New meta-analysis features in Stata 18

Gabriela Ortiz

StataCorp LLC

2023 Spanish Stata Conference
October 19, 2023

Introduction

New meta-analysis features in Stata 18

- Meta-analysis for prevalence
  - Stata's `meta` suite of commands now supports one-sample binary data, allowing you to estimate an overall proportion or prevalence of a symptom, disease, infection, or some other event
- Multilevel meta-analysis
  - You can now perform meta-analysis with effect sizes that are nested within higher-level groupings, such as regions or schools

Overview

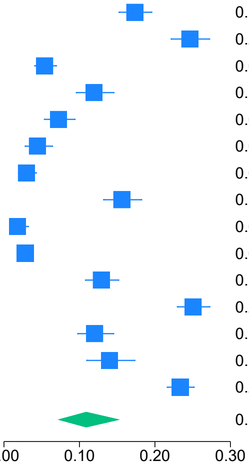
- Meta-analysis for prevalence
  - Effect-size computation
  - Summarizing meta-analysis data
- Multilevel meta-analysis
  - Meta-regression
  - Exploring heterogeneity at different levels
  - Sensitivity analysis

What is meta-analysis?

- This is a statistical technique for combining the results from several similar studies.
- The goal is to provide a single estimate of the effect of interest.
- If results vary widely across studies, the goal is then to understand the inconsistencies in the results.

Chronic kidney disease

Study	Number of events	Total	Proportion with 95% CI	Weight (%)
Study 1	208	1,200	0.17 [0.15, 0.20]	6.70
Study 2	277	1,125	0.25 [0.22, 0.27]	6.70
Study 3	54	1,000	0.05 [0.04, 0.07]	6.69
Study 4	80	670	0.12 [0.10, 0.15]	6.64
Study 5	47	650	0.07 [0.05, 0.09]	6.63
Study 6	23	520	0.04 [0.03, 0.06]	6.60
Study 7	25	840	0.03 [0.02, 0.04]	6.67
Study 8	128	820	0.16 [0.13, 0.18]	6.67
Study 9	9	500	0.02 [0.01, 0.03]	6.59
Study 10	57	2,000	0.03 [0.02, 0.04]	6.74
Study 11	118	915	0.13 [0.11, 0.15]	6.68
Study 12	401	1,600	0.25 [0.23, 0.27]	6.72
Study 13	89	740	0.12 [0.10, 0.14]	6.65
Study 14	65	465	0.14 [0.11, 0.17]	6.58
Study 15	528	2,260	0.23 [0.22, 0.25]	6.74
Overall			0.11 [0.07, 0.15]	



Meta-analysis goals

- The department of health needs to know the prevalence of chronic kidney disease (CKD) because it is a risk factor for cardiovascular disease
- Our goal is to report a single estimate of the prevalence of CKD
    - We assume that the effect sizes are independent across studies.
- If we observe substantial variation across the studies, we instead focus on trying to explain this variation
- Perhaps the age of study participants or some other study-level covariates can explain the discrepancies

Meta-analysis for prevalence

Fictional chronic kidney disease (CKD) data

```
. use extremeprop

. describe

Contains data from extremeprop.dta
 Observations:            15
    Variables:             5                  5 Jul 2023 10:32
---------------------------------------------------------------------------
Variable      Storage   Display    Value
    name         type    format    label      Variable label
---------------------------------------------------------------------------
author          str20   %20s                  Author
year            float   %9.0g                 Year
mean_age        float   %9.0g                 Mean age of participants
ssize           float   %9.0g                 Sample size
events          float   %9.0g                 Number of participants with CKD
---------------------------------------------------------------------------
Sorted by:
```

Meta-analysis data

```
. list author year events ssize
```

	author	year	events	ssize
1.	Ortiz et al.	1975	0	300
2.	Reynolds et al.	2001	1	800
3.	Medina et al.	1980	2	840
4.	Krasinsky et al.	2002	16	520
5.	Cusack et al.	2000	4	105
6.	Kaling et al.	1995	47	650
7.	Johnson et al.	1992	80	670
8.	Villanueva et al.	1992	89	740
9.	Rogen et al.	2004	226	915
10.	Yeun et al.	2008	161	465
11.	Baldwin et al.	2011	348	820
12.	Andrews et al.	2012	72	150
13.	Simone et al.	2007	197	200
14.	Barker et al.	2016	219	220
15.	Young et al.	2004	299	300

Random effects meta-analysis model

K independent studies; each reports the number of events observed and the sample size of the study, allowing us to compute the following:

- an estimate, $\hat{\theta}_j$, of the true (unknown) effect size θ_j
- an estimate, $\hat{\sigma}_j$, of its standard error

$$\hat{\theta}_j = \theta + u_j + \epsilon_j$$

for $j = 1, 2, \ldots, K$, where $\epsilon_j \sim \mathcal{N}(0, \hat{\sigma}_j^2)$ and $u_j \sim \mathcal{N}(0, \tau^2)$.

The ϵ_js are the sampling errors and the u_js are the random effects

- The estimate of the overall effect size is the mean of the distribution of effect sizes, $\theta_{pop} = \mathbb{E}(\theta_j)$.

