Prevalence of disclosed and undisclosed financial conflicts of interest among systematic review authors regarding the management of proximal humerus fractures

Cole Verble, B.S., Office of Medical Student Research, Oklahoma State University Center for Health Sciences, Tulsa, Oklahoma
Matthew C. Ferrell, B.S., Office of Medical Student Research, Oklahoma State University Center for Health Sciences, Tulsa, Oklahoma
Arjun K. Reddy, B.A., Office of Medical Student Research, Oklahoma State University Center for Health Sciences, Tulsa, Oklahoma
J. Michael Anderson, B.S., Office of Medical Student *Research, Oklahoma State University Center for Health Sciences, Tulsa, Oklahoma*
Michael Weaver M.S., Kansas City University of Medicine and Biosciences, College of Osteopathic Medicine, Joplin, Missouri
Micah Hartwell PhD., Office of Medical Student Research, Oklahoma State University Center for Health Sciences, Tulsa, Oklahoma
Matt Vassar, PhD, Office of Medical Student Research, Oklahoma State University Center for Health Sciences, Tulsa, Oklahoma

Funding: Development of this protocol and study was funded by the Oklahoma State University Center for Health Sciences Presidential Mentor-Mentee Research Fellowship Grant

Conflicts of Interest: Dr. Vassar reports receipt of funding from the National Institute on Drug Abuse, the National Institute on Alcohol Abuse and Alcoholism, the US Office of Research Integrity, Oklahoma Center for Advancement of Science and Technology, and internal grants from Oklahoma State University Center for Health Sciences — all outside of the present work. Dr. Hartwell has grant funding from the National Institutes of Justice, unrelated to the current work.

Abstract:

Background: A systematic review is an important evidence synthesis technique used to collate results from individual studies, such as treatments for proximal humerus fractures. It is necessary to minimize bias in systematic reviews, including financial COIs, which have been shown to result in unreliable assessments of credibility.

Objective : The aim of this study was to characterize the influence of financial bias on the results and conclusions of systematic reviews of proximal humerus fracture treatments and to characterize the nature of disclosed and undisclosed COIs.

Methods: Ovid MEDLINE and Ovid Embase databases were searched to locate systematic reviews covering proximal humerus fracture treatments. Following these searches, title and abstract screening was performed in a duplicate, masked fashion. Data from the final reviews were extracted in a triplicate manner. The data from the final reviews included various author and article characteristics. These characteristics can be found under the *Data extraction* paragraph. All authors were screened for non-disclosed COIs.

Results: We found no relationship between authorial COI and the results and conclusions of the systematic reviews. Among the 17 included systematic reviews, 7 (41.2%) had at least one non-disclosed COI. Of the 7 reviews with a non-disclosed COI, 2 (28.6%) were found to have a high risk of bias.

Conclusions : Findings from this study have limited generalizability due to our small sample size. More studies are needed to fully elucidate the effect of financial bias on the results and conclusions of systematic reviews.

Keywords: proximal humerus fractures, conflicts of interest, financial conflicts of interest, systematic reviews, proximal humerus

Introduction :

Proximal humerus fractures account for 6% of all fractures and are commonly seen in patients with osteoporotic disease following low impact falls.[1–3] Proximal humerus fractures are commonly managed conservatively, as most injuries heal without more invasive intervention. However, in more severe cases, the best course of treatment is subject to debate, and has been the topic of discussion throughout the orthopedic literature.[4–6] With an aging population, the incidence of osteoporotic fractures – including proximal humerus fractures – are expected to increase in the coming years.[7,8] Given the expected rise in disease burden, it is essential orthopedic surgeons critically appraise research outcomes, as well as the overall quality of evidence, from studies regarding the treatment of proximal humerus fractures.

The *American Academy of Orthopedic Surgeons (AAOS)* consider systematic reviews of Level 1 randomized controlled trials (RCTs) among the highest level of evidence in clinical research.[9,10] Given their spot atop the hierarchy of evidence, systematic reviews often serve as the foundation upon which clinical practice guideline recommendations are based. Despite the potential utility of systematic reviews in helping achieve optimal patient outcomes, previous studies have demonstrated that systematic reviews published in the orthopedic literature are not free of potential forms of bias. For example, Scott, et al., found a large percentage of studies published in high impact orthopedic journals failed to assess for publication bias; and, when studied, nearly one-third demonstrated evidence of publication bias.[11] Systematic reviews failing to account for sources of bias may result in misguided clinical decisions, with the potential to affect patient care.[12] Another potential source of bias that may call into question the validity of study outcomes is the presence of conflicts of interest (COI), among systematic review authors.

According to the International Committee of Medical Journal Editors (ICMJE), a COI exists when "... a professional judgment concerning a primary interest (such as patients' welfare or the validity of research) may be influenced by a secondary interest (such as financial gain)".[13] These industry relationships carry the potential to influence the nature of study outcomes, and calls to question the reliability and validity of such results. Take for example one study which found authors disclosing significant COIs with pharmaceutical industries were more likely to report favorable outcomes compared to authors without a COIs. Given the potential harm these COIs may have in medicine, further investigation into the extent that systematic review authors disclose COIs – as well as determine the influence these COIs have on the nature of outcomes reported in systematic reviews in the orthopedic literature – is warranted.

