Mathematics
& Statistics
Lancaster
University

Meta-analytic structural equation modelling

Application to Mendelian randomization studies

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Outline

- Meta-analytic structural equation modelling
- SEMs - RAM specification
- linear IV - single study and meta-analysis (two-stage structural equation modelling)
- Mediation model with IVs - single study and meta-analysis
- Conclusion

Meta-analytic structural equation modelling

- Studies report cov/corr matrices between variables (N, $\overline{x}$)
- SEMs and causal inference: Vanderweele (2012), De Stavola *et al.* (2015)
- SEMs for MR: Shin *et al.* (2014); Burgess *et al.* (2015); Evans & Davey Smith (2015); Ziegler *et al.* (2015)
- Cheung & Chan (2005); Meta-analytic structural equation modeling: A two stage approach
- Cheung (2015a) Meta-analysis: A structural equation modeling approach.
- `metaSEM` package for R (Cheung, 2015b); calls `OpenMx` (Boker *et al.* , 2011)

SEMs and meta-analysis models

- Using GLMM commands to fit meta-analysis models:
  1. random effects - numerical integration
  2. constraints - especially on residual variance - correct SEs

  - Normand (1999) - SAS `proc mixed`
  - Van Houwelingen *et al.* (2002) - SAS `proc mixed`
  - Stijnen *et al.* (2010) - SAS `proc nlmixed`
  - Bagos (2015) - Stata `gllamm`
- Using SEM commands to fit meta-analysis models:
  - Cheung (2008) - Mplus
  - Cheung (2010) - LISREL
  - Cheung (2013) - R `metaSEM`, OpenMx; MPlus
  - Palmer & Sterne (2015) - Stata `sem`, `gsem`

SEMs: RAM specification

- SEM specifications: LISREL, EQS, Mplus, RAM (OpenMx & `metaSEM`)
- 4 matrices ***F***, ***M***, ***A***, and ***S***, and a vector v
- v represents all variables in the model.
- ***A*** specifies regression coefficients and factor loadings (single headed arrows).
- ***S*** var-covar matrix or corr matrix of variables (double headed arrows).
- ***M*** means of the variables.
- ***F*** selection matrix indicating the observed variables.

RAM speicification II

- SEM implied means, $\mu(\theta)$, and covariance matrix $\Sigma(\theta)$, where $\boldsymbol{I}$ is an identity matrix, are

$$\mu(\theta) = \boldsymbol{F}(\boldsymbol{I} - \boldsymbol{A})^{-1}\boldsymbol{M}$$
$$\Sigma(\theta) = \boldsymbol{F}(\boldsymbol{I} - \boldsymbol{A})^{-1}\boldsymbol{S}((\boldsymbol{I} - \boldsymbol{A})^{-1})'\boldsymbol{F}'.$$

Mendelian randomization using SEM

- (Full information) ML estimation of linear instrumental variable model

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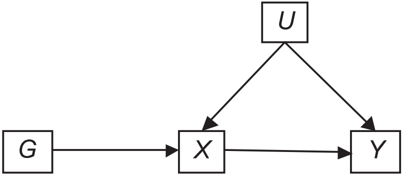
DAG



Mendelian randomization using SEM

- (Full information) ML estimation of linear instrumental variable model

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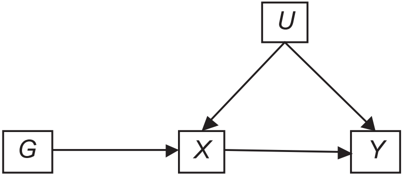
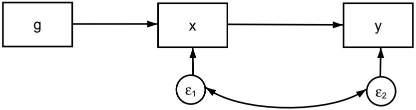


Path diagram (Burgess *et al.* , 2015, Figure 4)



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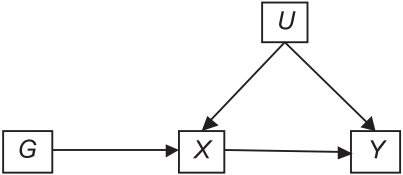

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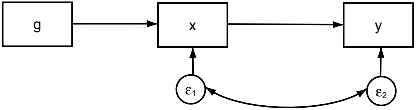


$$Y = \beta_0 + \beta_1 X + \varepsilon_1, \quad X = \alpha_0 + \alpha_1 G + \varepsilon_2, \qquad \begin{pmatrix} \varepsilon_1 \\ \varepsilon_2 \end{pmatrix} \sim MVN(0, \Sigma)$$

