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Review article

Nanofilled/nanohybrid and hybrid resin-based composite in patients with direct restorations in posterior teeth: A systematic review and meta-analysis

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ABSTRACT

Objective: A systematic review and a meta-analysis were performed to answer the following research question: Are there differences in the color match and surface texture of nanofilled/nanohybrid and hybrid composite in patients with direct posterior restorations?
Data: Randomized clinical trials that compared nanofilled/nanohybrid and hybrid composite in direct restoration in posterior teeth were included. For the analysis of the bias the risk of bias tool (RoB) was used. Meta-analyses of different pairs (nanofilled vs. hybrid and nanohybrid vs. hybrid composite) were conducted for surface texture and color match and other secondary outcomes at different follow-ups, using a random effects model. Heterogeneity was assessed with the Cochran Q test and I^2 statistics. GRADE was used to assess the quality of the evidence.
Sources: A search was performed in PubMed, Scopus, Web of Science, LILACS, BBO, Cochrane Library and SIGLE, without restrictions. IADR abstracts (2001–2019), unpublished and ongoing trials registries, dissertations and theses were also searched.
Study selection: 28 studies remained. No study was considered to be at low RoB; four studies were judged to have high RoB, and the remaining were judged to have unclear RoB.
Results: For the primary and secondary outcomes variables no significant differences were detected between nanofilled/nanohybrid restorations and hybrid composite restorations in any of the study follow-ups ($p > 0.08$). The body of evidence for surface texture and color match was classified as moderate or low.
Conclusion: No evidence of difference was found between nanofilled/nanohybrid and hybrid composite in any of the clinical parameters evaluated.

1. Introduction

Due to the increasing demand for esthetic restorations in recent decades, composites have gained a prominent role in modern restorative dentistry. Composite restorations are considered to be the first option to restore anterior teeth [1,2] and their use in posterior restorations is increasing worldwide [3], due to the phase-down of the use of dental amalgam [4].

The current state of the art of composites has evolved significantly since the introduction of these materials into dentistry [5]. The most significant changes in commercial composites in the last decades have been made predominantly by improving the monomer, the filler and the initiator system [5]. The type of fillers influences both the radiopacity and the mechanical properties of the material, enhance translucency

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and improve handling properties, especially consistency, polishability and gloss stability [5–7]. Composites have usually been classified according to filler specifications, such as type, distribution and average particle size [5].

The size of filler particles has decreased continuously, from the hybrid, microhybrid and microfilled composite to the nano-sized composites [8], in an effort to improve initial polishability and gloss retention [9,10]. Nowadays, there are mainly two nano-sized composite categories in the market: nanofilled and nanohybrid composites [11].

Nanofilled composites consist of nanometer-sized particles in the composite matrix [6,9], which are mostly clustered into larger secondary particles [5], and nanohybrid composites take the approach of combining nanometer and micrometer-sized fillers [11].

Although the nanofilled and nanohybrid composites represent the state of the art in terms of filler formulation [6,7], a recent systematic review of in vitro studies showed that there is no evidence to support that nano-sized composites have improved their mechanical properties [12], better surface smoothness, gloss, and polishing retention after in vitro simulation [10]. Clinical studies that evaluated nanofilled and nanohybrid composites in comparison to hybrid composites in posterior restorations have yielded controversial results [13–15]. A recent systematic review [16], compared the nanofilled/nanohybrid vs. hybrid composites. In this study it was, however, impossible to carry out a meta-analysis due to its simple search strategy, and due to the fact that is was thus impossible to provide an estimate of the effect size. Clinicians who must decide between these different types of composite resins can benefit from a systematic review that compares the nanofilled composite with conventional microhybrid composites.

Therefore, the present systematic review of the literature aimed to answer the following question, based on the acronym PICO (P – participant; I – intervention; C – comparator; O – outcome): Are there differences in color match, surface texture and overall survival of nanofilled/nanohybrid vs. hybrid posterior composite restoration?

2. Materials and methods

2.1. Protocol and registration

This systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD42018093182. The present study was reported according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [17].

2.2. Information sources and search strategy

The first search strategy used the MEDLINE database via PubMed (Table 1), with controlled vocabulary (MeSH terms) and free keywords for each concept of the PICO question described at the end of the introduction section.

The MEDLINE search strategy was adapted to other electronic databases (Cochrane Library, Brazilian Library in Dentistry, Latin American and Caribbean Health Sciences Literature database (LILACS)) and citation databases (Scopus, and Web of Science) (Table 1). Additionally, we searched the grey literature by examining the abstracts of the annual conference of the International Association for Dental Research (IADR) and its regional divisions (2001–2019), the database System for Information on Grey Literature in Europe and dissertations and theses using the ProQuest Dissertations and Theses full-text database, as well as the Periódicos CAPES Theses database.

Ongoing studies were searched in the following clinical trial registries: Current Controlled Trials, International Clinical trials registry platform, ClinicalTrials.gov, ReBEC, and EU Clinical Trials Register. Additionally, we hand-searched the reference lists of all primary sources and eligible studies of this systematic review for additional relevant publications. The first two pages of the related articles link of each primary study in the PubMed database were also searched. In the whole search process, we did not restrict studies based on publication date. To minimize publication bias, no year or language restrictions were applied.

2.3. Study selection and data collection process

Parallel and split-mouth randomized clinical trials (RCTs), conducted in patients with permanent dentition, that compared direct restorations with nanofilled/nanohybrid composites with hybrid composites were included. The articles retrieved by the literature search were revised in three phases. All studies were initially scanned for relevance by title, and the abstracts of those that were not excluded at this stage were appraised. The next step was the evaluation of the abstract, and the studies that could not be excluded, according to our eligibility criteria in the abstract review. The full texts were then read by two reviewers to determine whether they met the inclusion criteria. Finally, the eligible articles received a study identification label (ID), combining first author and year of publication.

Two reviewers independently summarized and categorized data, such as study design, number of patients, interventions, and outcomes. In cases of disagreement, a decision was reached by consulting a third reviewer. If there were multiple reports of the same study (i.e., reports with different follow-ups), data of all reports were extracted directly into a single data-collection form to avoid multiple data entry.

2.4. Data

The primary outcome variables were surface texture and color match, that were clinically evaluated by the United States Public Health Service (USPHS) criteria [18]. Anatomic form/fracture, marginal discoloration, marginal adaptation, postoperative sensitivity, loss of restoration, and secondary caries were secondary variables. For each of these criteria, restorations were scored as Alpha, Bravo, and Charlie. Data were dichotomized into Alpha vs. Bravo/Charlie for each criterion. In the USPHS criteria, Alpha represents the ideal clinical situation; Bravo is the score attributed to restorations with some defects but still clinically acceptable, and Charlie represents a clinically unacceptable restoration that needs replacement. For studies that employed the FDI (World Dental Federation) criteria, restorations were clinically graded into very good, good and sufficient/satisfactory vs. unsatisfactory but repairable, and poor (replacement required) [19]. When more than one commercial brand of the same composite was included in the study, their values were combined to make a single entry. In each study, the commercial brand of the composite was classified as nanohybrid, nanofiller or hybrid, based on categorization published by Ilie, Hickel [20] and Kaizer et al. [10].

2.5. Risk of bias in individual studies

Quality assessments of the selected trials were carried out by three independent reviewers, using the Cochrane Collaboration tool for assessing the risk of bias in RCTs [21]. The assessment criteria contain six items: selection bias (adequate sequence generation and allocation concealment), performance bias (blinding of patients and operators), detection bias (blinding of evaluators), attrition bias (incomplete outcome data), reporting bias (selective reporting), and other bias. The latter domain was not assessed in this systematic review. Disagreements among the reviewers were solved through discussion, and if needed, by consulting a fourth reviewer.

For each aspect of the quality assessment, the risk of bias was scored following the recommendations of the Risk of Bias tool (RoB) of the Cochrane Handbook for Systematic Reviews of Interventions 5.0.2 (http://handbook.cochrane.org). Each domain level was judged as low, high, or unclear risk of bias. Two domains of the RoB tool were considered as key domains: adequate sequence generation and allocation

Table 1
Search strategy in Pubmed database conducted in April 08, 2018 (updated on April 24, 2020).

Pubmed

#1 ((((((((((((((molar[MeSH Terms]) OR bicuspid [MeSH Terms]) OR dental restoration, permanent [MeSH Terms]) OR "dental restoration, permanent"[Title/Abstract]) OR "posterior teeth"[Title/Abstract]) OR "posterior tooth"[Title/Abstract]) OR "occlusal restoration"[Title/Abstract]) OR "occlusal restorations"[Title/Abstract]) OR "posterior restoration"[Title/Abstract]) OR "posterior restorations"[Title/Abstract]) OR "class 1"[Title/Abstract]) OR "class 2"[Title/Abstract]) OR "class I"[Title/Abstract]) OR "class II"[Title/Abstract]) OR molar [Title/Abstract]) OR bicuspid [Title/Abstract]

#2 ((((((((((((((((((((((((((dentin-bonding agents[MeSH Terms]) OR hybrid bond[Supplementary Concept]) OR "hybrid bond"[Title/Abstract]) OR "adhesive system"[Title/Abstract]) OR "adhesive systems"[Title/Abstract]) OR "bonding agent"[Title/Abstract]) OR "bonding agents"[Title/Abstract]) OR "dental adhesive"[Title/Abstract]) OR "dental adhesives"[Title/Abstract]) OR "adhesive material"[Title/Abstract]) OR "adhesive materials"[Title/Abstract]) OR "etch-and-rinse adhesive"[Title/Abstract]) OR "etch-and-rinse adhesives"[Title/Abstract]) OR "total-etch adhesive"[Title/Abstract]) OR "total-etch adhesives"[Title/Abstract]) OR "self-etch adhesive"[Title/Abstract]) OR "self-etch adhesives"[Title/Abstract]) OR "self-etching adhesive"[Title/Abstract]) OR "self-etching adhesives"[Title/Abstract]) OR "all-in-one adhesive"[Title/Abstract]) OR "all-in-one adhesives"[Title/Abstract]) OR "all-in-one adhesive"[Title/Abstract]) OR "all-in-one adhesives"[Title/Abstract]) OR "one-bottle adhesive"[Title/Abstract]) OR "one-bottle adhesives"[Title/Abstract]) OR "filled adhesive"[Title/Abstract]) OR “unfilled adhesive"[Title/Abstract]) OR "unfilled adhesives"[Title/Abstract]) OR "hybrid bond"[Title/Abstract]

