MRC | Biostatistics Unit

An overview of meta-analysis in Stata
Part II: multivariate meta-analysis

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London, 10th September 2010

Plan

- Example 1: Berkey data
- Multivariate random-effects meta-analysis model
- Situations where it could be used
- Software: **`mvmeta`**
- A problem: unknown within-study correlation
- Example 2: fibrinogen
  - software: **`mvmeta_make`**
- Multivariate vs. univariate

Example from Berkey et al (1998)

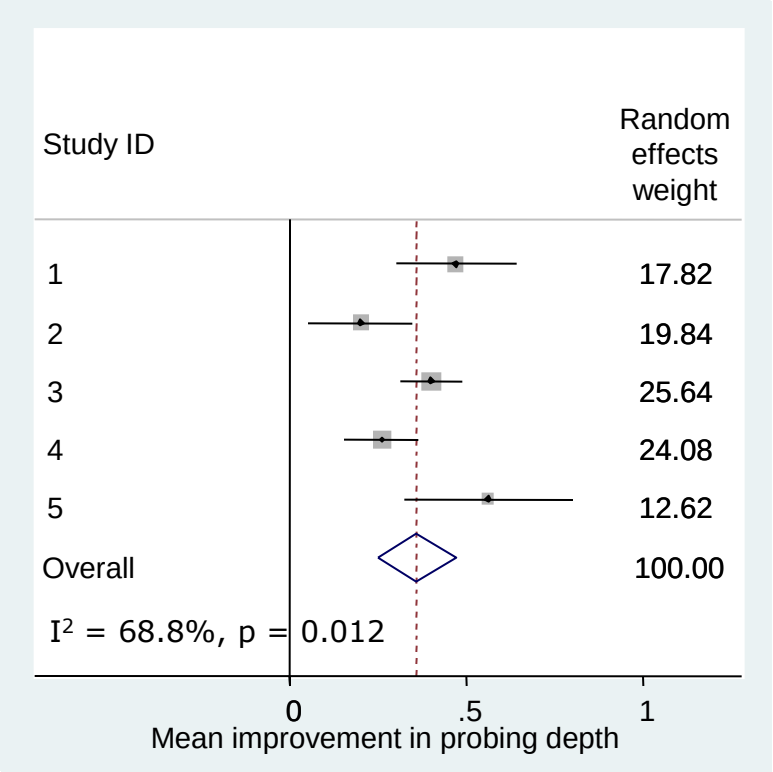
- 5 trials comparing a surgical with a non-surgical procedure for treating periodontal disease
- 2 outcomes:
  - "probing depth" (PD)
  - "attachment level" (AL)

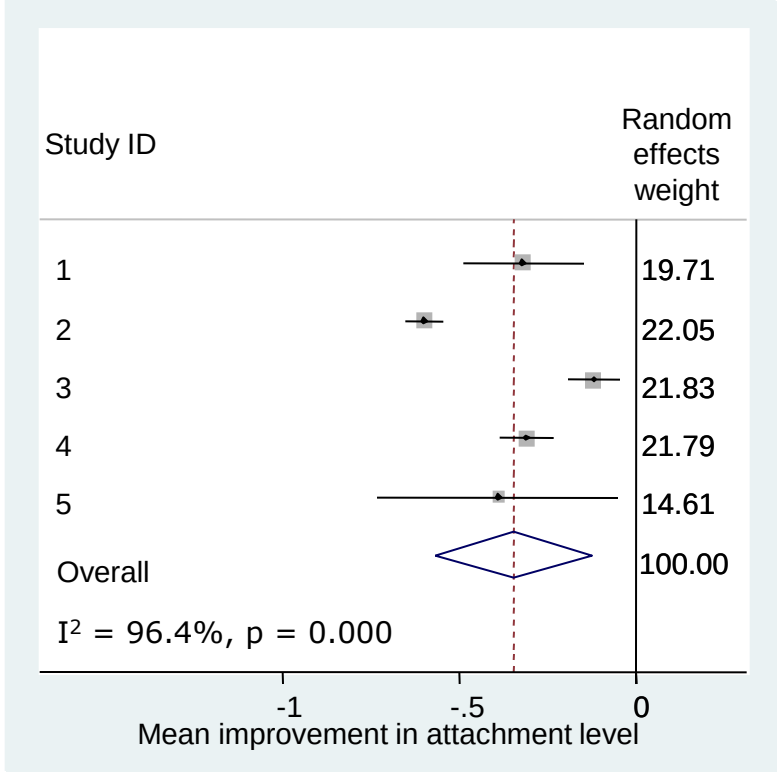
trial	y1	s1	y2	s2	corr
1	0.47	0.09	-0.32	0.09	0.39
2	0.20	0.08	-0.60	0.03	0.42
3	0.40	0.05	-0.12	0.04	0.41
4	0.26	0.05	-0.31	0.04	0.43
5	0.56	0.12	-0.39	0.17	0.34

