Psychology Department
University of Ioannina

Course in Pairwise and Network Meta-Analysis

20-24 October 2025

Synthesizing Randomized and non-randomized evidence

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EVIDENCE SYNTHESIS METHODS
STATISTICS TEAM

Randomized controlled trials (RCTs)

RCTs are considered the ‘gold standard’

- Participants are randomly assigned to treatment or control groups.
- This randomization helps control for confounders and bias.
- Provides high internal validity (i.e., strong causal inference).

✓ Minimizes bias

✓ Balances confounding

Non-Randomized Studies (NRS)

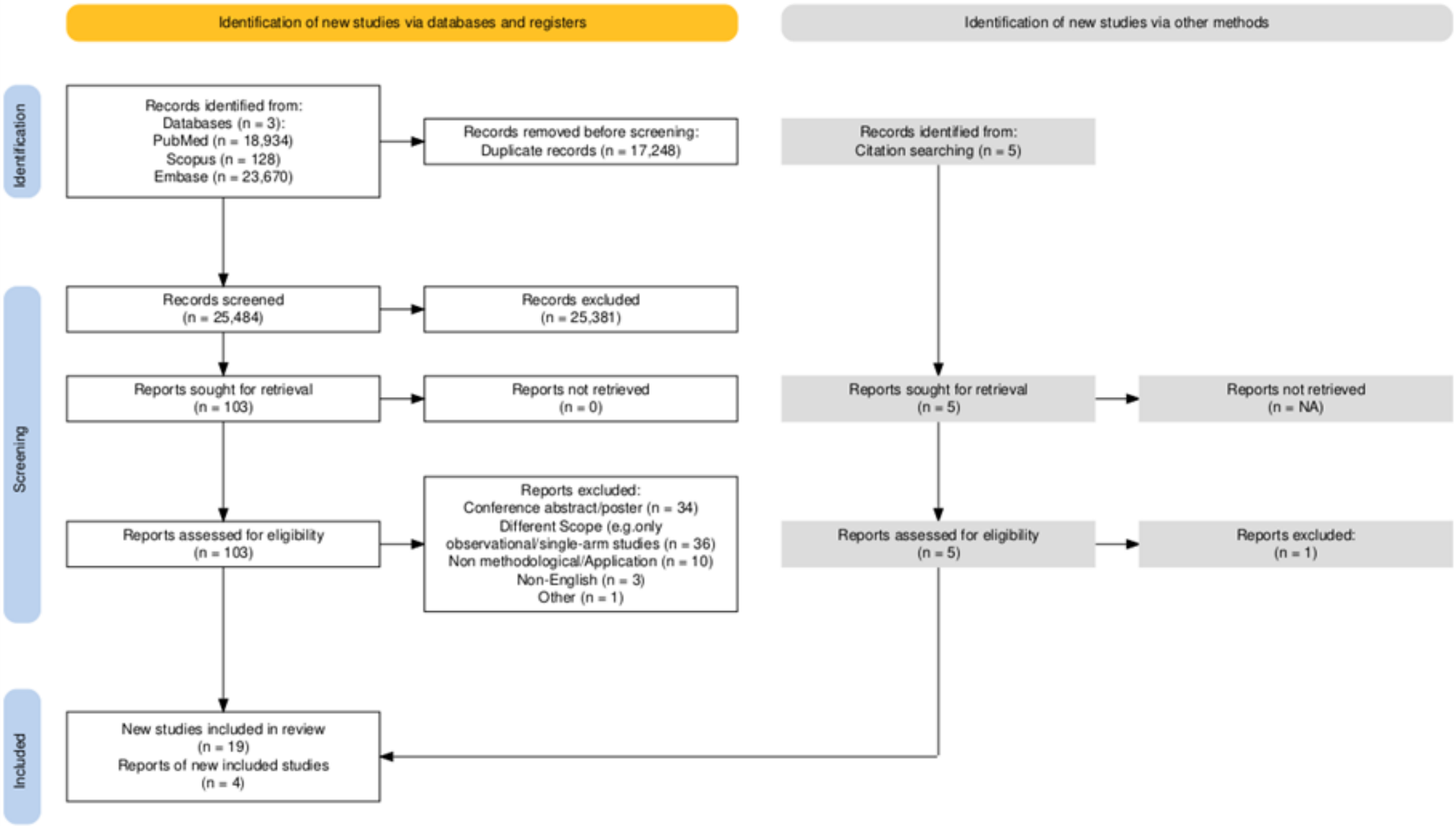
Non-RCTs provide *real world evidence* (RWE) and offer valuable insights especially when RCT data are limited.