#3 ((((((((((((((((((((composite resins[MeSH Terms]) OR nanoparticle[MeSH Terms]) OR nanocomposites[MeSH Terms]) OR "resin composite"[Title/Abstract]) OR "resin composites"[Title/Abstract]) OR "composite resin"[Title/Abstract]) OR "composite resins"[Title/Abstract]) OR "resin restoration"[Title/Abstract]) OR "resin restorations"[Title/Abstract]) OR "composite restoration"[Title/Abstract]) OR "composite restorations"[Title/Abstract]) OR "restorative technique"[Title/Abstract]) OR "restorative techniques"[Title/Abstract]) OR nanoparticle[Title/Abstract]) OR nanoparticles [Title/Abstract]) OR nanocomposite[Title/Abstract]) OR nanocomposites[Title/Abstract]) OR hybrid[Title/Abstract]) OR hybrids[Title/Abstract]) OR nanofilled[Title/Abstract]) OR nanohybrid[Title/Abstract]

#4 (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials [mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR ("clinical trial"[tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR (placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR comparative study[pt] OR evaluation studies as topic[mh] OR follow-up studies[mh] OR prospective studies[mh] OR control*[tw] OR prospective*[tw] OR volunteer*[tw]) NOT (animals[mh] NOT humans [mh])

#1 and #2 and #3 and #4

Cochrane

#1 MeSH descriptor: [Molar] explode all treesbicuspid
#2 MeSH descriptor: [Bicuspid] explode all treesdental next #3 MeSH descriptor: [Dental Restoration, Permanent] explode all trees
#4dental next restoration, permanent:ti,ab,kw or posterior near t*th:ti,ab,kw or occlusal near restoration*:ti,ab,kw or posterior near restoration*:ti,ab,kw or "class 1″:ti,ab,kw (Word variations have been searched)
#5″class 2″:ti,ab,kw or "class I":ti,ab,kw or "class II":ti,ab,kw or molar:ti,ab,kw or bicuspid:ti,ab,kw (Word variations have been searched)
#6 #1 or #2 or #3 or #4 or #5

#7 MeSH descriptor: [Dentin-Bonding Agents] explode all trees
#8 hybrid next bond:ti,ab,kw or adhesive next system*:ti,ab,kw or bonding near agent*:ti,ab,kw or dental next adhesive:ti,ab,kw or adhesive next material:ti,ab,kw (Word variations have been searched
#9″etch and rinse":ti,ab,kw or total etch*:ti,ab,kw or self etch*:ti,ab,kw or "all in one":ti,ab,kw or "one bottle":ti,ab,kw (Word variations have been searched)
#10 *filled adhesive*:ti,ab,kw (Word variations have been searched)
#11 #7 or #8 or #9 or #10

#12 MeSH descriptor: [Composite Resins] explode all trees
#13 MeSH descriptor: [Nanoparticles] explode all trees
#14 MeSH descriptor: [Nanocomposites] explode all trees
#15 resin near composite*:ti,ab,kw or composite next resin*:ti,ab,kw or resin near restoration*:ti,ab,kw or composite next restoration*:ti,ab,kw or restorative next technique*:ti,ab,kw (Word variations have been searched)
#16 nanoparticle*:ti,ab,kw or nanocomposite*:ti,ab,kw or *hybrid*:ti,ab,kw or nanofilled:ti,ab,kw (Word variations have been searched)
#17 #12 or #13 or #14 or #15 or #16

#18 #6 AND #11 AND #17

Lilacs/BBO

#1 (MH:molar OR MH:bicuspid OR MH:dental restoration permanent OR "dental restoration permanent" OR "restauración dental permanente" OR "restauração dental permanente" OR "posterior teeth" OR "dientes posteriores" OR "dentes posteriores" OR "posterior tooth" OR "diente posterior" OR "dente posterior" OR "occlusal restoration" OR "restauración oclusal" OR "restauração oclusal" OR "occlusal restorations" OR "restauraciones oclusales" OR "restaurações oclusais" OR "posterior restoration" OR "restauración posterior" OR "restauração posterior" OR "posterior restorations" OR "restauraciones posteriores" OR "restaurações posteriores" OR "class 1" OR "clase 1" OR "classe 1" OR "class 2" OR "clase 2" OR "classe 2" OR "class I" OR "clase I" OR "classe I" OR "class II" OR "clase II" OR "classe II" OR molar OR bicuspid OR bicúspide)

#2 (MH:"dentin-bonding agents" OR "hybrid bond" OR "enlace híbrido" OR "ligação híbrida" OR "adhesive system" OR "sistema adhesivo" OR "sistema adesivo" OR "adhesive systems" OR "sistemas adhesivos" OR "sistemas adesivos" OR "bonding agent" OR "agente adhesivo" OR "agente adesivo" OR "bonding agents" OR "agentes adhesivos" OR "agentes adesivos" OR "dental adhesive" OR "adhesive dental" OR "adesivo dental" OR "dental adhesives" OR "adhesivos dentales" OR "adesivos dentais" OR "adhesive material" OR "material adhesivo" OR "material adesivo" OR "adhesive materials" OR "materiales adhesivos" OR "materiais adesivos" OR "etch-and-rinse adhesive" OR "adhesive de grabado y enjuague" OR "adesivo convencional" OR "etch-and-rinse adhesives" OR "adhesives de grabado y enjuage" OR "adesivos convencionais" OR "total-etch adhesive" OR "total-etch adhesives" OR "self-etch adhesive" OR "adhesive autograbado" OR "adesivo autocondicionante" OR "self-etch adhesives" OR "adhesivos autograbados" OR "adesivos autocondicionantes" OR "self-etching adhesive" OR "self-etching adhesives" OR "all-in-one adhesive" OR "adhesivo todo en uno" OR " adesivo de um passo" OR "adesivos de um passo" OR "adhesive de dos pasos" OR "adhesivos de dos pasos" OR "adesivos de dois passos" OR "adhesive de uno paso" OR "adesivo de passo único" OR "all-in-one adhesives" OR "all-in-one adhesive" OR "all-in-one adhesives" OR "one-bottle adhesive" OR "adesivos de frasco único" OR "adesivo de fraco único")

#3 (MH:"composite resins" OR MH:nanoparticle OR MH:nanocomposites OR "resin composite" OR "resina compuesta" OR "resin composites" OR "resinas compuestas" OR "resinas compostas" OR "composite resin" OR "compuesto de resina" OR "compósito de resina" OR "composite resins" OR "compuestos de resina" OR "compósitos de resina" OR "resin restoration" OR "restauración de resina" OR "restauração de resina" OR "resin restorations" OR "restauraciones de resina" OR "restaurações de resina" OR "composite restoration" OR "restauraciones compuestas" OR "restaurações compostas" OR "composite restorations" OR "restorative technique" OR "técnica restauradora" OR "técnicas restauradoras" OR "restorative techniques" OR nanoparticle OR nanopartícula OR nanopartículas OR nanocomposites OR nanocompósito OR nanocompósitos OR hybrid OR híbrido OR nanofilled)

(continued on next page)

Table 1 (*continued*)

#1 and #2 and #3		
Scopus		
#1 (TITLE-ABS-KEY (molar) OR TITLE-ABS-KEY (bicuspid) OR TITLE-ABS-KEY ("dental restoration permanent") OR TITLE-ABS-KEY ("posterior t??th") OR TITLE-ABS-KEY ("occlusal restoration*") OR TITLE-ABS-KEY ("posterior restoration*") OR TITLE-ABS-KEY ("class 1") OR TITLE-ABS-KEY ("class 2") OR TITLE-ABS-KEY ("class I") OR TITLE-ABS-KEY ("class II"))	#2 (TITLE-ABS-KEY ("hybrid bond") OR TITLE-ABS-KEY ("adhesive system*") OR TITLE-ABS-KEY ("bonding agent*") OR TITLE-ABS-KEY ("dental adhesive*") OR TITLE-ABS-KEY ("adhesive material*") OR TITLE-ABS-KEY ("etch-and-rinse") OR TITLE-ABS-KEY ("total-etch") OR TITLE-ABS-KEY ("self-etch*") OR TITLE-ABS-KEY ("all-in-one") OR TITLE-ABS-KEY ("one-bottle") OR TITLE-ABS-KEY ("*filled adhesive") OR TITLE-ABS-KEY ("unfilled adhesive*"))	#3 (TITLE-ABS-KEY ("composite resin*") OR TITLE-ABS-KEY (nanoparticle*) OR TITLE-ABS-KEY (nanocomposite*) OR TITLE-ABS-KEY ("resin composite*") OR TITLE-ABS-KEY ("resin restoration*") OR TITLE-ABS-KEY ("composite restoration*") OR TITLE-ABS-KEY ("restorative technique*") OR TITLE-ABS-KEY (*hybrid) OR TITLE-ABS-KEY (hybrid*) OR TITLE-ABS-KEY (nanofilled))
#1 and #2 and #3		
Web of Science		
#1 Tópico: (Molar) OR Tópico: (Bicuspid) OR Tópico: ("dental restoration permanent") OR Tópico: ("posterior t??th") OR Tópico: ("occlusal restoration*") OR Tópico: ("posterior restoration*") OR Tópico: ("class 1")OR Tópico: ("class 2") OR Tópico: ("class I") OR Tópico: ("class II")	#2 Tópico: ("hybrid bond") OR Tópico: ("adhesive system*") OR Tópico: ("bonding agent*") OR Tópico: ("dental adhesive*") OR Tópico: ("adhesive material*") OR Tópico:("etch-and-rinse") OR Tópico: ("total-etch") OR Tópico: ("self-etch*") OR Tópico: ("all-in-one") OR Tópico: ("one-bottle") OR Tópico: ("*filled adhesive*")	#3 (TITLE-ABS-KEY ("composite resin*") OR TITLE-ABS-KEY (nanoparticle*) OR TITLE-ABS-KEY (nanocomposite*) OR TITLE-ABS-KEY ("resin composite*") OR TITLE-ABS-KEY ("resin restoration*") OR TITLE-ABS-KEY ("composite restoration*") OR TITLE-ABS-KEY ("restorative technique*") OR TITLE-ABS-KEY (*hybrid) OR TITLE-ABS-KEY (hybrid*) OR TITLE-ABS-KEY (nanofilled))
#1 and #2 and #3		

concealment (aimed to prevent selection bias) and blinding of evaluators (aimed to prevent detection bias).