`y1,y2` - treatment effects for PD, AL; `s1,s2` - standard errors

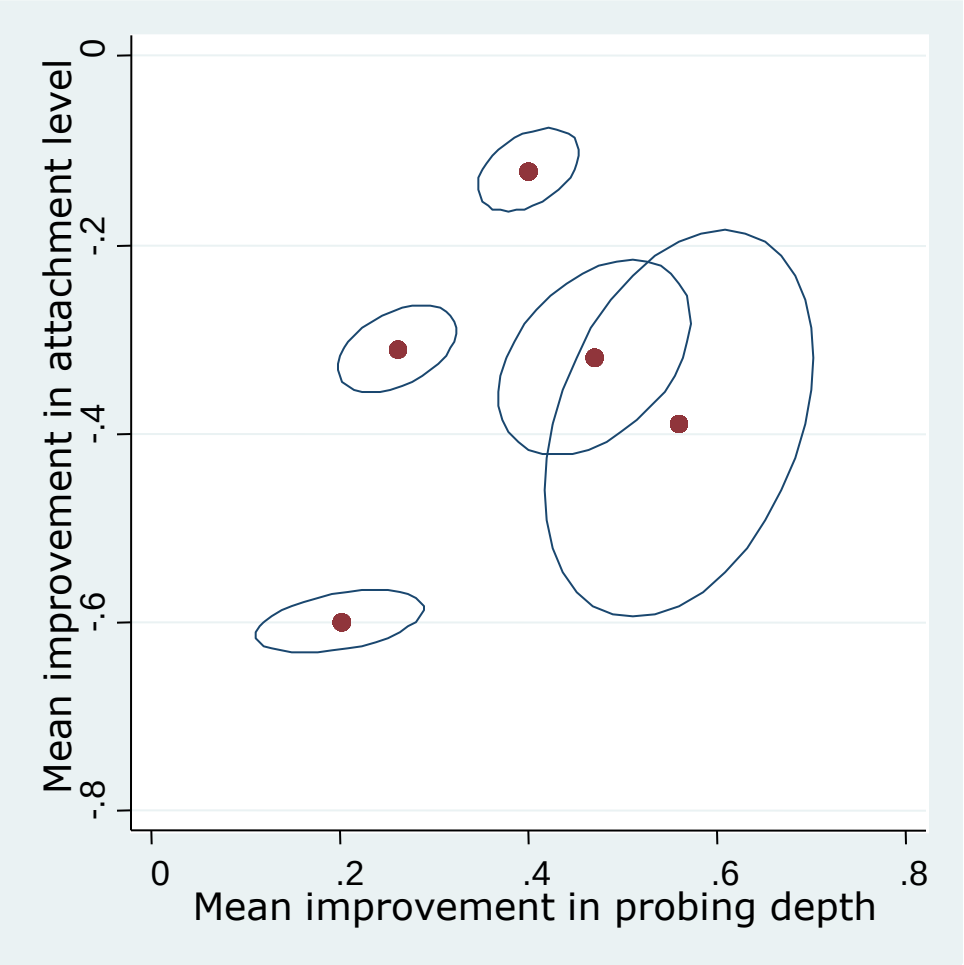
Berkey data (1)

- Could analyse the outcomes one by one





Berkey data (2)



- Dots mark the point estimates for the 5 studies
- Bubbles show 50% confidence regions
- Note the positive within-study correlation (0.3-0.4 for all studies)

- **`bubble.ado`**, available on my website

One or two stages?

