©Operative Dentistry, 2018, **43-4,** E191-E209

Do Nanofilled/Nanohybrid Composites Allow for Better Clinical Performance of Direct Restorations Than Traditional Microhybrid Composites? A Systematic Review

D Angerame • M De Biasi

Clinical Relevance

The effectiveness of direct restorations performed with nanofilled/nanohybrid composites was similar to that obtainable with traditional microhybrid composites. The weight of the available evidence supports the free choice in the clinical setting between these two classes of restorative materials.

SUMMARY

This systematic review was carried out to assess the clinical effectiveness of nanofilled and nanohybrid composites used for direct restorations in comparison with microhybrid composites. The guidelines for the preferred reporting items for systematic reviews and meta-analyses were followed. A search of articles published from July 1996 to February 2017 was performed in PubMed, SciVerse Scopus, Latin American and Caribbean Health Sciences, the Scientific Electronic Library Online, and the Cochrane Library. The present review selected only randomized controlled trials comparing the clinical performance of a nanofilled or nanohybrid composite for direct restorations with that of a microhybrid composite. The research found 201 studies. Twenty-one articles fulfilled the criteria of the present review. However, the included studies were characterized by great methodological diversities. As a general trend, nanofilled and nanohybrid composites were found to be capable of clinical performance, marginal quality, and resistance to wear similar to that of traditional composites without showing improved surface characteristics. The risk of bias of included studies was judged unclear or high. The clinical performance of nanofilled/nanohybrid composites was found to be comparable to that of traditional composites in the posterior area. The data concerning anterior and cervical restorations were insufficient. With regard to the esthetic properties, there is a compelling

Daniele Angerame, MD, DDS, University Clinical Department of Medical, Surgical and Health Sciences, University of Trieste, Trieste, Italy

*Matteo De Biasi, DDS, MS, PhD, University Clinical Department of Medical, Surgical and Health Sciences, University of Trieste, Trieste, Italy

*Corresponding author: Piazza Ospedale 1, Trieste, I-34125 Italy; e-mail: teiodebiasi@gmail.com

DOI: 10.2341/17-212-L

need for studies on anterior teeth in which the operators are kept unaware of the restorative material. Nanofilled/nanohybrid composites seem to be a valid alternative to traditional microhybrid composites, and at the moment, there is low-level evidence attesting a lack of their superiority.

INTRODUCTION

Among the several resin-based materials used for direct dental restorations, manufacturers offer a wide array of composites suitable for anterior and posterior teeth. These materials greatly differ from each other in terms of characteristics of their inorganic filler, which is known to influence the viscosity and handling of the material,[1] as well as its physical properties,[2,3] hence affecting the clinical performance of the restoration.[4,5] The composite strength is maximized when a substantial amount of evenly dispersed filler particles is embedded in the resin matrix.[6] Even if in a manner that lacks consistency in the plethora of dental literature, resin-based composites are usually classified according to their filler characteristics, such as chemical composition, shape, and especially particle size.[7]

By following the general belief that composites with smaller filler particles prevent the wear of the resin matrix and minimize the surface alteration deriving from the particles' detachment,[8] several new filler formulations have been proposed. Specifically, the evolution of filler has recently turned to the fabrication of nanofilled and nanohybrid composites, which are regarded as the state of the art in terms of filler formulation.[7] The size of the filler is surely one of the main determining factors for the most clinically relevant surface properties, such as smoothness and gloss.[9,10]

Despite the endeavor of the manufacturers that produce nanofilled and nanohybrid composites to grant better initial surface smoothness and provide superior gloss retention, doubt still remains as to whether the clinician should prefer these new-generation materials over traditional universal microhybrid composites.[11] A systematic review of *in vitro* studies assessing the difference in surface characteristics between composites with nano- or submicron-sized fillers and conventional composites concluded that, currently, there is insufficient evidence attesting the superiority of nanofilled or submicron materials in terms of surface smoothness and gloss.[11] However, laboratory investigations are very abundant in the literature, and this inevitably implies huge methodological variability. The comparisons among materials or findings of different studies are frequently impeded by differences in the materials being tested, as well as in the qualitative and quantitative assessment methods of surface characteristics. In light of the aforementioned drawbacks, the reliability of the clinical implications deriving from the information gathered in *in vitro* studies might be questionable.

To delineate evidence-based guidelines for the update and the practice of the clinician involved in restorative dentistry,[12,13] the aim of this systematic review was to assess the effectiveness of nanofilled and nanohybrid composite resins by selecting randomized clinical trials (RCTs) that compare these materials with traditional composite resins in the middle and long term. The primary outcome measure was the annual failure rate (AFR). The secondary outcome measures were the United States Public Health Service (USPHS) criteria for Clinical Evaluation of Restorations scores, the marginal quality, and the resistance to surface wear.

The present review followed the criteria of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses, the PRISMA statement (http://prisma-statement.org/).[14]

METHODS AND MATERIALS

Search Methods for Identification of Studies

Each phase of the review was carried out by two calibrated reviewers acting independently, who discussed the cases of disagreement to reach a consensual decision.

The inclusion criteria chosen to consider the trials for the present review are RCTs considering patients who received direct tooth restoration with a nanofilled/nanohybrid composite compared with a traditional one. The following databases were searched for relevant studies: PubMed, SciVerse Scopus, Latin American and Caribbean Health Sciences (LILACS), The Scientific Electronic Library Online (SciELO), and the Cochrane Library. Records from July 1996 to February 2017 were included. There was no restriction in terms of language. The details of the database consultation process are reported in Table 1.

Additional manual research of eligible articles was carried out by searching 1) related citations of selected articles via the PubMed dedicated function, 2) the references of the included articles, and 3) the articles published during the past 10 years in the following scientific journals, which were regarded authoritative because of the topics they treat and their impact factor: *Journal of Dental Research*,

Table 1: *Research Algorithms Used for Each Electronic Database*

Database	Web Address	Algorithm
PubMed	http://www.ncbi.nlm.nih.gov	((((nanocomposite) OR nanofilled) OR nanohybrid) OR submicron) AND clinical trial
SciVerse Scopus	http://www.scopus.com	(TITLE-ABS-KEY(((nanocomposite) OR (nanofilled) OR (nanohybrid) OR (submicron)) AND (clinical trial)))
LILACS	http://lilacs.bvsalud.org/en	(nanocomposite or nanofilled or nanohybrid or submicron) AND (clinical trial)
SciELO	http://www.scielo.org	(nanocomposite or nanofilled or nanohybrid or submicron) AND (clinical trial)
Cochrane Library	http://www.thecochranelibrary.com	(nanocomposite or nanofilled or nanohybrid or submicron) AND (clinical trial)

Dental Materials, *Journal of Dentistry*, and *Clinical Oral Investigations*.

Study Selection

The duplicated records were removed. Then, the two reviewers simultaneously and independently read the title and abstract of the identified articles to select the articles meeting all these criteria:

- Is it an RCT?
- Does it involve the assessment of direct restorations with nanofilled and/or nanohybrid composites?
- Are the failure rate, the USPHS criteria, and the marginal quality or the surface wear evaluated and reported at the end of the follow-up period?

A restoration was deemed a failure according to the criteria adopted in the trials.

To proceed to the screening of eligible articles, the full text was retrieved if all the criteria were met by the article or if the reviewers could not extrapolate sufficient information from the title and abstract.

Data Extraction

The two reviewers independently filled out a previously designed spreadsheet to perform data extraction. From the selected studies, the two reviewers extracted the following information: study design, length of follow-up, restoration type, outcome of interest, type of analysis, characteristics of the sample, operator(s) performing the interventions, field isolation technique, marginal preparation, lining technique, definition of groups and restorative materials, adhesive strategy, polishing protocol, and final recall rate.

For each experimental group, the AFR of the restorations was calculated according to the following formula:

$$AFR = \frac{failed\,restorations}{evaluated\,restorations \cdot years\,of\,follow-up}$$

Moreover, to combine the data of the included studies and compare the failure rate of traditional and nanofilled/nanohybrid composites, the normalized failure index (NFI)[15] was calculated according to the formula

$$NFI = \frac{\sum_i^n (AFR_i \cdot evaluated\,restorations_i)}{\sum_i^n evaluated\,restorations_i}$$

where n is the number of included studies. NFI calculation was performed distinguishing between the following categories: anterior, posterior, or cervical restoration and traditional or nanofilled/nanohybrid composite. If the same research was identified in distinguished papers, the paper with the longest follow-up period was considered for the calculation.

The continuous secondary outcomes were summarized calculating the mean values and 95% confidence intervals.