At study level, the study was at low risk of bias if all five domains of the RoB tool (previously described) for each outcome were at low risk of bias. If one or more domains were judged to have an unclear risk, the study as a whole was judged to have an unclear risk; if at least one item was considered at high risk of bias, the study was considered to have a high risk of bias.

2.6. Summary measures and synthesis of results

Data have been analyzed using Revman 5.3 (Review Manager Version 5.3, The Cochrane Collaboration, Copenhagen, Denmark). Meta-analyses were performed in studies classified as at low or at unclear risk of bias in the key domains; studies judged to be at high risk of bias in the key domains were not included in the meta-analysis. Data of eligible studies have been summarized by calculating the risk difference and the 95 % confidence interval. As studies reported outcomes from different follow-ups, the meta-analysis was performed in range periods of 12–18 months, 24–31 months, 36–60 months, and 72 months or more. When one study reported data twice within the same range period, data of the longest follow-up period have been taken into account.

For all meta-analyses, we used the random-effects model, as this is the most appropriate model for studies from different populations. Heterogeneity was evaluated using the Cochran Q test and I^2 statistics, but as this is a measure of dispersion, it was only presented in the discussion section when more than five studies were included in the meta-analysis. The 95 % prediction interval was calculated in all meta-analyses with at least five studies. Sensitivity analyses have been conducted to investigate the reasons for high heterogeneity, whenever detected.

2.7. Assessment of the quality of the evidence using GRADE

We graded the quality of evidence for primary outcomes across the studies (body of evidence) by using the Grading of Recommendations: Assessment, Development, and Evaluation (GRADE) (http://www.gradeworkinggroup.org/) to determine the overall strength of evidence for each meta-analysis [22]. The GRADE pro Guideline Development Tool (available online at www.gradepro.org) was used to create a summary-of-findings table, as suggested in the Cochrane Handbook for Systematic Reviews of Interventions 5.0.2 (http://handbook.cochrane.org) for the primary outcomes in two study follow-ups.

The GRADE approach to RCTs addresses five reasons (risk of bias, imprecision, inconsistency, indirectness of evidence, and publication bias) to downgrade the quality of evidence (1 or 2 levels). In order to categorize the quality of the evidence into high, moderate, low, and very low each topic has been assessed as having “no limitations,” “serious limitations,” or “very serious limitations”.

3. Results

3.1. Study selection

The search strategy was conducted initially on April 08, 2018 (updated on April 24, 2020). After database screening and duplicate removal, 5213 studies were identified (Fig. 1). After title screening, 748 studies remained, and after abstract screening, 44 studies remained. This number was reduced to 28 after careful examination of the full-text studies.

Eleven studies (16 articles) were excluded, as they: (1) evaluated indirect composite restorations [23]; (2) were in vitro studies [24,25]; (3) had only a group with a nanohybrid composite [26–29]; (4) evaluated only the clinical wear of the composite [30]; (5) were *ex-vivo* studies [31,32]; and (6) compared nanofilled vs. nanohybrid

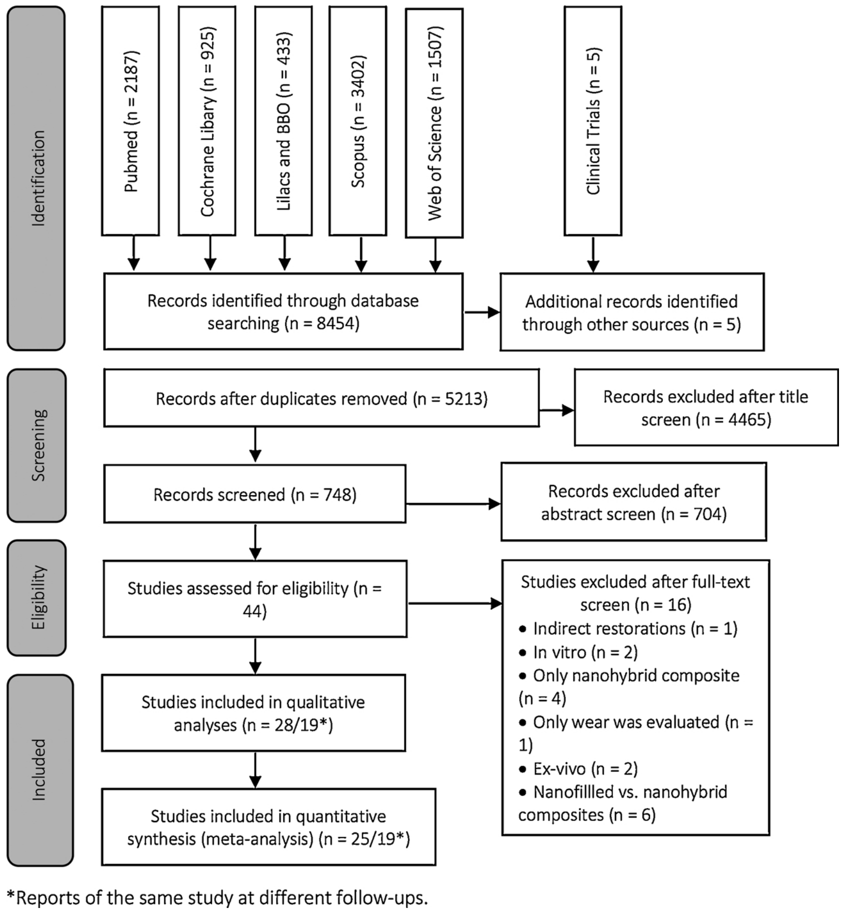

Fig. 1. Flow diagram of study identification.

composites [33–38].

Among the 28 remaining articles, there were multiple reports of the same study with different follow-ups. Data of studies with different follow-ups were collected in a single form, resulting in a total of 19 studies.

3.2. Characteristics of included articles

The characteristics of the 19 eligible studies are listed in Table 2. All studies were published in full-text format. In 18 studies USPHS criteria were used for clinical evaluation [13–15,39–62]. Only one study used the FDI criteria [63].

3.3. Study design

In the majority of the studies multiple restorations were placed in the same patient. Only one study reported a parallel study design [45].

3.4. Age and gender of the patients in the primary RCTs

The age of the patients ranged from 13 years to 82 years; the mean age was 32.7 years. Except for one study [13,39,40], more females were included than males. Four studies did not report on the sex of the patients [44,53,54,56].

3.5. Protocol of restoration

Ten studies reported that the operators were dentists [14,41,42,48–52,54–60,62,63], and one study reported that the operator was a dental student [43]. The other studies did not report on the type of operator [13,15,39,40,44–47,53,61]. The number of operators for each study varied from one to seven.

Seven studies included Class I and Class II restorations [41–44,53,55,56,59,60], seven studies only Class I restorations [13,15,39,40,45–47,54,61], and five only Class II restorations [14,48–52,57,58,62,63].

The mean cavity width was one-third of the intercuspal distance in nine studies [13,15,39–42,45–47,53,59–61], and one-quarter of the intercuspal distance in only one study [44]. The rest of the studies did not report on this item.

Nine studies used rubber dam isolation [13,39,40,44,47–52,55–60,62], and ten studies used cotton rolls and saliva ejectors [14,15,41–43,45,46,53,54,61,63].

In twelve studies restorations were made due to primary carious lesions or unsatisfactory restorations [13,15,39–46,53,54,57–60,62], and seven studies did not report on this item [14,47–52,55,56,61,63].

Twelve studies reported that beveling of the enamel margins was not performed [41,42,45,47–54,57,58,61–63], while it was the case in two studies [55,56].

Etch-and-rinse adhesive systems had been used in fourteen studies [13,39,40,43–46,48–62], self-etch strategy adhesive systems in three studies [41,42,47,63], and two studies used both types of adhesive systems [14,15].

In three studies a glass ionomer cement was applied for the protection of the dentin-pulp complex [13,39,40,54,55], in two studies a calcium hydroxide cement [41–43], and in five both materials [14,44,53,56]. In the other studies either did not use such materials [15,45–47,57–63] or did not report on whether or not it has been used [48–52].

In the majority of the studies the incremental technique has been

Table 2
Summary of the primary studies included in this systematic review.

