

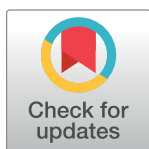
RESEARCH ARTICLE

Methodological approaches for assessing certainty of the evidence in umbrella reviews: A scoping review

Saranrat Sadoyu¹, Kaniz Afroz Tanni², Nontaporn Punrum³, Sobhon Paengtra³, Warittakorn Kategaew⁴, Nattiwat Promchit³, Nai Ming Lai^{5,6}, Ammarin Thakkinstian^{7,8}, Surachat Ngorsuraches², Mukdarut Bangpan⁹, Sajesh Veettil⁴, Nathorn Chaiyakunapruk^{4,10*}

1 Pakchongnana Hospital, Nakhon Ratchasima, Thailand, **2** Department of Health Outcomes Research and Policy, Harrison College of Pharmacy, Auburn University, Auburn, Alabama, United States of America, **3** Faculty of Pharmacy, Chiangmai University, Chiang Mai, Thailand, **4** Department of Pharmacotherapy, College of Pharmacy, University of Utah, Salt Lake City, Utah, United States of America, **5** School of Medicine, Taylor's University, Subang Jaya, Malaysia, **6** School of Pharmacy, Monash University Malaysia, Bandar Sunway, Malaysia, **7** Department of Clinical Epidemiology and Biostatistics, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand, **8** Mahidol University Health Technology Assessment Graduate Program, Bangkok, Thailand, **9** The Evidence for Policy and Practice Information and Co-ordinating Centre (EPPI-Centre), Social Research Institute, University College London, London, United Kingdom, **10** IDEAS Center, Veterans Affairs Salt Lake City Healthcare System, Salt Lake City, Utah, United States of America

* Nathorn.Chaiyakunapruk@utah.edu



OPEN ACCESS

Citation: Sadoyu S, Tanni KA, Punrum N, Paengtra S, Kategaew W, Promchit N, et al. (2022)

Methodological approaches for assessing certainty of the evidence in umbrella reviews: A scoping review. PLoS ONE 17(6): e0269009. <https://doi.org/10.1371/journal.pone.0269009>

Editor: Muhammad Shahzad Aslam, Xiamen University - Malaysia Campus, Xiamen University - Malaysia, MALAYSIA

Received: January 30, 2022

Accepted: May 12, 2022

Published: June 8, 2022

Copyright: © 2022 Sadoyu et al. This is an open access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Data Availability Statement: All relevant data are within the article and its [Supporting information](#) files.

Funding: The authors received no specific funding for this work.

Competing interests: The authors have declared that no competing interests exist.

Abbreviations: AMSTAR, A Measurement Tool to Assess systematic Reviews; GRADE, Grading of

Abstract

Introduction

The number of umbrella reviews (URs) that compiled systematic reviews and meta-analysis (SR-MAs) has increased dramatically over recent years. No formal guidance for assessing the certainty of evidence in URs of meta-analyses exists nowadays. URs of non-interventional studies help establish evidence linking exposure to certain health outcomes in a population. This study aims to identify and describe the methodological approaches for assessing the certainty of the evidence in published URs of non-interventions.

Methods

We searched from 3 databases including PubMed, Embase, and The Cochrane Library from May 2010 to September 2021. We included URs that included SR-MAs of studies with non-interventions. Two independent reviewers screened and extracted data. We compared URs characteristics stratified by publication year, journal ranking, journal impact factor using Chi-square test.

Results

Ninety-nine URs have been included. Most were SR-MAs of observational studies evaluating association of non-modifiable risk factors with some outcomes. Only half (56.6%) of the included URs assessed the certainty of the evidence. The most frequently used criteria is

Recommendations, Assessment, Development and Evaluations; IQR, Interquartile range; JBI, Joanna Bring Institute; JIF, journal impact factors; MA, meta-analysis; OQAQ, Oxman and Guyatt Overview Quality Assessment Questionnaire; RCT, randomized controlled trials; ROBIS, A Risk of Bias Assessment Tool for Systematic Reviews; SR, systematic reviews; UR, umbrella review.

credibility assessment (80.4%), followed by GRADE approach (14.3%). URs published in journals with higher journal impact factor assessed certainty of evidence than URs published in lower impact group (77.1 versus 37.2% respectively, $p < 0.05$). However, criteria for credibility assessment used in four of the seven URs that were published in top ranking journals were slightly varied.

Conclusions

Half of URs of MAs of non-interventional studies have assessed the certainty of the evidence, in which criteria for credibility assessment was the commonly used method. Guidance and standards are required to ensure the methodological rigor and consistency of certainty of evidence assessment for URs.

Introduction

The number of systematic review (SR) and umbrella reviews (UR) and meta-analysis (MAs) has increased dramatically over recent years [1]. Most SRs and MAs focus on answering a question such as the effect of a single treatment comparison on an outcome, this leaves a big gap of lacking an overall summary of evidence addressing broader related questions. URs, also known as overview or review of reviews, evolved in the last decade, can summarize and even synthesize the findings into single comprehensive evidence answering the broader picture of all existing findings [1, 2]. As a result, URs are considered as one of the highest levels of evidence summary in biomedical literature [2]. URs of epidemiological investigations and non-interventional studies help establish evidence linking exposure to certain health outcomes in a population. Therefore, these studies are expected to play a key role in gauging the burden of diseases, understand the risk or protective factors, delineating guideline for prevention as well as streamlining the treatment development process [3, 4].

Some steps for performing URs are generally similar to SR-MAs (e.g., search strategy, study selection, data extraction), yet some others especially assessment of uncertainty methods are not applicable owing to the difference in types of included studies [5]. Recently, there is a methodological guidance focusing on conducting and reporting an UR [6]. However, it does not cover every single aspect of the process including assessment methods for certainty of the evidence.

The certainty of the evidence from URs is an essential component as it demonstrates the confidence of the findings found across studies leading to support a decision or recommendations. Several approaches have been used in literature. For instance, some URs adopted Grading of Recommendation, Assessment, Development and Evaluation (GRADE) approach, which was originally designed for assessing the certainty of evidence of primary studies included in SRs, not URs [7]. In contrast, some URs reported the certainty of included SRs and MAs as originally reported from each study without further assessment [8–10]. Furthermore, the UR of MAs is more challenging as they usually report summary statistical data as one of the objective criteria to grade the certainty of evidence. Recently, the relatively strict criteria for stratifying the certainty of evidence using several statistical parameters (i.e., degree of statistical significance, predictive interval, small-study effects, and excess significance bias) have also been used and suggested as the good practical tips for conducting good URs [2]. Currently, there is no formal guidance for assessing the certainty of evidence in URs. Therefore, this scoping review aims to identify and describe the methodological approaches for assessing the certainty of the evidence in published URs that included MAs of non-interventions.

Methods

This review was conducted according to the methods pre-specified in a registered protocol (PROSPERO registration: CRD42020203273), following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension for scoping reviews ([S1 Table in S1 File](#)).

Search strategy and selection criteria

We searched three databases including PubMed, Embase, and The Cochrane Library from May 2010 to Sep 2021. The keyword ‘umbrella review’ was used. The full search strategies without language restriction are described in [S2 Table in S1 File](#). Manual searches of the reference lists of the eligible articles were also performed. We defined an UR as the review that is designed to summarize the evidence from multiple SR-MAs that were labeled as ‘umbrella review’ in the title or abstract of the article.

At least two reviewers (SS, KT, NP, SN, WK, NP, and SP) independently reviewed the titles, abstracts, and full texts for their potential inclusion against the eligibility criteria. Any disagreement was resolved by consensus with a third reviewer (NC). No language restriction was applied. URs, overview of SR-MAs, review of SR-MAs were selected if they included (a) MAs of interventions and (b) MAs of non-interventions involving diagnostic/prognostic factors and non-modifiable risk factors of diseases or health conditions, disease etiology, prevalence or incidence; in which most studies were observational studies, e.g., cohort, case-control, and cross-sectional studies. In this current study, we focus only umbrella reviews that included MAs of non-intervention studies.

Other types of studies or reviews (e.g., handbooks, guidelines, commentaries, editorials, and methodological studies), materials for poster presentations, UR of SRs without MAs, and protocols of URs were excluded. URs with network MAs were also excluded because these studies might use different methodological approaches.

Data extraction

At least two reviewers (SS, NP, SN, KT, WK, MP, and SP) independently extracted the data from each UR into a customized data extraction table. Any disagreement was resolved by consensus with a third reviewer (NC). Details of data extraction are described in [S1 File](#).

The assessment of the certainty of evidence was defined as any of evaluation of the totality or strength of the evidence such as the GRADE approach, criteria for credibility assessment, and other approaches used to grade the overall body of the UR evidence.

Data synthesis and analysis

A descriptive analysis of the methodological approaches for assessing the certainty of evidence in the URs was performed by frequencies and percentage. The included URs were classified into high and low impact sources based on the journal impact factors (JIF) reported by the Institute of Scientific Information’s Journals Citation Report in 2021 accessed on October 21, 2021. The journals reported as the top 100 highest ranking were defined as the high, otherwise they were classified as low impact groups. In addition, we also classified based on a median JIF, i.e., high if the URs were published in $JIF \geq \text{median}$, otherwise the URs were classified as lower impact groups. According to the previous study [11] that suggested the usefulness of URs according to the higher number of citations after 2015 and the release of tools for the methodological quality assessment in 2016 [12]. Thus, we further compared URs published between 2010 to 2016 with those published from 2017 to 2021, when feasible. Chi-square or

Fisher's exact test where appropriated was applied to compare characteristics of URs between groups. All analyses were performed using STATA version 15.0 (College Station, TX), p -value ≤ 0.05 was considered as statistical significance.

