Fitting fixed and random effects meta-analysis models using structural equation models

Tom M. Palmer Jonathan A. C. Sterne

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Mathematics & Statistics | Lancaster University

Outline

- Introduction

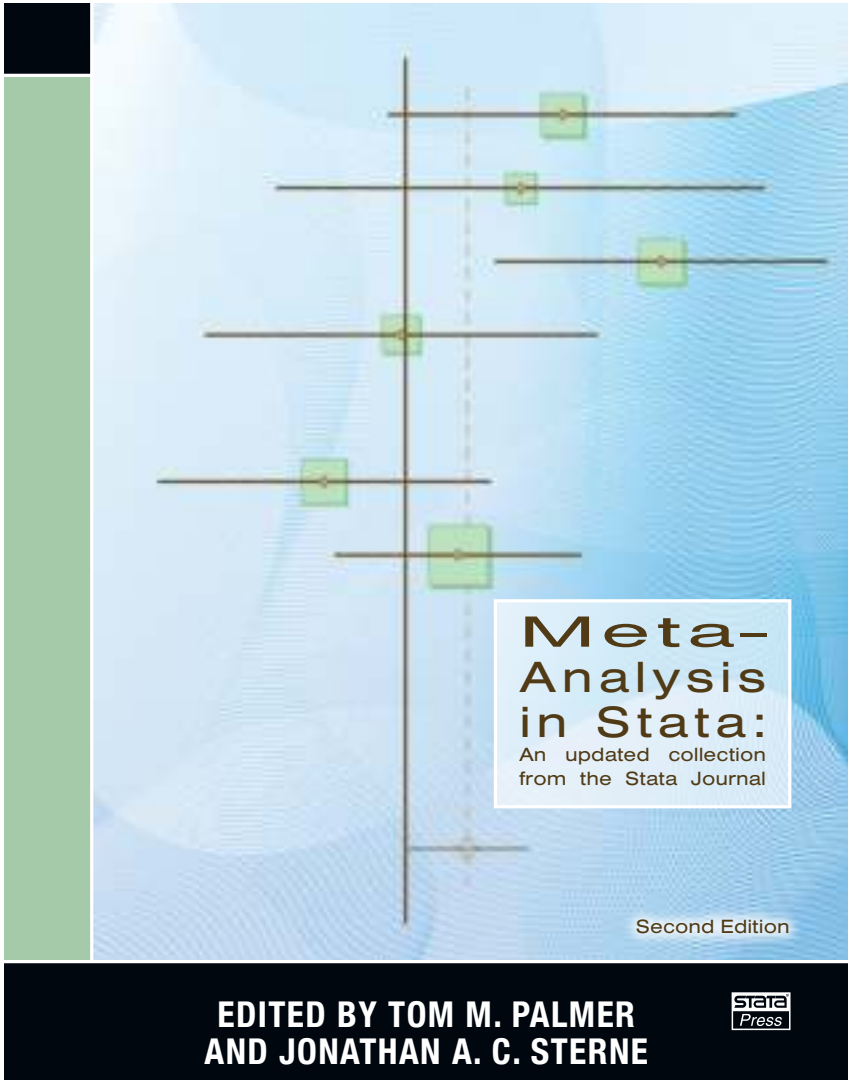
1. Univariate fixed effect meta-analysis
2. Univariate random effects meta-analysis
3. Multivariate meta-analysis with non-zero within study covariances

- Summary

Introduction I

- This talk focuses on the use of Stata and follows Palmer & Sterne (Stata Journal, forthcoming)

Stata Journal meta-analysis book 2nd ed. coming soon



- 27 Stata Journal articles, 11 new since 1st ed. (3 forthcoming)

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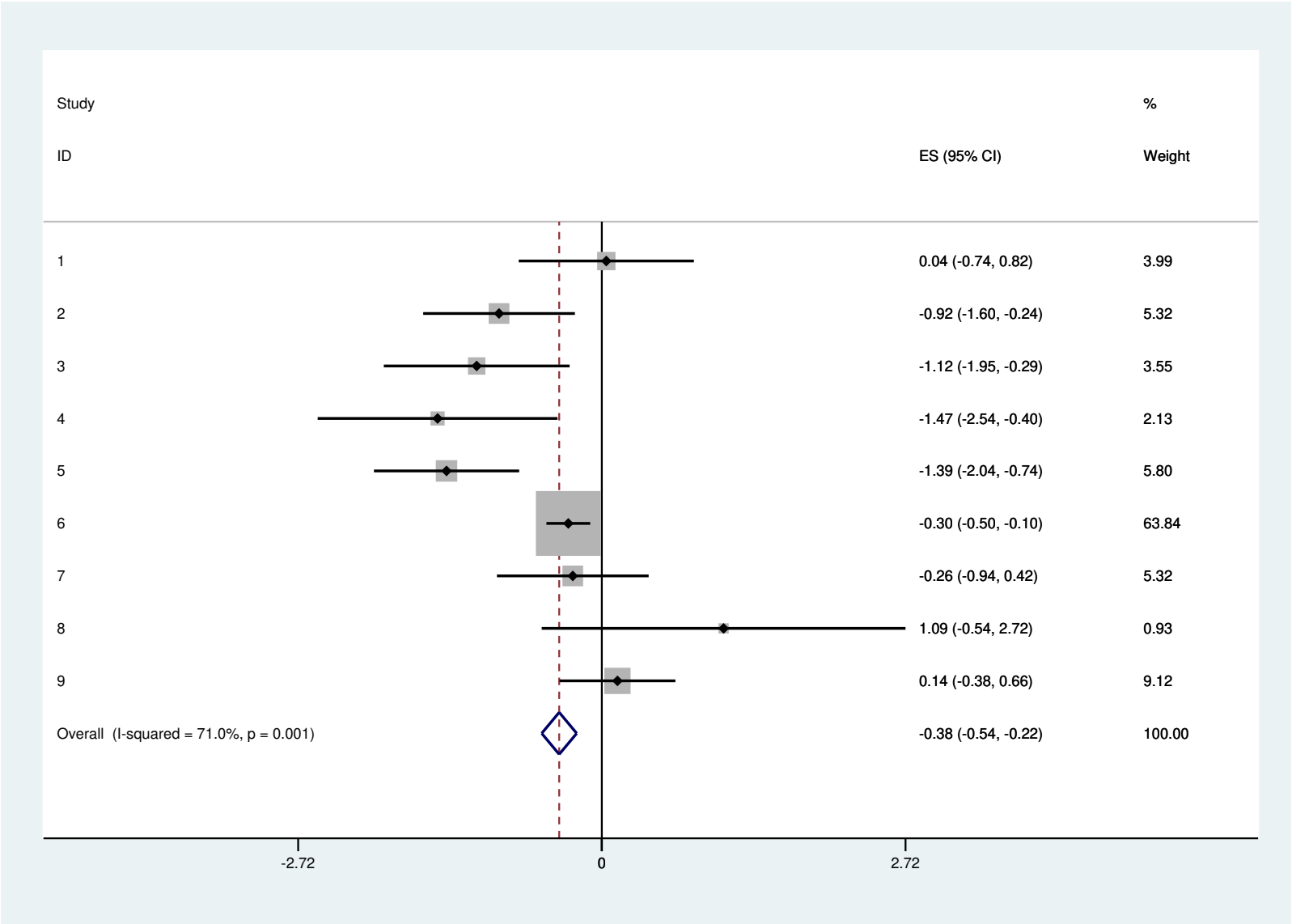
- Using SEM for meta-analysis well developed in Psychology
- Discussed in articles (and a new book) by Cheung (2008, 2010, 2013a, 2013b, 2013c, 2015)
- `metaSEM` package in R (automates use of `OpenMx`) also by Cheung