If the text of the article reported incomplete information about the data of interest, the corresponding author was contacted via e-mail and asked to provide the missing data, as e-mail has been described as the written method that requires the fewer numbers of attempts and the shortest time to obtain unpublished content.[16] To deal with nonreplying authors, a reminder was sent after two weeks. In the case of failure to get in touch with the corresponding author, the data were considered not reported.

Quality Assessment

For the quality assessment of included RCTs, the two reviewers made use of the Cochrane risk of bias tool. The following criteria were taken into consideration:

1. Random sequence generation (protection against selection bias)
   a. Criterion "met": the method used to generate the allocation sequence is described in sufficient detail to allow an assessment of whether it should produce comparable groups.

   b. Criterion "unclear": such information is not reported.
   c. Criterion "unmet": the method used to generate the allocation sequence is not described or inadequate to produce comparable groups.
2. Allocation concealment (protection against selection bias)
   a. Criterion "met": patients' recruitment and assignment were randomized, and the researcher recruiting participants was unaware of the allocation sequence, which was concealed before and until assignment.
   b. Criterion "unclear": such information is not reported.
   c. Criterion "unmet": the allocation schedule was not kept concealed to the researcher recruiting participants.
3. Blinding of participants and personnel (protection against performance bias)
   a. Criterion "met": the participants and the personnel involved in the study were kept blind; alternatively, the impossibility of blinding was deemed noninfluential to determine bias.
   b. Criterion "unclear": such information is not reported.
   c. Criterion "unmet": the participants and the personnel involved in the study were not kept blind.
4. Blinding of outcome assessment (protection against detection bias)
   a. Criterion "met": the researcher assessing the treatment outcomes was kept blind.
   b. Criterion "unclear": such information is not reported.
   c. Criterion "unmet": the researcher was not blind to the outcomes.
5. Incomplete outcome data (protection against attrition bias)
   a. Criterion "met": no dropouts or withdrawals took place, and all outcome data are reported. Alternatively, missing outcome data are evenly distributed among groups and missing for similar reasons.
   b. Criterion "unclear": such information is not reported.
   c. Criterion "unmet": relevant outcome data are not reported and/or missing data are imbalanced in either number or reasons among groups.
6. Selective reporting (protection against reporting bias)
   a. Criterion "met": the study protocol is available, and all of the primary and secondary outcomes that are taken into account in the review have been reported in a prespecified way; if the study protocol is not available, the published reports include all expected outcomes.
   b. Criterion "unclear": such information is not reported.
   c. Criterion "unmet": not all of the prespecified primary outcomes of the study have been reported; one or more primary outcomes are reported but were not prespecified or are reported using measurements, methods, or subsets of the data that were not prespecified.
7. Protection against other bias.
   a. Criterion "met": the study appears to be free of other sources of bias.
   b. Criterion "unclear": insufficient information to assess whether an identified problem will introduce bias.
   c. Criterion "unmet": there is a potential source of bias related to the specific study design used, or the study stopped early due to some data-dependent process or has been claimed to have been fraudulent.

The validity of the studies was established by classifying each one as follows:

1. Low risk of bias: all of the criteria met
2. Moderate risk of bias: one or more criteria unclear; the others met
3. High risk of bias: one or more criteria unmet

Other methodological aspects were taken into consideration and analyzed, namely, the description of sample size calculation (if present) and the clarity of inclusion and exclusion criteria.

RESULTS

Literature Search

The search found 201 studies; the review of the title and abstract caused the exclusion of 173 of them, as shown in Figure 1. Full-text articles were obtained for the remaining 28, which were all in English.

Seven articles were discarded because they did not fulfil the inclusion criteria of the present review. Two studies with the same first author[17,18] were excluded from the review because the authors assessed direct and indirect restorations but did not make use of a control group with a direct traditional restorative material for the comparison with nanofilled/nanohybrid composites. Two studies were excluded because they did not consider a control group with a microhybrid composite: in the study of Karaman and others,[19] the authors com-

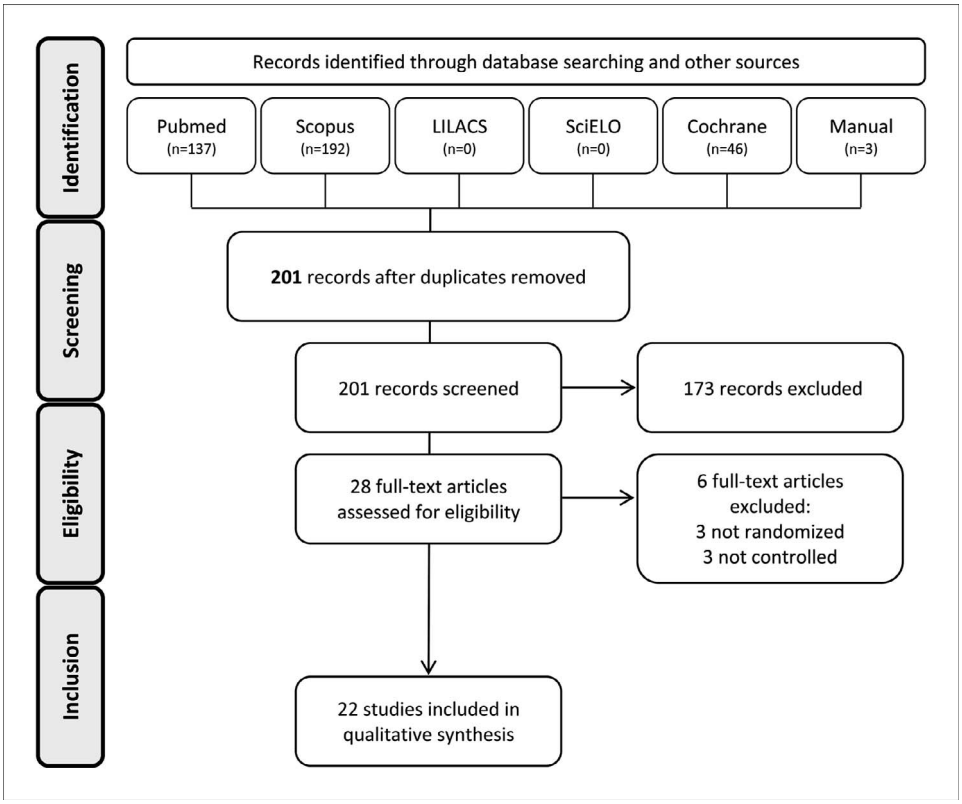

Figure 1. *Flow diagram of study inclusion.*

pared a nanofilled composite with a flowable nanofilled composite, without further control groups; the study of Türkün and Celik[20] used a polyacid modified resin composite (Dyract eXtra, Dentsply, York, PA, USA) as sole control. Three other studies were not randomized.[21-23]

As the selected studies were heterogeneous in terms of several methodological variables and they considered different clinical criteria for analysis, a meta-analysis was not feasible.

Study Characteristics

The data sets arranged in Tables 2, 3, and 4 describe in detail the information obtained from the included studies regarding the primary and secondary outcomes of the present review on anterior, posterior, and cervical restorations, respectively. The oldest study was published in 2006 and the most recent one in 2015. The nationality of the patients involved in the trials and most of the authors were Brazilian (six articles, three trials), German (six articles, two trials), Belgian (four articles, two trials), Swedish (two articles, one trial), Chinese (one article, one trial), Turkish (one article, one trial), and Iranian (one article, one trial). As expected, there was a remarkable variety of materials, techniques, and combination of them across studies. Several of the examined articles are subsequent reports of the same trial. Despite little differences in the determination of groups, all of the included articles had a split-mouth design.

Evaluation Criteria in the Selected Studies

RCTs appraising the clinical performance of nanofilled or nanohybrid composite restorations as primary objective were the clear majority of included studies.[24-32] Clinical evaluation of restored teeth was consistently carried out according to one of the modified versions of the USPHS criteria. Given the intrinsic variation among the different versions and the interpretability of the scores, the concept of failure of a restoration was not uniformly shared among the included articles. The attribution of Charlie or Delta scores corresponded to the most common and consistent events that caused a restoration to be classified as failures, such as lack of retention, secondary decay, bulk restoration fracture, restoration fracture with exposed dentin, and pain. Restorations scored as Bravo according to the USPHS criteria were considered functional and, thus, not failed.