Results

Search results

We identified 2405 articles, of which 302 and 1573 articles were excluded due to duplicates and during screening titles/abstracts, respectively: leaving 530 studies for the full-text review. A total of 447 URs matched with the eligibility criteria. Finally, 348 and 99 URs of intervention and non-therapy/non-intervention studies were eligible but only 99 URs were focused and reported in our scoping review (Fig 1) [13–111]. The reasons for exclusion of the articles after full-text review were described in detail in S3 Table in S1 File.

Characteristics of included URs

Table 1 summarize the characteristics of the 99 included URs. The number of URs increased over time from 1 in 2015 to 32 in 2021, with the majority being published in the recent 5 years (2017–2021), (N = 90, 90.9%).

Most URs (n = 78, 76.8%) included individual SR-MAs of observational studies evaluating risk or protective effects of risk factors, association, and non-modifiable risk factors of a disease

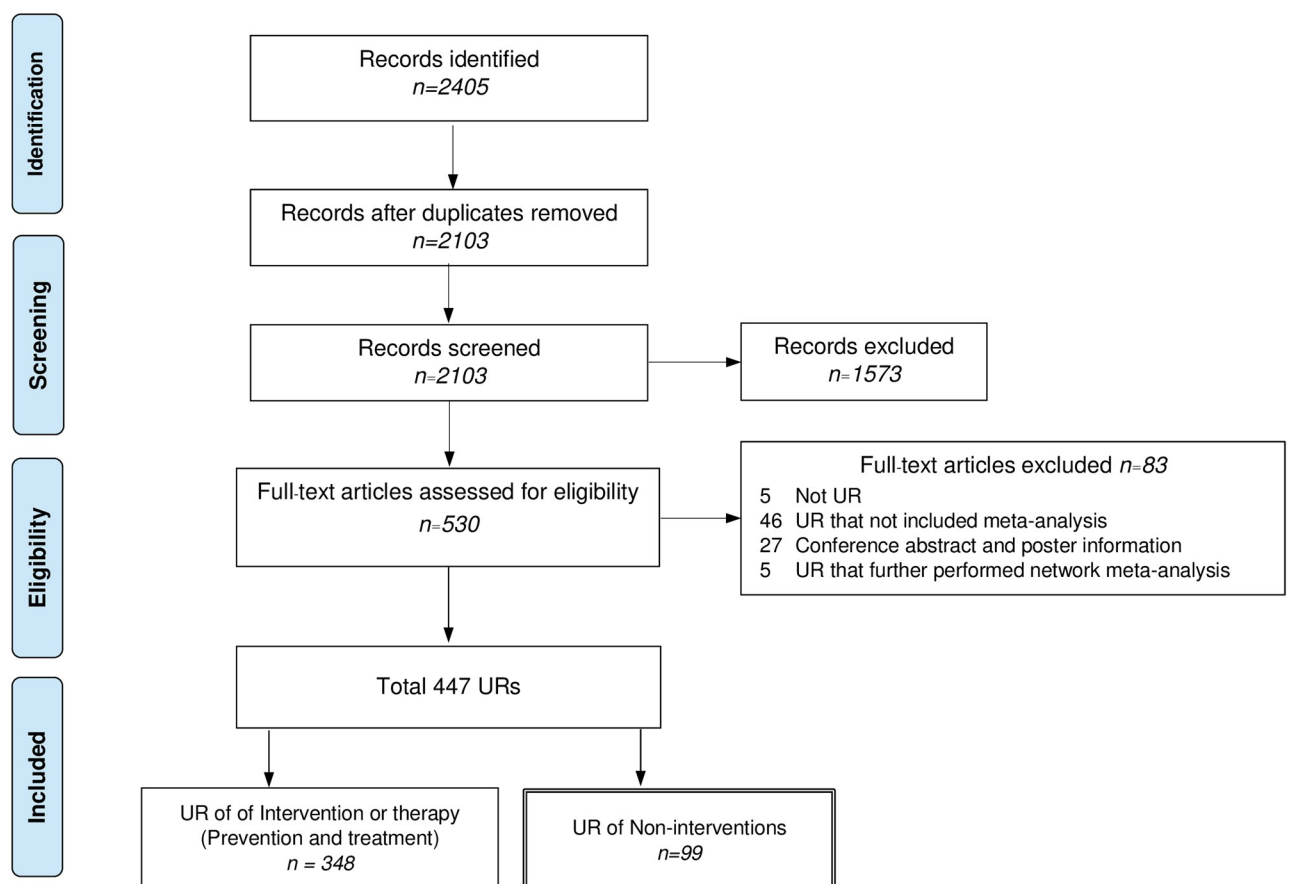


Fig 1. Evidence search and selection.

<https://doi.org/10.1371/journal.pone.0269009.g001>

or health condition, followed by URs that focused on prevalence/ incidence ($n = 11$, 11.1%), and etiology, diagnosis/prognostic biomarkers ($n = 6$, 6.1%). The median number of MAs included in these corresponding URs were 12 (Interquartile range (IQR): 5–42), The median of total number of primary studies included were 243 (IQR: 174–683). The median JIF of URs that included in this study was 4.45 (3.01–7.72). Seven of the 99 URs (7.1%) were published in top-100 ranking journals [30, 31, 41, 71, 95, 100, 103] according to the JIF in 2021.

Methodological approaches for assessing certainty of the evidence

Of 99 URs, only half of them ($N = 56$, 56.6%) assessed the certainty of the evidence, see Table 1, S4 and S5 Tables in S1 File. Criteria for credibility assessment was the most frequently used method ($N = 45$, 80.4%) followed by GRADE approach ($N = 8$, 14.3%), see Fig 2. Almost all URs used one tool ($N = 55$, 98.2%), only 1 URs (1.8%) used both criteria for credibility assessment and GRADE approach [61].

Table 2 showed the certainty and methodological quality assessment in URs. Based on the median of JIFs, the percent URs that assessed the certainty of evidence was significantly higher in the high impact group ($JIF > 4.45$) than the lower impact group ($JIF \leq 4.45$), i.e., 77.1% vs 37.3%, $p < 0.0001$. The number of URs that published in top-100 journals group also assessed the certainty of evidence more than the lower impact group, although it was not significant (71.4% vs 55.4%, $p = 0.70$). Comparing the period of 2010–2016 with 2017–2021, the percent of URs with certainty of the evidence assessments was higher in a period of 2010–2016 in than 2017–2021 but no statistically significant was found (66.7% vs 55.6%, $p = 0.73$). In addition, Fig 3 showed the direction that the proportion of URs that performed the certainty of evidence assessment was increase over time. Except that only 1 UR that published in 2015 meet our criteria and the author performed certainty of evidence assessment, thus, the proportion of URs that assess the certainty was 100%.

Of 7 URs published in top-100 ranking journals group [30, 31, 41, 71, 95, 100, 103], the assessment of certainty of the evidence was performed in 5 studies. The most used tools were criteria for credibility assessment ($n = 4$) followed by 1 study using GRADE approach. However, criteria for credibility assessment used in these URs were varied across studies, as shown in Table 3. For instance, 2 URs used the retained statistical significance in 10% credibility ceiling and the largest study with statistically significant effect as criteria for convincing class (the highest certainty). Four URs classified the certainty of evidence into 5 levels including “Convincing,” Highly suggestive,” Suggestive,” “Weak,” or “Not significant” but 1 UR used this tool to identified associations that had the strongest validity and were not suggestive of bias. Moreover, convincing evidence was graded based on the number of cases included in each MA of ≥ 350 to ≥ 5000 or p -values of $< 10^{-6}$ or even < 0.001 , as shown in S6 Table in S1 File.

Methodological quality assessment

Most of the included URs performed the methodological quality assessment of included MAs ($n = 74$, 74.8%). Of these, the most frequently used tool was AMSTAR 2 ($n = 34$, 46%), followed by its old version called AMSTAR ($n = 20$, 27%), and Joanna Bring Institute (JBI) critical appraisal checklist for SRs ($n = 13$, 17.6%), as shown in Table 1 and Fig 2.

Among 7 URs that published in top-100 journal ranking group [30, 31, 41, 71, 95, 100, 103], 5 of them (71.4%) assessed the methodological quality using AMSTAR [100, 103] and AMSTAR 2 [30, 41, 95]. The proportion of URs in the high-impact journal group, based on the median of journal impact factor, that performed the methodological quality assessment was lower than those published in the lower impact journal group, but it was not statistically significant (72.9% vs 74.6%, $p = 0.69$), as shown in Table 3. The more recent URs published in

Table 1. Description of included umbrella reviews.

Description	Response	
	N	%
1. Year published		
2010–2016	9	9.1
2017–2021	90	90.9
2. Number of included studies and participants		
Number of meta-analyses included in URs, median (IQR)	12 (5–42)	
Number of primary studies included in meta-analysis, median (IQR)	243 (174–683)	
Number of study participants, range	8–19,207,552	
Journal impact factor (IF), median (IQR)	4.45 (3.01–7.72)	
3. Journal publication		
3.1 Classified by Top 100 journal ranking		
Published in High impact groups (Top 100 journal ranking)	7	7.1
Published in lower impact groups	92	92.9
3.2 Classified by median journal impact factor of included URs		
Published in High JIF group	48	48.5
Published in lower JIF group	51	51.5
4. Characteristics of Included meta-analysis		
URs with meta-analysis of observational studies	78	78.8
URs with meta-analysis of both observational and experimental studies	10	10.1
URs that not reported the study design of primary studies	11	11.1
5. Certainty of the evidence assessment		
Assessment was done	56	56.6
5.1 Tools used for assessing certainty of the evidence (n = 56)		
Criteria for credibility assessment	45	80.4
GRADE approach	8	14.3
Performed both credibility assessment and GRADE approach	1	1.8
Authors used their own criteria	2	3.6
6. Methodological quality assessment		
Assessment was done	74	74.8
6.1 Tools used for assessing methodological quality		
AMSTAR	20	27
AMSTAR 2	34	46
JBI critical appraisal checklist for SRs	13	17.6
ROBIS	3	4.1
Other tools	4	5.4
Oxman and Guyatt Overview Quality Assessment Questionnaire (OQAQ)	1	
Authors used their own criteria	1	
A tool developed from the Centre for Reviews and Dissemination (CRD) checklist	1	
Newcastle Ottawa Scale	1	

<https://doi.org/10.1371/journal.pone.0269009.t001>

2017–2021, performed a methodological quality assessment more often than those published in 2010–2016 significantly, (78.9% vs 33.3%, $p < 0.05$). Furthermore, Fig 3 also showed the inclination of the proportion of URs that performed the methodological assessment over time.

