Microleakage of Direct Restorations—Comparison between Bulk-Fill and Traditional Composite Resins: Systematic Review and Meta-Analysis

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Abstract

Since the bulk-fill composites were produced, there was a progressive diffusion of their use for direct conservative treatment in posterior teeth. Their chemical structure increases the depth of cure and decreases the polymerization contraction; in this manner, bulk-fill composites can be placed in 4 mm single layers and the treatment times are considerably reduced. However, aesthetic and mechanical properties and impact on microleakage of bulk-fill resins are still unclear.

This systematic review and meta-analysis aimed to assess the risk of microleakage of direct posterior restorations made of bulk-fill versus conventional composite resins.

Researches were performed on PubMed and Scopus databases. Eligible in vivo studies, published since 2006, were reviewed. Outcomes of marginal discoloration, marginal adaptation, and recurrent caries were considered to conduct the systematic review and meta-analysis. Secondary data were examined to implement additional analysis and assess the risk of bias.

Eight randomized clinical trials were analyzed, involving 778 direct restorations. The summary of RCTs led to significant but inconsistent results; the marginal discoloration and recurrent caries were found to be improved respectively by 5.1 and 1.4%, whereas the marginal adaptation was reduced of 6.5%. Secondary analyses revealed that follow-up periods, the adhesive system used and the class of carious lesions evaluated are confounding factors, and they result in a risk of bias across studies.

Bulk-fill composites are innovative materials for conservative dentistry and they can be used to reduce treatment steps and duration of operative times. There are insufficient data to explore the relationship between bulk-fill composites and microleakage and further investigations are needed.

Keywords
- bulk-fill composites
- microleakage
- marginal discoloration
- marginal adaptation
- recurrent caries
- direct restorations

Introduction

The key role of dental restoration is covering the exposed dentine to protect it from the oral environment. However, this coverage could be lacking overtime with consequent gaps at the tooth-restoration interface known as microleakage.[1] This could result from polymerization shrinkage stress of the composite resins; the stress overcomes the bond strength of

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restoration causing the passage of fluids and bacterial infiltration between walls of the cavity and filling material.[2]

The presence or absence of microleakage is one of the outcomes accountable for the success of fillings overtime[3]; oral microorganisms invade the tooth-restoration gap in a short time and they can reach dental tissues causing a biological damage.[4] The microleakage could result in discoloration[5] of the margins of restoration, dentin hypersensitivity, secondary caries, and also pulp affections.[6] Thus, the progression of the disease could be accountable for therapeutic failure.[4]

Bulk-fill composite resins are recognized to have a low polymerization shrinkage, and therefore, they seem to be able to reduce the stress at the tooth-restoration interface.[7] Because of this, they are used in direct restoring of dental elements, allowing to be packed in the dental cavity in a single dose (3 mm+) or greater dimension dose compared to conventional composites.[8] On the other side, literature reports that bulk-fill composites are inferior to conventional ones in terms of wear resistance and fracture toughness[9]; accordingly, it may be advisable to cover their surface by using macrofilled resins, especially for flowable ones.[10] Moreover, color and translucency performances of bulk-fill resins are limited if compared with those of conventional resins with a subsequent lower aesthetic result.[10] In light of this, using bulk-fill composites is indicated for posterior restorations (Black class I and II) with deep and voluminous cavities, taking advantages from packing more resins into preparations; this allows making simpler and faster the restorative procedures with decreasing clinical steps.[11]

Although bulk-fill composite resins are claimed to exhibit low polymerization shrinkage, there are not enough evidences concerning the effects of gap formation of these composites using an intermediate liner.[2]

This systematic review with meta-analysis aimed:

- To evaluate the difference of microleakage between dental restorations performed with bulk-fill and conventional composites resins.
- To assess the entity of marginal discoloration, marginal adaptation, and secondary caries of restorations made by the two different composites resins.

The clinical question in the PICO (population, intervention, control, and outcomes) format was "in direct dental restorations, does the bulk-fill resins use compared to that of conventional composites affect the microleakage?

Materials and Methods

The protocol of this systematic review was developed according to the Cochrane Handbook and the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA).[12]

Eligibility Criteria

The following criteria were considered eligible for inclusion in this review:

- Randomized clinical trials (RCTS) in vivo with a 1-year minimum follow-up
- Papers published between January 2006 and June 2020
- Abstract and full-length text available for reading

The exclusion criteria were articles which have not been published in English or Italian, experimental in vitro studies, and studies that evaluated microleakage of bulk-fill composites without comparison with those conventional.

Data Sources and Search Strategy

The search was performed by using PubMed and Scopus in the period between April and June 2020.

Combinations of MeSH terms and free text words have been combined by using Boolean operators.

The search strategies for each database are represented in ►**Table 1**.

An additional search was carried out through cross-check on references of selected articles.

Study Selection

Two independent researchers (F.E. and Z.F.) performed the electronic search. The first evaluation was performed by reading only the title and abstract of the studies.

Later, all studies considered eligible were included for full-text evaluation and only studies considered eligible by both authors were included in the review.

In case of discordance, a third author (C.G.) was included in the evaluation.

