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Clinical Performance of Filled/ Nanofilled Versus Nonfilled Adhesive Systems in Noncarious Cervical Lesions: A Systematic Review and Meta-analysis

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Clinical Relevance

The use of filled adhesive systems does not influence the clinical performance of the adhesive restoration in noncarious cervical lesions.

SUMMARY

Objective: The aim of this meta-analysis was to investigate the clinical performance of filled vs unfilled adhesive systems when applied in noncarious cervical lesions.

Methods and Materials: A systematic search was performed in PubMed, Scopus, Web of Science, LILACS, BBO, Cochrane Library, and SIGLE. Gray literature was also screened. Only randomized controlled clinical trials were included. The risk of bias of the studies was evaluated using the Cochrane Collaboration's tool. A random-effects meta-analysis was conducted to compare the retention rate, marginal discoloration, and secondary caries of noncarious cervical lesions restored with filled adhesives vs unfilled adhesives. The quality of the body of evidence was assessed using the GRADE approach.

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Results: A total of 3662 studies were identified after removal of duplicates. Twenty-nine studies remained for qualitative analyses and 28 studies for the meta-analysis. Only one study was judged to have a low risk of bias, and the other 28 were considered to have unclear risk of bias. There was no statistically significant difference between filled adhesives compared with unfilled adhesives in relation to loss of retention, marginal discoloration, or secondary caries at any of the follow-up periods (12-18 months, 24-30 months, 3 years, and 5 years or longer). The quality of evidence was graded as moderate for most outcomes at the respective follow-ups, except when there was an explained heterogeneity, which occurred mainly for loss of retention at the 12-month to 3-year follow-up. The results did not depend on whether microfilled or nanofilled adhesives had been investigated.

Conclusions: The addition of fillers into the composition of adhesive systems did not increase the clinical performance (retention rates, marginal discoloration, or secondary caries) of composite restorations placed in noncarious cervical lesions when compared with unfilled adhesives.

INTRODUCTION

In recent decades, because of an increasing demand for esthetic restorations, composite resins have gained a prominent role in modern restorative dentistry. Nowadays, composite resins are the most widely used dental material, representing 65% of the restorations currently placed in the United States.[1,2] However, it is worth mentioning that 50% to 70% of newly placed restorations are the result of failure of preexisting restorations, which results in millions of dental care dollars spent annually on replacement of these restorations.[2-4] Many of those replacements, however, are unnecessary as either the defects that led to the replacement of the restoration could be repaired adhesively with composite resins or the restorations are replaced due to economic reasons or false diagnosis by the dentist (eg, confusion of discolored margin with caries at the margins).[5-7]

Among several clinical problems of esthetic restorations, the bonding interface between the dentin and the direct restorative material is considered one of the Achilles' heels of esthetic restorations. Recently published reviews have reported that although an improvement in the clinical performance of adhesive restorations has been observed, the retention rates of composite restorations placed in noncarious cervical lesions are still a clinical problem.[8,9]

Although the exact mechanism responsible for bond degradation is not completely understood,[2] one contributing factor for debonding may arise from the low mechanical properties of the adhesive layer that bonds the composite resin material to the dental substrate. Indeed, among the substrates of this bonded interface, the adhesive layer has the lowest elastic modulus.[10,11] When submitted to masticatory stresses, the adhesive layer suffers the greatest level of strain among the components. Stress that exceeds the inherent strength of the adhesive layer results in defects, cracks, or abrupt catastrophic failure of the resin-dentin bond.[12,13]

Adhesive systems traditionally do not contain filler particles.[14] However, from a theoretical perspective and by analogy with resin composites, the addition of fillers increases the mechanical properties of the adhesive layer.[15,16] This concept was called the elastic cavity wall concept.[17,18] In the past, manufacturers added varying proportions of glass filler particles (microfiller 1-5 μm) in the hydrophobic bonding bottle of three-step etch-and-rinse adhesives.[16,19,20] These filled adhesives were loaded up to 40-50 wt%,[19] for example, of Optibond FL (Kerr Co, Orange, CA, USA) and PermaQuick (Ultradent, South Jordan, UT, USA). Because of the very good clinical performance in long-term clinical trials of these highly filled adhesives,[21-24] the same strategy was used in simplified versions of two-step etch-and-rinse adhesives and in the self-etch adhesives.[8]

In simplified adhesives, hydrophobic resins are combined with priming and/or acidic monomers, which do not allow the addition of a large filler amount. For example, two-step etch-and-rinse adhesives contain about 8.5-15 wt% of fillers in their composition (OptiBond Solo, Kerr Co.; One-Step Plus, Bisco Inc, Schaumburg, IL, USA),[16,25-27] which is less than half of the amount that is added in three-step etch-and-rinse systems. By adding large filler amounts, adhesives become more viscous, and this jeopardizes the wettability of the dental substrates.[15,16]

Instead of microfillers, nanofillers have been added into the adhesive systems.[28] Apart from improving the strength of the adhesive layers, nanofillers can penetrate into dentin tubules and into the collagen network.[16,27] Nanometer-sized silica (pure silicon dioxide) smaller than 20 nm are usually added.[26,29] Some two-step etch-and-rinse

systems (Prime & Bond NT and XP Bond, Dentsply Sirona and Adper Scotchbond 2 XT, 3M OralCare) and one-step self-etch adhesive systems (Clearfil S3 Bond, Kuraray and G-Bond, GC Corp) that contain nanofillers are available on the market; the amount usually ranges between 5 wt% and 10 wt%.[16]

Studies have shown that simplified adhesives with nanofillers may have better mechanical properties compared with unfilled adhesive systems; however, the improvement is material dependent.[30,31] In addition, studies have also proven that the addition of nanofillers does not increase the bond strength to dentin.[32-35] A closer view showed inconclusive results when clinical studies evaluating filled vs unfilled adhesives were evaluated.[36-45] Therefore, the aim of this systematic review and meta-analysis was to answer the following focused PICO question- (P, participant; I, intervention; C, comparator; O, outcome): "Are the retention rates, marginal discoloration, and secondary caries of composite resin restorations placed in noncarious cervical lesions of patients superior when bonded with filled/nanofilled adhesives compared with unfilled adhesives?"

METHODS AND MATERIALS

The methodology described in the present study follows the PRISMA requirements (Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement).[46]

Protocol and Registration

The study was registered in the PROSPERO database (CRD42018093198) and performed from May to August 2018 at the State University of Ponta Grossa, Paraná, Brazil.

Information Sources and Search Strategy

The search strategy used in the PubMed database was developed based on the concepts of patient and intervention from the focused PICO question described at the end of the Introduction section. Within each concept, the controlled vocabulary (Medical Subject Headings terms) and free keywords were combined with the Boolean operator "OR." Then, the concepts were combined with the Boolean operator "AND" to restrict the search. A filter for randomized clinical trials was also used for the PubMed database (Table 1). Table 1 also lists other electronic databases that were searched (Web of Science, Scopus, Cochrane Library, Latin American and Caribbean Health Sciences Literature database [LILACS] and Brazilian Library in Dentistry [BBO]). The reference lists of all primary studies were hand searched for additional relevant publications as well as links to related articles of each primary study in the PubMed database. No restrictions on publication date or languages were made.

The gray literature was also inspected by looking up abstracts of the International Association for Dental Research and their regional divisions (1990-2016), the System for Information on Grey literature in Europe (SIGLE), dissertations and theses using the ProQuest Dissertations and Theses full-text database, as well as the *Periodicos* Capes Theses database. Ongoing trials were searched in the following clinical trials registries: Current Controlled Trials (www.controlled-trials.com), International Clinical trials registry platform (http://apps.who.int/trialsearch/), ClinicalTrials.gov (www.clinicaltrials.gov), Rebec (www.rebec.gov.br), and EU Clinical Trials Register (https://www.clinicaltrialsregister.eu).

Eligibility Criteria

We included randomized clinical trials (RCTs) with parallel and split-mouth designs that compared the retention rates or other secondary outcomes (caries at restorative margins and marginal discoloration) of filled/nanofilled adhesives vs unfilled adhesives for bonding composite resin restorations in noncarious cervical lesions. RCTs were excluded if they 1) compared the same type of adhesive, 2) compared the association among different adhesives in the same restorations, or 3) compared filled vs nanofilled adhesives.

Study Selection and Data Collection Process

After database screening, duplicates were removed and possible eligible articles were selected according to title and abstracts. Full-text articles were obtained by two authors (JLG and BMM), and they were classified according to the inclusion criteria. Pilot-tested, customized extraction forms were used to register details about the studies, such as study design, participants, interventions, and outcomes. Each study received an identification number (study ID), combining the first author name and the publication year. Authors were not contacted for further information to avoid recall bias.

Data Items

When there were multiple reports of the same study (ie, reports with different follow-ups), data from all reports were extracted directly into a single data

Table 1: *Electronic Database and Search Strategy*

PubMed, March 22, 2018: 2980			
#1 (tooth erosion[MeSH Terms] OR tooth abrasion[MeSH Terms] OR tooth cervix[MeSH Terms] OR "cervical lesion"[Title/Abstract]) OR "cervical lesions"[Title/Abstract]) OR "class V'[Title/Abstract] OR "class 5′[Title/Abstract] OR abfraction[Title/Abstract] OR "tooth cervix"[Title/Abstract])	**#2** (dentin-bonding agents[mh:noexp]) 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 "dentin bonding agent"[Title/Abstract] OR "dentin bonding agents"[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 "one-bottle adhesive"[Title/Abstract] OR "one-bottle adhesives"[Title/Abstract] OR "filled adhesive" [Title/Abstract]OR "unfilled adhesive" [Title/Abstract])	**#3** (dental restoration, permanent[MeSH Terms] OR composite resins[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])	**#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]))
Scopus: March 22, 2018: 742			
#1 (TITLE-ABS-KEY (**"tooth erosion"**) OR TITLE-ABS-KEY (**"tooth abrasion"**) OR TITLE-ABS-KEY (**"tooth cervix"**) OR TITLE-ABS-KEY (**"cervical lesion"**) OR TITLE-ABS-KEY (**"class V"**) OR TITLE-ABS-KEY (**"class 5"**) OR TITLE-ABS-KEY (**abfraction**))	**#2** 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("resin composite") OR TITLE-ABS-KEY("resin restoration") OR TITLE-ABS-KEY("composite restoration")OR TITLE-ABS-KEY (**"dental restoration"**) AND (LIMIT-TO (SUBJAREA , **"DENT"**))	
Web of Science search: March 22, 2018: 515			
Tópico: ("tooth erosion") *OR***Tópico:** ("tooth abrasion") *OR***Tópico:** ("tooth cervix") *OR***Tópico:** ("cervical lesion*") *OR***Tópico:** ("class V") *OR***Tópico:** ("class 5") *OR***Tópico:** (abfraction)	**#2**Topic: ("adhesive system*") OR Topic: ("bonding agent*") OR Topic: ("dental adhesive*") OR Topic: ("dentin bonding") OR Topic: ("adhesive material*") OR Topic: ("etch and rinse") OR Topic: ("total etch") OR Topic: ("self etch*") OR Topic: ("all in one") OR Topic: ("one bottle") OR Topic: ("*filled adhesive*")	**#3**Topic: ("resin composite*") *OR***Tópico:** ("dental restoration*")OR Topic: ("composite resin*") OR Topic: ("resin restoration*") OR Topic: ("composite restoration*")	