1. Univariate outcome meta-analysis models: fixed effect

$$y_i \sim N(\theta,\ \sigma_i^2)$$

i.e. y_i and σ_i^2 estimated in each study.

- Example, Turner et al. (2000)
- 9 trials investigating effect of taking diuretics during pregnancy on risk of pre-eclampsia
- log odds ratios for association between pre-eclampsia and diuretics from each study and SE



Pooled OR: 0.68 (95% CI 0.58, 0.80) – lower risk of pre-eclampsia for diuretic group

Syntax 1

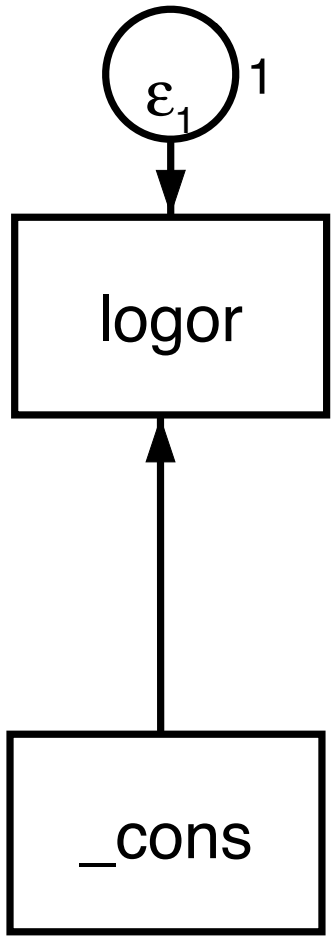
To fit the model in `sem` we generate a weighting variable of inverse variances:

- $Y \sim N(X\theta,\ \sigma^2 W^{-1})$
- WLS estimate:
  $\widehat{\theta} = (X'WX)^{-1}X'WY = (\sum_{i=1}^{N} w_i y_i)/(\sum_{i=1}^{N} w_i)$
- Variance of WLS estimate $= \sigma^2(X'WX)^{-1}$
- But we require the pooled variance to be:
  $1/\sum_{i=1}^{N} w_i = (X'WX)^{-1}$
- Hence we constrain $\sigma^2 = 1$.

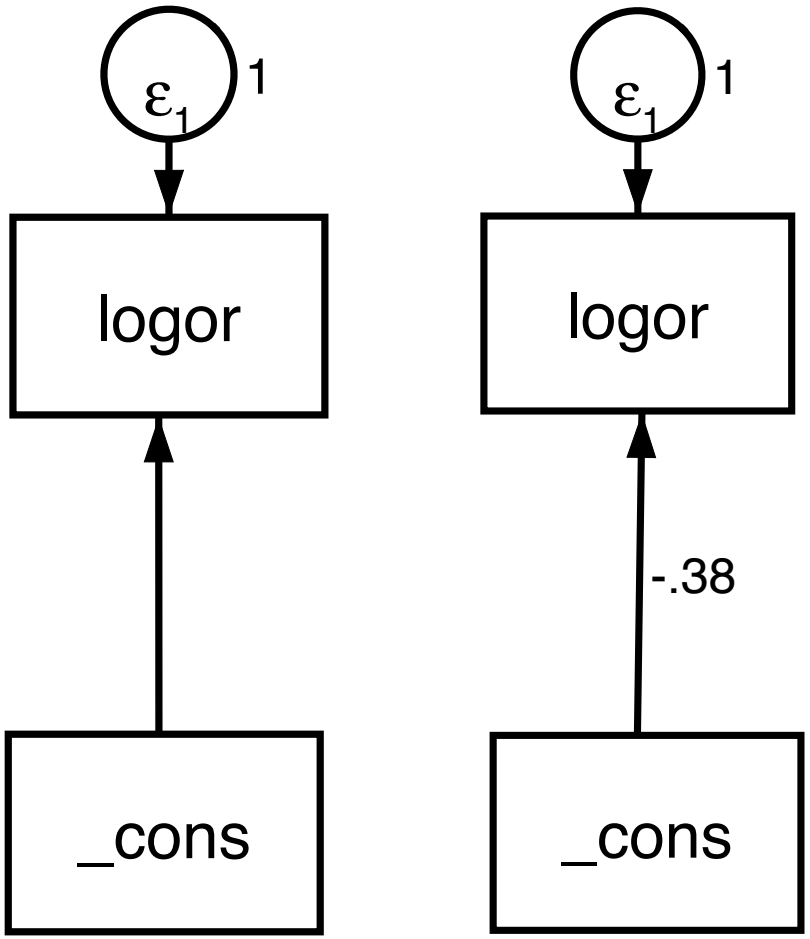
Syntax 1

```
.  gen double weight = 1/varlogor
.  sem (logor <- ) [iw=weight], var(e.logor@1) nodescribe nocnsreport nolog

Structural equation model                       Number of obs      =         9
Estimation method  = ml
Log likelihood     = -157.71614

------------------------------------------------------------------------------
             |                 OIM
             |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
Structural   |
  logor <-   |
       _cons |  -.3815467   .0799025    -4.78   0.000    -.5381527   -.2249406
-------------+----------------------------------------------------------------
 var(e.logor)|          1  (constrained)
------------------------------------------------------------------------------
LR test of model vs. saturated: chi2(1)   =    143.07, Prob > chi2 = 0.0000
```