Study ID	Study design [Settings]	Nº of patients	Subject age's mean ± SD [range] (years)	Nº of males [%]	Clinical experience [number of operators]	type of cavity	Groups/Nº of restorations per group	Mean cavity size	Isolation method	Enamel beveling
Andrade et al.* [13,39,40]	Split-mouth [n.r.]	41	13.4 ± 2.22 [n.r.-n.r.]	27 [65.9]	n.r. [1]	Class I	I: Filtek Z250$^{a\ Hy}$/41 II: Filtek Z350$^{a\ Na}$/41 III: Esthet-X$^{b\ Hy}$/41	One-third intercuspal	Rubber dam	n.r.
Arhun and Çelik et al.* [41,42]	Split-mouth [University]	31	26 ± n.r. [16–60]	10 [32.3]	Dentist [1]	Class I or II	I: Grandio$^{c\ Nh}$/41 II: Quixfil$^{b\ Hy}$/41	One-third intercuspal	Cotton rolls Saliva ejectors	None
Beck et al. [43]	Split-mouth [University]	456	33.9 ± 11.2 [n.r.-n.r.]	198 [43.4]	Students [n.r]	Class I or II	I: Ceram X$^{b\ Nh}$/528 II: Tetric Ceram$^{d\ Hy}$/580	n.r.	Cotton rolls Saliva ejectors	n.r.
Dresch et al. [44]	Split-mouth [University]	42	n.r. ± n.r. [n.r.-n.r.]	n.r. [n.r.]	n.r. [2]	Class I or II	I: Filtek Supreme$^{a\ Na}$/37 II: Pyramid$^{e\ Hy}$/37 III: Esthet-X$^{b\ Hy}$/37 IV: Tetric Ceram$^{d\ Hy}$/37	One-quarter intercuspal	Rubber dam	n.r.
Efes^{I} et al.** [45]	Parallel [University]	90	n.r. ± n.r. [18–48]	42 [46.7]	n.r. [1]	Class I	I: Admira$^{c\ Hy}$/30 II: Filtek Supreme$^{a\ Na}$/30 III: Renew$^{f\ Hy}$/30	One-third intercuspal	Cotton rolls Saliva ejectors	None
Efes^{II} et al.** [46]	Split-mouth [University]	54	n.r. ± n.r. [18–48]	25 [46.3]	n.r. [1]	Class I	I: Admira$^{c\ Hy}$/27 II: Admira$^{c\ Hy}$ + Admira Flow$^{c\ Hy}$/27 III: Filtek Supreme$^{a\ Na}$/27 IV: Filtek Supreme$^{a\ Na}$ + Filtek Flow$^{a\ Na}$/27	One-third intercuspal	Cotton rolls Saliva ejectors	None
Efes^{III} et al.** [47]	Split-mouth [University]	50	32.9 ± 6.34 [24–59]	23 [46]	n.r. [1]	Class I	I: Filtek Silorane$^{a\ Hy}$/50 II: Ceram.X Duo$^{b\ Na}$/50	One-third intercuspal	Rubber dam	None
Ernst et al. [62]	Split-mouth [n.r.]	50	35.7 ± 11.3 [13–48]	24 [49]	Dentist [6]	Class II	I: Filtek Supreme$^{a\ Na}$/56 II: Tetric Ceram$^{d\ Hy}$/56	n.r.	Rubber dam	None
Krämer and Frankenberger et al.* [48–52]	Split-mouth [Private practice]	30	32.9 ± n.r. [24–59]	7 [23.3]	Dentist [1]	Class II	I: Grandio$^{c\ Nh}$/36 II: Tetric Ceram$^{d\ Hy}$/32	n.r.	Rubber dam	None
Mahmoud^{I} et al.** [54]	Split-mouth [University]	40	n.r. ± n.r. [n.r.-n.r.]	n.r. [n.r.]	Dentist [2]	Class I	I: Admira$^{c\ Hy}$/35 II: Tetric EvoCeram$^{d\ Nh}$/35 III: Filtek Supreme$^{a\ Na}$/35 IV: Tetric Ceram$^{d\ Hy}$/35	n.r.	Cotton rolls Saliva ejectors	None
Mahmoud^{II} et al.** [53]	Split-mouth [University]	40	33 ± n.r. [20–54]	n.r. [n.r.]	n.r. [1]	Class I or II	I: Admira$^{c\ Hy}$/40 II: Filtek Supreme$^{a\ Na}$/40 III: Ceram X$^{b\ Nh}$/40 IV: Tetric Ceram$^{d\ Hy}$/40	One-third intercuspal	Cotton rolls Saliva ejectors	None
Özturk-Bozkurt et al. [14]	Split-mouth [n.r.]	29	24 ± 5 [n.r.-n.r.]	8 [27.6]	Dentist [1]	Class II	I: Filtek Silorane$^{a\ Hy}$/29 II: Filtek Z550$^{a\ Nh}$/29	n.r.	Cotton rolls Saliva ejectors	n.r.
Palaniappan^{I} et al.** [55]	Split-mouth [n.r.]	16	34.5 ± n.r. [n.r.-n.r.]	7 [43.7]	Dentist [2]	Class I or II	I: Filtek Supreme$^{a\ Na}$/18 II: Filtek Z100$^{a\ Hy}$/19	n.r.	Rubber dam	Yes
Palaniappan^{II} et al.** [56]	Split-mouth [n.r.]	15	n.r. ± n.r. [n.r.-n.r.]	n.r. [n.r.]	Dentist [2]	Class I or II	I: Tetric EvoCeram$^{d\ Nh}$/17 II: Tetric Ceram$^{d\ Hy}$/16 III: Gradia Direct Posterior$^{g\ Hy}$/16	n.r.	Rubber dam	Yes
Sadeghi et al. [61]	Split-mouth [University]	35	n.r. ± n.r. [18 – 29)	15 [42.9]	n.r. [1]	Class I	I: Nanofilled Premise$^{h\ Na}$/35 II: Point 4$^{h\ Hy}$/35 III: Packable Premise$^{h\ Hy}$/35	One-third intercuspal	Cotton rolls Saliva ejectors	None
Schirrmeister et al.* [59,60]	Split-mouth [University]	43	n.r. ± n.r. [n.r.-n.r.]	20 [46.5]	Dentist [1]	Class I or II	I: Ceram.X$^{b\ Na}$/43 II: Tetric Ceram$^{d\ Hy}$/43	One-third intercuspal	Rubber dam	n.r.
Van Dijken and Pallesen* [57,58]	Split-mouth [Private practice]	52	53 ± n.r. (29 – 82)	25 [48.1]	Dentist [1]	Class II	I: Tetric EvoCeram$^{d\ Nh}$/61 II: Tetric Ceram$^{d\ Hy}$/61	n.r.	Rubber dam	None
Walter et al. [63]	Split-mouth [University]	31	44.3 ± 12.7 [22–61]	6 [19.3]	Dentist [7]	Class II	I: Filtek Silorane$^{a\ Hy}$/41 II: Tetric Evo Ceram$^{d\ Nh}$/41	n.r.	Cotton rolls Saliva ejectors	None
Yazici et al. [15]	Split-mouth [University]	28	29.3 ± n.r. [18–52]	11 [39.3]	n.r. [1]	Class I	I: Filtek Supreme$^{a\ Na}$/28 II: P60$^{a\ Hy}$/28 II: Filtek Silorane$^{a\ Hy}$/28	One-third intercuspal	Cotton rolls Saliva ejectors	n.r.

Study ID	Cavity preparation	Adhesive system (number of steps)	Cement used in deep cavities	Resin placement technique	Light activation unit [Intensity (mW/cm^2)/Time (s)]	Finish time/ Polish time	Conflict of interest	Evaluation criteria used	Follow-up [Drop-outs]
Andrade et al.* [13,39,40]	Limited to carious tissue or unsatisfactory restorations	ER (2)	Glass Ionomer	Incremental 2 mm thick layer	LED [600/20]	Next session/ Next session	None	USPHS	6 m [0] 12 m [0] 30 m [4]
Arhun and Çelik et al.* [41,42]	Limited to carious tissue	I: SE (1) II: SE (1)	Calcium Hidroxide	Incremental 2 mm thick layer	Halogen light [500/n.r.]	Immediately/ Immediately	n.r.	USPHS	6 m [0] 12 m [0] 24 m [5] 36 m [10]

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Table 2 (*continued*)

Study ID	Cavity preparation	Adhesive system (number of steps)	Cement used in deep cavities	Resin placement technique	Light activation unit [Intensity (mW/cm^2)/Time (s)]	Finish time/ Polish time	Conflict of interest	Evaluation criteria used	Follow-up [Drop-outs]
Beck et al. [43]	Limited to carious tiusse	I: ER (2) II: ER (2)	Calcium Hidroxide	Incremental 2 mm thick layer	n.r. [≥500/20]	n.r./ Immediately	n.r.	USPHS	12 m [177]
Dresch et al. [44]	Limited to carious tissue	I: ER (2) II: ER (2) III: ER (2) IV: ER (2)	Calcium Hidroxide Glass Ionomer	Incremental 2 mm thick layer	Halogen light [550/40]	1 week after/ 1 week after	n.r.	USPHS	12 m [0]
Efes[I] et al.** [45]	Limited to carious tissue	I: ER (2) II: ER (2) III: ER (2)	None	Incremental	Halogen light [450/40]	Immediately/ 1 week after	n.r.	USPHS	6 m [0] 12 m [2] 24 m [3]
Efes[II] et al.** [46]	Limited to carious tissue	I and II: ER (2) III and IV: ER (2)	None	Incremental oblique	Halogen light [450/40]	Immediately/ 1 week after	n.r.	USPHS	6 m [1] 12 m [1] 24 m [4]
Efes[III] et al.** [47]	n.r.	I: SE (2) II: SE(1)	None	Incremental 2 mm thick layer	LED I: [650/40] II: [650/20]	Immediately/ 1 week after	None	USPHS	6 m [0] 12 m [0] 24 m [0]
Ernst et al. [62]	Limited to carious tissue or unsatisfactory restorations	ER (2)	None	Incremental 2 mm thick layer	LED [n.r./40]	n.r./ n.r	Yes	USPHS	6 m [0] 12 m [0] 24 m [0]
Krämer and Frankenberger et al.* [48–52]	n.r.	I: ER (2) II: ER (4)	n.r.	Incremental 2 mm thick layer	LED [650/40]	Immediately/ Immediately	None	USPHS	24 m [0] 48 m [0] 72 m [0] 96 m [0] 120 m [1]
Mahmoud[I] et al.** [54]	Limited to carious tissue or unsatisfactory restorations	I: ER (2) II: ER (2) III: ER (2) IV: ER (2)	Glass Ionomer	Incremental oblique	Halogen light [530/40]	Immediately/ 1 week after]	n.r.	USPHS	6 m [0] 12 m [0] 24 m [0]
Mahmoud[II] et al.** [53]	Limited to carious tissue	I: ER (2) II: ER (2) III: ER (2) IV: ER (2)	Calcium Hidroxide Glass Ionomer	Incremental oblique	Halogen light [530/40]	Immediatelly/ Immediately	None	USPHS	12 m [0] 24 m [0] 36 m [0]
Özturk-Bozkurt et al. [14]	n.r.	I: SE (2) II: ER (2)	Calcium Hidroxide Glass Ionomer	Incremental 2 mm thick layer	LED [≥400/40]	Immediately/ Immediately	None	USPHS	6 m [0] 31 m [0]
Palaniappan[I] et al.** [55]	n.r.	ER (2)	Glass Ionomer	Incremental 2 mm thick layer	LED [≥400/n.r.]	Immediately/ Immediately	Yes	USPHS	6 m [0] 12 m [0] 24 m [0] 36 m [1]
Palaniappan[II] et al.** [56]	n.r.	I and II: ER (2) II: ER (2)	Calcium Hidroxide Glass Ionomer	Incremental 2 mm thick layer	Halogen light [n.r./n.r.]	n.r./ n.r.	None	USPHS	6 m [0] 12 m [0] 24 m [0] 36 m [0]
Sadeghi et al. [61]	n.r.	ER (2)	None	Incremental 2 mm thick layer	LED [n.r./40]	n.r./ n.r	None	USPHS	6 m [0] 12 m [0] 18 m [0]
Schirrmeister et al.* [59,60]	Limited to carious tissue or unsatisfactory restorations	I: ER (2) II: ER (4)	None	Incremental 2 mm thick layer	LED I: [750/20]II: [750/40]	Immediately/ Immediately	Yes	USPHS	12 m [6] 24 m [12] 48 m [16]
Van Dijken and Pallesen* [57,58]	Limited to carious tissue or unsatisfactory restorations	ER (2)	None	Incremental 2 mm thick layer		Immediately/ Immediately	Yes	USPHS	12 m [0] 36 m [4] 72 m [4] 120 m [4]
Walter et al. [63]	n.r.	I: SE (2) II: SE (2)	None	Incremental 2 mm thick layer	LED [n.r./20]	Immediately/ Immediately	Yes	FDI	6 m [0] 12 m [3] 24 m [3] 36 m [3]