Table 1: *Electronic Database and Search Strategy (cont.)*

PubMed, March 22, 2018: 2980		
#1 AND #2 AND #3		
Lilacs and BBO: March 22, 2018: 358		
(MH:"tooth erosion" OR MH:"tooth abrasion" OR MH:"tooth cervix" OR "cervical lesion" OR "lesão cervical" OR "lesión cervical" OR "cervical lesions" OR "lesões cervicais" OR "lesiones cervicales" OR "class V" OR "classe V" OR "clase V" OR "class 5" OR "classe 5" OR "clase 5" OR abfraction OR "abfração" OR "abfracción")	#2(MH:"dentin-bonding agents" OR "adhesive system" OR "adhesive systems" OR "sistema adesivo" OR "sistemas adesivos" OR "sistema adhesivo" OR "sistemas adhesivos" OR "bonding agent" OR "bonding agents" OR "agentes de união" OR "agentes de unión" OR "agentes de ligación" OR "agentes de enlace" OR "dental adhesive" OR "dental adhesives" OR "adesivo dental" OR "adhesivo dental" OR "adesivos dentais" OR "adhesivos dentales" OR "adhesive material" OR "material adesivo" OR "material adhesivo" OR "adhesive materials" OR "materiais adesivos" OR "materiales adhesivos" OR "adesivo dentinário" OR "adesivos dentinários" OR "adhesives dentinarios" OR "adhesive material" OR "adhesive materials" OR "dentin bonding agent" OR "dentin bonding agents" OR "etch-and-rinse adhesive" OR "etch-and-rinse adhesives" OR "adesivo convencional" OR "adesivos convencionais" OR "adhesive convencional" OR "adhesives convencionales" OR "total-etch adhesive" OR "total-etch adhesives" OR "condicionamento ácido total" OR "adhesivo de grabado total" OR "adhesivos de grabado total" OR "self-etch adhesive" OR "self-etch adhesives" OR "adesivo autocondicionante" OR "adesivos autocondicionantes" OR "adhesive autograbado" OR "adhesives autograbados" OR "self-etching adhesive" OR "self-etching adhesives" OR "all-in-one adhesive" OR "all-in-one adhesives" OR "adesivo de passo único" OR "adesivos de passo único" OR "adhesivo de paso unico" OR "adhesivos de passo unico" OR "one-bottle adhesive" OR "one-bottle adhesives" OR "adesivo de frasco único" OR "adesivos de frasco único" OR "filled adhesive" OR "unfilled adhesive" OR "filled adhesives" OR "unfilled adhesives")	**#3** (MH: "composite resins" OR MH:"dental restoration, permanent" OR "resin composite" OR "resin composites" OR "resina composta" OR "resinas compostas" OR "resina compuesta" OR "resinas compuestas" OR "composite resin" OR "composite resins" OR "compósito" OR "compósitos" OR "resin restoration" OR "resin restorations" OR "restauração de resina" OR "restauração de resinas" OR "restauración de resina" OR "restauraciones de resina" OR "composite restoration" OR "composite restorations" OR "restauração de compósito" OR "restaurações de compósitos" OR "restauração de resina composta" OR "restaurações de resinas compostas")

Table 1: *Electronic Database and Search Strategy (cont.)*

PubMed, March 22, 2018: 2980		
#1 AND #2 AND #3		
Cochrane Library: March 22, 2018: 286		
#1MeSH descriptor: [Tooth Erosion] explode all trees	#12MeSH descriptor: [Dentin-Bonding Agents]	#23*filled adhesive*
#2MeSH descriptor: [Tooth Abrasion] explode all trees	#13adhesive next system*:ti,ab,kw	#24 #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23
#3MeSH descriptor: [Tooth Cervix] explode all trees	#14bonding next agent*:ti,ab,kw	#25MeSH descriptor: [Composite Resins]
#4cervical next lesion?:ti,ab,kw	#15dental next adhesive*:ti,ab,kw	#26MeSH descriptor: [Dental Restoration, Permanent]
#5"class V":ti,ab,kw	#16dentin bonding agent*:ti,ab,kw	#27resin near composite*:ti,ab,kw
#5"class 5":ti,ab,kw	#17adhesive next material*:ti,ab,kw	#28composite next resin*
#7abfraction:ti,ab,kw	#18"etch and rinse":ti,ab,kw	#29resin near restoration*
#8tooth next cervix:ti,ab,kw	#19total next etch*:ti,ab,kw	#30composite next restoration*:ti,ab,kw
#9 tooth next erosion:ti,ab,kw	#20"self etch*":ti,ab,kw	#31#25 or #26 or #27 or #28 or #29 or #30
# 10 tooth next abrasion:ti,ab,kw	#21"all in one":ti,ab,kw	#32#11 and #24 and #31
#11 #1 or #2 or #3 or #4 0r #5 or #6 or #7 or #8 or #9 or #10	#22"one bottle":ti,ab,kw	

collection form to avoid overlapping data. We collected data about retention rates, marginal discoloration, and secondary caries. Usually, clinical studies on restorative materials use USPHS criteria, which are classified as Alpha, Bravo, and Charlie. We dichotomized the ordinal data into Alpha+Bravo/Charlie. For clinical studies using World Dental Federation criteria, the ordinal data were dichotomized as clinically acceptable or clinically unacceptable. The data were collected into different follow-up evaluations: 12 to 18 months, 24 to 30 months, 3 years, and 5 years or longer. When more than one adhesive of each type was included in the study, their values were combined to make a single entry. In the case of data inconsistencies between reports of different follow-up evaluations of the same study, data were collected from the most recent article. Subgroup analysis based on the type of filler (regular or nanofillers) was performed whenever data were available.

Risk of Bias in Individual Studies

Two authors (JLG and BMM) independently assessed the risk of bias of the studies selected using the Cochrane Collaboration's tool for assessing risk of bias in randomized trials.[47] The risk of bias tool contains six domains: sequence generation, allocation concealment, blinding of the outcome assessors, incomplete outcome data, selective outcome reporting, and other possible sources of bias. Each domain was judged to be at low, unclear, or high risk of bias according to the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0 (http://handbook.cochrane.org).

The key domains of this study were sequence generation, allocation concealment, and examiner blinding. At the study level, the study was at low risk of bias if all key domains were at low risk of bias. If one key domain was judged as having high risk of bias, the study was considered as having a high risk of bias. If at least one key domain was judged as at unclear risk among other low-risk of bias domains, the study was considered as having unclear risk of bias. During data selection and quality assessment, any disagreements between the reviewers were solved through discussion and if needed by consulting a third reviewer (ADL).

Summary Measures and Synthesis of the Results

Dichotomous data (loss of retention, marginal discoloration, and secondary caries) were meta-analyzed to obtain a combined estimate of the overall risk difference (RD) with a 95% confidence interval. This procedure was done in different follow-ups: 12 to 18 months, 24 to 30 months, 3 years, and 5 years or longer. Subgroup analysis based on the type of filler (microfillers or nanofillers) was performed whenever data were available in each follow-up. Random effect models were used for all meta-analyses, and we assessed heterogeneity (which represents any kind of variability among studies) by using the Cochran Q test and I^2 statistics. We carried out the analyses by using the software RevMan 5.3 (Review Manager version 5, The Cochrane Collaboration, Copenhagen, Denmark).