The following data were extracted:

- Sample features (number of restorations performed and followed-up; Black's classification)

Table 1 Search strategy

1: – Dental restoration, permanent [MeSH Terms] – Dental caries [MeSH Terms] – Tooth restoration – Teeth restoration – Class i – Class 1 – Class ii – Class 2 – Posterior restoration – Molar restoration	2: – Bulk fill – Bulk-fill – Bulk fill – Bulk filled – Bulk filling – Bulk
3: – Composite resins [MeSH Terms] – Composite resin – Resin composite – Resin composites – Resin restoration – Resin restorations – Composite restoration – Composite restorations	4: – Dental leakage [MeSH Terms] – Microleakage – Leakage – Secondary caries – Recurrent decay – Recurrent caries – Recurrent decay
((((((((((((dental restoration, permanent[MeSH Terms]) OR dental caries[MeSH Terms]) OR tooth restoration) OR teeth restoration) OR class i) OR class 1) OR class ii) OR class 2) OR posterior restoration) OR molar restoration)) AND ((((((bulkfill) OR bulk-fill) OR bulk fill) OR bulk filled) OR bulk filling) OR bulk)) AND (((((((((composite resins[MeSH Terms]) OR composite resin) OR resin composite) OR resin composites) OR resin restoration) OR resin restorations) OR composite restoration) OR composite restorations)) AND (((((((dental leakage[MeSH Terms]) OR microleakage) OR leakage) OR secondary decay) OR secondary caries) OR recurrent decay) OR recurrent caries)	

- Operative procedures (adhesive system, type and viscosity of the composite used and the control groups, prospective capping layer)
- Assessment method (follow-up, evaluation criteria, included variables)
- Outcomes[21] to assess microleakage. Three observable, and measurable clinical variables were taken into account:
  - Marginal discoloration
  - Marginal adaptation
  - Secondary caries

To perform a meta-analysis, all variables were turned into dichotomous variables:

- No clinical sign: only restorations that received the best score of the criterion used Alpha scoring of Ryge criteria; 0 of US Public Health Service (USPHS) modified criteria.
- Clinical sign: all restorations did not receive the best score of the criterion used, Bravo, or Charlie scoring of Ryge criteria; 1 to 5 of USPHS modified criteria.

In this way, four groups were created for evaluating each clinical variable in each selected study:

- Group A: bulk-fill resin restoration without a clinical sign
- Group B: conventional resin restoration without a clinical sign
- Group C: bulk-fill resin restoration with a clinical sign
- Group D: conventional resin restoration with a clinical sign

Risks of Bias

To determine the validity and the quality of each RCT selected, from the full-text were assessed the following criteria:

- Adequacy of randomization
- Adequacy of allocation
- Selection criteria of patients and restorations
- Number of operators who performed restorations
- Patients and assessor blinding
- Drop-out at follow-up, impossibility to assess outcomes and reasons for this
- Experience of assessors

All criteria used to assess the quality of RCTs were taken into account (the list above); furthermore, for each variable, a funnel plot was designed by using the relative risk and the weight of each study. The symmetry of the plot excludes the publication bias, assuming that error decreases with the increasing of precision and quality of experimental studies.[13] Therefore, the studies with considerable weight are near to midline and those with poor weight are farther from this.

Further determinants could influence the symmetry of the funnel plot:

- Differences among the observational periods of the studies
- Experience of the operator: the learning curve is responsible for differences among studies, both for the proper performance of clinical procedures and for the knowledge about the new class of Bulk-fill composite resins and the feasibility to assess microleakage using the measurement criteria.
- Adhesive system: different adhesive protocols are accountable for confounding results due to different performances of different generation of adhesive systems,[14]
- Capping layer: some manufacturer, especially those of flowable resins, advice to cover the bulk-fill restoration with a conventional composite layer. In these cases, the comparison of micro-leakage signs is unavoidably altered.
- Black's classification of restorations: class II restorations have tooth-filling interface placed in the interproximal area, this represents a greater risk overtime[15]; therefore, the studies assessing exclusively class II could produce less encouraging results.

Meta-Analysis

Statistical analysis was performed by using Stata Software (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC).

Relative risk (RR) and 95% confidence interval were calculated, fixing significance at $\alpha = 0.05 = 5\%$, to assess heterogeneity of studies in the forest plot. This evaluation was confirmed by Chi-square test. The random-effect model was used.

Combined relative risk (CRR) for outcomes represents differences between composites:

- CRR = 1: no differences between two type of resins for the considered variable
- CRR > 1: bulk-fill composites show more favorable clinical performances than conventional for the considered variable
- CRR < 1: bulk-fill composites show less favorable clinical performances than conventional for the considered variable

Z-test was run to assess the significance of the three results and *p*-values >0.05 were considered statistically significant.

Additional Analyses

Additional analyses were performed to better elucidate the effect of peculiar features of studies included:

- Differences of carious lesions (only class I or class I and II restorations)
- Viscosity of composite resin and differences of restorative procedures, especially capping layer placement
- Differences of adhesive systems used (1 step or 2 steps)

Results

Study Selection

From the first search 1,050 works resulted, duplicates were checked, and according to inclusion and exclusion criteria, 22 studies were included. Application of eligibility criteria resulted in eight papers evaluated. The literature selection process was reported in the diagram (►**Fig. 1**).

Results were synthesized in ►**Table 2**.