Discussion

To the best of our knowledge, this is the first study identifying the methodological approaches for assessing the certainty of evidence in URs of SR-MAs considering 99 URs of non-

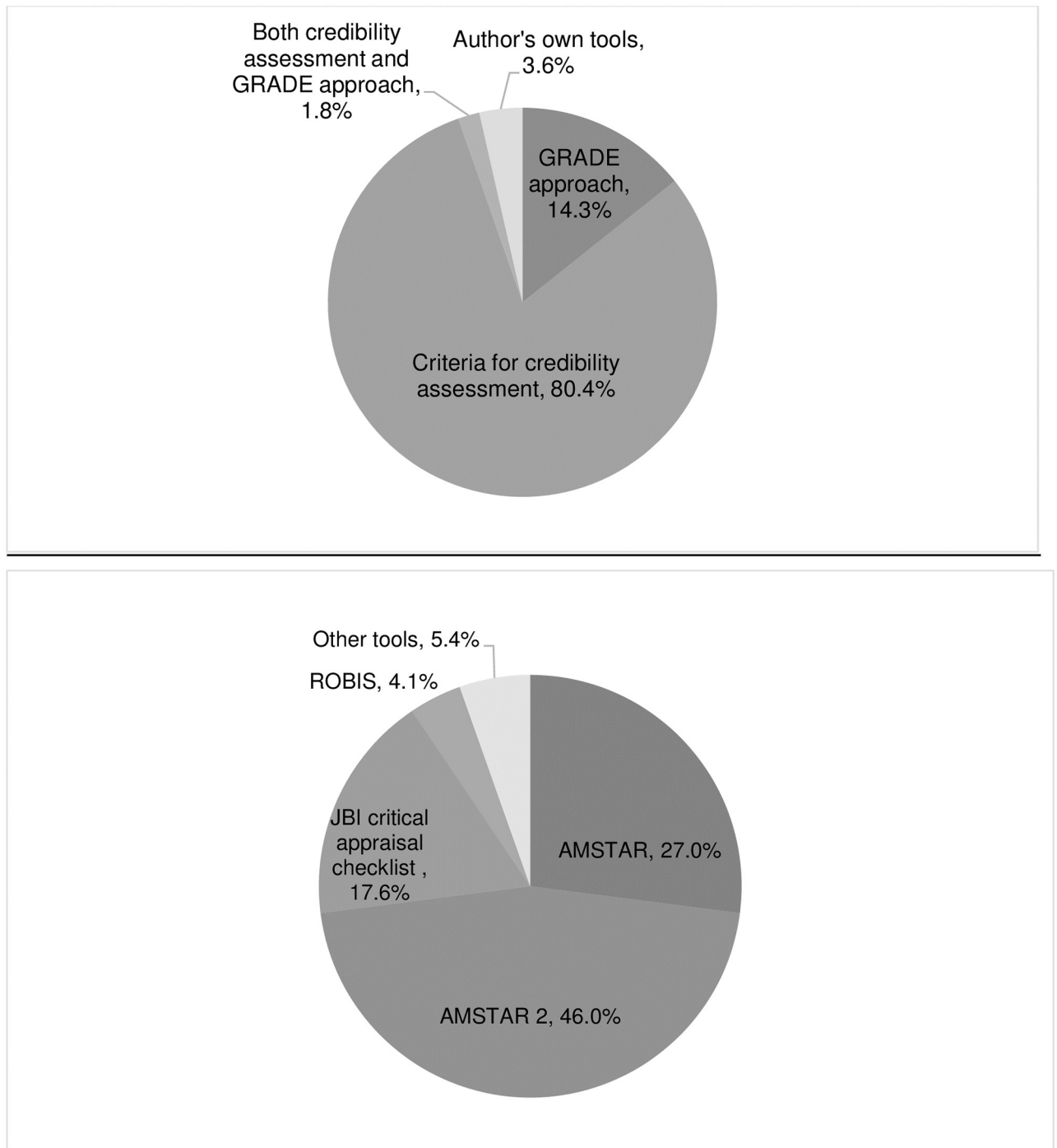


Fig 2. Percent used of methodological approaches for certainty and methodological quality assessment. (A) Methodological approaches for certainty of evidence assessment. (B) Methodological approaches for methodological quality assessment.

<https://doi.org/10.1371/journal.pone.0269009.g002>

intervention studies. Our finding suggested that only nearly half of the included URs assessed certainty of evidence, in which the criteria of credibility assessment was a mainly used tool. URs that were published in high JIFs and high-ranking journals are more likely to assess the certainty of evidence than URs published in lower JIFs and lower-ranking journals. Nearly

Table 2. Certainty and methodological quality assessment in included URs.

Study characteristics	Assessment	P-value
1. Performed a certainty assessment		
1.1 Classified by the median of impact factor		
Published in Higher impact journals (JIF > 4.45)	37/48 (77.1%)	<0.05 ^a
Published in Lower impact journals (JIF ≤ 4.45)	19/51 (37.3%)	
1.2 Classified by ranking of journal		
Published in higher impact group (top 100 ranking)	5/7 (71.4%)	0.70 ^b
Published in lower impact journals	51/92 (55.4%)	
1.3 Classified by year of publication		
2010–2016	6/9 (66.7%)	0.73 ^b
2017–2021	50/90 (55.6%)	
2. Performed a methodological quality assessment		
2.1 Classified by the median of impact factor		
Published in Higher impact journals (JIF > 4.45)	35/48 (72.9%)	0.69 ^a
Published in Lower impact journals (JIF ≤ 4.45)	39/51 (74.6%)	
2.2 Classified by ranking of journal		
Published in higher impact group (top 100 ranking)	5/7 (71.4%)	0.99 ^b
Published in lower impact journals	69/92 (75%)	
2.3 Classified by year of publication		
2010–2016	3/9 (33.3%)	<0.05 ^b
2017–2021	71/90 (78.9%)	

^a Chi-square test,

^b Fisher's exact test.

<https://doi.org/10.1371/journal.pone.0269009.t002>

80% of the URs performed a methodological quality assessment and the AMSTAR 2 was the most frequently used tool for this process.

URs were increasingly published over the last decade to compile evidence and provide broad pictures of information from SR-MAs [2]. URs of epidemiological investigations and non-interventional studies also help in establish evidence linking exposure to the incidence of certain health condition in a population. Consequently, these studies are expected to play a key role in gauging the burden of diseases, understand the risk or protective factors, delineating guidelines for prevention as well as streamlining the treatment development process [3, 4]. The certainty of the evidence from these URs, which is the extent of confidence to support a decision or recommendations, may further be used as supportive evidence in develop clinical practice guidelines and recommendations. High certainty in evidence means that the investigators are very confident that the effect they found across studies is close to the true effect and vice versa [11]. URs of these studies should aim to provide the highest certainty of evidence to facilitate better health outcomes. Despite the necessity of assessing the certainty of the evidence in URs, there is no consensus that which approach should be the method of choice. Although Aromataris et al.—a methodology working group formed by the JBI (formerly named the URs Working Group)—published the guidance on how to conduct and report an UR [6], the methodology for the certainty assessment was not provided. Hence, we included URs of non-interventional studies in this scoping review to provide information the methodology for the certainty assessment that used these days.

According to our findings, approximately half of the included URs assessed the certainty of evidence, with the criteria of credibility assessment being the most commonly utilized tool. In contrast to the results from a previous study by Hartling et al [1] indicating that described the

Certainty and Methodological quality assessment in published URs

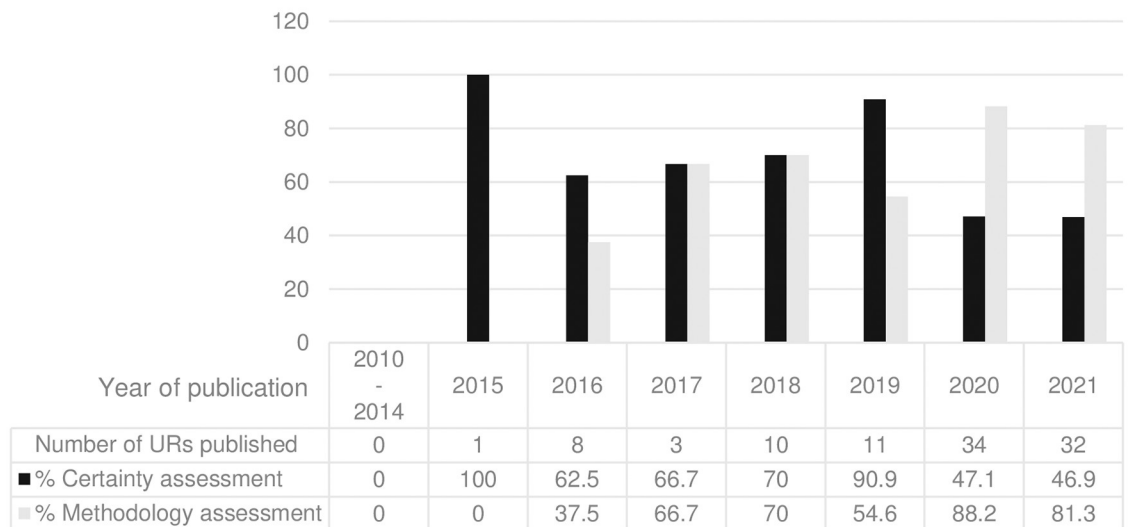


Fig 3. The proportion of studies employing certainty and methodological quality assessment over time.

