REVIEW ARTICLE

# Guideline for systematic reviews

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Meta-analysis, Preferred Reporting Items for Systematic Review and Meta-analysis, quality of reporting meta-analysis, systematic review

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## Abstract

Systematic reviews and meta-analyses form the basis for evidence-based dentistry. Evidence-based dentistry has become popular in recent years, which utilizes the best available research evidences with clinical experience and patient needs. In the hierarchy of studies, meta-analysis and systematic reviews occupy the highest levels. Systematic reviews and meta-analyses are the essential tools as they help in summarizing different available information reliably so as to draw the conclusion more accurately. A systematic review is the process of searching clinical evidence on a particular topic and selecting quality articles, appraising, and synthesizing to draw conclusion. Conducting a systematic review involves proper methodology as described in the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA).[1] There are some guidelines that should be followed by conducting and reporting systematic reviews. Items are described in sufficient details with clarity somewhere in the text. These guidelines were provided by a group of different review authors, methodologists, and medical editors, etc. The original guidelines for conducting a systematic review were given by QUOROM quality of reporting meta-analysis. After improving QUOROM, a new guideline has been developed as the PRISMA.[1] This is essential for transparent reporting of systematic review so as that one can check its strength and weakness. The potential usefulness is compromised without proper key information. The rationale behind this article is to explain checklist items with appropriate dental example. This would help new researchers in better understanding of the proper methodology to conduct and report systematic reviews. Certain extensions to PRISMA guideline have also been given for improving systematic review such as PRISMA-Equity 2012, PRISMA-IPD, PRISMA-Abstract, and PRISMA-Harm. To visit various extensions of the PRISMA, one can visit http://www.equator-network.org/?post_type=eq_guideline&eq_guideline_study_design=systematic-review-and-meta-analyses&eq_guideline_clinical_specialty=0&eq_guideline.

## Introduction

Systematic review summarizes different researches with the same aim more accurately and reliably. Systematic reviews are not only essential for clinicians for keeping them updated regarding treatment, but also to policymakers to judge risk and benefits of any intervention. In meta-analysis, we combine the results of different independent studies and apply statistical tests. Systematic review may or may not contain meta-analysis. Initially, the entire process was termed meta-analysis. Now, meta-analysis is considered as a component of systematic review. It is not always possible to perform meta-analysis due to clinical, methodological, and statistical differences across individual studies.

Thus, a systematic review is an overview of primary studies of high quality. There are some guidelines that should be followed while writing a systematic review article so as to correctly interpret the result. Systematic review combines information from individual studies, and thus, it has an overall sample size that is greater than that of any other studies and it synthesizes all relevant studies on a specific topic. Systematic review methods can be applied to any type of study – may it be epidemiological or randomized trials or any other type. Meta-analysis is the statistical method to explain and combine the results of studies included in review articles.

The key features of a systematic review involve: (a) Formulating the objective (b) searching different studies

which would fulfill the eligibility criteria; (c) assessing the validity of these included studies by assessing the risk of bias; and (d) presentation of the findings.

Following are the characteristic features of a systematic review as per the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guideline (explained with an appropriate example in Table 1).

## Title

The title of a systematic review should reflect the study design, population under study, and the term systematic review or meta-analysis as the inclusion of the terms in the title improves indexing and identification.

## Abstract

A structured abstract involves summary of all available information, objective of the study, sources from where data are collected, eligibility criteria, number of participants, treatment provided, study details, results, limitations, and conclusions, along with the registration number of the systematic review.

## Introduction

An introduction includes objective of the review along with the statement regarding the necessity of review. It should be brief and should clearly state the aim of the review and questions being addressed with reference population under study such as age of participants, type of study, exposure, control group, and type of study design.

## Methods

*Protocol and registration*

A protocol sets the objective and method for conducting a systematic review article.

The methods for study searching, screening, data extraction, and analysis should be contained in a proper written document to minimize bias before starting the study search. Registration of systematic review helps in reducing the publication bias. The Cochrane collaboration has established the Cochrane-controlled trials register, which contains records of controlled trials. If all trials are registered, the results of all trials (positive as well negative) are available for reporting systematic reviews. This avoids publication bias so that meta-analyses and systematic reviews are not affected adversely. Registration can be done on the following sites:

www.clinicaltrials.gov, www.lib.umi.com/dissertations, and www.controlled-trials.com.