Data Extraction: Characteristics of Included Studies

- Sample features: papers included evaluated a total amount of 778 restorations from a minimum of 56 in Heck et al[16] to a maximum of 196 fillings in the van Dijken et al work.[17] In all studies classification of restorations was

Table 2 Synthesized results

Author, year	Sample	Black's classification	Study group	Control group	Adhesive system	Follow-up	Evaluation criteria
Van Dijken et al, 2015[16]	196	Class I (74) and class II (122)	SDR flowable RC + capping CeramX– max 4mm+2mm	CeramX – 2mm - packable	1 step	3 years	USPHS criteria
Alkurdi et al, 2016[17]	58	Class II	Tetric N Ceram Bulk-fill – 4mm – packable Sonic Fill – 5mm - sonic	TetricEvo Ceram – 2mm - packable	2 stepsetch and rinse	1 year	USPHS criteria
Van Dijken et al, 2016[19]	183	Class I (68) and class II (115)	SDR flowable RC + capping CeramX – max 4mm+2mm	CeramX – 2mm - packable	1 step	5 years	USPHS criteria
Colak et al, 2017[19]	70	Class II	TetricEvoCeram bulk-fill – 4mm - packable	TetricEvoCeram – 2mm - packable	2 stepsetch and rinse	1 year	USPHS criteria
Yazici et al, 2017[20]	81	Class II	TetricEvoCeram Bulk Fill – 4mm - packable	Filtek Ultimate - packable	2 stepsetch and rinse	3 years	USPHS criteria
Heck et al,2018[22]	56	Class I (74) and class II (45)	QuiXfil – 4mm - packable	Tetric Ceram – 2mm - packable	1 step 2 steps etch and rinse	10 years	USPHS criteria
Balkaya et al, 2019[23]	71	Class II	Filtek Bulk Fill Posterior Restorative - 4mm - packable	Charisma Smart Composite - 2mm - packable	1 step	1 year	USPHS criteria
Balkaya et al, 2020[24]	63	Class II	Filtek Bulk Fill Posterior Restorative - 4mm - packable	Charisma Smart Composite - 2mm - packable	1 step	2 years	USPHS criteria

Abbreviation: USPHS, U.S. Public Health Service.

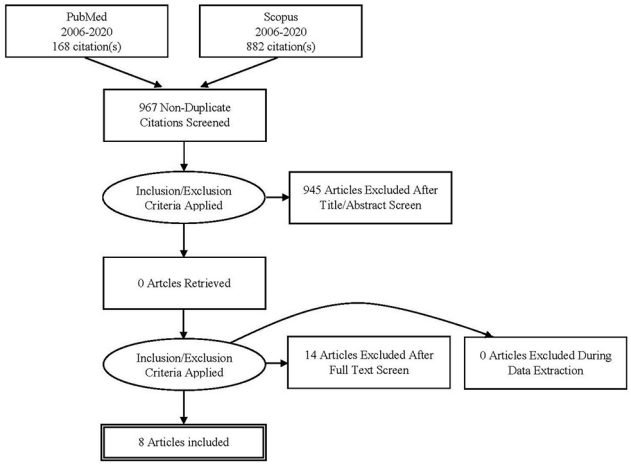


Fig. 1 Literature selection process.

reported, specifically five studies[18-20,22,23]considered only class II fillings and three studies both class I and II restorat ions.[16,17,24]

- Operative procedures: restorations of the study group are made by bulk-fill composites both packable, flowable, and sonic; in two van Dijken et al[17,24] studies, the flowable bulk-fill was capped with 2 mm layer of conventional composite resin as advised by the manufacturer. Alkurdi et al[18] evaluated two bulk-fill composites in two different study groups, one packable resin and a sonic one: the two groups were here considered as a unique one, by uniting results. Both 1-step and 2-step etch and rinse adhesive systems were used in the studies evaluated. All authors used the same adhesive system for the two groups, except in Heck et al[16] where the 1-step system was used in the study group and 2-step system in the control group.
- Assessment method: Studies selected followed-up results between 1 and 3 years, except for Dijken et al[24] and Heck et al[16] who compared groups at 5 and 10 years, respectively. This difference in the observation period might cause differences in outcomes.

All restorations were evaluated by using USPHS modified criteria: in seven studies all three outcomes were assessed, whereas in the research by Yazici et al[20] only marginal discoloration and marginal adaptation were considered.

The studies analyzed used different scoring in some studies Alpha, Bravo, and Charlie were used; in others, a numerical score from 0 to 4 was assigned. Except in the two studies by van Dijken et al,[17,24] where the percentage of outcomes incidence is reported in all studies, the absolute values were

shown in tables. The values reported by van Dijken et al were turned into absolute values.

Outcomes

Marginal Discoloration

A decrease of marginal discoloration was noticed in 5.1% of bulk-fill composites restorations. All studies are not significant. Only Alkurdi et al[18] and Yazici et al[20] showed RR values >1, indicating a greater discoloration rate in conventional restorations compared to those made of bulk-fill composites (►**Table 3**).

Marginal Adaptation

An increase of poor marginal adaptation was noticed in 6.5% in bulk-fill composites restorations. The study by Yazici et al[20] resulted statistically significant. Only van Dijken et al,[17] Alkurdi et al[18], Heck et al[16] reported RR values <1 (►**Table 4**).

Secondary Caries

A decrease of secondary caries was noticed in 1.4% in bulk-fill composites restorations.