In other articles, the researchers performed indirect analyses on positive replicas of the restored teeth. Some of them focused on the assessment of marginal quality via scanning electron microsco-

Table 2: *Characteristics of the Included Study on Anterior Restorations*

Author and Year	Population and Follow-up Duration	Outcome of Interest and Type of Analysis	Intervention	Polishing Protocol	Comparison	Conclusions	Quality Assessment
Loguercio, 2007[29]	38 Brazilian adult patients, 114 maxillary anterior teeth followed up for one year	Clinical performance assessed by clinical evaluation and USPHS criteria	Class III restorations Two instructed experienced dentists Rubber dam Bevelled buccal enamel of the cavosurface margins Lining with calcium hydroxide (Dycal, Dentsply) and/or glass ionomer cement (Vitrebond, 3M ESPE, St. Paul, MN, USA)	Sof-Lex Pop-On disks (3M ESPE)	MH: Filtek Z250 (3M ESPE), 38 restorations NF: Filtek Supreme (3M ESPE), 38 restorations Microfilled: Durafill VS (Heraeus Kulzer), 38 restorations AS: Clearfil SE Bond (Kuraray) with or without enamel etching in all groups	Excellent immediate and 12-mo color match of the microhybrid composite resin, which was superior to the nanofilled and microfilled composites tested	No detail of the randomization procedure. Quote: "The resin composite used in each cavity was randomly selected before the beginning of the restorative procedure." It is not specified whether the patients were aware of the materials used for each tooth. The operators performing the restorations were not blind. The outcome data obtained with the two different adhesive protocols (with or without enamel etching) is unclearly and insufficiently reported.

Abbreviations: AS, adhesive system; MH, microhybrid; NF, nanofilled; USPHS, United States Public Health Service.

py.[33,34] Another research group took into consideration in different articles the evaluation of the occlusal wear of Class I and II restorations, by three-dimensional laser scanning positive gypsum replicas and observing them with scanning electron microscopy for the analysis of microwear patterns.[35,36]

Main Findings From the Selected Studies

Table 5 reports the mean AFRs, the failure indices (number of evaluated restorations × AFR), and the NFI calculated from the included studies. The data for all the included studies were combined, distinguishing between anterior, posterior, and cervical restorations. There was only one study[29] comparing the clinical performance on anterior teeth of traditional and nanofilled/nanohybrid composites over a period of one year; the NFI for the former was calculated to be 0, with the corresponding value for the latter being 5.26. A larger amount of longer-lasting studies (1 to 10 years of follow-up)[24-28,31,32,35,36] performed the same comparison in the posterior area. The NFI for traditional composites was equal to 1.20, while that of nanofilled/nanohybrid composites was 0.91. With respect to cervical restorations of Class V noncarious lesions, only one study was included in the present review[30]; the NFI for traditional and nanofilled/nanohybrid composites was 0 and 2.68, respectively. A summary of the most relevant findings of each included study is reported below.

The research group of de Andrade and coworkers published four articles[24,33,37,38] on their 54-month trial, designed to compare the clinical effectiveness of Class I restorations made either with a nanofilled or a nanohybrid composite, using a microhybrid composite control group. Their sample was constituted of 41 adolescent patients in a state of poverty. In synthesis, all of the investigated materials led to acceptable clinical performance, even if the authors reported a trend of better surface smoothness associated with the tested nanofilled composite.

The two-year trial by Arhun and others[25] was designed to compare the clinical performance of posterior restorations with a low-shrinkage microhybrid composite with a nanohybrid one in 31 adult patients. The two materials demonstrated similar

and acceptable clinical performance. The authors observed increased surface texture deterioration on the nanohybrid composite restorations.

Dresch and coworkers[26] published an article on the comparison among four materials (a nanofilled, a nanohybrid, a packable, and a microhybrid composite) used for Class I and II restorations in 37 dental students. Presenting recall and success rates of 100%, the authors found no difference among materials. Several methodological characteristics of the study raise questions about the reliability of the data in the article, since clarity and rigor were often lacking, especially in the description of the enrollment phase.

In the two-year trial by Ernst and others,[27] the clinical performance of a nanofilled composite was compared with that of a microhybrid composite for the restoration of Class II cavities. By comparing the outcome of 112 restorations placed by six different dentists in 50 adult patients, the authors concluded that both restorative materials showed acceptable clinical performance (98% success rate) without observing differences between them.

A German research group presented in five different papers[28,34,39-41] the findings of a trial investigating the clinical performance of a microhybrid and a nanofilled composite after 2, 4, 6, 8, and 10 years. A private practitioner placed 68 Class II composite restorations in 30 adult patients. At each reevaluation time point, including the last 10-year recall of 29 of the 30 involved patients, there were no differences in the success rate of all restorations between the two tested materials, with an overall success rate equal to 96.9%. The only reported differences in clinical performance between the control microhybrid composite and the nanofilled composite concerned the worse surface smoothness and color match of the latter (Grandio, Voco GmbH, Indian Land, SC, USA).

Loguercio and others[29] published the only study presenting outcomes that are of interest in the present review specifically focused on anterior teeth. The authors evaluated the clinical performance of a microhybrid, a nanofilled, and a microfilled composite for the restoration of Class III defects in maxillary anterior teeth. Even if after one year of clinical service high success rates were recorded in all groups (95%-100%), the authors reported better scores for the item "color match" in the microhybrid composite group, compared with the other two.

The research group of Palaniappan and others produced four articles that met the inclusion criteria of the present review. These two sets of coupled-articles report the findings at subsequent time points of two distinct trials with a similar setup. The first two articles[35,42] compared the clinical performance and, more specifically, the surface wear of a microhybrid and a nanofilled composite used for the restoration of teeth in the posterior area. Sixteen dental students were involved in the study as patients. The researchers carried out the measurement of surface wear by taking precision impressions of the area of interest of the restored teeth and laser scanning the positive gypsum replicas. The comparisons made after three and five years led to the conclusion that vertical loss in height and volume loss on the restoration surface in the nanofilled group were not significantly different from the microhybrid group. The latter two publications,[36,43] which were conducted with similar aim and methodology, report the three-year and five-year wear data registered on restorations performed with other materials, namely, a microhybrid, a traditional hybrid, and a nanohybrid. The authors concluded that the wear resistance of the three tested materials complies with American Dental Association specification minimum requirements for posterior composite restorations (vertical loss <50 μm/y) and that the nanohybrid composite Tetric EvoCeram showed significantly lower volume loss than the other two materials.

In the study by Qin and others,[30] 116 cervical noncarious lesions on anterior and premolar teeth belonging to 46 adult patients were restored either with a microhybrid or a nanofilled composite and followed up for two years. The authors found that the restorations performed with both investigated materials demonstrated acceptable clinical effectiveness in noncarious cervical lesions without significant differences in their clinical performance.

The 18-month trial by Sadeghi and others[31] compared the clinical performance of Class I restorations received by 35 dental and oral hygiene students. For each patient, a single operator performed one restoration per material type: microhybrid, packable, and nanofilled composite. All materials showed acceptable clinical performance, with 94%-97% success rates; the differences among materials were not significant.

In two different publications reporting the findings of the same trial enrolling 52 patients,[32,44] van Dijken and Pallesen tested the clinical performance of a microhybrid and a nanohybrid composite used in Class II restorations. This 10-year trial reported a remarkably high recall rate (93%). With a success rate higher

Table 3: *Characteristics of the Included Studies on Posterior Restorations*

Author and Year	Population and Follow-up Duration	Outcome of Interest and Type of Analysis	Intervention	Polishing Protocol
de Andrade, 2014[24]	41 destitute Brazilian adolescent students, 123 permanent molars followed up for 4.5 y	Clinical performance assessed by clinical evaluation and USPHS criteria	Class I restorations One operator "absolute isolation of the operative field" Cavities prepared with carbide burs, no details on margin characteristics Lining with glass ionomer cement (Vitrebond, 3M ESPE) in deep cavities	Multi-bladed bur (FG7714F, KG Sorensen, Cotia, Brazil), rubber cups and points (FlexiCups and FlexiPoints, Cosmedent Inc, Chicago, IL, USA), Enamelize Polishing Paste (Cosmedent Inc), diamond felt disk (FGM Produtos Odontologicos, Joinville, Brazil)
Arhun, 2010[25]	31 Turkish patients, 82 posterior teeth followed up for 2 years	Clinical performance assessed by clinical evaluation and USPHS criteria	Class I and II restorations One clinician of the research team Cotton rolls and saliva ejectors No bevelling Lining with calcium hydroxide (Dycal, Dentsply Caulk) for deep cavities	Fine and super fine diamond points (KG Finishing Kit, Karensen Ltd) and rubber polishing kits (Eveflex Polisher, EVE Ernst Vetter GmbH)
Dresch, 2006[26]	37 Brazilian dental students (42 according to the abstract), 148 permanent molars followed up for one year	Clinical performance assessed by clinical evaluation and USPHS criteria	Class I and II restorations Two calibrated operators Rubber dam Cavities prepared with stainless steel burs, no details on margin characteristics Lining with calcium hydroxide (Dycal, Dentsply) and/or glass ionomer cement (Vitrebond, 3M ESPE)	Fine-grit diamond burs (KG Sorensen) and aluminium oxide polishing paste (Kerr, Orange, CA, USA) in rubber cups on the occlusal surfaces
Ernst, 2006[27]	50 German adult patients, 112 posterior teeth followed up for two years	Clinical performance assessed by clinical evaluation and USPHS criteria	Class II restorations Six experienced dentists placing approximately the same number of restorations Rubber dam Margins, quote: "Occlusal and lateral enamel margins and cervical cementum margins received no bevel preparations, except for cervical enamel margins if enough enamel was left." No lining	Flexible discs (Soflex, 3M ESPE), Enhance polishing tips (Dentsply DeTrey), and polishing brushes (Soflex Brush, 3M ESPE)

Table 3: Extended.

