OHDSI Tutorial:

15 min. Meta-analysis

Chungsoo Kim

Prerequisites

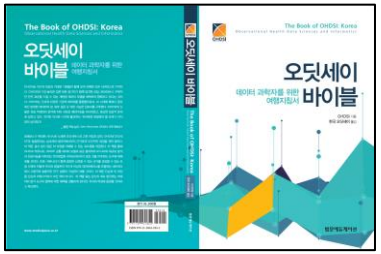
- Familiar with R codes
- Familiar with OHDSI frameworks (OMOP-CDM, ATLAS, HADES)
- At least 2 results of the population-level estimation package from different sites (databases)

Goal of the Tutorial

- Meta-analysis in 15 minutes
- Understanding basic concepts (without equations)
- Interpreting a forest plot
- Give an example using PLE results and its forest plot

Book of OHDSI

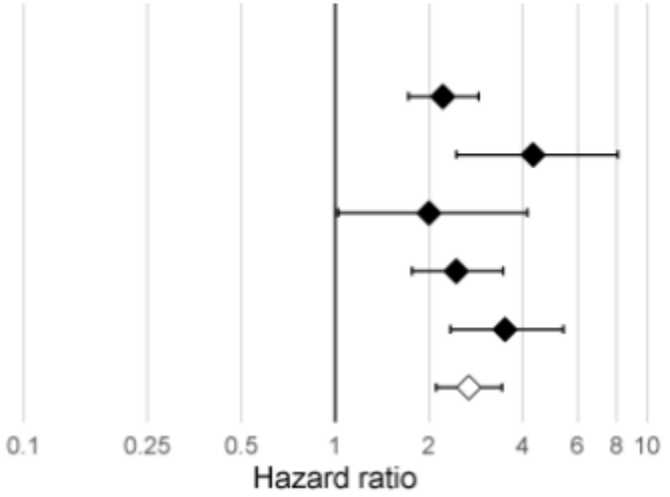
book.ohdsi.org



18.3.6 Between-Database Heterogeneity

Just as we executed our analysis on one database, in this case the IBM MarketScan Medicaid (MDCD) database, we can also run the same analysis code on other databases that adhere to the Common Data Model (CDM). Figure 18.7 shows the forest plot and meta-analytic estimates (assuming random effects) (DerSimonian and Laird 1986) across a total of five databases for the outcome of angioedema. This figure was generated using the `plotMetaAnalysisForest` function in the EvidenceSynthesis package.

Source	Hazard ratio (95% CI)
CCAE	2.22 (1.72-2.88)
MDCD	4.32 (2.45-8.08)
MDCR	2.00 (1.02-4.14)
Optum	2.45 (1.76-3.46)
Panther	3.51 (2.34-5.40)
Summary (I^2 = 0.42)	2.69 (2.11-3.43)