*Inclusion criteria of study*

Eligibility criteria are essential in knowing the validity, applicability, and comprehensiveness of issues. They influence search strategy and then serve to ensure that studies are selected in a systematic and unbiased manner. Strict inclusion and exclusion criteria for studies are recommended. Study eligibility criteria likely to include are the participants under study, interventions, control group, outcomes, and study designs of interest. Inclusion criteria may also be language of publication, publication status whether unpublished material also used or not, and year of publication.

*Information sources (search)*

It requires description of all information sources (databases, platform, or search media, e.g., Ovid, Dialog, and PubMed). The start and end dates of coverage of the search and contact with different study authors should also be described. Interested reader accesses comprehensiveness and completeness of search and may try to duplicate it. Unpublished literature can be searched through various sites such as:

www.clinicaltrials.gov, www.lib.umi.com/dissertations, and www.controlled-trials.com.

*Study selection*

There is no standard process of selecting the studies for systematic review article, yet it should be described. Author records large number of studies from different search engines and includes the relevant study according to the eligibility criteria and excludes the studies that do not meet the eligibility criteria. PRISMA flow diagram is used to describe the selection processes of different studies. Two reviewers independently select the studies. Any disagreement is resolved by general concusses. The views of two investigators reduce the possibility of missing a relevant study.

*Data items and data collection process*

Authors draw information from different selected studies so as to summarize and present evidence of a systematic review. Some authors use data collection form. The data collection forms vary for different systematic reviews. Depending on the particular systematic review, more specific data collection items may need to be extracted for appropriate review. Data items should include the list of all variables, for which data were extracted such as age of participants, severity of disease, method of diagnosis, inclusion and exclusion criteria, duration of treatment, and any assumptions and simplifications made about missing or unclear information.

*Risk of bias in individual studies*

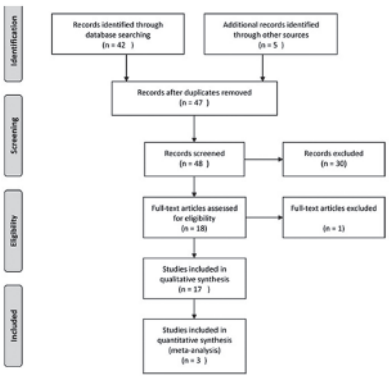
The result of systematic review is closure to the truth if the included studies are valid. The risk of bias in an individual study is assessed by assessing its methodology because the treatment effect reported in any study is true when the study is valid. The methodological characteristics may affect the effect sizes. Hence, it is necessary to describe the method so as to access the risk of bias (whether the results are actual or biased). Validity of a method depends on random allocation sequence, concealment of allocation sequence, blinding (participants, treating doctor, data collector or analyzer, and outcome adjudicators), number of patients lost to follow-up, stopping of trials early for benefits, and whether analysis is followed with intention-to-treat principle or not.

