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Single Day Event

Meta-Analytical Framework for Proportions using R

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Disclaimer

I confirm that, the opinions and thoughts discussed in this presentation are subject to my own independent views and are not subject to the opinions of the organization that I represent.

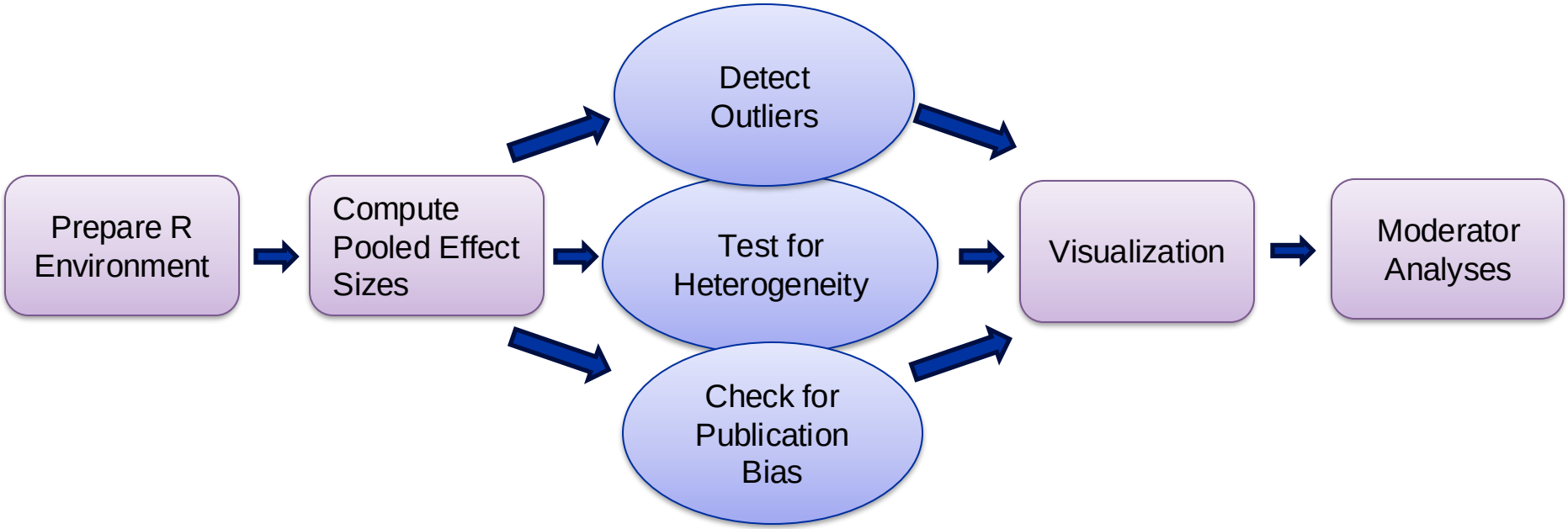
Meta-Analysis

- Meta-analysis is often used to evaluate the **clinical effectiveness of healthcare interventions**.
- Reasons for doing meta-analysis are the need **to increase sample size**, **to establish statistical significance with better accuracy**, to **extrapolate to broader population**.
- Components of a good meta-analysis are **complete coverage of all relevant studies**, look for the **presence of heterogeneity**, and **explore the robustness of the main findings** using sensitivity analysis.

Tools to implement Meta-Analysis:

SAS	Python	STATA	OTHERS	R
PROC MIXED	PythonMeta	Meta commands	Comprehensive Meta-Analysis Software (CMA)	metafor
PROC MCM	PyMARE		MetaWin	meta
PROC BGLIMM	zEpid		MetaStat	netmeta
PROC GLIMMIX	NiMARE		OpenMeta (Analyst)	bayesmeta
PROC MEANS				MetaStan