Thus, the aim of this study was to characterize the nature of disclosed and undisclosed COIs of systematic review authors, specifically with regard to the treatment of proximal humerus fracture. Additionally, we sought to determine whether the direction of narrative results and/or conclusions from these reviews are influenced by authors receiving significant financial compensation.

Methods:

Transparency, Reproducibility, and Reporting
Institutional review board oversight was not required for this cross-sectional study as it did not involve human subjects.[14] To facilitate reproducibility and transparency of our results, we have supplied the study protocol, materials, and data sets on Open Science Framework.[15] The *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) guidelines were used in the process of drafting this manuscript.[16] Additionally, we referred to Murad and Wang's guidelines for conducting meta-epidemiological research.[17]

Deviations from study protocol
Due to the essence of our final data, we could not determine whether industry-funded systematic reviews were more or less likely to find positive results and conclusions with regard to an intervention than systematic reviews funded by other sources (including those that did not receive funding support). Not a single industry-funded systematic review was found in our sample, which precluded us from determining whether associations in outcome reporting may exist. This topic may need further investigation.

Study Objectives
Our primary objectives were to (1) determine the frequency of COIs (both disclosed undisclosed) among authors of systematic reviews and meta-analyses focusing on the treatment of proximal humerus fractures; and (2) determine if author COI affects the overall narrative results and conclusions. As secondary objectives, we evaluated (1) whether an association exists between risk of bias and COI among review authors and (2) whether the presence of study sponsorship influenced reported results and conclusions.

Search Strategy
MEDLINE (Ovid) and Embase (Ovid) databases were searched using the same strategies developed by a systematic review librarian, as that outlined in a previous protocol, for a prior study within our research group.[18] The search was performed June 2, 2020 to identify systematic reviews with or without meta-analyses using a search strategy in Supplemental File 1. Following the execution of these searches, the resulting records were uploaded to Rayyan (https://rayyan.qcri.org/), a systematic review platform for title and abstract screening.

Supplemental File 1

Ovid MEDLINE:	**Ovid Embase:**
1. exp Humeral Fractures/	1. exp humerus fracture/
2. (proximal adj1 humer* adj1 fracture*).mp.	2. (proximal adj1 humer* adj1 fracture*).mp.
3. 1 or 2	3. 1 or 2
4. exp "Systematic Review"/	4. exp "systematic review"/
5. exp Meta-Analysis/	5. exp meta-analysis/
6. ("systematic review" or "meta-analysis" or (systematic* adj1 review*)). ti,ab.	6. ("systematic review" or "meta-analysis" or (systematic* adj1 review*)). ti,ab.
7. 4 or 5 or 6	7. 4 or 5 or 6
8. 3 and 7	8. 3 and 7

Screening

The initial results for the search strategy were screened from a previous study to include systematic reviews concerning treatments for proximal humerus fractures. Specific screening criteria can be found in the protocol.[15] We further refined our inclusion criteria for screening by AR, CV, and MF in a masked, triplicate manner based upon these additional criteria which are outlined below. All discrepancies were resolved in a group meeting after the screening process was completed.

Eligibility Criteria

A study was deemed eligible for inclusion if it (1) met the PRISMA-P definition of a systematic review and/or meta-analysis; (2) was a head-to-head comparison of one treatment to either another treatment (or combination) or a placebo/standard of care; (3) focused on treatments for proximal humerus fractures; (4) was published between September 1, 2016 and June 2, 2020; (5) was published in the English language; and (5) synthesized data from systematic reviews using human data. As prespecified in the study protocol, if more than 200 studies were eligible for inclusion, studies were uploaded to STATA for randomization. Data were subsequently extracted from the first 200 randomized studies.

Training

All investigators completed training, online and in-person, before study commencement. Training was recorded and is available online.[15] In short, this training session consisted of the study design and objectives, study materials, and a step-by-step explanation of how to perform data extraction using an example systematic review.

Data extraction

Three authors (AR, CV, and MF) were assigned with data extraction. Data were pulled independently in a masked, triplicate fashion using a pilot-tested Google form. Full-text of each systematic review or meta-analysis was examined and the following data items were extracted: (1) PubMed identification number and/or DOI, (2) journal name, (3) publication date, (4) name of authors, compared treatment interventions, (5) first and last author affiliation(s), (6) source of funding, (7) full COI statement, (8) risk of bias assessment within the systematic review or meta-analysis, (9) the verbatim risk of bias statement, (10) whether systematic review author(s) were also an author on any of the primary studies included in the review, (11) amount of self-cited primary studies, (12) the systematic reviews primary outcome or the first outcome reviewed, (13) whether an overall pooled effect estimate was calculated, (14) pooled effect estimate for the primary outcome, (15) type of calculated pooled effect estimate (eg, mean difference, risk ratio, odds ratio), (16) statistical significance of pooled effect estimate, (17) the primary outcomes favorability of pooled effect estimate in regards to the primary outcome, and (18) whether narrative results and conclusions favored the comparison or treatment group (e.g., placebo, standard of care, control). For the purpose of this study, “conclusion” was used to represent a review’s discussion and conclusion.