In four studies out of seven, the incidence of secondary caries was reported to be 0 in both groups. These studies were not included in the meta-analysis because they did not inform on the effect of treatment.[18-20,22,23] Thus, for this outcome, only van Dijken et al[17,24] and Heck et al[16] researches were analyzed and found to be statistically significant. The RR was reported to be 1, indicating the same incidence of secondary caries among both groups (►**Table 5**).

Intra-Studies Risk of Bias

Randomization and allocation were specified in seven studies; Alkurdi et al[18] did not provide information.

Blinding of operators and assessors was clearly mentioned in six studies,[15,19,20,22,23] except in those by Alkurdi et al[18] and Heck et al.[16] The six studies further indicated the training of assessors.

All eight studies exhaustively reported inclusion and exclusion criteria, specifying factors related to patients (hygiene habits and comorbidity) and those related to carious lesions (dimension and vitality of teeth).

Dropout of restorations varies depending on the duration of observation period; in the 1-year follow-up studies, Alkurdi et al[18] reported 3.33% of not-followed restorations, Colak et al[19] reported 5.41%, and Balkaya et al[22] reported 5.50%. In 2-year follow-up studies, Balkaya et al[23] reported a percentage of 22.94. In studies with a 3-year follow-up, dropout of 2% was reported by Dijken et al[17] and 22.12% by Yazici et al.[20] Studies with longer observation period reported having loss sample of 8.5% in the 5-year van Dijken et al[24] research and of 41.67% in the Heck et al[16] work. Reasons for these dropouts were specified only in van Dijken et al[17,24] and Alkurdi et al[18] studies.

Experience of assessors in using USPHS modified criteria was attested in all studies; in Alkurdi et al,[18] Colak et al,[19] Yazici et al,[20] and Balkaya et al,[22,23] the assessment was performed by the same operator and in the studies by van Dijken et al[17,24] and in that by Heck,[16] two and three operators were used, respectively.

None of the eight studies showed a high risk of bias; therefore, all were considered qualitatively eligible for meta-analysis (►**Fig. 2**).

Inter-Studies Risk of Bias

Funnel plots for publication bias are reported in table (►**Fig. 3**).

Funnel plots for marginal discoloration and secondary caries showed regular distribution indicating that precision of estimation of effect increases with increasing of the weight of each study. Conversely, the plot for marginal adaptation appeared altered, considering that two works by Dijken et al[17,24] are out of traced segments.

Additional Analyses

Differences of Carious Lesions (Only Class I or Class I and II Restorations)

Percentage of restorations positive for all three outcomes in both groups (study and control) is greatly higher in the three studies analyzing both I and II class restorations, as reported in ►**Tables 3**–**5**.

Therefore, determining clinical signs of microleakage in the interproximal areas is difficult to be performed, with consequent distortion of results due to those false negatives.

Viscosity of Composite Resin and Differences of Restorative Procedures (Especially Capping Layer Placement)

Only studies by van Dijken et al[17,24] used flowable resins and conventional composite layer capping to perform restorations. Results were 0.91[17] and 0.92[24] for marginal discoloration and 0.90[17] and 1.24[24] for marginal adaptation. These findings are consistent with those from other researches indicating a difference between study and control group even if a flowable resin capped is used. This means that meta-analysis is not affected by the inclusion of these experimentations.

In Alkurdi et al,[18] four cases of marginal discoloration and four cases of poor marginal adaptation in the group restored with packable bulk-fill resin were reported. In the group restored by sonic composite, two cases of margin discoloration and one of poor marginal adaptation were highlighted. For the outcome of secondary caries, both groups reported 0 cases. Thus, the findings with a 1-year follow-up draw the attention on the better performances of sonic resin.[18]

Differences of Adhesive System Used (1 Step or 2 Steps)

The number of steps in adhesive procedures can affect the outcomes of restorations[25]: adhesives of sixth and seventh-generation lead to less satisfying microscopical results compared to those of fourth and fifth generation.[26,27]

Studies by van Dijken et al[17,24] and Balkaya et al[22,23] used all-in-one adhesive systems, those by Alkurdi et al,[18] Colak et al,[19] and Yazici et al[20] used 2-step etch and rinse.

The research by Heck et al[16] used 1-step adhesive in the study group and 2-step adhesive in the control group, this issue negatively affected the quality of research due to the different condition of two group tested.

Results showed lower RR compared to those from other researches for the three outcomes (0.69 for marginal discoloration; 0.73 for marginal adaptation; 0.69 for secondary

Table 3 (**A**) Marginal discoloration results; (**B**) marginal discoloration statistical analysis; (**C**) marginal discoloration forest plot

(A)

Author (Year)	Bulk-fill resin restorations without clinical sign	Conventional resin restorations without clinical sign	Bulk-fill resin restorations with clinical sign	Conventional resin restorations with clinical sign
Van Dijken et al (2015)[16]	82.1%	90.5%	17.9%	9.5%
Alkurdi et al (2016)[17]	83.8%	78.9%	16.2%	21.2%
Van Dijken et al (2016)[18]	73.6%	80.2%	26.4%	19.8%
Colak et al (2017)[19]	88.6%	97.1%	11.4%	2.9%
Yazici et al (2017)[20]	90.2%	75%	9.8%	25%
Heck et al (2018)[22]	85.7%	66.7%	14.3%	33.3%
Balkaya et al (2019)[23]	94.4%	100%	5.6%	0%
Balkaya et al (2020)[24]	93.5%	96.9%	6.5%	3.1%

Note: All outcomes are expressed as a percentage.