Random-effects meta-analysis

- For each study, we'll compute an estimate of the proportion, $\hat{\theta}_j$, and an estimate, $\hat{\sigma}_j$, of its standard error
- The overall estimate of the prevalence is a weighted average of the study-specific estimates

$$\hat{\theta}^* = \frac{\sum_{j=1}^{K} w_j \hat{\theta}_j}{\sum_{j=1}^{K} w_j}$$

where $w_j = \frac{1}{\hat{\sigma}_j^2 + \hat{\tau}^2}$ and $\hat{\tau}^2$ is the variance of the random effects

Effect sizes for a proportion

Effect size	Estimate	Variance
Raw proportion	$\hat{p} = \frac{e}{n}$	$\frac{\hat{p}(1-\hat{p})}{n}$
Freeman–Tukey	$\hat{p}_{FT} = \arcsin(\sqrt{\frac{e}{n+1}}) + \arcsin(\sqrt{\frac{e+1}{n+1}})$	$\frac{1}{n+0.5}$
Logit	$\text{logit}(\hat{p}) = \ln(\frac{\hat{p}}{1-\hat{p}})$	$\frac{1}{n\hat{p}} + \frac{1}{n-n\hat{p}}$

Summary

- We are now familiar with
  - the random-effects meta-analysis model
  - how the overall estimate is computed (weighted average of the study-specific estimates)
  - effect sizes for proportions
- We can now begin working with our data

Declare meta-analysis data

```
. meta esize events ssize

Meta-analysis setting information

 Study information
    No. of studies: 15
       Study label: Generic
        Study size: _meta_studysize
      Summary data: events ssize

       Effect size
              Type: ftukeyprop
             Label: Freeman–Tukey's p
          Variable: _meta_es

         Precision
         Std. err.: _meta_se
                CI: [_meta_cil, _meta_ciu]
          CI level: 95%

  Model and method
             Model: Random effects
            Method: REML
```

System variables

```
. describe

Contains data from extremeprop.dta
 Observations:            15
    Variables:            12                  5 Jul 2023 10:32
------------------------------------------------------------------------------------
Variable      Storage   Display    Value
    name         type    format    label      Variable label
------------------------------------------------------------------------------------
author          str20   %20s                  Author
year            float   %9.0g                 Year
mean_age        float   %9.0g                 Mean age of participants
ssize           float   %9.0g                 Sample size
events          float   %9.0g                 Number of participants with CKD
_meta_id        byte    %9.0g                 Study ID
_meta_studyla~l str8    %9s                   Study label
_meta_es        double  %10.0g                Freeman–Tukey's p
_meta_se        double  %10.0g                Std. err. for Freeman–Tukey's p
_meta_cil       double  %10.0g                95% lower CI limit for Freeman–Tukey's p
_meta_ciu       double  %10.0g                95% upper CI limit for Freeman–Tukey's p
_meta_studysize int     %9.0g                 Sample size per study
------------------------------------------------------------------------------------
Sorted by:
     Note: Dataset has changed since last saved.
```

Summary of meta-analysis data

```
. meta summarize

  Effect-size label: Freeman–Tukey's p
        Effect size: _meta_es
          Std. err.: _meta_se

Meta-analysis summary                     Number of studies =     15
Random-effects model                      Heterogeneity:
Method: REML                                          tau2 =  1.0909
                                                    I2 (%) =   99.82
                                                        H2 =  549.89

       Effect size: Freeman–Tukey's p

--------------------------------------------------------------------
           Study |  Effect size    [95% conf. interval]  % weight
-----------------+--------------------------------------------------
        Study  1 |        0.058     -0.055       0.171       6.66
        Study  2 |        0.085      0.016       0.155       6.68
        Study  3 |        0.109      0.041       0.176       6.68
        Study  4 |        0.358      0.272       0.444       6.67
        Study  5 |        0.414      0.224       0.605       6.63
        (output omitted)
        Study 11 |        1.419      1.351       1.488       6.68
        Study 12 |        1.531      1.371       1.691       6.64
        Study 13 |        2.878      2.739       3.016       6.65
        Study 14 |        2.979      2.847       3.111       6.66
        Study 15 |        3.002      2.889       3.115       6.66
-----------------+--------------------------------------------------
           theta |        1.139      0.610       1.669
--------------------------------------------------------------------
Test of theta = 0: z = 4.01                       Prob > |z| = 0.0001
Test of homogeneity: Q = chi2(14) = 5004.80         Prob > Q = 0.0000
```

Summary of meta-analysis data

```
. meta summarize, proportion

  Effect-size label: Freeman–Tukey's p
        Effect size: _meta_es
          Std. err.: _meta_se

Meta-analysis summary                     Number of studies =      15
Random-effects model                      Heterogeneity:
Method: REML                                          tau2 =  1.0909
                                                    I2 (%) =   99.82
                                                        H2 =  549.89

--------------------------------------------------------------------
            Study |    Proportion   [95% conf. interval]   % weight
------------------+-------------------------------------------------
         Study  1 |         0.000      0.000      0.006       6.66
         Study  2 |         0.001      0.001      0.005       6.68
         Study  3 |         0.002      0.000      0.007       6.68
         Study  4 |         0.031      0.017      0.048       6.67
         Study  5 |         0.038      0.008      0.085       6.63
         (output omitted)
         Study 11 |         0.424      0.391      0.458       6.68
         Study 12 |         0.480      0.400      0.560       6.64
         Study 13 |         0.985      0.962      0.998       6.65
         Study 14 |         0.995      0.981      0.997       6.66
         Study 15 |         0.997      0.986      0.997       6.66
------------------+-------------------------------------------------
  invftukey(theta)|         0.290      0.089      0.549
--------------------------------------------------------------------
Test of theta = 0: z = 4.01                      Prob > |z| = 0.0001
Test of homogeneity: Q = chi2(14) = 5004.80        Prob > Q = 0.0000
```