Author and Year	Comparison	Conclusions	Quality Assessment
de Andrade, 2014[24]	MH: Filtek Z250 (3M ESPE), 41 restorations NF: Filtek Z350 (3M ESPE), 41 restorations NH: Esthet-X (Dentsply Caulk), 41 restorations AS: Adper Single Bond 2 (3M ESPE) in all groups	The three tested materials showed similar and acceptable clinical performance in Class I restorations after 12 mo of clinical service.	The methods of the randomization procedure are not described. Unclear allocation concealment. Quote: "To ensure randomness, a drawing was held using sealed envelopes, to establish in which group a certain tooth would be placed." The details of the draw are missing (use of a random sequence, sequential numbered envelopes, assignment procedure, etc). The patients were unaware of the restorative material used for each tooth. The operator performing the restorations was not blinded.
Arhun, 2010[25]	Low-shrinkage MH: Quixfil (Dentsply Caulk), 41 restorations; AS: Xeno III (Dentsply Caulk) NH: Grandio (Voco GmbH), 41 restorations; AS: Futurabond NR (Voco GmbH)	Nanohybrid and low-shrinkage posterior composite restorations demonstrated similar and acceptable clinical performance after two years. Increased surface texture deterioration in nanohybrid composite restorations.	Not properly randomized. Quote: "Interference in the randomization procedure within patients was performed to equally distribute materials into some important variables." Quote: "The distribution of materials and tooth locations were randomly determined by tossing a coin." In trials with relatively small samples, simple randomization often results in an allocation sequence leading to groups that differ, by chance, substantially. The patients were unaware of the restorative material used for each tooth. The operator performing the restorations was not blinded. The authors did not report the reasons for the patients lost to follow-up. The statistical unit of the study is unclear, since some patients participated with more than one couple of restorations.
Dresch, 2006[26]	NF: Filtek Supreme (3M ESPE), 37 restorations; AS: Single Bond (3M ESPE) Packable composite: Pyramid (Bisco), 37 restorations; AS: One Step Plus (BISCO) NH: Esthet-X (Dentsply DeTrey), 37 restorations; AS: Prime & Bond NT (Dentsply DeTrey) MH:Tetric Ceram (Ivoclar Vivadent), 37 restorations; AS: Excite (Ivoclar Vivadent)	Excellent one-year clinical performance and no significant difference among materials	Not properly randomized. Quote: "Interference in the randomization procedure within patients was performed to equally distribute materials into some important variables." The randomization is not meant to be adjusted by the researchers. Quote: "Randomization of the materials was performed on each patient by tossing a coin." In trials with relatively small samples and with more than two groups, simple randomization often results in an allocation sequence leading to groups that differ, by chance, substantially. Not mentioned whether the patients or the operator were aware of the composite type used for each restoration. It is not specified in the materials and methods section how many patients were enrolled, so we have no information on withdrawals/dropouts. The study design is unclear and contradictory: the study enrolled patients requiring at least five Class V restorations, but the authors declare also that 148 restorations were placed in 37 patients (148/37 = 4).
Ernst, 2006[27]	MH: Tetric Ceram (Ivoclar), 56 restorations NF: Filtek Supreme (3M ESPE), 56 restorations AS: Scotchbond 1 (3M ESPE) in all groups	Both restorative materials investigated showed acceptable clinical performance; no significant differences were observed between both types of dental composites.	The allocation sequence was not prepared before the start of the trial. The researchers tossed a coin just before performing each pair of restorations to decide the cavity to start with and then the restorative material. The operators performing the restorations and the patients were not blinded.

Table 3: Continued.

Author and Year	Population and Follow-up Duration	Outcome of Interest and Type of Analysis	Intervention	Polishing Protocol
Krämer, 2015[28]	30 German adult patients, 68 posterior teeth followed up for 10 y	Clinical performance assessed by clinical evaluation and USPHS criteria	Class II restorations One dentist in a private practice Rubber dam Cavities finished with a 25-μm diamond bur and not bevelled No lining	Super-fine discs (3M ESPE), polishing brushes (Hawe-Neos Dental), and a fluoride varnish (Elmex Fluid)
Palaniappan, 2011[35]	16 Belgian dental student volunteers, 37 molar teeth followed up for five years	Resistance to wear assessed by 3D laser scanning and scanning electron microscopy analysis of positive replicas of restored teeth	Class I and II restorations Two dentists Rubber dam Enamel margins bevelled with diamond-coated bevel tips (Sonic-Sys, KaVo Company, Orange, CA, USA) Lining with glass ionomer cement (Vitrebond, 3M ESPE) to cover preparations closer than 0.5 mm to the pulp	Diamond composite finishing kit (Komet) and Sof-Lex (3M ESPE) finishing and polishing set
Palaniappan, 2012[36]	15 Belgian dental student volunteers, 49 molar teeth followed up for five years	Resistance to wear assessed by 3D laser scanning and scanning electron microscopy analysis of positive replicas of restored teeth	Class I and II restorations Two dentists Rubber dam Enamel margins bevelled with diamond-coated bevel tips (Sonic-Sys, KaVo Company) Lining with glass ionomer cement (Vitrebond, 3M ESPE) to cover preparations closer than 0.5 mm to the pulp	Sof-Lex discs and strips (3M ESPE), polishing kit (Komet, Rock Hill, SC, USA), Prisma gloss paste on polishing cup (Dentsply), and Prisma gloss extra-fine paste on polishing cup (Dentsply).
Sadeghi, 2010[31]	35 Iranian dental and oral hygiene students, 105 permanent molars followed up for 1.5 y	Clinical performance assessed by clinical evaluation and USPHS criteria	Class I restorations One operator Cotton rolls No enamel bevel No lining	Microfine diamond finishing burs for contouring and removal of excess restorative material, followed by abrasive aluminium oxide disks

Table 3: Continued. Extended.

Author and Year	Comparison	Conclusions	Quality Assessment
Krämer, 2015[28]	MH: Filtek Z250 (3M ESPE), 32 restorations; AS: Adper Single Bond 2 (3M ESPE) NF: Grandio (Voco GmbH), 36 restorations; AS: Solobond M (Voco GmbH)	After 10 y, Grandio showed worse surface smoothness and color match.	No detail of the randomization procedure is reported. Quote: "fillings to be replaced in different quadrants received at least two different restorations in a random decision" Allocation concealment not mentioned. After contacting the authors, they stated that they made used of envelopes without providing further details. It is not specified whether the patients were aware of the materials used for each tooth. The operator performing the restorations was not blind.
Palaniappan, 2011[35]	MH: Z100 (3M ESPE), 19 restorations NF: Filtek Supreme (3M ESPE), 18 restorations AS: Scotchbond Adhesive (3M ESPE) in all groups	Vertical loss in height and volume loss on the restoration surface in the nanofilled group was not significantly different from the microhybrid group at the five-year recall. Generalized vertical loss (mean; 95% CI): MH, 0.870 μm/mo [0.830; 0.910]; NF, 0.925 μm/mo [0.887; 0.963] Generalized volume loss (mean; 95% CI): MH, 0.014 mm^3/mo [0.014; 0.014]; NF, 0.011 mm^3/mo [0.010; 0.011]	The patients were unaware of the materials used for each tooth. The operators performing the restorations were not blind.
Palaniappan, 2012[36]	MH: Gradia Direct Posterior (GC), 16 restorations; AS: UniFil Bond (GC) Traditional hybrid: Tetric Ceram (Ivoclar), 16 restorations; AS: AdheSe (Ivoclar) NH: Tetric EvoCeram (Ivoclar), 17 restorations; AS: AdheSe (Ivoclar)	The wear resistance of the three materials complies with ADA specification of minimum requirements for posterior composite restorations: vertical loss (<50 μm/y). Tetric EvoCeram (NH) showed significantly lower volume loss than the other two materials. Generalized vertical loss (mean; 95% CI): MH, 1.830 μm/mo [1.777; 1.883]; traditional hybrid, 1.411 μm/mo [1.364; 1.458]; NH, 1.401 μm/mo [1.369; 1.433] Generalized volume loss (mean; 95% CI): MH, 0.018 mm^3/mo [0.017; 0.019]; traditional hybrid, 0.017 mm^3/mo [0.016; 0.017]; NH, 0.011 mm^3/mo [0.010; 0.012]	The filling materials were randomized over cavity groups in an unspecified way. After contacting the authors, they stated that they performed a block randomization. No details on allocation concealment. The patients were unaware of the materials used for each tooth. The operators performing the restorations were not blind. It is not specified if the personnel involved in the wear analysis is aware of the materials used for each tooth. After contacting the authors, they stated that the evaluator was kept blind.
Sadeghi, 2010[31]	MH: Point 4 (Kerr), 35 restorations Packable composite: Packable Premise (Kerr), 35 restorations NF: Nanofilled Premise (Kerr) AS: OptiBond Solo Plus (Kerr) in all groups	Acceptable clinical performance, no significant difference among materials	No detail of the randomization procedure is reported. Quote: "Three cavities of each patient were randomly restored with three types of light-cured resin composites." No details on allocation concealment. It is not specified whether the operators were aware of the materials used for each tooth. The patients were kept blind. All the restorations are performed in a single increment, but this is usually not advisable except in the case of extremely small cavities filled with low-shrinkage composites.