Meta analysis

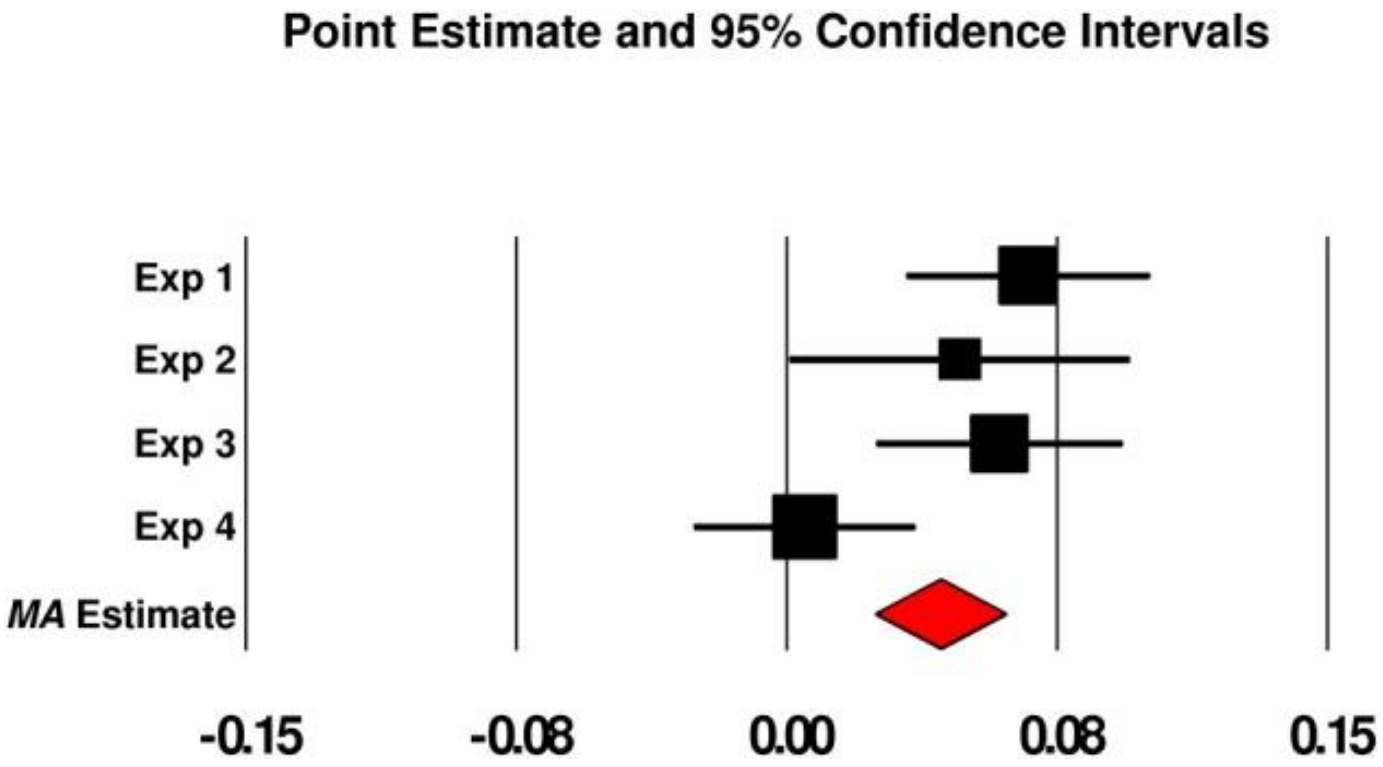
- Meta-analysis quantifies the results of individual studies and presents them as an integrated effect size
- Meta-analysis has become popular for a number of reasons
  - The adoption of evidence-based medicine requires that all reliable information is considered.
  - The desire to avoid narrative reviews which are often misleading.
  - The desire to interpret the large number of studies that may have been conducted about a specific treatment.
  - The desire to increase the statistical power of the results by combining many small-size studies.

- Software capable of meta-analysis includes STATA, R, SAS, MIX, CMA, RevMan, and Meta-Analyst.

Shim SR, Kim S-J. Intervention meta-analysis: application and practice using R software. Epidemiol Health. 2019;41(0):e2019008-0.
알기쉬운 메타분석의 이해, 황성동 저, 학지사
NCSS Statistical Software, NCSS.com

Meta analysis

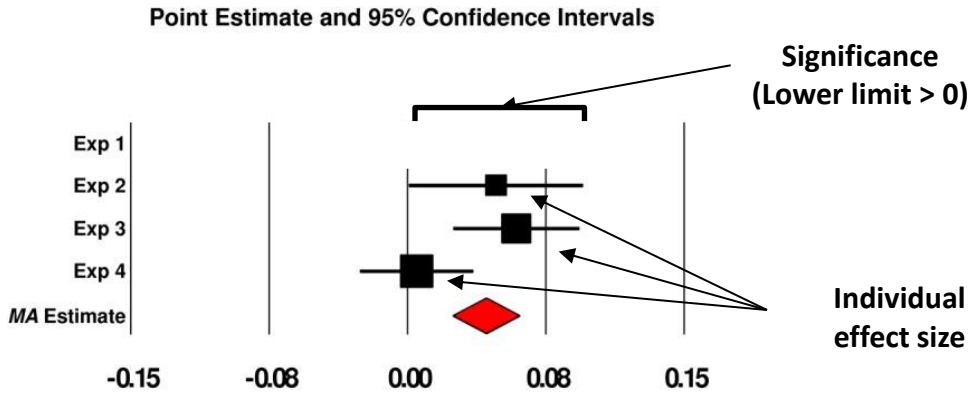
- Forest plot
  - Presenting individual effect sizes, statistical significance, precision, weight, summary effect size and its significance



Meta analysis

- Effect size
  - The unit of currency in a meta-analysis
  - Point estimates:
    - Risk ratio (RR), Odds ratio (OR), Risk difference
    - Cohen's d, Hedges' g

- Statistical significance
  - When the 95% confidence interval does not contain "0"
  - Shorter the confidence interval, the more precise