Favorability of narrative results and conclusions

We reviewed the favorability of the narrative results and conclusions by designating them as favorable, unfavorable, or mixed/inconclusive. While reviewing results we considered favorable when only positive results reported for all study populations. Unfavorable was assigned when only negative results reported for at least one study population. Mixed/inconclusive was assigned if both positive and negative results reported for the study populations within the narrative. While reviewing conclusions, favorable was assessed when authors reported either explicitly or implicitly in favor of the target intervention. Conversely unfavorable was assessed if the authors explicitly or implicitly favored the control group. Mixed/inconclusive was assessed if we are unable to meet criteria for favorable or unfavorable (e.g., reporting negative population outcome but positive subgroup analysis).

Identification of undisclosed conflicts of interest

Our stepwise strategy of the search for undisclosed COI is located in Figure 1. For this process, we modified the methodology by Mandrioli et al,[19] by incorporating 3 additional databases – the Open Payments database, Dollars for Profs, and the United States Patent and Trademark Office (USPTO). Table 1 describes each database. All authors for each systematic review were searched for undisclosed COI, regardless of disclosed COIs. Database-specific search strings were generated by a custom program created by MW using the Python programming language (Python Software Foundation, https://www.python.org/) for Google Patents, the United States Patent and Trademark Office (USPTO) Database, and PubMed to ensure reproducibility and accuracy of data extraction. We chose to limit searches of patents to 10 years prior to the review's publication due to the longevity of patents. If we were unable to verify if the patents from our searches belonged to the author for whom we searched, we did not consider it an undisclosed COI. PubMed searches for each author reviewed the conflict statement of all of the authors published works up to 36 months prior to the publication of the original review. If more than 10 manuscripts were found during the initial PubMed search, then random numbers were assigned to all PubMed manuscripts returned for an author. After, data was extracted from the first 10 randomized manuscripts starting with the lowest number. AR, CV, and MF all generated their own random samples to broaden the search strategy. The search process was continued until it reached its conclusion or an undisclosed conflict of interest was found. This termination process was also used by Mandrioli et al.[19]

Figure 1

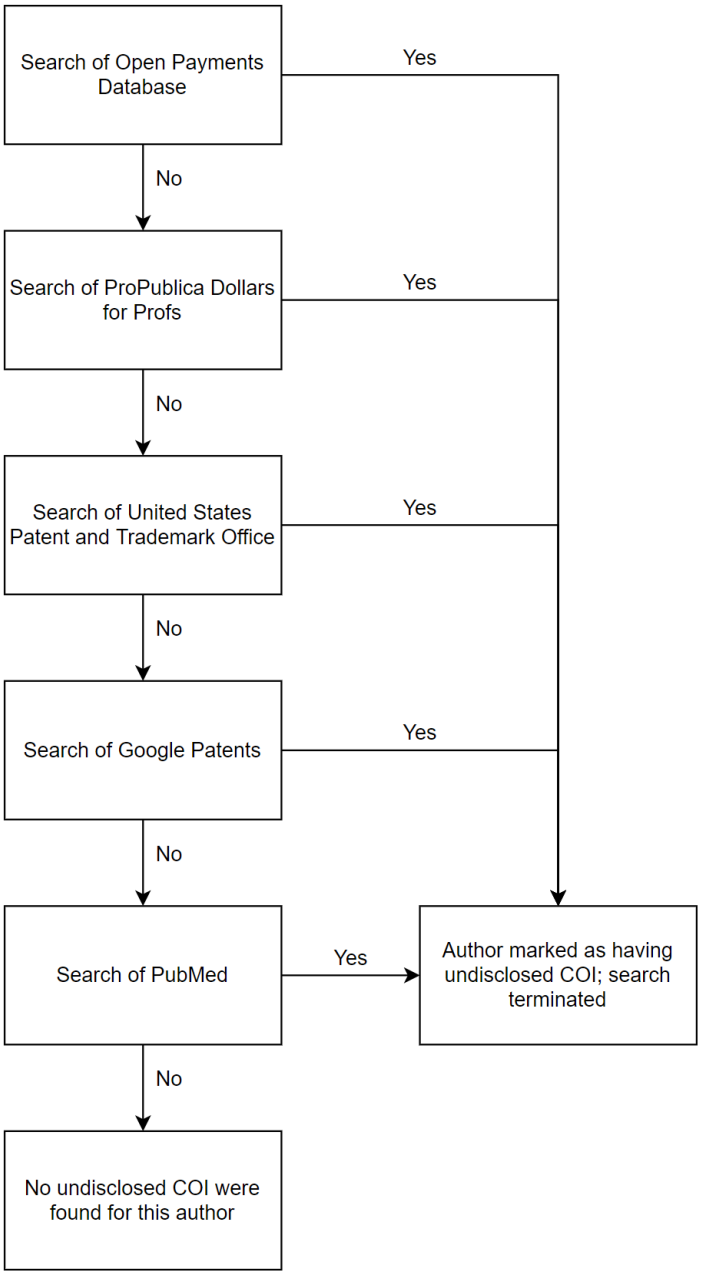

Figure 1. Stepwise search for undisclosed COI among systematic review authors

Table 1. Description of databases used to search for undisclosed COI among systematic review authors