Stata SEM builder path diagrams I



Stata SEM builder path diagrams I



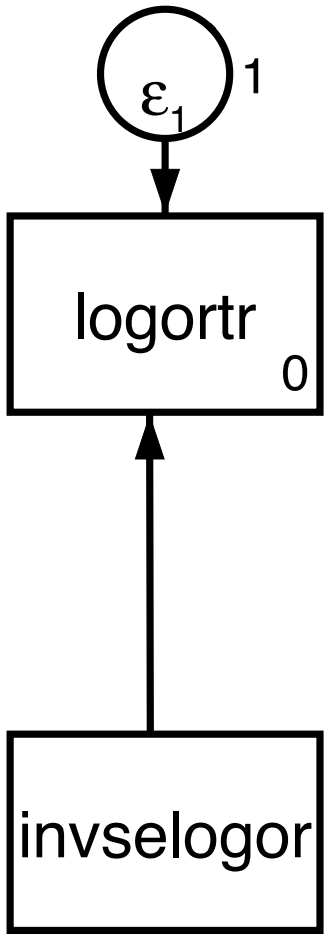
After fitting the estimated coefficient is shown

Syntax 2

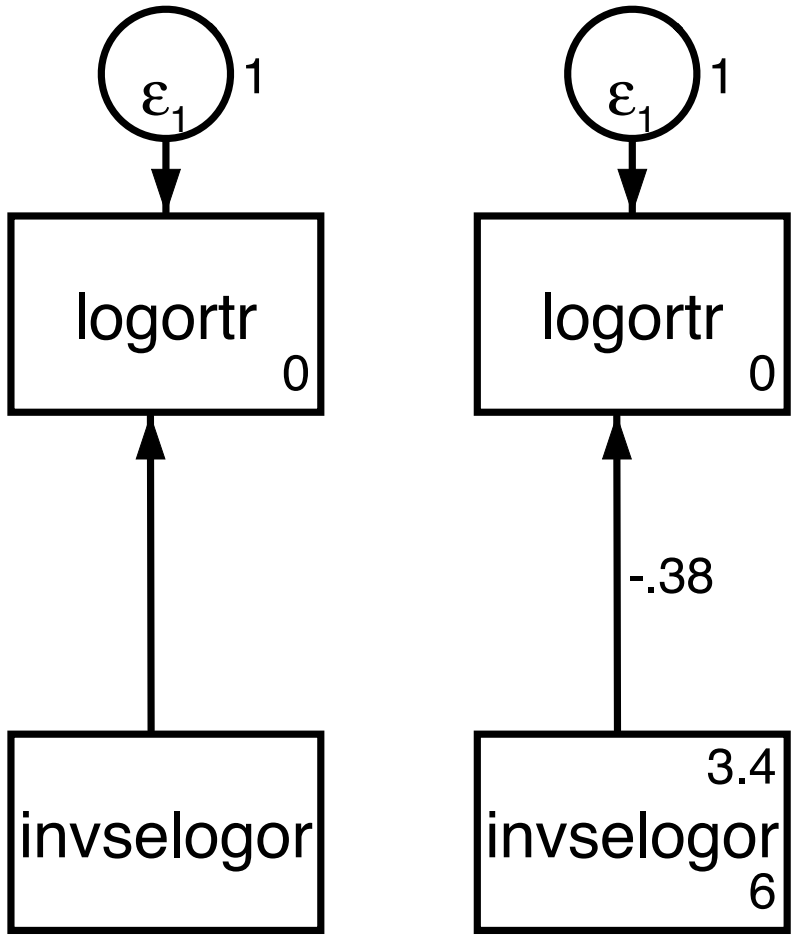
- Fit the same model by scaling all the variables by 1/SEs
- Scale the vector of 1's for the intercept
- Constrain $\sigma^2 = 1$

```
. gen double invselogor = 1/selogor
. gen double logortr = logor*invselogor
. sem (logortr <- invselogor, nocons), noheader nodescribe nocnsreport nolog var(e.logortr@1)

------------------------------------------------------------------------------
             |                 OIM
             |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
Structural   |
  logortr <- |
   invselogor |  -.3815467   .0799025    -4.78   0.000    -.5381527   -.2249406
        _cons |          0  (constrained)
-------------+----------------------------------------------------------------
var(e.logortr)|          1  (constrained)
------------------------------------------------------------------------------
LR test of model vs. saturated: chi2(2)   =      9.10, Prob > chi2 = 0.0106
```

Stata SEM builder path diagrams II



Stata SEM builder path diagrams II



After fitting the estimated coefficient is shown, along with mean and variance of covariate (scaled intercept)

Heterogeneity test

- Remove constraint from σ^2.

```
. sem (logortr <- invselogor, nocons), noheader nodescribe nocnsreport nolog
------------------------------------------------------------------------------
             |                 OIM
             |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
Structural   |
  logortr <- |
   invselogor |  -.3815467   .1398305    -2.73   0.006    -.6556094    -.107484
        _cons |           0  (constrained)
-------------+----------------------------------------------------------------
var(e.logortr)|   3.062546   1.443698                      1.215689     7.715122
------------------------------------------------------------------------------
LR test of model vs. saturated: chi2(1)   =      0.61, Prob > chi2 = 0.4344
```

- $Q = \widehat{\sigma^2} N = 3.016 \times 9 = 27.56,\ P = 0.00056$
- $I^2 = \frac{Q-df}{Q} = (27.56 - 8)/27.56 = 0.71$

2. Univariate outcome random effects meta-analysis

$$y_i \sim N(\theta + \nu_i,\ \sigma_i^2)$$
$$\nu_i \sim N(0,\ \tau^2)$$

- Syntax 1: 9 studies – 9 random effects
- Syntax 2: interact 1 random effect with standard errors (untransformed variables)
- Syntax 3: interact 1 random effect with the inverse standard error transformed variables
- Same example meta-analysis
- `metan` RE DL pooled log OR: -0.516 (95% CI -0.908, -0.124)
- $Q = 27.56$ (p=0.001), $I^2 = 71\%$, $\tau^2 = 0.2185$