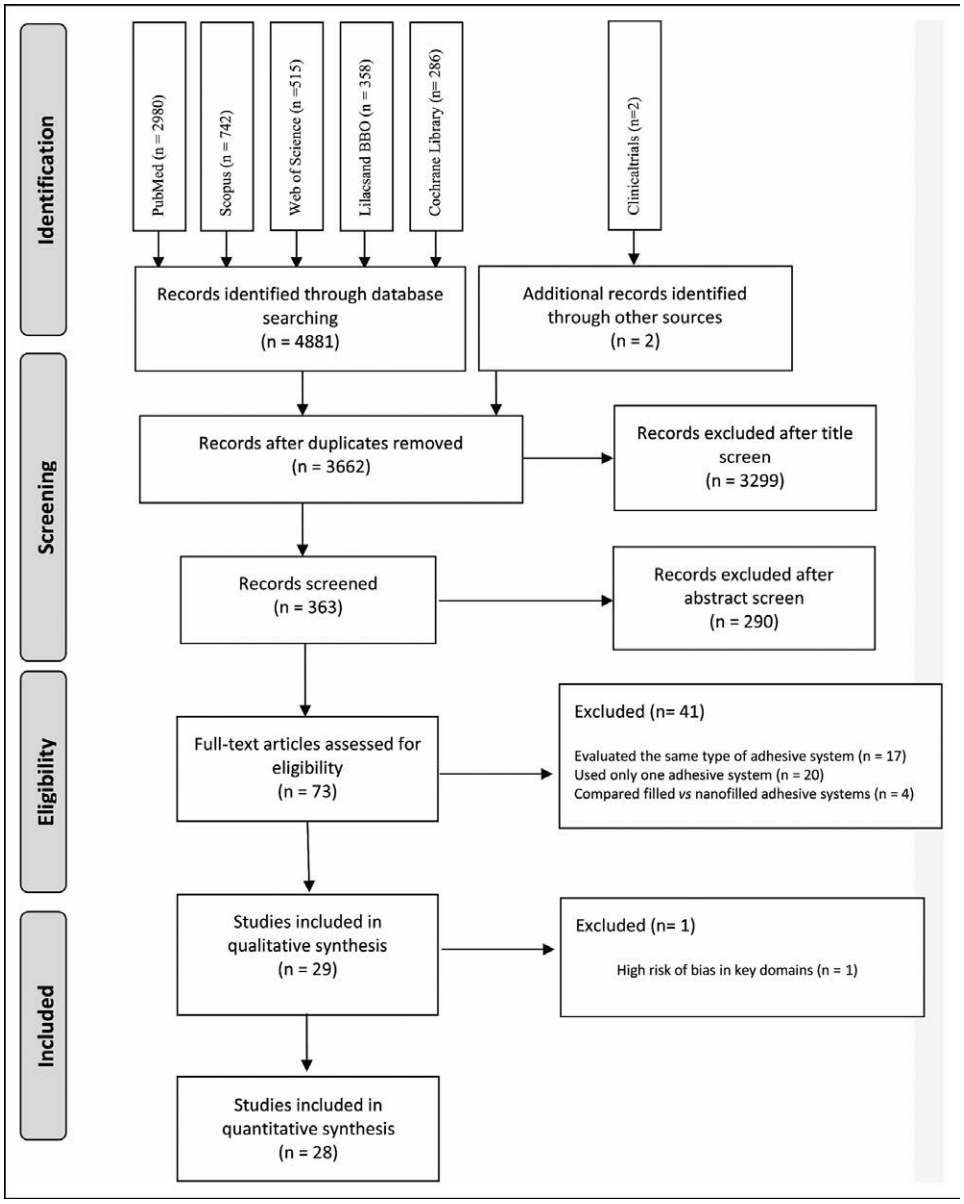

Figure 1. *Flowchart diagram showing the number of articles obtained in the different phases of the study.*

In case of heterogeneity, a sensitivity analysis was performed.

Assessment of the Quality of Evidence Using GRADE

The quality of the evidence was graded for each outcome variable across studies (body of evidence) using the Grading of Recommendations: Assessment, Development and Evaluation (GRADE; http://www.gradeworkinggroup.org/) to determine the overall strength of evidence. The GRADE approach is used to contextualize or justify intervention recommendations with four levels of evidence quality, ranging from high to very low.

The GRADE approach begins with the study design (RCTs or observational studies) and then addresses five reasons (risk of bias, imprecision, inconsistency, indirectness of evidence, and publication bias) to possibly rate down the quality of evidence (one or two levels) and three to possibly rate up the quality (large effect, management of confounding factors, dose-response gradient).[48] Each one of these topics was assessed as "no limitation," "serious limitations," or "very serious limitations" to allow categorization of the quality of the evidence for

Table 2: *Summary of the Studies Included in the Systematic Review*

Study ID	Follow-up, mo	Study Design	Subjects' Age, Mean ± SD [range], y	Total Number of Subjects [Male]	Number of Restorations per Group at Baseline
Abdalla and Garcia-Godoy [105]	12 and 24	Multiple restorations	n.r. ± n.r. [35-52]	48 [n.r.]	AB – 65 CSE – 65 HB – 65
Aw and others [94]	6, 12, 24, and 36	Multiple restorations	51 ± n.r. [29-75]	57 [n.r.]	SB – 47 SM – 51 OCB – 48
Boushell and others [95]	6, 18, 36, and 72	Multiple restorations	55.4 ± 9.5 [30-75]	39 [13]	XIII – 39 XIV – 40 XP – 41
Burrow and Tyas [96]	6, 12, 24, and 36	Multiple restorations	61 ± n.r. [n.r.-n.r.]	20 [n.r.]	SB – 30 CSE – 31
Eliguzeloglu, Dalkilic, and Omurlu [43]	3, 12, and 24	Multiple restorations	n.r. ± n.r. [30-70]	29 [16]	SB – 60 CSE – 102 XIII – 90
De Araújo and others [91]	6 and 12	Multiple restorations	n.r. ± n.r. [23-54]	17 [n.r.]	SM – 31 EO – 31
Dutra-Correa and others [97]	6 and 18	Multiple restorations	48.7 ± n.r. [27-79]	37 [n.r.]	XV – 30 XP – 30
Hafer and others [98]	6, 12, 24, and 36	Multiple restorations	46.7 ± 14.1 [18-66]	40 [n.r.]	FM – 40 SoM – 40 SC – 30
Hansen and others [37,38]	36, 48, and 60	Multiple restorations	n.r. ± n.r. [n.r. ± n.r.]	n.r. [n.r.]	G – 75 SM – 30
Horsted-Bindslev and others [36]	6, 12, 18, and 24	Multiple restorations	n.r. ± n.r. [n.r. ± n.r.]	10 [n.r.]	G – 26 SM – 26
Jang and others [45]	6, 12, 18, and 24	Multiple restorations	55 ± n.r. [30-73]	35 [n.r.]	CSE – 83 XV– 81
Jordan and Suzuki [92]	6 and 12	Multiple restorations	n.r. ± n.r. [n.r. ± n.r.]	n.r. [n.r.]	G2000 – 95 T – 115 PUB 3 – 100 AB2 – 101
Kubo and others [99]	12, 24, 36, 48, and 60	Multiple restorations	61.3 ± n.r. [45-78]	8 [4]	CLB – 36 SB – 35
Kurokawa and others [93]	3, 6, and 12	Multiple restorations	46 ± n.r. [31-82]	46 [20]	APL – 21 AQ – 21 GB – 14 OBF – 18
Lawson and others [106]	6, 12, and 24	Multiple restorations	n.r. ± n.r. [n.r. ± n.r.]	37 [n.r.]	SM – 42 SU – 84
Matis and others [100]	6, 12, and 36	Multiple restorations	45 ± n.r. [30-75]	30 [12]	FL – 40 SM – 40
Neo and others [42]	18	Multiple restorations	47 ± n.r. [n.r.-n.r.]	10 [4]	PUB 3 – 21 IB –20
Pena and others [102]	3, 6, 12, 18, and 24	Multiple restorations	n.r. ± n.r. [n.r. ± n.r.]	25 [13]	CSE – 56 XV– 56
Perdigão and others [89]	6 and 18	Multiple restorations	n.r. ± n.r. [24-63]	35 [16]	PBNT – 63 SB – 65
Perdigão and others [44]	6 and 18	Multiple restorations	47.6 ± n.r. [22-78]	39 [n.r]	SM – 29 SSE – 30 SBP – 32 EB – 34

Table 2: *Summary of the Studies Included in the Systematic Review (ext.)*

Rubber Dam?	Mechanical Preparation?	Materials [Type of Particles]	Type of Adhesive
Yes	No	Admira Bond[a] – AB [FI] Clearfil SE Bond[b] – CSE [NA] Hybrid Bond[c] – HB [UN]	AB – two-step etch and rinse CSE – two-step self-etch HB – one-step self-etch
No	Bevel	Single Bond[d] – SB [UN] Scotchbond Multipurpose[d] – SM [UN] One Coat Bond[e] – OCB [FI]	SB – two-step etch and rinse SM: three-step etch and rinse OCB two-step etch and rinse
No	No	Xeno III[f] – XIII [UN] Xeno IV[f] – XIV [UN] XP Bond[f] – XP [NA]	XIII – one-step self-etch XIV – one-step self-etch XP – two-step etch and rinse
n.r.	n.r.	Single Bond[d] – SB [UN] Clearfil SE Bond[b] – CSE [NA]	SB – two-step etch and rinse CSE – two-step self-etch
No	No	Single Bond[d] – SB [UN] Clearfil SE Bond[b] – CSE [NA] Xeno III[f] – XIII [UN]	SB – two-step etch and rinse CSE – two-step self-etch XIII – one-step self-etch
No	No	Scotchbond Multipurpose[d] – SM [UN] Easy One[d] – EO [NA]	SM – three-step etch and rinse EO – one-step self-etch
No	No	Xeno V[f] – XV [UN] XP Bond[f] – XP [NA]	XV – one-step self-etch XP – two-step etch-and-rinse
Yes	No	Futurabond M[a] – FM [NA] Solobond M[a] – SoM [UN] Syntac Classic[g] – SC [UN]	FM – one-step self-etch SoM – two-step etch and rinse SC – four-step etch and rinse
No	Bevel	Gluma[h] – G [FI] Scotchbond Multipurpose[d] – SM [UN]	G – two-step self-etch SM – three-step etch and rinse
n.r.	n.r.	Gluma[h] – G [FI] Scotchbond Multipurpose[d] – SM [UN]	G – two-step self-etch SM – three-step etch and rinse
No	No	Clearfil SE Bond[b] – CSE [NA] Xeno V[f] – XV [UN]	CSE – two-step self-etch XV– one-step self-etch
Yes	n.r.	Gluma 2000[i] – G2000 [FI] Tenure[j] – T [FI] Prisma Universal Bond 3[f] – PUB3 [UN] AllBond 2[k] – AB2 [UN]	G2000 – two-step etch and rinse T – two-step self-etch PUB 3 – two-step etch and rinse AB2 – three-step etch and rinse
No	Bevel	Clearfil Liner Bond II[b] – CLB [FI] Single Bond[d] – SB [UN]	CLB – two-step self-etch SB –two-step etch and rinse
No	No	Adper Prompt L-Pop[d] – APL [UN] AQ bond plus[c] – AQ [UN] G Bond[l] – GB [NA] One-up Bond F Plus[m] – OBF [FI]	APL – one-step self-etch AQ – one-step self-etch GB – one-step self-etch OBF – one-step self-etch
Yes	n.r.	Scotchbond Multipurpose[d] – SM [UN] Scotchbond Universal[d] – SM [NA]	SM – three-step etch and rinse SU – one-step self-etch or two-step etch and rinse
Yes	No	FL Bond[n] – FL [FI] Scotchbond Multipurpose[d] – SM [UN]	FL – two-step self-etch SM – three-step etch and rinse
No	No	Prisma Universal Bond 3[f] – PUB3 [UN] Imperva Bond[n] – IB [FI]	PUB 3 – two-step self-etch IB – three-step etch and rinse
No	Bevel	Clearfil SE Bond[b] – CSE [NA] Xeno V[f] – XV [UN]	CSE – two-step self-etch XV– one-step self-etch
Yes or No	No	Prime & Bond NT[f] – PBNT [NA] Single Bond[d] – SB [UN]	PBNT – two-step etch and rinse SB – two-step etch and rinse
No	No	Scotchbond Multipurpose[d] – SM [UN] Scotchbond SE[d] – SSE [NA] Single Bond Plus[d] – SBP [NA] Easy-Bond[d] – EB [NA]	SM – three-step each and rinse SSE – two-step self-etch SBP – two-step etch and rinse EB – one-step self-etch