Framework for Meta-analysis for Proportions using R



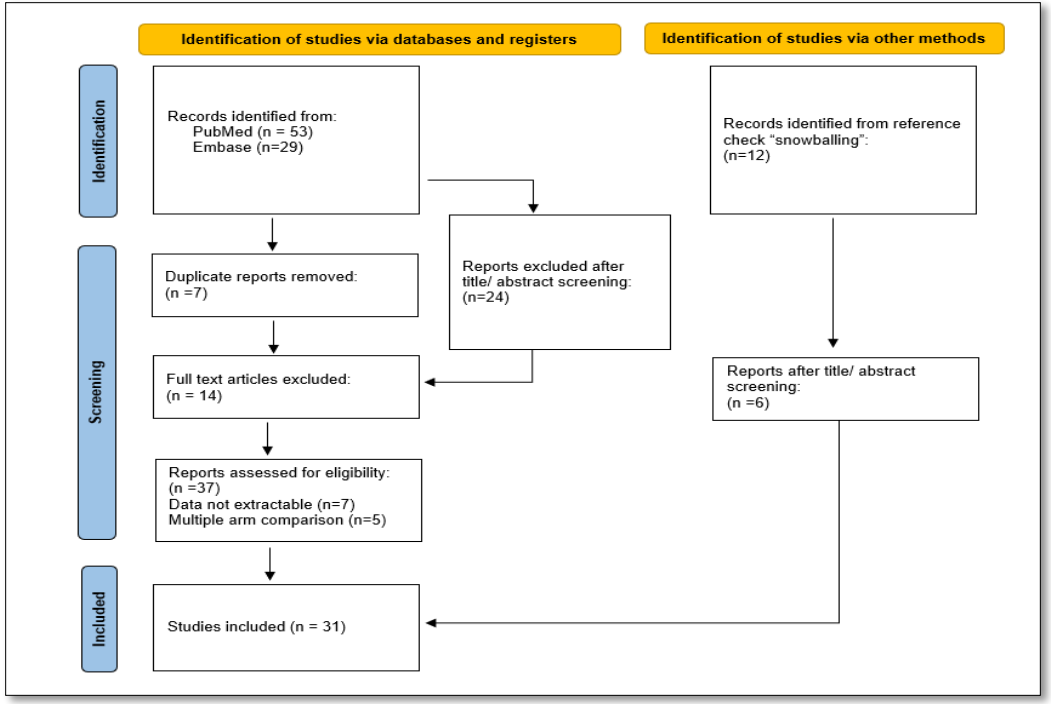
Case Study

Acute Graft Rejection among patients who have undergone renal transplantation in India – a Systematic Review and Meta-Analysis

- To find pooled estimate of Acute Graft Rejection among Renal Transplant patients in India
- To evaluate the risk factors related to Acute Graft Rejection

Pre-Processing

- Search Strategy- using PRISMA guidelines



Data Points:

- *Author*
- *Year*
- *Location of Study*
- *Total Population*
- *Acute Graft Rejection Rate*
- *Donor characteristics*
- *Type of Hospital*

1. Prepare R Environment

i. Installing packages : **metafor, meta**

ii. Calling libraries

iii. Importing datasets

```
install.packages(c("metafor", "meta"))
library(meta)
library(metafor)
meta_data <- read.csv("D:/Conferences/PHUSE/obj1.csv", header=T, sep=",")
```

2. Compute Pooled Effect Size

Pre-requisites:

1. Transformation of data
2. Using appropriate model

```
  pred  ci.lb  ci.ub  pi.lb  pi.ub
0.1626 0.1044 0.2443 0.0161 0.6979
```

```r
ind_eff <- escalc(xi=AGR, ni=N, data=meta_data, measure="PLO")
pool_eff <- rma(yi, vi, data=ind_eff, method="DL")
eff_size <-predict(pool_eff, transf=transf.ilogit)
print(eff_size)
```

3. Test for Heterogeneity

Analysing variance:

- T^2 statistic
- Q- statistic
- I^2 statistic

```
ind_eff <- escalc(xi=AGR, ni=N, data=dat, measure="PLO")
pool_eff <- rma(yi, vi, data=ind_eff, method="DL")
print(pool_eff)
confint(pool_eff)
```

3. Test for Heterogeneity

```
Random-Effects Model (k = 24; tau^2 estimator: DL)

tau^2 (estimated amount of total heterogeneity): 1.5287 (SE = 0.5135)
tau (square root of estimated tau^2 value):      1.2364
I^2 (total heterogeneity / total variability):   95.31%
H^2 (total variability / sampling variability):  21.30

Test for Heterogeneity:
Q(df = 23) = 489.9923, p-val < .0001

Model Results:

estimate      se     zval    pval    ci.lb    ci.ub
 -1.6390  0.2602  -6.2988  <.0001  -2.1490  -1.1290  ***

---
Signif. codes:  0 '***' 0.0
```

	estimate	ci.lb	ci.ub
tau^2	1.5287	1.2248	4.3127
tau	1.2364	1.1067	2.0767
I^2(%)	95.3060	94.2088	98.2841
H^2	21.3040	17.2675	58.2799