(*continued on next page*)

Table 2 (*continued*)

Study ID	Cavity preparation	Adhesive system (number of steps)	Cement used in deep cavities	Resin placement technique	Light activation unit [Intensity (mW/cm^2)/Time (s)]	Finish time/ Polish time	Conflict of interest	Evaluation criteria used	Follow-up [Drop-outs]
Yazici et al. [15]	Limited to carious tissue	I and II: ER (2) III: SE (2)	None	Incremental 2 mm thick layer	Halogen light [600/40]	Immediately/ Immediately	None	USPHS	6 m [0] 12 m [0] 24 m [1] 36 m [8]

Abbreviations: ID–identification; Nº–number; SD–standard deviation; n.r.–not reported in the study; Hy–Hybrid composite; Na–nanofilled composite; Nh–nanohybrid composite; ER–etch-and-rinse; USPHS–United States Public Health Service; m–months; SE–self etch; LED–Light-Emitting Diode.

* Reports of the same study at different follow-ups.

** Reports of the same author, but different studies.

[a] 3 M Oral Care (St Paul, MN, USA).

[b] Denstply Sirona (Kostanz, Germany).

[c] Voco GmbH (Cuxhaven, Germany).

[d] Ivoclar Vivadent (Schaan, Liechtenstein).

[e] Bisco (Schaumburg, IL, USA).

[f] Komet (Lemgo, Germany).

[g] GC Corporation (Tokyo, Japan).

[h] Kerr Co. Orange, CA, USA.

applied. In nine studies finishing and polishing of the restoration was performed immediately after composite placement [14,15,41,42,48–53,55,57–60,63], while in two studies the restorations had been finished and polished in the next clinical appointment or one week after [13,39,40,44]. In four studies the restorations had been finished immediately after placement, while the restorations were polished only one week after [45–47,54]. Four studies did not report on this procedure [43,56,61,62].

3.6. Assessment of the risk of bias

For the majority of studies, bias was judged as unclear, as allocation concealment was not reported or the patient and/or operator were not blinded during assessment (Fig. 2). On the other hand, the majority of studies reported blinding of the evaluator, with exception of two studies that did not report on this item [43,56]. At study level, of the 19 studies, none was considered to be at low risk of bias; four [13,39–42,44,55] were considered to be at high risk of bias and the remaining were judged to be at unclear risk of bias (Fig. 2).

3.7. Meta-analyses

Meta-analyses included all studies of low and unclear risk of bias and for which data on color match and surface texture were present. Three studies were excluded from the meta-analysis, due to high risk of bias in the key domains [41,42,44,55] (Fig. 1).

Meta-analysis was grouped as follow: 1) nanofilled vs. hybrid composite, including ten studies [13,15,39,40,45–47,53,54,59–62] and 2) nanohybrid vs. hybrid including eight studies [14,43,48–54,56–58,63]. Variations in the number of studies in the meta-analysis of the different follow-ups depended on the follow-ups reported by the investigators and whether the specific outcome was reported by authors.

3.8. Surface texture

Risk differences for the comparison between nanofilled and hybrid composite varied from -1% (95 % CI -4% to 1%) at the 12–18 months follow-up (Fig. 3A) to -2% (-8% to 3%) at the 36–60 months recall (Fig. 3C). Risk ratios for the comparison between nanohybrid and hybrid composite, varied from -3% (-10 % to 3%) at the 12- to 18 months follow-up (Fig. 4A) to 0% (-3% to 3%) at the 72 months or more recall (Fig. 4D). None of the comparisons yielded statistically significant differences ($p > 0.05$; Figs. 3 and 4). Surface texture showed a trivial heterogeneity, varying from 27 % to 81 %.

3.9. Color match

Risk differences for the comparison between nanofilled and hybrid composite varied from -2% (-6% to 2%) at the 12–18 months recall (Fig. 5A) to -4% (95 % CI -9% to 2%) at the 36 months or more-follow-up (Fig. 5C). Risk ratios for the comparison between nanohybrid and hybrid composite, varied from -7% (-21 % to 7%) at the 12- to 18 months recall (Fig. 6A) to -1% (95 % CI -5% to 4%) at the 72 months or more follow-up (Fig. 6D). None of the comparisons yielded statistically significant differences ($p > 0.05$; Figs. 5 and 6). Color match showed a trivial heterogeneity in the nanofilled vs hybrid composite comparison and a substantial heterogeneity in the nanohybrid vs. hybrid composite comparisons. Heterogeneity not due to chance varied from 0% to 100 % between studies.

3.10. Secondary outcomes variables

Other secondary outcomes variables, such as anatomic form/fracture, marginal discoloration, marginal adaptation, postoperative sensitivity, loss of restoration, and secondary caries had also been

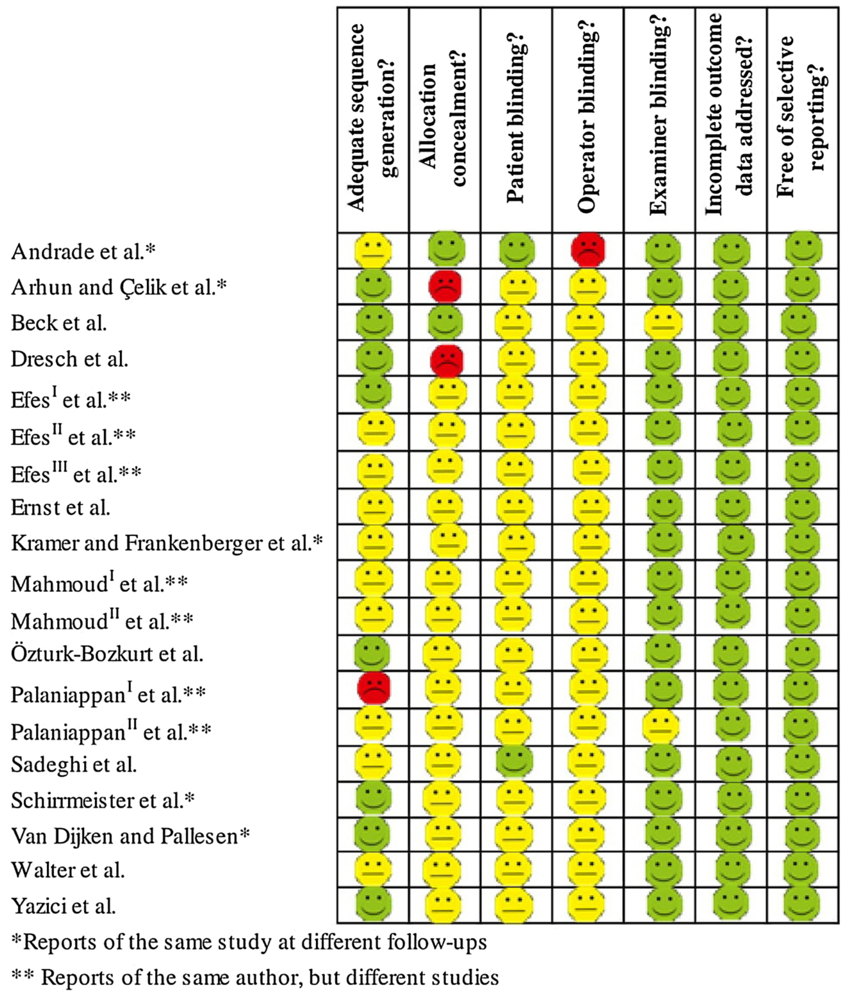

Fig. 2. Summary of the risk of bias assessment according to the Cochrane Collaboration tool.

evaluated.

The risk difference and the confidence intervals for the pairs nanofilled vs. hybrid composite and nanohybrid vs. hybrid composite can be seen in Tables 3 and 4. There were no statistically significant differences for the above mentioned secondary outcomes variables.

3.11. Sensitivity analysis

There is some heterogeneity in all meta-analyses. A non-significant p-value for heterogeneity does not mean an absence of heterogeneity, but that the variation may be trivial. In cases of significant heterogeneity, we found specific characteristics in some studies that differ from the others studies.

In a sensitivity analysis, we attempted to identify the studies that were responsible for the heterogeneity in the meta-analysis. This fact was not pre-specified in the protocol registered in PROSPERO and these findings should only be considered as speculative (Table 5).

3.12. Assessment of the quality of evidence

3.12.1. Surface texture

The body of evidence for surface texture was classified as moderate or low. This classification is shown in Figs. 3 and 4. Observed that some meta-analyses were classified as moderate, due to the unclear risk of bias for most included studies (Fig. 3 and 4). However, other meta-analyses were classified as low, due to two aspects: unclear risk of bias associated with inaccurate data and low number of included studies.

