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ORIGINAL RESEARCH ARTICLE

Are Causal Statements Reported in Pharmacovigilance Disproportionality Analyses Using Individual Case Safety Reports Exaggerated in Related Citations? A Meta-epidemiological Study

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Abstract

Background Previous meta-epidemiological surveys have found considerable misinterpretation of results of disproportionality analyses. We aim to explore the relationship between the strength of causal statements used in title and abstract conclusions of pharmacovigilance disproportionality analyses and the strength of causal language used in citing studies.

Methods On March 30, 2022, we selected the 30 disproportionality studies with the highest Altmetric Attention Scores. For each article, we extracted all citing studies using the Dimension database ($n = 1434$). In parallel, two authors assessed the strength of causal statements in the title and abstract conclusions of source articles and in the paragraph of citing studies. Based on previous studies, the strength of causal language was quantified based on a four-level scale (1—appropriate interpretation; 2—ambiguous interpretation; 3—conditionally causal; 4—unconditionally causal). Discrepancies were solved by discussion until consensus among the team. We assessed the association between the strength of causal statements in source articles and citing studies, separately for the title and abstract conclusions, through multinomial regression models.

Results Overall, 27% ($n = 8$) of source studies used unconditionally causal statements in their title, 30% ($n = 9$) in their abstract conclusion, and 17% ($n = 5$) in both. Only 20% ($n = 6$) used appropriate statements in their title and in their abstract's conclusions. Among the 622 citing studies analyzed, 285 (45.8%) used unconditionally causal statements when referring to the findings from disproportionality analysis, and only 164 (26.4%) used appropriate language. Multinomial models found that the strength of causal statements in citing studies was positively associated with the strength of causal language used in abstract conclusions of source articles (Likelihood Ratio Test (LogLRT) $p < 0.00001$) but not in the titles. In particular, among studies citing source articles with appropriate interpretation, 30.2% (95% confidence interval [CI] 22.8–37.6) contained unconditionally causal statements in their abstract conclusions, versus 56.4% (95% CI 48.7–64.2) for studies citing source articles with unconditionally causal statements.

Conclusions Nearly half of the studies citing pharmacovigilance disproportionality analyses results used causal claims, particularly when the causal language used in the source article was stronger. There is a need for higher caution when writing, interpreting, and citing disproportionality studies.

Key Points

Disproportionality analyses are often misinterpreted.

Causal statements are reiterated and exaggerated in citations.

Citation bias may canonize hypothesis-generating results as demonstrated facts.

1 Introduction

Continual monitoring of the safety of medications and vaccines after marketing authorization is essential to ensure that the benefit–risk balance of medications remains favorable in routine conditions of use [1]. Individual case safety reports of suspected adverse drug reactions reported by healthcare professionals and patients, collected in pharmacovigilance databases such as the Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) or the World Health Organization (WHO) pharmacovigilance database (VigiBase), constitute the main

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data source for detecting unknown adverse drug reactions after marketing authorization [2–5]. Disproportionality analyses have been developed for mining these databases in the attempt to generate hypotheses about unexpected adverse drug reactions (the so-called signals of disproportionate reporting) [6–9]. They are widely used by pharmaceutical companies and regulatory agencies, but signals of disproportionate reporting are subject to many biases [10], including differential motivation to report, country-specific regulatory aspects, confounding by indication, channeling bias and other methodological aspects [11–13]. Therefore, signals of disproportionate reporting need to be validated (e.g., through a qualitative case-by-case analysis), and contextualized within other sources of evidence, before being considered for regulatory actions or further assessment [14, 15]. Indeed, given the lack of exposure data and the unknown extent of selective reporting, disproportionality analyses cannot be used to estimate drug-related risk or incidence of adverse drug reactions [12]. Yet, previous meta-epidemiological surveys (i.e., studies in which the unit of analysis is a study and not a patient) have found considerable misinterpretation of results of disproportionality analyses by authors themselves, by overstating the strength of causal links, lacking proper handling and discussion of biases, providing unsupported clinical recommendations, or comparing drug safety profiles [12, 16–18]. A notable example is represented by the case of pancreatitis with glucagon-like peptide-1–based therapies: the original online version of disproportionality analysis, published in *Gastroenterology* and claiming an "increased incidence" in the title, was withdrawn following concerns raised by a drug company, and the title of the manuscript was subsequently reformulated in the print version [19, 20].