- I'm assuming a *two-stage meta-analysis* (as in the Berkey data):
  - 1st stage: compute results for each study
  - 2nd stage: use these results as "data"
  - makes a Normal approximation to the within-study log-likelihoods
- *One-stage meta-analysis* is possible if we have individual participant data (IPD), but can be computationally horrible (Smith et al 2005)
  - we'll use the two-stage method even with IPD

Bivariate meta-analysis: data

- Data from *i*th study:
  - y_{i1}, y_{i2} – estimates for 1st, 2nd outcomes
  - s_{i1}, s_{i2} – their standard errors
  - but we also need the correlation ρ_{Wi} of y_{i1} and y_{i2}
- It's often most convenient to use matrix notation:

  estimate $$y_i = \begin{pmatrix} y_{i1} \\ y_{i2} \end{pmatrix}$$

  with within-study variance

$$S_i = \text{var}\begin{pmatrix} y_{i1} \\ y_{i2} \end{pmatrix} = \begin{pmatrix} s_{i1}^2 & \rho_{Wi} s_{i1} s_{i2} \\ \rho_{Wi} s_{i1} s_{i2} & s_{i2}^2 \end{pmatrix}$$

- NB y_{i1} or y_{i2} can be missing.

Bivariate meta-analysis: the model

- Data from *i*th study:
  - y_i – vector of estimates
  - S_i – variance-covariance matrix
- Model is $y_i \sim N(\mu, S_i+\Sigma)$
- Total variance = within + between variance:

$$\text{var}\begin{pmatrix} y_{i1} \\ y_{i2} \end{pmatrix} = \begin{pmatrix} s_{i1}^2 & \rho_{Wi} s_{i1} s_{i2} \\ \rho_{Wi} s_{i1} s_{i2} & s_{i2}^2 \end{pmatrix} + \begin{pmatrix} \tau_1^2 & \rho_B \tau_1 \tau_2 \\ \rho_B \tau_1 \tau_2 & \tau_2^2 \end{pmatrix}$$

known to be estimated

Bivariate meta-analysis: 2 correlations

$$\text{var}\begin{pmatrix} y_{i1} \\ y_{i2} \end{pmatrix} = \begin{pmatrix} s_{i1}^2 & \rho_{Wi} s_{i1} s_{i2} \\ \rho_{Wi} s_{i1} s_{i2} & s_{i2}^2 \end{pmatrix} + \begin{pmatrix} \tau_1^2 & \rho_B \tau_1 \tau_2 \\ \rho_B \tau_1 \tau_2 & \tau_2^2 \end{pmatrix}$$

- Within-study correlation ρ_{Wi}
  - one per study
  - should be known from 1st stage of meta-analysis
  - but often unknown: discussed later
- Between-study correlation ρ_B
  - overall parameter
  - to be estimated

Multivariate meta-analysis: the model

- Data from *i*th study:
  - y_i – vector of estimates (p-dimensional)
  - S_i – variance-covariance matrix (pxp)
- Model is again $y_i \sim N(\mu, S_i+\Sigma)$

- Can also extend to meta-regression:
  e.g. $y_i \sim N(\beta x_i, S_i+\Sigma)$
  - x_i is a q–dimensional vector of explanatory variables
  - β is a pxq matrix containing the regression coefficients for each of the p outcomes
  - more generally, can allow different x's for different outcomes

When could multivariate meta-analysis be used? (1)

- Original applications: meta-analysis of randomised controlled trials (RCTs)
  - several outcomes of interest
  - some trials report more than one outcome
  - "data" are treatment effects on each outcome in each study (some may be missing)
  - data are correlated within studies because outcomes are correlated
  - also used in health economics for cost and effect (Pinto et al, 2005)

When could multivariate meta-analysis be used? (2)

- Meta-analysis of diagnostic accuracy studies
  - "data" are sensitivity and specificity in each study
  - data are uncorrelated within studies because they refer to different subgroups
  - still likely to be correlated between studies
- See Roger's talk
  - sparse data often invalidates Normal approximation
  - best to use **`metandi`**

When could multivariate meta-analysis be used? (3)

- Meta-analysis of RCTs comparing more than two treatments
  - "data" are treatment effects for each treatment compared to same control
  - data are correlated within studies because they use same control group
- Similarly multiple treatments meta-analysis
  - my current area of research

When could multivariate meta-analysis be used? (4)

- Meta-analysis of observational studies exploring shape of exposure-disease relationship
  - if exposure is categorised, "data" could be contrasts between categories
  - if fractional polynomial model is used, "data" would be coefficients of different model terms

Stata software for multivariate random-effects meta-analysis

- Can almost use **`xtmixed`**
  - but you need to constrain the level 1 (co)variances
  - not possible in **`xtmixed`**
- So I wrote **`mvmeta`** (White, 2009)