<https://doi.org/10.1371/journal.pone.0269009.g003>

methodological approaches in overviews of interventions. They indicated that only 16% of the overview of reviews published between 2000 and 2011 assessed the certainty of the evidence and the most frequently used method is the GRADE approach. One of the reasons could be that the GRADE approach is a well-established tool developed to determine the certainty of evidence-based on several factors namely risk of bias, imprecision, indirectness, inconsistency, and publication bias [111]. However, GRADE approach was primarily designed for assessing the quality of the evidence from primary studies. Further guidance is needed to ensure appropriate use and interpretation of the GRADE tool when it is applied to assess the quality of evidence of SRs, instead of primary studies [1]. The other reasons that our study differs from the previous study likely because we specifically considered the URs that included MAs of non-interventions. The criteria for credibility assessment classified the certainty of the evidence according to several statistical criteria, which usually reported in MAs. This method was recently released [6, 112], might be specific to URs of MAs of non-interventions, and was being used more commonly.

Because most researchers generally aspire to publish their research findings in the top journal publishers. We then classified URs that included in our study into high and lower impact groups using journal impact factors (JIFs) to find the impact of methodological approaches on journal publication. The JIFs help reflect several factors such as the high frequency of citations, media promotion of articles and journals, and the increase in speed of the review and publication process [113, 114]. Although JIFs could not be used to reflect the full impact of journals on formal implications, it remains an acceptable objective and quantifiable measure of knowledge dissemination nowadays [113–115]. This study demonstrated that a higher number of URs with a certainty assessment was published in higher impact and higher-ranking journals. One of the reasons could be that the assessment helped to reflect the certainty of results and facilitate the translation of the evidence into guideline recommendations.

When focusing in the URs that published in top-100 ranking journal, criteria for credibility assessment was also the most used method. However, levels of evidence and a series of

Table 3. Details of the criteria of credibility assessment used in umbrella reviews published in the top-100 ranking journals*.

Details of criteria	Criteria for credibility assessment of each study			
	Belbasis L, 2015 [71]	Radua J, 2018 [103]	Kim JY, 2019 [95]	Kim JH, 2020 [30]
1. Number of categories (Label used)	2 Identified associations that had the strongest validity and were not suggestive of bias	5 (Convincing, Highly suggestive, Suggestive, Weak, Not significant)	5 (Convincing, Highly suggestive, Suggestive, Weak, Not significant)	5 (Convincing, Highly suggestive, Suggestive, Weak, Not significant)
2. Details of each category				
2.1 Convincing/class I				
• Number of cases	> 1000	> 1000	> 1000	> 1000
• P-value	fixed-effects and random-effects at $p < 0.05$ and at $p < 0.001$	$P < 10^{-6}$	$P < 10^{-6}$	Random effects $P < 10^{-6}$
• 95% prediction interval excluded null	Used	Used	Used	Used
• Heterogeneity	$I^2 < 50\%$	$I^2 < 50\%$	$I^2 < 50\%$	$I^2 < 50\%$
• No evidence of small-study effects	Used	Used	Used	Used
• No evidence of excess significance bias	Not Used	Not Used	Used	Used
• Retained statistical significance in 10% credibility ceiling	Not Used	Not Used	Used	Used
• Largest study with statistically significant effect	Not Used	Not Used	Used	Used
2.2 Highly suggestive/class II				
• Number of cases	No category	> 1000	> 1000	> 1000
• P-value	No category	$P < 10^{-6}$	$P < 10^{-6}$	Random effects $P < 10^{-6}$
• Largest study with statistically significant effect	No category	Used	Used	Used
2.3 Suggestive/class III				
• Number of cases	No category	> 1000	> 1000	> 1000
• P-value	No category	$P < 10^{-3}$	$P < 10^{-3}$	$P < 10^{-3}$
2.4 Weak/class IV				
• P-value	No category	$P \leq 0.05$	$P \leq 0.05$	$P \leq 0.05$
2.5 Non-significant				
P-value	No category	$P > 0.05$	$P > 0.05$	$P > 0.05$

* Of 7 umbrella reviews published Top-100 ranking journals group that included in this study, 4 studies used the criteria of credibility assessment to assess the certainty of the evidence.

<https://doi.org/10.1371/journal.pone.0269009.t003>

statistical tests in these URs using the arbitrary cut-off values and the cut point of each component in these criteria varied slightly. As shown in Table 3, UR that published earlier start using criteria for credibility assessment to identify associations that had the strongest certainty or not. Then, the URs published later used criteria for credibility assessment to categorize the certainty of evidence into several levels from convincing (the highest level) to weak (the lowest level). Their classification was obtained through strict criteria including number of cases and several statistical parameters. The degree of statistical significance (p-value) was used despite the lack of consensus on what might be and optimal threshold and p-value thresholds might need to be tailored to the specific research setting and even to a specific database [2, 116]. Some URs used $p < 0.05$ or $p < 0.001$, but several URs used the stricter level of $P < 10^{-6}$ to be categorized as the highest certainty of evidence. Several other parameters also have been used including a heterogeneity, predictive interval, and small-study effect test. The excess

significance bias, which evaluates whether the number of observed studies with statistically significant results differs from the expected number of positive studies [117], has also been used to be a criterion in some of the URs. The credibility ceiling is a method to test whether the observational studies can survive the specific level that the likelihood of summary effect being in a specific direction [118]. Two URs that published more recently used the retained statistical significance in 10% credibility ceiling as criteria for convincing class (the highest certainty) likely because this method was published more recently [118, 119]. Moreover, criteria of credibility assessment were generally reproduced following previous URs, where some of the published URs were repeatedly cited [71, 79, 80]. Therefore, our findings highlighted the importance of guidance for assessing the certainty of the evidence in URs to recommend the most appropriate tools to provide standards for those conducting URs.

This study also demonstrated that majority of the included URs performed a methodological quality assessment. This was more frequent than a previous study [1] that reported the assessment of methodological quality in only 37% of the overviews of reviews. One of the reasons could be that this process has been strongly recommended in the methodological guidance for producing URs [2] and has been implemented longer than the certainty assessment. This process is essential to ensure that the methodological quality of SR-MAs that included in URs are adequately assessed and incorporated into the results and conclusions. Besides, we found that the most often used tool for methodological quality assessment changed from the Oxman and Guyatt Overview Quality Assessment Questionnaire (OQAQ) to AMSTAR. The AMSTAR tool has been recommended since 2007 and the revised version-AMSTAR 2 was released in 2016 [12]. Given that the revised tool introduced recently, the method advocated in published guidance have evolved over time and the variation of tool used for methodological quality assessment reported in this study confirms the need for updated guidance for conducting URs. In addition, our findings also highlighted that many of the published URs of non-intervention studies performed the certainty of evidence and/or methodological quality assessments, particularly in the more recent published URs and URs that published in journals with higher impact factor. In the current time, the criteria for credibility assessments is the most commonly used methods for certainty assessment and AMSTAR-2 is the most used methods for methodological quality assessments. These results help emphasize the future researchers to apply these assessments in their studies.

Our study has some limitations. First, the definition of included studies was restricted to URs. This might not cover all types of other kinds of reviews for example- overview of reviews, and review of reviews. Therefore, our findings with regards to terminology used to describe “umbrella reviews” and methods used might not be comprehensive or wholly representative. However, there is no universally accepted technical term for this new type of reviews that summarize or synthesize findings from systematic reviews. The term URs has been used increasingly and studies that describe the methodological approach regarding the URs are sparse to date. Second, this study is confined to only URs of non-intervention studies. The methods used for assessing the certainty of evidence and methodological quality in URs that contained other study designs might be different from our findings and could be extended in future research. Third, our study focused on describing the method used in previously published URs and most of them did not provide the reasons for methods selection. Thus, we could not assess the reasons why each UR used different approaches for assessing the certainty of evidence and methodological quality. Although this study could not endorse which method is the best for the certainty of the evidence assessment in URs, a major strength of our study is that it provides a broad picture of the certainty assessment methods used in URs and the commonly used tools to perform this assessment.

Conclusions

This study revealed that only half of URs that included MAs of non-interventional studies have assessed the certainty of the evidence. The criteria of credibility assessment were the most used method. Moreover, URs that published in higher impact journals assessed the certainty of evidence more than the lower impact group. Therefore, guidance and standards are required to ensure the methodological rigor and consistency of certainty of evidence assessment for URs.

Supporting information

S1 File.
(DOCX)

Acknowledgments

The authors gratefully acknowledge Asst.Prof. Peerawat Jinatongthai for his help on databases searching and search strategy suggestion.

Author Contributions

Conceptualization: Saranrat Sadoyu, Kaniz Afroz Tanni, Nontaporn Punrum, Sobhon Paengtraï, Nai Ming Lai, Ammarin Thakkinstian, Nathorn Chaiyakunapruk.

Data curation: Saranrat Sadoyu, Kaniz Afroz Tanni, Nontaporn Punrum, Sobhon Paengtraï, Nathorn Chaiyakunapruk.

Formal analysis: Saranrat Sadoyu, Kaniz Afroz Tanni, Nontaporn Punrum, Sobhon Paengtraï, Nattiwat Promchit.

Funding acquisition: Nathorn Chaiyakunapruk.

Investigation: Saranrat Sadoyu.