Several hundreds of disproportionality analyses are now published each year [21, 22], especially by academic researchers, receiving in some instances considerable attention from other researchers, social media, or newspapers [23, 24]. The related potential for misinterpretation of studies may have serious consequences when interpreted at face value by prescribers and patients. Indeed, misinterpretation in articles, notably in abstract conclusions, has been shown to modify the readers' perceptions on the strength of evidence inferred from a study's results [25–27].

We therefore hypothesize that causal statements are exaggerated when disseminated by other researchers, journalists, or health-related news, potentially even affecting the general public behavior regarding medications [28–31]. In this study, we aimed at evaluating the association between the causal language used when reporting pharmacovigilance disproportionality analyses and the causal language used by other researchers when quoting and referring to these articles.

2 Methods

The protocol of this meta-research study has been published on Open Science Framework [32]. We initially planned to analyze, in parallel, the causal statements used in newspapers reporting results of disproportionality analyses. However, three reasons led us to forgo this objective: (1) it was often impossible to identify the sentence or paragraph referring to the source study (i.e., references are displayed at the end of the article but are not indexed in the text); (2) numerous articles relayed the news from another source without adding new content; (3) we had no full access to a significant proportion of journal articles. We reported this study according to the guideline for reporting meta-epidemiological methodology research [33].

2.1 Identification of Source Articles

On March 30, 2022, we identified pharmacovigilance signal detection studies in the Altmetric explorer database using a PubMed query: ("case-non case" OR "case/no-case" OR "disproportionality" OR "pharmacovigilance analysis" OR "pharmacovigilance study" OR "FAERS" OR "Vigibase" OR "Eudravigilance" OR "VAERS"). We used Altmetric scores to identify articles that attracted significant attention from other researchers and the public. Then we identified the first 30 original studies that presented solely results of disproportionality analyses with the highest Altmetric Attention Scores (i.e., articles which have received presumably the highest interaction by other researchers, newspapers, social media, and the general public). We excluded articles without disproportionality analyses, non-original investigations, cases series, and mixed study designs.

For each source article, we extracted the journal name, specialty (pharmacological versus clinical), year of publication, journal impact factor on the year of publication (extracted from Clarivate's Journal Citation Reports), and gender of the last author [34]. For each source article, we assessed the level of causal statements in the title and abstract conclusions (see below), whether methodological limitations were described, and whether clinical recommendations for healthcare professionals and patients were provided. We chose to evaluate the causality status of the title

and the conclusion of the abstract, as these are what authors read first to select the articles cited in their paper.

2.2 Identification of Citing Studies

We identified all the studies (any publication date) citing the selected 30 source articles using the Dimensions database (https://www.dimensions.ai/), which allowed the retrieval and extraction of all citations of an article. We excluded citations for which access to the full article was impossible through our institutional access. We then analyzed a maximum of 50 random citing studies for each source article (selected through ordering all citations from one to *n* and generating 50 random numbers). We extracted all sentences related to the source articles in each citing article in an Excel file and excluded citations not directly discussing study results (e.g., method or context), after consensus among three authors (BR, CB, and CK).

For each citing study, we assessed the level of causal language used (see below), whether methodological limitations of the source study were described (i.e., individual case safety report database), and whether they provided clinical recommendations for healthcare professionals and patients.

2.3 Gradation of Causal Statements

Judgement about the strength of causal statements of all abstracts of source articles and citations was performed in parallel by two authors (BR, CB, or CK) and discrepancies discussed among the team in dedicated meetings until the three authors (BR, CB, and CK) reached a consensus. Analyses of citations was performed blinded from the source article.