Database	Description of Database
Open Payments Database (https://openpaymentsdata.cms.gov)	Open Payments Database – which was created on September 1, 2013 – is a Congressionally-mandated, openly accessible resource designed to increase the transparency within the United States healthcare system. This database collects and publishes information regarding industry relationships between healthcare providers (e.g., physicians and teaching hospitals) and industry (e.g., drug and device manufacturers). Physicians and teaching hospitals report industry payments received in the form of research, food and beverage, travel, and consulting or speaking fees.
Pro Publicas Dollars for P rofs (https://projects.propublica.org/dollars-for-profs)	Dollars for Profs provides information from state universities and the National Institutes of Health (NIH) regarding industry payments and conflicts of interest of academic professors, researchers, and other support personnel. Rationale for including this database was based on the knowledge that searching for non-healthcare professionals listed as an author of a systematic review included in our sample would not return beneficial information.
United States Patent and Trademark Office (USPTO) (https://www.uspto.gov)	The United States Patent and Trademark Office (USPTO) is responsible for the registration of US patents and trademarks in accordance with the commerce clause (Article I, Section 8, Clause 3) of the US Constitution. In addition, the USPTO “furthers effective intellectual property protection for U.S. innovators and entrepreneurs worldwide by working with other agencies to secure strong IP provisions in free trade and other international agreements.” (https://www.uspto.gov/about-us)
Google Patents (https://patents.google.com)	Google Patents is a database consisting of greater than 120 million patent publications from more than 100 different patent offices worldwide. In addition, Google Patents provides access to technical documents and books indexed in Google Scholar and Google Books, as well as documents included in the Prior Art Archive.
PubMed (https://pubmed.ncbi.nlm.nih.gov)	PubMed was launched in January 1996 and is one of the most widely used databases for academic research. The entire MEDLINE collection includes more than 30 million citations from biomedical literature. As part of the Enterz system of informational retrieval, PubMed is maintained by The United States National Library of Medicine at the National Institutes of Health. (https://pubmed.ncbi.nlm.nih.gov/)

Risk of bias evaluations
We assessed the risk of funding bias within the systematic reviews using the Cochrane Collaboration's criteria, which included the following 4 items from Mandrioli et al[19]: (1) whether replicable and "well-defined" criteria for study inclusion/exclusion were used; (2) whether multiple assessors took part in selecting studies for inclusion/exclusion; (3) whether authors used a comprehensive search strategy; and (4) whether potential sources of bias were controlled for in the primary studies included in the review. Investigators assigned a yes, no, or unclear response to each of the inquiries. Overall risk of bias was considered low if 3 or more of the aforementioned criteria were met. If not, we considered the systematic review to have a high risk of bias.

Statistical Analysis
When necessary, the results were quantified using illustrative statistics and analyzed with Fisher's exact tests. Fisher's exact tests were used to compare the presence of relationships between industry and authors of systematic reviews. Stata 16.1 (StataCorp, LLC, College Station, TX) was used for all analyses.

Results:
Our search provided 505 potential records. Following removal of duplicates and other ineligible studies based on title and abstract screening, 107 studies were included for full-text review. Following full-text screening, 17 systematic reviews regarding proximal humerus fracture treatment were included for data extraction. (Figure 2)