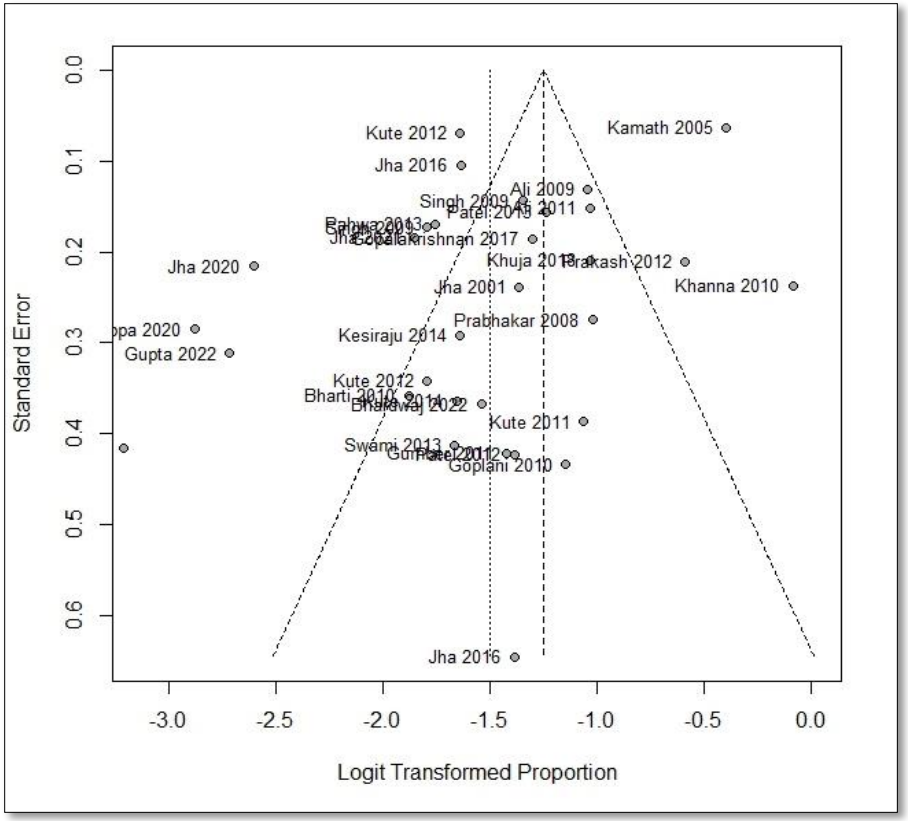
- *T^2 statistic indicates systematic differences in effects across studies.*
- *Q-test and its p-value serve as a test of significance to address the null hypothesis that the effects across studies are homogeneous.*
- *I^2 statistic is the ratio of between-study variance to the observed variance. It conveys the cause of heterogeneity.*

4. Publication bias

Funnel Plot:

```
funnel(pool_eff, atransf=transf.ilogit)
funnel(pool_eff, yaxis="ni")
```

- *Even though the plot shows asymmetrical nature , detecting publication bias using funnel plot is rather subjective in nature.*
- *Other objective ways to identify publication bias is the rank correlation test, Egger's regression test.*



5. Detecting Outliers

Detecting outliers:

- Externally studentized residuals
- Difference in fits values (DFFITS)
- Cook's distances
- Leave-one-out estimates

```
stud_res <- rstudent(pool_eff)
abs_res <- abs(stud_res$z)
stud_res[order(-abs_z)]
```

```
L1O <- leave1out(pool_eff, transf=transf.ilogit)
print(L1O, digits=6)
```