Methodology: Saranrat Sadoyu, Kaniz Afroz Tanni, Warittakorn Kategaew, Nai Ming Lai, Ammarin Thakkinstian, Surachat Ngorsuraches, Mukdarut Bangpan, Nathorn Chaiyakunapruk.

Project administration: Saranrat Sadoyu, Warittakorn Kategaew, Nathorn Chaiyakunapruk.

Resources: Nathorn Chaiyakunapruk.

Software: Nattiwat Promchit.

Supervision: Nai Ming Lai, Ammarin Thakkinstian, Surachat Ngorsuraches, Sajesh Veettil, Nathorn Chaiyakunapruk.

Validation: Warittakorn Kategaew, Ammarin Thakkinstian.

Visualization: Warittakorn Kategaew, Mukdarut Bangpan, Sajesh Veettil, Nathorn Chaiyakunapruk.

Writing – original draft: Saranrat Sadoyu, Kaniz Afroz Tanni, Sobhon Paengtraï, Warittakorn Kategaew, Nattiwat Promchit.

Writing – review & editing: Saranrat Sadoyu, Nai Ming Lai, Ammarin Thakkinstian, Surachat Ngorsuraches, Mukdarut Bangpan, Sajesh Veettil, Nathorn Chaiyakunapruk.

References

1. Hartling L, Chisholm A, Thomson D, Dryden DM. A descriptive analysis of overviews of reviews published between 2000 and 2011. *PLoS One*. 2012; 7(11):e49667. <https://doi.org/10.1371/journal.pone.0049667> PMID: 23166744
2. Fusar-Poli P, Radua J. Ten simple rules for conducting umbrella reviews. *Evidence Based Mental Health*. 2018; 21(3):95–100. <https://doi.org/10.1136/ebmental-2018-300014> PMID: 30006442
3. Mishra D, Vora J. Non interventional drug studies in oncology: Why we need them? Perspectives in clinical research. 2010; 1(4):128–33. <https://doi.org/10.4103/2229-3485.71770> PMID: 21350727
4. Committee on the Analysis of Cancer Risks in Populations near Nuclear Facilities-Phase I, Nuclear, Radiation Studies B, Division on E, Life S, National Research C. Analysis of Cancer Risks in Populations Near Nuclear Facilities: Phase I. Washington (DC): National Academies Press (US) Copyright 2012 by the National Academy of Sciences. All rights reserved.; 2012.
5. Lunny C, Brennan SE, McDonald S, McKenzie JE. Evidence map of studies evaluating methods for conducting, interpreting and reporting overviews of systematic reviews of interventions: rationale and design. *Systematic Reviews*. 2016; 5(1):4. <https://doi.org/10.1186/s13643-015-0178-0> PMID: 26739283
6. Aromataris E, Fernandez R, Godfrey CM, Holly C, Khalil H, Tungpunkom P. Summarizing systematic reviews: methodological development, conduct and reporting of an umbrella review approach. *Int J Evid Based Healthc*. 2015; 13(3):132–40. <https://doi.org/10.1097/XEB.000000000000055> PMID: 26360830
7. Lunny C, Brennan SE, McDonald S, McKenzie JE. Toward a comprehensive evidence map of overview of systematic review methods: paper 2-risk of bias assessment; synthesis, presentation and summary of the findings; and assessment of the certainty of the evidence. *Syst Rev*. 2018; 7(1):159. <https://doi.org/10.1186/s13643-018-0784-8> PMID: 30314530
8. De Freitas L, Goodacre S, O'Hara R, Thokala P, Hariharan S. Interventions to improve patient flow in emergency departments: an umbrella review. *Emerg Med J*. 2018; 35(10):626–37. <https://doi.org/10.1136/emered-2017-207263> PMID: 30093379
9. Papageorgiou PN, Deschner J, Papageorgiou SN. Effectiveness and Adverse Effects of Deep Brain Stimulation: Umbrella Review of Meta-Analyses. *J Neurol Surg A Cent Eur Neurosurg*. 2017; 78(2):180–90. <https://doi.org/10.1055/s-0036-1592158> PMID: 27642815
10. Seifo N, Cassie H, Radford JR, Innes NPT. Silver diamine fluoride for managing carious lesions: an umbrella review. *BMC Oral Health*. 2019; 19(1):145. <https://doi.org/10.1186/s12903-019-0830-5> PMID: 31299955
11. Hossain M. Umbrella Review as an Emerging Approach of Evidence Synthesis in Health Sciences: A Bibliometric Analysis. *SSRN Electronic Journal*. 2020.
12. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, 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. <https://doi.org/10.1136/bmj.j4008> PMID: 28935701
13. Abou Ghayda R, Duck-Young Park D, Lee JY, Kim JY, Lee KH, Hong SH, et al. Body mass index and mortality in patients with cardiovascular disease: an umbrella review of meta-analyses. *Eur Rev Med Pharmacol Sci*. 2021; 25(1):273–86. https://doi.org/10.26355/eurrev_202101_24393 PMID: 33506916
14. Arias-de la Torre J, Puigdomenech E, García X, Valderas JM, Eiroa-Orosa FJ, Fernández-Villa T, et al. Relationship Between Depression and the Use of Mobile Technologies and Social Media Among Adolescents: Umbrella Review. *J Med Internet Res*. 2020; 22(8):e16388. <https://doi.org/10.2196/16388> PMID: 32663157
15. Avşar TS, McLeod H, Jackson L. Health outcomes of smoking during pregnancy and the postpartum period: an umbrella review. *BMC Pregnancy Childbirth*. 2021; 21(1):254. <https://doi.org/10.1186/s12884-021-03729-1> PMID: 33771100
16. Balante J, Broek DVD, White K. How does culture influence work experience in a foreign country? An umbrella review of the cultural challenges faced by internationally educated nurses. *Int J Nurs Stud*. 2021; 118:103930. <https://doi.org/10.1016/j.ijnurstu.2021.103930> PMID: 33819641
17. Bertelsen AS, Florisson S, Aagesen EK, Rosholm J-U, Nielsen LP. Are older adults insufficiently included in clinical trials?-An umbrella review. *Basic and Clinical Pharmacology and Toxicology*. 2021; 128(2):213–23. <https://doi.org/10.1111/bcpt.13536> PMID: 33210799
18. Blume KS, Dietermann K, Kirchner-Heklau U, Winter V, Fleischer S, Kreidl LM, et al. Staffing levels and nursing-sensitive patient outcomes: Umbrella review and qualitative study. *Health Serv Res*. 2021.

19. Bonaccorsi G, Manzi F, Del Riccio M, Setola N, Naldi E, Milani C, et al. Impact of the Built Environment and the Neighborhood in Promoting the Physical Activity and the Healthy Aging in Older People: An Umbrella Review. *Int J Environ Res Public Health*. 2020; 17(17).
20. Bramley P, McArthur K, Blayney A, McCullagh I. Risk factors for postoperative delirium: An umbrella review of systematic reviews. *Int J Surg*. 2021; 93:106063. <https://doi.org/10.1016/j.ijsu.2021.106063> PMID: 34411752
21. Burns CJ, Juberg DR. Cancer and occupational exposure to pesticides: an umbrella review. *Int Arch Occup Environ Health*. 2021; 94(5):945–57. <https://doi.org/10.1007/s00420-020-01638-y> PMID: 33495906
22. Carvalho AF, Solmi M, Sanches M, Machado MO, Stubbs B, Ajnakina O, et al. Evidence-based umbrella review of 162 peripheral biomarkers for major mental disorders. *Transl Psychiatry*. 2020; 10(1):152. <https://doi.org/10.1038/s41398-020-0835-5> PMID: 32424116
23. Fan J, Senthana S, Macpherson RA, Sharpe K, Peters CE, Koehoorn M, et al. An Umbrella Review of the Work and Health Impacts of Working in an Epidemic/Pandemic Environment. *Int J Environ Res Public Health*. 2021; 18(13).
24. Farazi M, Jayedi A, Shab-Bidar S. Dietary inflammatory index and the risk of non-communicable chronic disease and mortality: an umbrella review of meta-analyses of observational studies. *Crit Rev Food Sci Nutr*. 2021:1–10. <https://doi.org/10.1080/10408398.2021.1943646> PMID: 34176394
25. Gatti M, Bianchin M, Raschi E, De Ponti F. Assessing the association between fluoroquinolones and emerging adverse drug reactions raised by regulatory agencies: An umbrella review. *Eur J Intern Med*. 2020; 75:60–70. <https://doi.org/10.1016/j.ejim.2020.01.009> PMID: 31983604
26. Hossain MM, Sultana A, Tasnim S, Fan Q, Ma P, McKyer ELJ, et al. Prevalence of mental disorders among people who are homeless: An umbrella review. *Int J Soc Psychiatry*. 2020; 66(6):528–41. <https://doi.org/10.1177/0020764020924689> PMID: 32460590
27. Iqbal S, Ali S, Ali I. Maternal pesticide exposure and its relation to childhood cancer: an umbrella review of meta-analyses. *Int J Environ Health Res*. 2021:1–19. <https://doi.org/10.1080/09603123.2021.1900550> PMID: 33745400
28. Kelly MM, Griffith PB. The Influence of preterm birth beyond infancy: Umbrella review of outcomes of adolescents and adults born preterm. *J Am Assoc Nurse Pract*. 2020; 32(8):555–62. <https://doi.org/10.1097/JXX.0000000000000248> PMID: 31651585
29. Kelly MM, Griffith PB. Umbrella Review of School Age Health Outcomes of Preterm Birth Survivors. *J Pediatr Health Care*. 2020; 34(5):e59–e76. <https://doi.org/10.1016/j.pedhc.2020.05.007> PMID: 32660808
30. Kim JH, Kim JY, Lee J, Jeong GH, Lee E, Lee S, et al. Environmental risk factors, protective factors, and peripheral biomarkers for ADHD: an umbrella review. *Lancet Psychiatry*. 2020; 7(11):955–70. [https://doi.org/10.1016/S2215-0366\(20\)30312-6](https://doi.org/10.1016/S2215-0366(20)30312-6) PMID: 33069318
31. Kim MS, Kim WJ, Khera AV, Kim JY, Yon DK, Lee SW, et al. Association between adiposity and cardiovascular outcomes: an umbrella review and meta-analysis of observational and Mendelian randomization studies. *Eur Heart J*. 2021; 42(34):3388–403. <https://doi.org/10.1093/eurheartj/ehab454> PMID: 34333589
32. Lee KS, Choi YJ, Cho J, Lee H, Lee H, Park SJ, et al. Environmental and Genetic Risk Factors of Congenital Anomalies: an Umbrella Review of Systematic Reviews and Meta-Analyses. *J Korean Med Sci*. 2021; 36(28):e183. <https://doi.org/10.3346/jkms.2021.36.e183> PMID: 34282604
33. Li W, Pan J, Wei M, Lv Z, Chen S, Qin Y, et al. Non-ocular influence factors for primary glaucoma: an umbrella review of meta-analysis. *Ophthalmic Res*. 2021.
34. Lopez-Leon S, González-Giraldo Y, Wegman-Ostrosky T, Forero DA. Molecular genetics of substance use disorders: An umbrella review. *Neurosci Biobehav Rev*. 2021; 124:358–69. <https://doi.org/10.1016/j.neubiorev.2021.01.019> PMID: 33556390
35. Magnavita N, Chirico F, Garbarino S, Bragazzi NL, Santacroce E, Zaffina S. SARS/MERS/SARS-CoV-2 Outbreaks and Burnout Syndrome among Healthcare Workers. An Umbrella Systematic Review. *Int J Environ Res Public Health*. 2021; 18(8).
36. Solmi M, Dragioti E, Arango C, Radua J, Ostinelli E, Kilic O, et al. Risk and protective factors for mental disorders with onset in childhood/adolescence: An umbrella review of published meta-analyses of observational longitudinal studies. *Neurosci Biobehav Rev*. 2021; 120:565–73. <https://doi.org/10.1016/j.neubiorev.2020.09.002> PMID: 32931804
37. Martinez-Calderon J, Flores-Cortes M, Morales-Asencio JM, Luque-Suarez A. Which Psychological Factors Are Involved in the Onset and/or Persistence of Musculoskeletal Pain? An Umbrella Review of Systematic Reviews and Meta-Analyses of Prospective Cohort Studies. *Clin J Pain*. 2020; 36(8):626–37. <https://doi.org/10.1097/AJP.0000000000000838> PMID: 32379072