3.12.2. Color match

Similarly, the body of evidence for color match was classified as moderate or low (Figs. 5 and 6), for the same reasons that were elucidated for surface texture (s. above).

4. Discussion

Pursuant to the general concept that composites with smaller filler particles tend to wear less and minimize the surface alteration deriving from the particles' detachment [64,65], several new filler formulations have been developed. These changes in filler morphology, with reduction in size, are the most significant changes in commercial composites in recent decades [5].

A continuous decrease in particle filler size has occurred over the years, from the traditional to the nanohybrid and nanofilled materials, to obtain materials with improved mechanical properties and aesthetics [12]. These variations in average size, amount, and volume created a large variety of composite categories, confusing clinical practitioners when choosing the restorative material that best balances several requirements, such as price, ease of use, ease of polishing, clinical efficacy and scientific evidence. The variety and amount of commercial composites available today makes a direct comparison of their efficiency in clinical studies impossible [66].

A meta-analysis that comprise data of many single clinical studies provide better estimate of the effect size than single studies [67]. As the primary studies present their data in different follow-ups, data of studies were grouped in similar follow-up periods. This was done because

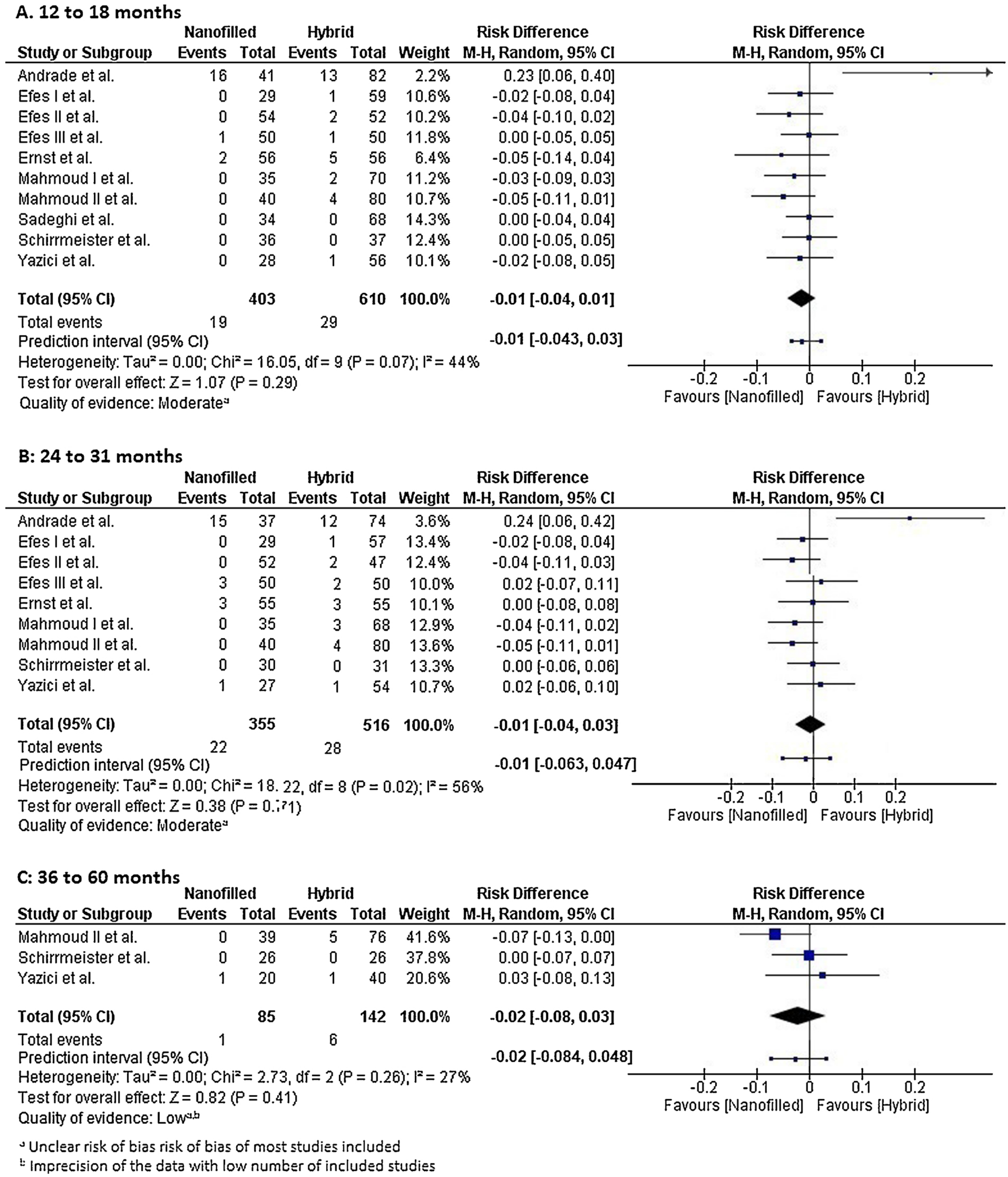

Fig. 3. Forest plot of surface texture comparing *nanofilled vs. hybrid* composite at different follow-ups.

the composite resins have different mechanical, physical and handling properties and this can affect their longevity [20]. Thus, knowing the clinical performance of these materials at the longest follow-ups is important for clinicians and researchers. Another important piece of information is that, as reported in the results section, the great majority of the studies involved multiple restorations placed per patient, and they considered the restoration, not the patient, to be the experimental unit of their studies. In the present meta-analyses, we had to make the same assumptions as in the primary studies, i.e., we had to consider the restorations as the experimental units. Though not ideal, as restorations placed within the same patient are clustered, this clustering could not be taken into consideration, given the limitations in the data reports of the primary studies.

Surface texture and color match were selected as primary outcomes variables because nanohybrid and nanofilled composites reportedly have a smoother surface [67] and lower susceptibility to color change [68] over time than the traditional hybrid composites. These advantages are seen as positive from a clinical perspective, as lower surface roughness reduces bacterial adhesion and improves color match, consequently contributing to the reduction of other types of restoration failures [42,69]. All of these aspects can be partially observed in a systematic review of resin composite in posterior restorations published by Heintze, Rousson [3]. The authors demonstrated a clear tendency of microfiller composites to show a more rapid loss of color match than

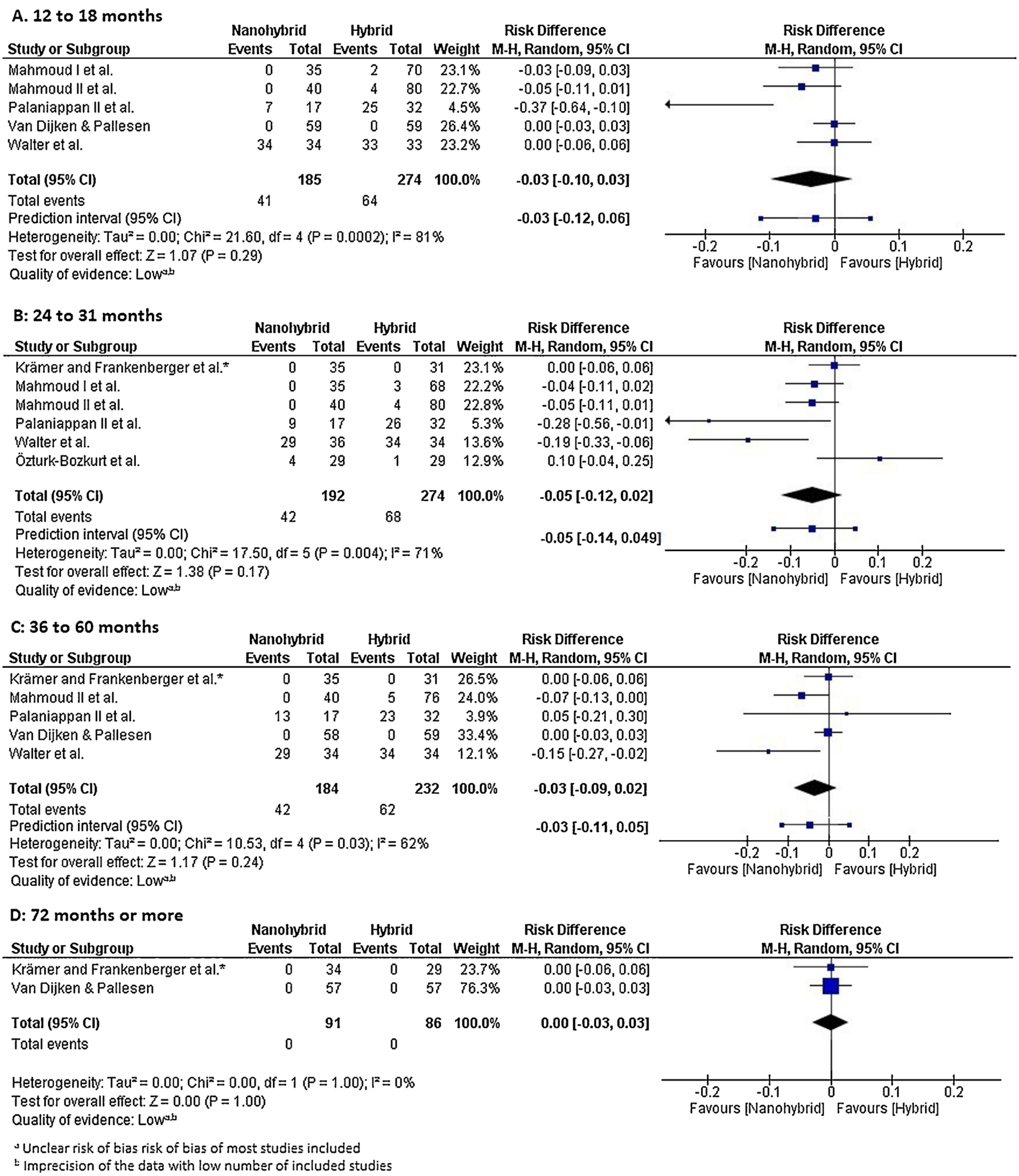

Fig. 4. Forest plot of surface texture comparing *nanohybrid vs. hybrid* composite at different follow-ups.

hybrid composites. However, the claimed advantages of nanofilled and nanohybrid composites [70], in terms of improved surface texture, were not confirmed in the present study. There was a very low difference in the risks for inadequate surface texture between both groups.