Based on previous studies assessing the strength of causal claims in scientific articles and a pilot study, we first decided to use a six-level gradation system. However, after retrieving all the citing studies, we decided to simplify the gradation to a four-level scale, given the difficulty of differentiating certain causal gradations and the low number of citations in some of them (Table 1) [30, 35, 36].

2.4 Statistical Analyses

Categorical data were described using relative frequencies and continuous data using medians with interquartile ranges (IQRs).

Differences in pre-specified covariates (i.e., journal specialty, year of publication, number of citations per year, Altmetric Attention Scores, journal impact factor, gender of the last author) according to the level of causal statements in the title and abstract conclusions were explored through Fisher exact test for categorial variables and analysis of variance (ANOVA) test for continuous variables.

Associations with regard to the level of causal statements between source articles (title or abstract conclusions) and related citing studies were explored through distinct multinomial regression models. An ordinal regression model was deemed inappropriate given that the proportional odds assumption was unlikely in our study. Marginal probabilities of levels of causal statements in citing studies according to the level of causal language used in the source article were also estimated.

Given the exploratory nature of these analyses, a p value < 0.05 was considered significant, without adjusting for the multiplicity of comparisons. All analyses were performed using R (version 3.6.1) and Jamovi (2.3.18.0).

3 Results

3.1 Literature Searches and Selection of Source Articles

Using the pre-specified query, we retrieved 1611 studies from PubMed, which were sorted according to their Altmetric Attention Scores. We screened the first 97 articles to identify 30 studies complying with the inclusion criteria.

These 30 source studies were published in journals with a median impact factor of 5.5 (IQR 4.3–14.6) and had a median publication year of 2020 (IQR 2018–2021) and a median number of citations of 32 (IQR 13.5–50.0). Only 30% of the journals ($n = 9$) belonged to the field of

Table 1 Levels of strength of causal statements from disproportionality analyses

Strength	Statement
Level 1—Appropriate interpretation	Description of number/characteristics of reported cases (e.g., XXX cases were reported…)
	Discussing signals (e.g., a signal has been identified for an adverse event/drug combination…)
Level 2—Ambiguous interpretation	Correlational expressions (e.g., the drug is associated with…), without considering that the association was found only between the reporting of a drug and the reporting of an event
Level 3—Conditionally causal	Probably or conditionally causal (e.g., drug exposure could/may/might/can increase the risk of …or cause the adverse drug reaction…)
Level 4—Unconditionally causal	Unconditionally causal (e.g., drug exposure increases the risk of adverse event…)

pharmacology, and the last authors were men in 76.7% of cases ($n = 23$) (Supplementary Table 1; see the electronic supplementary material). Most of these studies explored adverse events following immunization ($n = 10$) or were related to coronavirus disease 2019 (COVID-19) treatments (e.g., remdesivir, hydroxychloroquine) ($n = 11$). The median Altmetric Attention Score was 272.5 (IQR 146–329), with the highest score being 3742 for an article entitled, "Serious bradycardia and remdesivir for coronavirus 2019 (COVID-19): a new safety concerns" [24].

3.2 Causal Statements in Titles and Abstracts of Source Articles

Most of the included studies used ambiguous, conditionally causal, or unconditionally causal statements in their titles or abstract conclusions (Fig. 1). The two reviewers similarly rated causal statement strength in 83.3% of the abstract conclusions ($n = 25$) and 80.0% of the titles of source articles ($n = 24$). Overall, nine studies (30%) used unconditionally causal claims in their conclusion, eight studies (27%) used them in their titles, and five studies (17%) used them in both. In addition, 43% of studies ($n = 13$) provided recommendations for clinical practice, and the vast majority did not describe any study limitations in their abstracts ($n = 27/30$).

The characteristics of articles according to their level of causal statements in abstract conclusions and in the title are presented in Table 2 and Supplementary Table 2 (see the electronic supplementary material), respectively.

We did not find any significant and meaningful differences between the level of causal statements in titles and abstracts with any of the pre-specified covariates (i.e., journal specialty, year of publication, number of citations per year, Altmetric Attention Scores, journal impact factor, and gender of last author).