Freeman–Tukey-transformed proportions

- Freeman–Tukey-transformed proportions have two advantages:
  - The back-transformed CIs are guaranteed to be in the $[0, 1]$ range
  - The variance does not depend on the number of events, which means it will not assign artificially large or small weights to studies with $\hat{p}$ close to 0 or 1

Declare meta-analysis data

- Compute effect sizes

  `meta esize` *events samplesize* [, *model* `esize(`*estype*`)` `zerocells(`*spec*`)`]

  model: `random`, `common`, or `fixed`

  estype: raw proportion, Freeman–Tukey-transformed proportion, logit-transformed proportion

Raw proportions

```
. meta esize events ssize, esize(proportion)
Meta-analysis setting information
 Study information
    No. of studies: 15
       Study label: Generic
        Study size: _meta_studysize
      Summary data: events ssize

       Effect size
              Type: proportion
             Label: Proportion
          Variable: _meta_es
   Zero-cells adj.: 0.5, only0

         Precision
         Std. err.: _meta_se
                CI: [_meta_cil, _meta_ciu]
          CI level: 95%

  Model and method
             Model: Random effects
            Method: REML
```

Effect sizes for a proportion

Effect size	Estimate	Variance
Raw proportion	$\hat{p} = \frac{e}{n}$	$\frac{\hat{p}(1-\hat{p})}{n}$
Freeman–Tukey	$\hat{p}_{FT} = \arcsin(\sqrt{\frac{e}{n+1}}) + \arcsin(\sqrt{\frac{e+1}{n+1}})$	$\frac{1}{n+0.5}$
Logit	$\text{logit}(\hat{p}) = \ln(\frac{\hat{p}}{1-\hat{p}})$	$\frac{1}{n\hat{p}} + \frac{1}{n-n\hat{p}}$

CIs for raw proportions

```
. meta summarize, level(97)

  Effect-size label: Proportion
        Effect size: _meta_es
          Std. err.: _meta_se

Meta-analysis summary                     Number of studies =     15
Random-effects model                      Heterogeneity:
Method: REML                                          tau2 =  0.1435
                                                    I2 (%) =   99.99
                                                        H2 = 9871.81

--------------------------------------------------------------------
           Study |   Proportion    [97% conf. interval]    % weight
-----------------+--------------------------------------------------
        Study  1 |        0.002      -0.003       0.007        6.68
        Study  2 |        0.001      -0.001       0.004        6.68
        Study  3 |        0.002      -0.001       0.006        6.68
        Study  4 |        0.031       0.014       0.047        6.68
        Study  5 |        0.038      -0.002       0.079        6.66
        (output omitted)
        Study 11 |        0.424       0.387       0.462        6.66
        Study 12 |        0.480       0.391       0.569        6.60
        Study 13 |        0.985       0.966       1.000        6.67
        Study 14 |        0.995       0.986       1.000        6.68
        Study 15 |        0.997       0.989       1.000        6.68
-----------------+--------------------------------------------------
           theta |        0.324       0.112       0.536
--------------------------------------------------------------------
Test of theta = 0: z = 3.31                      Prob > |z| = 0.0009
Test of homogeneity: Q = chi2(14) =   1.3e+05      Prob > Q = 0.0000
```

Effect sizes for a proportion

- Logit transformation
  - Like the Freeman–Tukey transformation, guarantees that back-transformed confidence intervals will be in the $[0, 1]$ range
  - However, it assigns small weights to studies with $\hat{p}$ close to 0 or 1 for common-effect models
- Raw proportions
  - Can produce confidence limits outside the $[0, 1]$ range
  - Tends to assign large weights to studies with $\hat{p}$ close to 0 or 1 for common-effect models
- Freeman–Tukey-transformed proportions solve both of these problems; they are variance stabilizing and produce a reasonable CI range

Fictional CKD data

- Let's continue with a modified version of the CKD data with less extreme values for the proportions

```
. use myprop1, clear

. list author ssize events mean_age
```

	author	ssize	events	mean_age
1.	Andrews & Thompson	1200	208	37.2
2.	Barker et al.	1125	277	57.4
3.	Cusack & Golds	1000	54	30.1
4.	Johnson & Johnson	670	80	35.3
5.	Kaling et al.	650	47	32.4
6.	Krasinsky & Blunt	520	23	28.2
7.	Medina et al.	840	25	26.5
8.	Ortiz & Baldwin	820	128	36.5
9.	Ortiz et al.	500	9	26.1
10.	Reynolds et al.	2000	57	24.5
11.	Rogen et al.	915	118	36.2
12.	Simone et al.	1600	401	48.6
13.	Villanueva & Blunt	740	89	34.7
14.	Yeun et al.	465	65	37.3
15.	Young et al.	2260	528	62.6