Example fit in OpenMx I

- Simulate a single study

$$\begin{aligned} n &= 10000 \\ G &= \text{Binomial}(2,\ p = 0.3) \\ Y &= 1 + X + \varepsilon_1, \\ X &= 1 + G + \varepsilon_2, \end{aligned}$$

$$\begin{pmatrix} \varepsilon_1 \\ \varepsilon_2 \end{pmatrix} \sim MVN\left(0,\ \mathbf{\Sigma} = \begin{bmatrix} 1 & 0.75 \\ 0.75 & 1 \end{bmatrix}\right)$$

- Observed means and covariances (first stage $R^2 = 0.3$)

$$\text{Means} = \begin{bmatrix} y : 2.60 \\ x : 1.61 \\ g : 0.61 \end{bmatrix} \quad \text{Covariances} = \begin{bmatrix} 3.92 & 2.17 & 0.43 \\ 2.17 & 1.43 & 0.42 \\ 0.43 & 0.42 & 0.42 \end{bmatrix}$$

Example fit in OpenMx II

$$\boldsymbol{A} = \begin{bmatrix} 0 & \beta_1 & 0 \\ 0 & 0 & \alpha_1 \\ 0 & 0 & 0 \end{bmatrix}, \boldsymbol{S} = \begin{bmatrix} \sigma^2_{\varepsilon_1} & \sigma_{\varepsilon_1\varepsilon_2} & 0 \\ \sigma_{\varepsilon_1\varepsilon_2} & \sigma^2_{\varepsilon_2} & 0 \\ 0 & 0 & \sigma^2_g \end{bmatrix}, \boldsymbol{M} = \begin{bmatrix} \beta_0 \\ \alpha_0 \\ \bar{g} \end{bmatrix}, \boldsymbol{F} = \boldsymbol{I}(3)$$

```
library(OpenMx)

# define model
tsls.model <- mxModel("TSLS", mxData(observed=my.cov, type="cov",
    numObs=n, means=my.means), A1, S1, M1, F1,
    mxExpectationRAM(A="A1", S="S1", F="F1", M="M1",
      dimnames = c("y","x","g")), mxFitFunctionML())

# fit model
tsls.fit <- mxRun(tsls.model)
if (tsls.fit$output$status$code <= 1) summary(tsls.fit)
```

Example fit in OpenMx III

```
> summary(tsls.fit)
Summary of TSLS

free parameters:
     name matrix row col Estimate Std.Error A
1   beta1     A1   1   2 1.0018335 0.015291192
2  alpha1     A1   2   3 1.0064283 0.015391885
3  errory     S1   1   1 0.9987171 0.026822173
4 errorxy     S1   1   2 0.7455682 0.019717928
5  errorx     S1   2   2 0.9991108 0.014130145
6    varg     S1   3   3 0.4218099 0.005965600
7   beta0     M1   1   y 0.9870826 0.026577242
8  alpha0     M1   1   x 0.9950869 0.013729530
9   meang     M1   1   g 0.6115000 0.006494691
...
```

- Estimation using standardised variables (correlations) $\beta_{1s} = \beta_1 \frac{\mathrm{sd}(x)}{\mathrm{sd}(y)} = 1.002 \times 1.19/1.98 = 0.604$

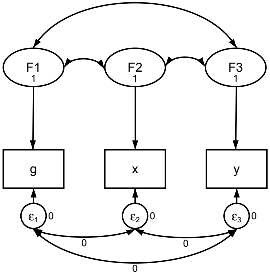
Meta-analysis

Approaches:

- Fit TSLS in each study and then meta-analyse
- Estimate numerator (YG) and denominator (XG) in each study, meta-analyse, then calculate ratio
- Fit SEM to all studies (parameters constrained equal across studies, e.g. Stata `ssd` framework)
- METASEM:
  1. Meta-analyse corr/covs (GLS) then weighted SEM
  2. TSSEM: multi-group SEM then weighted SEM

TSSEM - stage 1

- Stage 1: estimate pooled correlations/covariances using a multigroup SEM
- Correlations/covariances constrained equal in each study
- Estimation weighted by the var-covar matrices of each study's corr/cov matrix