My program: **`mvmeta`**

- Analyses a data set containing point estimates with their (within-study) variances and covariances
- Utility **`mvmeta_make`** creates a data set in the correct format (demo later)
- Fits random-effects model
  - uses **`ml`** to maximise the (restricted) likelihood using numerical derivatives
  - between-studies variance-covariance matrix is parameterised via its Cholesky decomposition
  - CIs are based on Normal distribution
  - also offers method of moments estimation (Jackson et al, 2009)

Data format for **mvmeta**: Berkey data

trial	y1	y2	V11	V22	V12
1	0.47	-0.32	0.0075	0.0077	0.003
2	0.2	-0.6	0.0057	0.0008	0.0009
3	0.4	-0.12	0.0021	0.0014	0.0007
4	0.26	-0.31	0.0029	0.0015	0.0009
5	0.56	-0.39	0.0148	0.0304	0.0072

y1, y2	treatment effects for PD, AL
V11, V22	squared standard errors (s_{i1}^2, s_{i2}^2)
V12	covariance ($\rho_{Wi} s_{i1} s_{i2}$)

Running **mvmeta**: Berkey data

```
. mvmeta y V
Note: using method reml
Note: using variables y1 y2
Note: 5 observations on 2 variables

[5 iterations]
                                                Number of obs    =          5
                                                Wald chi2(2)     =      93.15
Log likelihood =  2.0823296                     Prob > chi2      =     0.0000

------------------------------------------------------------------------------
             |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
Overall_mean |
          y1 |   .3534282    .061272     5.77   0.000     .2333372    .4735191
          y2 |  -.3392152     .08927    -3.80   0.000    -.5141811   -.1642493
------------------------------------------------------------------------------

Estimated between-studies SDs and correlation matrix:
           SD         y1         y2
y1   .1083191          1  .60879876
y2   .1806968  .60879876          1
```

Running **mvmeta**: method of moments

```
. mvmeta y V, mm
Note: using method mm (truncated)
Note: using variables y1 y2
Note: 5 observations on 2 variables

Multivariate meta-analysis
Method = mm                                     Number of dimensions    =     2
                                                Number of observations  =     5
------------------------------------------------------------------------------
             |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
          y1 |   .3478429   .0557943     6.23   0.000       .238488    .4571978
          y2 |  -.3404843   .1131496    -3.01   0.003    -.5622534   -.1187152
------------------------------------------------------------------------------

Estimated between-studies SDs and correlation matrix:
            SD         y1         y2
y1  .10102601          1  .74742532
y2  .23937024  .74742532          1
```

Running **mvmeta**: I^2

- I^2 measures the impact of heterogeneity (Higgins & Thompson, 2002)

```
. mvmeta1 y V, i2

[output omitted]

I-squared statistics:
------------------------------------------------------
Variable          I-squared   [95% Conf. Interval]
------------------------------------------------------
y1                    72%        -45%         94%
y2                    94%         76%         98%
------------------------------------------------------
(computed from estimated between and typical within variances)
```

- Requires updated **mvmeta1**

Running **mvmeta**: meta-regression

```
. mvmeta1 y V publication_year, reml dof(n-2)
Note: using method reml
Note: using variables y1 y2
Note: 5 observations on 2 variables
Variance-covariance matrix: unstructured

[4 iterations]

Multivariate meta-analysis
Method = reml                                   Number of dimensions    =     2
Restricted log likelihood = -5.3778317          Number of observations  =     5
                                                Degrees of freedom      =     3
------------------------------------------------------------------------------
             |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
y1           |
publicatio~r |   .0048615   .0222347     0.22   0.841    -.0658992    .0756221
       _cons |   .3587569   .0740749     4.84   0.017     .1230175    .5944963
-------------+----------------------------------------------------------------
y2           |
publicatio~r |  -.0115367   .0303001    -0.38   0.729     -.107965    .0848917
       _cons |  -.3357368   .0985988    -3.41   0.042    -.6495222   -.0219513
------------------------------------------------------------------------------
```

`mvmeta`: programming

- Basic parameters: Cholesky decomposition of the between-studies variance Σ
- Eliminate fixed parameters from (restricted) likelihood
- Maximise using `ml`, method `d0` (can't use `lf` for REML)
- Likelihood now coded in Mata
  - Stata creates matrices y_i, S_i for each study & sends them to Mata

Estimating the within-study correlation ρ_{wi}

- Sometimes known to be 0
  - e.g. in diagnostic test studies where sens and spec are estimated on different subgroups
- Estimation usually requires IPD
  - even then, not always trivial: e.g. for 2 outcomes in RCTs, can fit seemingly unrelated regressions, or observe ρ_{wi} = correlation of the outcomes
- Published literature never (?) reports ρ_{wi}
  - not the objective of the original study
  - difficult to estimate from summary data
- What do we do in a published literature meta-analysis if ρ_{wi} values are missing?