Table 3: Continued.

Author and Year	Population and Follow-up Duration	Outcome of Interest and Type of Analysis	Intervention	Polishing Protocol
van Dijken, 2014[32]	52 Swedish adult patients, 122 posterior teeth followed for 10 y	Clinical performance assessed by clinical evaluation and USPHS criteria	Class II restorations One operator (first author) Cotton rolls and suction device No bevels No lining	Enhance finishing system (Dentsply DeTrey) or brownie points (Shofu Co) and proximal finishing strips

Abbreviations: 3D, three dimensional; ADA, American Dental Association; AS, adhesive system; CI, confidence interval; MH, microhybrid; NF, nanofilled; NH, nanohybrid; USPHS United States Public Health Service.

than 80% in both groups, the authors concluded that the two materials did not differ in clinical performance.

Risk of Bias Assessment

The item-by-item analysis of the critical points of the quality assessment of included studies according to the Cochrane Quality Assessment tool is reported and justified in Tables 2, 3, and 4. All the included studies showed some flaws, as most of them were judged at high risk of bias and the remaining four at unclear risk of bias, as synthetically depicted in Figures 2 and 3. More specifically, only a few articles[27,35,36,42,43] properly described an adequate method to generate the allocation sequence, judged capable of producing comparable groups. Further, the issue of allocation concealment has been totally ignored by the included studies, with none of them furnishing information about the procedure for keeping the researcher recruiting participants unaware of the allocation sequence. Also, the risk of performance bias appeared to be relevant in the included studies, because even though the participants involved in the trials were often blind to the restorative material being used, the operative personnel other than the evaluators were never kept blind to the restorative material. The included articles generally fulfilled the criteria to ensure blinding of outcome assessment, selective reporting, and completeness of outcome data, with the exception of two studies, in which a substantial number of dropouts was observed[25] or less than one-fourth of enrolled patients were subjected to the analysis.[33] Sporadic minor sources of study-specific methodological biases were identified and are reported in the relevant sections of Tables 2, 3, and 4.

DISCUSSION

The present review demonstrated that there is low-level evidence attesting the absence of differences between the clinical effectiveness of nanofilled/nanohybrid composites and traditional microhybrid composites. Primary and secondary studies that do not provide significant differences between the treatments being compared are often labeled as *negative*, but it is known that a systematic review that does not find evidence of difference is very different from one that finds evidence of no difference.[45] Indeed, the findings of the present review have some clinical significance, because until a sufficient number of high-quality RCTs are conducted, filling a cavity either with a traditional microhybrid composite or a nanofilled/nanohybrid composite can still be left to the choice of the operator, who can select the material that better matches his or her preferences.

There are, however, some reasons to exercise caution when drawing conclusions from the present review, both in consideration to its primary outcome (AFR) or its secondary outcomes (USPHS scores, marginal quality, and surface wear). It is known that heterogeneity of the data may cause problems when combining the results of a number of studies to provide an overview, for example, with a meta-analysis.[15] Using the NFI is an alternative way to systematically compare results obtained in heterogeneous studies, which weights the sample size and the AFR of the individual studies. Nonetheless, the present review included a reasonable number of studies involving posterior restorations but very few involving cervical and anterior restorations. In these conditions, the mere comparison of NFI values to assess the clinical effectiveness of nanofilled and nanohybrid composite resins can only be indicative in delineating a general trend, until a larger number

Table 3: Continued. Extended.

Author and Year	Comparison	Conclusions	Quality Assessment
van Dijken, 2014[32]	MH: Tetric Ceram (Ivoclar), 61 restorations NH: Tetric EvoCeram (Ivoclar), 61 restorations AS: Excite (Ivoclar) in all groups	No significant difference between the two tested materials	The restorative material was randomly chosen by casting a coin in a split-mouth design. No details on allocation concealment. The patients were unaware of the restorative material used for each tooth. The operator performing the restorations was not blinded. Blinding of outcome is unclear. Quote: "The restorations were evaluated direct after placement (baseline), six months, and then annually during the following six years by the treating dentist. At different recalls, two calibrated dentists without knowledge of earlier assessments evaluated part of the restorations."

of well-conducted RCTs becomes available and a meta-analysis feasible. Although all the trials that fulfilled the inclusion criteria of the present review reported optimistic findings, with overall success rates ranging from 80% to 100% in relation to the length of the follow-up period regardless of the experimental group, none of them were judged at low risk of bias.

As to the risk of bias assessment, there were some criteria that were never met by the included studies. The random sequence generation or the use of a known random sequence is seldom described or appropriate. The included studies often describe the use of simple randomization procedures achieved via coin tossing, but this approach is generally not advisable in trials with fewer than 100 subjects per randomized group.[46] The allocation concealment, which should prevent selection bias in intervention assignment by protecting the allocation sequence before and until assignment and can always be implemented regardless of the study,[47] was never taken into account in the selected articles. In some articles, a certain tooth is assigned to a designated restorative material by means of a draw of envelopes, but the details of the draw organization and management were not described or retrievable. Moreover, it is known that using envelopes is more susceptible to manipulation than other approach-

Table 4: *Characteristics of the Included Study on Cervical Restorations*

Author and Year	Population and Follow-up Duration	Outcome of Interest and Type of Analysis	Intervention	Polishing Protocol	Comparison	Conclusions	Quality Assessment
Quin, 2013[30]	46 Chinese adult patients, 116 teeth (not molars) followed up for two years	Clinical performance assessed by clinical evaluation and USPHS criteria	Class V restorations Two experienced dentists Cotton rolls and retraction cords Quote: "The incisal enamel margins of the cervical lesions were bevelled to 1-mm area with a diamond bur at high speed." No lining	Not specified extra-fine diamond point	MH: Clearfil AP-X (Kuraray), 58 restorations; AS: Clearfil SE Bond (Kuraray) NF: Filtek Z350 (3M ESPE), 58 restorations; AS: Adper Prompt (3M ESPE)	Both the Clearfil AP-X and Filtek Z350 restorations demonstrated acceptable clinical effectiveness in noncarious cervical lesions without significant differences in their clinical performance.	No detail of the randomization procedure is reported. Quote: "Each patient received at least one pair of restorations that were randomly allocated." No details on allocation concealment. It is not specified whether the patients or the operators were aware of the materials used for each tooth.

Abbreviations: AS, adhesive system; MH, microhybrid; NF, nanofilled; USPHS, United States Public Health Service.