Table 2: *Summary of the Studies Included in the Systematic Review (cont.)*

Study ID	Follow-up, mo	Study Design	Subjects' Age, Mean ± SD [range], y	Total Number of Subjects [Male]	Number of Restorations per Group at Baseline
Ritter and others [90]/ Swift and others [114]	6, 18, 36, and 96	Multiple restorations	53 ± 12.4 [27-77]	33 [19]	OS – 48 PB – 51
Sartori and others [103]	6, 18, and 30	Multiple restorations	n.r. ± n.r. [n.r. ± n.r.]	27 [n.r.]	FNR – 30 SoM – 33
Stojanac and others [104]	12 and 24	Multiple restorations	n.r. ± n.r. [18-50]	30 [n.r.]	PBNT – 30 A – 30 XIII – 30
Turkun [101]	3, 6, 9, and 12	Multiple restorations	44 ± n.r. [26-59]	35 [16]	CPB – 85 XIII – 78
Tyas [109]	3, 6, 12, 24, and 36	Multiple restorations	n.r. ± n.r. [n.r. ± n.r.]	36 [n.r.]	G – 20 SM – 20 PUB – 20
Van Dijken [115]	6, 12, 18, 24, 30, 36, 42, and 48	Multiple restorations	56.4 ± n.r. [26-82]	81 [44]	T – 47 Tri – 53 S2 – 53
Van Dijken [41]	6, 12, 18, and 24	Multiple restorations	58 ± n.r. [46-72]	90 [51]	CLB – 46 OCB – 46 APL – 52
Van Meerbeek and others [107]	6, 12, and 24	Multiple restorations	n.r. ± n.r. [n.r. ± n.r.]	35 [n.r.]	T – 32 Tri – 40
Van Meerbeek and others [108]	6, 12, 24, and 36	Multiple restorations	n.r. ± n.r. [20-79]	125 [n.r.]	G2000 – 103 CLB – 110 SM – 107

Abbreviations: FI, filled adhesive system; ID, identification; NA, nanofilled adhesive system; n.a., not applicable; n.r., not reported in the study; SD, standard deviation; UN, unfilled adhesive system.
[a] *Voco, Cuxhaven, Germany.*
[b] *Kuraray Medical, Tokyo, Japan.*
[c] *Sun Medical, Moriyama City, Chiga, Japan.*
[d] *3M Oral CAre, St Paul, MN, USA.*
[e] *Coltène Whaledent, Cuyahoga Falls, OH, USA.*
[f] *Dentsply Sirona, York, PA, USA.*
[g] *Ivoclar Vivadent, Schaan, Liechtenstein.*
[h] *Bayer, Leverkusen, Germany.*
[i] *Columbus Dental, St Louis, MO, USA.*
[j] *DenMat Corp., Santa Maria, CA, USA.*
[k] *Bisco Inc. Schaumburg, IL, USA.*
[l] *GC Corp., Tokyo, Japan.*
[m] *Tokuyama Dental, Tokyo, Japan.*
[n] *Shofu Inc., Kyoto, Japan.*
[o] *Kerr, Orange, CA, USA.*
[p] *ICI Dental, Macclesfield, UK.*

each outcome into high, moderate, low, and very low. The "high-quality" level suggests that we are very confident that the true effect lies close to the estimate of the effect. On the other extreme, a study of "very low quality" suggests that we have very little confidence in the effect estimate and the estimate reported can be substantially different from what was measured.

RESULTS

Characteristics of Included Studies

After the database screening and removal of duplicates, 3662 articles were identified (Figure 1). After title screening, 363 articles remained, and this number was reduced to 75 articles after careful examination of the abstracts (Figure 1). Among these articles, 41 were excluded for the following reasons:

Table 2: *Summary of the Studies Included in the Systematic Review (ext.)*

Rubber Dam?	Mechanical Preparation?	Materials [Type of Particles]	Type of Adhesive
No	No	Optibond Solo° – OS [FI] Prime & Bond[f] – PB [UN]	OS – two-step etch and rinse PB – two-step etch and rinse
No	n.r.	Futurabond NR[a] – FNR [NA] Solobond M[a] – SoM [UN]	FNR – one-step self-etch SoM – two-step etch and rinse
No	No	Prime & Bond NT[f] – PBNT [NA] AdheSE[g] – A [NA] Xeno III[f] – XIII [UN]	PBNT – two-step etch and rinse A – two-step self-etch XIII – one-step self-etch
No	No	Clearfil Protect Bond[b] – CPB [NA] Xeno III[f] – XIII [UN]	CPB – two-step self-etch XIII – one-step self-etch
n.r.	n.r.	Gluma[h] – G [FI] Scotchbond Multipurpose[d] – SM [UN] Prisma Universal Bond[f] – PUB [UN]	G – two-step etch and rinse SM – three-step etch and rinse PUB – two-step etch and rinse
No	No	Tenure[j] – T [FI] Tripton[p] – Tri [UN] Scotchbond 2[d] – S2 [UN]	T – two-step self-etch Tri – two-step self-etch S2 – two-step self-etch
n.r.	No	Clearfil Liner Bond II[b] – CLB [FI] One Coat Bond[e] – OCB [FI] Adper Prompt L-Pop[d] – APL [UN]	CLB – two-step self-etch OCB – two-step etch-and-rinse APL – one-step self-etch
Yes	Bevel	Tenure[j] – T [FI] Tripton[p] – Tri [UN]	T – two-step self-etch Tri – two-step self-etch
Yes	With or without bevel	Gluma 2000[i] – G2000 [FI] Clearfil Liner Bond II[b] – CLB [FI] Scotchbond Multipurpose[d] – SM [UN]	G2000 – two-step self-etch CLB – two-step self-etch SM – three-step etch and rinse

1) the studies compared the same type of adhesive system (n=19),[40,49-66] 2) the studies used the same type of adhesive system in both study groups (n=18),[67-84] and 3) the studies compared filled vs nanofilled adhesive systems (n=4).[85-88]

A total of 32 articles remained for qualitative evaluation. From these 32 articles, 3 articles[38,89,90] reported longer follow-ups of earlier studies. Therefore, there were 29 studies among 32 publications. Tables 2, 3, and 4 characterize the 29 included studies. The follow-up time of the studies varied from 12 months[91-93] to 8 years.[90] All studies placed multiple restorations per patient. In this design, any patient could receive as many restorations as possible, depending on the number of available noncarious cervical lesions.

The mean age of the participants was approximately 50 (±7) years.[a] Most of the studies (n=17, 59%) used cotton rolls and a saliva ejector to prevent contamination during the restorative protocol,[b] while 8 studies used a rubber dam.[89,92,98,100,105-108]

In few studies (n=6), the enamel was beveled.[38,94,99,102,107,108] Different types of adhesive systems were used in the studies, varying from three-step etch-and-rinse adhesives (n=11)[c] to one-step self-etch adhesives (n=14).[d] The number of restorations per adhesive system used in the studies evaluated varied from 14 restorations[93] to 189 restorations.[107]

[a] *References 39, 41, 42, 44, 45, 90, 93-101.*

[b] *References 38, 39, 42-45, 90, 91, 93-95, 97, 99, 101-104.*

[c] *References 36, 38, 42, 44, 91, 92, 94, 100, 106, 108, 109.*

[d] *References 41, 43-45, 91, 93, 95, 97, 98, 101-105.*

Table 3: *Summary of the Studies Included in the Systematic Review: Part 2*

Study ID	Conditioner	Wet-Bonding Adhesion Technique?	Application Under Agitation?
Abdalla and Garcia-Godoy [105]	AB – 36% phosphoric acid[n.s.] CSE – Cleafil SE [primera] HB – n.a.	AB – yes CSE – n.r. HB – n.r.	AB – n.r. CSE – n.r. HB – n.r.
Aw and others [94]	SB – 35% phosphoric acid[n.s.] SM – 35% phosphoric acid[n.s.] OCB – 15% phosphoric acid[n.s.]	SB – yes SM – yes OCB – yes	SB – n.r. SM – n.r. OCB – yes
Boushell and others [95]	XIII – n.a. XIV – n.a. XP – Caulk 34% Conditioner Gel[e]	XIII – yes XIV – yes XP – yes	XIII – n.r. XIV – n.r. XP – n.r.
Burrow and Tyas [96]	SB – n.r. CSE – Cleafil SE primer[a]	SB – yes CSE – yes	SB – n.r. CSE – n.r.
Eliguzeloglu, Dalkilic, and Omurlu [43]	SB – 35% phosphoric acid[f] CSE – Cleafil SE primer[a] or 37% phosphoric acid[n.s.] XIII – n.a. or 37% phosphoric acid[n.s.]	SB – yes CSE – yes XIII – yes	SB – n.r. CSE – n.r. XIII – n.r.
De Araújo and others [91]	SM – 35% phosphoric acid[n.s.] EO – n.a.	SM – yes EO – yes	SM – n.r. EO – n.r.
Dutra-Correa and others [97]	XV – n.a. XP – 36% phosphoric acid[n.s.]	XV – n.r. XP – yes	XV – yes XP – n.r.
Hafer and others [98]	FM – n.a. SoM – 35% phosphoric acid[f] SC – 37% phosphoric acid[g]	FM – yes SoM – yes SC – yes	FM – n.r. SoM – n.r. SC – n.r.
Hansen and others [37, 38]	G – n.r. SM – n.r.	G – n.r. SM – n.r.	G – n.r. SM – n.r.
Horsted-Bindslev and others [36]	G – 35% phosphoric acid[h] SM – 35% phosphoric acid[h]	G – yes SM – yes	G – n.r. SM – n.r.
Jang and others [45]	CSE – Cleafil SE primer[a] XV– n.a.	CSE – n.r. XV– n.r.	CSE – n.r. XV– yes
Jordan and Suzuki [92]	G2000 – n.r. T – n.r. PUB 3 – n.r. AB2 – n.r.	G2000 – n.r. T – n.r. PUB 3 – n.r. AB2 – n.r.	G2000 – n.r. T – n.r. PUB 3 – n.r. AB2 – n.r.
Kubo and others [99]	CLB – 37% phosphoric acid[a] SB – 37% phosphoric acid[a]	CLB – yes SB –n.r.	CLB – n.r. SB –n.r.
Kurokawa and others [93]	APL – n.a. AQ – n.a. GB – n.a. OBF – n.a.	APL – n.r. AQ – n.r. GB – n.r. OBF – n.r.	APL – yes AQ – n.r. GB – n.r. OBF – yes
Lawson and others [106]	SM – 37% phosphoric acid[c] SU – n.a. or 37% phosphoric acid[c]	SM – yes SU – yes	SM – yes SU – yes
Matis and others [100]	FL – n.a. SM – 37% phosphoric acid[n.s.]	FL – yes SM – yes	FL – n.r. SM – n.r.
Neo and others [42]	PUB 3 – n.r. IB – n.r.	PUB 3 – n.r. IB – n.r.	PUB 3 – n.r. IB – n.r.
Pena and others [102]	CSE – Cleafil SE primer[a] XV– n.a.	CSE – n.r. XV– n.r.	CSE – n.r. XV– n.r.
Perdigão and others [89]	PBNT – 34% phosphoric acid[e] SB – 37% phosphoric acid[c]	PBNT – yes or not SB – yes or not	PBNT – n.r. SB – n.r.
Perdigão and others [44]	SM – 35% phosphoric acid[c] SSE – n.a. SBP – 35% phosphoric acid[c] EB – n.a.	SM – n.r. SSE – yes SBP – n.r. EB – yes	SM – n.r. SSE – yes SBP – n.r. EB – n.r.
Ritter and others [90]/Swift and others [114]	OS – 37% phosphoric acid[n.s.] PB – 34% phosphoric acid[n.s.]	OS – yes PB – yes	OS – yes PB – n.r.
Sartori and others [103]	FNR – n.a. SoM – 35% phosphoric acid[f]	FNR – yes SoM – yes	FNR – n.r. SoM – n.r.