Unknown ρ_{wi}: possible solutions

- Ignore within-study correlation (set $\rho_{wi} = 0$)
  - not advisable (Riley, 2009)
- Sensitivity analysis using a range of values
  - can be time-consuming & confusing
- Use external evidence (e.g. IPD on one study)
- Bayesian approach (Nam et al., 2004)
  - e.g. $\rho_{wi} \sim U(0,1)$
- Some special cases where it can be done
  - % survival at multiple time-points
  - nested binary outcomes?
- Use an alternative model that models the 'overall' correlation (Riley et al., 2008)

Alternative bivariate model

$$\begin{pmatrix} Y_{i1} \\ Y_{i2} \end{pmatrix} \sim N\left(\begin{pmatrix} \mu_1 \\ \mu_2 \end{pmatrix}, V_i \right)$$

Standard model with overall ρ_B and one ρ_{Wi} per study:

$$V_i = \begin{pmatrix} s_{i1}^2 + \tau_1^2 & \rho_{Wi} s_{i1} s_{i2} + \rho_B \tau_1 \tau_2 \\ \rho_{Wi} s_{i1} s_{i2} + \rho_B \tau_1 \tau_2 & s_{i2}^2 + \tau_2^2 \end{pmatrix}$$

Alternative model with one 'overall' correlation ρ:

$$V_i = \begin{pmatrix} s_{i1}^2 + \tau_1^2 & \rho\sqrt{\left(s_{i1}^2 + \tau_1^2\right)\left(s_{i2}^2 + \tau_2^2\right)} \\ \rho\sqrt{\left(s_{i1}^2 + \tau_1^2\right)\left(s_{i2}^2 + \tau_2^2\right)} & s_{i2}^2 + \tau_2^2 \end{pmatrix}$$

`mvmeta1: corr(riley)` option

Example: Fibrinogen

- Fibrinogen Studies Collaboration (2005)
  - assembled IPD from 31 observational studies
  - 154211 participants
  - to explore the association between fibrinogen levels (measured in blood) and coronary heart disease
- We focus on exploring the shape of the association using grouped fibrinogen
- Data (IPD):
  - Variable **`fg`** contains fibrinogen in 5 groups
  - Studies are identified by variable **`cohort`**
  - Time to CHD has been **`stset`**
  - In each cohort, I want to run the Cox model
    `xi: stcox age i.fg, strata(sex tr)`

1st stage of meta-analysis: **`mvmeta_make`**

- Getting IPD into the right format can be the hardest bit
- I wrote **`mvmeta_make`** to do this
- It assumes the 1st stage of meta-analysis involves fitting a regression model

Fibrinogen data: using **mvmeta_make**

- Stata command within each study:
  - **xi: stcox age i.fg, strata(sex tr)**
- Create meta-analysis data set:
  - **xi: mvmeta_make stcox age i.fg, strata(sex tr) by(cohort) usevars(i.fg) name(b V) saving(FSC2)**
- Creates file **FSC2.dta** containing
  - coefficients: **b_Ifg_2, b_Ifg_3, b_Ifg_4, b_Ifg_5**
  - variances and covariances: **V_Ifg_2_Ifg_2, V_Ifg_2_Ifg_3** etc.
- We then run **mvmeta b V** on file **FSC2.dta**.

