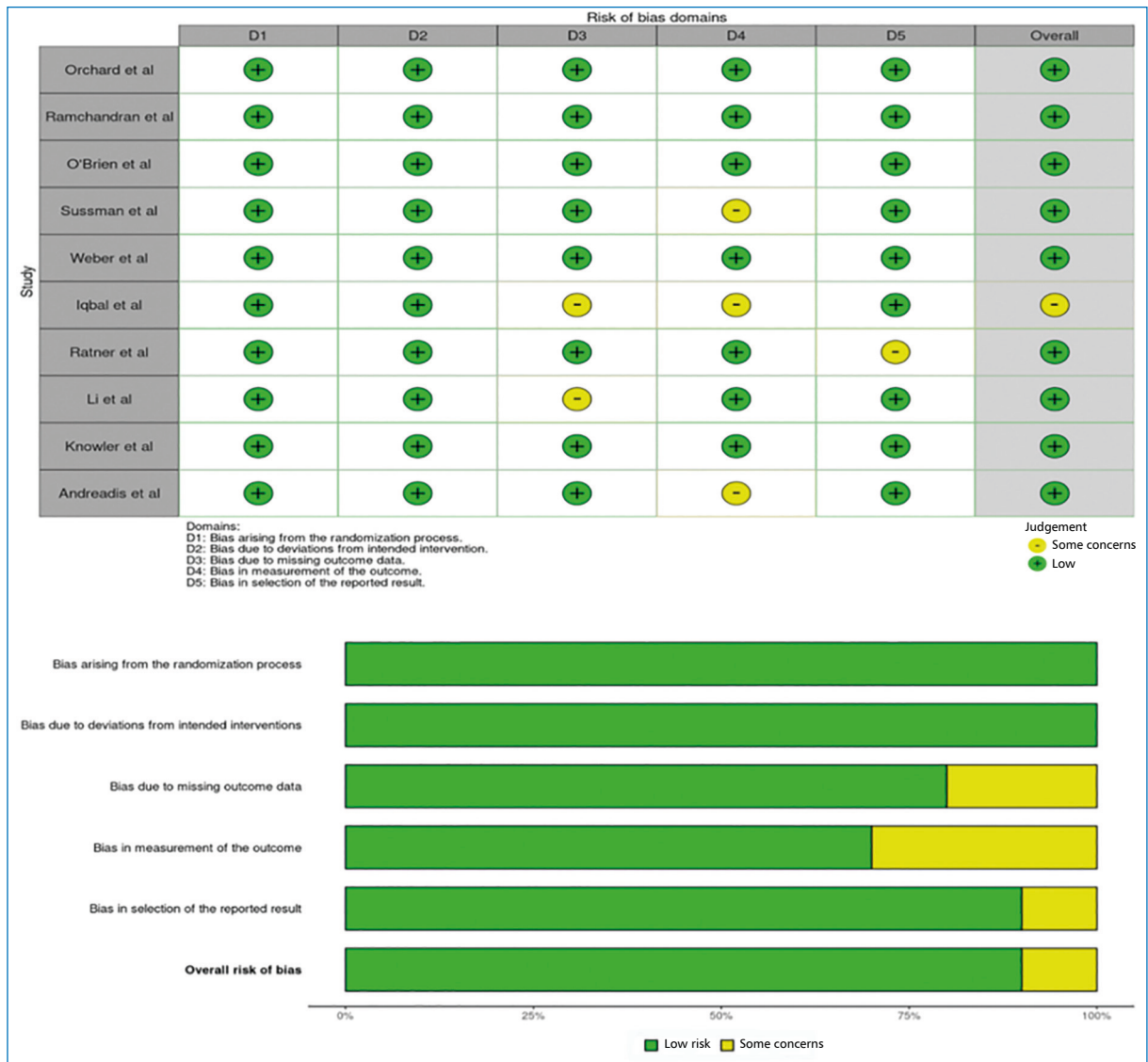


Supplementary File 1. Web Search for Citations Using the Cochrane Library

Search Name: Metformin in Prediabetes
 Date Run: 10/11/2023 04:00:53
 Comment:

ID	Search	hits
#1	MeSH descriptor: [Prediabetic State] explode all trees	1572
#2	MeSH descriptor: [Glucose Intolerance] explode all trees	1503
#3	(IFG):ti,ab,kw (Word variations have been searched)	739
#4	("impaired fasting glucose"):ti,ab,kw (Word variations have been searched)	856
#5	(IGT):ti,ab,kw (Word variations have been searched)	1202
#6	("impaired glucose tolerance"):ti,ab,kw (Word variations have been searched)	3745
#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6	5946
#8	MeSH descriptor: [Metformin] explode all trees	4991
#9	#7 AND #8 in Trials	304

Supplementary File 2. Cochrane Risk of Bias Algorithm



Supplementary File 3. Codes for Analysis

A. Libraries required

```
library(dmetar)
library(tidyverse)
library(meta)
library(metafor)
```

B. Creating a basic model for analysis

```
data = PreDM4
m.bin <- metabin(event.e = Ee,
  n.e = Ne,
  event.c = Ec,
  n.c = Nc,
  studlab = Studies,
  data = data,
  sm = "RR",
  method = "MH",
  MH.exact = TRUE,
  fixed = FALSE,
  random = TRUE,
  method.tau = "PM",
  hakn = TRUE)
summary(m.bin)
```

C. Funnel plot

```
funnel(m.bin, method = "linreg")
metabias(m.bin, method.bias = „peters“)
```

D. Influence analysis

```
m.bin.inf <- InfluenceAnalysis(m.bin, random = TRUE)
plot(m.bin.inf, "baujat")
plot(m.bin.inf, "influence")
plot(m.bin.inf, „es“)
plot(m.bin.inf, "i2")
```

E. Forest plot

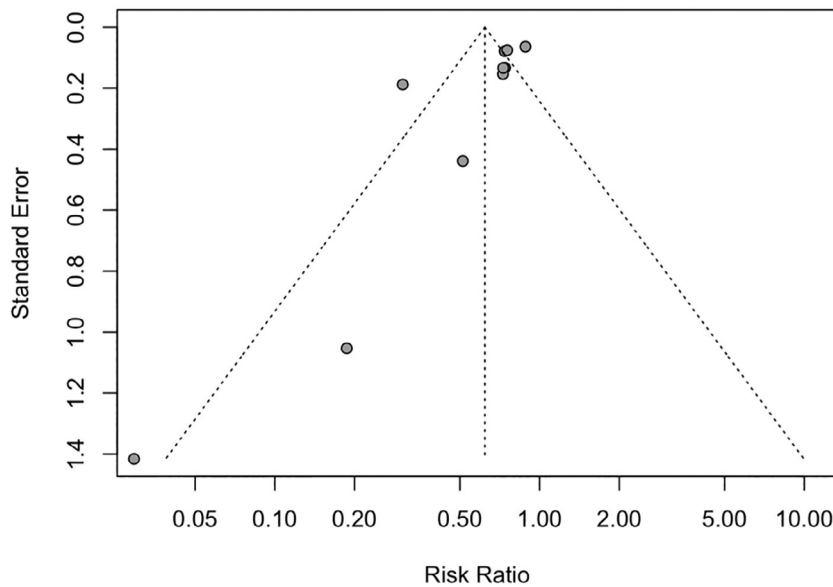
```
forest(m.bin,
  prediction = TRUE,
  layout = "RevMan5",
  xlab = c("Metformin Placebo"))
```

F. Subgroup analysis

```
update.meta(m.bin,
  byvar = Low_dose,
  tau.common = FALSE)
m_subgroup <- update.meta(m.bin, byvar = Low_dose, tau.common = FALSE)
forest(m_subgroup)
```

Supplementary File 4. Selection of Studies Based on Funnel Plot Asymmetry and Heterogeneity

A. Funnel plot



Linear regression test of funnel plot asymmetry

Test result: $t = -2.84$, $df = 8$, $p\text{-value} = 0.0218$

Sample estimates:

bias	se.bias	intercept	se.intercept
-2.4214	0.8526	-0.0552	0.0967

B. Heterogeneity

Number of studies: $k = 10$

Number of observations: $o = 8869$

Number of events: $e = 2189$

	RR	95% CI	t	p-value
Random effects model	0.6212	[0.4287; 0.9001]	-2.90	0.0175

Quantifying heterogeneity

$\tau^2 = 0.1944$ [0.0318; 2.3302]; $\tau = 0.4409$ [0.1784; 1.5265]