5. Detecting Outliers

Statistics measuring impact of outliers

	rstudent	dffits	cook.d	cov.r	tau2.del	QE.del	hat	weight	dfbs
1	0.8006	0.1658	0.0276	1.0491	1.5383	478.3537	0.0412	4.1164	0.1658
2	-1.3194	-0.2688	0.0717	1.0330	1.5154	475.5595	0.0399	3.9924	-0.2688
3	0.1467	0.0300	0.0009	1.0879	1.5970	488.5439	0.0422	4.2200	0.0300
4	0.3085	0.0642	0.0044	1.1028	1.6188	483.9002	0.0429	4.2916	0.0642
5	-1.7780	-0.3757	0.1244	0.9250	1.3421	402.7500	0.0430	4.3024	-0.3749
6	-0.5721	-0.1223	0.0159	1.1082	1.6269	481.1925	0.0431	4.3107	-0.1225
7	1.5718	0.3264	0.1015	0.9928	1.4508	452.4422	0.0411	4.1149	0.3266
8	0.1698	0.0348	0.0013	1.0788	1.5836	488.6151	0.0417	4.1724	0.0348
9	2.5705	0.5100	0.2409	0.9556	1.3980	443.1459	0.0382	3.8160	0.5119
10	0.7995	0.1671	0.0281	1.0513	1.5404	474.5477	0.0419	4.1911	0.1671
11	-0.9752	-0.2048	0.0424	1.0556	1.5468	474.4200	0.0421	4.2146	-0.2048
12	-1.5462	-0.3057	0.0923	1.0253	1.5070	476.3987	0.0378	3.7788	-0.3059
13	-0.7619	-0.1617	0.0271	1.0816	1.5861	476.4329	0.0428	4.2828	-0.1618
14	0.1433	0.0292	0.0009	1.0990	1.6134	488.2056	0.0426	4.2605	0.0292
15	0.2037	0.0419	0.0019	1.1032	1.6197	486.8872	0.0428	4.2786	0.0420
16	0.5818	0.1212	0.0150	1.0652	1.5621	480.9942	0.0419	4.1900	0.1212
17	-1.0097	-0.2122	0.0454	1.0534	1.5431	472.3053	0.0422	4.2250	-0.2122
18	-1.0019	-0.2107	0.0448	1.0542	1.5444	472.1210	0.0423	4.2302	-0.2108
19	-0.4833	-0.1033	0.0113	1.1052	1.6227	485.1338	0.0429	4.2911	-0.1034
20	2.1904	0.4502	0.1854	0.9501	1.3856	435.5361	0.0404	4.0418	0.4509
21	0.2204	0.0454	0.0021	1.0800	1.5852	487.9355	0.0419	4.1882	0.0454
22	-0.3048	-0.0659	0.0047	1.1223	1.6489	488.4424	0.0431	4.3072	-0.0660
23	-1.7068	-0.3443	0.1156	1.0141	1.4870	468.2710	0.0393	3.9328	-0.3445
24	2.1048	0.4497	0.1680	0.8712	1.2595	387.0910	0.0425	4.2505	0.4489

R 4.2.2 · ~/

```
> abs.z=abs(stud.res$z)
> abs.z=abs(stud.res$z)
> stud.res[order(-abs.z)]
```

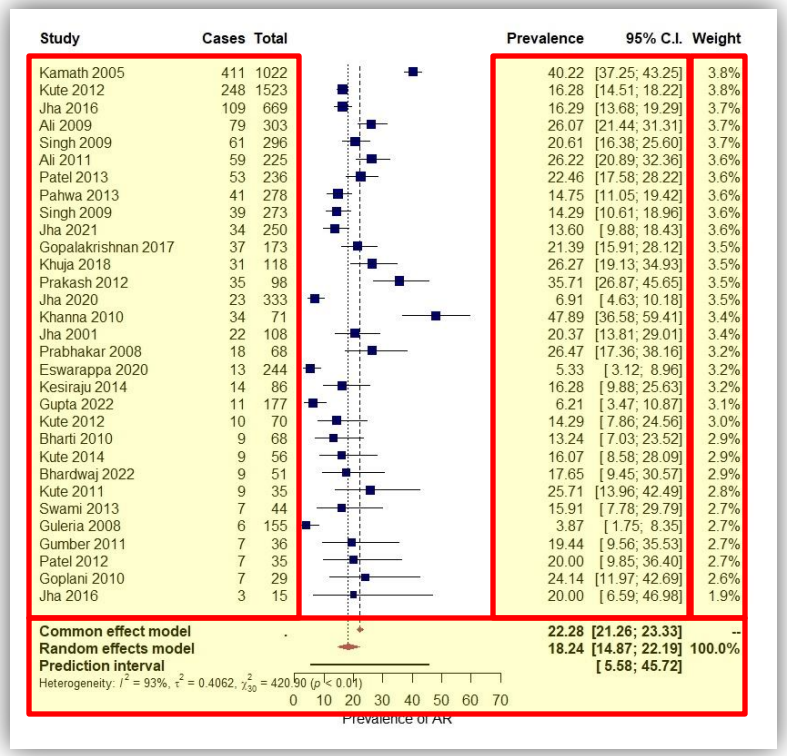
	resid	se	z
30	1.1378	0.4761	2.3901
10	-1.7603	0.7585	-2.3206
21	1.4642	0.6795	2.1548
20	-1.4244	0.6890	-2.0674
1	-1.2538	0.7079	-1.7713
24	-1.1421	0.6608	-1.7284
28	0.9450	0.6840	1.3816
19	0.4838	0.6823	0.7091
3	0.4853	0.6908	0.7025
4	0.4762	0.6830	0.6973
26	0.4946	0.7104	0.6962
17	0.4519	0.7589	0.5955
9	-0.3617	0.6781	-0.5334
6	-0.3918	0.7429	-0.5274
7	0.3645	0.7837	0.4652
14	-0.3024	0.6771	-0.4466
18	-0.3007	0.7358	-0.4087
16	0.2714	0.6841	0.3967
15	-0.2637	0.6775	-0.3893
25	0.2061	0.6870	0.3000
11	0.1579	0.6837	0.2310
27	-0.1696	0.7713	-0.2199
13	-0.1574	0.7471	-0.2107
31	-0.1408	0.6798	-0.2071
23	-0.1408	0.6914	-0.2036
12	0.1418	0.6992	0.2028
2	-0.1420	0.7159	-0.1984
5	0.1169	0.7775	0.1504
29	0.1159	0.9170	0.1264
22	0.0809	0.7767	0.1041