Table 3: *Summary of the Studies Included in the Systematic Review: Part 2 (ext.)*

Time of Evaporation of the Solvent (s)	Type of Solvent	Composite Resin Used	Operator(s) Experience (Graduate, Dentist, or Postgraduate)
AB – 2 - 3 CSE – n.r. HB – 5	AB – acetone CSE – water HB – acetone/water	Clearfil APX[a]	Dentist
SB – 5 SM – 5 OCB – 2	SB – ethanol SM – water OCB – water	SB – Silux Plus[b] SM – Silux Plus[b] OCB – Synergy[c]	n.r.
XIII – 5 XIV – 2 XP – 5	XIII – ethanol XIV – ethanol XP – tert-butanol	TPH[d]	Dentist
SB – n.r. CSE – n.r.	SB – ethanol CSE – water	SB – Filtek A110[b] CSE – Clearfil ST[a]	n.r.
SB – n.r. CSE – n.r. XIII – n.r.	SB – ethanol CSE – ethanol XIII – water	Filtek Supreme[b]	n.r.
SM – 5 EO – 5	SM – water EO – ethanol/water	Z350[c]	n.r.
XV – 5 XP – 5	XV – ethanol XP – tert-butanol	Exthet X[d]	n.r.
FM – 5 SoM – n.r. SC – n.r.	FM – water SoM – water/acetone SC – water/acetone	FM – Amaris[h] SoM – Amaris[h] SC – Tetric EvoCeram[f]	n.r.
G – n.r. SM – n.r.	G – ethanol SM – water	Silux Enamel Bond[b]	n.r.
G – n.r. SM – n.r.	G – ethanol SM – water	P-30[b]	n.r.
CSE – n.r. XV– 5	CSE – water XV– ethanol	Z250[b]	n.r.
G2000 – n.r. T – n.r. PUB 3 – n.r. AB2 – n.r.	G2000 – ethanol T – acetone PUB 3 – ethanol AB2 – acetone	G2000 – Pekafil[i] T – Marathon[j] PUB 3 – Prisma APH[d] AB2 – Bisfil M[k]	n.r.
CLB – n.r. SB –n.r.	CLB – water SB – ethanol	Clearfil APX[a]	Dentist
APL – n.r. AQ – n.r. GB – n.r. OBF – n.r.	APL – water AQ – water/acetone GB – water OBF – water	APL – Filtek Supreme[b] AQ – Metafil C[n] GB – Gradia Direct[l] OBF – Palfique Estelite[o]	n.r.
SM – 5 SU – 5	SM – water SU – water/ethanol	Filtek Supreme Ultra[b]	Dentist
FL – 10 SM – 5	FL – water SM – water	FL – Beautifil[p] SM – Silux Plus[b]	n.r.
PUB 3 – n.r. IB – n.r.	PUB 3 – ethanol IB – water/ethanol	PUB 3 – APH[d] IB – Lite Fil II[p]	n.r.
CSE – n.r. XV– n.r.	CSE – water XV– ethanol	Esthet X[d]	Dentist
PBNT – 5 SB – n.r.	PBNT – acetone SB – ethanol	Filtek A110[b]	Dentist
SM – 5 SSE – 5 SBP – 10 EB – 5	SM – water SSE – ethanol SBP – water EB – water/ethanol	Filtek Supreme Plus[b]	n.r.
OS – n.r. PB – 5	OS – ethanol PB – acetone	OS – Prodigy[m] PB – TPH Spectrum[d]	Dentist
FNR – 5 SoM – 5	FNR – water SoM – water/acetone	Polofil M[h]	Graduate

Table 3: *Summary of the Studies Included in the Systematic Review: Part 2 (Cont.)*

Study ID	Conditioner	Wet-Bonding Adhesion Technique?	Application Under Agitation?
Stojanac and others [104]	PBNT – 36% orthophosphoric acid[e] A – AdheSE primer[g] XIII – n.a.	PBNT – yes A – yes XIII – yes	PBNT – n.r. A – n.r. XIII – n.r.
Turkun [101]	CPB – CPB primer[a] XIII – n.a.	CPB – n.r. XIII – n.r.	CPB – n.r. XIII – n.r.
Tyas [109]	G – n.r. SM – n.r. PUB – n.r.	G – n.r. SM – n.r. PUB – n.r.	G – n.r. SM – n.r. PUB – n.r.
Van Dijken [115]	T – n.r. Tri – n.r. S2 – n.r.	T – n.r. Tri – n.r. S2 – n.r.	T – n.r. Tri – n.r. S2 – n.r.
Van Dijken [41]	CLB – CLB primer[a] OCB – 15% phosphoric acid gel[n.s.] APL – n.a.	CLB – n.r. OCB – n.r. APL – n.r.	CLB – n.r. OCB – n.r. APL – yes
Van Meerbeek and others [107]	T – 37% phosphoric acid[c] Tri – 37% phosphoric acid[c]	T – yes Tri – n.r.	T – n.r. Tri – n.r.
Van Meerbeek and others [108]	G2000 – n.r. CLB – n.r. SM – n.r.	G2000 – n.r. CLB – n.r. SM – n.r.	G2000 – n.r. CLB – n.r. SM – n.r.

Abbreviations: ID, identification; n.a., not applicable; n.r., not reported in the study; n.s., not specified.
[a] *Kuraray Medical, Tokyo, Japan.*
[b] *3M Oral Care, St Paul, MN, USA.*
[c] *Coltène Whaledent, Cuyahoga Falls, OH, USA.*
[d] *Dentsply Sirona, York, PA, USA.*
[e] *Benlioglu Dental Inc., Ankara, Turkey.*
[f] *IvoclarVivadent, Schaan, Liechtenstein.*
[g] *DMC, Joinvile, SC, Brazil.*
[h] *Voco, Cuxhaven, Germany.*
[i] *Columbus Dental, St Louis, MO, USA.*
[j] *DenMat Corp, Santa Maria, CA, USA.*
[k] *Bisco Inc, Schaumburg, IL, USA.*
[l] *GC Corp, Tokyo, Japan.*
[m] *Kerr, Danbury, CT, USA.*
[n] *Sun Medical, Moriyama City, Chiga, Japan.*
[o] *Tokuyama Dental, Tokyo, Japan.*
[p] *Shofu Inc, Kyoto, Japan.*
[q] *SDI, Bayswater, Australia.*
[r] *Degussa, Düsseldorf, Germany.*
[s] *ICI Dental, Macclesfield, UK.*

The wet bonding technique was applied in 18 studies.[e] Some studies (n=8) mentioned that the application of the adhesive system was done while the adhesive was actively moved on the surface (agitation).[f] The time to evaporate the solvent was 5 seconds in most studies (n=14).[g] Adhesives were composed of different solvents such as water, ethanol, acetone, and tert-butanol. Most of the studies did not report on the operator experience (graduate, postgraduate, academic dentist, general practitioner), but for those for which this information was reported, most of the operators were academic dentists.[89,90,95,99,102,105-108] Only one study reported that the operator was a graduate student.[103] No study was conducted with general practitioners.

[e] *References 36, 43, 44, 89-91, 94-100, 103-107.*

[f] *References 41, 44, 45, 90, 93, 94, 97, 106.*

[g] *References 41, 44, 45, 90, 91, 94, 95, 97, 98, 100, 101, 103, 105, 106.*

Meta-analysis

A meta-analysis was performed that included all studies with exception of one,[98] which was considered at high risk of bias in the key domain examiner blinding. The risk of bias assessment is provided in Figure 2. Some follow-ups could not be integrated into the meta-analysis because of lack of information. If data were not available or could not be extracted, the study was not considered for the meta-analysis. No difference was observed between the

Table 3: *Summary of the Studies Included in the Systematic Review: Part 2 (Cont.)*

Time of Evaporation of the Solvent (s)	Type of Solvent	Composite Resin Used	Operator(s) Experience (Graduate, Dentist, or Postgraduate)
PBNT – n.r. A – n.r. XIII – n.r.	PBNT – acetone A – water XIII – ethanol	PBNT – Esthet X[d] A – Tetric EvoCeram[f] XIII – Dyract Extra[d]	n.r.
CPB – 5 XIII – n.r.	CPB – water XIII – ethanol	Esthet X[d]	n.r.
G – n.r. SM – n.r. PUB – n.r.	G – ethanol SM – water PUB – ethanol	G – Lumifor[b] SM – Silux[b] PUB – Prismafine[d]	n.r.
T – n.r. Tri – n.r. S2 – n.r.	T – acetone Tri – water S2 – water	T – Opalux[s] Tri – Opalux[s] S2 – Silux[b]	n.r.
CLB – 3 - 5 OCB – 3 APL – 5	CLB – water OCB – water APL – water	CLB – Clearfil APX[a] OCB – Synergy[c] APL – Pertac Hybrid[b]	n.r.
T – n.r. Tri – n.r.	T – acetone Tri – water	T – Herculite XR[m] Tri – Opalux[l]	Dentist
G2000 – n.r. CLB – n.r. SM – n.r.	G2000 – ethanol CLB – water SM – water	G2000 – Pekafill[b] CLB – Clearfil Photo Anterior[a] SM – Silux Plus[b]	Dentist

subgroup analysis in any of the meta-analyses that had been conducted.