- Also called observational studies or non-experimental studies.
- No random assignment → so there is potential for selection bias and confounding.
- But they often have better external validity (they reflect real-world practice).

Why combine RCTs and Non-RCTs?

- **Limited RCT evidence**: In some areas, few or no RCTs exist (e.g., rare diseases, surgical techniques).
- **Ethical or practical problems**: Sometimes RCTs can not be done (e.g., smoking exposure).
- **Generalizability**: Non-RCTs can reflect real-world populations better than highly controlled RCTs.
- **Complementary evidence**: Non-RCTs may help explore long-term outcomes, rare events, or subgroups.

Flowchart


Identification of new studies via databases and registers
Identification of new studies via other methods
Identification
Screening
Included
Records identified from:
Databases (n = 3):
PubMed (n = 18,934)
Scopus (n = 128)
Embase (n = 23,670)
Records removed before screening:
Duplicate records (n = 17,248)
Records identified from:
Citation searching (n = 5)
Records screened
(n = 25,484)
Records excluded
(n = 25,381)
Reports sought for retrieval
(n = 103)
Reports not retrieved
(n = 0)
Reports sought for retrieval
(n = 5)
Reports not retrieved
(n = NA)
Reports assessed for eligibility
(n = 103)
Reports excluded:
Conference abstract/poster (n = 34)
Different Scope (e.g.only observational/single-arm studies (n = 36)
Non methodological/Application (n = 10)
Non-English (n = 3)
Other (n = 1)
Reports assessed for eligibility
(n = 5)
Reports excluded:
(n = 1)
New studies included in review
(n = 19)
Reports of new included studies
(n = 4)

Systematic review findings

Out of the 23 included articles, **17 are methodological** papers focused on the combination of RE and NRE information in MA or NMA, while the remaining 6 were reviews of methods addressing the same topic.

Among these 17 methodological studies:

- ✓ 11 (64.7%) focused on combining RE and NRE in standard MA
- ✓ 5 (29.4%) in NMA alone and
- ✓ 1 (5.9%) addressed both approaches

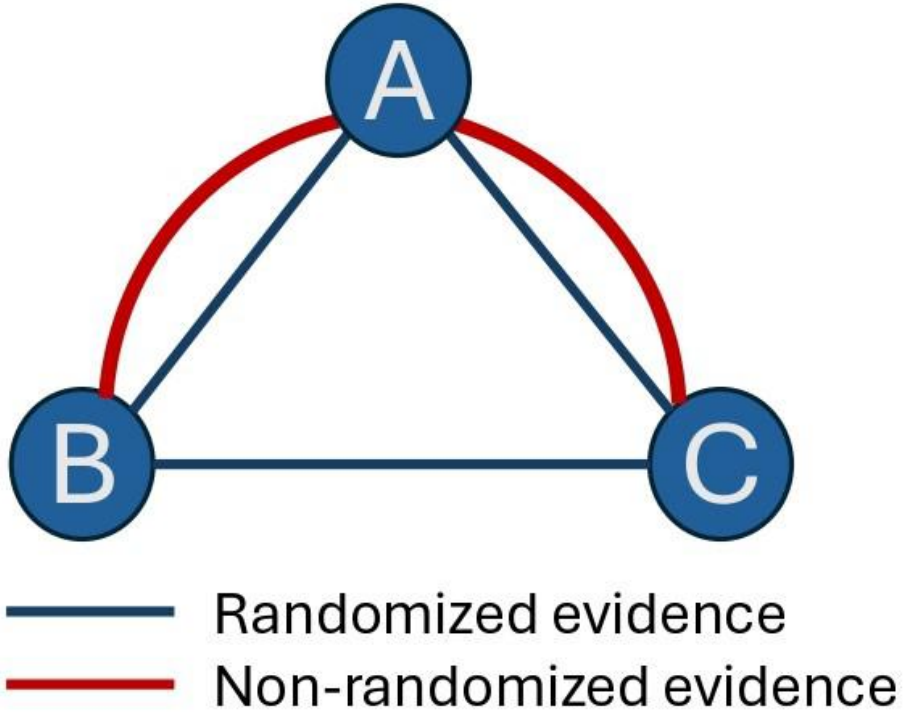
The majority - 15 articles (88.2%) - adopted a Bayesian framework.