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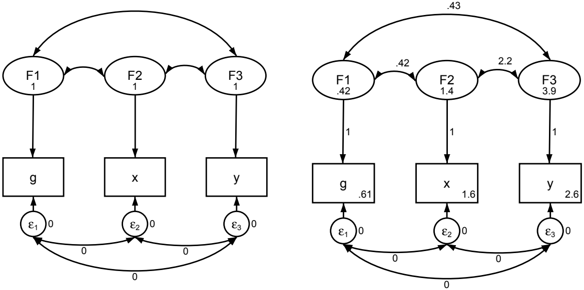

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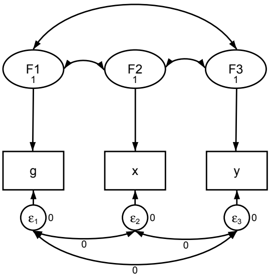
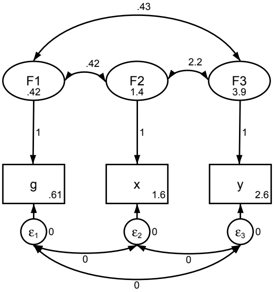
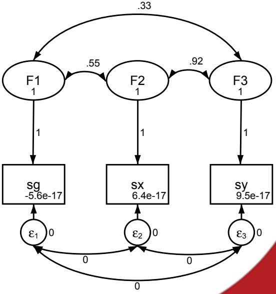




Standardized



TSSEM - stage 2

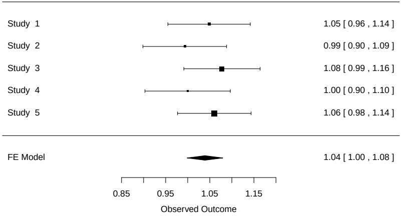
- Fit SEM using ADF (GMM) estimation weighted by inverse of var-cov matrix of pooled correlation matrix

$$\begin{aligned} r_F &= \text{vechs(Stage 1 pooled cov/corr matrix)} \\ \boldsymbol{V}_F &= \text{Var-covar matrix of Stage 1 pooled cov/corr matrix} \\ \rho(\theta) &= \text{vechs}(\Sigma) = \text{vechs}(\boldsymbol{F}(\boldsymbol{I} - \boldsymbol{A}_\theta)^{-1}\boldsymbol{S}_\theta((\boldsymbol{I} - \boldsymbol{A}_\theta)^{-1})'\boldsymbol{F}') \\ \text{ADF minimises: } & (r_F - \rho(\theta))'\boldsymbol{V}_F^{-1}(r_F - \rho(\theta)) \end{aligned}$$

TSSEM example

- Simulate 5 studies from same model ($N = 1000$, $\overline{R}^2 = 0.3$)
- Fit TSLS in each study and meta-analyse

Unstandardised variables



TSSEM example

- Simulate 5 studies from same model ($N = 1000$, $\overline{R}^2 = 0.3$)
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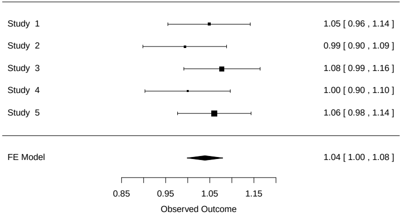
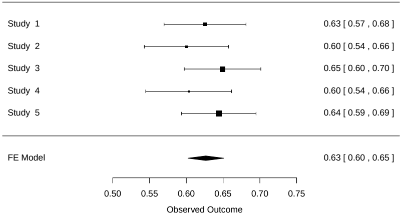
Unstandardised variables



Standardised variables



TSSEM example
Stage 1: covariances

```
> fixed1 <- tssem1(scovs, sampsizes, method="FEM", cor.analysis=FALSE)
> summary(fixed1)
...
Coefficients:
       Estimate Std.Error z value Pr(>|z|)
S[1,1] 4.0290830 0.0806222 49.975 < 2.2e-16 ***
S[1,2] 2.2430250 0.0467777 47.951 < 2.2e-16 ***
S[1,3] 0.4400050 0.0191257 23.006 < 2.2e-16 ***
S[2,2] 1.4639978 0.0292948 49.975 < 2.2e-16 ***
S[2,3] 0.4246214 0.0124470 34.114 < 2.2e-16 ***
S[3,3] 0.4054322 0.0081127 49.975 < 2.2e-16 ***
---
Signif. codes: 0 *** 0.001 ** 0.01 * 0.05 . 0.1   1
...
> coef(fixed1)
        y         x         g
y 4.029083 2.2430250 0.4400050
x 2.243025 1.4639978 0.4246214
g 0.440005 0.4246214 0.4054322
```