Loss of Retention—This analysis was based on 27 studies.[h] In the overall analysis, which took into consideration both subgroups (filled vs unfilled and nanofilled vs unfilled), no significant difference between the two groups was detected in the follow-ups of 12 to 18 months (RD=–0.01; 95% confidence interval [CI], –0.03 to 0.02; p=0.60; Figure 3), 24 to 30 months (RD=0.00; 95% CI, –0.03 to 0.03; p=0.95; Figure 3), 3 years (RD=–0.04; 95% CI, –0.10 to 0.03; p=0.26; Figure 4), and 5 or more years (RD=–0.01; 95% CI, –0.10 to 0.07; p=0.77; Figure 4). Analysis of heterogeneity revealed that data were heterogeneous at 12 to 18 months, 24 to 30 months, and 3-year follow-ups ($p<0.03$; $I^2>45\%$; Figures 3 and 4) but not at the 5-year recall (p=0.28; I^2=21%; Figure 4).

Marginal Discoloration—This analysis was based on 22 studies.[i] In the overall analysis, which took into consideration both subgroups, no significant difference between the two groups was detected in the follow-ups of 12 to 18 months (RD=–0.02; 95% CI, –0.04 to 0.00; p=0.07; Figure 5), 24 to 30 months (RD=–0.04; 95% CI, –0.10 to 0.02; p=0.18; Figure 5), or 3 years (RD=0.01; 95% CI, –0.06 to 0.09; p=0.75; Figure 5). Analysis of heterogeneity revealed that data were heterogeneous at 12 to 18 months (p=0.16; I^2=22%; Figure 5), and 3-year follow-up (p=0.84; I^2=0%; Figure 6) but not at the 24 to 30 months recall ($p<0.0002$; I^2=69%; Figure 5).

Secondary Caries—This analysis was based on 17 studies.[j] In the overall analysis, which took into consideration both subgroups, no significant difference between groups was detected in the follow-ups of 12 to 18 months (RD=–0.00; 95% CI, –0.01 to 0.01; p=0.88; Figure 7), 24 to 30 months (RD=–0.00; 95% CI, –0.02 to 0.01; p=0.59; Figure 7), or 3 years (RD=–0.02; 95% CI, –0.06 to 0.01; p=0.16; Figure 8). Analysis of heterogeneity revealed that data were not heterogeneous at any given recall time ($p>0.32$; $I^2<13\%$; Figures 7 and 8).

Assessment of the Quality of Evidence—In the summary of findings in Table 4, we can observe that for the outcome variable loss of retention, most of the follow-ups were graded as having a low quality of evidence, except for 5 or more year recalls, which were graded as moderate. Unclear risk of bias and unexplained heterogeneity were the reasons for downgrading the level of evidence. For the outcome variable marginal discoloration, the 12- to 18-month recall and the 3-year recall were graded as moderate (unclear risk of bias of the eligible studies) and the 24- to 30-month recall was graded as having a low quality of evidence (unclear risk of bias and

[h] *References 36, 38, 39, 41-45, 89-94, 96, 97, 99-109.*

[i] *References 41-45, 89-94, 96, 97, 100-108.*

[j] *References 36, 41, 43-45, 89, 90, 93, 97, 100-106, 108.*

Table 4: *Summary of Findings*[a]

Outcome	Anticipated Absolute Effects[b] (95% CI)		Relative Effect (95% CI)	No. of Restorations (studies)	Quality of the Evidence (GRADE)[c]
	Filled/Nanofilled Adhesives	Unfilled Adhesives			
Loss of retention (1 year): dichotomous scale (yes/no)	54 per 1000 (−54 to 107)	65 per 1000	RR −0.01 (−0.03 to 0.02)	2801 (25 RCTs)	⊕⊕○○ LOW[d,e]
Loss of retention (2 years): dichotomous scale (yes/no)	78 per 1000 (−234 to 234)	88 per 1000	RD −0.00 (−0.03 to 0.03)	1601 (15 RCTs)	⊕⊕○○ LOW[d,e]
Loss of retention (3 years): dichotomous scale (yes/no)	88 per 1000 (−66 to 220)	166 per 1000	RD −0.04 (−0.10 to 0.03)	759 (7 RCTs)	⊕⊕○○ LOW[d,e]
Loss of retention (5 or more years): dichotomous scale (yes/no)	169 per 1000 (−241 to 1690)	241 per 1000	RD −0.01 (−0.10 to 0.07)	215 (3 RCTs)	⊕⊕⊕○ MODERATE[d]
Marginal discoloration (1 year): dichotomous scale (yes/no)	68 per 1000 (−68 to 136)	104 per 1000	RD −0.02 (−0.04 to 0.00)	2273 (21 RCTs)	⊕⊕⊕○ MODERATE[d]
Marginal discoloration (2 years): dichotomous scale (yes/no)	172 per 1000 (−86 to 430)	223 per 1000	RD −0.04 (−0.10 to 0.02)	1327 (12 RCTs)	⊕⊕○○ LOW[d,e]
Marginal discoloration (3 years): dichotomous scale (yes/no)	306 per 1000 (−1836 to 2754)	302 per 1000	RD 0.01 (−0.06 to 0.09)	516 (4 RCTs)	⊕⊕⊕○ MODERATE[d]
Secondary caries (1 year): dichotomous scale (yes/no)	5 per 1000 (−5 to 10)	7 per 1000	RD −0.00 (−0.01 to 0.01)	1857 (16 RCTs)	⊕⊕⊕○ MODERATE[d]
Secondary caries (2 years): dichotomous scale (yes/no)	2 per 1000 (−2 to 4)	6 per 1000	RD −0.00 (−0.02 to 0.01)	1137 (10 RCTs)	⊕⊕⊕○ MODERATE[d]
Secondary caries (3 years): dichotomous scale (yes/no)	0 per 1000	30 per 1000	RD −0.02 (−0.06 to 0.01)	390 (3 RCTs)	⊕⊕⊕○ MODERATE[d]

[a] *Patient or population: noncarious cervical lesions; intervention: filled/nanofilled adhesives; comparison: unfilled adhesives.*
[b] *The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*
[c] *GRADE Workgroup grades of evidence:*
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.
[d] *Unclear risk of bias.*
[e] *Unexplained statistical heterogeneity.*

unexplained heterogeneity). All meta-analyses of the outcome variable secondary caries were graded as moderate because of the unclear risk of bias of the studies.

DISCUSSION

Systematic reviews and meta-analyses are important for resolving controversies between clinical trials and to provide clinical input for guidelines that address adequate clinical care delivered by oral health personnel, especially general practitioners.[110] According to the results of the present study, the addition of fillers or nanofillers in adhesive systems does not significantly improve the clinical performance of the retention rate, marginal discoloration, or secondary caries.

When the first filled adhesive systems emerged in the market, the theoretical concept was that

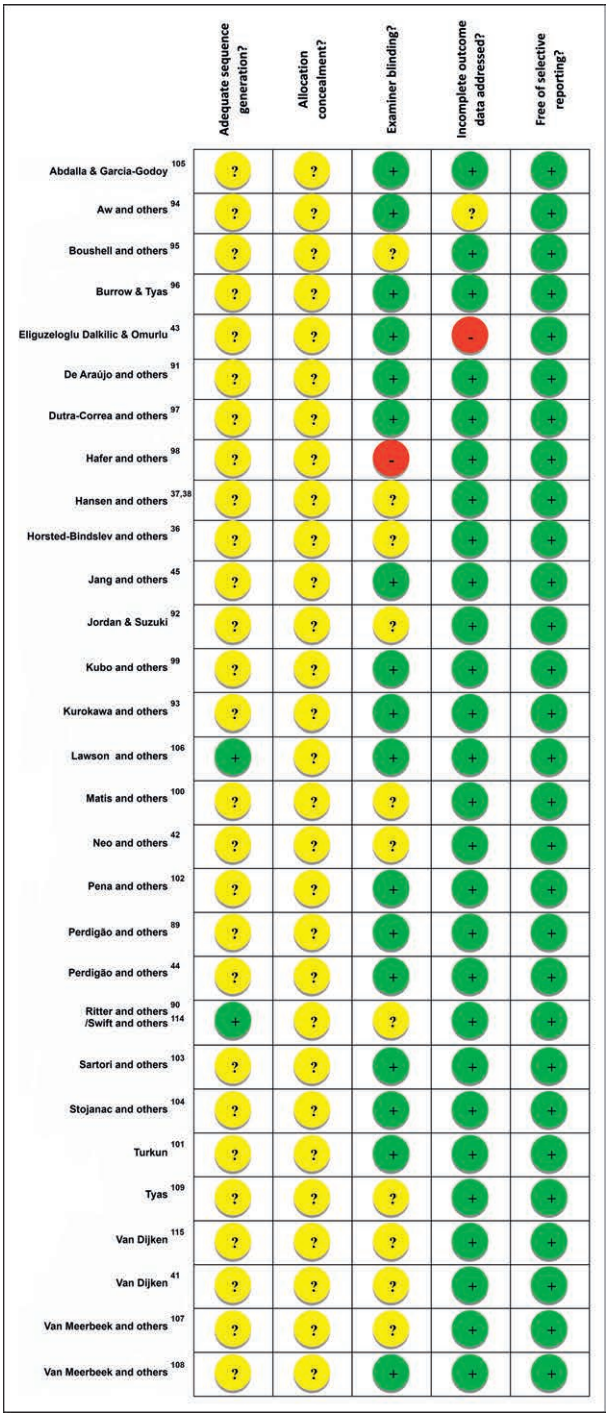

Figure 2. *Summary of the risk of bias assessment for the 27 studies included in the meta-analysis according to the Cochrane Collaboration tool. The risk of bias tool contains six domains: sequence generation, allocation concealment, blinding of the outcome assessors, incomplete outcome data, selective outcome reporting, and other possible sources of bias. Each domain was judged to be at low, unclear, or high risk of bias according to the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0*

filled adhesive systems act as thickening agents within the adhesive layer. The formation of a thick layer of adhesive interface will improve the mechanical properties, and[15,16] according to the so-called elastic bonding concept,[17,18] the adhesive layer should absorb the compression produced by the tooth-flexure stress, thus reducing interfacial stresses and preserving the marginal integrity,[17,18,111] which eventually should result in better retention rate of the adhesively bonded restorations.[12,13]

There are, however, options to increase the thickness of the adhesive layer: first, to apply two layers of adhesive, and second, to use a separate hydrophobic layer such as the three-step etch-and-rinse or two-step self-etch adhesive systems.[8,112] Some systematic reviews came to the conclusion that simplified adhesive systems such as the one-step self-etch systems reduce the retention rates and increase marginal discoloration of Class V composite resin restorations.[8,113] However, a closer view of the RCTs of the present study showed that although 16 studies evaluated filled vs unfilled adhesives, only a few compared a filled or unfilled adhesive within the same adhesive system group.[k] This prevented us from investigating this variable by a subgroup analysis or meta-regression.