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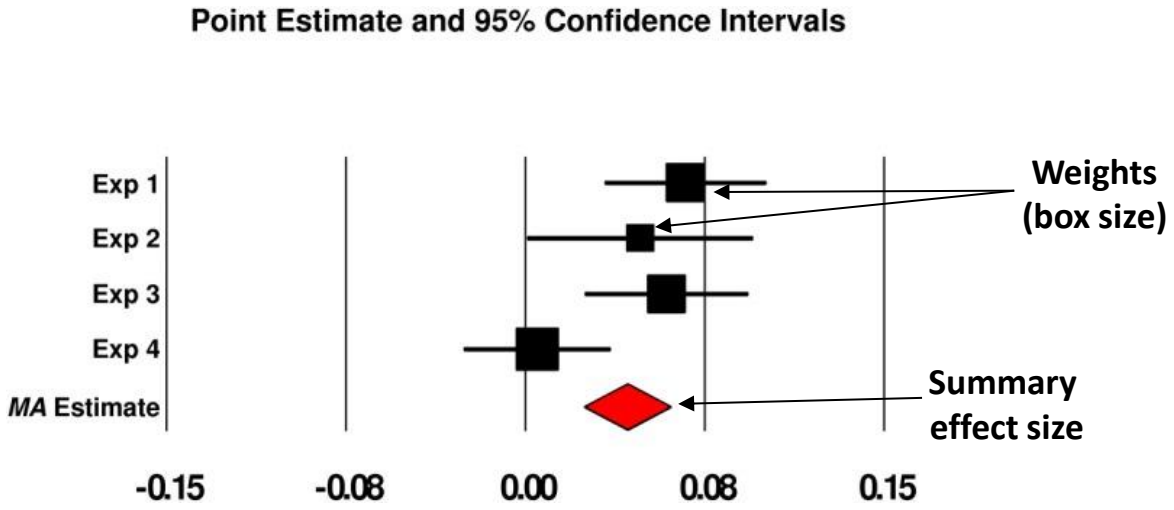
알기쉬운 메타분석의 이해, 황성동 저, 학지사; NCSS Statistical Software, NCSS.com;

Meta analysis

- Weights
  - Generally, inverse of the variance
  - Higher weight when the sample size is large

- Summary effect size
  - Overall effect, weighted mean effect, mean effect size



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알기쉬운 메타분석의 이해, 황성동 저, 학지사; NCSS Statistical Software, NCSS.com