**Table 1:** Relevant example of checklist item

| Check list | Content | Item | Checklist items of PRISMA with relevant example |
|---|---|---|---|
| Title | Title of systemic review article includes term systemic review or meta-analysis, which help in improving article search (identification and indexing). | 1 | Malocclusion, orthodontic treatment, and the oral health impact profile (OHIP-14): Systematic review and meta-analysis.<br>"This title includes both term which is good for identification of this article while searching articles."[6] |
| Abstract | Abstract is structured to include the summary of background, objective, data sources, study eligibility criteria, number of subjects and treatment provided, study appraisal and synthesis methods, results, limitations, and conclusions along with registration number of systematic review. | 2 | **Objectives**: To evaluate the effectiveness of fluoride in preventing white spot lesion (WSL) demineralization during orthodontic treatment and compare all modes of fluoride delivery.<br>**Data Sources**: The search strategy for the review was carried out according to the standard Cochrane systematic review methodology. The following databases were searched for RCTs or CCTs: Cochrane Clinical Trials Register, Cochrane Oral Health Group Specialized Trials Register, MEDLINE, and EMBASE. Inclusion and exclusion criteria were applied when considering studies to be included. Authors of trials were contacted for further data.<br>**Data Selection**: The primary outcome of the review was the presence or absence of WSL by patients at the end of treatment. Secondary outcomes included any quantitative assessment of enamel mineral loss or lesion depth.<br>**Data Extraction**: Six reviewers independently, in duplicate, extracted data, including an assessment of the methodological quality of each trial.<br>**Data Synthesis**: Fifteen trials provided data for this review, although none fulfilled all the methodological quality assessment criteria. One study found that a daily NaF mouthrinse reduced the severity of demineralization surrounding an orthodontic appliance (lesion depth difference −70.0 mm; 95% CI: −118.2 to−21.8 mm). One study found that use of a glass ionomer cement (GIC) for bracket bonding reduced the prevalence of WSL (Peto OR: 0.35; 95% CI: 0.15-0.84) compared with a composite resin. None of the studies fulfilled all the methodological quality assessment criteria.<br>**Conclusions**: There is some evidence that the use of a daily NaF mouthrinse or a GIC for bonding brackets might reduce the occurrence and severity of WSL during orthodontic treatment. More high quality, clinical research is required into the different modes of delivering fluoride to the orthodontic patients.[2] |
| Introduction | Rationale: Introduction includes the rationale for the review in the context of what is already known. | 3 | The most compelling potential advantages attributed to self-ligating brackets are a reduction in overall treatment time and less associated subjective discomfort. Other improvements include more efficient chairside manipulation and promotion of periodontal health due to poorer biohostability. Preliminary retrospective research has pointed to a definite advantage, with a reduction in overall treatment time of 4-7 months and a similar decrease in required appointments. Consequently, the use of SLBs has increased exponentially; over 42% of American practitioners surveyed reported using at least one system in 2008.[9] This figure was just 8.7% in 2002.[3] |
| | Objective | 4 | The purpose of this systematic review is to evaluate the clinically significant effects of SLBs on orthodontic treatment with respect to the quality of scientific evidence and the methodology of those reports.[3] |
| Methods | Protocol and registration | 5 | Protocol is important as it specify the objective and method of systemic review article. Registration of systemic reduces the publication bias. The Cochrane Collaboration has established the Cochrane Controlled Trials Register, which contains the records of controlled trials. |
| | Eligibility criteria | 6 | TABLE 1. Initial Inclusion and Exclusion Criteria for the Retrieved Studies [4]<br>Inclusion Criteria / Exclusion Criteria<br>Human studies / Case reports and case series<br>Primary and early mixed dentition with posterior crossbite / Review articles and abstracts<br>Randomized controlled trials, prospective and retrospective observational studies with concurrent untreated/normal controls / Treatment in late mixed and permanent dentition, adults<br>Clinical trials comparing at least two treatment strategies / Treatment combined with extractions or full-fixed appliances<br>Articles written in English, German, French, and Scandinavian languages / Surgically assisted treatments<br>Anterior crossbite, Angle Class III<br>Cleft lip and/or palate or other craniofacial syndrome diagnosis |

*(Contd...)*

**Table 1:** *(Continued)*

| Check list | Content | Item | Checklist items of PRISMA with relevant example |
|---|---|---|---|
| | Information sources and search strategy | 7, 8 | This systemic review was done to evaluate the clinical differences in relation to the use of self-ligating brackets in orthodontics. The electronic databases that were searched for this review are MEDLINE via OVID (1950 to April 2009; see Appendix), EMBASE (1980 to April 2009), and Cochrane Central Register of Controlled Trials (The Cochrane Library, 2009). Language restrictions were not applied. Unpublished or "gray" literature was searched using ClinicalTrials.gov (www.clinicaltrials.gov) and the National Research Register (www.controlled-trials.com) using the term, "orthodontic and bracket." In addition, Pro-Quest Dissertation Abstracts and Thesis database was searched +++++++. (www.lib.umi.com/dissertations) using "orthodontic*" and "ligat*." Conference proceedings and abstracts were also searched. Authors were contacted to identify unpublished or ongoing clinical trials and to clarify data as required. Reference lists of the included studies were screened for relevant research.[3] |
| | Study selection | 9 (Described in result section as item number) | This systemic review was done to evaluate the clinical differences in relation to the use of self-ligating brackets in orthodontics.<br>Forty-three trials were initially deemed potentially relevant to the review, 42 being derived from MEDLINE via OVID and 1 study from the National Research. Register 11 (www.controlled-trials.com). Following detailed assessment, 13 satisfied the inclusion criteria. One of these was subsequently omitted following retrieval of the full-text article; the remaining 30 studies were also excluded. However, after contacting the authors of published trials, a further five studies were also included. Of the 17 papers selected, 6 were randomized controlled trials.[3]<br>PRISMA flow diagram to summarize study selection processes:<br>  <br> |
| | Data collection process and data items | 10, 11 | This study was done to perform a meta-analysis of the literature concerning the optimal force or range of forces for orthodontic tooth movement. After applying the exclusion criteria, 17 of 161 articles on animal studies and 12 of 305 articles on human studies included in the review.<br>From each study that remained after application of the exclusion criteria, the data were extracted as follows:<br>1. Title description<br>2. Number of experimental conditions<br>3. Number of individuals or sites per experimental condition<br>4. Age or weight of the experimental participants<br>5. Method for measuring tooth movement<br>6. Method for measuring force<br>7. System of force control<br>8. Frequency of reactivation of appliance (if applicable)<br>9. Type of appliance<br>10. Initial force magnitude in cN<br>11. Direction of force<br>12. Type of tooth movement<br>13. Duration of experimental period in weeks.<br>Mean rate of tooth movement over experimental period in mm/wk, etc.[5] |