Computing Freeman–Tukey-transformed proportions

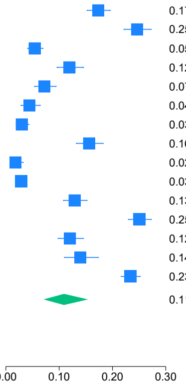
- Let's compute Freeman–Tukey-transformed proportions

```
. meta esize events ssize
Meta-analysis setting information
 Study information
    No. of studies: 15
       Study label: Generic
        Study size: _meta_studysize
      Summary data: events ssize
       Effect size
              Type: ftukeyprop
             Label: Freeman–Tukey's p
          Variable: _meta_es
         Precision
         Std. err.: _meta_se
                CI: [_meta_cil, _meta_ciu]
          CI level: 95%
  Model and method
             Model: Random effects
            Method: REML
```

Forest plot

```
. meta forestplot, proportion
```

Study	Number of successes	Total	Proportion with 95% CI	Weight (%)
Study 1	208	1,200	0.17 [0.15, 0.20]	6.70
Study 2	277	1,125	0.25 [0.22, 0.27]	6.70
Study 3	54	1,000	0.05 [0.04, 0.07]	6.69
Study 4	80	670	0.12 [0.10, 0.15]	6.64
Study 5	47	650	0.07 [0.05, 0.09]	6.63
Study 6	23	520	0.04 [0.03, 0.06]	6.60
Study 7	25	840	0.03 [0.02, 0.04]	6.67
Study 8	128	820	0.16 [0.13, 0.18]	6.67
Study 9	9	500	0.02 [0.01, 0.03]	6.59
Study 10	57	2,000	0.03 [0.02, 0.04]	6.74
Study 11	118	915	0.13 [0.11, 0.15]	6.68
Study 12	401	1,600	0.25 [0.23, 0.27]	6.72
Study 13	89	740	0.12 [0.10, 0.14]	6.65
Study 14	65	465	0.14 [0.11, 0.17]	6.58
Study 15	528	2,260	0.23 [0.22, 0.25]	6.74
Overall			0.11 [0.07, 0.15]	



Heterogeneity: $\tau^2 = 0.07$, $I^2 = 98.53\%$, $H^2 = 67.86$

Test of $\theta_i = \theta_j$: Q(14) = 1136.27, p = 0.00

Test of $\theta = 0$: z = 9.50, p = 0.00

Random-effects REML model

CIs for individual studies

- By default, `meta summarize` and `meta forestplot` compute Wald intervals for the proportion of each individual study
- However, it has been argued that the coverage probability of the Wald interval does not meet the nominal level for extreme values of the proportion and for small sample sizes

Alternative CIs for individual studies

- Alternative CI computations include the Clopper–Pearson, Wilson, Agresti–Coull, and Jeffreys and can be obtained with the `citype()` option
- Brown, Cai, and DasGupta (2001) recommend either the Wilson or Jeffreys interval for a sample size of 40 or less
- For sample sizes greater than 40, they found the Wilson, Jeffreys, and Agresti–Coull intervals to behave similarly

Forest plot with alternative CI

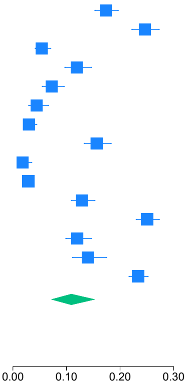
```
. meta forestplot, proportion citype(agresti)
```

Study	Number of successes	Total	Proportion with Agresti–Coull 95% CI	Weight (%)
Study 1	208	1,200	0.17 [0.15, 0.20]	6.70
Study 2	277	1,125	0.25 [0.22, 0.27]	6.70
Study 3	54	1,000	0.05 [0.04, 0.07]	6.69
Study 4	80	670	0.12 [0.10, 0.15]	6.64
Study 5	47	650	0.07 [0.05, 0.09]	6.63
Study 6	23	520	0.04 [0.03, 0.07]	6.60
Study 7	25	840	0.03 [0.02, 0.04]	6.67
Study 8	128	820	0.16 [0.13, 0.18]	6.67
Study 9	9	500	0.02 [0.01, 0.03]	6.59
Study 10	57	2,000	0.03 [0.02, 0.04]	6.74
Study 11	118	915	0.13 [0.11, 0.15]	6.68
Study 12	401	1,600	0.25 [0.23, 0.27]	6.72
Study 13	89	740	0.12 [0.10, 0.15]	6.65
Study 14	65	465	0.14 [0.11, 0.17]	6.58
Study 15	528	2,260	0.23 [0.22, 0.25]	6.74
Overall			0.11 [0.07, 0.15]	

Heterogeneity: $\tau^2 = 0.07$, $I^2 = 98.53\%$, $H^2 = 67.86$

Test of $\theta_i = \theta_j$: Q(14) = 1136.27, p = 0.00

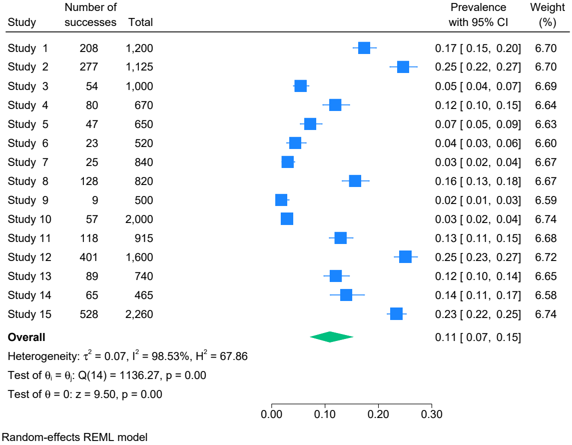
Test of $\theta = 0$: z = 9.50, p = 0.00