$I^2 = 76.1\%$ [55.7%; 87.1%]; $H = 2.04$ [1.50; 2.78]

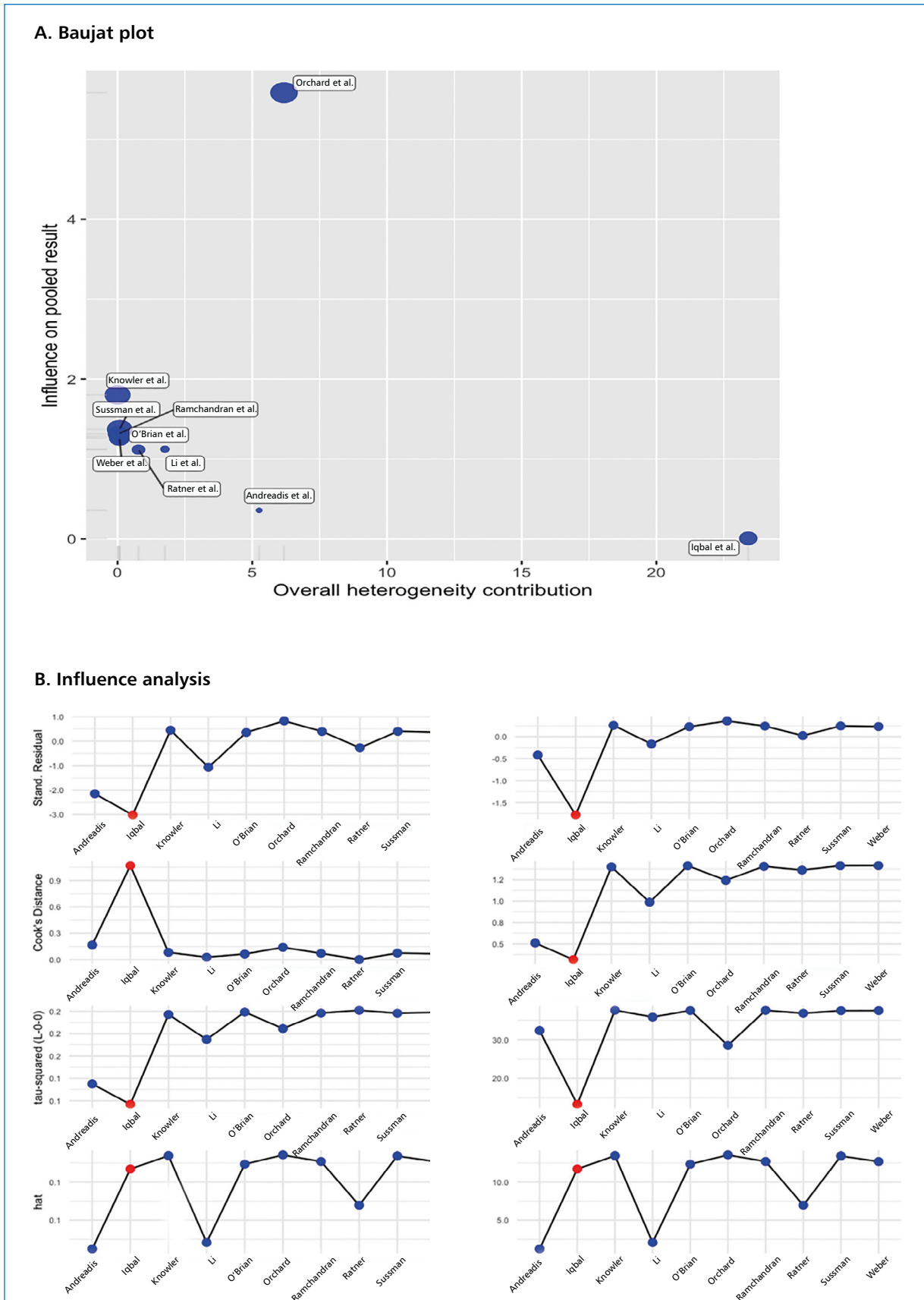
Test of heterogeneity

Q	d.f.	p-value
37.60	9	< 0.0001

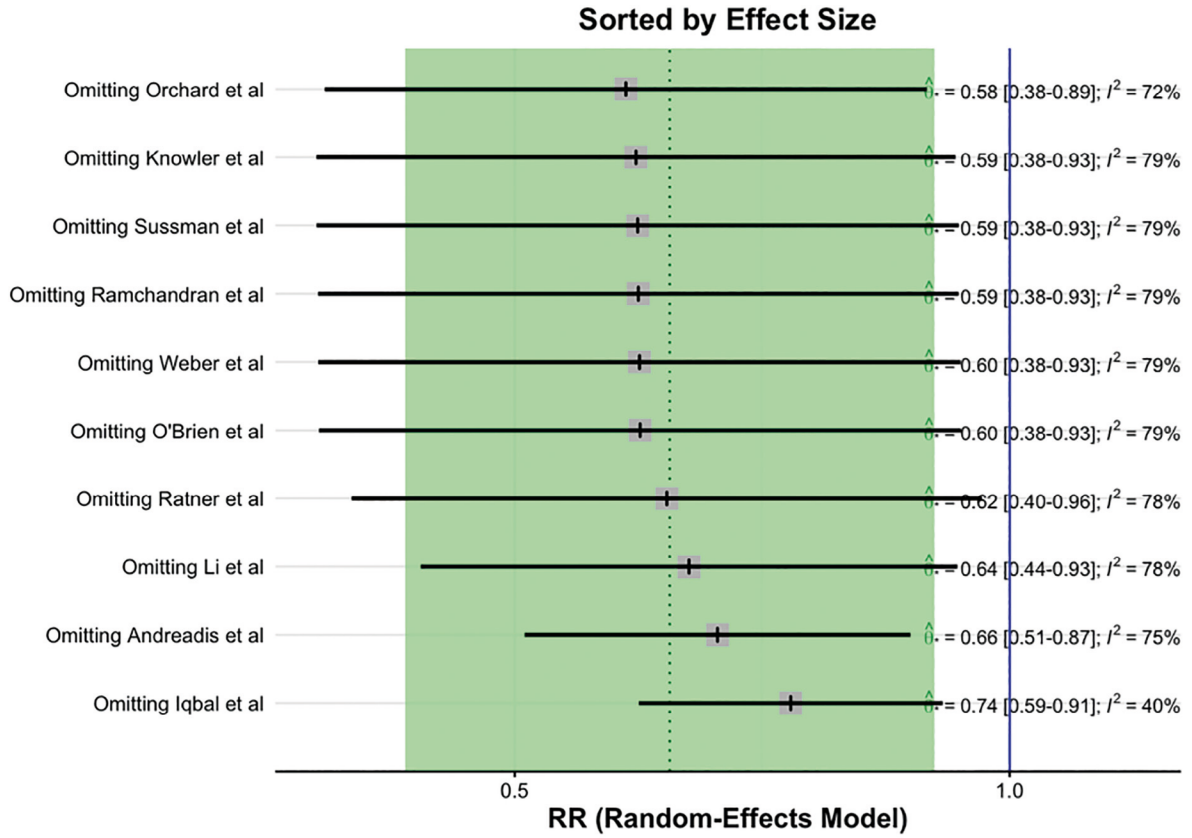
Details on meta-analytical method:

- Inverse variance method
- Paule-Mandel estimator for τ^2
- Q-Profile method for confidence interval of τ^2 and τ
- Hartung-Knapp adjustment for random effects model ($df = 9$)
- Continuity correction of 0.5 in studies with zero cell frequencies

Supplementary File 5. Identification of the Study Adversely Influencing the Meta-Analysis