It is worthwhile to mention that flowable composites are also used with the goal of absorbing occlusal stress ("elastic bonding concept").[17,18] However, several systematic reviews have shown that the use of flowable resin composite compared with high-viscous resin composites did not affect the retention rate or marginal discoloration of Class V restorations.[8,113,116] Microfillers in adhesive systems (1-5 μm) do not penetrate into the interfibrillar spaces but are observed within the adhesive layer.[117] Therefore, there are adhesive systems with glass particles of 20-nm size or lower (pure silicon dioxide, from either colloidal or pyrogenic origin).[26,29] According to the manufacturers, the nanofillers are small enough to penetrate into dentin tubules and infiltrate the interfibrillar spaces of demineralized dentin. Furthermore, it was suggested that infiltration of the interfibrillar channels could provide a strengthening element for demineralized dentin.[16,27]

However, the nanofillers must be physically and chemically stabilized to prevent them from aggregating during storage and/or during the application of the adhesive, which makes these "filler clusters"

[k] *References 89, 93, 94, 105, 107-109, 114, 115.*

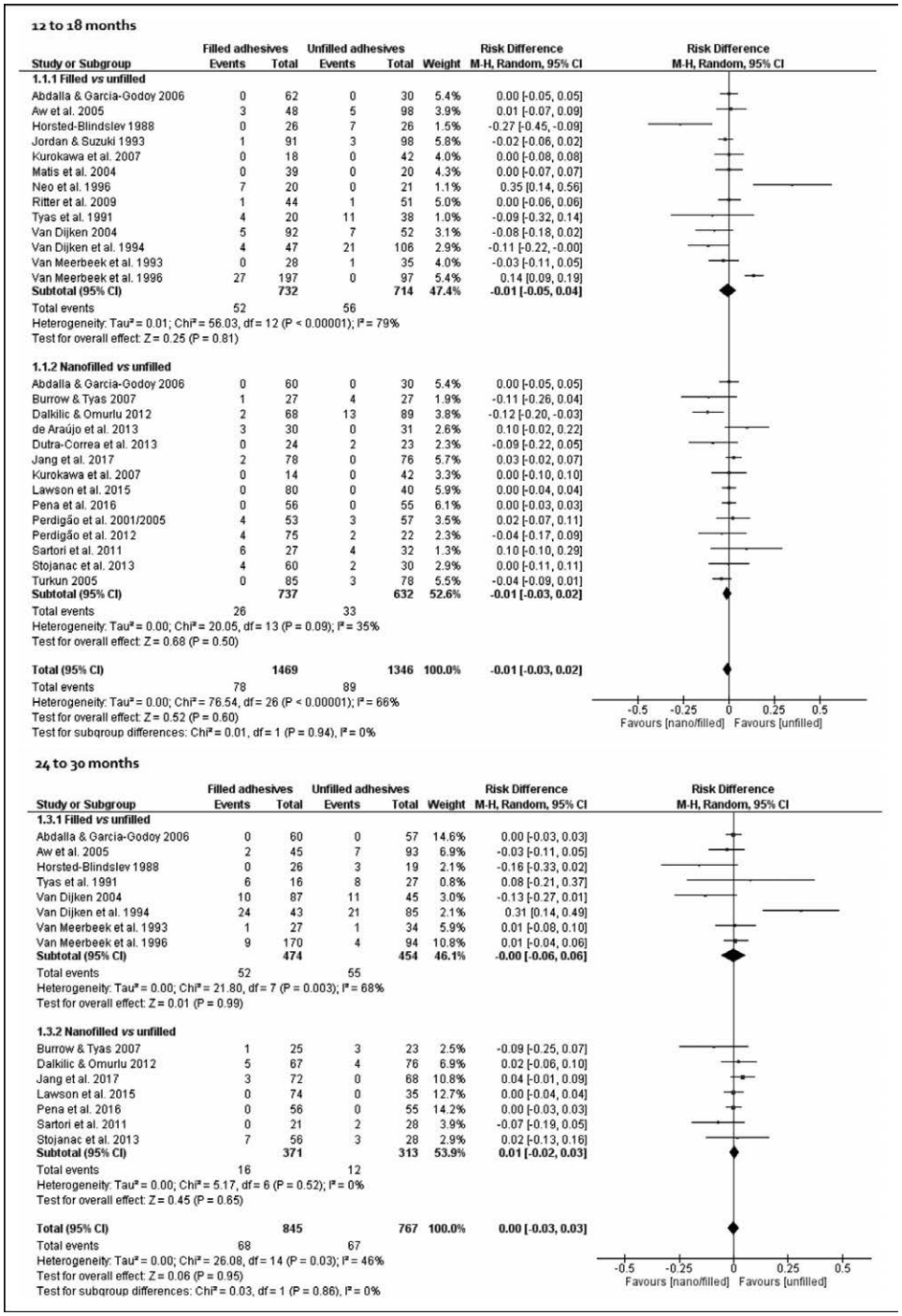

Figure 3. *Forest plot of restorations that suffered retention loss comparing filled/nanofilled vs unfilled adhesives at 12 to 18 months and 24 to 30 months.*

too large to infiltrate the interfibrillar spaces.[27,118] However, several studies showed that no nanofiller had been found inside the hybrid layer or the demineralized dentin.[27,119,120] Furthermore, it has been reported that exposed collagen may function as a filter[121] that does not allow the nanofillers to penetrate. The molecular weight of the nanofillers and the resin monomers of the adhesives differ substantially. Therefore, the diffusion rate is very different, which inhibits the complete infiltration of the nanofillers into the interfibrillar space.[27,122] Some authors claim that in demineralizing dentin, there is a formation of a hydrogel of residual substance, proteoglycans, and noncollagenous pro-

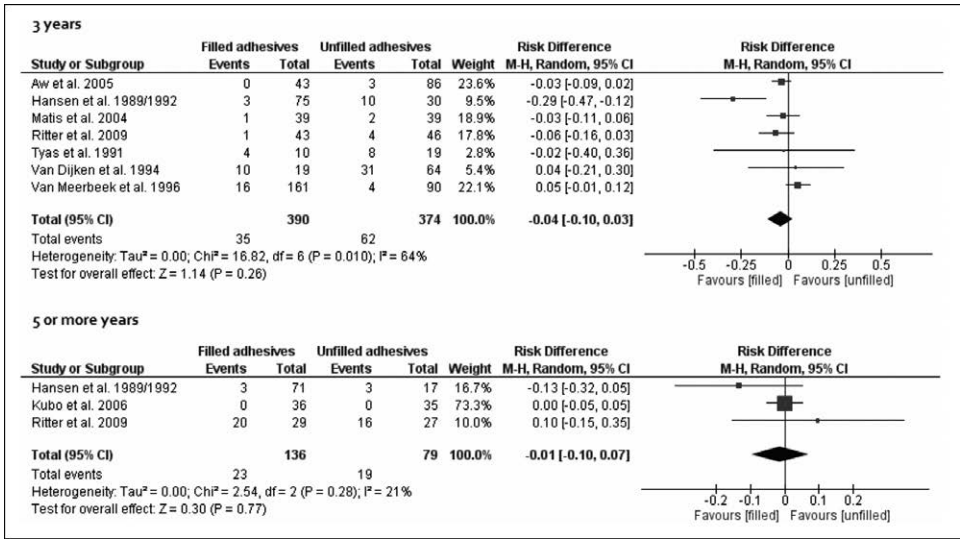

Figure 4. *Forest plot of restorations that suffered retention loss comparing filled vs unfilled adhesives at 3 and 5 or more years.*

teins that may physically impede the infiltration of nanofillers.[123]

Also due to the natural tendency to aggregate, micrometric electrodense filler clusters will form that are larger than the interfibrillar spaces.[16,27] Osorio and others[119] showed that in self-etch adhesive systems, large clusters were observed that were beyond the dimensions of the interfibrillar spaces of the collagen fibers. Some authors suggested that if the volume of the nanofillers within the adhesive was lower than 3.0 wt%, they did not aggregate that easily and would increase the bond strength to dentin.[124] However, in commercial simplified etch-and-rinse and self-etch adhesives, more than 5 wt% is found.[16] On the other hand, the lower amount of nanofillers did not significantly improve the mechanical properties of the adhesive layer.[20,30,31] Other researchers used specific techniques to produce nonaggregated nanoparticles with high antimicrobial potential.[125,126] These facts may also explain why no significant increase in the bond strength to dentin could be observed when nanofilled-containing simplified adhesives had been tested compared with unfilled simplified adhesives.[32-35]

The results of the present study should be interpreted with caution because they represent an overall comparison without taking into consideration specific variations in the products (monomer and solvent composition, application technique, evaporation solvent time, and moisture control). However, if one of these factors has an important role in the clinical performance of an adhesive, merging studies in a meta-analysis will increase the power to detect the role of such a variable. This would not be possible in primary studies with low sample sizes.

Also, the inadequate randomization of some clinical studies may have led to the fact that the chances of a patient being allocated to the test or control group were not the same for all patients, and known and unknown prognostic factors had not been balanced out among the groups.[47,110,127] The random sequence should be protected until implementation[127] (allocation concealment). Most of the eligible studies that had been included in this systematic review were classified as having unclear risk of bias. This judgment was based on the lack of clear description of the randomization and allocation concealment process. This is in accordance with what was recently published by Reis and others in 2018,[128] who reported that more than 60% of RCTs about adhesive systems that had been tested in noncarious cervical lesions had a high or unclear risk of bias for randomization and allocation concealment.