Random-effects REML model

Customizing the forest plot

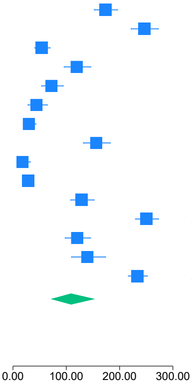
```
. meta forestplot, prevalence
```



Customizing the forest plot

```
. meta forestplot, columnopts(_e, title("patients with CKD"))
transform("No. of CKD patients per 1000": invftukey, scale(1000))
```

Study	Number of patients with CKD	Total	No. of CKD patients per 1000 with 95% CI	Weight (%)
Study 1	208	1,200	173.33 [152.42, 195.29]	6.70
Study 2	277	1,125	246.22 [221.47, 271.84]	6.70
Study 3	54	1,000	54.00 [40.79, 68.92]	6.69
Study 4	80	670	119.40 [95.89, 145.10]	6.64
Study 5	47	650	72.31 [53.57, 93.57]	6.63
Study 6	23	520	44.23 [28.07, 63.75]	6.60
Study 7	25	840	29.76 [19.24, 42.43]	6.67
Study 8	128	820	156.10 [132.03, 181.77]	6.67
Study 9	9	500	18.00 [7.91, 31.80]	6.59
Study 10	57	2,000	28.50 [21.63, 36.27]	6.74
Study 11	118	915	128.96 [107.99, 151.49]	6.68
Study 12	401	1,600	250.62 [229.68, 272.16]	6.72
Study 13	89	740	120.27 [97.77, 144.74]	6.65
Study 14	65	465	139.78 [109.67, 172.87]	6.58
Study 15	528	2,260	233.63 [216.41, 251.30]	6.74
Overall			109.00 [71.27, 153.52]	



Heterogeneity: $\tau^2 = 0.07$, $I^2 = 98.53\%$, $H^2 = 67.86$

Test of $\theta_i = \theta_j$: Q(14) = 1136.27, p = 0.00

Test of $\theta = 0$: z = 9.50, p = 0.00

Random-effects REML model

STATA 18

Prediction interval

- In addition to the CI for the estimate of the overall proportion, we can also compute the prediction interval
- The prediction interval estimates a plausible range for the proportion in a future study by incorporating the uncertainty of the between-study variance

Prediction interval and Agresti–Coull CI

```
. meta summarize, proportion citype(agresti) predinterval

  Effect-size label: Freeman–Tukey's p
        Effect size: _meta_es
          Std. err.: _meta_se

Meta-analysis summary                     Number of studies =     15
Random-effects model                      Heterogeneity:
Method: REML                                          tau2 =  0.0668
                                                    I2 (%) =   98.53
                                                        H2 =   67.86

------------------------------------------------------------------
                  |                  Agresti–Coull
            Study |   Proportion   [95% conf. interval]   % weight
------------------+-----------------------------------------------
         Study  1 |        0.173      0.153      0.196       6.70
         Study  2 |        0.246      0.222      0.272       6.70
         Study  3 |        0.054      0.042      0.070       6.69
         Study  4 |        0.119      0.097      0.146       6.64
         Study  5 |        0.072      0.055      0.095       6.63
         (output omitted)
         Study 11 |        0.129      0.109      0.152       6.68
         Study 12 |        0.251      0.230      0.272       6.72
         Study 13 |        0.120      0.099      0.146       6.65
         Study 14 |        0.140      0.111      0.174       6.58
         Study 15 |        0.234      0.217      0.252       6.74
------------------+-----------------------------------------------
  invftukey(theta)|        0.109      0.071      0.154
------------------------------------------------------------------
Note: Agresti CIs are reported only for individual studies.
95% prediction interval for invftukey(theta): [ 0.002, 0.343]
```

Exploring heterogeneity

- With `meta summarize` we can estimate the overall proportion and with `meta forestplot` we can see how effect sizes vary around the overall estimate
- We can also perform meta-regression to investigate whether between-study heterogeneity can be explained by one or more moderators

Random-effects meta-regression

Random-effects meta-regression model:

$$\hat{\theta}_j = x_j\beta + \epsilon_j^* = x_j\beta + u_j + \epsilon_j$$

where $\epsilon_j^* \sim \mathcal{N}(0,\, \hat{\sigma}_j^2 + \tau^2)$

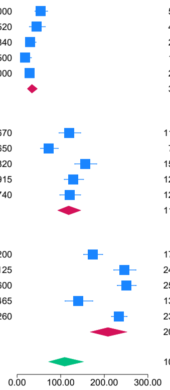
Meta-regression

```
. meta regress mean_age

  Effect-size label: Freeman–Tukey's p
        Effect size: _meta_es
          Std. err.: _meta_se

Random-effects meta-regression                    Number of obs   =         15
Method: REML                                      Residual heterogeneity:
                                                              tau2 =   .01087
                                                            I2 (%) =    91.14
                                                                H2 =    11.28
                                                     R-squared (%) =    83.72
                                                  Wald chi2(1)    =     66.74
                                                  Prob > chi2     =    0.0000

------------------------------------------------------------------------------
    _meta_es | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
    mean_age |   .0208473   .0025518     8.17   0.000     .0158459    .0258487
       _cons |  -.1068683   .1001801    -1.07   0.286    -.3032177    .0894812
------------------------------------------------------------------------------
Test of residual homogeneity: Q_res = chi2(13) = 179.99  Prob > Q_res = 0.0000
```