38. Mjaess G, Chebel R, Karam A, Moussa I, Pretot D, Abi Tayeh G, et al. Prognostic role of neutrophil-to-lymphocyte ratio (NLR) in urological tumors: an umbrella review of evidence from systematic reviews and meta-analyses. *Acta Oncol.* 2021; 60(6):704–13. <https://doi.org/10.1080/0284186X.2021.1886323> PMID: 33586577
39. Mohammed SH, Habtewold TD, Arero AG, Esmailzadeh A. The state of child nutrition in Ethiopia: an umbrella review of systematic review and meta-analysis reports. *BMC Pediatr.* 2020; 20(1):404. <https://doi.org/10.1186/s12887-020-02301-8> PMID: 32847552
40. Obaid M, Douiri A, Flach C, Prasad V, Marshall I. Can we prevent poststroke cognitive impairment? An umbrella review of risk factors and treatments. *BMJ Open.* 2020; 10(9):e037982. <https://doi.org/10.1136/bmjopen-2020-037982> PMID: 32912953
41. Okoth K, Chandan JS, Marshall T, Thangaratinam S, Thomas GN, Nirantharakumar K, et al. Association between the reproductive health of young women and cardiovascular disease in later life: umbrella review. *Bmj.* 2020; 371:m3502. <https://doi.org/10.1136/bmj.m3502> PMID: 33028606
42. Palmer Kelly E, Paredes AZ, Tsilimigras DI, Hyer JM, Pawlik TM. The role of religion and spirituality in cancer care: An umbrella review of the literature. *Surg Oncol.* 2020:101389. <https://doi.org/10.1016/j.suronc.2020.05.004> PMID: 34103240
43. Paraskevi L, Antigoni S, Kleanthi G. Stress and Anxiety Levels in Couples who Undergo Fertility Treatment: a Review of Systematic Reviews. *Mater Sociomed.* 2021; 33(1):60–4. <https://doi.org/10.5455/msm.2021.33.60-64> PMID: 34012353
44. Pelletier R, Ng K, Alkabbani W, Labib Y, Mourad N, Gamble JM. The association of sodium-glucose cotransporter 2 inhibitors with cancer: An overview of quantitative systematic reviews. *Endocrinol Diabetes Metab.* 2020; 3(3):e00145. <https://doi.org/10.1002/edm2.145> PMID: 32704566
45. Pelletier R, Ng K, Alkabbani W, Labib Y, Mourad N, Gamble JM. Adverse events associated with sodium glucose co-transporter 2 inhibitors: an overview of quantitative systematic reviews. *Ther Adv Drug Saf.* 2021; 12:2042098621989134. <https://doi.org/10.1177/2042098621989134> PMID: 33552467
46. Peruzzi M, Biondi-Zoccai G, Carnevale R, Cavarretta E, Frati G, Versaci F. Vaping Cardiovascular Health Risks: an Updated Umbrella Review. *Curr Emerg Hosp Med Rep.* 2020:1–7. <https://doi.org/10.1007/s40138-020-00219-0> PMID: 32837803
47. Pittara T, Vyrides A, Lamniso D, Giannakou K. Pre-eclampsia and long-term health outcomes for mother and infant: an umbrella review. *Bjog.* 2021; 128(9):1421–30. <https://doi.org/10.1111/1471-0528.16683> PMID: 33638891
48. Poveda-Moral S, Falcó-Pegueroles A, Ballesteros-Silva MP, Bosch-Alcaraz A. Barriers to Advance Care Planning Implementation in Health care: An Umbrella Review with Implications for Evidence-Based Practice. *Worldviews Evid Based Nurs.* 2021.
49. Rahmanian V, Rahmanian K, Jahromi AS, Bokaie S. Seroprevalence of toxoplasma gondii infection: An umbrella review of updated systematic reviews and meta-analyses. *J Family Med Prim Care.* 2020; 9(8):3848–55. https://doi.org/10.4103/jfmpc.jfmpc_753_20 PMID: 33110778
50. Román-Gálvez RM, Martín-Peláez S, Martínez-Galiano JM, Khan KS, Bueno-Cavanillas A. Prevalence of Intimate Partner Violence in Pregnancy: An Umbrella Review. *Int J Environ Res Public Health.* 2021; 18(2). <https://doi.org/10.3390/ijerph18020707> PMID: 33467538
51. Rydzewska E, Dunn K, Cooper SA. Umbrella systematic review of systematic reviews and meta-analyses on comorbid physical conditions in people with autism spectrum disorder. *Br J Psychiatry.* 2021; 218(1):10–9. <https://doi.org/10.1192/bjp.2020.167> PMID: 33161922
52. Sahebi A, Nejati-Zarnaqi B, Moayedi S, Yousefi K, Torres M, Golitaleb M. The prevalence of anxiety and depression among healthcare workers during the COVID-19 pandemic: An umbrella review of meta-analyses. *Prog Neuropsychopharmacol Biol Psychiatry.* 2021; 107:110247. <https://doi.org/10.1016/j.pnpbp.2021.110247> PMID: 33476692
53. Sahle BW, Reavley NJ, Li W, Morgan AJ, Yap MBH, Reupert A, et al. The association between adverse childhood experiences and common mental disorders and suicidality: an umbrella review of systematic reviews and meta-analyses. *Eur Child Adolesc Psychiatry.* 2021.
54. Shams Vahdati S, Ala A, Rahmanpour D, Sadeghi-Hokmabadi E, Tahmasbi F. Neurological manifestations of COVID-19 infection: an umbrella review. *Egypt J Neurol Psychiatr Neurosurg.* 2021; 57(1):113. <https://doi.org/10.1186/s41983-021-00366-5> PMID: 34483649
55. Solmi M, Civardi S, Corti R, Anil J, Demurtas J, Lange S, et al. Risk and protective factors for alcohol and tobacco related disorders: An umbrella review of observational studies. *Neurosci Biobehav Rev.* 2021; 121:20–8. <https://doi.org/10.1016/j.neubiorev.2020.11.010> PMID: 33248149
56. Solmi M, Dragioti E, Croatto G, Radua J, Borgwardt S, Carvalho AF, et al. Risk and protective factors for cannabis, cocaine, and opioid use disorders: An umbrella review of meta-analyses of observational