TSSEM example
Stage 2: covariances

```
> fixed2 <- tssem2(fixed1, Amatrix=A1, Smatrix=S1, Fmatrix=F1,
+ diag.constraints=TRUE, intervals.type="LB")
> summary(fixed2)
...
95% confidence intervals: Likelihood-based statistic
Coefficients:
      Estimate Std.Error lbound ubound z value Pr(>|z|)
beta1  1.03623       NA 1.01956 1.05249   NA       NA
alpha1 1.04733       NA 1.02950 1.06517   NA       NA
ey     0.95251       NA 0.90865 0.99738   NA       NA
exy    0.72599       NA 0.68835 0.76407   NA       NA
ex     1.01928       NA 0.97924 1.05927   NA       NA
```

- FE MA of TSLS estimates: 1.04 (1.00, 1.08)

TSSEM example
Stage 1: correlations

```
> fixed1s <- tssem1(sscovs, sampsizes, method="FEM", cor.analysis=TRUE)
> summary(fixed1s)
...
Coefficients:
       Estimate Std.Error z value Pr(>|z|)
S[1,2] 0.9235678 0.0020814 443.722 < 2.2e-16 ***
S[1,3] 0.3446074 0.0124713 27.632 < 2.2e-16 ***
S[2,3] 0.5514068 0.0098498 55.982 < 2.2e-16 ***
---
Signif. codes: 0 *** 0.001 ** 0.01 * 0.05 . 0.1   1
...
> coef(fixed1s)
          sy        sx        sg
sy 1.0000000 0.9235678 0.3446074
sx 0.9235678 1.0000000 0.5514068
sg 0.3446074 0.5514068 1.0000000
```

TSSEM example
Stage 2: correlations

```
> fixed2 <- tssem2(fixed1, Amatrix=A1, Smatrix=S1, Fmatrix=F1,
+                 diag.constraints=TRUE, intervals.type="z")
> summary(fixed2s)
...
95% confidence intervals: z statistic approximation
Coefficients:
       Estimate Std.Error  lbound   ubound z value Pr(>|z|)
beta1  0.6249602 0.0122872 0.6008779 0.6490426 50.863 < 2.2e-16 ***
alpha1 0.5514068 0.0116996 0.5284761 0.5743376 47.130 < 2.2e-16 ***
ey     0.2361890 0.0086635 0.2192090 0.2531691 27.263 < 2.2e-16 ***
exy    0.2986075 0.0114840 0.2760993 0.3211157 26.002 < 2.2e-16 ***
ex     0.6959505 0.0129382 0.6705921 0.7213089 53.790 < 2.2e-16 ***
---
Signif. codes: 0 *** 0.001 ** 0.01 * 0.05 . 0.1   1
...
```

- FE MA of standardised TSLS: 0.63 (0.60, 0.65)
- Convert to unstandardised scale: $\beta_1 = \beta_{1s}\frac{\text{sd}(y)}{\text{sd}(x)}$ – need average sd(x) and sd(y) to rescale

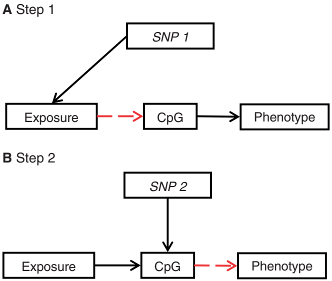
Mediation model: concept

- Concerns about possible measurement error/confounding in the mediator
- Cole & Preacher (2014) outline problems using imprecisely measured variables in path analysis:
  - Under or over-estimate effects
  - Reduced power
  - Valid models appear invalid
  - Differential measurement error in various parts of model can change conclusions
  - Problems get worse as models get more complex
- Instrument the mediator as well as the exposure
- Similar model proposed in clinical trials (Imai *et al.* , 2013)
- Non-parametric SEM / 3SLS estimation (Tchetgen Tchetgen & Lin, 2012)

Mediation model: definition

DAG

Relton & Davey Smith (2012)