*The studies with values **above 3** are those studies whose heterogeneity impact the pooled estimates adversely*

6. Visualization

Forest Plot

```
pool_summary <- metaprop(AR, N, authoryear, data=meta_data, sm="PLO",method = "Inverse",
                         method.tau="DL", method.ci="NAsm",random =
                           TRUE , prediction = TRUE)
precision <- sqrt(ind_eff$vi)
forest(pool_summary,
       xlim=c(0,70),pscale=100,
       rightcols=c("effect", "ci","w.random"),
       rightlabs=c("Prevalence", "95% C.I.", "Weight"),
       leftcols=c("studlab", "event", "n"),
       leftlabs=c("Study", "Cases", "Total"),
       xlab="Prevalence of AR", smlab="",weight.study="random", squaresize=0.5,
       col.square="navy", col.square.lines="navy",col.diamond="maroon",
       col.diamond.lines="maroon",comb.fixed=FALSE,comb.random=FALSE,
       pooled.totals=FALSE, fs.hetstat=10, print.tau2=TRUE, print.Q=TRUE,
       print.pval.Q=TRUE, print.I2=TRUE,digits=2,
       sortvar=precision)
```

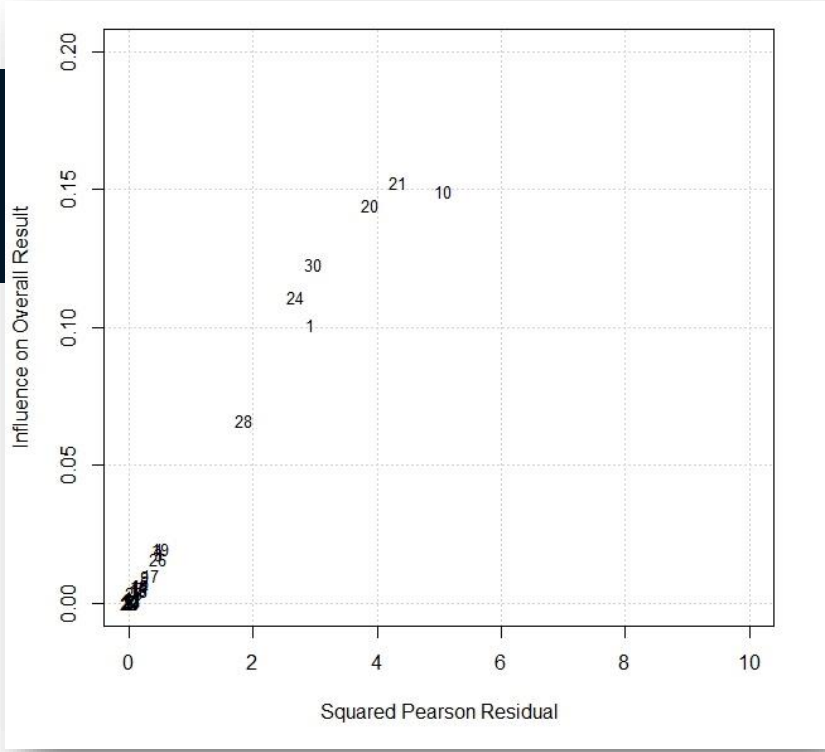


6. Visualization

Baujat Plot

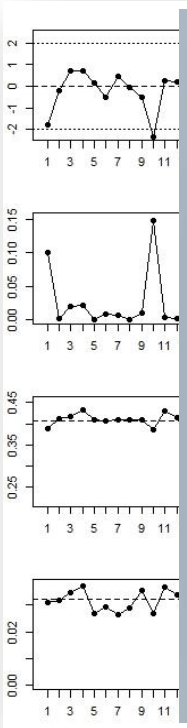
```
resd <- rma(yi, vi, data=ind_effect, method="DL")
baujat(resd, xlim=c(0,6), ylim=c(0,0.2))
```

- *The studies on the furthest end of the right quadrant show the most heterogeneity with the most impact on the pooled effect size.*

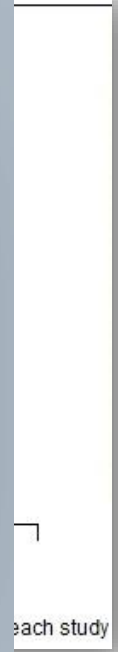