3.3 Causal Statements in Citations

Collectively, the 30 source articles were cited 1434 times. After excluding citing studies we could not access, those in non-English languages, and those not related to the results of disproportionality analyses, and after randomly selecting a maximum of 50 citing studies for each source article, we analyzed in total 622 citing studies (Fig. 2). Reviewers agreed in their rating of the strength of causal statements by providing the exact same category in 69.1% of cases ($n = 430$). Most of the citing studies analyzed used unconditionally causal claims when referring to the findings from disproportionality analyses ($n = 285$, 45.8%), and only 26.2% ($n = 163$) used appropriate statements (Fig. 3). Moreover, 44.9% of citing studies ($n = 279$) mentioned the study design (i.e., disproportionality analysis) or the data type (e.g., individual case safety reports or pharmacovigilance database) when citing the result of selected articles, and 27.3% of studies ($n = 170$) displayed numerical results in their citations.

3.4 Association Between Causal Statements in Citation and Source Articles

Overall, the level of causal statements from the abstract conclusions of source articles was exaggerated in 41.3%, was the same in 37.6%, and was minimized in 22.0% of related

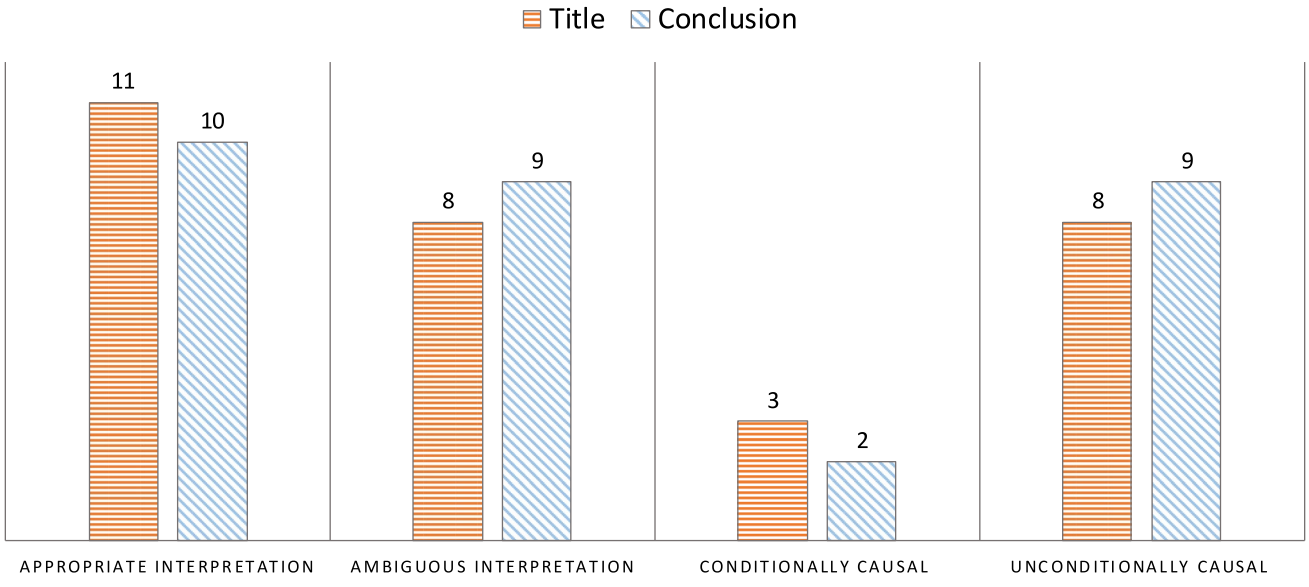

Fig. 1 Distribution of the number of source studies according to the level of causal statements in title and abstract conclusion

Table 2 Characteristics of the selected source articles according to level of causal statements in abstract conclusion

