Publication bias evaluations are not routinely conducted in clinical oncology systematic reviews.

C. WAYANT, D. HERRMANN, J. HOLMES, S. KHAN, C. KOLLER, P. SINNETT, M. VASSAR, PH.D

Publication bias and non-reporting found in majority of systematic reviews and meta-Analyses in anesthesiology journals.

A. DEMAND, R. HEDIN, MPH, B. UMBERHAM, B. DETWEILER, L. KOLLMORGEN, M. VASSAR, PH.D
Publication bias (PB) is an over-representation of statistically significant results in the published literature and may exaggerate summary effect estimates in systematic reviews (SR).
Publication bias is not adequately addressed in anesthesiology and oncology literature.
Key Message

- Publication bias is not adequately addressed in anesthesiology and oncology literature.
- Our results not only shed light on the current deficiency of publication bias assessments in anesthesiology & oncology reviews but also suggest that a significant number of non-reporting reviews likely have some degree of publication bias.
We investigate ways that systematic reviewers attempted to limit publication bias during the search process as well as the statistical methods used to evaluate it.
Introduction

- We investigate ways that systematic reviewers attempted to limit publication bias during the search process as well as the statistical methods used to evaluate it.

- In addition, we performed an evaluation of publication bias in those reviews that did not perform it originally.
Using the h5-index of Google Scholar Metrics, we identified the five highest ranking journals from the anesthesiology subcategory: Anesthesiology, Anesthesia & Analgesia, British Journal of Anaesthesia, Anaesthesia, and Regional Anesthesia and Pain Medicine.
Methods (continued)

- We searched PubMed for systematic reviews and/or meta-analyses published between 2007 and 2015.
Our initial search yielded 315 records.

207 articles were included in our final analysis.
Our initial search yielded 315 records.

207 articles were included in our final analysis.
Methods (continued)

- From the articles included in final analysis we used a data extraction form to assess certain aspects of publication bias including:
Methods (continued)

- From the articles included in final analysis we used a data extraction form to assess certain aspects of publication bias including:
  - Did the article discuss PB?
  - Was PB formally evaluated? If so, the method used to assess PB.
  - Was PB found?
  - Was a funnel plot published in the article?
For the articles that did not evaluate publication bias, we undertook that task provided that there were at least ten studies and measured a clinical outcome.

We then constructed funnel plots, used Duval and Tweedie’s trim and fill method, and performed Egger’s regression tests for each of the meta-analyses.
Results (continued)

- How do systematic reviewers attempt to limit PB?
Results (continued)

- *How do systematic reviewers attempt to limit PB?*

- Of the reviews that evaluated for PB, 88.8% (79/89) performed a **hand search** of the references.
How do systematic reviewers attempt to limit PB?

Of the reviews that evaluated for PB, 88.8% (79/89) performed a hand search of the references.

From our sample of SRs, approximately one fifth (20.3%, 42/207) included a grey literature search.
Results (continued)

- **How do systematic reviewers attempt to limit PB?**

- Of the reviews that evaluated for PB, 88.8% (79/89) performed a **hand search** of the references.

- From our sample of SRs, approximately one fifth (20.3%, 42/207) included a grey literature search.
  - The most common forms of grey literature searched were **clinicaltrials.gov** and **conference abstracts**.
Results (continued)

- How often is PB discussed and/or evaluated?
Results (continued)

How often is PB discussed and/or evaluated?

Of the 207 SRs in our study, just over half (55.1%, 114/207) discussed PB, while 89 evaluated (43%).
How often is PB discussed and/or evaluated?

Of the 207 SRs in our study, just over half (55.1%, 114/207) discussed PB, while 89 evaluated (43%).