Regarding data types:

- ✓ 13 articles (76.4%) synthesized only aggregated data (AgD)
- ✓ 2 (11.8%) required individual participant data (IPD)
- ✓ 2 (11.8%) incorporated both IPD and AgD

Methods for synthesizing RCTs and NRE in NMA

- The Naïve approach
- Design-adjusted analysis
- Informative priors from NRSs
- A three-level hierarchical model



Naïve approach

Pool all RCTs and NRE together without adjustments

- ✓ Simple and straightforward
- ✓ Increases the amount of data and network

- ✗ High risk of bias, because it assumes RCTs and NRE are equally reliable
- ✗ Results may be dominated by biased observational studies

Mainly as a sensitivity analysis

Design-adjusted analysis

A model that **down-weights NRE** by increasing their **variance** or by including a **bias term**.

$$y_{i,jk} \sim N(\theta_{i,j\mathrm{k}} + \boldsymbol{\beta_i}, \frac{S_{i,jk}}{w_i})$$

i: study

β_i: bias term

w_i: precision term $0 < w_i < 1$

Conduct a sensitivity analysis (use of range of values)

Using NRE as prior information

Predictive prior with down-weighted variance

This approach constructs a predictive distribution from NRS estimates and incorporates it a prior for μ_{jk}, but down-weights it by inflating the variance using a factor w_{jk}

$$\mu_{jk} \sim Normal(\hat{\mu}_{jk}^{NRS} + \beta_{jk}\,, \frac{\hat{V}_{jk}^{NRS}}{w_{jk}})$$

If $\beta_{jk} = 0$ and $w_{jk} = 1$ full trust in NRS

If $w_{jk} \ll 1$, NRE evidence is heavily down-weighted.

✓ Handles uncertainty and possible bias

✗ Requires specification of prior parameters and less useful with few NRS

Using NRE as prior information

Power Prior:

This method down-weights the contribution of NRE by raising its likelihood contribution to a power between $a_i \in [0, 1]$

$$L(\mu|NRE) = \prod_{i=1}^{k} [L(\mu|NRE_i)]^{a_i}$$

- ✓ Flexible
- ✗ Choosing a_i value can be subjective

Three-level hierarchical model

- First level, (within study differences)

$$y_{i,jk} \sim Normal(\theta_{i,jk}, s^2_{i,jk})$$

- Second level, (between study differences)

$$\theta_{i,jk} \sim Normal(\mu_{jk}^{design}, \tau^2)$$

- Third level, (between design differences)

$$\mu_{jk}^{design} \sim Normal(\mu_{jk}, \tau^2_{design})$$

✓ Accounts for design-specific effects and heterogeneity

✗ More complex, requires sufficient data per design

Empirical example

P (Population)	Elderly
I (Intervention)	23-valent pneumococcal polysaccharide vaccine (PPV23)
C (Comparator)	Placebo or no vaccination
O (Outcome)	Occurrence of invasive pneumococcal disease

- Design-adjusted analysis:

Low risk of bias ~Beta (0.25,1)
high risk of bias ~Beta (1.5,1)