	Appropriate interpretation ($n = 10$)	Ambiguous interpretation ($n = 9$)	Conditional causal ($n = 2$)	Unconditionally causal ($n = 9$)	Test p value*
Number of citations per year	11.79 (4.72–20.38)	5.12 (4.50–7.38)	32.30 (23.15–41.45)	9.88 (4.00–19.25)	0.496
Journal impact factor	5.55 (3.42–10.63)	4.90 (4.40–5.45)	26.55 (22.12–30.97)	11.50 (4.62–23.40)	0.180
Altmetric Attention Score	318.00 (251.25–666.75)	303.00 (174.50–330.75)	115.00 (108.00–122.00)	203.00 (126.50–273.00)	0.080
Years since publication (ref. 2023)	2.00 (2.00–4.25)	3.00 (2.75–5.25)	4.00 (3.50–4.50)	2.50 (2.00–4.00)	0.633
Last author gender (female/male)	20%/80%	11.1%/88.9%	0%/100%	11.1%/88.9%	1.000
Type of journal (clinical/pharmacological)	60%/40%	66.7%/33.3%	100%/0%	77.8%/22.2%	0.839

For qualitative data, we used relative frequencies (%), and for quantitative data, median and IQR

ANOVA analysis of variance, *IQR* interquartile range, *n* number of studies

*Fisher exact test for categorial variables and ANOVA test for continuous variables

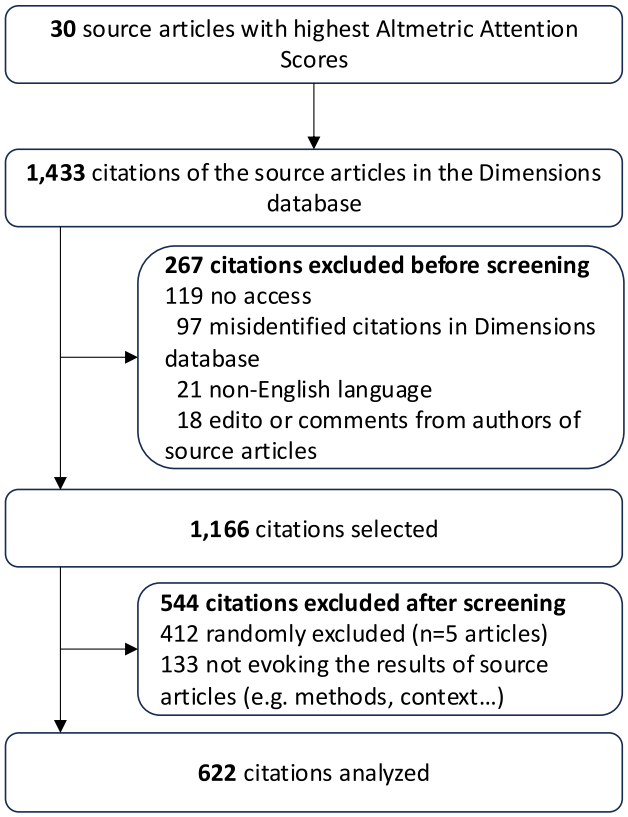

Fig. 2 Flowchart of the selection of citing studies

citations (Fig. 3). Examples of exaggeration and repetition of causal claims are provided in Table 3.

The results of the multinomial models found that the level of causal statements in citing studies was positively associated with the level of causal statements in the abstract conclusions of source articles (Likelihood Ratio Test (LogLRT) $p < 0.00001$) but not in the titles of source articles (full results are presented in Supplementary Table 3 and 4; see the electronic supplementary material).

Figure 4 shows the marginal probabilities of the level of causal statements in citing articles according to abstract conclusion. The probability of citing articles containing unconditionally causal statements was 30.2% (95% confidence interval [CI] 22.8–37.6) when referring to source articles using appropriate interpretation of their results, while it was 56.4% (95% CI 48.7–64.2) for conclusions containing unconditionally causal statements. Inversely, the marginal probabilities of citations using correct interpretation decreases from 40.7% (95% CI 32.7–48.6) to 22.6% (95% CI 16.0–29.1).