(B)

Meta-analysis summary Random-effect model method: REML		Number of studies = 8 Heterogeneity: $Tau^2 = 0.0000$ I^2 (%) = 0.00 $H^2 = 1.00$		
Author (Year)	**Effect size**	**95% CI**		**% Weight**
Van Dijken et al (2015)[16]	0.907	0.796	1.019	17.43
Alkurdi et al (2016)[17]	1.061	0.789	1.333	2.92
Van Dijken et al (2016)[18]	0.918	0.765	1.070	9.30
Colak et al (2017)[19]	0.912	0.780	1.044	12.44
Yazici et al (2017)[20]	1.203	0.998	1.409	5.13
Heck et al (2018)[22]	0.692	0.206	1.179	0.91
Balkaya et al (2019)[23]	0.944	0.865	1.024	34.45
Balkaya et al (2020)[24]	0.966	0.854	1.077	17.41
Summary	0.949	0.903	0.996	
Test of theta = 0: z = 40.01 Test of homogeneity: Q = χ^2 (7) = 8.72 Prob > |z| = 0.0000 Prob > Q = 0.2730				

Abbreviations: CI, confidence interval; REML, restricted maximum likelihood.

(C)

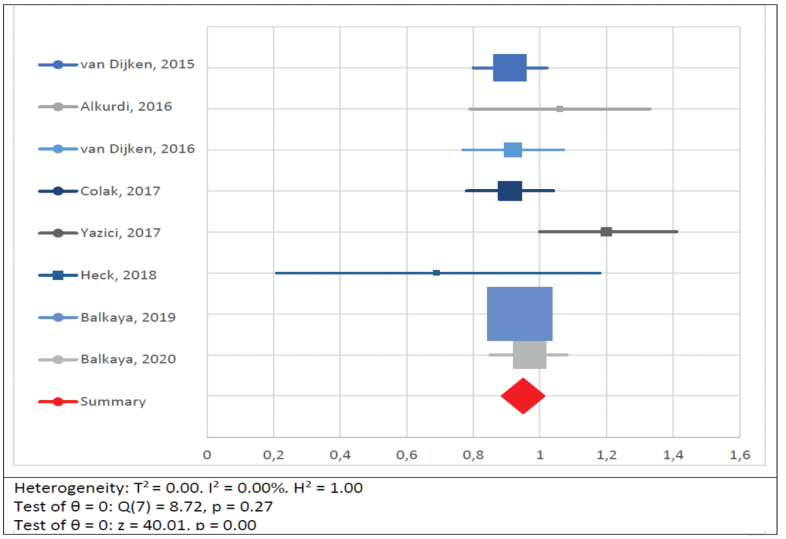


Table 4 (**A**) Marginal adaptation results; (**B**) marginal adaptation statistical analysis; (**C**) marginal adaptation forest plot

(A)

Author (Year)	Bulk-fill resin restorations without clinical sign	Conventional resin restorations without clinical sign	Bulk-fill resin restorations with clinical sign	Conventional resin restorations with clinical sign
Van Dijken et al (2015)[16]	87.8%	97%	12.2%	3%
Alkurdi et al (2016)[17]	86.5%	89.5%	13.5%	10.5%
Van Dijken et al (2016)[18]	92.9%	74.7%	7.1%	25.3%
Colak et al (2017)[19]	100%	97.1%	0%	2.9%
Yazici et al (2017)[20]	95.1%	80%	4.9%	20%
Heck et al (2018)[22]	53.8%	73.3%	46.2%	26.7%
Balkaya et al (2019)[23]	94.4%	85.7%	5.6%	14.3%
Balkaya et al (2020)[24]	87.1%	71.9%	12.9%	18.1%

Note: All outcomes are expressed as a percentage.

(B)

Meta-analysis summary Random-effect model Method: REML		Number of studies = 8 Heterogeneity: Tau^2 = 0.0136 I^2 (%) = 77.02 H^2 = 4.35		
Author (Year)	**Effect size**	**95% CI**		**% Weight**
Van Dijken et al (2015)[16]	0.905	0.824	0.986	17.23
Alkurdi et al (2016)[17]	0.967	0.767	1.167	10.96
Van Dijken et al (2016)[18]	1.244	1.117	1.370	14.84
Colak et al (2017)[19]	1.029	0.973	1.086	18.25
Yazici et al (2017)[20]	1.189	1.019	1.359	12.48
Heck et al (2018)[22]	0.734	0.318	1.150	4.48
Balkaya et al (2019)[23]	1.102	0.945	1.259	13.17
Balkaya et al (2020)[24]	1.212	0.956	1.467	8.60
Summary	1.065	0.964	1.165	
Test of theta = 0: z = 20.78 Test of homogeneity: Q = χ^2 (7) = 28.59 Prob > |z| = 0.0000 Prob > Q = 0.0002				

(C)