6. Visualization

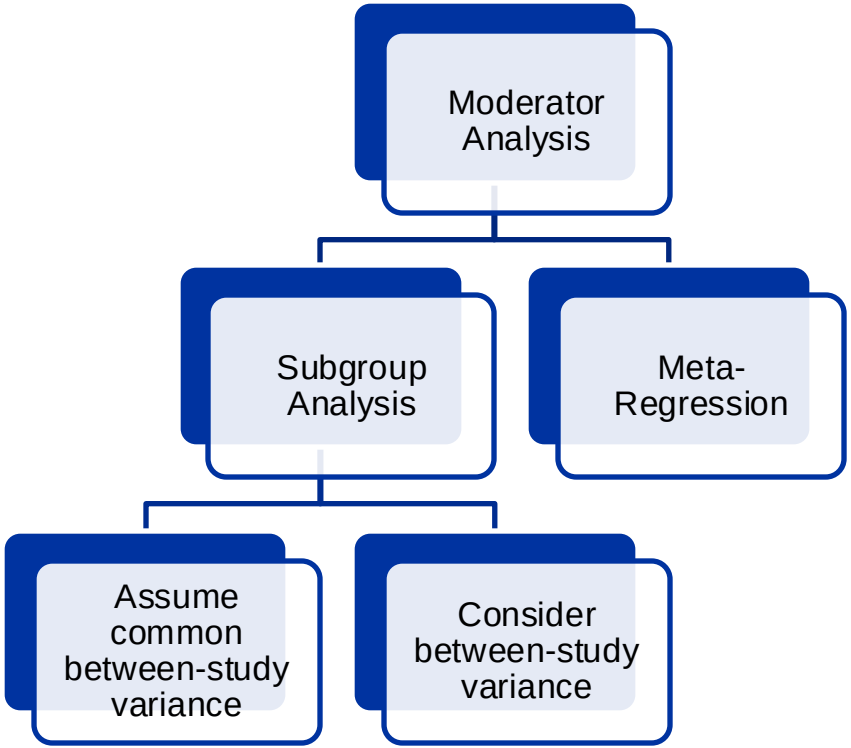
Plots showing leave1out estimates




```
forest(yi, vi, transf=transf.ilogit,
       slab=paste(dat$Author, dat$Year, sep=", "),
       refline=pes$pred,
       xlab="Summary proportions leaving out each study")
inf=influence(pes.logit)
plot(inf)
```



7. Moderator Analyses



7. Moderator Analyses

Subgroup analysis:

Subset data to include only the moderator groups and repeat earlier steps.

```
ind_effect <- escalc(xi=AR, ni=N, data=meta_data, measure="PLO")
pool_before <- rma(yi, vi, data=ind_eff, subset=S_A=="Before 2009")
pool_after <- rma(yi, vi, data=ind_eff, subset=S_A=="After 2009")
effsize_before <- predict(pool_before, transf=transf.ilogit)
effsize_after <- predict(pool_after, transf=transf.ilogit)
diffvar <- data.frame(estimate=c(pool_before$b, pool_after$b),
                      stderror=c(pool_before$se, pool_after$se),
                      moderator=c("Before 2009", "After 2009"),
                      tau2=round(c(pool_before$tau2,
                                   pool_after$tau2), 3))
subg_period <- rma(estimate, sei=stderror, mods=~moderator,
                   method="FE", data=diffvar)
pool_period <- rma(estimate, sei=stderror, method="FE", data=diffvar)
mtprop <- metaprop(AR,N,studlab=paste(dat$Author, dat$Year, sep=", "),data=meta_data, subgroup =
(S_A))
summary(mtprop)
forest.meta(mtprop, layout = "JAMA")
```