Figure 2

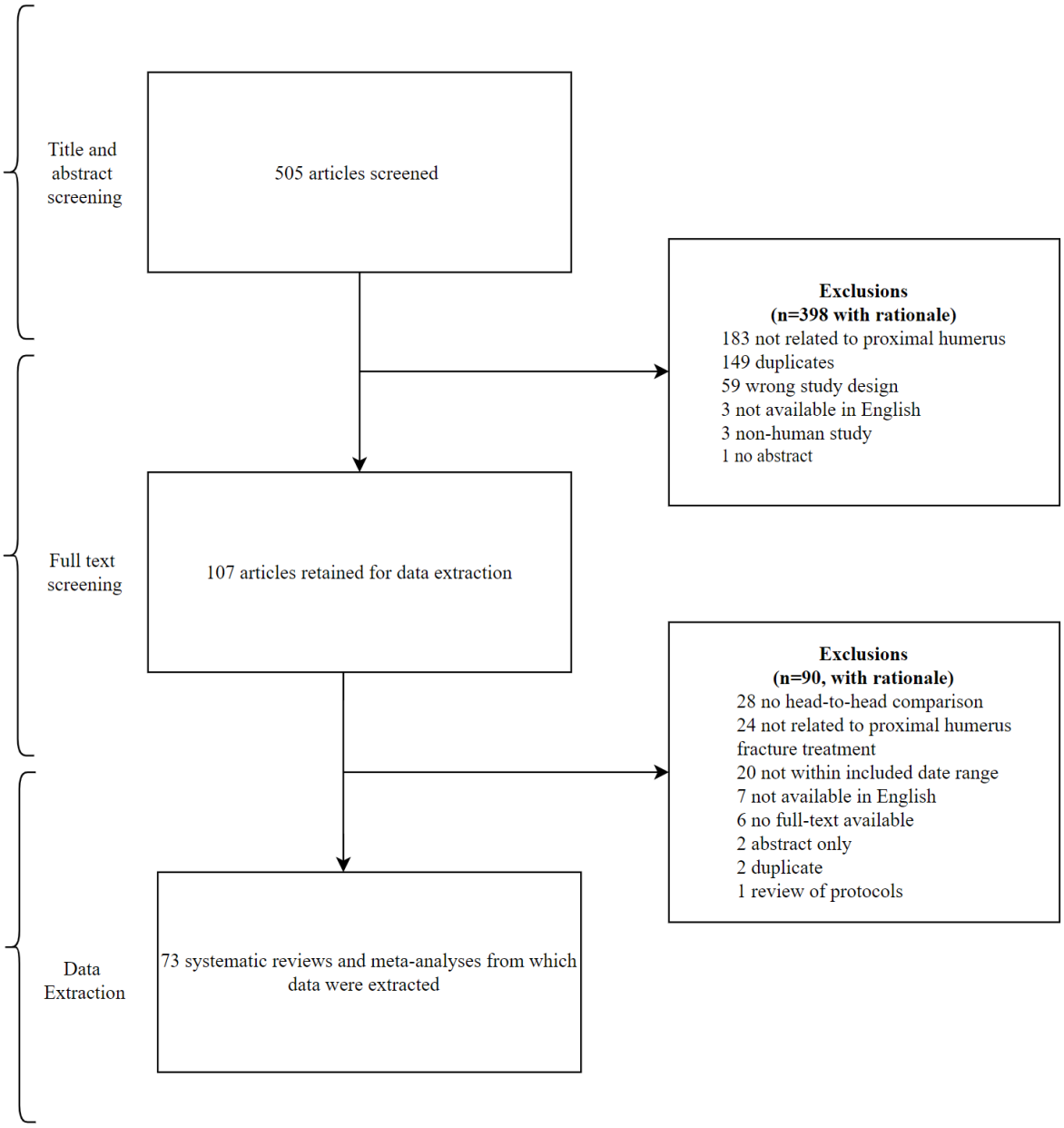

Figure 2. PRISMA Flowchart for included and excluded

Systematic Review Characteristics

Our study included 17 systematic reviews and meta-analyses conducted by 93 authors and published within 16 journals. The most common journal represented in our sample was *Orthopaedics & traumatology: Surgery and Research* (2; 11.8%). Most systematic reviews (11/17; 64.7%) evaluated surgical techniques or interventions and the most common source of sponsorship was public funding (5/17; 29.4%). (Table 2) Of the 17 systematic reviews, 7 (41.2%) had at least one author with a COI. (Table 3)

Table 2. Systematic review characteristics

Characteristic	Form Response	N (%)
Journal (n= 17)	BMC musculoskeletal disorders	1 (5.9)
	BioMed research international	1 (5.9)
	Bone & Joint Research	1 (5.9)
	International Journal of Clinical and..	1 (5.9)
	International orthopaedics	1 (5.9)
	Journal of Shoulder Elbow Surgery	1 (5.9)
	Journal of Shoulder and Elbow Surgery	1 (5.9)
	Journal of clinical orthopaedics and ..	1 (5.9)
	Journal of comparative effectiveness ..	1 (5.9)
	Journal of orthopaedic surgery (Hong ..	1 (5.9)
	Journal of orthopaedic surgery and re..	1 (5.9)
	Journal of orthopaedic trauma	1 (5.9)
	Journal of shoulder and elbow surgery	1 (5.9)
	Orthopaedic Surgery	1 (5.9)
	Orthopaedics & traumatology, surgery ..	2 (11.8)
	The Journal of international medical ..	1 (5.9)
Accuracy of author COI disclosure statement (n= 93)	No COI found	82 (88.2)
	All COI disclosed in systematic review	0 (0.0)
	No COI disclosed in systematic review, found to have one or more undisclosed COI	9 (9.7)
	Disclosed one or more COI in systematic review, found to have additional undisclosed COI	2 (2.2)

Intervention Type (n= 17)	Drug	0 (0)
	Device	3 (17.6)
	Surgical Technique/Intervention	11 (64.7)
	Multiple	3 (17.6)
	Other	0 (0)
Affiliation of First Author (n= 17)	Public academic institution	16 (94.1)
	Public academic institution, Government	1 (5.9)
Affiliation of Last Author (n= 17)	Government	1 (5.9)
	Non-Profit Institution	1 (5.9)
	Public academic Institution	15 (88.2)
Source of Funding (n= 17)	No funding received	8 (47.1)
	No statement listed	3 (17.6)
	Public	5 (29.4)
	Public, University	1 (5.9)
Conflict of Interest Statement (n= 17)	Includes 1 or more authors with a COI	1 (5.9)
	Reports no conflicts of interest	13 (76.5)
	There is no conflict statement	3 (17.6)

Table 3. Frequency of an SR having no COI or at least 1 author with a Non-Disclosed COI			
Review Outcomes		**COI Among Systematic Reviews**	
		No COI n= 10 (%)	**Non-Disclosed COI n= 7 (%)**
Favorability of Results			
	Results Favor Treatment Group	3 (30.0)	3 (42.8)
	Results are Mixed/Inconclusive	4 (40.0)	2 (28.6)
	Results Favor Placebo/Control Group	3 (30.0)	2 (28.6)
Favorability of Discussion/Conclusions			
	Discussion Favors Treatment Group	5 (50.0)	5 (71.4)
	Discussion is Mixed/Inconclusive	3 (30.0)	2 (28.6)
	Discussion Favors Placebo or Control Group	2 (20.0)	0 (0.0)
Risk of Bias			
	High Risk of Bias	0 (0.0)	2 (28.6)
	Low Risk of Bias	10 (100.0)	5 (71.4)

Author Characteristics

Of the 93 review authors, 11 (11.8%) were found to have some form of COI. Of these 11 authors, none completely disclosed all COI within the systematic review, 2 (2.2%) disclosed one or more COI but were found to have an additional undisclosed COI, and 9 (9.7%) were found to have only undisclosed COI. Additional author and study characteristics are provided in Table 2.