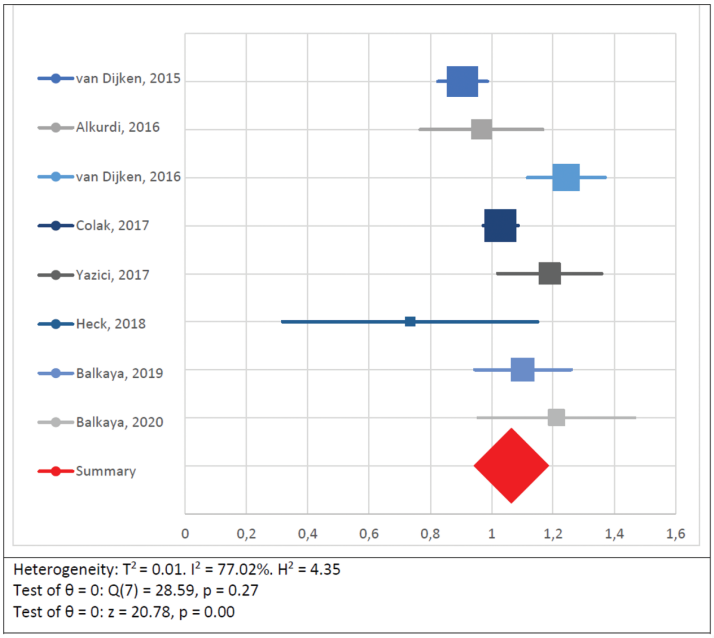


Table 5 (**A**) Secondary caries results; (**B**) secondary caries statistical analysis; (**C**) secondary caries forest plot

(A)

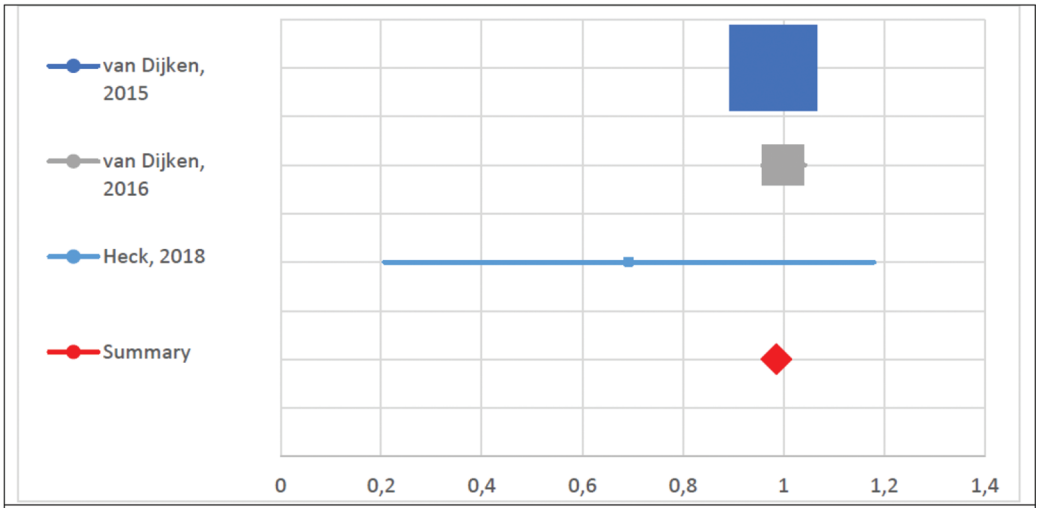
Author (Year)	Bulk-fill resin restorations without clinical sign	Conventional resin restorations without clinical sign	Bulk-fill resin restorations with clinical sign	Conventional resin restorations with clinical sign
Van Dijken et al (2015)[16]	98%	100%	2%	0%
Alkurdi et al (2016)[17]	100%	100%	0%	0%
Van Dijken et al (2016)[18]	97.8%	97.8%	2.2%	2.2%
Colak et al (2017)[19]	100%	100%	0%	0%
Yazici et al (2017)[20]	46.2%	66.7%	53.8%	33.3%
Heck et al (2018)[22]	100%	100%	0%	0%
Balkaya et al (2019)[23]	100%	100%	0%	0%
Balkaya et al (2020)[24]	100%	100%	0%	0%

Note: All outcomes are expressed as a percentage.

(B)

Meta-analysis summary **Random-effect model** **Method: REML**		**Number of studies = 3** **Heterogeneity:** **Tau² = 0.0000** **I² (%) = 0.04** **H² = 1.00**		
Author (Year)	**Effect Size**	**95% CI**		**% Weight**
Van Dijken et al (2015)[16]	0.980	0.952	1.008	68.62
Van Dijken et al (2016)[18]	1.000	0.958	1.042	31.15
Heck et al (2018)[22]	0.692	0.206	1.179	0.23
Summary	0.986	0.962	1.009	
Test of theta = 0: z = 83.23 Test of homogeneity: Q = χ^2 (7) = 2.01 Prob > |z| = 0.0000 Prob > Q = 0.3656				

(C)