*(Contd...)*

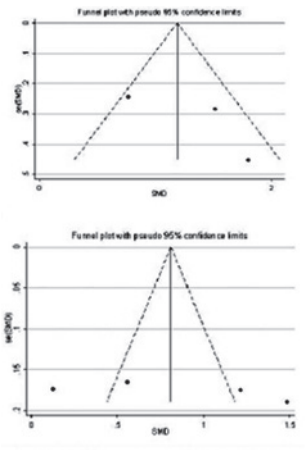
**Table 1:** *(Continued)*

| Check list | Content | Item | Checklist items of PRISMA with relevant example |
|---|---|---|---|
| | Risk of bias in individual studies | 12 (Method of assessing risk of bias described as item number 19) | This systemic review was done to evaluate the clinical differences in relation to the use of self-ligating brackets in orthodontics. Six key methodological criteria were assessed: Sample size calculation, random sequence generation, allocation concealment, reporting of withdrawals, blinding of measurement assessment, and the use of intention-to-treat analysis. An overall assessment of risk of bias (high, medium, and low) was undertaken for each included trial using Cochrane Collaboration criteria. When five or more quality items were met, studies were considered to have a low risk of bias; three or more had medium risk; studies fulfilling less than three criteria were deemed to have a high risk of bias. Only those at low-to-medium risk of bias were to be considered for meta-analysis.[3] |

**Table 2.** Methodological Assessment of Included Trials

| Study | Design | Sample Size Calculation | Random Sequence Generation | Allocation Concealment | Reporting of Withdrawals | ITT | Blinding of Measurement | Risk of Bias |
|---|---|---|---|---|---|---|---|---|
| Pringle et al (2009)[11] | RCT[b] | Yes | Yes | Yes | Yes | No | No | Low |
| Fleming et al (2009)[12] | RCT | Yes | Yes | Yes | Yes | No | Yes | Low |
| Miles et al (2006)[13] | CCT[c] | No | Alternate | No | Yes | No | No | High |
| Scott et al (2008)[14] | RCT[d] | Yes | Yes | Yes | Yes | No | Yes | Low |
| Miles (2005)[15] | CCT | No | Alternate | No | Yes | No | No | High |
| Pandis et al (2007)[16] | CCT | No | Alternate | No | None | – | No | Medium |
| Scott et al (2008)[17] | RCT | n/a[a] | Yes | Yes | Yes | No | No | Low |
| Fleming et al (2009)[18] | RCT | Yes | Yes | Yes | Yes | No | No | Low |
| Pandis et al (2006)[19] | CCT | No | Alternate | No | None | – | No | Medium |
| Pellegrini et al (2009)[20]* | CCT | No | Unclear | Unclear | Yes | No | Yes | Medium |
| Pandis et al (2008)[21] | CCT | Yes | Alternate | No | None | – | Yes | Medium |