The mechanical and esthetic properties of a restoration are dependent on many factors and not solely on the filler type and brand of the composite selected for the restorative procedures. Patient-related features, professional ability, and restorative protocol may be even more important than the filler type and brand itself. Irrespective of the composite brand selected, when placed under ideal circumstances, a long-lasting restoration can be produced [71].

Additionally, not only benefits should be expected when reducing the size of filler particles. For instance, the larger surface area to volume ratio of the fillers presented in nanofilled and nanohybrid materials may increase water uptake and degradation of the filler/matrix interface, affecting their mechanical properties, relative to the hybrid composites [72]. As such, the benefits that can be achieved with reduced filler size may not overcome these disadvantages sufficiently, so that improvements in clinical performance are not observed.

Another purported advantage of nanohybrid and nanofilled composites is that their staining susceptibility is lower [70,73] than that of hybrid composites, which was also not confirmed in the present study with the data on color match. All meta-analyses of color match failed to show differences between the different types of composites in any of the study follow-ups. Thus, this advantage, claimed by manufacturers, is neither confirmed by clinical data nor by laboratory studies [74,75].

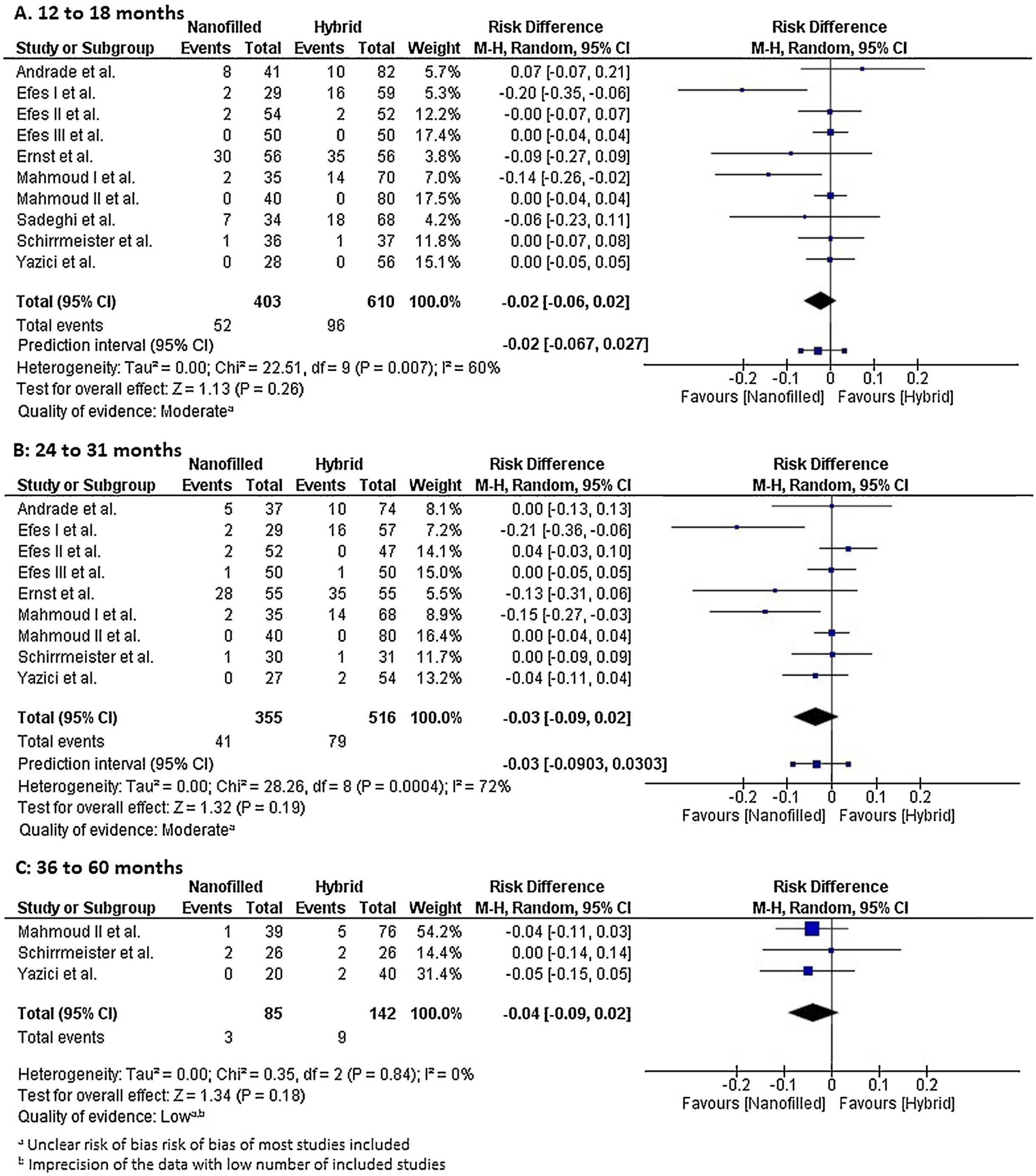

Fig. 5. Forest plot of color match comparing *nanofilled vs. hybrid* composite at different follow-ups.

Lee et al. [76] concluded that smoother surfaces were not necessarily the most stain resistant, as staining ability may also be influenced by composite monomers and filler composition. For all other secondary outcomes, there was no difference between types of composites.

The heterogeneity in some of the meta-analyses presented in this study needs further comments. Heterogeneity is not inherently good or bad in meta-analysis, but it casts doubt on the reasonability to believe in an overall estimate that applies to all the encompassed studies [77]. In the absence of between-study heterogeneity or the presence of trivial heterogeneity, we can consider that the mean effect size applies to all comparable populations. However, in the presence of heterogeneity, there is no common effect size that applies to all populations [78]. As expected in the meta-analyses of this study, substantial heterogeneity (significant p-value and moderate and high I^2 value) was observed meaning that there are other factors, apart from the ones investigated that affect the magnitude of the intervention effect size. It would not be justifiable to measure an average intervention effect if heterogeneity was observed in the direction of the effects: with some studies showing beneficial effects and others showing the opposite. As we did not observe heterogeneity in the direction of the effect sizes, it seems reasonable and useful to estimate an average intervention effect among studies. The treatment effect varies substantially among treatments, and future studies should therefore focus on the identification of factors that can explain this variability [79], to inform clinicians on the type of population that may benefit best from a specific treatment.

In spite of the heterogeneity of the clinical studies and the bias of many of them, it seems noneless reasonable to assume that there is no clinical effect of different filler concepts of materials (nano/

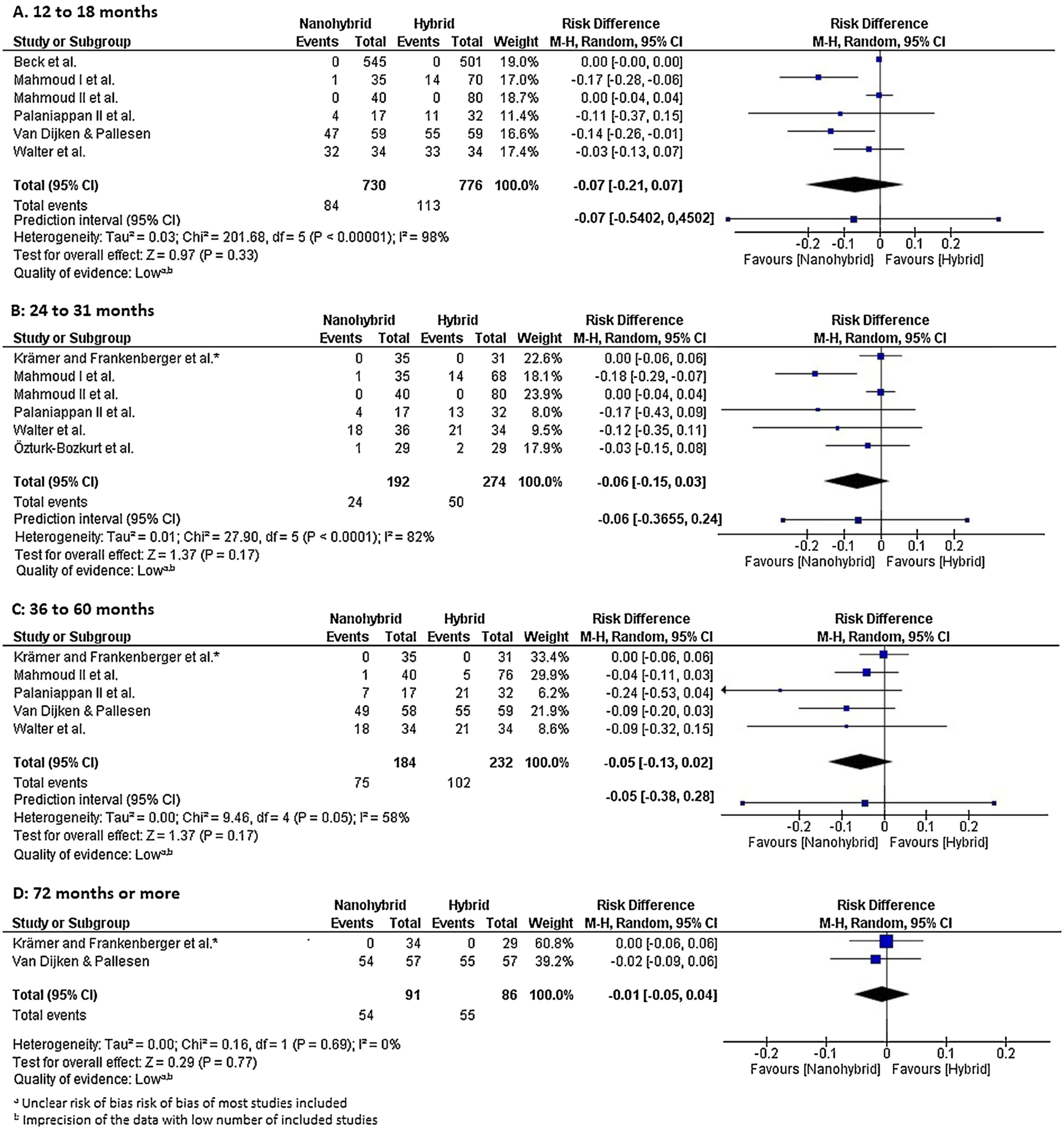

Fig. 6. Forest plot of color match comparing *nanohybrid vs. hybrid* composite at different follow-ups.

nanohybrid/microhybrid/hybrid) on color match, gloss stability, fracture incidence and overall longevity. The results might be different, if the same operator applies the same materials in the same patients; this would rule out or at least diminish patient- and operator-related effects. Also, the results might be different, if the analysis focuses on different brands which, however, would only be feasible if an adequate number of clinical studies with the same brands would be available for analysis. One can speculate about confounding factors, such as patient factors (diet, oral hygiene, caries activity, chewing forces), operator factors (skill of operator GP versus academic setting, shade selection) and tooth factors (type of tooth, extension of restoration) [80–82].