Subgroup-analysis forest plot

```
. meta forestplot, proportion subgroup(agegroup) ...
```

Study	Number of patients with CKD	Total	No. of CKD patients per 1000 with 95% CI	Weight (%)
Mean age < 30				
Study 3	54	1,000	54.00 [40.79, 68.92]	6.69
Study 6	23	520	44.23 [28.07, 63.75]	6.60
Study 7	25	840	29.76 [19.24, 42.43]	6.67
Study 9	9	500	18.00 [7.91, 31.80]	6.59
Study 10	57	2,000	28.50 [21.63, 36.27]	6.74
			33.98 [23.01, 46.95]	
30 <= Mean age < 40				
Study 4	80	670	119.40 [95.89, 145.10]	6.64
Study 5	47	650	72.31 [53.57, 93.57]	6.63
Study 8	128	820	156.10 [132.03, 181.77]	6.67
Study 11	118	915	128.96 [107.99, 151.49]	6.68
Study 13	89	740	120.27 [97.77, 144.74]	6.65
			118.31 [92.38, 146.95]	
40 <= Mean age				
Study 1	208	1,200	173.33 [152.42, 195.29]	6.70
Study 2	277	1,125	246.22 [221.47, 271.84]	6.70
Study 12	401	1,600	250.62 [229.68, 272.16]	6.72
Study 14	65	465	139.78 [109.67, 172.87]	6.58
Study 15	528	2,260	233.63 [216.41, 251.30]	6.74
			208.31 [166.88, 253.02]	
Overall			109.00 [71.27, 153.52]	



Random-effects REML model

Subgroup meta-analysis

```
. meta summarize, subgroup(agegroup) prop noheader nometashow
(output omitted)
Heterogeneity summary
```

Group	df	Q	P > Q	tau2	% I2	H2
Mean age < 30	4	18.40	0.001	0.004	79.43	4.86
30 <= Mean ~40	4	26.68	0.000	0.008	85.69	6.99
40 <= Mean age	4	51.69	0.000	0.014	94.54	18.31
Overall	14	1136.27	0.000	0.067	98.53	67.86

```
Test of group differences: Q_b = chi2(2) = 92.60          Prob > Q_b = 0.000
```

Multilevel meta-analysis

Multilevel data

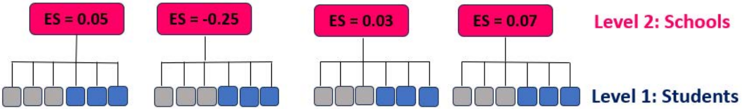
- In our previous example, we performed a standard random-effects meta-analysis in which we assumed that the effect sizes were independent across studies
- However, if your data have a multilevel (hierarchical) structure, you can perform multilevel meta-analysis to account for the correlation between effect sizes in the same group

Standard meta-analysis as a two-level model

- Consider a series of studies that examined whether students performed better under a modified school calendar, with frequent breaks, as opposed to the traditional schedule (Cooper et al. 2003).
- Each study was performed in a different school
- The effect size is the standardized mean difference in performance, with positive values indicating that students on the modified calendar performed better than students on the traditional calendar

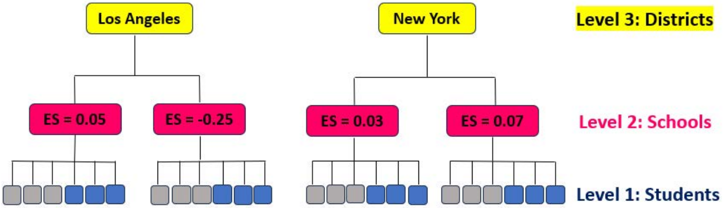
Standard meta-analysis as a two-level model

- Here we see the effect size reported by each study



Three-level model

- Now suppose that multiple studies belong to the same district
- Schools belonging to the same district will be more similar in terms of demographics and socioeconomical factors, resulting in a correlation between results within a district



- Here we see how studies are grouped by district

Modified school calendar data

```
. use schoolcal2, clear
(Effect of modified school calendar on student achievement)

. describe

Contains data from schoolcal2.dta
 Observations:            56                  Effect of modified school calendar on student achievement
    Variables:             9                  5 Jul 2023 11:06
                                              (_dta has notes)
---------------------------------------------------------------------------------------------------------
Variable      Storage   Display    Value
    name         type    format    label      Variable label
---------------------------------------------------------------------------------------------------------
district        int     %12.0g                District ID
school          byte    %9.0g                 School ID
study           byte    %12.0g                Study ID
stdmdiff        double  %10.0g                Standardized difference in means of achievement test scores
var             double  %10.0g                Within-study variance of stdmdiff
year            int     %12.0g                Year of the study
se              double  %10.0g                Within-study standard-error of stdmdiff
year_c          byte    %9.0g                 Year of the study centered around 1990
mean_exp        float   %9.0g                 Mean teacher experience
---------------------------------------------------------------------------------------------------------
Sorted by: district
```

Modified school calendar data

```
. list district school study stdmdiff mean_exp in 1/11, sepby(district)
```

	district	school	study	stdmdiff	mean_exp
1.	11	1	1	-.18	6.394918
2.	11	2	2	-.22	1.820014
3.	11	3	3	.23	7.86858
4.	11	4	4	-.3	8.369441
5.	12	1	5	.13	10.48499
6.	12	2	6	-.26	10.73829
7.	12	3	7	.19	2.892403
8.	12	4	8	.32	6.689758
9.	18	1	9	.45	5.5483
10.	18	2	10	.38	13.40538
11.	18	3	11	.29	3.927117