Table 5: *Comparison Between Failure Rate of Restoration With Traditional and Nanofilled/Nanohybrid Composites*

Site	Composite Material	Study	Study Duration, y	No. of Evaluated Restorations	No. of Restorations Reported as Having Failed	Mean Annual Failure Rate, %	Failure Index (No. of Restorations × Mean Annual Failure Rate)	Normalized Failure Index
Anterior	Traditional	Loguercio, 2007[29]	1	38	0	0	0	
		Total		38			0	0
	Nanofilled/ nanohybrid	Loguercio, 2007[29]	1	38	2	5.3	200.0	
		Total		38			200.0	5.26
Posterior	Traditional	de Andrade, 2014[24]	4.5	31	2	1.4	44.4	
		Arhun, 2010[25]	2	35	2	2.9	100.0	
		Dresch, 2006[26]	1	37	0	0	0	
		Ernst, 2006[27]	2	56	1	0.9	50.0	
		Krämer, 2015[28]	10	32	1	0.3	10.0	
		Palaniappan, 2011[35]	5	19	0	0	0	
		Palaniappan, 2012[36]	5	16	0	0	0	
		Sadeghi, 2010[31]	1.5	35	1	1.9	66.7	
		van Dijken, 2014[32]	10	57	11	1.9	110.0	
		Total		318			381.1	1.20
	Nanofilled/ nanohybrid	de Andrade, 2014[24]	4.5	62	3	1.1	66.7	
		Arhun, 2010[25]	2	35	1	1.4	50.0	
		Dresch, 2006[26]	1	74	0	0	0	
		Ernst, 2006[27]	2	56	1	0.9	50.0	
		Krämer, 2015[28]	10	36	1	0.3	10.0	
		Palaniappan, 2011[35]	5	18	0	0	0	
		Palaniappan, 2012[36]	5	17	0	0	0	
		Sadeghi, 2010[31]	1.5	35	1	1.9	66.7	
		van Dijken, 2014[32]	10	57	11	1.9	110	
		Total		390			353.4	0.91
Cervical	Traditional	Qin, 2013[30]	2	58	0	0	0	
		Total		58			0	0
	Nanofilled/ nanohybrid	Qin, 2013[30]	2	56	3	2.7	150.0	
		Total		56			150.0	2.68

es.[48] The last main flaw that threatens the reliability of the findings of the included studies is the risk of performance bias deriving from defective blinding of participants and personnel. Most studies claimed to be "double-blind," specifically reporting that the patients were unaware of the restorative materials being used on each tooth. Only a few studies did not report this information; however, the blinding of patients is likely to have an impact only on the subjective outcomes (such as postoperative sensitivity) and not on those assessed by the evaluators. What is really noteworthy is that the operator performing the restorations was almost never kept blind to the restorative materials in use; in the other cases, these details were not specified at all, despite the recommendations in the CONSORT Statement to be explicit.[49] The lack of blinding, in this case, would probably introduce bias, as the operators placing the restorations could have differentiated their behavior when using different materials, especially whether strong beliefs or prejudices exist among operators. For future investigations, the blinding would be feasible with little effort, for instance by removing the producers' labels from the bottles and syringes and creating a standard reference color scale for shade choice, by preparing dedicated molds of known dimensions.

There are numerous other sources of variability capable of affecting the results reported in the included studies. In fact, it is known that the material can be a secondary factor for the determination of the prognosis of a restoration.[5] First, the characteristics of the participants involved in the study are likely to play a major role in determining the success of an adhesive restoration. In the selected studies, the samples varied hugely in terms

of age, culture, social status, wealth, dietary habits, quality of oral hygiene, and so forth; for example, one trial was conducted on Brazilian adolescents living in the suburbs (some of whom were without adequate supply of food),[24] another one on German adult patients of a private practitioner,[41] and other ones on dental students.[26,31] This probably reflects the different aims of the researchers, who wanted to test the performance of the materials in the most controlled conditions or, on the contrary, in the worst possible scenario. It is difficult to comprehend the complex interaction of the multitude of these elements and appraise their relevance since the studies included in the present review involved a relatively small number of patients.

It can be safely assumed that the USPHS criteria are the most widespread and used method to score the performance of tooth-colored restorative materials. One way to deal with ordinal data to produce a meta-analysis is binarization, meaning that some scores were to be considered acceptable and, hence, a clinical success, while the others unacceptable and, thus, restoration failure. This process can be strongly influenced by the arbitrary decision of both authors and reviewers and also because several modifications of the USPHS criteria exist and are further adapted by the authors of primary research. Some versions of the USPHS criteria include the variant of Cvar and Ryge,[50] the adaptation of Wilson and others,[51] and the color-match modification of Reusens and others.[52] The use of these multiple versions of the criteria is undesirable because it hinders the summary of the findings of different studies. Even if the evaluators are trained and calibrated, they always make a subjective estimate of the parameters of interest, and there is no guarantee of agreement among evaluators of different trials. This is particularly relevant when the different versions of the scoring system do not share the same amount of rating steps, with some scales contemplating four scores (from Alpha to Delta) and other ones three (from Alpha to Charlie) for the same parameter. Although, at the moment, no better evaluation methods have been proposed to overcome the problems relative to the subjectivity of the appraisal, the reliability of the rating of some items of the evaluation can be easily questioned. Specifically, a substantial difference in opinions is likely to arise when distinguishing among the scores relative to color match and surface roughness; these intrinsically subjective parameters were the most relevant outcomes of interest in the present review. Moreover, there are some methodological details that can

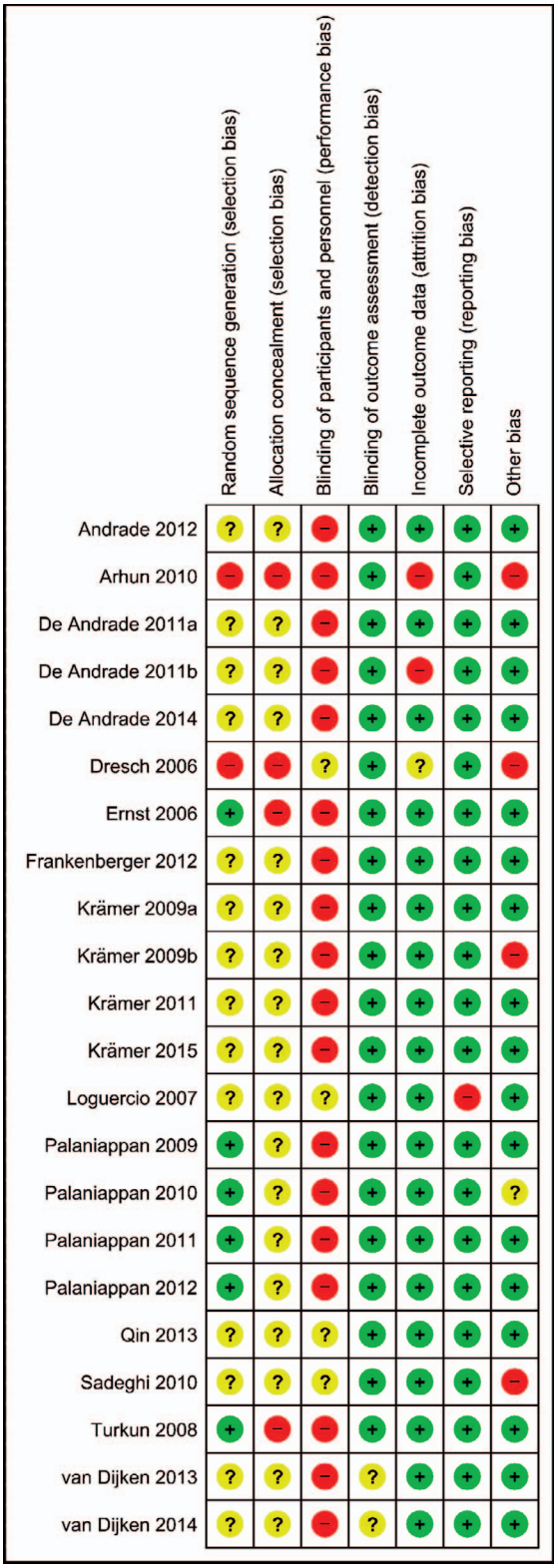

Figure 2. *Risk of bias summary: review authors' judgments about each risk of bias item for each included study.*

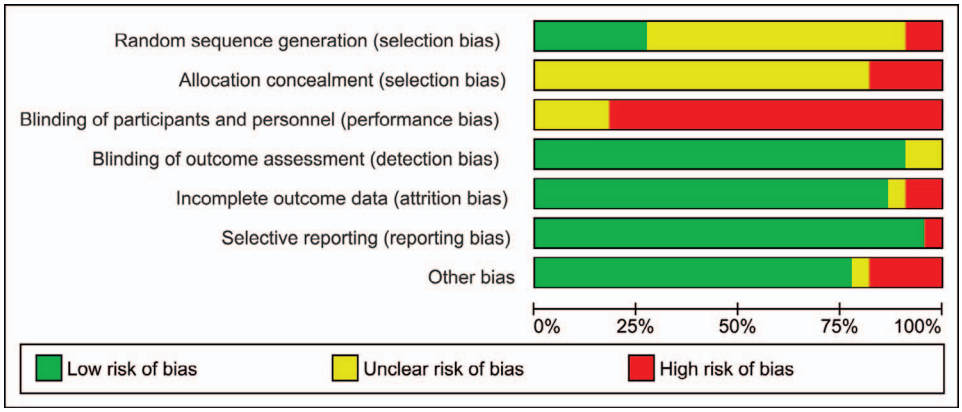

Figure 3. *Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.*

alter the scores of the USPHS criteria. Examples that support this statement are reported in Table 6.