Syntax 3 – use 1/SE transformed variables

- Constrain coefficient of interaction of inverse SEs and RE to 1.
- Constrain variance of residuals to 1.
- Variance of RE, `var(M)`, is estimate of τ^2.

```
. gsem (logortr <- invselogor c.invselogor#c.M@1, nocons), ///
>       var(e.logortr@1) latent(M) nolog nocnsreport

Generalized structural equation model           Number of obs   =          9
Log likelihood =   -18.8726

------------------------------------------------------------------------------
             |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
logortr <-   |
    invselogor |  -.5166151   .2059448    -2.51   0.012    -.9202594   -.1129708
             |
c.invselogor#c.M |          1  (constrained)
             |
       _cons |          0  (omitted)
-------------+----------------------------------------------------------------

        var(M) |  .2377469     .1950926                      .0476023     1.187413

-------------+----------------------------------------------------------------
 var(e.logortr)|          1  (constrained)
------------------------------------------------------------------------------
```

Syntax 3 – use 1/SE transformed variables

- Constrain coefficient of interaction of inverse SEs and RE to 1.
- Constrain variance of residuals to 1.
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```
.  gsem (logortr <- invselogor c.invselogor#c.M@1, nocons), ///
>        var(e.logortr@1) latent(M) nolog nocnsreport

Generalized structural equation model             Number of obs   =          9
Log likelihood =   -18.8726

------------------------------------------------------------------------------
             |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
logortr <-   |
  invselogor |  -.5166151   .2059448    -2.51   0.012    -.9202594   -.1129708
             |
c.invselogor#c.M |          1  (constrained)
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-------------+----------------------------------------------------------------

      var(M) |  .2377469     .1950926                      .0476023     1.187413

-------------+----------------------------------------------------------------
var(e.logortr)|          1  (constrained)
------------------------------------------------------------------------------
```
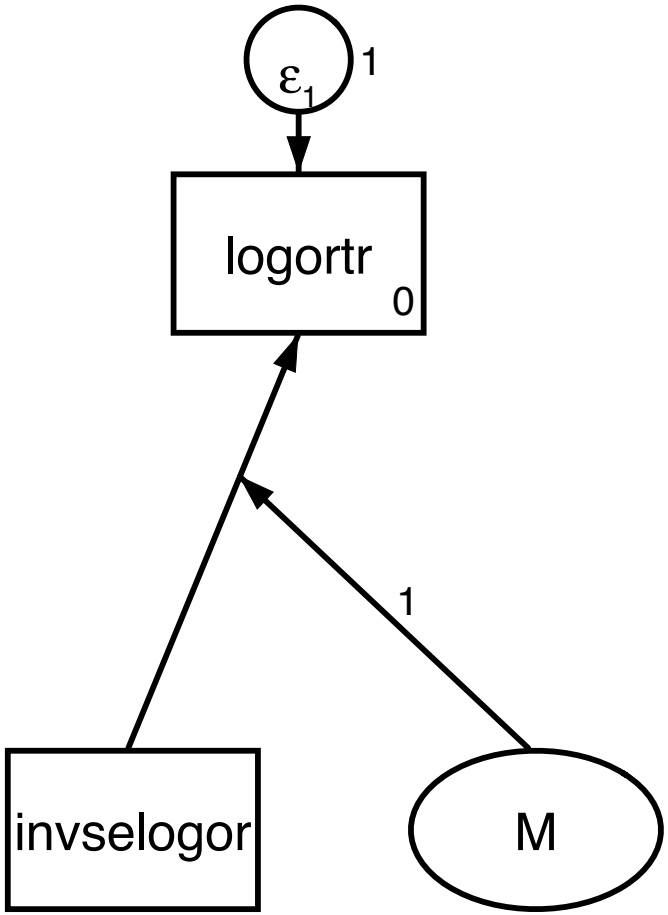
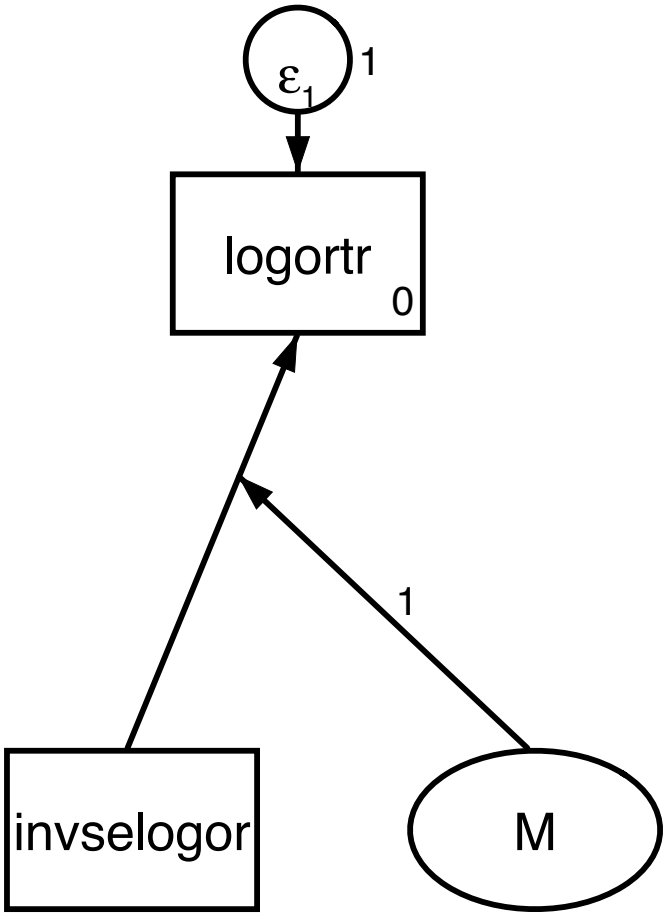
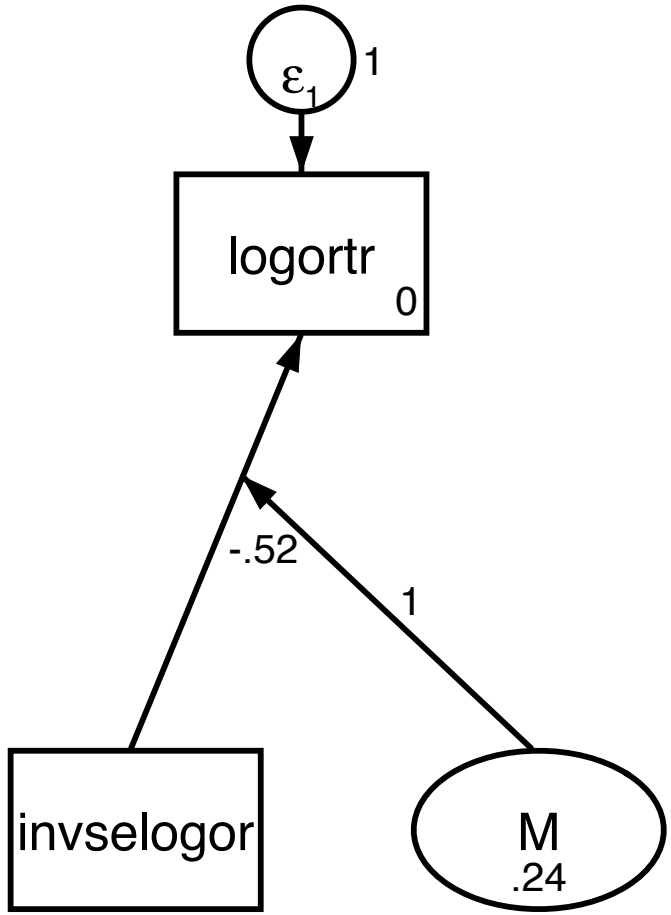

- `gsem` can't do REML estimation of τ^2 (`metaSEM` in R can).
- can derive a prediction interval for pooled estimate

Stata SEM builder syntax 3 path diagram



Stata SEM builder syntax 3 path diagram





3.1 Multivariate fixed effect meta-analysis with non-zero within study covariances

- $Y = \begin{bmatrix} y_{11} \\ y_{12} \\ \dots \\ y_{N1} \\ y_{N2} \end{bmatrix}$, $\boldsymbol{\theta} = \begin{bmatrix} \theta_1 \\ \theta_2 \end{bmatrix}$, $V_i = \begin{bmatrix} \sigma^2_{i,11} & \sigma_{i,12} \\ \sigma_{i,12} & \sigma^2_{i,22} \end{bmatrix}$
- $\Sigma = \begin{bmatrix} V_1 & 0 & 0 \\ 0 & \dots & 0 \\ 0 & 0 & V_N \end{bmatrix}$ $\quad Y \sim \text{MVN}(\boldsymbol{\theta},\ \Sigma)$
- Transformation multivariate equivalent of 1/SE scaling – Cholesky decomposition of inverse of within study covariance matrix, i.e. $W_i^{1/2} = V_i^{-1/2}$
- $W^{1/2}Y \sim \text{MVN}(W^{1/2}X\boldsymbol{\theta},\ W^{1/2}\Sigma(W^{1/2})')$
- Fibrinogen Studies Collaboration (2004): incidence of CHD (log hazard ratio), 31 studies using 2 outcomes

Multivariate fixed effect meta-analysis with non-zero within study covariances