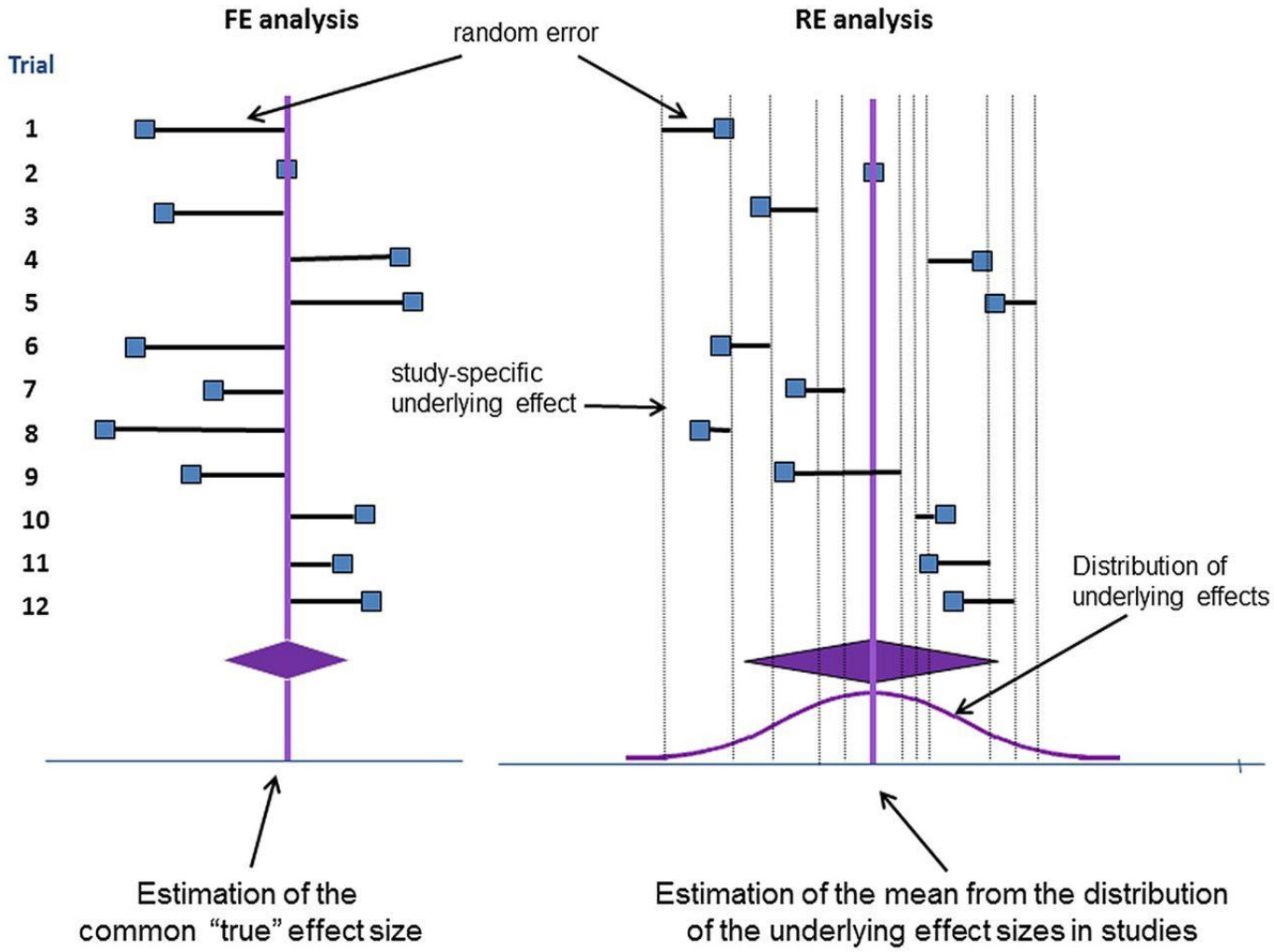
Meta analysis

- Fixed effect model
  - “One (Common) true effect” across all studies
  - Estimating true effect size
  - Sampling error

- Random effect model
  - Various effect sizes across studies because of real differences (Heterogeneity of effect size)
  - Estimating mean effect in relevant distribution
  - Sampling error + between-study variance

Shim SR, Kim S-J. Intervention meta-analysis: application and practice using R software. Epidemiol Health. 2019;41(0):e2019008-0.
알기쉬운 메타분석의 이해, 황성동 저, 학지사; NCSS Statistical Software, NCSS.com

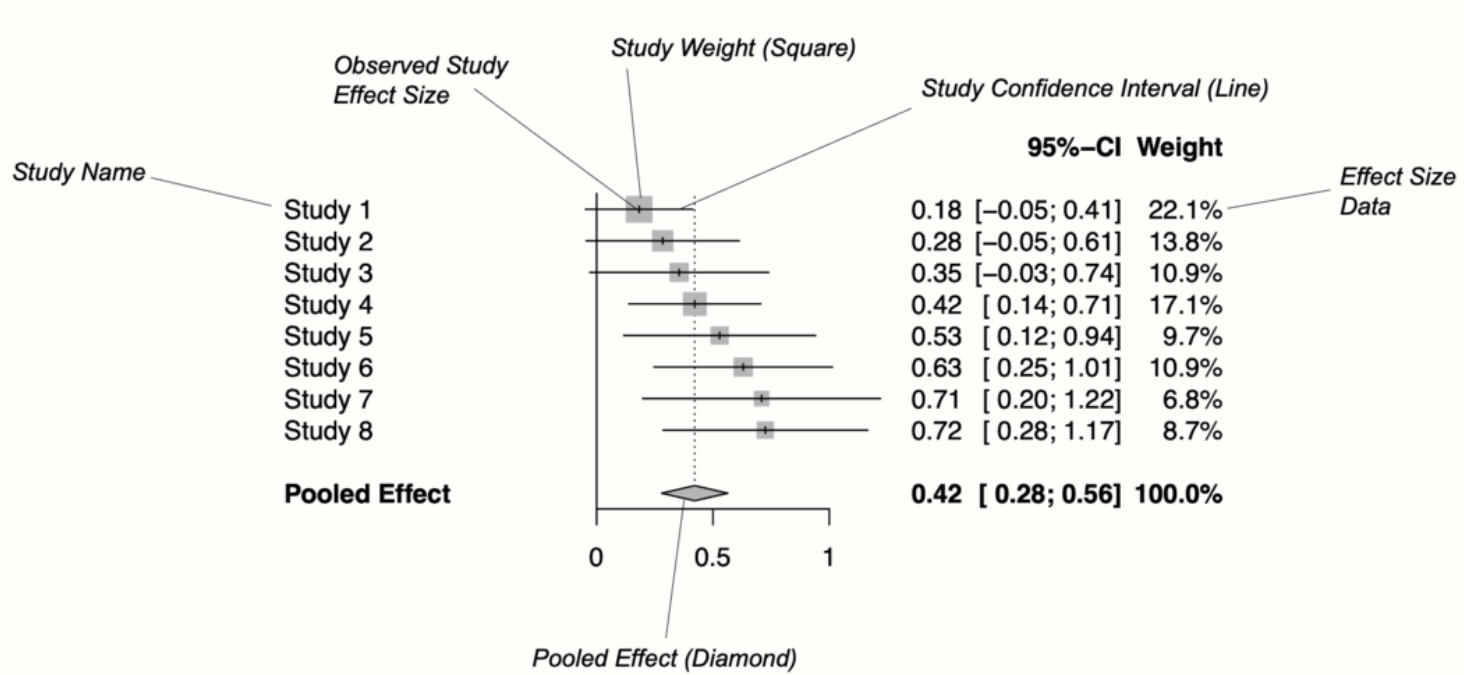
Meta analysis



*Nikolakopoulou A, Mavridis D, Salanti G Demystifying fixed and random effects meta-analysis Evidence-Based Mental Health 2014;**17**:53-57.*