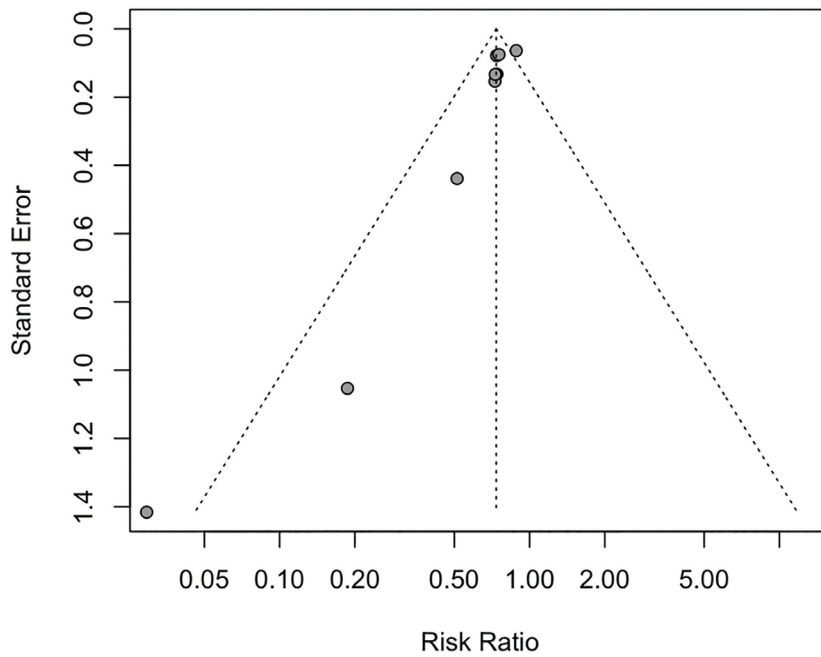


C. Leave-one-out sensitivity analysis



Supplementary File 6. Selection of Studies Based on Funnel Plot Asymmetry and Heterogeneity: Excluding Iqbal et al.

A. Funnel plot



Qualitative assessment reveals a study with small study effect capable of skewing the summary statistic.