```
. use FSCstage1, clear

. * code to generate transformed outcome and outcome indicator variables

. sem (ystarstack <- xstarstack1 xstarstack2, nocons), ///
>         var(e.ystarstack@1) nocapslatent nolog nocnsr nodescribe

Structural equation model                       Number of obs      =        62
Estimation method  = ml
Log likelihood     = -384.49772

------------------------------------------------------------------------------
                 |                 OIM
                 |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-----------------+------------------------------------------------------------
Structural       |
  ystarstack <-  |
     xstarstack1 |   .2042387   .0529888     3.85   0.000     .1003826    .3080947
     xstarstack2 |   .8639001   .0536208    16.11   0.000     .7588052     .968995
           _cons |          0  (constrained)
-----------------+------------------------------------------------------------
var(e.ystarstack)|          1  (constrained)
------------------------------------------------------------------------------
LR test of model vs. saturated: chi2(2)   =     15.87, Prob > chi2 = 0.0004
```

Heterogeneity test for both outcomes jointly

- Again remove constraint from variance of residuals

```
. quietly sem (ystarstack <- xstarstack1 xstarstack2, nocons), nocapslatent

. di "var(e.ystarstack) = " _b[var(e.ystarstack):_cons]
var(e.ystarstack) = 1.8483607

. local Q = _b[var(e.ystarstack):_cons]*e(N)

. local df = e(N) - 2

. di "Het. test statistic = " `Q'
Het. test statistic = 114.59836

. di "Het. test p-value = " chi2tail(`df', `Q')
Het. test p-value = .00002803
```

Decompose the heterogeneity test for each outcome

- `reshape` data to `wide` format
- Specify model using 2 equations – 1 for each outcome; each has a residual variance

```
qui sem (ystarstack1 <- xstarstack11 xstarstack21@c1) ///
>         (ystarstack2 <- xstarstack22@c1), nocons ///
>         nocaps nolog nocnsr nodescribe
```

Outcome	Approach	Q	*P*	I^2 (95% CI)
1	Multivariate	48.12	P=0.019 (`sem`)	18 (`mvmeta`)
1	Univariate	36.74	P=0.185	18 (0, 48)
2	Multivariate	66.50	P<0.0001 (`sem`)	55 (`mvmeta`)
2	Univariate	66.19	P<0.0001	55 (32, 70)

3.2 Random effects multivariate meta-analysis with non-zero within study covariance

- $Y \sim \text{MVN}(\boldsymbol{\theta} + \boldsymbol{\nu},\ \Sigma)$
- $\boldsymbol{\nu} \sim N(\mathbf{0},\ \boldsymbol{T^2})$, for a 2 outcome model $\boldsymbol{T^2} = \begin{bmatrix} \tau_1^2 & \tau_{12} \\ \tau_{12} & \tau_2^2 \end{bmatrix}$
- `long` format data – specify `study` level random effects

```
.  gsem (ystarstack <- c.xstarstack1#c.M1[study]@1 c.xstarstack2#c.M2[study]@1 ///
>        xstarstack1 xstarstack2, nocons), ///
>        latent(M1 M2) nocnsreport nolog ///
>        cov(e.ystarstack@1 (M1[study]*M2[study]))

Generalized structural equation model           Number of obs   =         62
Log likelihood = -101.66433

------------------------------------------------------------------------------
                             |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-----------------------------+------------------------------------------------------------------
ystarstack <-                |
                  xstarstack1 |   .1875603   .0690866     2.71   0.007     .0521531    .3229675
                  xstarstack2 |   .8585811   .0887304     9.68   0.000     .6846728    1.032489
 ...
-----------------------------+------------------------------------------------------------------
               var(M1[study])|   .0221546   .0324089                      .0012597    .3896245
               var(M2[study])|   .0945799   .0614174                      .0264883    .3377098
-----------------------------+------------------------------------------------------------------
cov(M2[study],M1[study])|   .0272542   .0382754     0.71   0.476    -.0477642    .1022726
-----------------------------+------------------------------------------------------------------
       var(e.ystarstack)|          1  (constrained)
------------------------------------------------------------------------------
```

Equivalent model for wide format data (2 equations).