It is hard to delineate robust evidence in favor of or against the use of nanofilled/nanohybrid composites, also because they belong to a class of materials with numerous commercial products. Furthermore, there is still debate and a certain extent of confusion about the classification of composite resins,[7] since the distinction between the different classes of materials can be vague and the attribution of a particular composite resin to a single class arduous. Because of the low quality of the evidence found in the present review, it was not possible to carry out any meta-analysis.

One of the limitations of the present review is that it might not have been sensitive enough to locate all the RCTs published on the clinical performance of nanofilled/nanohybrid composites in comparison to that of microhybrid composites. In fact, it can happen that the words *nanocomposites*, *nanofilled*, *nanohybrid*, or *submicron* do not appear in the title or in the abstract of the article. In the case of trials referring to the materials only with brand names, the probability of the trial to be missed is high; hence, the use of descriptive words that attribute the material to a specific class should be encouraged.

Table 6: *Factors Other Than the Restorative Material That Could Affect the Evaluation of the Clinical Performance of the Restorations Placed in the Included Studies*

Methodological Item	USPHS Criteria Being Affected
Marginal preparation	Marginal adaptation
	Marginal discoloration
	Color match
	Secondary caries
Field isolation	Secondary caries
	Postoperative sensitivity
Lining	Postoperative sensitivity
Adhesive system	Marginal discoloration
	Color match
	Secondary caries
	Postoperative sensitivity
Polishing protocol	Anatomic form
	Color match
	Surface roughness
	Secondary caries

Abbreviation: USPHS, United States Public Health Service.

Even if, nowadays, patients are demanding tooth-colored restorations with optimal esthetic properties in the posterior teeth, the most relevant area of the mouth from an esthetic point of view is undoubtedly the anterior area, especially in the maxilla. It is disappointing that a sole trial[29] among those that fulfilled the inclusion criteria of the present review was specifically designed to address the issue of the potential benefits of the use of nanofilled composite for Class III restoration of teeth in the esthetic area. The assessment of the hypothetical benefits of nanofilled/nanohybrid materials (ie, possible improved surface luster and prolonged gloss retention) would be particularly useful in this area of the mouth because it is the most esthetically relevant. Nevertheless, the authors reported that the hybrid control composite resin showed an immediate and 12-month color match that was superior to the nanofilled and microfilled composites tested. On the other hand, the nanofilled and microfilled composites obtained the best surface appearance after six months.

CONCLUSIONS

The present review assessed that there are several RCTs attesting that in the posterior area, nanofilled and nanohybrid composites are capable of satisfactory clinical effectiveness, which was similar to that of microhybrid composites. No substantial trend of

improved surface characteristics, marginal quality, or resistance to wear associated with nanofilled or nanohybrid composites emerged. Data concerning cervical and anterior restorations were extremely scarce.

Considering that the risk of bias was deemed to be unclear or high, the reader should interpret the findings of the present review with caution. The need should be stressed for further well-conducted long-term RCTs comparing nanofilled/nanohybrid composite resins with traditional ones, aiming at decreasing the risk of selection and performance bias.

At this time, the choice of restorative material between nanofilled/nanohybrid and microhybrid composite continues to be up to the clinician performing the restoration.

Disclaimer

This study was conducted in accordance with all the provisions of the local human subjects oversight committee guidelines and policies of the University of Trieste, in Trieste, Italy.

Conflict of Interest

The Authors of this article certify that they have no proprietary, financial, or other personal interest of any nature or kind in any product, service, and/or company that is presented in this article.

(Accepted 24 October 2017)

REFERENCES

1. Kaleem M, Satterthwaite JD, & Watts DC (2009) Effect of filler particle size and morphology on force/work parameters for stickiness of unset resin-composites *Dental Materials* **25(12)** 1585-1592, http://dx.doi.org/10.1016/j.dental.2009.08.002.
2. Karabela MM, & Sideridou ID (2011) Synthesis and study of properties of dental resin composites with different nanosilica particles size *Dental Materials* **27(8)** 825-835, http://dx.doi.org/10.1016/j.dental.2011.04.008.
3. Goncalves F, Kawano Y, & Braga RR (2010) Contraction stress related to composite inorganic content *Dental Materials* **26(7)** 704-709, http://dx.doi.org/10.1016/j.dental.2010.03.015.
4. Da Rosa Rodolpho PA, Donassollo TA, Cenci MS, Loguercio AD, Moraes RR, Bronkhorst EM, Opdam NJ, & Demarco FF (2011) 22-Year clinical evaluation of the performance of two posterior composites with different filler characteristics *Dental Materials* **27(10)** 955-963, http://dx.doi.org/10.1016/j.dental.2011.06.001.
5. Demarco FF, Correa MB, Cenci MS, Moraes RR, & Opdam NJ (2012) Longevity of posterior composite restorations: not only a matter of materials *Dental Materials* **28(1)** 87-101, http://dx.doi.org/10.1016/j.dental.2011.09.003.
6. Kahler B, Kotousov A, & Swain MV (2008) On the design of dental resin-based composites: a micromechanical approach *Acta Biomaterialia* **4(1)** 165-172, http://dx.doi.org/10.1016/j.actbio.2007.06.011.
7. Ferracane JL (2011) Resin composite—state of the art *Dental Materials* **27(1)** 29-38, http://dx.doi.org/10.1016/j.dental.2010.10.020.
8. Scougall-Vilchis RJ, Hotta Y, Hotta M, Idono T, & Yamamoto K (2009) Examination of composite resins with electron microscopy, microhardness tester and energy dispersive X-ray microanalyzer *Dental Materials Journal* **28(1)** 102-112.
9. Cavalcante LM, Masouras K, Watts DC, Pimenta LA, & Silikas N (2009) Effect of nanofillers' size on surface properties after toothbrush abrasion *American Journal of Dentistry* **22(1)** 60-64.
10. Heintze SD, Forjanic M, Ohmiti K, & Rousson V (2010) Surface deterioration of dental materials after simulated toothbrushing in relation to brushing time and load *Dental Materials* **26(4)** 306-319, http://dx.doi.org/10.1016/j.dental.2009.11.152.
11. Kaizer MR, de Oliveira-Ogliari A, Cenci MS, Opdam NJ, & Moraes RR (2014) Do nanofill or submicron composites show improved smoothness and gloss? A systematic review of *in vitro* studies *Dental Materials* **30(4)** e41-78, http://dx.doi.org/10.1016/j.dental.2014.01.001.
12. Oxman AD, Sackett DL, & Guyatt GH (1993) Users' guides to the medical literature. I. How to get started. The Evidence-Based Medicine Working Group *Journal of the American Association* **270(17)** 2093-2095.
13. Swingler GH, Volmink J, & Ioannidis JP (2003) Number of published systematic reviews and global burden of disease: database analysis *British Medical Journal* **327(7423)** 1083-1084, http://dx.doi.org/10.1136/bmj.327.7423.1083.
14. Moher D, Liberati A, Tetzlaff J, & Altman DG (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement *PLOS Medicine* **6(7)** e1000097, http://dx.doi.org/10.1371/journal.pmed.1000097.
15. Burke FJT, Singh V, & Wilson NHF (2013) The normalized failure index: a method for summarizing the results of studies on restoration longevity? *Operative Dentistry* **38(5)** 448-496.
16. Young T, & Hopewell S (2011) Methods for obtaining unpublished data *Cochrane Database of Systematic Reviews* **(11)** MR000027, http://dx.doi.org/10.1002/14651858.MR000027.pub2.
17. Cetin AR, Unlu N, & Cobanoglu N (2013) A five-year clinical evaluation of direct nanofilled and indirect composite resin restorations in posterior teeth *Operative Dentistry* **38(2)** E1-11, http://dx.doi.org/10.2341/12-160-C.
18. Cetin AR, & Unlu N (2009) One-year clinical evaluation of direct nanofilled and indirect composite restorations in posterior teeth *Dental Materials Journal* **28(5)** 620-626, http://dx.doi.org/JST.JSTAGE/dmj/28.620.
19. Karaman E, Yazici AR, Ozgunaltay G, & Dayangac B (2012) Clinical evaluation of a nanohybrid and a flowable resin composite in non-carious cervical lesions: 24-month

results *Journal of Adhesive Dentistry* **14(5)** 485-492, http://dx.doi.org/10.3290/j.jad.a27794.