- studies. *Neurosci Biobehav Rev.* 2021; 126:243–51. <https://doi.org/10.1016/j.neubiorev.2021.03.014> PMID: 33737104
57. Solmi M, Radua J, Stubbs B, Ricca V, Moretti D, Busatta D, et al. Risk factors for eating disorders: an umbrella review of published meta-analyses. *Braz J Psychiatry.* 2021; 43(3):314–23. <https://doi.org/10.1590/1516-4446-2020-1099> PMID: 32997075
 58. Solmi M, Veronese N, Galvano D, Favaro A, Ostinelli EG, Noventa V, et al. Factors Associated With Loneliness: An Umbrella Review Of Observational Studies. *J Affect Disord.* 2020; 271:131–8. <https://doi.org/10.1016/j.jad.2020.03.075> PMID: 32479308
 59. Thang Le VN, Kim JG, Yang YM, Lee DW. Risk Factors for Early Childhood Caries: An Umbrella Review. *Pediatr Dent.* 2021; 43(3):176–94. PMID: 34172110
 60. Townsend R, Sileo FG, Allotey J, Dodds J, Heazell A, Jorgensen L, et al. Prediction of stillbirth: an umbrella review of evaluation of prognostic variables. *Bjog.* 2021; 128(2):238–50. <https://doi.org/10.1111/1471-0528.16510> PMID: 32931648
 61. Trott M, Smith L, Xiao T, Veronese N, Koyanagi A, Jacob L, et al. Hearing impairment and diverse health outcomes: An umbrella review of meta-analyses of observational studies. *Wien Klin Wochenschr.* 2021.
 62. Tsiros MD, Tian EJ, Shultz SP, Olds T, Hills AP, Duff J, et al. Obesity, the new childhood disability? An umbrella review on the association between adiposity and physical function. *Obes Rev.* 2020; 21(12): e13121. <https://doi.org/10.1111/obr.13121> PMID: 32779327
 63. Wang Y, Zhong X, Zhou L, Lu J, Jiang B, Liu C, et al. Prognostic Biomarkers for Pancreatic Ductal Adenocarcinoma: An Umbrella Review. *Front Oncol.* 2020; 10:1466. <https://doi.org/10.3389/fonc.2020.01466> PMID: 33042793
 64. Weir NM, Preston K, Newham R, Bennie M. Development of a primary care pharmacy outcomes framework: An umbrella literature review. *Res Social Adm Pharm.* 2021.
 65. Xia L, Zhao R, Wan Q, Wu Y, Zhou Y, Wang Y, et al. Sarcopenia and adverse health-related outcomes: An umbrella review of meta-analyses of observational studies. *Cancer Med.* 2020; 9(21):7964–78. <https://doi.org/10.1002/cam4.3428> PMID: 32924316
 66. Xu W, He Y, Wang Y, Li X, Young J, Ioannidis JPA, et al. Risk factors and risk prediction models for colorectal cancer metastasis and recurrence: an umbrella review of systematic reviews and meta-analyses of observational studies. *BMC Med.* 2020; 18(1):172. <https://doi.org/10.1186/s12916-020-01618-6> PMID: 32586325
 67. Zhang TN, Wu QJ, Liu YS, Lv JL, Sun H, Chang Q, et al. Environmental Risk Factors and Congenital Heart Disease: An Umbrella Review of 165 Systematic Reviews and Meta-Analyses With More Than 120 Million Participants. *Front Cardiovasc Med.* 2021; 8:640729. <https://doi.org/10.3389/fcvm.2021.640729> PMID: 33791351
 68. Zhang X, Gill D, He Y, Yang T, Li X, Monori G, et al. Non-genetic biomarkers and colorectal cancer risk: Umbrella review and evidence triangulation. *Cancer Med.* 2020; 9(13):4823–35. <https://doi.org/10.1002/cam4.3051> PMID: 32400092
 69. Apóstolo J, Cooke R, Bobrowicz-Campos E, Santana S, Marcucci M, Cano A, et al. Predicting risk and outcomes for frail older adults: an umbrella review of frailty screening tools. *JBI Database System Rev Implement Rep.* 2017; 15(4):1154–208. <https://doi.org/10.11124/JBISRIR-2016-003018> PMID: 28398987
 70. Belbasis L, Bellou V, Evangelou E. Environmental Risk Factors and Amyotrophic Lateral Sclerosis: An Umbrella Review and Critical Assessment of Current Evidence from Systematic Reviews and Meta-Analyses of Observational Studies. *Neuroepidemiology.* 2016; 46(2):96–105. <https://doi.org/10.1159/000443146> PMID: 26731747
 71. Belbasis L, Bellou V, Evangelou E, Ioannidis JP, Tzoulaki I. Environmental risk factors and multiple sclerosis: an umbrella review of systematic reviews and meta-analyses. *Lancet Neurol.* 2015; 14(3):263–73. [https://doi.org/10.1016/S1474-4422\(14\)70267-4](https://doi.org/10.1016/S1474-4422(14)70267-4) PMID: 25662901
 72. Belbasis L, Dosis V, Evangelou E. Elucidating the environmental risk factors for rheumatic diseases: An umbrella review of meta-analyses. *Int J Rheum Dis.* 2018; 21(8):1514–24. <https://doi.org/10.1111/1756-185X.13356> PMID: 30146746
 73. Belbasis L, Köhler CA, Stefanis N, Stubbs B, van Os J, Vieta E, et al. Risk factors and peripheral biomarkers for schizophrenia spectrum disorders: an umbrella review of meta-analyses. *Acta Psychiatr Scand.* 2018; 137(2):88–97. <https://doi.org/10.1111/acps.12847> PMID: 29288491
 74. Belbasis L, Mavrogiannis MC, Emfietzoglou M, Evangelou E. Environmental factors, serum biomarkers and risk of atrial fibrillation: an exposure-wide umbrella review of meta-analyses. *Eur J Epidemiol.* 2020; 35(3):223–39. <https://doi.org/10.1007/s10654-020-00618-3> PMID: 32180061

75. Belbasis L, Savvidou MD, Kanu C, Evangelou E, Tzoulaki I. Birth weight in relation to health and disease in later life: an umbrella review of systematic reviews and meta-analyses. *BMC Med.* 2016; 14(1):147. <https://doi.org/10.1186/s12916-016-0692-5> PMID: 27677312
76. Belbasis L, Stefanaki I, Stratigos AJ, Evangelou E. Non-genetic risk factors for cutaneous melanoma and keratinocyte skin cancers: An umbrella review of meta-analyses. *J Dermatol Sci.* 2016; 84(3):330–9. <https://doi.org/10.1016/j.jdermsci.2016.09.003> PMID: 27663092
77. Bellou V, Belbasis L, Konstantinidis AK, Evangelou E. Elucidating the risk factors for chronic obstructive pulmonary disease: an umbrella review of meta-analyses. *Int J Tuberc Lung Dis.* 2019; 23(1):58–66. <https://doi.org/10.5588/ijtld.18.0228> PMID: 30674376
78. Bellou V, Belbasis L, Tzoulaki I, Evangelou E. Risk factors for type 2 diabetes mellitus: An exposure-wide umbrella review of meta-analyses. *PLoS One.* 2018; 13(3):e0194127. <https://doi.org/10.1371/journal.pone.0194127> PMID: 29558518
79. Bellou V, Belbasis L, Tzoulaki I, Evangelou E, Ioannidis JP. Environmental risk factors and Parkinson's disease: An umbrella review of meta-analyses. *Parkinsonism Relat Disord.* 2016; 23:1–9. <https://doi.org/10.1016/j.parkreldis.2015.12.008> PMID: 26739246
80. Bellou V, Belbasis L, Tzoulaki I, Middleton LT, Ioannidis JPA, Evangelou E. Systematic evaluation of the associations between environmental risk factors and dementia: An umbrella review of systematic reviews and meta-analyses. *Alzheimers Dement.* 2017; 13(4):406–18. <https://doi.org/10.1016/j.jalz.2016.07.152> PMID: 27599208
81. Bortolato B, Köhler CA, Evangelou E, León-Caballero J, Solmi M, Stubbs B, et al. Systematic assessment of environmental risk factors for bipolar disorder: an umbrella review of systematic reviews and meta-analyses. *Bipolar Disord.* 2017; 19(2):84–96. <https://doi.org/10.1111/bdi.12490> PMID: 28470927
82. Bouras E, Karakioulaki M, Bougioukas KI, Aivaliotis M, Tzimagiorgis G, Chourdakis M. Gene promoter methylation and cancer: An umbrella review. *Gene.* 2019; 710:333–40. <https://doi.org/10.1016/j.gene.2019.06.023> PMID: 31202904
83. Campbell JM, Bateman E, Peters M, Bowen JM, Keefe DM, Stephenson MD. Fluoropyrimidine and platinum toxicity pharmacogenetics: an umbrella review of systematic reviews and meta-analyses. *Pharmacogenomics.* 2016; 17(4):435–51. <https://doi.org/10.2217/pgs.15.180> PMID: 26894782
84. Campbell JM, Bateman E, Stephenson MD, Bowen JM, Keefe DM, Peters MD. Methotrexate-induced toxicity pharmacogenetics: an umbrella review of systematic reviews and meta-analyses. *Cancer Chemother Pharmacol.* 2016; 78(1):27–39. <https://doi.org/10.1007/s00280-016-3043-5> PMID: 27142726
85. Campbell JM, Stephenson MD, Bateman E, Peters MD, Keefe DM, Bowen JM. Irinotecan-induced toxicity pharmacogenetics: an umbrella review of systematic reviews and meta-analyses. *Pharmacogenomics J.* 2017; 17(1):21–8. <https://doi.org/10.1038/tpj.2016.58> PMID: 27503581
86. Carvalho AF, Köhler CA, Fernandes BS, Quevedo J, Miskowiak KW, Brunoni AR, et al. Bias in emerging biomarkers for bipolar disorder. *Psychol Med.* 2016; 46(11):2287–97. <https://doi.org/10.1017/S0033291716000957> PMID: 27193198
87. Cupp M, Cariolou M, Tzoulaki I, Evangelos E, Berlanga-Taylor A. Neutrophil counts and cancer prognosis: An umbrella review of systematic reviews and meta-analyses of observational studies. *British Journal of Cancer.* 2018; 119(1):26–7.
88. Fullana MA, Tortella-Feliu M, Fernández de la Cruz L, Chamorro J, Pérez-Vigil A, Ioannidis JPA, et al. Risk and protective factors for anxiety and obsessive-compulsive disorders: an umbrella review of systematic reviews and meta-analyses. *Psychol Med.* 2019; 1–16. <https://doi.org/10.1017/S0033291719001247> PMID: 31172897
89. Giannakou K, Evangelou E, Papatheodorou SI. Genetic and non-genetic risk factors for pre-eclampsia: umbrella review of systematic reviews and meta-analyses of observational studies. *Ultrasound Obstet Gynecol.* 2018; 51(6):720–30. <https://doi.org/10.1002/uog.18959> PMID: 29143991
90. Giannakou K, Evangelou E, Yiallourous P, Christophi CA, Middleton N, Papatheodorou E, et al. Risk factors for gestational diabetes: An umbrella review of meta-analyses of observational studies. *PLoS One.* 2019; 14(4):e0215372. <https://doi.org/10.1371/journal.pone.0215372> PMID: 31002708
91. Grabovac I, Veronese N, Stefanac S, Haider S, Jackson SE, Koyanagi A, et al. Human Immunodeficiency Virus Infection and Diverse Physical Health Outcomes: An Umbrella Review of Meta-analyses of Observational Studies. *Clin Infect Dis.* 2020; 70(9):1809–15. <https://doi.org/10.1093/cid/ciz539> PMID: 31401650
92. Hossain MM, Khan N, Sultana A, Ma P, McKyer ELJ, Ahmed HU, et al. Prevalence of comorbid psychiatric disorders among people with autism spectrum disorder: An umbrella review of systematic reviews and meta-analyses. *Psychiatry Res.* 2020; 287:112922. <https://doi.org/10.1016/j.psychres.2020.112922> PMID: 32203749