| | | | |
|---|---|---|---|
| | Summary measures | 13 | "A meta-analysis was performed using the metan command in Stata version 11.2 (StataCorp, College Station, Tex). As the studies selected in this analysis were carried out in different countries and populations, between-study variations were assumed *a priori*. Hence, random effect models were used in the meta-analysis, which takes into account both within- and between-study variations in effect sizes."[6] |
| | Synthesis of results | 14 | A meta-analysis was performed using the metan command in Stata version 11.2. As the studies selected in this analysis were carried out in different countries and populations, between-study variations were assumed *a priori*. Hence, random effect models were used in the meta-analysis, which takes into account both within- and between-study variations in effect sizes. To test whether there was more heterogeneity in the data than the chance, Q test was used. The heterogeneity measure I2 was also calculated to measure the percentage of heterogeneity in the data.[6] |
| | Risk of bias across studies | 15 (Describe it in result as item number 22) | Funnel plots are used to assess the publication bias visually" (A funnel plot is a graph designed to check for the existence of publication bias; funnel plots are commonly used in systematic reviews and meta-analyses. In the absence of publication bias, it assumes that the largest studies will be plotted near the average, and smaller studies will be spread evenly on both sides of the average, creating a roughly funnel-shaped distribution. Deviation from this shape can indicate publication bias). |




An example funnel plot, each dot represents a study; the y-axis represents the size of the study (e.g., number of experimental subjects) and the x-axis shows the study's result.[6]

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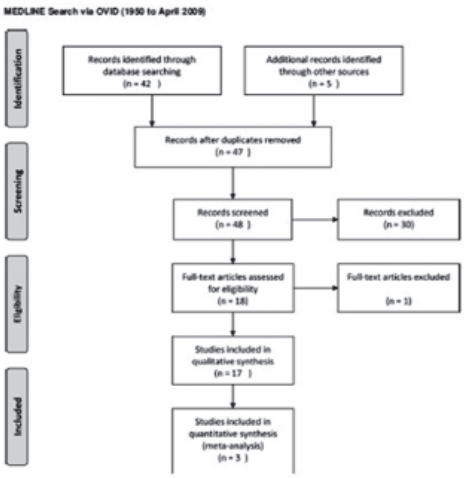
**Table 1:** *(Continued)*

| Check list | Content | Item | Checklist items of PRISMA with relevant example |
|---|---|---|---|
| | Additional analysis | 16 (describe in result as item number 23) | Interventions for accelerating orthodontic tooth movement: A systematic review<br>Hu Long[a]; Ujjwal Pyakurel[a]; Yan Wang[b]; Lina Liao[a]; Yang Zhou[a]; Wenli Lai[c]<br>Sensitivity analysis was done to test the robustness of the synthetic results in meta-analysis.[7] |
| Results | Study selection | 17 | Self-ligating brackets in orthodontics: A systematic review<br>Padhraig S. Fleming[a]; Ama Johal[b]<br>Forty-three trials were initially deemed potentially relevant to the review, 42 being derived from MEDLINE via OVID and 1 study from the National Research.<br>Register 11 (www.controlled-trials.com). Following detailed assessment, 13 satisfied the inclusion criteria. One of these was subsequently omitted following retrieval of the full-text article; the remaining 30 studies were also excluded. However, after we contacted the authors of published trials, a further five studies were included. Of the 17 papers selected, 6 were randomized controlled trials.[3] |
| | | |  |
| | Study characteristics | 18 | All 25 studies were observational and were organized into three groups according to the type of comparisons made: (1) 11 studies (9-19) comparing groups with and without malocclusion/orthodontic treatment need (independent groups design), (2) 10 studies (20-29) comparing the same group of individuals before and after treatment (labeled as pre-post design), and (3) four studies (30-33) comparing an orthodontically treated group with an independent group requiring treatment (treated-untreated) groups' design.[6] |
| | | | **Table 1.** Characteristics of the Studies on the Association of Malocclusion and Its Associated Treatment With OHIP-14[a,b]<br>Author, y | Study Design[a] | Sample Characteristics | Exposure[b] | Outcome | Statistical Analysis[c] | Main Findings<br>Anosike et al. (2010)[18] | Type 1 | 805 Schoolchildren, Nigeria, 12–16 y | DAI | Prevalence | Chi-square | No association<br>Bernabé et al. (2008)[9] | Type 1 | 200 Schoolchildren, UK, 16–17 y | DAI, IOTN | Mean (SD), prevalence | Nonparametric | Differences in total score and prevalence by DAI but not IOTN<br>Caglayan et al. (2009)[17] | Type 1 | 1090 Patients, Turkey, 18+ y | Complaints | Median | Nonparametric | Orthodontic/aesthetic patients had higher total scores than controls<br>de Oliveira and Sheiham (2003)[19] | Type 1 | 1675 Schoolchildren, Brazil, 15–16 y | IOTN | Prevalence | Logistic regression | Prevalence of impacts increased with IOTN severity<br>Freijman et al. (2013)[16] | Type 1 | 68 Patients, Brazil, 27.6 y | Class II/III malocclusion | Median | Nonparametric | Higher total score in patients with malocclusion<br>Hassan and Amin (2010)[14] | Type 1 | 366 Patients, Egypt, 21–25 y | IOTN | Prevalence | Chi-square | Higher prevalence as IOTN severity increased but not in all domains |
| | Risk of bias within studies | 19 (see item number 12) | Refer to item number 12. |