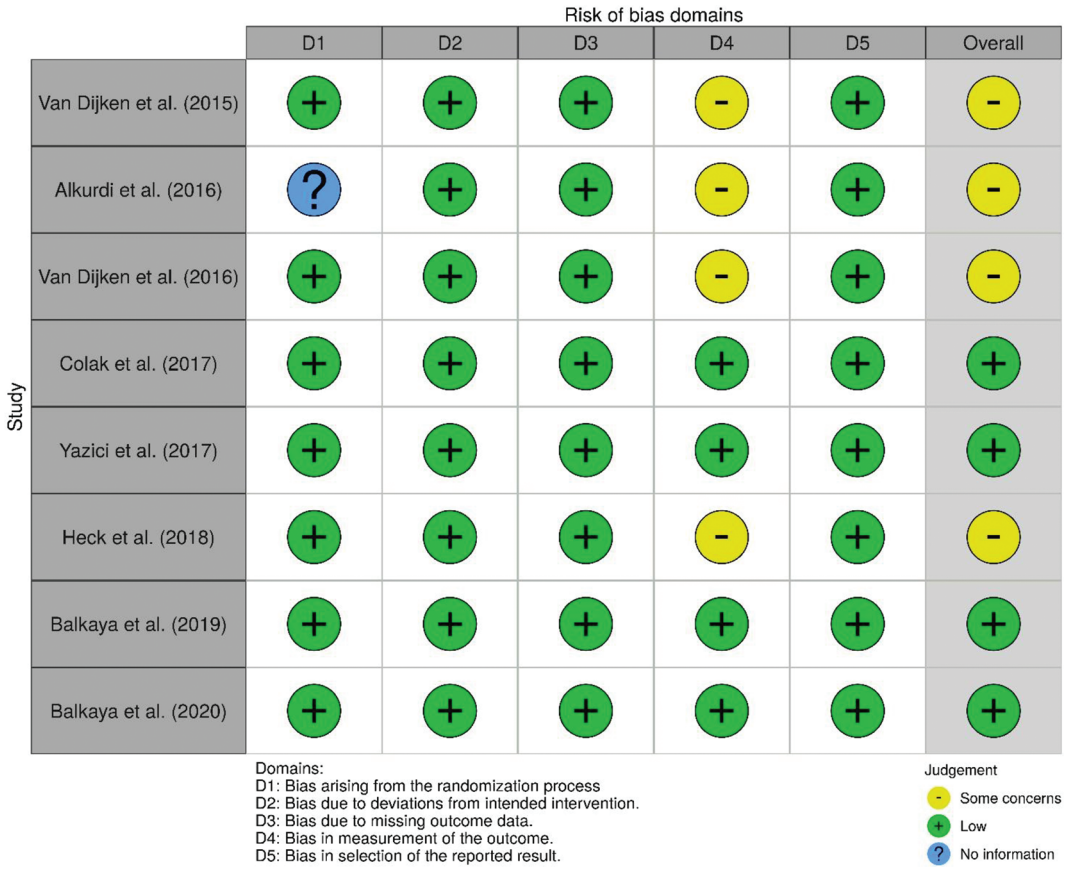


Fig. 2 Intra-studies risk of bias.

caries). Despite the long-term period of observation, this unfavorable condition of the experiment could affect the results, confirmed by the poor weight and the wide confidence interval.

Discussion

Since their market launch in 2006, bulk-fill composites were broadly used in restorative treatments of posterior teeth.[28] Their properties allow to puck more into the preparation and curing light to penetrate greater depth with a consequent clinical advantage in terms of time compared to conventional composite resins.[10] On the other hand, chemical and structural changes made could have determined weakness of resin properties; therefore, literature proposed in vivo and in vitro experimentation to assess this issue.[29,30] This systematic review and meta-analysis aimed to evaluate the behavior of bulk-fill composites concerning marginal discoloration, marginal adaptation and secondary caries occurrence, clinical signs of microleakage, in in vivo clinical trials.

Our findings showed a decrease of marginal discoloration and secondary caries of 5.1 and 1.4%, respectively; however, the poor marginal adaptation resulted to be increased of 6.5% using bulk-fill composites. Even if the results were found to be statistically significant, they are not in agreement in identifying the most suitable kind of composite resin to use for avoiding microleakage.

Therefore, our findings deserve deeper clarification because results of meta-analysis could be influenced by intra- and inter-studies bias.

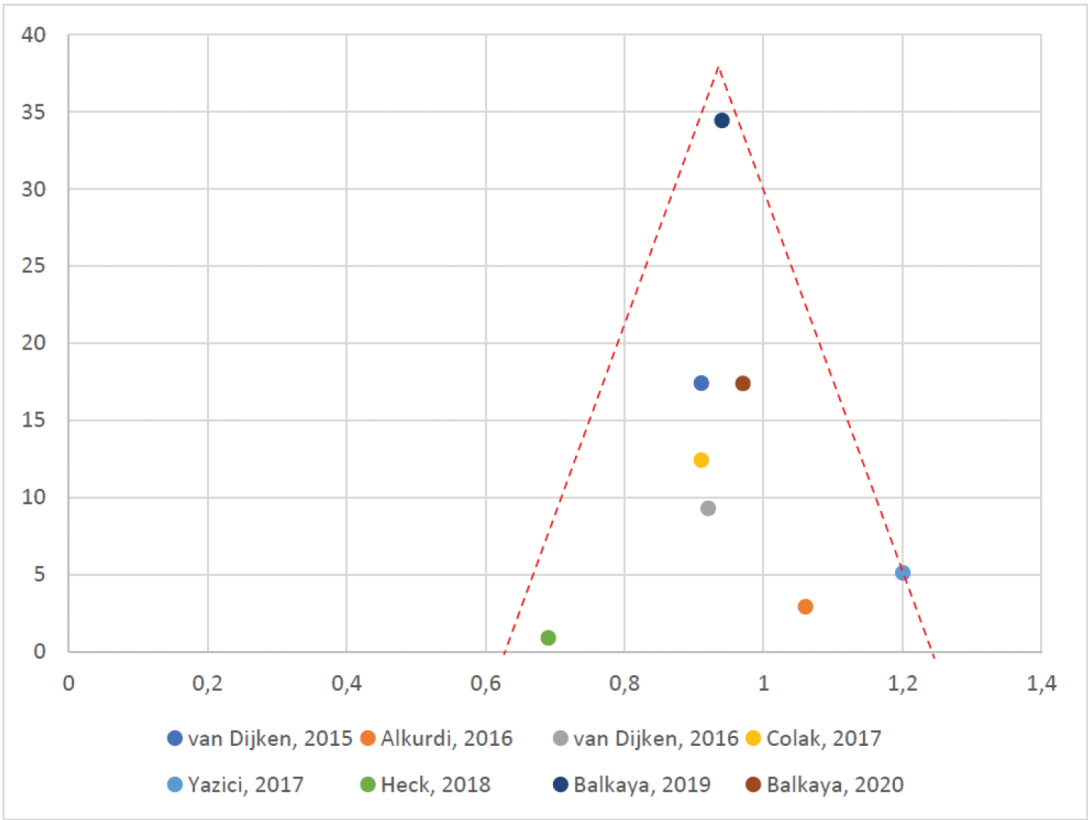
Concerning limitation of studies, authors evaluated randomization, blinding of patients, and assessors and the experience of practitioners and assessors in addition to the selection of patients and teeth restored and dropout.