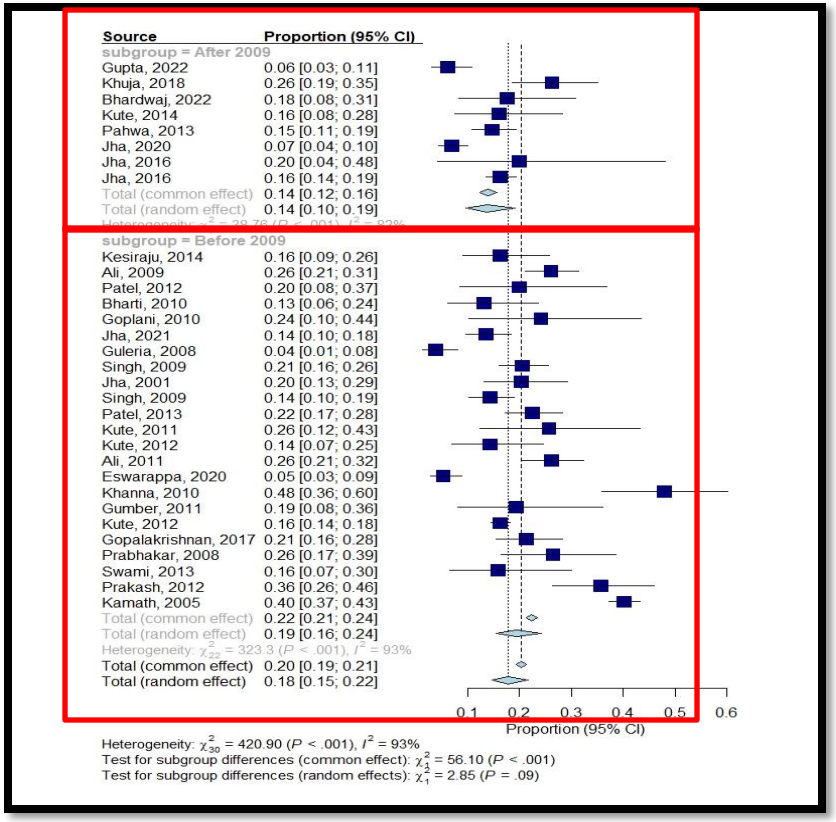
7. Moderator Analyses

Subgroups considered:

- Study Period (Before and After 2009)

The groups have been divided keeping 2009 as the point of division as that was the year when an outcome-altering drug Tacrolimus, an immunosuppressant, was introduced in India.

The forest plot shows that there is a significant difference between the two groups.



7. Moderator Analyses

Meta-Regression:

```
ind_eff <- escalc(xi=AR, ni=N, data=meta_data, measure="PLO")
pool_eff <- rma(yi, vi, data=ind_eff, method="DL")
eff_size <- predict(pool_eff, transf=transf.ilogit)
metareg <- rma(yi, vi, data=ind_eff, mods=~mod1+mod2+mod3+mod4)
print(metareg)
```