When we analyze heterogeneity, we tend to ask how much of the true effect size varies across studies. Unfortunately, none of the statistics that typically report on heterogeneity in meta-analysis (Q-statistics, p-value, tau^2, and I^2) directly addresses this question. Although the results were reported in the forest plots of this study, we also included the 95 % prediction interval that gives us information on how widely the effects are actually spread over the mean effect. In all meta-analyses that compared nanofilled vs. hybrids, the 95 % prediction interval was shown to be shorter than those reported in the meta-analyses that compared nanohybrids vs. hybrid composites. This probably reflects the fact that there are several brands of nanohybrid composites included in the present study and only one brand of nanofilled composite. The fact that the same type of composite was tested in all studies reduced this source of heterogeneity and may account for the reduced amount of heterogeneity observed.

Although sensitivity analysis tried to identify the causes of heterogeneity, as described in the results section of this paper, its results are observational, not causal. It is possible that some of the different features of the studies causing heterogeneity (reported in the results section) may be responsible for the observed variation in the effect sizes. However, it is also possible that the difference is due to some other unknown variable. This is the reason why these analyses should not be seen as definitive, but rather exploratory.

Table 3
Data and analyses for the secondary outcomes for the comparison *nanofilled vs. hybrid* composite.

Outcome	Follow-up (months)	Nanofilled (# events/total)	Hybrid (# events/total)	Effect Estimate RD [M-H; Random, 95 % CI]	Test for overall effect	Heterogeneity	
					p-value	Chi-square p-value	I^2
Anatomic form/fracture	12 to 18	2/403	16/610	−0.01 [-0.03, 0.00]	0.10	0.72	0%
	24 to 31	17/355	31/516	−0.01 [-0.03, 0.02]	0.56	0.99	0%
	36–60	4/85	9/142	−0.03 [-0.10, 0.03]	0.34	0.22	33%
Marginal discoloration	12 to 18	14/403	22/610	−0.00 [-0.02, 0.02]	0.94	0.89	0%
	24 to 31	16/355	28/516	−0.00 [-0.02, 0.02]	0.90	0.92	0%
	36–60	15/85	26/142	−0.02 [-0.08, 0.05]	0.57	0.75	0%
Marginal adaptation	12 to 18	20/403	45/610	−0.02 [-0.04, 0.00]	0.08	0.99	0%
	24 to 31	21/355	44/516	−0.02 [-0.04, 0.00]	0.12	0.91	0%
	36–60	9/85	21/142	−0.03 [-0.09, 0.03]	0.38	0.76	0%
Postoperative sensitivity	12 to 18	0/403	0/610	0.00 [-0.01, 0.01]	1.00	1.00	0%
	24 to 31	0/355	0/516	0.00 [-0.01, 0.01]	1.00	1.00	0%
	36–60	0/85	0/142	0.00 [-0.03, 0.03]	1.00	1.00	0%
Loss of restoration	12 to 18	0/403	0/610	0.00 [-0.01, 0.01]	1.00	1.00	0%
	24 to 31	1/356	5/521	−0.01 [-0.02, 0.01]	0.50	0.99	0%
	36–60	1/86	4/146	−0.01 [-0.05, 0.03]	0.66	0.84	0%
Secondary caries	12 to 18	0/403	0/610	0.00 [-0.01, 0.01]	1.00	1.00	0%
	24 to 31	1/355	0/516	0.00 [-0.01, 0.02]	0.85	1.00	0%
	36–60	0/85	0/142	0.00 [-0.03, 0.03]	1.00	1.00	0%

Abbreviations: RD–Risk Difference; M-H–Mantel-Haenszel; CI–Confidence Interval; I^2–Heterogeneity.

It is important to emphasize that no eligible study was classified as having a low risk of bias, mainly due to unclear reporting of sequence generation, allocation concealment and evaluators' blinding. The inadequate report of these domains was observed in many other systematic reviews in the dental field [83–86]. The unclear risk of bias of most studies, as well as the imprecision observed in all meta-analyses, make our confidence in the estimates and conclusion of this systematic review moderate to low. This highlights the need to conduct well-designed clinical trials, especially with longer follow-up periods, as only a few studies reported on clinical outcomes of periods longer than 6 years. The lack of studies with longer follow-up periods is explained by the high drop-out rates of patients after long periods of time. As it is difficult to predict the drop-out rates after long follow-up periods, studies with longer follow-ups are usually underpowered and do not offer precise information. Even so, they should be reported in the literature so that authors of systematic reviews can merge different study findings, thus increasing power and allowing the achievement of more precise conclusions.

5. Conclusions

The present meta-analysis revealed no significant differences between nanofilled/nanohybrid and hybrid composite in any of the investigated parameters (color match, surface texture, surface staining, fracture incidence, overall longevity). However most of the included studies showed some degree of bias which emphasized the need for well-conducted randomized controlled clinical trials.

Table 4
Data and analyses for the secondary outcomes for the comparison *nanohybrid vs. hybrid* composite.

Outcome	Follow-up (months)	Nanohybrid (# events/total)	Hybrid (# events/total)	Effect Estimate RR (M-H Random, 95 % CI)	Test for overall effect	Heterogeneity	
					p-value	Chi-square p-value	I^2
Anatomic form/fracture	12 to 18	35/185	40/274	−0.03 [-0.06, 0.01]	0.13	0.83	0%
	24 to 31	33/157	37/243	−0.03 [-0.06, 0.01]	0.21	0.60	0%
	36–60	35/149	42/201	−0.04 [-0.08, 0.01]	0.11	0.40	0%
Marginal discoloration	12 to 18	10/730	11/776	−0.00 [-0.02, 0.01]	0.64	0.29	19%
	24 to 31	12/157	8/243	0.02 [-0.03, 0.07]	0.38	0.30	18%
	36–60	8/149	9/201	0.00 [-0.06, 0.07]	0.90	0.09	54%
Marginal adaptation	12 to 18	54/730	58/776	−0.01 [-0.03, 0.01]	0.34	0.83	0%
	24 to 31	49/192	60/274	−0.05 [-0.12, 0.03]	0.24	0.007	69%
	36–60	64/184	61/232	−0.00 [-0.05, 0.04]	0.87	0.47	0%
	72 or more	45/91	33/86	0.09 [-0.01, 0.19]	0.07	0.69	0%
Postoperative sensitivity*	12 to 18	1/185	0/274	0.00 [-0.02, 0.02]	0.85	0.97	0%
	24 to 31	0/192	1/274	−0.00 [-0.02, 0.02]	0.83	0.99	0%
	36–60	0/184	1/232	−0.00 [-0.02, 0.02]	0.84	0.97	0%
	72 or more	0/91	0/86	0.00 [-0.03, 0.03]	1.00	1.00	0%
Loss of restoration	12 to 18	7/737	3/779	0.01 [-0.00, 0.01]	0.10	0.99	0%
	24 to 31	2/194	5/279	−0.01 [-0.03, 0.02]	0.54	0.96	0%
	36–60	4/188	7/239	−0.01 [-0.04, 0.03]	0.72	0.54	0%
	72 or more	1/92	1/87	−0.00 [-0.03, 0.03]	0.97	0.90	0%
Secondary caries	12 to 18	4/730	4/776	−0.00 [-0.01, 0.01]	0.87	1.00	0%
	24 to 31	0/192	3/274	−0.00 [-0.03, 0.02]	0.61	0.95	0%
	36–60	2/184	3/232	0.00 [-0.03, 0.03]	0.89	0.99	0%
	72 or more	4/91	7/86	−0.02 [-0.08, 0.05]	0.63	0.25	25%

Abbreviations: RD–Risk Difference; M-H–Mantel-Haenszel; CI–Confidence Interval; I^2-Heterogeneity.

* The study of Beck et al. [43] was not included in the evaluation of postoperative sensitivity in the comparison of *nanohybrid vs. hybrid* composite because the study included teeth with root canal treatment.

Table 5
Heterogeneity of the meta-analysis of the primary outcomes and the studies that may have been responsible for the heterogeneity.

Outcome	Comparison	Follow-up (months)	Heterogeneity		
			p-value	I^2 (%)	Studies likely responsible for the heterogeneity
Surface texture	*Nanofilled* vs *hybrid*	24 – 31	0.02	56	Andrade et al. [13,39,40] – the population of this study was composed only by teenagers of about 13 years
	Nanohybrid vs. *hybrid*	12 – 18	= 0.0002	81	Palaniappan et al. [56] – only that used a bevel in the cavities preparation
		24 – 31	= 0.0004	71	Reason not found
		36 – 60	= 0.03	62	Reason not found
Color match	*Nanofilled* vs *hybrid*	12 – 18	= 0.007	60	Efes et al. [45–47] and Mahmoud et al. [53,54] – at baseline, hybrid composite was already classified as bravo score.
		24 – 31	= 0.0004	72	Reason not found
	Nanohybrid vs. *hybrid*	12 – 18	< 0.00001	98	Reason not found
		24 – 31	< 0.0001	82	Reason not found

Declaration of Competing Interest

There was no conflict of interest present during the undertaking of this study. The study did not receive any internal or external funding.

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