Meta analysis

- Heterogeneity of effect size
  - Differences in effect sizes
  - Understanding the pattern of effects sizes



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NCSS Statistical Software, NCSS.com

Meta analysis

- Heterogeneity statistics
  - τ^2 (tau squared) : absolute value of between-studies variance
  - I^2 : the proportion of true variance (J. P. Higgins and Tompson, 2002), $I^2 = 0.25$ (low), $I^2 = 0.5$ (medium) $I^2 = 0.75$ (high)
  - Only calculated for fixed effect model

Source	Hazard ratio (95% CI)
CCAE	2.22 (1.72-2.88)
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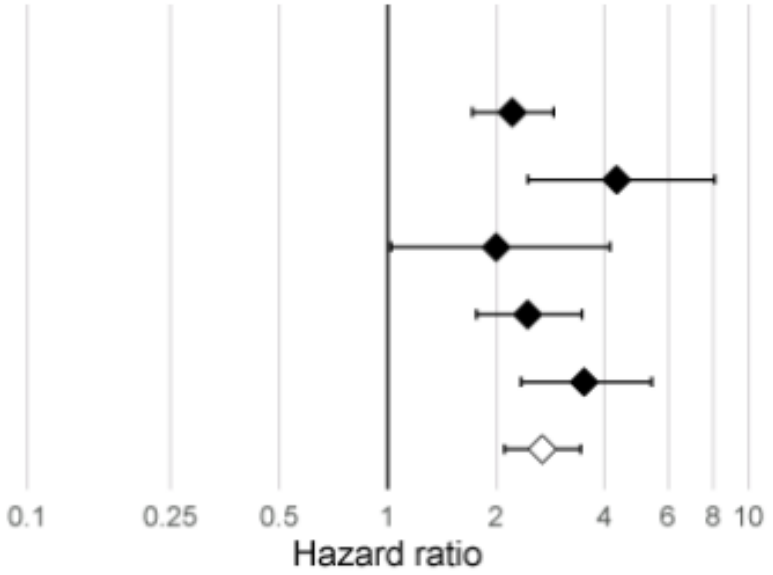
Summary ($I^2 = 0.42$)	2.69 (2.11-3.43)



Book of OHDSI Chap 18.;

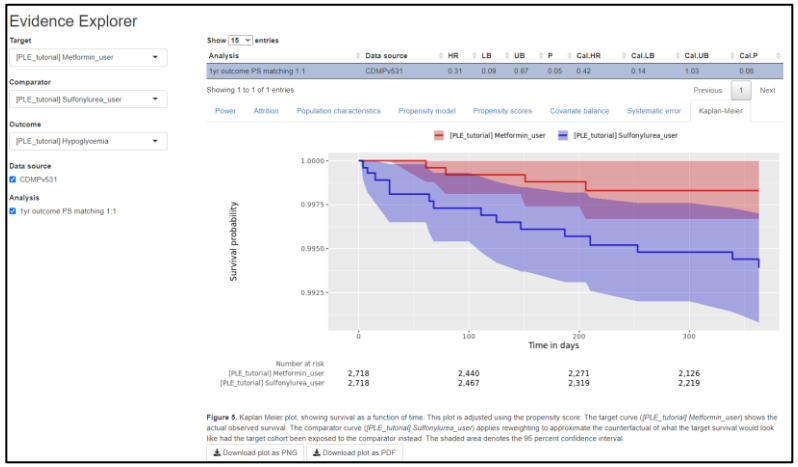
Shim SR, Kim S-J. Intervention meta-analysis: application and practice using R software. Epidemiol Health. 2019;41(0):e2019008-0.;