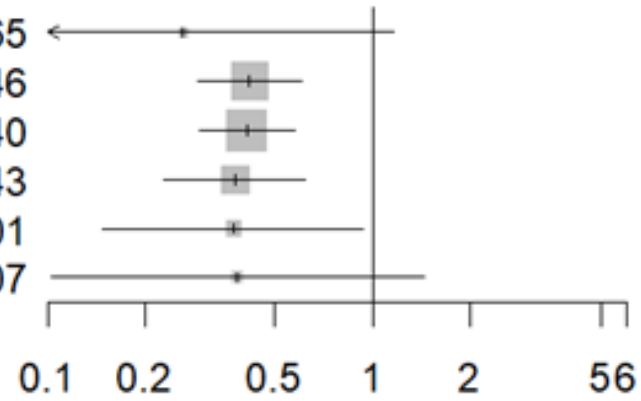
Finally, randomized clinical trials are not weighted.

No.	Study	LOG(OR)	SE	Total ppv23	Total number of vaccine	Design	Risk of bias
1	Honkanen 1999	-0.9722612	0.8367229	19549	18488	RCT	Unclear
2	Maruyama 2010	-1.9406631	1.5124362	1140	1149	RCT	Low
3	Ortqvist 1998	-1.5178076	1.0965467	793	873	RCT	Low
4	Hechter 2012	-1.0498000	0.8998000	3962	27320	Cohort	High
5	Jackson 2003	-0.5852000	0.2615000	84203	42977	Cohort	Low
6	Ochoa-Gondar 2014	-0.9676000	0.7584000	28662	30000	Cohort	Low
7	Tsai 2015	-1.4271000	0.3342000	229181	229181	Cohort	High
8	Vila-Corcoles 2006	-0.5108000	0.5161000	17401	16504	Cohort	Low
9	Dominguez 2005	-1.1882000	0.2687000	149	447	Case-control	Low
10	Leventer-Roberts 2015	-0.5463000	0.1712000	212	848	Case-control	Low
11	Vila-Corcoles 2009	-1.0850000	0.3416000	94	188	Case-control	Low

Falkenhorst G, Remschmidt C, Harder T, Hummers-Pradier E, Wichmann O, Bogdan C. Effectiveness of the 23-Valent Pneumococcal Polysaccharide Vaccine (PPV23) against Pneumococcal Disease in the Elderly: Systematic Review and Meta-Analysis. PLoS One. 2017;12(1):e0169368. Published 2017 Jan 6. doi:10.1371/journal.pone.0169368

Results

Study	logOR	SE(logOR)	OR	95%-CI
only RCTs	-1.3411	0.7565	0.26	[0.06; 1.15]
only RWE	-0.8719	0.1846	0.42	[0.29; 0.60]
naive	-0.8902	0.1740	0.41	[0.29; 0.58]
design-adjusted L(Beta(0.25,1)), H(Beta(1.5,1))	-0.9773	0.2543	0.38	[0.23; 0.62]
prior model	-0.9863	0.4701	0.37	[0.15; 0.94]
3-level hierarchical model	-0.9556	0.6707	0.38	[0.10; 1.43]




WORK IN
PROGRESS

References

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[3] *Falkenhorst G, Remschmidt C, Harder T, Hummers-Pradier E, Wichmann O, Bogdan C. Effectiveness of the 23-Valent Pneumococcal Polysaccharide Vaccine (PPV23) against Pneumococcal Disease in the Elderly: Systematic Review and Meta-Analysis. PLoS One. 2017;12(1):e0169368. Published 2017 Jan 6. doi:10.1371/journal.pone.0169368*

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H.F.R.I.
Hellenic Foundation for Research & Innovation

Greece 2.0
NATIONAL RECOVERY AND RESILIENCE PLAN

Funded by the European Union
NextGenerationEU

Thank you!
Questions?

UNIVERSITY of IOANNINA

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SCAN ME

EVIDENCE SYNTHESIS METHODS
STATISTICS TEAM

This project is carried out within the framework of the National Recovery and Resilience Plan Greece 2.0, funded by the European Union – NextGenerationEU (Implementation body: HFRI). Project Number: 015467