Relationship between COI and favorability of results and conclusions

Of the 7 systematic reviews with non-disclosed COIs, 3 (42.8%) reported narrative results in favor of the treatment group. Additionally, 5 (71.4%) reported discussions/conclusions favoring the treatment group. With respect to the 10 systematic reviews with no conflicted authors, 3 (30.0%) reported results favoring the treatment group and 5 (50.0%) reported discussions/conclusions favoring the treatment group. (Table 3) Fisher's exact did not show a statistically significant association between COI and favorability of results and conclusions.

Relationship between sponsorship and favorability of results and conclusions
Six systematic reviews (of 17; 35.3%) received external sponsorship, 8 (of 17; 47.1%) did not receive external sponsorship, and 3 (of 17; 17.6%) did not disclose whether the review was supported by an external sponsor. No significant relationship between favorability of the results or discussion/conclusions and article sponsorship was found. Considering none of the systematic reviews in our sample were industry-sponsored, we were unable to assess if a relationship exists between industry vs non-industry-sponsorship and outcomes of systematic reviews. (Table 4).

Table 4. Relationship between sponsorship and favorability of results and discussions/conclusions

Review Outcomes		Funding Sponsor			
		Industry (%)	Non-industry n= 6 (%)	No funding received n= 8 (%)	No statement listed n= 3 (%)
Favorability of Results					
	Results Favor Treatment Group	0 (0.0)	1 (16.7)	4 (50.0)	1 (33.3)
	Results are Mixed/Inconclusive	0 (0.0)	3 (50.0)	2 (25.0)	1 (33.3)
	Results Favor Placebo or Control Group	0 (0.0)	2 (33.3)	2 (25.0)	1 (33.3)
Favorability of Discussion/Conclusions					
	Discussion Favors Treatment Group	0 (0.0)	3 (50.0)	5 (62.5)	2 (66.7)
	Discussion is Mixed/Inconclusive	0 (0.0)	2 (33.3)	2 (25.0)	1 (33.3)
	Discussion Favors Placebo or Control Group	0 (0.0)	1 (16.7)	1 (12.5)	0 (0.0)
Risk of Bias					
	High risk of bias	0 (0.0)	0 (0.0)	2 (25.0)	0 (0.0)
	Low risk of bias	0 (0.0)	6 (100.0)	6 (75.0)	3 (100.0)

Relationship between risk of bias and industry sponsorship and conflicts of interest
None of the systematic reviews were funded by industry, thus an association between industry sponsorship and risk of bias was not assessed for. Of the systematic reviews with no COI among authors, none (0%) were considered to have high risk of bias. In contrast, 2 systematic reviews (of 7; 28.6%) with at least one conflicted author were found to have a high risk of bias. (Table 3) Due to low sample size, no statistically significant association between COI and review outcomes was detected.

Discussion:
Approximately two out of five systematic reviews regarding the treatment of proximal humerus fractures had at least one author with an undisclosed COI. Despite high rates of nondisclosure, we found no significant association between the presence of author COI—either disclosed or undisclosed—with the favorability of systematic review results and conclusions. Due to a lack of industry-funded systematic reviews in our sample, we were unable to ascertain whether industry-sponsorship increased the likelihood of reporting favorable results and conclusions.

Author COI, whether disclosed or undisclosed, carries the potential to introduce bias into the medical literature. For example, Okike et al. found podium presentations at conferences within the field of orthopedic surgery were more likely to present positive findings when individuals had conflicts of interest related to royalties, stock options, and consultant or employee status.[20] Narain et al. also found that orthopedic research articles on cervical disc arthroplasty more often presented positive outcomes when conflicts of interest were present.[21] Kjaergaard and Als-Nielson found that RCTs were more likely to reach significant results favoring the experimental group when financial competing interests were declared.[22] In our sample, a similar association between author COI and the favorability of results and conclusions was not identified; however, our findings suggest the completeness of author COI disclosure is low and poses as an actionable item by which research stakeholders may improve upon in order to better the quality of research and public trust in research outcomes.