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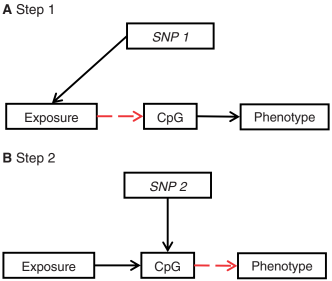
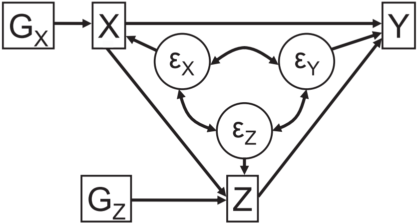


Path diagram

Burgess *et al.* (2015)



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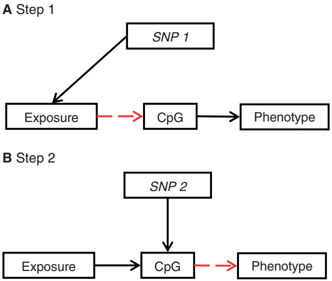

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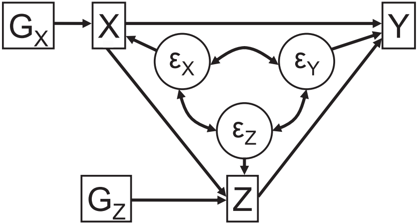
Burgess *et al.* (2015)



$$
\begin{aligned}
Y &= \beta_0 + \beta_1 X + \beta_2 Z + \varepsilon_1, \\
X &= \alpha_0 + \alpha_1 G1 + \varepsilon_2, \\
Z &= \gamma_0 + \gamma_1 G2 + \gamma_2 X + \varepsilon_3
\end{aligned}
\qquad
\begin{pmatrix} \varepsilon_1 \\ \varepsilon_2 \\ \varepsilon_3 \end{pmatrix} \sim MVN(0, \Sigma)
$$

Mediation model: single study fit in OpenMx I

$$\boldsymbol{A} = \begin{bmatrix} 0 & \beta_1 & \beta_2 & 0 & 0 \\ 0 & 0 & 0 & \alpha_1 & 0 \\ 0 & \gamma_1 & 0 & 0 & \gamma_2 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix}, \quad \boldsymbol{S} = \begin{bmatrix} \sigma^2_{\varepsilon_1} & \sigma_{\varepsilon_1\varepsilon_2} & \sigma_{\varepsilon_1\varepsilon_3} & 0 & 0 \\ \sigma_{\varepsilon_1\varepsilon_2} & \sigma^2_{\varepsilon_2} & \sigma_{\varepsilon_1\varepsilon_3} & 0 & 0 \\ \sigma_{\varepsilon_1\varepsilon_3} & \sigma_{\varepsilon_2\varepsilon_3} & \sigma^2_{\varepsilon_3} & 0 & 0 \\ 0 & 0 & 0 & \sigma^2_{G1} & 0 \\ 0 & 0 & 0 & 0 & \sigma^2_{G2} \end{bmatrix}$$

$$\boldsymbol{M} = \begin{bmatrix} \beta_0 \\ \alpha_0 \\ \gamma_0 \\ \overline{G1} \\ \overline{G2} \end{bmatrix}, \quad \boldsymbol{F} = \boldsymbol{I}(5)$$

- $R^2_X = 0.3$, $R^2_{Z,G2} = 0.16$

Mediation model: single study fit in OpenMx II

```
> mxTryHard(mediation.model)
> summary(mediation.fit2)
...
free parameters:
      name matrix row col  Estimate   Std.Error
1    beta1     A1   1   2 1.0109453 0.018136100
2   gamma1     A1   3   2 1.0209632 0.015113946
3    beta2     A1   1   3 1.0019530 0.009864446
4   alpha1     A1   2   4 1.0155065 0.015515166
5   gamma2     A1   3   5 1.0259136 0.013303523
6   errory     S1   1   1 0.9793607 0.027248906
7  errorxy     S1   1   2 0.7425581 0.020213100
8   errorx     S1   2   2 1.0150569 0.014356109
9  erroryz     S1   1   3 0.3855889 0.021258490
10 errorxz     S1   2   3 0.4930445 0.018988609
11  errorz     S1   3   3 0.9931549 0.020481237
12   varg1     S1   4   4 0.4218099 0.005965607
13   varg2     S1   5   5 0.4260051 0.006024941
14   beta0     M1   1   y 0.9849710 0.030509203
15  alpha0     M1   1   x 1.0037412 0.013839038
16  gamma0     M1   1   z 0.9588452 0.027641798
17  meang1     M1   1  g1 0.6115000 0.006494691
18  meang2     M1   1  g2 0.6088000 0.006526907
...
```