20. Türkün LS, & Celik EU (2008) Noncarious class V lesions restored with a polyacid modified resin composite and a nanocomposite: a two-year clinical trial *Journal of Adhesive Dentistry* **10(5)** 399-405.
21. Dukic W, Dukic OL, Milardovic S, & Delija B (2010) Clinical evaluation of indirect composite restorations at baseline and 36 months after placement *Operative Dentistry* **35(2)** 156-164, https://doi.org/10.2341/09-133-C.
22. Mahmoud SH, El-Embaby AE, & AbdAllah AM (2014) Clinical performance of ormocer, nanofilled, and nanoceramic resin composites in Class I and Class II restorations: a three-year evaluation *Operative Dentistry* **39(1)** 32-42, http://dx.doi.org/10.2341/12-313-C.
23. Mahmoud SH, El-Embaby AE, AbdAllah AM, & Hamama HH (2008) Two-year clinical evaluation of ormocer, nanohybrid and nanofill composite restorative systems in posterior teeth *Journal of Adhesive Dentistry* **10(4)** 315-322.
24. de Andrade AK, Duarte RM, Medeiros e Silva FD, Batista AU, Lima KC, Monteiro GQ, & Montes MA (2014) Resin composite class I restorations: a 54-month randomized clinical trial *Operative Dentistry* **39(6)** 588-594, http://dx.doi.org/10.2341/14-067-C.
25. Arhun N, Celik C, & Yamanel K (2010) Clinical evaluation of resin-based composites in posterior restorations: two-year results *Operative Dentistry* **35(4)** 397-404, http://dx.doi.org/10.2341/09-345-C.
26. Dresch W, Volpato S, Gomes JC, Ribeiro NR, Reis A, & Loguercio AD (2006) Clinical evaluation of a nanofilled composite in posterior teeth: 12-month results *Operative Dentistry* **31(4)** 409-417, http://dx.doi.org/10.2341/05-103.
27. Ernst CP, Brandenbusch M, Meyer G, Canbek K, Gottschalk F, & Willershausen B (2006) Two-year clinical performance of a nanofiller vs a fine-particle hybrid resin composite *Clinical Oral Investigations* **10(2)** 119-125, http://dx.doi.org/10.1007/s00784-006-0041-8.
28. Kramer N, Reinelt C, & Frankenberger R (2015) Ten-year clinical performance of posterior resin composite restorations *Journal of Adhesive Dentistry* **17(5)** 433-441, http://dx.doi.org/10.3290/j.jad.a35010.
29. Loguercio AD, Lorini E, Weiss RV, Tori AP, Picinatto CC, Ribeiro NR, & Reis A (2007) A 12-month clinical evaluation of composite resins in class III restorations *Journal of Adhesive Dentistry* **9(1)** 57-64.
30. Qin W, Song Z, Ye YY, & Lin ZM (2013) Two-year clinical evaluation of composite resins in non-carious cervical lesions *Clinical Oral Investigations* **17(3)** 799-804, http://dx.doi.org/10.1007/s00784-012-0780-7.
31. Sadeghi M, Lynch CD, & Shahamat N (2010) Eighteen-month clinical evaluation of microhybrid, packable and nanofilled resin composites in Class I restorations *Journal of Oral Rehabilitation* **37(7)** 532-537, http://dx.doi.org/10.1111/j.1365-2842.2010.02073.x.
32. van Dijken JW, & Pallesen U (2014) A randomized 10-year prospective follow-up of Class II nanohybrid and conventional hybrid resin composite restorations *Journal of Adhesive Dentistry* **16(6)** 585-592, http://dx.doi.org/10.3290/j.jad.a33202.
33. de Andrade AK, Duarte RM, Guedes Lima SJ, Passos TA, Lima KC, & Montes MA (2011) Nanohybrid versus nanofill composite in class I cavities: margin analysis after 12 months *Microscopy Research and Technique* **74(1)** 23-27, http://dx.doi.org/10.1002/jemt.20867.
34. Kramer N, Reinelt C, Richter G, Petschelt A, & Frankenberger R (2009) Nanohybrid vs. fine hybrid composite in Class II cavities: clinical results and margin analysis after four years *Dental Materials* **25(6)** 750-759, http://dx.doi.org/10.1016/j.dental.2008.12.003.
35. Palaniappan S, Bharadwaj D, Mattar DL, Peumans M, Van Meerbeek B, & Lambrechts P (2011) Nanofilled and microhybrid composite restorations: five-year clinical wear performances *Dental Materials* **27(7)** 692-700, http://dx.doi.org/10.1016/j.dental.2011.03.012.
36. Palaniappan S, Elsen L, Lijnen I, Peumans M, Van Meerbeek B, & Lambrechts P (2012) Nanohybrid and microfilled hybrid versus conventional hybrid composite restorations: 5-year clinical wear performance *Clinical Oral Investigations* **16(1)** 181-190, http://dx.doi.org/10.1007/s00784-010-0500-0.
37. Andrade AK, Duarte RM, Silva FD, Batista AU, Lima KC, Pontual ML, & Montes MA (2012) Clinical evaluation of nanofill and nanohybrid composite in Class I restorations: a 12-month randomized trial *General Dentistry* **60(4)** e255-262.
38. de Andrade AK, Duarte RM, FD, Medeiros e Silva Batista AU, Lima KC, Pontual ML, & Montes MA (2011) 30-Month randomised clinical trial to evaluate the clinical performance of a nanofill and a nanohybrid composite *Journal of Dentistry* **39(1)** 8-15, http://dx.doi.org/10.1016/j.jdent.2010.09.005.
39. Kramer N, Reinelt C, Garcia-Godoy F, Taschner M, Petschelt A, & Frankenberger R (2009) Nanohybrid composite vs. fine hybrid composite in extended Class II cavities: clinical and microscopic results after 2 years *American Journal of Dentistry* **22(4)** 228-234.
40. Krämer N, Garcia-Godoy F, Reinelt C, Feilzer AJ, & Frankenberger R (2011) Nanohybrid vs. fine hybrid composite in extended Class II cavities after six years *Dental Materials* **27(5)** 455-464, http://dx.doi.org/10.1016/j.dental.2011.01.004.
41. Frankenberger R, Reinelt C, & Kramer N (2014) Nanohybrid vs. fine hybrid composite in extended class II cavities: 8-year results *Clinical Oral Investigations* **18(1)** 125-137, http://dx.doi.org/10.1007/s00784-013-0957-8.
42. Palaniappan S, Bharadwaj D, Mattar DL, Peumans M, Van Meerbeek B, & Lambrechts P (2009) Three-year randomized clinical trial to evaluate the clinical performance and wear of a nanocomposite versus a hybrid composite *Dental Materials* **25(11)** 1302-1314, http://dx.doi.org/10.1016/j.dental.2009.06.001.
43. Palaniappan S, Elsen L, Lijnen I, Peumans M, Van Meerbeek B, & Lambrechts P (2010) Three-year randomised clinical trial to evaluate the clinical performance, quantitative and qualitative wear patterns of hybrid composite restorations *Clinical Oral Investigations* **14(4)** 441-458, http://dx.doi.org/10.1007/s00784-009-0313-1.
44. van Dijken JW, & Pallesen U (2013) A six-year prospective randomized study of a nano-hybrid and a conven-

tional hybrid resin composite in Class II restorations *Dental Materials* **29(2)** 191-198, http://dx.doi.org/10.1016/j.dental.2012.08.013.

45. Altman DG, & Bland JM (1995) Absence of evidence is not evidence of absence *British Medical Journal* **311(7003)** 485.
46. Schulz KF, & Grimes DA (2002) Generation of allocation sequences in randomised trials: chance, not choice *Lancet* **359(9305)** 515-519, http://dx.doi.org/S0140-6736(02)07683-3.
47. Juni P, Altman DG, & Egger M (2001) Systematic reviews in health care: assessing the quality of controlled clinical trials *British Medical Journal* **323(7303)** 42-46.
48. Schulz KF, Chalmers I, Hayes RJ, & Altman DG (1995) Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials *Journal of the American Medical Association* **273(5)** 408-412.
49. Moher D, Schulz KF, & Altman DG (2001) The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials *Lancet* **357(9263)** 1191-1194, http://dx.doi.org/S0140673600043373.
50. Cvar JF, & Ryge G (2005) Reprint of criteria for the clinical evaluation of dental restorative materials. 1971 *Clinical Oral Investigations* **9(4)** 215-232, http://dx.doi.org/10.1007/s00784-005-0018-z.
51. Wilson MA, Cowan AJ, Randall RC, Crisp RJ, & Wilson NH (2002) A practice-based, randomized, controlled clinical trial of a new resin composite restorative: one-year results *Operative Dentistry* **27(5)** 423-429.
52. Reusens B, D'Hoore W, & Vreven J (1999) *In vivo* comparison of a microfilled and a hybrid minifilled composite resin in Class III restorations: 2-year follow-up *Clinical Oral Investigations* **3(2)** 62-69.