Therefore, long-term and well-conducted RCTs that comply with the requirements of an RCT are needed to evaluate possible technological improvements of adhesive systems such as the addition of nanofillers to improve the longevity of the bonding interface to dentin.

CONCLUSIONS

The addition of micro or nanofillers to the composition of adhesive systems did not increase the clinical performance (retention rates, marginal discoloration, or secondary caries) in noncarious cervical lesions compared with unfilled adhesive systems.

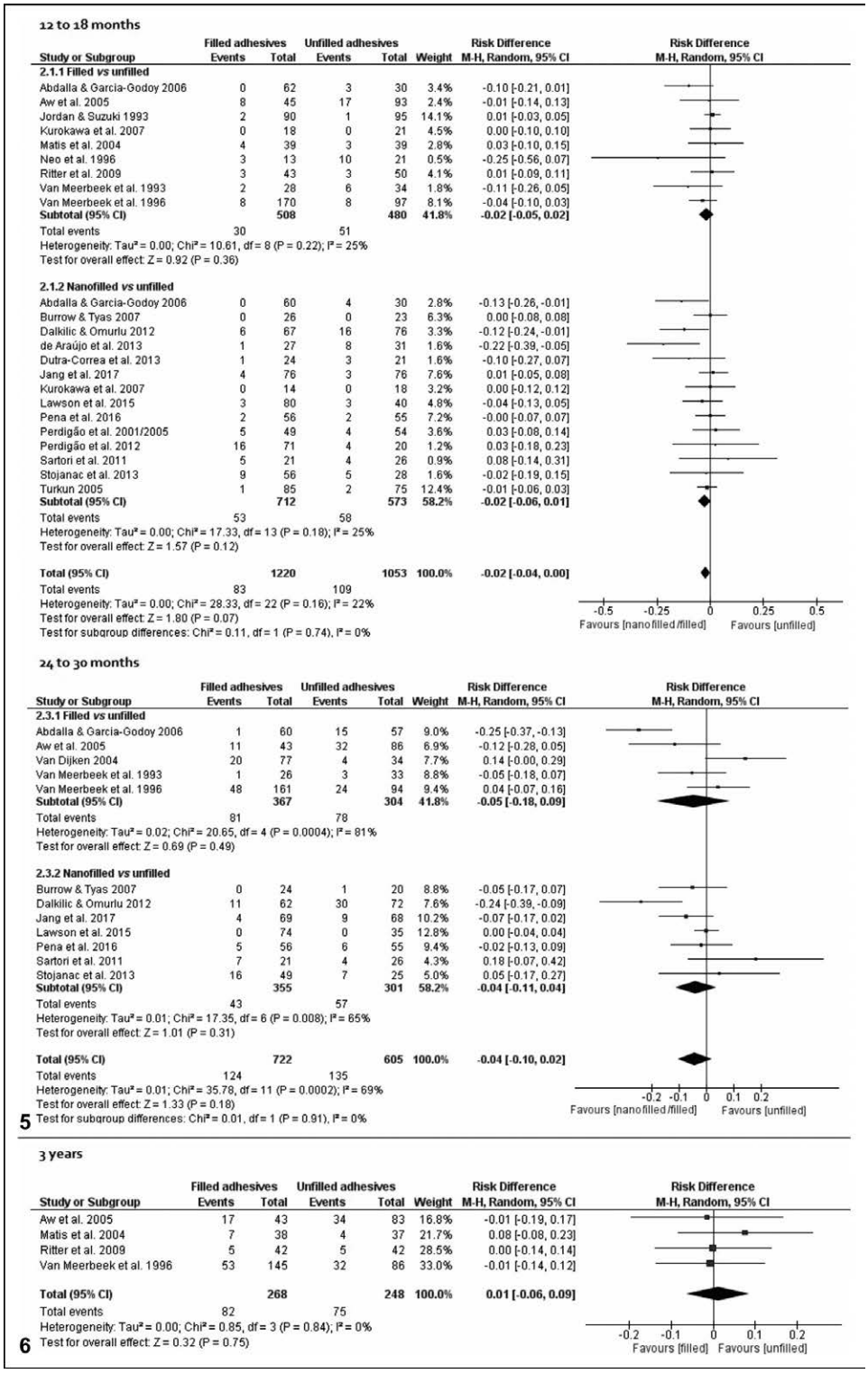

Figure 5. *Forest plot of restorations with marginal discoloration comparing filled/nanofilled vs unfilled adhesives at 12 to 18 months and 24 to 30 months.*

Figure 6. *Forest plot of restorations with marginal discoloration comparing filled vs unfilled adhesives at 3 years.*

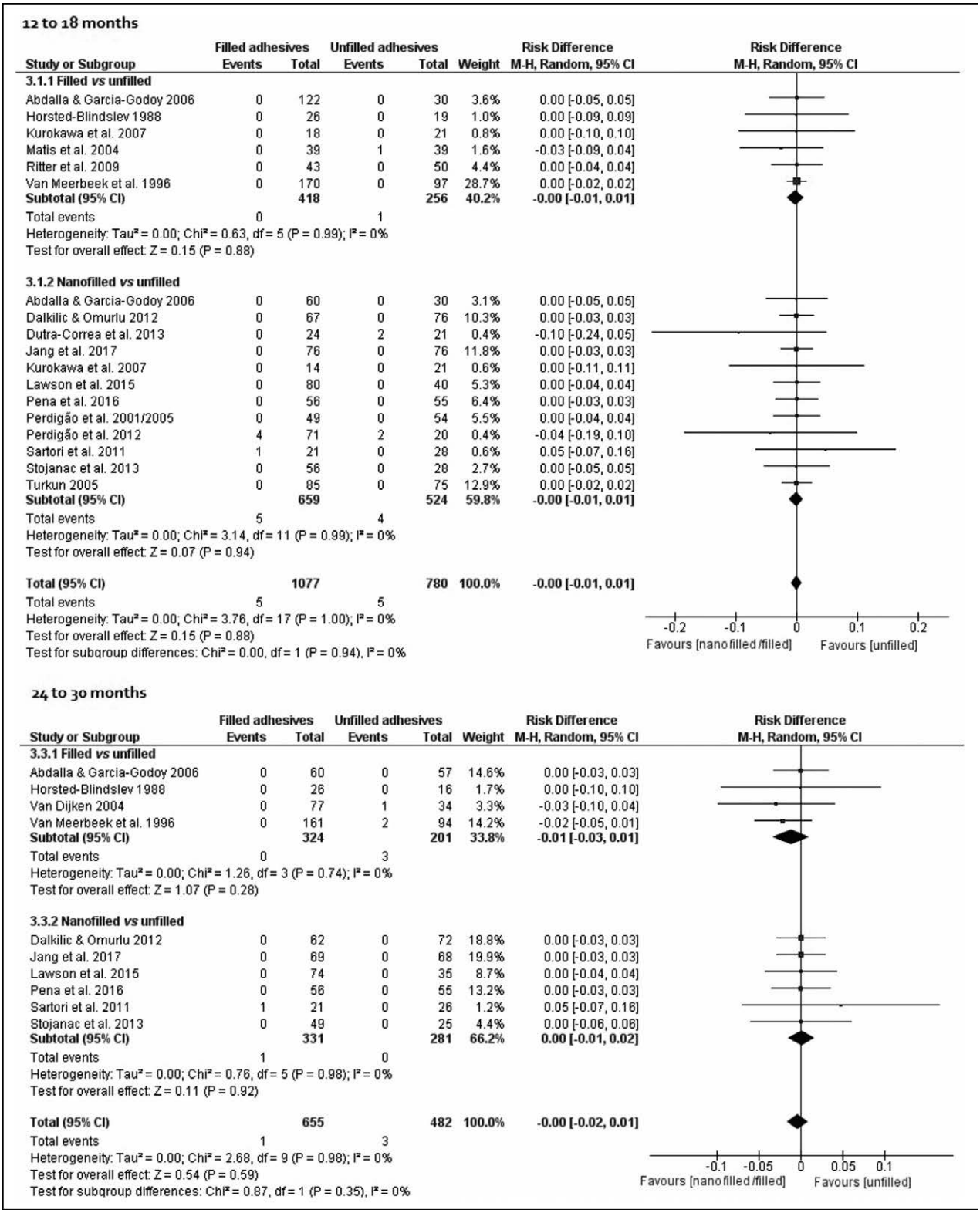

Figure 7. *Forest plot of restorations with secondary caries comparing filled/nanofilled vs unfilled adhesives at 12 to 18 months and 24 to 30 months.*

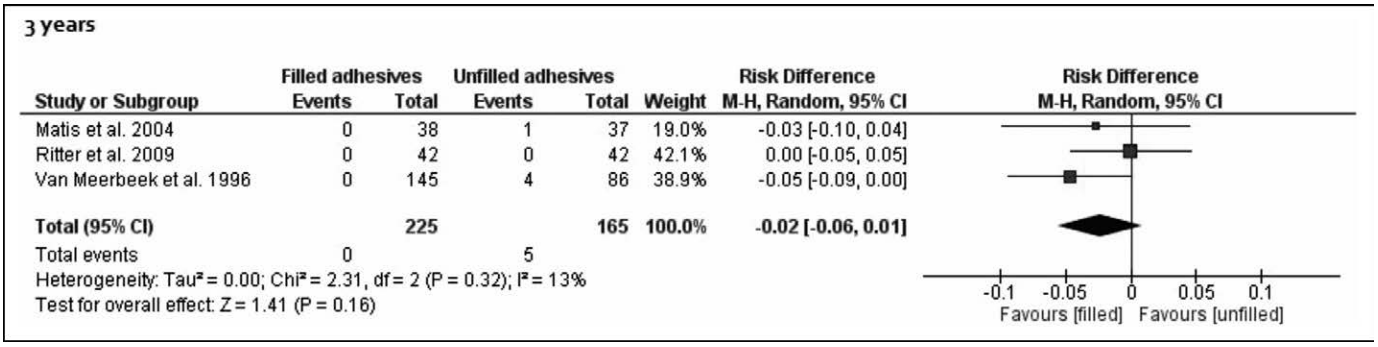

Figure 8. *Forest plot of restorations with secondary caries comparing filled vs unfilled adhesives at 3 years.*

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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.

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