The main funding sponsors in the systematic reviews studied included public grants and university funding. A disconnect from industry alludes to the lower likelihood that these systematic reviews contain inherent bias.[23,24] Although it is suggested that industry plays a crucial role in furthering orthopedic research,[25] industry funding is still vulnerable to a variety of biases, such as intentionally or unintentionally searching for data significance. Previous studies have shown that industry sponsorship is associated with an increased likelihood of positive outcome reporting.[23,24] For example, a 2017 Cochrane review found industry sponsorship was associated with increased likelihood of reporting efficacious results and conclusions demonstrating favorability towards a sponsor's drug or device despite similar harm results when compared to non-industry sponsored drug and device studies.[26] In the same review, drug and device industry-sponsored studies had higher rates of discordance between results and conclusions than in non-industry sponsored studies. Another study found that 85% of orthopedic clinical trials reporting industry funding reported favorable outcomes to the novel treatment.[27] Given the lack of industry sponsored studies in our sample, a clinically significant association between study sponsorship and favorability of results and conclusions could not be identified. Despite the implications of industry-funded studies, Hozack et al. argued that the connections made by physician-scientists could bring ample opportunity for research output by the individual or institute.[28] Nevertheless, Friedberg et al. reported, within the field of oncology, industry funding was significantly associated with studies yielding negative results going unpublished. While more funding could increase research output, ensuring that all data are published and readily available is of great importance. Unpublished negative results, in the industry's favor, can allude to a rise in unreliable overall results within systematic reviews.[29,30]

Recommendations

COIs may lead to alterations in the data presented by authors. Open Payments Database and Dollars for Profs are beneficial tools that may help patients, colleagues, and researchers distinguish reliability of medical professionals within the United States (US). Although our study did not find significant evidence of skewed results within our included papers due to COIs, the lack of awareness leaves proximal humerus fracture studies vulnerable to potential bias in the future. Journals should compare and align authors with databases such as Open Payments Database and Dollars for Professors to make sure that disclosures are being addressed in articles. There were also certain articles that had no comments on disclosures for COIs, therefore there should be a strong emphasis to require that all published literature have a disclosed COIs section. Additionally, a large portion of authors in our study had international affiliations with countries including China, the United Kingdom, Sweden and the Netherlands, and they were not found on either OpenPayments Database or Dollars for Profs. If a universal database were to be made accessible, the process of locating an author's COIs would be less challenging.

Strengths and Limitations

As for our strengths, all authors completed training prior to commencement of data extraction. Completion of calibration exercises amongst data extractors increased the inter-rater reliability between respondents. In addition, data was extracted in a masked, triplicate fashion, ensuring accurate information was collected. Finally, our protocol – which was developed *a priori* – and study materials have been provided on a public repository, thus increasing the transparency and reproducibility of our results. As for our limitations, Open Payments Database and Dollars for Professors restricted our search to only the U.S.-affiliated authors. Moreover, this study was cross-sectional in design and was limited to studies published between September 2016 and June 2020. Use of a different date range may result in differing outcomes. Lastly, our study was specific to literature pertaining to the treatment of proximal humerus fractures. Choosing to focus on a different topic in the orthopedic literature may result in contrasting results. Thus, careful interpretation of our results on the frequency and influence of author COI in the orthopedic literature is warranted.

Conclusion:

In conclusion, our data shows a moderate rate of COIs in literature related to proximal humerus fracture treatments. COIs can result in design, analysis, and reporting bias, all of which can skew results. In contrast, our study found little reporting bias when there was a COI. It would be difficult to have physicians stop from getting incentives from industry and it has been suggested that industry payments help with the progression of research.[25] As long as there is complete transparency with their COIs, authors of systematic reviews over proximal humerus fracture treatments should not be scrutinized for their bias affecting the results.

References

1. Horak J, Nilsson BE. Epidemiology of fracture of the upper end of the humerus. *Clin Orthop Relat Res*. 1975;(112):250-253.

2. Court-Brown CM, Caesar B. Epidemiology of adult fractures: A review. *Injury*. 2006;37(8):691-697.

3. Lind T, Krøner K, Jensen J. The epidemiology of fractures of the proximal humerus. *Arch Orthop Trauma Surg*. 1989;108(5):285-287.

4. Fjalestad T, Hole MØ, Hovden IAH, Blücher J, Strømsøe K. Surgical treatment with an angular stable plate for complex displaced proximal humeral fractures in elderly patients: a randomized controlled trial. *J Orthop Trauma*. 2012;26(2):98-106.

5. Olerud P, Ahrengart L, Ponzer S, Saving J, Tidermark J. Internal fixation versus nonoperative treatment of displaced 3-part proximal humeral fractures in elderly patients: a randomized controlled trial. *J Shoulder Elbow Surg*. 2011;20(5):747-755.

6. Bell J-E, Leung BC, Spratt KF, et al. Trends and variation in incidence, surgical treatment, and repeat surgery of proximal humeral fractures in the elderly. *J Bone Joint Surg Am*. 2011;93(2):121.

7. Dall TM, Gallo PD, Chakrabarti R, West T, Semilla AP, Storm MV. An Aging Population And Growing Disease Burden Will Require ALarge And Specialized Health Care Workforce By 2025. *Health Aff*. 2013;32(11):2013-2020.

8. van Eck CF, Klein CM, Rahmi H, et al. Morbidity, mortality and cost of osteoporotic fractures—should proximal humerus fractures be taken as seriously as hip fractures? *Annals of Joint*. 2019;4:4-4. doi:10.21037/aoj.2019.01.01

9. Marx RG, Wilson SM, Swiontkowski MF. Updating the assignment of levels of evidence. *J Bone Joint Surg Am*. 2015;97(1):1-2.