*(Contd...)*

**Table 1:** *(Continued)*

| Check list | Content | Item | Checklist items of PRISMA with relevant example |
|---|---|---|---|
| | Results of individual studies | 20 | Forest plot is the graphical display of results of meta-analysis. Results of individual study are presented with effect estimates and confidence intervals, ideally with a forest plot. Forest plots are commonly presented with two columns-left-hand column names of the studies in chronological order from the top downward, right-hand column-plot of the measure of effect, for example, an odds ratio has confidence intervals represented by horizontal lines. Area of each square is proportional to the study's weight in the meta-analysis. Overall, meta-analyzed measure of effect is often represented on the plot as a dashed vertical line. This meta-analyzed measure of effect is commonly plotted as a diamond, the lateral points of which indicate confidence intervals for this estimate.[7] |
| | Synthesis of results | 21 | Among the studies that used OHIP-14, only a few used the same type and details of reporting. Only eight of the 25 studies included in the review (32%) provided information on the OHIP-14 mean and standard deviation as well as the sample size of the groups compared, namely, three of the 11 using the pre-post design, four of the 10 using the independent groups design, and one of the four using the treated-untreated groups' design. The three and four studies in the first and second study designs were amenable to meta-analysis. The remaining 18 studies were excluded from the meta-analysis. The contribution of each study to the meta-analysis is given as a percentage of weight. For the four studies that used the pre-post study design, the standardized mean difference (SMD) was 1.29 (95% CI: 0.67-1.92), indicating that the OHIP-14 score decreased after treatment. Similarly, for the three studies that used the independent groups study design, the SMD was 0.84 (95% CI: 0.25-1.43), indicating that people without malocclusion had lower OHIP-14 scores compared with their counterparts. The mean SMD score was significantly different from 0 in both cases ($P$<0.001 and 0.005, respectively). The studies involved in each meta-analysis were heterogeneous, and the heterogeneity was statistically significant (($P$<0.047 and, 0.001) for the first and second meta-analysis, respectively). The variations in SMD measured as a percentage were 67.2% (pre-post study design) and 91.6% (independent group study design). The between-study variance was 0.20 and 0.34 for the pre-post and independent-group study designs, respectively.[6] |
| | Risk of bias across study | 22 | See item number 15. |
| | Additional analysis: Give results of additional analysis if done | 23 (refer item number 16) | "The sensitivity analysis indicated that the omission of any of the studies led to a new estimate of 0.81 (95% CI: 0.25-1.43) that findings varied widely between the populations and countries where the primary studies were conducted." Sensitivity analyses are used to explore the degree to which the main findings of a systematic review are affected by changes in its methods or in the data used from individual studies (e.g., study inclusion criteria, results of risk of bias assessment.[6] |

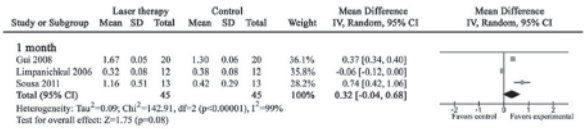



**Table 2.** Sensitivity Analysis for the Meta-Analysis of Studies Comparing Groups With and Without Malocclusion (Independent Groups Study Design)

| Study Omitted | Estimate | 95% Confidence Interval |
|---|---|---|
| Bernabé et al. (2008)[9] | 1.04 | 0.84 to 1.24 |
| Sutinen et al. (2007)[11] | 0.91 | 0.71 to 1.11 |
| Masood et al. (2013)[10] | 0.68 | 0.48 to 0.87 |
| Lee et al. (2007)[19] | 0.63 | 0.43 to 0.82 |
| Combined | 0.81 | 0.64 to 0.98 |