The most common method employed was a funnel plot, and 38 reviews (46.3%) presented their funnel plot graphically in their study.
Results (continued)

- **British Journal of Anesthesia**
  - Discussed: 57.3%, 43/75
  - Evaluated: 42.7%, 32/75

- **Anesthesia and Analgesia**
  - Discussed: 55.8%, 24/43
  - Evaluated: 48.8%, 21/43
Results (continued)

- **Anesthesiology**
  - Discussed: 52.8%, 19/36
  - Evaluated: 41.7%, 15/36

- **Anaesthesia**
  - Discussed: 51.2%, 22/41
  - Evaluated: 43.9%, 18/41

- **Regional Anesthesia and Pain Medicine**
  - Discussed: 50%, 6/12
  - Evaluated: 25%, 3/12
Use of appropriate reporting guidelines

- **Total SRs that evaluated PB:** 114
  - **PRISMA:** 68 SRs
  - **MOOSE & QUOROM** were also used.
Results

- We analyzed the 25 SRs, containing 45 total meta-analyses, that did not evaluate PB originally.
Results

- We analyzed the 25 SRs, containing 45 total meta-analyses, that did not evaluate PB originally.
  - Using trim and fill, we found that 36 (80%) showed evidence of PB.
  - Egger’s regression showed evidence of PB in 23 (51.1%) of meta-analyses.
Discussion

Our research highlights that while many anesthesia SRs report following appropriate guidelines, not enough adhere to PB assessment requirements.
Our research highlights that while many anesthesia SRs report following appropriate guidelines, not enough adhere to PB assessment requirements.

Although, use of reporting guidelines does increase the likelihood of discussing and/or evaluating PB.

- The PRISMA statement recommends an appropriate bias assessment (e.g., publication bias).
Our analysis of PB in anesthesia literature shows that there is significant evidence of PB.
Our analysis of PB in anesthesia literature shows that there is significant evidence of PB.

In most of the PB analyses that we conducted on non-reporting SRs, effect size decreased.
The American Society of Anesthesiologists considers SRs with sufficient numbers of RCTs that perform and report meta-analyses as Level 1a evidence.
The American Society of Anesthesiologists considers SRs with sufficient numbers of RCTs that perform and report meta-analyses as Level 1a evidence. This places a great importance on the assessment of PB in SRs, because any evidence of PB can affect treatment guidelines and resource allocation.
Cancer trials provide unique challenges due to the high number of studies that never reach publication.
Cancer trials provide unique challenges due to the high number of studies that never reach publication.

In a review of adult cancer clinical trials from ClinicalTrials.gov (N=7,776 trials), authors found a seven-year cumulative incidence of failure to complete of approximately 20%.
Cancer trials provide unique challenges due to the high number of studies that never reach publication.

In a review of adult cancer clinical trials from ClinicalTrials.gov (N=7,776 trials), authors found a seven-year cumulative incidence of failure to complete of approximately 20%.

Poor accrual was the most common reason for failure to complete, followed by logistics (e.g., cancellation by the trial sponsor, inadequate budget), and unacceptable toxicity or poor interim results.
A second challenge is the scientific impact of positive results of cancer clinical trials.
A second challenge is the scientific impact of positive results of cancer clinical trials.

Recent evidence indicates that trials with positive results are published in journals with higher impact factors and cited twice as often as cancer trials with negative results.²
Urrútia, et al., 7 May, 2016³

“The objective of the current study was to determine the publication rate of cancer RCTs and to analyse the determinants of the publication, as well as to estimate the possible existence of a location and time lag bias”
Urrútia, et al., 7 May, 2016

“The objective of the current study was to determine the publication rate of cancer RCTs and to analyse the determinants of the publication, as well as to estimate the possible existence of a location and time lag bias”

Study characteristics

303 RCTs identified, 168 reached publication (55.4%)
Background (continued)

Urrútia, et al., 7 May, 2016³

“The objective of the current study was to determine the publication rate of cancer RCTs and to analyse the determinants of the publication, as well as to estimate the possible existence of a location and time lag bias”

Study characteristics

- 303 RCTs identified, 168 reached publication (55.4%)
- International studies (78.2%, 237/303) were published 85.7% of the time (144/168)
Background (continued)