10. Wright JG, Swiontkowski MF, Heckman JD. Introducing levels of evidence to the journal. *J Bone Joint Surg Am*. 2003;85(1):1-3.

11. Scott J, Checketts JX, Cooper CM, Boose M, Wayant C, Vassar M. An Evaluation of Publication Bias in High-Impact Orthopaedic Literature. *JB JS Open Access*. 2019;4(2):e0055.

12. Lavis JN. How Can We Support the Use of Systematic Reviews in Policymaking? *PLoS Med*. 2009;6(11):e1000141.

13. ICMJE | Recommendations | Author Responsibilities—Disclosure of Financial and Non-Financial Relationships and Activities, and Conflicts of Interest. Accessed June 25, 2020. http://www.icmje.org/recommendations/browse/roles-and-responsibilities/author-responsibilities--conflicts-of-interest.html

14. Electronic Code of Federal Regulations- US Department of Health and Human Services' Code of Federal Regulation 45 CFR 46.102(d). https://www.ecfr.gov/cgi-bin/retrieveECFR?gp=&SID=83cd09e1c0f5c6937cd9d7513160fc3f&pitd=20180719&n=pt45.1.46&r=PART&ty=HTML#se45.1.46_1102 in effect July 19, 2018

15. Ferrell M, Verble C, Anderson M, Weaver M, Hartwell M, Vassar M. Evidence of financial conflicts of interest in authors of proximal humerus repair systematic reviews and meta-analyses. Published online July 1, 2020. Accessed July 3, 2020. https://osf.io/4tzwy/

16. PRISMA. Accessed July 2, 2020. http://prisma-statement.org/

17. Murad MH, Wang Z. Guidelines for reporting meta-epidemiological methodology research. *Evid Based Med*. 2017;22(4):139-142.

18. Rulon Z, Jones CW, Ottwell RL. Evaluation of Spin in Systematic Reviews Related to the Management of Proximal Humerus Fractures. Published online May 29, 2020. Accessed July 3, 2020. https://osf.io/cvgtm/

19. Mandrioli D, Kearns CE, Bero LA. Relationship between Research Outcomes and Risk of Bias, Study Sponsorship, and Author Financial Conflicts of Interest in Reviews of the Effects of Artificially Sweetened Beverages on Weight Outcomes: A Systematic Review of Reviews. *PLOS ONE*. 2016;11(9):e0162198. doi:10.1371/journal.pone.0162198

20. Okike K, Kocher MS, Mehlman CT, Bhandari M. Conflict of Interest in Orthopaedic Research. *The Journal of Bone & Joint Surgery*. 2007;89(3):608-613. doi:10.2106/jbjs.f.00994

21. Narain AS, Hijji FY, Yom KH, Kudaravalli KT, Singh K. Cervical disc arthroplasty: do conflicts of interest influence the outcome of clinical studies? *Spine J*. 2017;17(7):1026-1032.

22. Kjaergard LL, Als-Nielsen B. Association between competing interests and authors' conclusions: epidemiological study of randomised clinical trials published in the BMJ. *BMJ*. 2002;325(7358):249.

23. Bhandari M, Busse JW, Jackowski D, et al. Association between industry funding and statistically significant pro-industry findings in medical and surgical randomized trials. *CMAJ*. 2004;170(4):477-480.

24. Shnier A, Lexchin J, Romero M, Brown K. Reporting of financial conflicts of interest in clinical practice guidelines: a case study analysis of guidelines from the Canadian Medical Association Infobase. *BMC Health Serv Res*. 2016;16(a):383.

25. Boddapati V, Sachdev R, Fu MC, Camp CL, Marx RG, Dines JS. Increasing Industry Support Is Associated with Higher Research Productivity in Orthopaedic Surgery. *J Bone Joint Surg Am*. 2018;100(6):e36.

26. Lundh A, Lexchin J, Mintzes B, Schroll JB, Bero L. Industry sponsorship and research outcome. *Cochrane Database Syst Rev*. 2017;2:MR000033.

27. Khan SN, Mermer MJ, Myers E, Sandhu HS. The roles of funding source, clinical trial outcome, and quality of reporting in orthopedic surgery literature. *Am J Orthop* . 2008;37(12):E205-E212; discussion E212.

28. Hozack WJ, Ranawat C, Rothman RH. Corporate sponsorship and research. *The Journal of Arthroplasty*. 2003;18(8):953. doi:10.1016/j.arth.2003.10.009

29. Oostrom T. Funding of Clinical Trials and Reported Drug Efficacy.". Published online 2020. https://pdfs.semanticscholar.org/ad9d/a7bf3d061116c6ae7515c651bb8c276b44df.pdf&hl=de&sa=X&d=2481165454991070009&scisig=AAGBfm0pU2GBj7xIJKqQECD8GYT0KYhv-Q&nossl=1&oi=scholaralrt&hist=76cO6AEAAAAJ:6061284773987871490:AAGBfm3WthEa5PhImJpHiGN_0yYVD3ZCNw

30. Friedberg M, Saffran B, Stinson TJ, Nelson W, Bennett CL. Evaluation of conflict of interest in economic analyses of new drugs used in oncology. *JAMA*. 1999;282(15):1453-1457.