4 Discussion

The title and abstract of an article carry the most important message for end-users, and are often the only parts of the paper that are freely accessible to everyone online [37]. Our results suggest that the causal language used in abstract conclusions, but not in titles, is related to the causal language used by other researchers when citing pharmacovigilance signal detection studies using disproportionality analysis. Given the inherent limitations of adverse events reporting databases (e.g., lack of exposure data, selective reporting of adverse events) and of disproportionality analyses (e.g., competition between drugs and events), incidence and drug- or vaccine-related risks cannot be quantified [10, 38]. For these reasons, disproportionality analyses should be typically considered as hypothesis-generating studies. Yet, approximately one third of the source articles selected in our study claimed the demonstration of a causal link between an adverse event and a drug, and another third used vague and

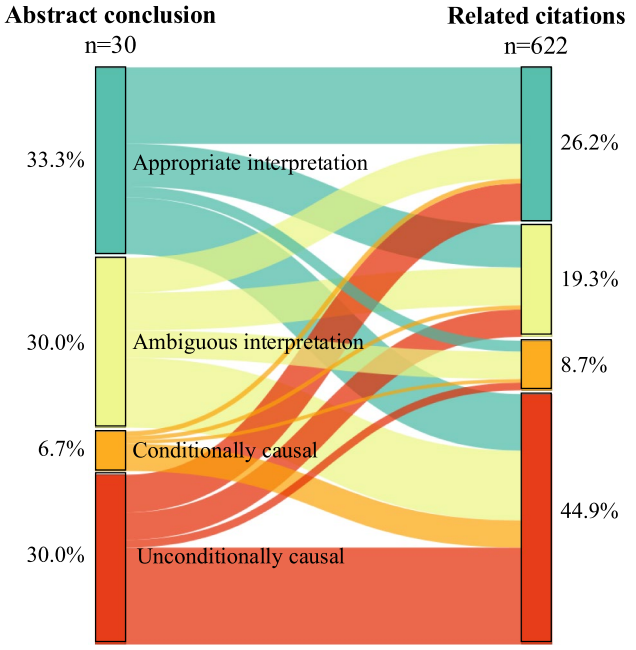

Fig. 3 Sankey plot presenting the distribution of the levels of causal statements in citing articles according to the level of causal statements in the abstract conclusions of source articles

ambiguous language in their abstract conclusion. Moreover, our results show that these causal claims are often repeated, sometimes by directly copy-pasting a sentence from the conclusion, or exaggerated when articles are subsequently cited by other researchers. This tendency, in conjunction with publication bias, selective outcome reporting, selective citation of significant results, and citation cascades, may canonize hypothesis-generating results as demonstrated facts [39–42].

Responsibility, therefore, lies primarily with authors and publishers to ensure adequate interpretation of findings in peer-reviewed publications [43]. The development of specific reporting guidelines for disproportionality analyses (REporting of A Disproportionality analysis for drUg Safety signal detection using spontaneously reported adverse events in PharmacoVigilance [READUS-PV]) may hopefully help authors, peer reviewers, and editors in this task [44, 45]. These guidelines may also promote a wider adoption of explicit statements about limitations, pre-registration of protocols, full reporting of outcomes, and sensitivity analyses. Of note, the item 14b in the READUS-PV checklist for abstracts was specifically devoted to limitations (*acknowledge that the disproportionality analysis is a hypothesis-generating or refinement approach*). This could represent the first step to support readers in the proper interpretation of results. To this end, we advocate for wide dissemination and global endorsement by pharmacology journals of the READUS-PV guidelines [46]. To our view, it is fundamental to

Table 3 Examples of abstract conclusions at different levels of strength of causal statement leading to unconditionally causal claims in related citations