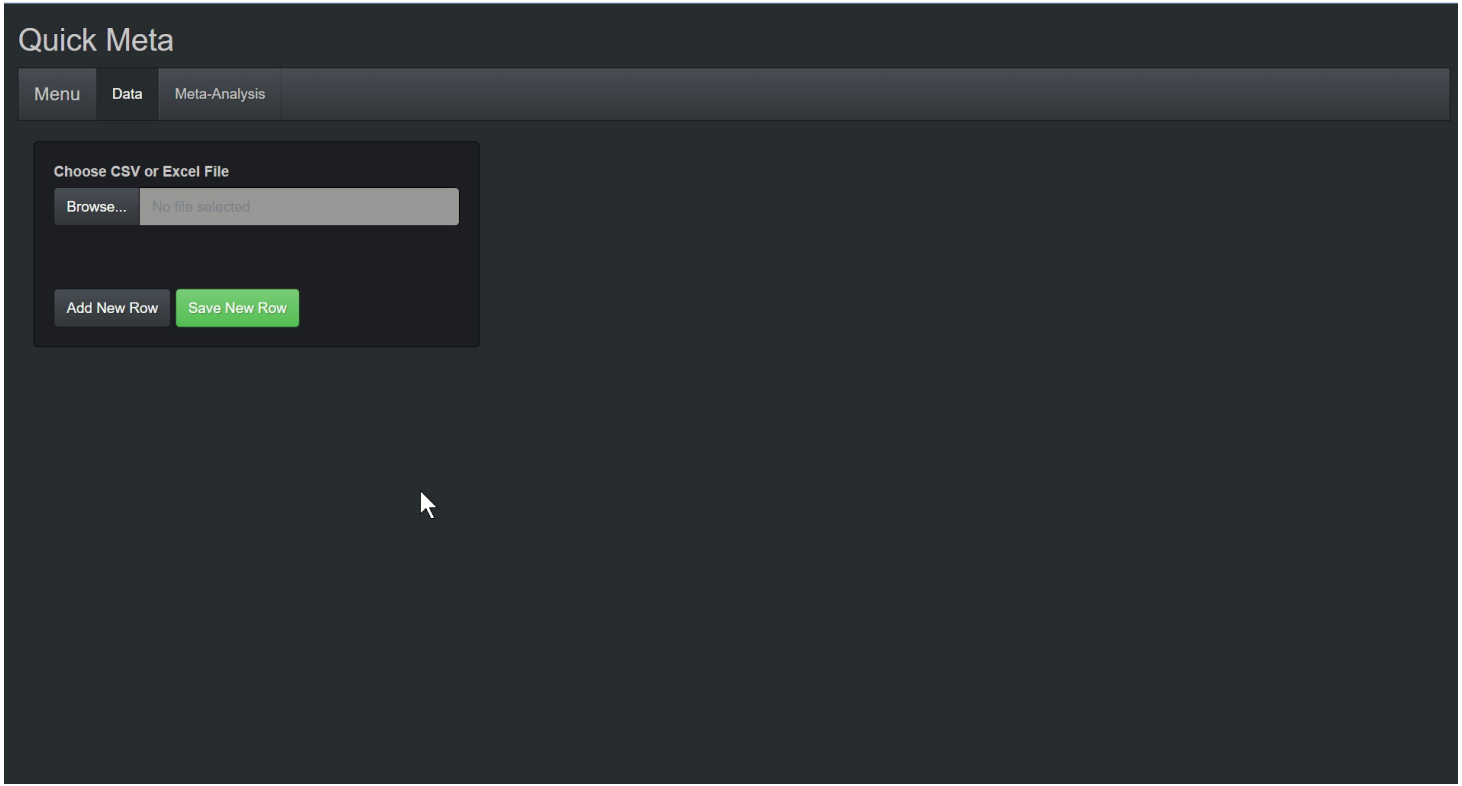
Outcomes

- The estimated higher prevalence of Acute Graft Rejection, compared to other developed countries, **provides impetus to further research into the conditions leading to the risk of AGR**.
- The estimated prevalence of AGR **provides a reasonable data to calculate sample size** for clinical trials in this domain.
- Study of risk factors **provide for inclusion/exclusion criteria for patients** to be included in clinical trials.
- Helps in **understanding the region in the country where the patients could benefit from the drug** produced.

Applications in Pharma Industry

- Finding patient groups for clinical trials
- Basic Inputs to Design a study
- Sample Size Calculation
- Inclusion/Exclusion Criteria
- Used in pharmacometrics to decide baseline dosage
- Understand the demand area of a drug to market it better

Dashboard


Quick Meta
Menu
Data
Meta-Analysis
Choose CSV or Excel File
Browse...
No file selected
Add New Row
Save New Row

Conclusion

Tailored Approach to Statistical Analysis: The flexibility of R allows us to customize our analyses, tailoring our approaches to fit the specific nuances of our data.

Deliver Impactful Insights: Use R Shiny to create interactive dashboards that not only visualize your findings but also empower stakeholders to explore the data themselves.

Engage with the Community: The true power of R lies not just in the code itself but in the community behind it. By tapping into a wealth of resources and shared knowledge, we can continue to enhance our analytical skills and expand our understanding of the world around us.

Next Steps: As you integrate R into your research workflows, experiment, innovate, collaborate, and share your findings.

THANK YOU!

The Global Healthcare Data Science Community

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