- Urrútia, et al., 7 May, 2016³
  - “The objective of the current study was to determine the publication rate of cancer RCTs and to analyse the determinants of the publication, as well as to estimate the possible existence of a location and time lag bias”

- Study characteristics
  - 303 RCTs identified, 168 reached publication (55.4%)
  - **International studies** (78.2%, 237/303) were published 85.7% of the time (144/168)
  - **Pharmaceutical sponsored studies** (74.6%, 226/303) were published 75% of the time (126/168).
Urrútia, et al., 7 May, 2016

"The objective of the current study was to determine the publication rate of cancer RCTs and to analyse the determinants of the publication, as well as to estimate the possible existence of a location and time lag bias"

Study characteristics
- 303 RCTs identified, 168 reached publication (55.4%)
- International studies (78.2%, 237/303) were published 85.7% of the time (144/168)
- Pharmaceutical sponsored studies (74.6%, 226/303) were published 75% of the time (126/168).

Mean length of time to publication
- Pharmaceutical sponsors (6.1 years vs. 7.6 years, p=0.002)
- Favorable results according to hypothesis (6.1 vs. 7.0, p=0.04)
- Less than 1000 patients (6.3 years vs. 7.9 years, p=0.03)
Design

- We examined systematic reviews from the top six oncology journals according to Google Scholar metrics.
- 182 SRs were included in our study.
Design

- We examined systematic reviews from the top six oncology journals according to Google Scholar metrics.
- 182 SRs were included in our study.
In our second analysis, a re-analysis of reviews not initially evaluating for publication bias was performed using the trim-and-fill method and Egger’s regression.
How do systematic reviewers attempt to limit PB?
Results (continued)

- **How do systematic reviewers attempt to limit PB?**

- From our sample of SRs, over half (52%, 94/182) included a **hand search** of the references of included articles.
Results (continued)

- **How do systematic reviewers attempt to limit PB?**

- From our sample of SRs, over half (52%, 94/182) included a **hand search** of the references of included articles.

- **Conference abstracts** were the most common form of grey literature searched (27%, 49/182) followed by **clinical trials registries** (8%, 15/182).
Results (continued)

- **How do systematic reviewers attempt to limit PB?**
  - From our sample of SRs, over half (52%, 94/182) included a **hand search** of the references of included articles.
  - **Conference abstracts** were the most common form of grey literature searched (27%, 49/182) followed by **clinical trials registries** (8%, 15/182).
  - Thirty percent (55/182) expanded their search to include **foreign language**.
How often is PB discussed and/or evaluated?
Results (continued)

- **How often is PB discussed and/or evaluated?**

- Of the 182 systematic reviews in our study, less than one third (28%, 51/182) performed an evaluation of publication bias, while 40% discussed PB (73/182).
Results (continued)

- **How often is PB discussed and/or evaluated?**

- Of the 182 systematic reviews in our study, less than one third (28%, 51/182) performed an evaluation of publication bias, while 40% discussed PB (73/182).
  - Of the SRs that did assess PB, most used multiple methods (69%, 35/51).
How often is PB discussed and/or evaluated?

Of the 182 systematic reviews in our study, less than one third (28%, 51/182) performed an evaluation of publication bias, while 40% discussed PB (73/182).

- Of the SRs that did assess PB, most used multiple methods (69%, 35/51).
- The most common method was the funnel plot (80%, 41/51) followed by Egger’s regression (59%, 30/51) and Begg’s test (43%, 22/51).
Results (continued)

- **Clinical Cancer Research**
  - Discussed: **58%**, 10/17
  - Evaluated: **41%**, 7/17

- **The Journal of Clinical Oncology**
  - Discussed: **39%**, 41/106
  - Evaluated: **27%**, 29/106

- **The Lancet Oncology**
  - Discussed: **38%**, 22/58
  - Evaluated: **26%**, 15/58
Results (continued)