Strength of causal statements in abstract conclusions	Conclusions of source article	Example of exaggerated related citations
Level 1—Appropriate interpretation	[We] detected a *statistically significant pharmacovigilance signal* of [adverse event X] associated with [drug A], deserving a thorough qualitative assessment of all available data	[…] revealed a statistically significant [adverse event X] signal, demonstrating a *20-fold higher risk* of [adverse event X] with [drug A] use than that associated with other drugs frequently used in COVID-19
Level 2—Ambiguous	These data demonstrate that [drug A] *is associated with* [adverse event X]	In recent years, studies have reported that [drug A], *has caused a series of* [adverse event X] disorders
Level 3—Conditionally causal	[Drug A] *may carry a clear potential* for serious AEs, which deserves urgent clarification by means of further prospective studies	A recent study of postmarketing safety data on [drug A] that analyzed reports made to the United States Food and Drug Administration Adverse Event Reporting System found a *24.0 increased odds for development of* [adverse event X] during treatment with [drug A]
Level 4—Unconditionally causal	[Adverse events X] *often occurred* early after [drug A] administration. Importantly, [adverse events X] were associated with *fatalities that ranged* from ~ 10% […] to ~ 20%. […] *Severe and occasionally fatal* [adverse events X] *occur* in patients exposed to [drug A]. These events should be considered in patient care and in clinical trial designs	Retrospective toxicity studies indicate that its current treatment schedule is associated with an *increased risk* of [adverse events X]

AE adverse event, *COVID-19* coronavirus disease 2019

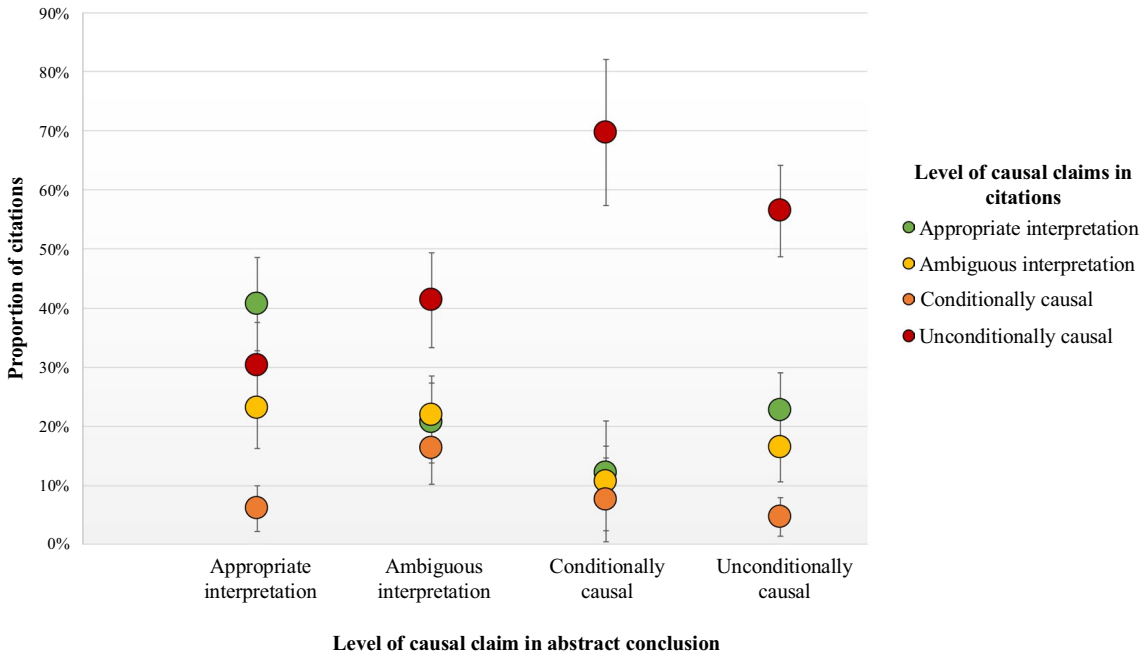

Fig. 4 Marginal probabilities of the level of causal statements in citations according to abstract conclusion