93. Hossain MM, Purohit N, Sultana A, Ma P, McKyer ELJ, Ahmed HU. Prevalence of mental disorders in South Asia: An umbrella review of systematic reviews and meta-analyses. *Asian J Psychiatr*. 2020; 51:102041. <https://doi.org/10.1016/j.ajp.2020.102041> PMID: 32315966
94. Hutchens BF, Kearney J. Risk Factors for Postpartum Depression: An Umbrella Review. *J Midwifery Womens Health*. 2020; 65(1):96–108. <https://doi.org/10.1111/jmwh.13067> PMID: 31970924
95. Kim JY, Son MJ, Son CY, Radua J, Eisenhut M, Gressier F, et al. Environmental risk factors and biomarkers for autism spectrum disorder: an umbrella review of the evidence. *Lancet Psychiatry*. 2019; 6(7):590–600. [https://doi.org/10.1016/S2215-0366\(19\)30181-6](https://doi.org/10.1016/S2215-0366(19)30181-6) PMID: 31230684
96. Li L, Tan J, Liu L, Li J, Chen G, Chen M, et al. Association between *H. pylori* infection and health Outcomes: an umbrella review of systematic reviews and meta-analyses. *BMJ Open*. 2020; 10(1): e031951. <https://doi.org/10.1136/bmjopen-2019-031951> PMID: 31924635
97. Lucaroni F, Ciccirella Modica D, Macino M, Palombi L, Abbondanzieri A, Agosti G, et al. Can risk be predicted? An umbrella systematic review of current risk prediction models for cardiovascular diseases, diabetes and hypertension. *BMJ Open*. 2019; 9(12):e030234. <https://doi.org/10.1136/bmjopen-2019-030234> PMID: 31862737
98. Lucaroni F, Morciano L, Rizzo G, F DA, Buonuomo E, Palombi L, et al. Biomarkers for predicting spontaneous preterm birth: an umbrella systematic review. *J Matern Fetal Neonatal Med*. 2018; 31(6):726–34. <https://doi.org/10.1080/14767058.2017.1297404> PMID: 28274163
99. Machado MO, Veronese N, Sanches M, Stubbs B, Koyanagi A, Thompson T, et al. The association of depression and all-cause and cause-specific mortality: an umbrella review of systematic reviews and meta-analyses. *BMC Med*. 2018; 16(1):112. <https://doi.org/10.1186/s12916-018-1101-z> PMID: 30025524
100. O'Sullivan JW, Muntinga T, Grigg S, Ioannidis JPA. Prevalence and outcomes of incidental imaging findings: umbrella review. *Bmj*. 2018; 361:k2387. <https://doi.org/10.1136/bmj.k2387> PMID: 29914908
101. Parreira P, Maher CG, Steffens D, Hancock MJ, Ferreira ML. Risk factors for low back pain and sciatica: an umbrella review. *Spine J*. 2018; 18(9):1715–21. <https://doi.org/10.1016/j.spinee.2018.05.018> PMID: 29792997
102. Piovani D, Danese S, Peyrin-Biroulet L, Nikolopoulos GK, Lytras T, Bonovas S. Environmental Risk Factors for Inflammatory Bowel Diseases: An Umbrella Review of Meta-analyses. *Gastroenterology*. 2019; 157(3):647–59.e4. <https://doi.org/10.1053/j.gastro.2019.04.016> PMID: 31014995
103. Radua J, Ramella-Cravaro V, Ioannidis JPA, Reichenberg A, Phipphothasane N, Amir T, et al. What causes psychosis? An umbrella review of risk and protective factors. *World Psychiatry*. 2018; 17(1):49–66. <https://doi.org/10.1002/wps.20490> PMID: 29352556
104. Raglan O, Kalliala I, Markozannes G, Cividini S, Gunter MJ, Nautiyal J, et al. Risk factors for endometrial cancer: An umbrella review of the literature. *Int J Cancer*. 2019; 145(7):1719–30. <https://doi.org/10.1002/ijc.31961> PMID: 30387875
105. Smith L, Luchini C, Demurtas J, Soysal P, Stubbs B, Hamer M, et al. Telomere length and health outcomes: An umbrella review of systematic reviews and meta-analyses of observational studies. *Ageing Res Rev*. 2019; 51:1–10. <https://doi.org/10.1016/j.arr.2019.02.003> PMID: 30776454
106. Tortella-Feliu M, Fullana MA, Pérez-Vigil A, Torres X, Chamorro J, Littarelli SA, et al. Risk factors for posttraumatic stress disorder: An umbrella review of systematic reviews and meta-analyses. *Neurosci Biobehav Rev*. 2019; 107:154–65. <https://doi.org/10.1016/j.neubiorev.2019.09.013> PMID: 31520677
107. Van Der Burg N, Bakker PR, Van Os J, Van Harten P, Al Hadithy A. The genetics of drug-related movement disorders an umbrella review of meta-analyses. *Schizophrenia Bulletin*. 2018; 44:S295.
108. Veronese N, Demurtas J, Soysal P, Smith L, Torbahn G, Schoene D, et al. Sarcopenia and health-related outcomes: an umbrella review of observational studies. *European Geriatric Medicine*. 2019; 10(6):853–62. <https://doi.org/10.1007/s41999-019-00233-w> PMID: 34652767
109. Yang T, Li X, Montazeri Z, Little J, Farrington SM, Ioannidis JPA, et al. Gene-environment interactions and colorectal cancer risk: An umbrella review of systematic reviews and meta-analyses of observational studies. *Int J Cancer*. 2019; 145(9):2315–29. <https://doi.org/10.1002/ijc.32057> PMID: 30536881
110. Zhou C, Zhong X, Song Y, Shi J, Wu Z, Guo Z, et al. Prognostic Biomarkers for Gastric Cancer: An Umbrella Review of the Evidence. *Front Oncol*. 2019; 9:1321. <https://doi.org/10.3389/fonc.2019.01321> PMID: 31850212
111. Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol*. 2011; 64(4):401–6. <https://doi.org/10.1016/j.jclinepi.2010.07.015> PMID: 21208779
112. Schlesinger S, Schwingshackl L, Neuenschwander M, Barbaresco J. A critical reflection on the grading of the certainty of evidence in umbrella reviews. *Eur J Epidemiol*. 2019; 34(9):889–90. <https://doi.org/10.1007/s10654-019-00531-4> PMID: 31222608

113. Ali MJ. Questioning the Impact of the Impact Factor. A Brief Review and Future Directions. *Semin Ophthalmol*. 2022; 37(1):91–6. <https://doi.org/10.1080/08820538.2021.1922713> PMID: 33969807
114. Rizkallah J, Sin DD. Integrative Approach to Quality Assessment of Medical Journals Using Impact Factor, Eigenfactor, and Article Influence Scores. *PLOS ONE*. 2010; 5(4):e10204. <https://doi.org/10.1371/journal.pone.0010204> PMID: 20419115
115. Saginur M, Fergusson D, Zhang T, Yeates K, Ramsay T, Wells G, et al. Journal impact factor, trial effect size, and methodological quality appear scantily related: a systematic review and meta-analysis. *Systematic Reviews*. 2020; 9(1):53. <https://doi.org/10.1186/s13643-020-01305-w> PMID: 32164791
116. Gianfredi V, Nucci D, Amerio A, Signorelli C, Odone A, Dinu M. What Can We Expect from an Umbrella Review? *Advances in Nutrition*. 2022; 13(2):684–5.
117. Ioannidis JP, Trikalinos TA. An exploratory test for an excess of significant findings. *Clin Trials*. 2007; 4(3):245–53. <https://doi.org/10.1177/1740774507079441> PMID: 17715249
118. Salanti G, Ioannidis JP. Synthesis of observational studies should consider credibility ceilings. *J Clin Epidemiol*. 2009; 62(2):115–22. <https://doi.org/10.1016/j.jclinepi.2008.05.014> PMID: 19131013
119. Papatheodorou SI, Tsilidis KK, Evangelou E, Ioannidis JP. Application of credibility ceilings probes the robustness of meta-analyses of biomarkers and cancer risk. *J Clin Epidemiol*. 2015; 68(2):163–74. <https://doi.org/10.1016/j.jclinepi.2014.09.004> PMID: 25433443