Mediation model: meta-analysis – stage 1 covs

- Simulate 5 studies from same model ($N = 1000$)

```
> fixed1 <- tssem1(scovs, sampsizes, method="FEM", cor.analysis=FALSE)
> summary(fixed1)
...
Coefficients:
        Estimate Std.Error z value Pr(>|z|)
S[1,1] 14.0847613 0.2818307 49.9760 <2e-16 ***
S[1,2] 4.1042813 0.0861058 47.6655 <2e-16 ***
S[1,3] 7.0914238 0.1465197 48.3991 <2e-16 ***
S[1,4] 0.8598434 0.0365179 23.5458 <2e-16 ***
S[1,5] 0.6208533 0.0429352 14.4602 <2e-16 ***
S[2,2] 1.4335084 0.0286838 49.9762 <2e-16 ***
S[2,3] 1.9145515 0.0435214 43.9911 <2e-16 ***
S[2,4] 0.4252767 0.0125247 33.9550 <2e-16 ***
S[2,5] -0.0094234 0.0134083 -0.7028 0.4822
S[3,3] 4.0431484 0.0809034 49.9750 <2e-16 ***
S[3,4] 0.4272514 0.0194131 22.0084 <2e-16 ***
S[3,5] 0.6332306 0.0242343 26.1295 <2e-16 ***
S[4,4] 0.4204346 0.0084129 49.9749 <2e-16 ***
S[4,5] -0.0087257 0.0072621 -1.2015 0.2295
S[5,5] 0.6263648 0.0125336 49.9748 <2e-16 ***
---
Signif. codes: 0 *** 0.001 ** 0.01 * 0.05 . 0.1   1
```

Mediation model: meta-analysis – stage 2 covs

```
> fixed2 <- tssem2(fixed1, Amatrix=A1, Smatrix=S1, Fmatrix=F1,
+                 diag.constraints=TRUE, intervals.type="LB")
> summary(fixed2)
...
95% confidence intervals: Likelihood-based statistic
Coefficients:
       Estimate Std.Error lbound ubound z value Pr(>|z|)
beta1   1.02087        NA 0.99777 1.04377    NA       NA
beta2   0.99634        NA 0.98214 1.01051    NA       NA
alpha1  1.01150        NA 0.99349 1.02951    NA       NA
gamma1  1.02570        NA 1.00810 1.04302    NA       NA
gamma2  1.02683        NA 1.00763 1.04595    NA       NA
ey      0.97624        NA 0.92966 1.02415    NA       NA
exy     0.73331        NA 0.69452 0.77253    NA       NA
ex      1.00333        NA 0.96390 1.04269    NA       NA
eyz     0.35686        NA 0.32107 0.39343    NA       NA
exz     0.45387        NA 0.41927 0.48883    NA       NA
ez      0.96391        NA 0.92302 1.00517    NA       NA
```

Conclusion

- MASEM (inc. TSSEM) implemented in `metaSEM` R package
- Stage 1: estimate pooled correlation/covariance matrix
- Stage 2: SEM (ADF weighted by inverse Stage 1 var-cov)
- TSSEM can be used for MR analyses and complex mediation models
- `sem` (Stata) can't fit Stage 2
- Using correlations returns estimates for standardized variables
- Bayesian approach of Prevost *et al.* (2007) (Fisher's z)
- MR using path analysis could help uptake by researchers in psychology

References I

Bagos, Pantelis G. 2015. Meta-analysis in Stata using gllamm. *Research Synthesis Methods*, **6**(4), 310–332.

Boker, S, Neale, M, Maes, H, Wilde, M, Spiegel, M, Brick, T, Spies, J, Estabrook, R, Kenny, S, Bates, T, Mehta, P, & Fox, J. 2011. OpenMx: An Open Source Extended Structural Equation Modeling Framework. *Psychometrika*, **76**(2), 306–317.

Burgess, Stephen, Daniel, Rhian M, Butterworth, Adam S, & Thompson, Simon G. 2015. Network Mendelian randomization: using genetic variants as instrumental variables to investigate mediation in causal pathways. *International Journal of Epdiemiology*, **44**(2), 484–95.

Cheung, Mike. 2010. Fixed-Effects Meta-Analyses as Multiple-Group Structural Equation Models. *Structural Equation Modeling: A Multidisciplinary Journal*, **17**(3), 481–509.