```
. gsem (ystarstack1 <- c.xstarstack11#c.M1@1 c.xstarstack21#c.M2@1 ///
>                 xstarstack11 xstarstack21@c1, nocons) ///
>         (ystarstack2 <- c.xstarstack22#c.M2@1 xstarstack22@c1, nocons), ///
>         cov(e.ystarstack1@1 e.ystarstack2@1) latent(M1 M2) ///
>         collinear nocnsreport nolog

Generalized structural equation model             Number of obs   =         31
Log likelihood = -101.66433

------------------------------------------------------------------------------
                     |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
---------------------+--------------------------------------------------------------
ystarstack1 <-       |
       xstarstack11 |   .1875603   .0690866     2.71   0.007     .0521531    .3229675
       xstarstack21 |   .8585811   .0887304     9.68   0.000     .6846728    1.032489
...
---------------------+--------------------------------------------------------------
ystarstack2 <-       |
       xstarstack22 |   .8585811   .0887304     9.68   0.000     .6846728    1.032489
...
---------------------+--------------------------------------------------------------
             var(M1)|   .0221546   .0324089                      .0012597    .3896245
             var(M2)|   .0945799   .0614174                      .0264883    .3377098
---------------------+--------------------------------------------------------------
          cov(M2,M1)|   .0272542   .0382754     0.71   0.476    -.0477642    .1022726
---------------------+--------------------------------------------------------------
  var(e.ystarstack1)|          1  (constrained)
  var(e.ystarstack2)|          1  (constrained)
------------------------------------------------------------------------------
. di "corr(M1,M2)=", _b[cov(M2,M1):_cons]/sqrt(_b[var(M1):_cons]*_b[var(M2):_cons])

corr(M1,M2)= .59539071
```

Summary

- Can fit these models using `metan`; `metareg`; `mvmeta` (White, 2009, 2011)
- Fixed effect meta-analysis – 2 syntaxes
- Random effect meta-analysis – 3 syntaxes
- Meta-regression – FE and RE
- Multivariate outcome – FE and RE – with zero and non-zero within study covariances
- (and by extension) Multivariate meta-regression
- For RE models `gsem` cannot perform REML estimation – `metaSEM` in R can.
- Cochran heterogeneity test after FE models (joint test and test for each multivariate outcome)

References

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- Mike Cheung (National University of Singapore)
- Rebecca Pope, Stephanie White, and the development team of the `gsem` command at StataCorp
- Medical and Pharmaceutical Statistics (MPS) Research Unit, Lancaster University

RE MA syntax 1: 9 random effects

- Constrain coefficients of study and RE interactions to 1.
- Constrain the studies to be independent with variance as estimated in each study.
- Variance of residuals `var(e.logor)` is estimate of τ^2

Syntax 1: 9 random effects

```
. mkmat varlogor, mat(f)

. mat f = diag(f)

. qui tabulate trial, gen(tr)

. gsem (logor <- M1#c.tr1@1 M2#c.tr2@1 M3#c.tr3@1 ///
>          M4#c.tr4@1 M5#c.tr5@1 M6#c.tr6@1 ///
>          M7#c.tr7@1 M8#c.tr8@1 M9#c.tr9@1) ///
>         , covstructure(_LEx, fixed(f)) intmethod(laplace) nocnsreport nolog

Generalized structural equation model             Number of obs   =          9
Log likelihood = -9.4552759

------------------------------------------------------------------------------
             |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
logor <-     |
  c.tr1#c.M1 |          1  (constrained)
  ...
       _cons |  -.5166151   .2059448    -2.51   0.012    -.9202594   -.1129707
-------------+----------------------------------------------------------------
      var(M1)|        .16  (constrained)
      var(M2)|        .12  (constrained)
      var(M3)|        .18  (constrained)
      var(M4)|         .3  (constrained)
      var(M5)|        .11  (constrained)
      var(M6)|        .01  (constrained)
      var(M7)|        .12  (constrained)
      var(M8)|        .69  (constrained)
      var(M9)|        .07  (constrained)
-------------+----------------------------------------------------------------
 var(e.logor)|   .2377469   .1950926                      .0476023    1.187413
------------------------------------------------------------------------------
```

- Can derive 95% prediction interval for pooled effect

```
. local setotal = sqrt(_se[logor:_cons]^2 + _b[var(e.logor):_cons])

. local pilow = _b[logor:_cons] - invt(e(N) - 2, .975)*‘setotal’

. local piupp = _b[logor:_cons] + invt(e(N) - 2, .975)*‘setotal’

. di "95% Prediction interval:", ‘pilow’, ‘piupp’
95% Prediction interval: -1.7682144 .73498424
```

Syntax 2: 1 random effect interacted with SEs

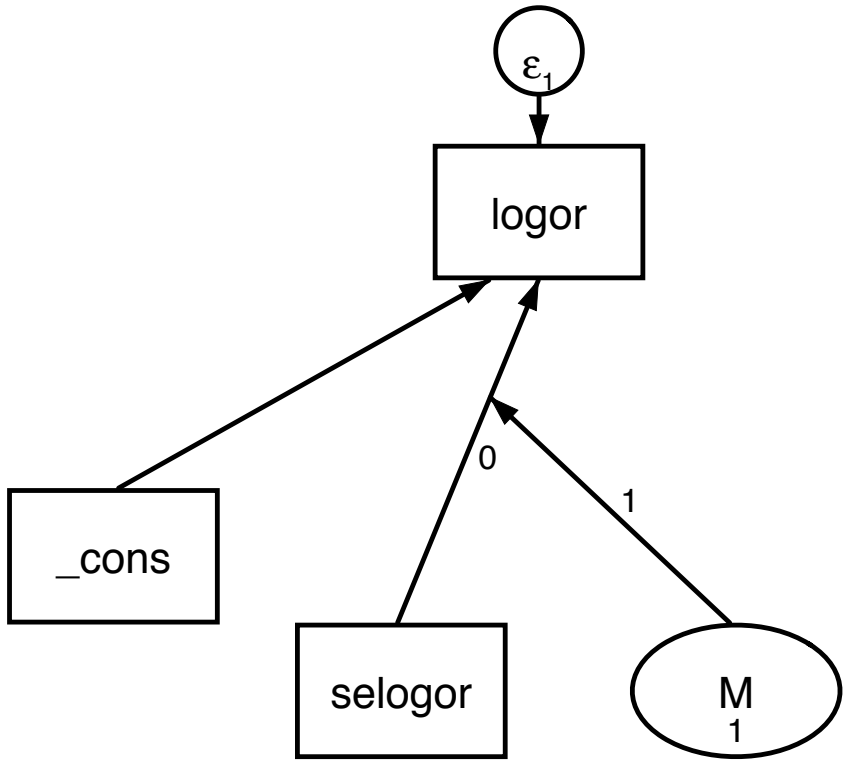
- Constrain interaction coefficients to 1.
- Constrain variance of REs to 1.
- Variance of residuals `var(e.logor)` is estimate of τ^2.