Multilevel meta-analysis model

By performing a multilevel meta-analysis, we can

- estimate the effect size more precisely by accounting for the dependence between observations within a group
- assess the heterogeneity between schools within a district and between districts
- estimate how each district varies from the overall mean
  - This will help us decide whether the modified calendar should be applied to some districts and not others

Multilevel meta-analysis model

We'll fit a three-level random-intercepts model

$$\hat{\theta}_{jk} = \theta + u_j^{(3)} + u_{jk}^{(2)} + \epsilon_{jk}$$

where $u_j^{(3)} \sim \mathcal{N}(0, \tau_3^2)$, $u_{jk}^{(2)} \sim \mathcal{N}(0, \tau_2^2)$, and $\epsilon_{jk} \sim \mathcal{N}(0, \hat{\sigma}_{jk}^2)$. Note that j represents the third level (district), k represents the second level (school within district), and ϵ_{jk} represents the sampling errors.

Three-level meta-analysis

```
. meta multilevel stdmdiff, relevels(district school) essevariable(se) nolog
Multilevel REML meta-analysis                              Number of obs = 56

        Grouping information
        ---------------------------------------------------------------
                    |     No. of       Observations per group
         Group variable |     groups    Minimum    Average    Maximum
        ----------------+----------------------------------------------
               district |         11          3        5.1         11
                 school |         56          1        1.0          1
        ---------------------------------------------------------------

                                                           Wald chi2(0)   =  .
Log restricted-likelihood = -7.9587239                     Prob > chi2    =  .

------------------------------------------------------------------------------
    stdmdiff | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
       _cons |   .1847132   .0845559     2.18   0.029     .0189866    .3504397
------------------------------------------------------------------------------
Test of homogeneity: Q_M = chi2(55) = 578.86               Prob > Q_M = 0.0000

-----------------------------------------
  Random-effects parameters  |   Estimate
-----------------------------+-----------
district: Identity           |
                   sd(_cons) |   .2550724
-----------------------------+-----------
school: Identity             |
                   sd(_cons) |   .1809324
-----------------------------------------
```

Assess variability among effect sizes

```
. estat heterogeneity

Method: Cochran
Joint:
  I2 (%) = 90.50

Method: Higgins–Thompson
district:
  I2 (%) = 63.32

school:
  I2 (%) = 31.86

Total:
  I2 (%) = 95.19
```

Fit a two-level model

- We want to test whether there is a nonnegligible amount of heterogeneity between the schools within a district
- First, we store our results from the previous model

```
. meta multilevel stdmdiff, ///
 relevels(district school) essevariable(se)
. estimates store full_model
```

- We now fit a two-level model with district as the second level

```
. meta multilevel stdmdiff, ///
 relevels(district) essevariable(se)
. estimates store school_effect
```

Likelihood-ratio test

```
. lrtest full_model school_effect

Likelihood-ratio test
Assumption: school_effect nested within full_model

 LR chi2(1) =  48.52
Prob > chi2 = 0.0000

Note: The reported degrees of freedom assumes the null hypothesis is not on the boundary of
      the parameter space. If this is not true, then the reported test is conservative.
Note: LR tests based on REML are valid only when the fixed-effects specification is identical
      for both models.
```

Sensitivity analysis

- Suppose we're interested in exploring how different magnitudes of the school-level variation impact our estimates of the overall standardized mean difference and the district-level variation
- To answer this question, we'll refit our model, each time setting the random-effects standard deviations for the school level to a different value

Random-intercepts standard deviations

```
. meta multilevel stdmdiff, ///
 relevels(district school, sd(.  0.01)) esse(se)
. estimates store fixsd1
. meta multilevel stdmdiff, ///
 relevels(district school, sd(.  0.18)) esse(se)
. estimates store fixsd2
. meta multilevel stdmdiff, ///
 relevels(district school, sd(.  0.60)) esse(se)
. estimates store fixsd3
```

Comparing effect sizes

```
. estimates table _all, stats(sd2) keep(stdmdiff:_cons) b(%8.3f) se(%8.3f)
```

Variable	fixsd1	fixsd2	fixsd3
_cons	0.196	0.185	0.123
	0.090	0.085	0.083
sd2	0.010	0.180	0.600

Legend: b/se

Comparing random-effects standard deviations for districts

```
. estimates table _all, stats(sd2) keep(lns1_1_1:_cons) b(%8.3f) eform
```