A problem: perfect prediction

```
. tab fg allchd if cohort=="KORA_S3"

Fibrinogen |    Any CHD event?
    groups |         0          1 |     Total
-----------+----------------------+----------
         1 |       546          0 |       546
         2 |       697          3 |       700
         3 |       715          2 |       717
         4 |       677          4 |       681
         5 |       482          8 |       490
-----------+----------------------+----------
     Total |     3,117         17 |     3,134
```

- No events in the reference category
- Fit Cox model: HR for 2 vs 1 is 21.36 (se 0.91) – wrong

mvmeta_make: handling perfect prediction

- Recall:
  - no events in **fg=1** (reference) group
  - **stcox**'s "fix" can yield large hazard ratios with small standard errors – and disaster for **mvmeta**!
- **mvmeta_make** implements a different "fix" in any study with perfect prediction:
  - add a few observations, with very small weight, that "break" the perfect prediction
  - all contrasts with **fg=1** are large with large s.e.
  - all other contrasts (e.g. **fg=3** vs. **fg=2**) are correct
- Works fine for likelihood-based procedures (REML, ML, fixed-effect model) but not for method of moments

FSC: partial results of **mvmeta_make**

```
. l c b* V_Ifg_2_Ifg_2 V_Ifg_3_Ifg_3 , clean noo
```

cohort	b_Ifg_2	b_Ifg_3	b_Ifg_4	b_Ifg_5	V_Ifg_~2	~3_Ifg_3
ARIC	0.252	0.532	0.946	1.401	0.036	0.033
BRUN	-0.184	-0.032	0.119	0.567	0.348	0.344
CAER	0.001	-0.529	-0.339	0.416	0.375	0.323
CHS	0.066	0.184	0.407	0.645	0.058	0.053
COPEN	0.078	0.406	0.544	1.088	0.101	0.083
EAS	-0.113	0.456	0.456	0.875	0.065	0.054
FINRISKI	-2.149	-0.264	-0.494	0.169	1.336	0.421
FRAM	-0.039	0.170	0.420	1.053	0.042	0.038
GOTO	0.443	0.595	0.922	0.797	0.202	0.175
GOTO33	0.356	1.312	0.628	2.133	1.500	1.170
GRIPS	1.297	1.052	1.421	1.752	0.559	0.542
HONOL	0.323	0.545	0.681	0.540	0.132	0.122
KIHD	-0.042	0.509	0.560	0.998	0.088	0.072
KORA_S2	-2.667	-2.524	-2.010	-1.767	1.337	0.584
KORA_S3	5.946	5.420	6.088	7.057	189.088	189.271
MALMO	0.123	0.371	0.506	0.936	0.071	0.058

...

Study with no events in fg=1 group: "perfect prediction"