```
. gsem (logor <- ibn.trial#c.selogor#c.M@1), var(M@1) nolog nocnsreport

Generalized structural equation model             Number of obs   =          9
Log likelihood = -9.4552759

------------------------------------------------------------------------------
                     |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
---------------------+--------------------------------------------------------------
logor <-             |
trial#c.selogor#c.M  |
                  1  |          1  (constrained)
                  2  |          1  (constrained)
                  3  |          1  (constrained)
                  4  |          1  (constrained)
                  5  |          1  (constrained)
                  6  |          1  (constrained)
                  7  |          1  (constrained)
                  8  |          1  (constrained)
                  9  |          1  (constrained)
                     |
               _cons |  -.5166151   .2059448    -2.51   0.012    -.9202594   -.1129708
---------------------+--------------------------------------------------------------
               var(M)|          1  (constrained)
---------------------+--------------------------------------------------------------
        var(e.logor)|   .2377469   .1950926                      .0476023    1.187413
------------------------------------------------------------------------------
```

Stata SEM builder random effects syntax 2 path diagram



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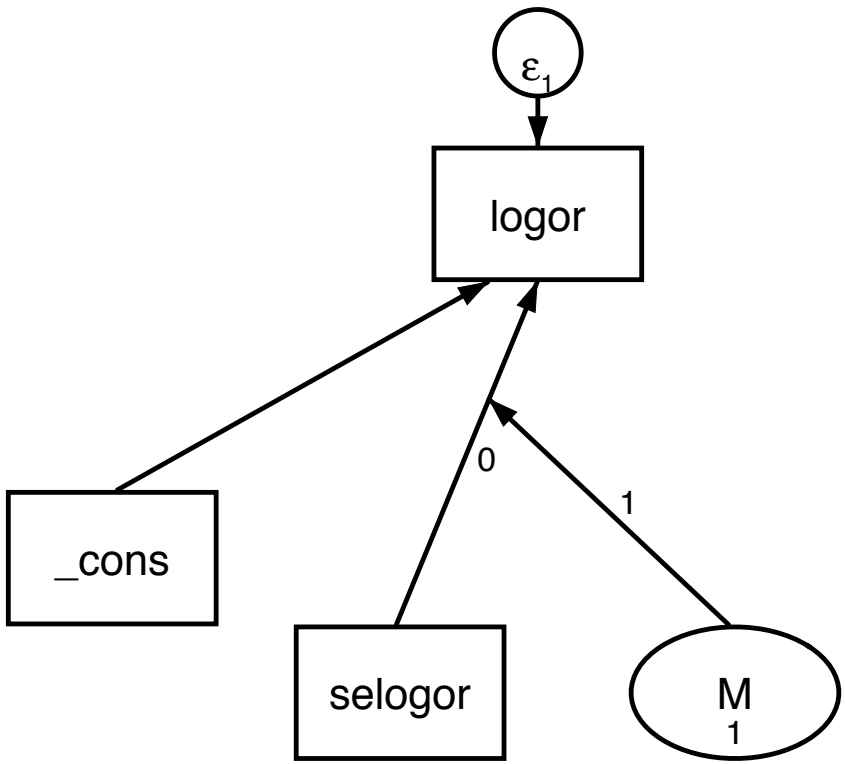

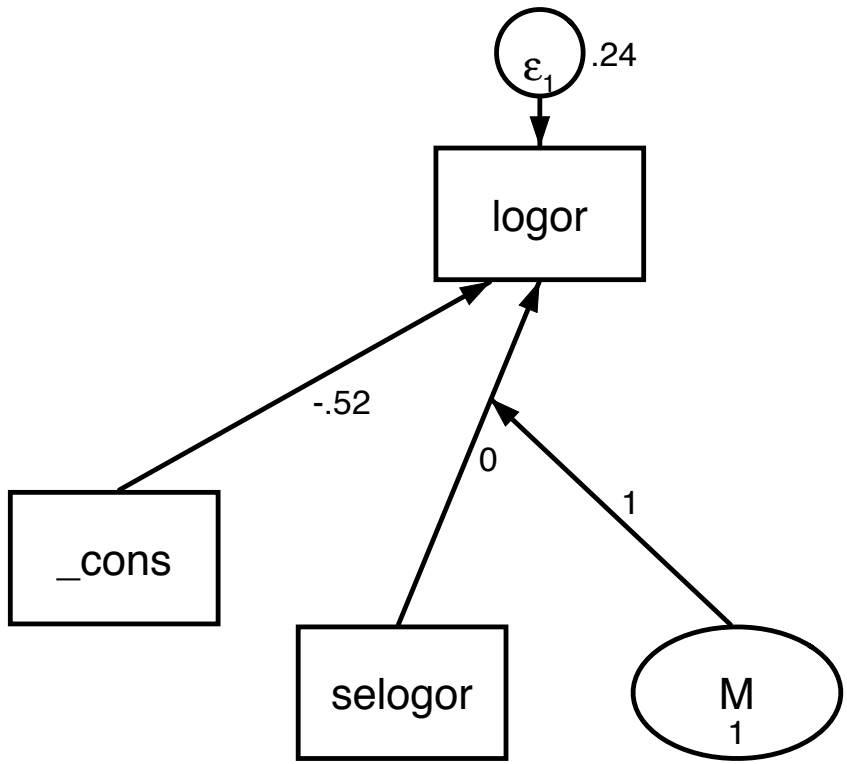

2.1 Fixed effect meta-regression

- $y_i \sim N(X_i\theta,\ \sigma_i^2)$
- Not recommend – assumes het. explained by covariates
- Tends to give too small SEs with moderate/large heterogeneity
- We need to fit it to obtain heterogeneity test
- Example data (Thompson & Sharp 1999) 28 RCTs of cholesterol lowering interventions for reducing risk of IHD.
- Each study reports log odds ratio and its SE, and a variable summarising the cholesterol reduction in each trial.

Fixed effect meta-regression