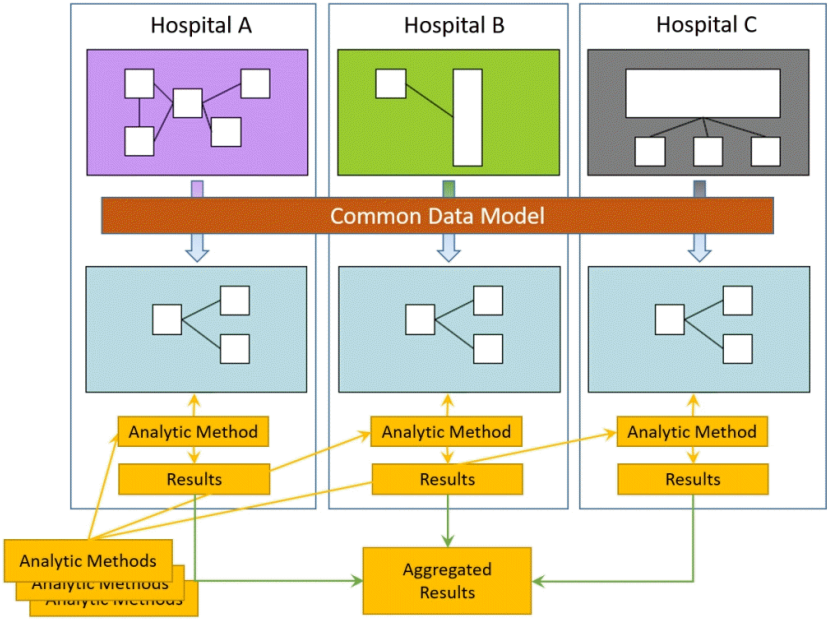
알기쉬운 메타분석의 이해, 황성동 저, 학지사; NCSS Statistical Software, NCSS.com

Study example

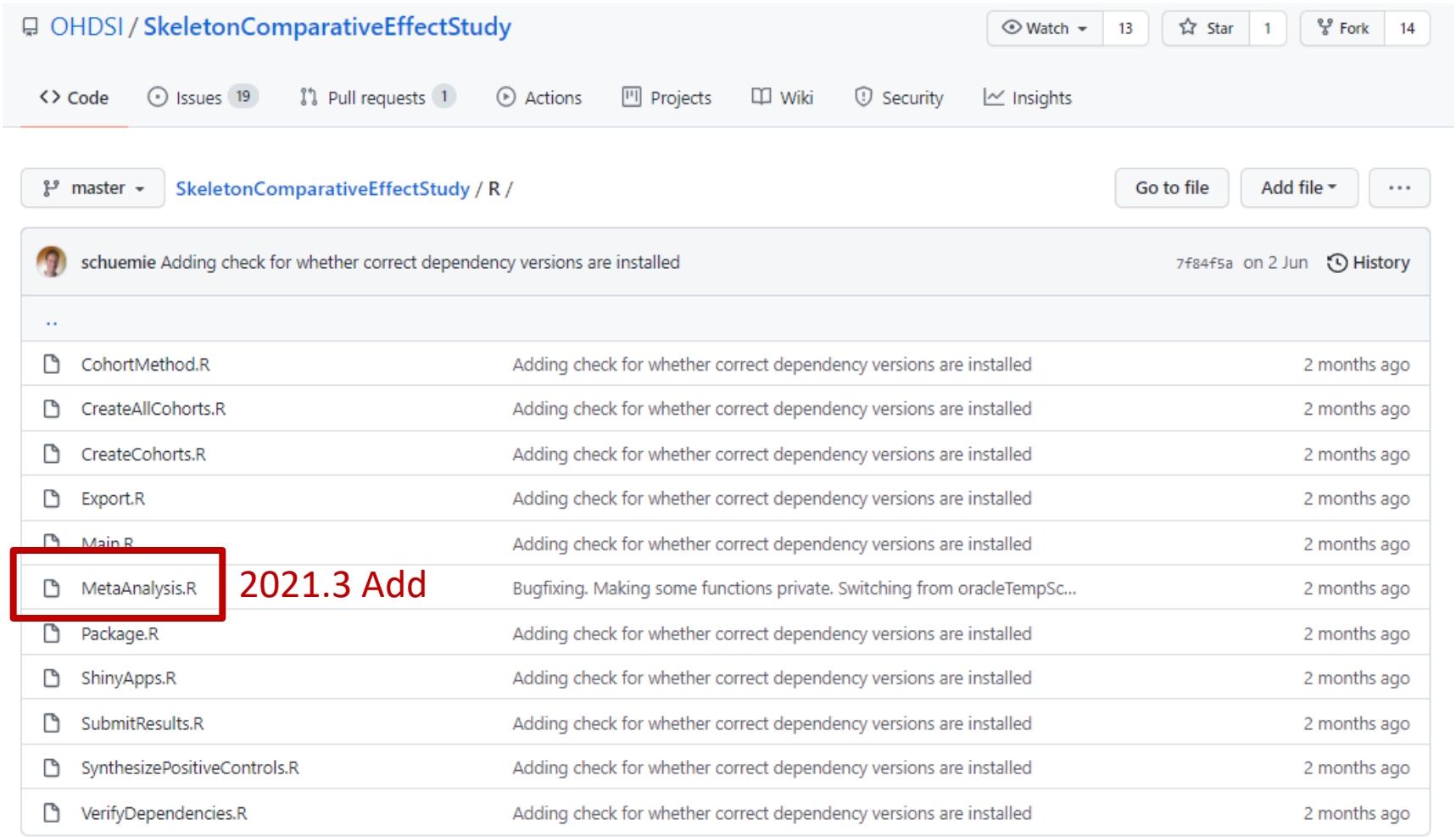
- **OHDSI Journey**

Choice	Value
Target Cohort	New users of Metformin in the type 2 diabetes mellitus
Comparator Cohort	New users of Sulfonylurea in the type 2 diabetes mellitus
Outcome Cohort	Hypoglycemia
Time-at-risk	1 days ~ 365 days from cohort start date
Model	Cox proportional hazards model
PS adjustment	1:1 matching