FSC: results of **mvmeta**

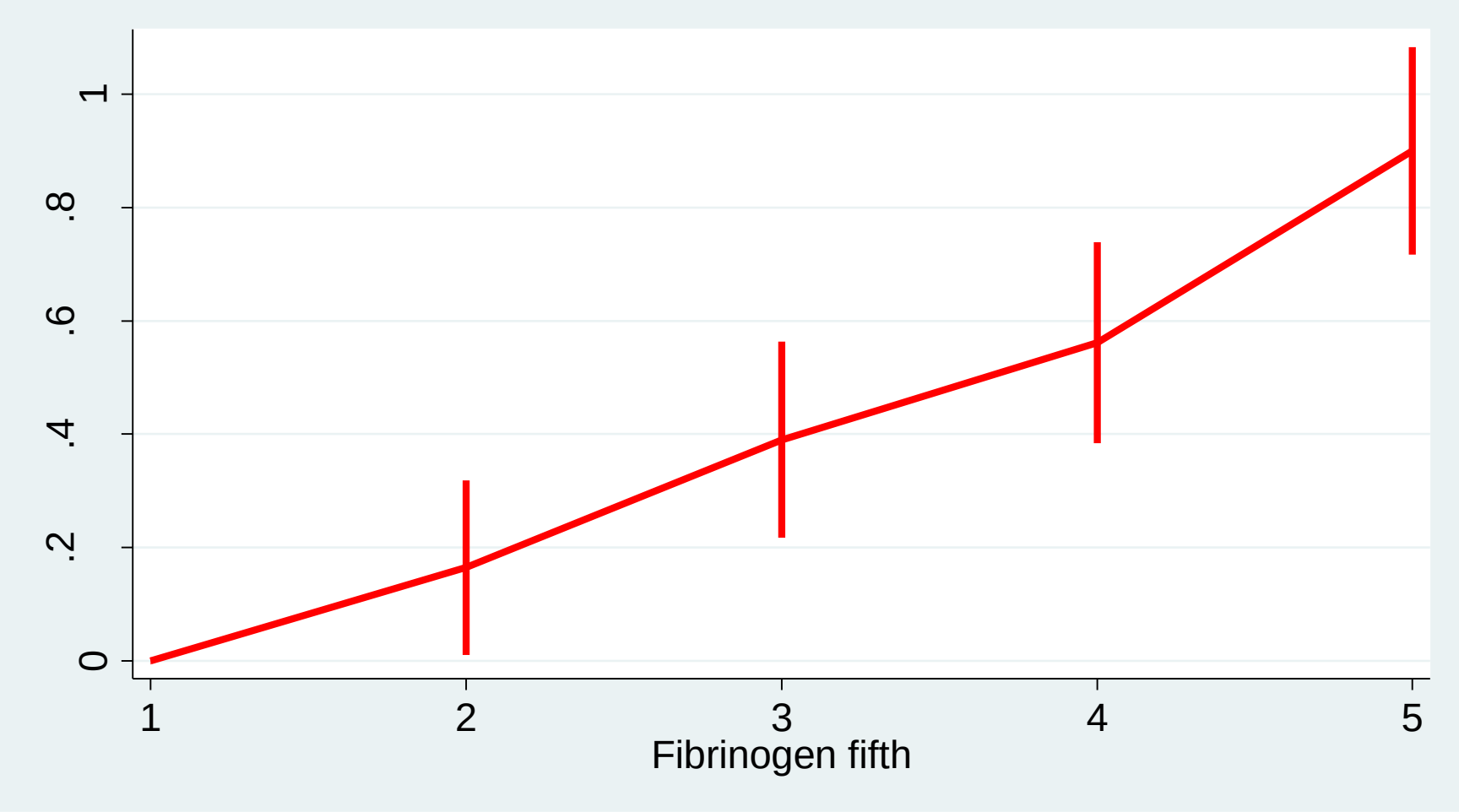
```
. mvmeta b V

                                                Number of obs    =         31
                                                Wald chi2(4)     =     142.62
Log likelihood = -79.129029                     Prob > chi2      =     0.0000

------------------------------------------------------------------------------
             |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Int.]
-------------+----------------------------------------------------------------
Overall_mean |
     b_Ifg_2 |   .1646353   .0787025     2.09   0.036     .0103813    .3188894
     b_Ifg_3 |   .3905063    .088062     4.43   0.000     .2179080    .5631047
     b_Ifg_4 |   .5612908   .0904966     6.20   0.000     .3839206    .7386609
     b_Ifg_5 |   .8998468   .0932989     9.64   0.000     .7169843    1.082709
------------------------------------------------------------------------------

Estimated between-studies variance matrix Sigma:
           b_Ifg_2    b_Ifg_3    b_Ifg_4    b_Ifg_5
b_Ifg_2   .04945818
b_Ifg_3   .06355581    .0836853
b_Ifg_4   .06689067   .08920553   .09570788
b_Ifg_5    .0506146   .07530983   .08501967   .1041611
```

FSC: graphical results



Other choices of reference category give the same results.

Example 2: borrowing strength

Study	Log hazard ratio (mutant vs. normal p53 gene)			
	Disease-free survival		Overall survival	
	y_1	s_1	y_2	s_2
1	-0.58	0.56	-0.18	0.56
2			0.79	0.24
3			0.21	0.66
4	-1.02	0.39	-0.63	0.29
5			1.01	0.48
6	-0.69	0.40	-0.64	0.40

- $y_2>0 \Rightarrow y_1$ missing
- $y_2<0 \Rightarrow y_1$ observed
- Pooling the observed y_1 can't be a good way to estimate μ_1
- Bivariate model helps:
  - assumes a linear regression of μ_1 on μ_2
  - assumes data are missing at random
- Bivariate model can avoid bias & increase precision ("Borrowing strength")

Multivariate vs. univariate meta-analysis

- Advantages:
  - "borrowing strength"
  - avoiding bias from selective outcome reporting
  - Joint confidence / prediction intervals
  - Functions of estimates
  - Longitudinal data
  - Coherence
- Disadvantages:
  - more computationally complex
  - boundary solutions for ρ_B
  - unknown within-study correlations
  - more assumptions

Getting **mvmeta**

- **mvmeta** is in the SJ
- Current update **mvmeta1** is available on my website (includes meta-regression, I^2, structured Σ, speed & other improvements)
  - **net from http://www.mrc-bsu.cam.ac.uk/IW_Stata**
  - **bubble** is also available

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