- **Clinical Cancer Research**
  - Discussed: **58%**, 10/17
  - Evaluated: **41%**, 7/17
- **The Journal of Clinical Oncology**
  - Discussed: **39%**, 41/106
  - Evaluated: **27%**, 29/106
- **The Lancet Oncology**
  - Discussed: **38%**, 22/58
  - Evaluated: **26%**, 15/58
- **Cancer Research** only contained one (1) SR. **Nature Reviews Cancer** and **Cancer Cell** did not contain any SRs.
Use of appropriate reporting guidelines

Total SRs that evaluated PB: 51

- PRISMA: 38 SRs
- MOOSE: 10 SRs
- QUOROM: 10 SRs
Results

- We analyzed the 19 SRs (42 total meta-analyses) that did not evaluate PB originally.
Results

- We analyzed the 19 SRs (42 total meta-analyses) that did not evaluate PB originally.
  - Using trim-and-fill, it was found in 36 of 42 meta-analyses (86%) revealed statistically significant results.
Results

- We analyzed the 19 SRs (42 total meta-analyses) that did not evaluate PB originally.
  - Using trim-and-fill, it was found in **36 of 42 meta-analyses (86%)** revealed statistically significant results.
  - Only **9 meta-analyses (21%)** revealed statistically significant results using Egger’s regression.
Results (continued)
Our research calls into question the use and/or adherence of reporting guidelines in clinical oncology.

- PRISMA, MOOSE, & QUOROM all recommend appropriate assessments of bias (e.g., publication bias).
Future research is needed to evaluate PB in other clinical specialties, using larger sample sizes of SRs, to see how it compares with oncology.
Future research is needed to evaluate PB in other clinical specialties, using larger sample sizes of SRs, to see how it compares with oncology.

- **Souza’s et al.** study in reproductive health and **Onishi and Furukawa**’s study in general medicine are good examples.
There is also a need to look at how clinical trials registries can be used to find unpublished data for mitigating PB.
There is also a need to look at how clinical trials registries can be used to find unpublished data for mitigating PB.

- Sinnett et al.⁶ in neurology, Jones et al.⁷ in general medical journals, and Keil et al.⁸ in emergency medicine all assessed the use of trial registry searches in SRs and found discouraging results.
Based on our sample, we recommend future SRs in oncology make use of more robust methods to evaluate publication bias.
Based on our sample, we recommend future SRs in oncology make use of more robust methods to evaluate publication bias.

- **Cumulative meta-analysis by precision** should be used to assess for suppression of small effect sizes from small samples through evidence of "drift" in the cumulative point estimate.⁹
Recommendations

Based on our sample, we recommend future SRs in oncology make use of more robust methods to evaluate publication bias.

- **Cumulative meta-analysis by precision** should be used to assess for suppression of small effect sizes from small samples through evidence of “drift” in the cumulative point estimate.\(^9\)
- **Deek’s test for diagnostic accuracy** should be used to test for publication bias specific to diagnostic accuracy studies.\(^10\)
Recommendations

- Based on our sample, we recommend future SRs in oncology make use of more robust methods to evaluate publication bias.
  - **Cumulative meta-analysis by precision** should be used to assess for suppression of small effect sizes from small samples through evidence of “drift” in the cumulative point estimate.\(^9\)
  - **Deek’s test for diagnostic accuracy** should be used to test for publication bias specific to diagnostic accuracy studies.\(^10\)
  - **Contour-enhanced funnel plots** should be used to differentiate publication bias as a cause of funnel-plot asymmetry over other causes of asymmetry such as observed differences between large and small sample sizes.\(^11\)
Conclusion

Our study shows publication bias assessments are not frequently used in anesthesiology nor in oncology systematic reviews.
Conclusion

- Our study shows publication bias assessments are not frequently used in anesthesiology nor in oncology systematic reviews.
- Furthermore, evidence of publication bias was found in a subset of non-reporting reviews.
Conclusion

- Our study shows publication bias assessments are not frequently used in anesthesiology and oncology systematic reviews.

- Furthermore, evidence of publication bias was found in a subset of non-reporting reviews.

- The evidence of unreported PB and lack of analysis of PB in SRs can potentially affect clinical outcomes and decisions.
References