*(Contd...)*

**Table 1:** *(Continued)*

| Check list | Content | Item | Checklist items of PRISMA with relevant example |
|---|---|---|---|
| Discussion | Summary of evidence | 24 | Authors should summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health-care providers, users, and policymakers).<br>"This review has found some evidence that a daily sodium fluoride mouthrinse will reduce the severity of demineralization associated with orthodontic appliances and that GIC used for bonding reduces the incidence and severity of WSL compared with a composite resin.<br>However, considering the widespread use of fluoride products during orthodontic treatment, there is little evidence as to which method or combination of methods to deliver the fluoride is the most effective for orthodontic patients.[2] |
| | Limitations | 25 | Discuss the limitations at study and outcome level (e.g., risk of bias) and at review level (e.g., incomplete retrieval of identified research, reporting bias).<br>"In the quality analysis, 6 of the 22 studies were judged to be of medium/high quality [Table 4]. Four of these 6 articles were RCTs. The reason for a medium/high quality score instead of a high score is that these studies had some methodological limitations.<br>• The article by O'Brien *et al.* gave no statistical analysis for the mandibular skeletal changes.<br>• The RCTs by Jakobsson, Nelson *et al*., and Tulloch *et al*., did not use blinding in measuring the cephalometric parameters.<br>• On the other hand, 2 CCTs were judged to be of medium/high quality, whereas most CCTs were judged to be of medium quality.[8] |
| | Conclusion: Conclusion should be realistic and not too optimistic in the context of other evidence and give idea for future research | 26 | "Titanium TSADs do offer direct structural and functional anchorage according to the Branemark's definitions. Future research should target specific issues by using well-controlled experimental models."<br>"Titanium skeletal anchorage device offers direct structural and functional anchorage even with a level of osteointegretion as low as 5%. Future research about optimum loading for stability is required for different specific issues with well-controlled experimental design."[9] |
| Funding | | 27 | Author should describe the sources of funding or other support (e.g., supply of data) for the systematic review; role of funders for the systematic review. |

PRISMA: Preferred Reporting Items for Systematic Review and Meta-analysis

*Summary measures*

When planning a systematic review, it is advised that author should pre-specify the outcome measure. Most common summary measures are the risk ratio, odds ratio, and risk difference for binary outcomes. For continuous outcomes, we measure difference in means.

*Planned methods of analysis*

The data gathered from the studies are analyzed to decide whether meta-analysis can be performed or not. In case of heterogeneity between included studies, meta-analysis cannot be performed. If it is included, the authors should mention the effect measure (e.g., relative risk or mean difference). The statistical consideration is most technical and evidence-based. For combining data in a meta-analysis, two types of statistical models are used commonly: (1) Fixed effects model (common treatment effect for all included studies) (2) Random effects model (variation of effects across studies).

*Risk of bias across studies*

Publication bias may distort meta-analysis and systematic reviews because these reviews rely on a large number of studies. Publication bias is caused by the fact that results showing significant findings are published and the results that are negative are not published. Thus, studies with significant results do not appear to be superior with respect to the quality of design. To avoid publication bias, registration of trials is done, and thus, studies with unfavorable results are also available to be included and are not withheld from publication.

Authors should examine results from the available studies for missing studies (publication bias) or missing data in the included studies (selective reporting bias). Bias toward reporting significant results despite the fact that number of studies with negative results are higher is known as publication bias.

There are certain other analysis (sensitivity analysis, subgroup analysis, meta-regression analysis, etc.), which are applied depending on the aim of review.

## Results

*Study selection*

Authors should give the total numbers of studies screened along with that the information of whether they are selected or rejected with reason of their acceptance or rejection with a flow diagram.

*Study characteristics*

This helps in knowing the validity and applicability of a systematic review. Authors should provide a source of information of the included studies. Authors should describe sufficient details of different included studies to make their own judgment. Author should not assume any information that is missing in the study (e.g., sample size and method of randomization).