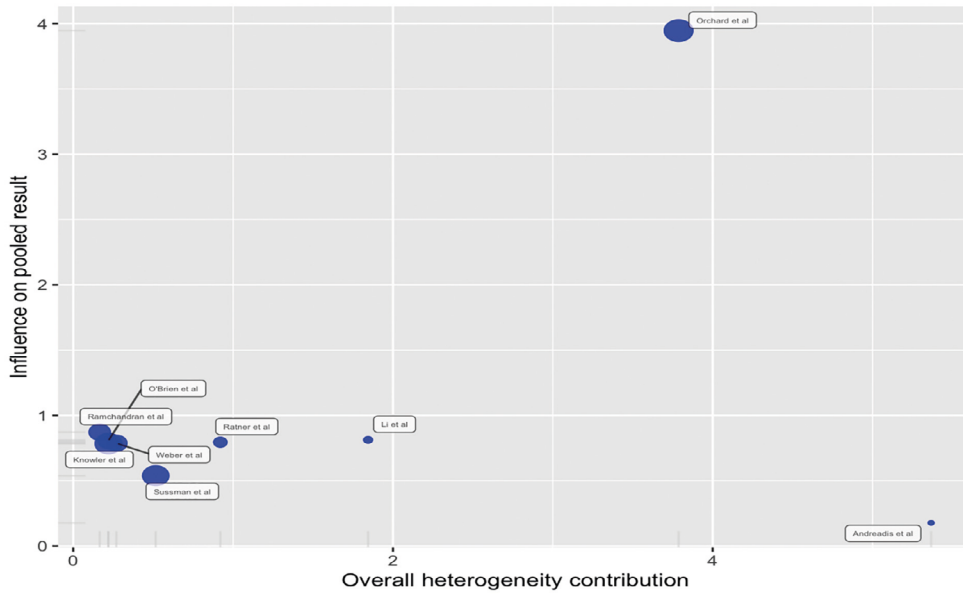
B. Heterogeneity

Study	Experimental		Control		Weight	Risk Ratio		Risk Ratio MH, Random, 95% CI
	Events	Total	Events	Total		MH, Random, 95% CI		
Orchard et al	236	503	260	490	18.4%	0.88	[0.78; 1.00]	
Ramchandran et al	52	128	73	133	14.2%	0.74	[0.57; 0.96]	
O'Brien et al	68	983	92	967	13.0%	0.73	[0.54; 0.98]	
Sussman et al	215	1027	292	1030	17.6%	0.74	[0.63; 0.86]	
Weber et al	69	283	98	293	14.2%	0.73	[0.56; 0.95]	
Ratner et al	7	111	15	122	3.6%	0.51	[0.22; 1.21]	
Li et al	1	33	6	37	0.7%	0.19	[0.02; 1.47]	
Knowler et al	233	1073	313	1087	17.8%	0.75	[0.65; 0.87]	
Andreadis et al	0	92	50	274	0.4%	0.03	[0.00; 0.47]	
Total (95% CI)	4233		4433		100.0%	0.74	[0.59; 0.91]	
Prediction interval							[0.43; 1.25]	

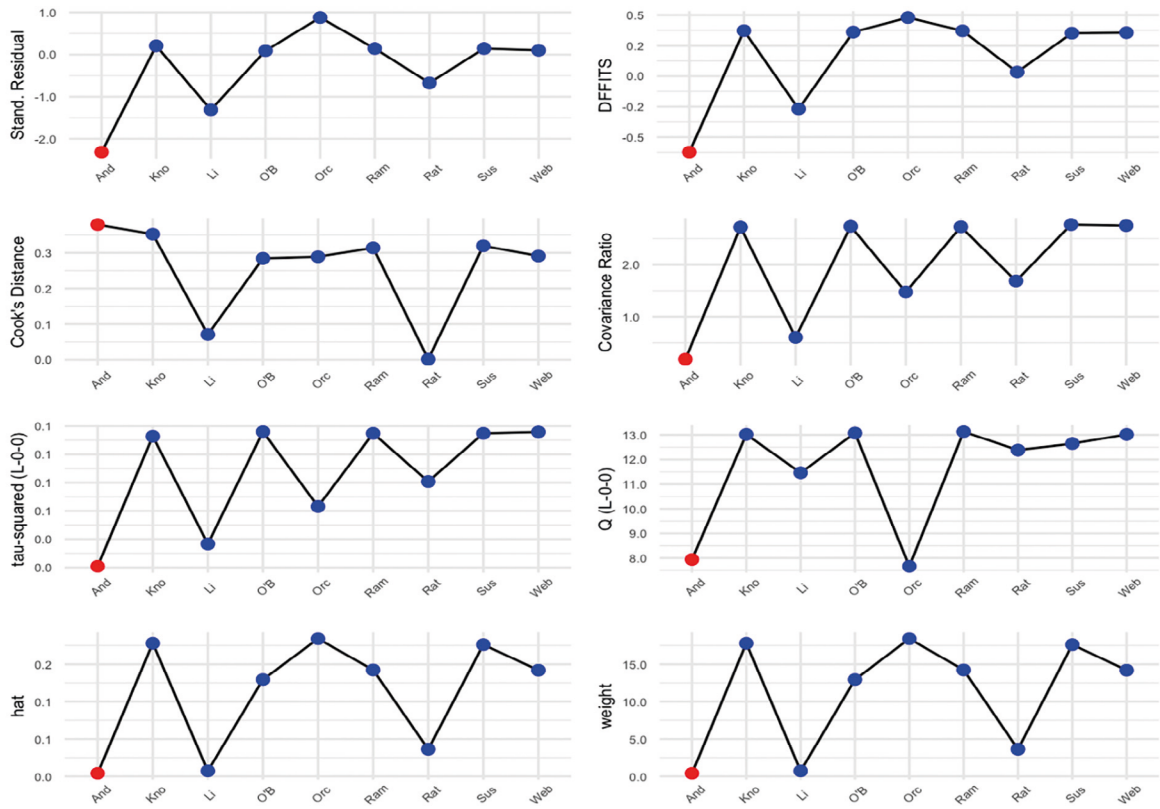
Heterogeneity: $\tau^2 = 0.0422$; $\chi^2 = 13.31$, $df = 8$ ($P = 0.10$); $I^2 = 40\%$

Supplementary File 7. Identification of the Study Adversely Influencing the Meta-Analysis: Excluding Iqbal et al.

A. Baujat plot



B. Influence analysis



C. Leave-one-out sensitivity analysis

Sorted by Effect Size