```
. use cholesterol, clear
(Serum cholesterol reduction & IHD)

. gen double invselogor = 1/sqrt(varlogor)

. gen double logortr = logor*invselogor

. gen double cholreductr = cholreduc*invselogor

. sem (logortr <- cholreductr invselogor, nocons), ///
>         nodescribe nolog nocnsreport var(e.logortr@1)

Structural equation model                       Number of obs      =        28
Estimation method  = ml
Log likelihood     = -165.21497

------------------------------------------------------------------------------
             |                 OIM
             |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
Structural   |
  logortr <- |
  cholreductr |  -.4752451   .1382083    -3.44   0.001    -.7461284   -.2043617
   invselogor |   .1207613   .0972033     1.24   0.214    -.0697538    .3112763
        _cons |          0  (constrained)
-------------+----------------------------------------------------------------
var(e.logortr)|          1  (constrained)
------------------------------------------------------------------------------
LR test of model vs. saturated: chi2(2)   =      1.42, Prob > chi2 = 0.4907
```

Heterogeneity test for meta-regression

- Remove constraint from variance of residuals

```
. quietly sem (logortr <- cholreductr invselogor, nocons), ///
>         nodescribe nolog nocnsreport

. local Q = _b[var(e.logortr):_cons]*e(N)

. local df = e(N) - 2

. di "Het. test statistic = " `Q'
Het. test statistic = 37.866258

. di "Het. test p-value = " chi2tail(`df', `Q')
Het. test p-value = .06231403
```

3.1 Fixed effect multivariate MA with zero within study covariances

- $Y = \begin{bmatrix} y_{11} \\ y_{12} \\ ... \\ y_{N1} \\ y_{N2} \end{bmatrix}$, $\boldsymbol{\theta} = \begin{bmatrix} \theta_1 \\ \theta_2 \end{bmatrix}$, $V_i = \begin{bmatrix} \sigma^2_{i,11} & 0 \\ 0 & \sigma^2_{i,22} \end{bmatrix}$
- $\Sigma = \begin{bmatrix} V_1 & 0 & 0 \\ 0 & ... & 0 \\ 0 & 0 & V_N \end{bmatrix}$
- $Y \sim \text{MVN}(\boldsymbol{\theta}, \Sigma)$
- Example meta-analysis (Riley et al. 2007) 10 studies, diagnostic accuracy of tumour marker for bladder cancer, each report logit of sensitivity and specificity

```
. use telomerase, clear
(Riley's telomerase data)

. reshape long y s, i(study) j(outcome)
(note: j = 1 2)

Data                               wide   ->   long
-----------------------------------------------------------------------------
Number of obs.                       10   ->      20
Number of variables                   5   ->       4
j variable (2 values)                     ->   outcome
xij variables:
                                  y1 y2   ->   y
                                  s1 s2   ->   s
-----------------------------------------------------------------------------

. gen byte y2cons = (outcome == 2)

. gen double invse = 1/s

. gen double ytr = y*invse

. gen double y2constr = y2cons*invse
```

```
. sem (ytr <- y2constr invse, nocons), nocaps nodescribe nolog nocnsr var(e.ytr@1)

Structural equation model                       Number of obs      =        20
Estimation method  = ml
Log likelihood     = -116.12748

------------------------------------------------------------------------------
             |                 OIM
             |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
Structural   |
  ytr <-     |
    y2constr |   .0834338   .2104572     0.40   0.692    -.3290547    .4959223
       invse |   1.126318   .1177527     9.57   0.000     .8955267    1.357109
       _cons |          0  (constrained)
-------------+----------------------------------------------------------------
   var(e.ytr)|          1  (constrained)
------------------------------------------------------------------------------
LR test of model vs. saturated: chi2(2)   =     47.82, Prob > chi2 = 0.0000

. lincom [ytr]invse + [ytr]y2constr

 ( 1)  [ytr]y2constr + [ytr]invse = 0

------------------------------------------------------------------------------
             |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         (1) |   1.209751    .174432     6.94   0.000      .867871    1.551632
------------------------------------------------------------------------------
```

Heterogeneity test

- Remove constraint from variance of residuals

```
. quietly sem (ytr <- y2constr invse, nocons), nocaps nodescribe nolog nocnsr

. local Q = _b[var(e.ytr):_cons]*e(N)

. local df = e(N) - 2

. di "Het. test statistic = " `Q'
Het. test statistic = 90.865377

. di "Het. test p-value = " chi2tail(`df', `Q')
Het. test p-value = 1.009e-11
```

3.2 Random effects multivariate outcomes with zero within study covariances

- $Y \sim \text{MVN}(\boldsymbol{\theta} + \boldsymbol{\nu},\ \Sigma)$
- $\boldsymbol{\nu} \sim N(\mathbf{0},\ \boldsymbol{T^2})$, for a 2 outcome model $\boldsymbol{T^2} = \begin{bmatrix} \tau_1^2 & \tau_{12} \\ \tau_{12} & \tau_2^2 \end{bmatrix}$

```
. use telomerase, clear

. gen double y1tr = y1/s1

. gen double invs1 = 1/s1

. gen double y2tr = y2/s2

. gen double invs2 = 1/s2
```

```
. gsem (y1tr <- c.invs1#c.M1@1 invs1, nocons) ///
>         (y2tr <- c.invs2#c.M2@1 invs2, nocons), ///
>         cov(e.y1tr@1 e.y2tr@1 e.y1tr*e.y2tr@0) ///
>         latent(M1 M2) nolog nocnsreport

Generalized structural equation model             Number of obs   =         10
Log likelihood = -37.273657

------------------------------------------------------------------------------
             |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
y1tr <-      |
       invs1 |   1.158561   .1616837     7.17   0.000     .8416669    1.475455
             |
...
-------------+----------------------------------------------------------------
y2tr <-      |
       invs2 |    2.00511   .4581216     4.38   0.000     1.107208    2.903012
             |
...
-------------+----------------------------------------------------------------
      var(M1)|   .1179669   .0000813                      .1178077    .1181264
      var(M2)|   1.628624   .0018461                       1.62501    1.632246
-------------+----------------------------------------------------------------
   cov(M2,M1)|  -.4383192   .0001342 -3265.57   0.000    -.4385823   -.4380561
-------------+----------------------------------------------------------------
  var(e.y1tr)|          1  (constrained)
  var(e.y2tr)|          1  (constrained)
------------------------------------------------------------------------------
```