use cautious wording and take into account the whole body of evidence supporting or not a potential adverse drug reaction when interpreting results of disproportionality analyses. In addition, displaying caveats about estimates generated by these methods is essential for a credible research field and may encourage regulatory agencies and stakeholders to further consider some significant signals of disproportionate reporting [47]. Although these analyses are exploratory and potentially affected by selection bias, reassuringly, we did not find any positive association between exaggerated causal statement in the title and abstract conclusion and journal impact factors, subsequent citations, or attention from the public. Further studies could be worthwhile to explore the pattern of causal language used in publications depending on the type of scientific journal. Given the exponential increase in the number of articles dealing with disproportionality analysis, also in clinical journals, developing interventions specifically tailored to support the correct perception of readers on the difference between association (i.e., a detected signal of disproportionate reporting only subtending a statistical significance) and causation (a plausible adverse drug reaction) would probably be the most impactful.

Another important finding is that even when authors correctly reported and interpreted their study results, exaggeration of the findings in citing studies is common (i.e., 59.3% of citing studies). These numbers underline the importance of better communication between, and the acculturation of, the scientific community and the lay public regarding pharmacovigilance signal detection studies, and the importance of improving the peer reviewing of citations in scientific articles [42]. Presumably, outside of the scientific literature, among healthcare practitioners not adequately informed to critically interpret disproportionality analyses and the lay public, the rate of misinterpretation is even higher. For example, during the COVID-19 pandemic, disproportionality signals and the number of reports in pharmacovigilance databases (with no proven causal link with drug exposure) have been used by antivax movements to support claims about the supposed toxicity of vaccines [48–50]. Understanding the extent and the type of misinterpretation of these studies by the lay public is crucial to improve our ability to communicate on safety signals generated by pharmacovigilance disproportionality analyses. Future studies may leverage advances in machine learning and natural language processing to find ways to do so, starting with social media [51].

4.1 Limitations

First, we selected source articles among those published in Medline-indexed journals that have high Altmetric Attention Scores, in order to assess articles with a high probability of being cited by other researchers and reaching the public. While Altmetric Attention Scores have been found to be weakly correlated with citation counts, we have certainly missed some highly quoted articles in the field [52]. Moreover, one third of publications were related to COVID-19 vaccines or treatments; however, no interaction was found between this topic and the level of causal statements in the

conclusions of source articles in the multinomial model ($p = 0.197$). This sample is, therefore, unlikely to be representative of all published disproportionality analyses, and we encourage other researchers to replicate our findings in different samples of studies. In addition, we were unable to access around 10% of citations due to restricted access to journals. Second, we categorized causal statements from associational to unconditionally causal based on previous research [30]. However, other studies have shown that associations can be perceived by some readers as unconditionally causal claims, and it is worth noting that these ambiguous formulations prompted much discussion within the team [36, 53]. Moreover, it is of the utmost importance to conduct research to further quantify and account for biases affecting disproportionality analyses and to develop a gradation system to assess the robustness of safety signals generated by disproportionality analyses. Last, the assessment of causal claims is obviously a subjective task, involving interpretation and judgements of authors influenced by personal belief and context. We have tried to minimize this issue by involving two independent reviewers to evaluate each article according to a defined methodology, blinded from the source articles, and in resolving discrepancies by consensus.

5 Conclusion

This meta-research study found that nearly half of the studies citing pharmacovigilance disproportionality analyses results used (and exaggerated) causal language, particularly when causal statements were stronger in the source article, thus creating and perpetuating a citation bias. Ambiguous and correlational statements are the most important source of exaggerated causal claims in citations, and we call for the development of specific interventions aimed at supporting their perception and interpretation by readers. Researchers working with and exploiting results from pharmacovigilance disproportionality analyses need to exert great caution in interpreting, communicating, and citing relevant findings.

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Declarations

Availability of data and materials The datasets used in this study are available on request from the corresponding author.

Code availability The codes used in this study are available on request from the corresponding author.

Conflict of interests Francesco Salvo is an editorial board member of *Drug Safety*. Francesco Salvo was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions. The other authors declare no conflict of interest related to this study.

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Authors' contributions CB, BR, and CK extracted and analyzed the data. All authors participated in the interpretation of results. CK was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

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