Cheung, Mike W. 2013. Multivariate Meta-Analysis as Structural Equation Models. *Multivariate Meta-Analysis as Structural Equation Models*, **20**(3), 429–454.

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

Cheung, Mike W.-L. 2015a. *Meta-analysis: A structural equation modeling approach*. Chichester, UK: John Wiley & Sons, Ltd.

Cheung, Mike W.-L. 2015b. metaSEM: An R Package for Meta-Analysis using Structural Equation Modeling. *Frontiers in Psychology*, **5**, 01521.

Cheung, Mike W L, & Chan, Wai. 2005. Meta-Analytic Structural Equation Modeling: A Two-Stage Approach. *Psychological Methods*, **10**(1), 40–64.

Cole, David A, & Preacher, Kristopher J. 2014. Manifest variable path analysis: Potentially serious and misleading consequences due to uncorrected measurement error. *Psychological methods*, **19**(2), 300–15.

References II

De Stavola, Bianca L., Daniel, Rhian M., Ploubidis, George B., & Micali, Nadia. 2015. Mediation analysis with intermediate confounding: Structural equation modeling viewed through the causal inference lens. *American Journal of Epidemiology*, **181**(1), 64–80.

Evans, David M, & Davey Smith, George. 2015. Mendelian Randomization: New Applications in the Coming Age of Hypothesis-Free Causality. *Annual Review of Genomics and Human Genetics*, 1–24.

Imai, Kosuke, Tingley, Dustin, & Yamamoto, Teppei. 2013. Experimental designs for identifying causal mechanisms. *Journal of the Royal Statistical Society. Series A: Statistics in Society*, **176**(1), 5–51.

Normand, Sharon Lise T. 1999. Tutorial in biostatistics meta-analysis: Formulating, evaluating, combining, and reporting. *Statistics in Medicine*, **18**(3), 321–359.

Palmer, T M, & Sterne, J A C. 2015. Fitting fixed- and random-effects meta-analysis models using structural equation modeling with the sem and gsem commands. *Stata Journal*, **15**(3), 645–671.

Prevost, A T, Mason, D, Griffin, S, Kinmonth, A L, & Sutton, S. 2007. Allowing for correlations between correlations in random-effects meta-analysis of correlation matrices. *Psychological Methods*, **12**(4), 434–450.

Relton, Caroline L., & Davey Smith, George. 2012. Two-step epigenetic mendelian randomization: A strategy for establishing the causal role of epigenetic processes in pathways to disease. *International Journal of Epidemiology*, **41**(1), 161–176.

Shin, So-Youn, Petersen, Ann-Kristin, Wahl, Simone, Zhai, Guangju, Romisch-Margl, Werner, Small, Kerrin, Doring, Angela, Kato, Bernet, Peters, Annette, Grundberg, Elin, Prehn, Cornelia, Wang-Sattler, Rui, Wichmann, H Erich, Hrabe de Angelis, Martin, Illig, Thomas, Adamski, Jerzy, Deloukas, Panos, Spector, Tim, Suhre, Karsten, Gieger, Christian, & Soranzo, Nicole. 2014. Interrogating causal pathways linking genetic variants, small molecule metabolites and circulating lipids. *Genome Medicine*, **6**(3), 25.

References III

Stijnen, Theo, Hamza, Taye H., & Özdemir, Pinar. 2010. Random effects meta-analysis of event outcome in the framework of the generalized linear mixed model with applications in sparse data. *Statistics in Medicine*, **29**(29), 3046–3067.

Tchetgen Tchetgen, Eric J, & Lin, Sheng Hsuan. 2012. *Robust Estimation of Pure / Natural Direct Effects with Mediator Measurement Error*. Tech. rept. Harvard University Biostatistics Working Paper Series Paper 152.

Van Houwelingen, Hans C., Arends, Lidia R., & Stijnen, Theo. 2002. Advanced methods in meta-analysis: Multivariate approach and meta-regression. *Statistics in Medicine*, **21**(4), 589–624.

Vanderweele, Tyler J. 2012. Invited commentary: Structural equation models and epidemiologic analysis. *American Journal of Epidemiology*, **176**(7), 608–612.

Ziegler, A, Mwambi, H, & König, I R. 2015. Mendelian randomization versus path models: Making causal inferences in genetic epidemiology. *Human Heredity*, **79**(3-4), 194–204.