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Heterogeneity of systematic reviews with meta-analyses of pharmacological, surgical and radiotherapeutic interventions in patients with advanced cancer – a meta-epidemiological study (SCOPE)

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1. Background

- Taking heterogeneity in meta-analyses into account is crucial for drawing conclusions, e.g. for treatment guidelines.
- An analysis of 95% prediction intervals (PIs) and the way of considering heterogeneity in meta-analyses of advanced cancer patients has not yet been performed.

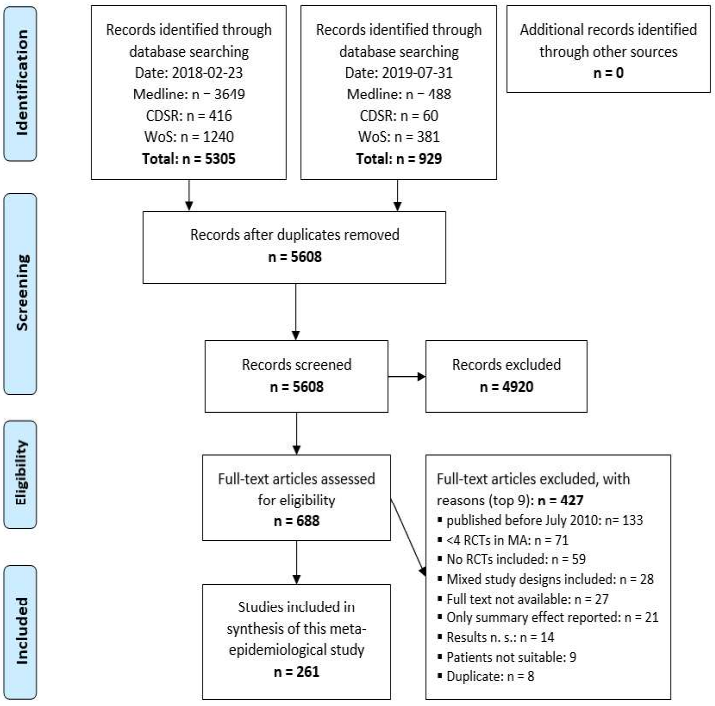
Aims:

i. To calculate and analyze 95%-PIs, and
ii. to assess the way heterogeneity in meta-analyses is considered.

3. Results

- Of 5608 hits screened, 261 were included (Figure 1).
- Results regarding heterogeneity are shown in the Table below.

Figure: Flow diagram



2. Methods

Study design:

- Meta-epidemiological study (PROSPERO-ID: CRD42019134904)

Unit of analysis:

- Systematic reviews (SRs) and their first reported, statistically significant meta-analysis in the abstract with at least four randomized controlled trials.
- SRs had to include pharmacological, surgical or radiotherapeutic interventions in advanced cancer patients.

95%-PI calculation and interpretation

- A 95%-PI indicates the 95% probability range for the true effect of a similar future study [1].
- As relevance assessment, we checked if *no effect* (e.g. risk ratio [RR]=1) or the *opposite effect* (e.g. RR=0.5 and 95%-PI overlaps RR=2) was included by the 95%-PI of the meta-analyses [2].
- Formula:

$$\hat{\mu} \pm t^{\alpha}_{k-2} \sqrt{\{\hat{\tau}^2 + \widehat{SE}(\hat{\mu})^2\}}$$

$\hat{\mu}$: pooled estimate of the random effects model
t^{α}_{k-2}: 100(1−α/2)% percentile of *t*-distribution with *k*−2 degrees of freedom
$\hat{\tau}^2$: estimate of between study variance in meta-analysis
$\widehat{SE}(\hat{\mu})^2$: variance of pooled estimate of the random effects model

Consideration of heterogeneity in meta-analyses

- Heterogeneity was assessed in the meta-analyses, in which the 95%-PI included the null effect (n=196).
- The consideration of clinical (i.e. PICO-scheme) and methodological (i.e. risk of bias) heterogeneity in results or discussion was explored [3, 4].

Table: Results for 95%-PIs and consideration of heterogeneity

Outcome	Sample
Prediction interval: no effect	N=261
included	196 (75.1%)
excluded	65 (24.9%)
Prediction interval: opposite effect	N=261
included	98 (37.5%)
excluded	163 (62.5%)
Consideration of heterogeneity where 95%-PI included null effect	n=196
heterogeneity not explored	34 (17.3%)
clinical heterogeneity explored	93 (47.4%)
methodological heterogeneity explored	10 (5.1%)
clinical and methodological heterogeneity explored	59 (30.1%)

4. Conclusion

- The 95%-PIs indicated that more than one third of future similar studies of the statistically significant meta-analyses may include the opposite treatment effect, i.e. many patients in these studies may experience negative or even opposite treatment effects.
- Heterogeneity was not adequately described in many SRs, e.g. only "exclusively statistically" in about one fifth of the SRs.
- We strongly encourage review authors to consider 95%-PIs and heterogeneity in future SRs and meta-analyses.

References

1. Higgins, J. P. T., Thompson, S. G., & Spiegelhalter, D. J. (2009). A re-evaluation of random-effects meta-analysis. *Journal of the Royal Statistical Society. Series A, (Statistics in Society)*, *172*(1), 137–159.
2. IntHout, J., Ioannidis, J. P. A., Rovers, M. M., & Goeman, J. J. (2016). Plea for routinely presenting prediction intervals in meta-analysis. *BMJ Open*, *6*(7), e010247.
3. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.0 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook.
4. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ*. 2017;358:j4008.