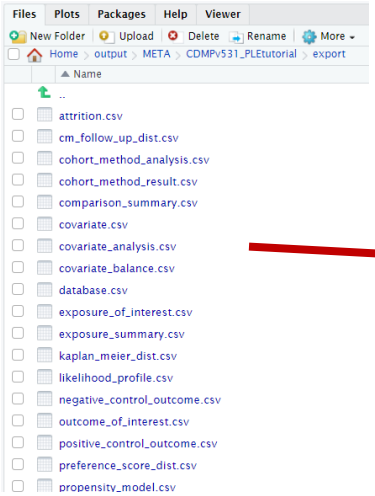


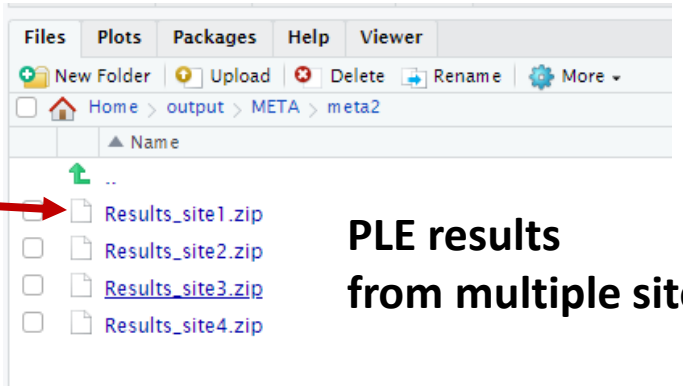
Study example



Study example

Single PLE result





PLE results from multiple sites

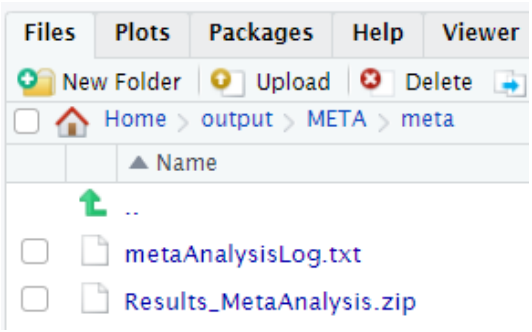
```
> synthesizeResults(allDbsFolder = '/home/ted9219/output/META/meta2',
+                   maExportFolder = '/home/ted9219/output/META/meta2',
+                   maxCores = maxCores,
+                   method = "BayesianNonNormal",
+                   resultsZipPattern = "^Results_.*\\.zip",
+                   addTraditional = TRUE)
Found 4 zip files matching pattern ^Results_.*\.zip for synthesizing
Loading results from Results_site1.zip for evidence synthesis
Loading results from Results_site2.zip for evidence synthesis
Loading results from Results_site3.zip for evidence synthesis
Loading results from Results_site4.zip for evidence synthesis
Loading likelihood profiles from Results_site1.zip for evidence synthesis
Loading likelihood profiles from Results_site2.zip for evidence synthesis
Loading likelihood profiles from Results_site3.zip for evidence synthesis
Loading likelihood profiles from Results_site4.zip for evidence synthesis
Performing cross-database evidence synthesis
  |=========================================================================================================| 100%
Creating database table
Adding results to zip file
Results are ready for sharing at:/home/ted9219/output/META/meta2/Results_MetaAnalysis.zip
```


1. *DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986 Sep;7(3):177-88. doi: 10.1016/0197-2456(86)90046-2.*

2. *Schuemie M, Chen Y, Madigan D, Suchard M, Combining Cox Regressions Across a Heterogeneous Distributed Research Network Facing Small and Zero Counts. arXiv: 2101.01551, 2021*

Study example

Not OHDSI official now!