Variable	fixsd1	fixsd2	fixsd3
_cons	0.288	0.255	0.000
sd2	0.010	0.180	0.600

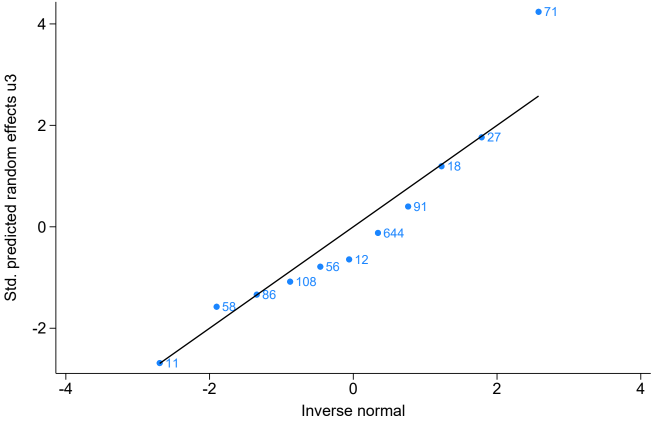
Predictions of random effects

```
. qui: meta multilevel stdmdiff, relevels(district school) esse(se)
. predict double u3 u2, reffects reses(se_u3 se_u2, diagnostic)
. by district, sort: generate tolist = (_n==1)
. list district u3 se_u3 if tolist
```

	district	u3	se_u3
1.	11	-.18998596	.07071817
5.	12	-.08467077	.13168501
9.	18	.1407273	.11790486
12.	27	.24064814	.13641505
16.	56	-.1072942	.13633364
20.	58	-.23650899	.15003184
31.	71	.53427781	.12606072
34.	86	-.2004695	.1499012
42.	91	.05711692	.14284823
48.	108	-.14168396	.13094894
53.	644	-.01215679	.10054689

Normal quantile plot

```
. generate double ustan3 = u3/se_u3

. qnorm ustan3 if tolist, mlabel(district)
```



Models with random slopes

- `meta multilevel` allows us to fit random-intercepts meta-analysis models

```
. meta multilevel stdmdiff, relevels(district school) esse(se)
```

- We can also fit this model as follows:

```
. meta meregress stdmdiff || district:  || school:, esse(se)
```

- If we wish to include random slopes, we can instead use `meta meregress`

```
. meta meregress stdmdiff x1 || district:  x1 || school:, esse(se)
```

  - The `me` in `meregress` refers to mixed effects

Three-level meta-regression with random slopes

```
. meta meregress stdmdiff mean_exp ///
>   || district: mean_exp ///
>   || school:, essevariable(se) nolog nogroup

Multilevel REML meta-regression                    Number of obs =      56
                                                   Wald chi2(1)  =    8.37
Log restricted-likelihood = -3.3635425             Prob > chi2   =  0.0038

------------------------------------------------------------------------------
    stdmdiff | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
    mean_exp |  -.0262054    .009058    -2.89   0.004    -.0439587   -.0084521
       _cons |   .3580009   .0981127     3.65   0.000     .1657036    .5502982
------------------------------------------------------------------------------
Test of homogeneity: Q_M = chi2(54) = 558.47               Prob > Q_M = 0.0000

------------------------------------------
  Random-effects parameters |   Estimate
----------------------------+-------------
district: Independent       |
               sd(mean_exp) |   .0156308
                  sd(_cons) |   .2605429
----------------------------+-------------
school: Identity            |
                  sd(_cons) |    .146955
------------------------------------------
```

Display variance components

```
. estat sd, variance
```

Random-effects parameters	Estimate
district: Independent	
var(mean_exp)	.0002443
var(_cons)	.0678826
school: Identity	
var(_cons)	.0215958

Conclusion

Summary

- Today, we learned how to do the following in Stata:
  - Compute different effect sizes for meta-analysis of prevalence.
  - Summarize meta-analysis data in both a table and a graph.
  - Perform meta-regression with effect sizes that have hierarchical structures.
  - Assess heterogeneity at different levels of the hierarchy.

Resources

- Overview of meta-analysis features in Stata
- Video tutorial on performing meta-analysis in Stata
- *Stata Meta-Analysis Reference Manual*

References

Barker, T. H., C. B. Migliavaca, C. Stein, V. Colpani, M. Falavigna, E. Aromataris, and Z. Munn. 2021. Conducting proportional meta-analysis in different types of systematic reviews: A guide for synthesisers of evidence. *BMC Medical Research Methodology* 21.

Berkey, C. S., D. C. Hoaglin, F. Mosteller, and G. A. Colditz. 1995. A random effects regression model for meta analysis. *Statistics in Medicine* 14: 395–411.

Borenstein, M., L. V. Hedges, J. P. T. Higgins, and H. R. Rothstein. 2009. *Introduction to Meta-Analysis.* Chichester, UK: Wiley.

Brown, L. D., T. T. Cai, and A. DasGupta. 2001. Interval estimation for a binomial proportion. *Statistical Science* 16: 101–133.

Colditz, G. A., T. F. Brewer, C. S. Berkey, M. E. Wilson, E. Burdick, H. V. Fineberg, and F. Mosteller. 1994. Efficacy of BCG vaccine in the prevention of tuberculosis: Meta analysis of the published literature. *Journal of the American Medical Association* 271: 698–702.

Glass, G. V. 1976. Primary, secondary, and meta-analysis of research. *Educational Researcher* 5: 3–8.

Hill, N. R., S. T. Fatoba, J. L. Oke, J. A. Hirst, C. A. O'Callaghan, D. S. Lasserson, and F. D. R. Hobbs. 2016. Global prevalence of chronic kidney disease - A systematic review and meta-analysis. *PLoS One* 11(7).

Moore, R. A., M. R. Tramèr, D. Carroll, P. J. Wiffen, and H. J. McQuay. 1998. Quantitative systematic review of topically applied non-steroidal anti-inflammatory drugs. *British Medical Journal* 316: 333–338.

Rabe-Hesketh, S., and A. Skrondal. 2022. *Multilevel and longitudinal modeling using Stata.* 4th ed. College Station, TX: Stata Press.