The PICOS framework (population, intervention, comparator, outcome, and study design) is useful in reporting the clinical characteristics, disease, methods of the intervention, and of the comparison group.

*Risk of bias within studies*

Assessment of the risk of bias of included studies can be performed using any standard approach. For example - Cochrane collaboration's criteria for assessing the risk of bias.

*Results of individual studies and its synthesis*

Authors should give unadjusted estimates and confounder-adjusted estimates and their precision (e.g., 95% confidence interval) in individual studies. Make clear which confounders were adjusted for and why they were included. For continuous outcomes, the mean, standard deviation, and sample size for each group are described. To know time-to-event ratio, the authors should determine the log hazard ratio (it is the limits of the number of event per unit time divided by the number of risk, as the time interval approach zero) and standard error for included study.

The main result of the review should be presented at first. If meta-analyses are done, confidence intervals and measures of consistency are included. Meta-analysis is neither always indicated nor feasible because of clinical heterogeneity between studies with regard to populations, interventions, or form of outcome assessment. If meta-analysis was not performed, possible explanation should be given for not performing meta-analysis, and inferences should be presented systematically.

*Additional analyses*

Additional analyses such as sensitivity analysis, subgroup analysis, and meta-regression (if done) should be reported, whether the result is statistically significant or not, to avoid selective outcome reporting bias within the review.

## Discussion

*Summary of evidence and limitations*

Authors should explain the main findings for each outcome along with their pertinence to key groups (e.g., health-care providers, users, and policymakers). While interpreting results, one should keep in mind that statistical significant results may not be necessary clinically significant and thus, may not suggest clinical or policy relevance. Similarly, statistically non-significant results may not indicate that a treatment is ineffective. Authors should also discuss the limitations of the study such as risk of bias and reporting bias. Publication bias might account for the effects observed. Asymmetric funnel plot suggests the selective reporting, which cause the overestimation of effect size. Limitation addresses validity (risk of bias) and reporting or information of the included study, limitation of review process, and generalizability and reliability of review. Limitation of review process includes: (a) Limitation of the search restricting to few search engines (b) Any other particular language publication (English only).

## Conclusion

Authors should give a brief and balanced statement on findings of the review. Drawing conclusion should be realistic and should not be too optimistic. If conclusion is not drawn because of insufficient number of reliable study or because of uncertainty, it should be declared in the study. Such a finding can be as important as finding consistent effects from several large studies. Authors should also make explicit recommendations for further research. Systematic reviews have capability for guiding future clinical research.

*Funding*

Authors should describe the role of funding source and role of funder in the study design, collection of data, analysis, interpretation of data, or writing of report, etc., with transparency in systematic review. Whether they accept the responsibility of content or not should be mentioned. Sometimes, funding will be provided by ICMR, CDC center, or the department of science and technology.

*PRISMA extensions*

Certain extensions to PRISMA guidelines have been proposed for improving systematic review, such as PRISMA-Equity 2012. Healthy equity refers to study and cause of difference and quality of health and health care across different populations. Hence, equity refers to the absence of disparity in controllable or remedial aspect of health. Inequity implies some kind of social injustice. PRISMA extension provides structured guidance on transparently reporting the methods and results and to legitimize and emphasize the importance of reporting health equity.[10]

Despite published guidance on writing the abstract in the PRISMA statement, there is a poor reporting of abstracts. Hence, an extension to the PRISMA statement for good reporting of abstracts is developed.[11]

Another extension called PRISMA-individual participants data (IPD), which includes integrity of IPD (in method and result), for explanation of variation in effect is developed.[12]

PRISMA-Harm has also been developed as an extension to PRISMA to improve reporting and to encourage a balance statement of benefits and harms of different interventions, for example, length of follow-up of treatment, measurement of any associated risk factor, etc.[13]

Traditionally, meta-analyses have compared only two interventions at a time. Hence, another extension of the PRISMA

statement was developed specifically to improve the reporting of systematic reviews, which incorporated network meta-analysis that allows comparisons between more than two interventions. Five new items were added in this extension (32-item PRISMA extension checklist).[14]

PRISMA guidelines are developed to reduce flaws and to improve the clarity and transparency in reviews. Here, we have provided a brief step-by-step explanation of the principles for all the items of PRISMA guidelines. This review paper provides a brief, simple, step-by-step guideline, which will help researchers to conduct systematic reviews.

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