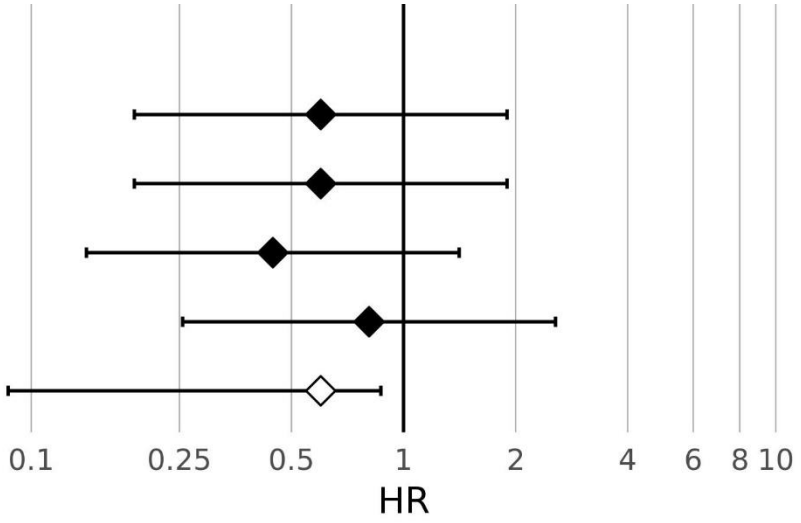


Meta-analysis results

```
> plotMetaAnalysisForest (allDbsFolder,
+                         maExportFolder,
+                         labels = c("Site1", "Site2", "Site3", "Site4"),
+                         xLabel = "HR",
+                         summaryLabel = "Summary",
+                         limits = c(0.1, 10),
+                         alpha = 0.05,
+                         fileName = '/home/ted9219/output/META/meta/figure1.jpg')
Found 4 zip files matching pattern ^Results_.*\.zip for synthesizing
Loading results from Results_site1.zip for evidence synthesis
Loading results from Results_site2.zip for evidence synthesis
Loading results from Results_site3.zip for evidence synthesis
Loading results from Results_site4.zip for evidence synthesis
Loading results from Results_MetaAnalysis.zip for forest plot
```

Forest plot

Source	HR (95% CI)
Site1	0.60 (0.19 - 1.90)
Site2	0.60 (0.19 - 1.90)
Site3	0.45 (0.14 - 1.41)
Site4	0.81 (0.26 - 2.56)
Summary	0.60 (0.09 - 0.87)

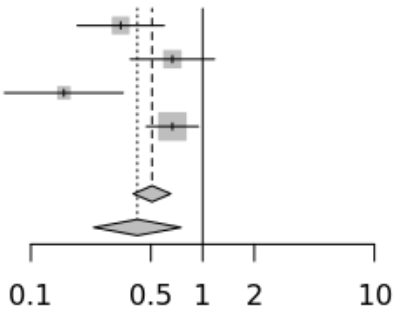


Study example for meta analysis

```
> library(meta)
> resultsZipPattern = "^Results_.*\\.zip"
> resultSets <- list.files(path = allDbsFolder, pattern = resultsZipPattern)
> mainResults <- lapply(resultSets, loadDatabaseResults, allDbsFolder = allDbsFolder)
Loading results from Results_site1.zip for evidence synthesis
Loading results from Results_site2.zip for evidence synthesis
Loading results from Results_site3.zip for evidence synthesis
Loading results from Results_site4.zip for evidence synthesis
> data = do.call(rbind, mainResults)
> data = data[data$outcomeId == getOutcomesOfInterest(),]
> FR.fit <- metabin(event.e = data$targetOutcomes,
+                   n.e = data$targetSubjects,
+                   event.c = data$comparatorOutcomes,
+                   n.c = data$comparatorSubjects, method = "I")
> forest.meta(FR.fit)
```

Study	Experimental Events	Experimental Total	Control Events	Control Total	Risk Ratio	RR	95%-CI	Weight (fixed)	Weight (random)
1	15	2718	45	2718		0.33	[0.19; 0.60]	18.6%	24.8%
2	20	2771	30	2771		0.67	[0.38; 1.17]	19.8%	25.2%
3	7	3127	45	3127		0.16	[0.07; 0.34]	10.0%	20.5%
4	52	5432	78	5432		0.67	[0.47; 0.94]	51.7%	29.5%
Fixed effect model		**14048**		**14048**		**0.51**	**[0.39; 0.65]**	**100.0%**	--
Random effects model						**0.42**	**[0.23; 0.75]**	--	**100.0%**

Heterogeneity: I^2 = 78%, τ^2 = 0.2711, p < 0.01



Concluding remarks

- Offering a sneak peek of meta-analysis

- HADES package + R offer large flexibility
- 80% of studies are 'cookie-cutter' design
- For remaining 20%, will need to modify code generated by ATLAS

- Further subjects
  - Multiple outcomes
  - Meta-ANOVA, Meta regression
  - Publication bias, funnel plot

- Materials
  - 알기쉬운 메타분석의 이해, 황성동 저, 한나래아카데미
  - Doing Meta-Analysis in R https://bookdown.org/MathiasHarrer/Doing_Meta_Analysis_in_R
  - https://github.com/OHDSI/EvidenceSynthesis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OBSERVATIONAL HEALTH DATA SCIENCES AND INFORMATICS

Thank you