In the RCTs, the randomization, blinding, and allocation play different roles in different moments. Allocation of carious lesions and patients to different groups aim to avoid the selection bias allowing to create a homogeneous group where confounding factors should be similar. Blinding, on the other hand, prevent spoiled behaviors of patients and clinicians. These aspects, recommended when a clinical trial is carried out, are specified in all studies, except those from Alkurdi et al[18] and Heck et al.[16]

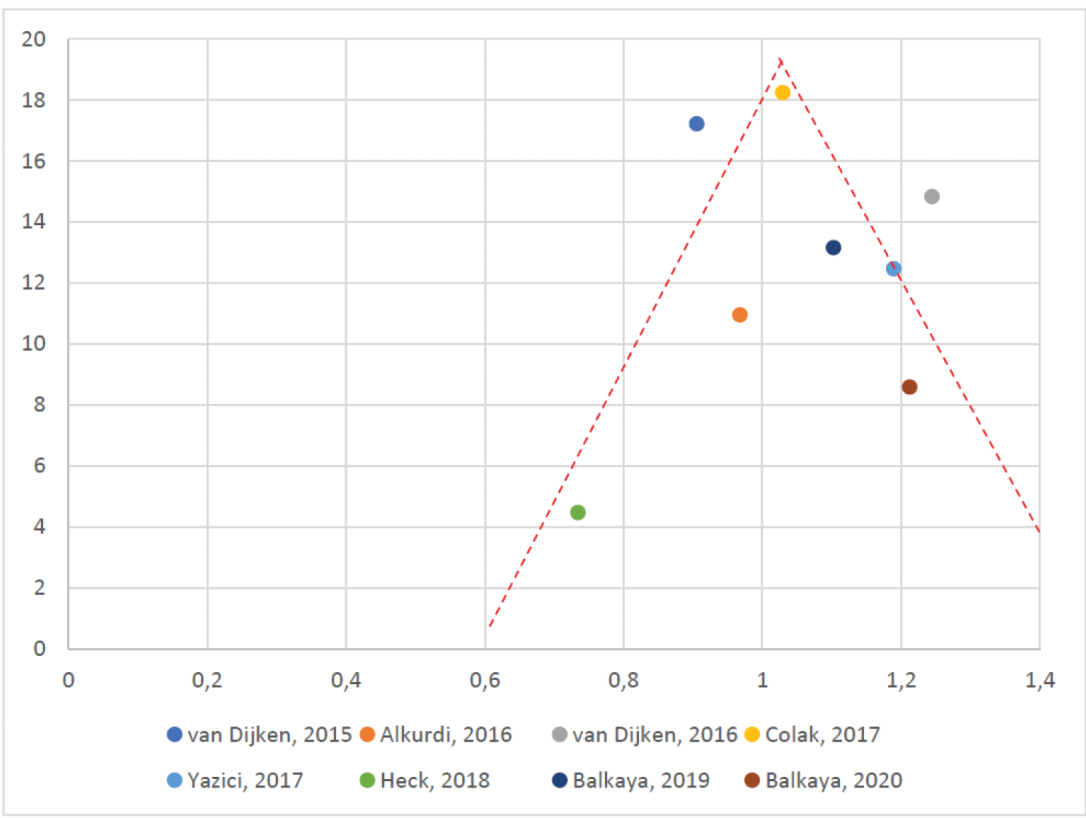
Experience of clinicians and assessors is an important criterion strictly related to the learning curve and to the subsequent ability in performing restorations; therefore, this issue should be taken into account in choosing figures involved in the study. All studies selected in the present meta-analysis reported that procedures were performed by trained operators, this ensures the minimization of technical errors and outcomes evaluation.

Inclusion and exclusion criteria were specified in all RCTs included in this work, even if with some difference. The most appropriate and clear criteria were listed by Balkaya et al.[22,23]

(A)



(B)



(*Continued*)

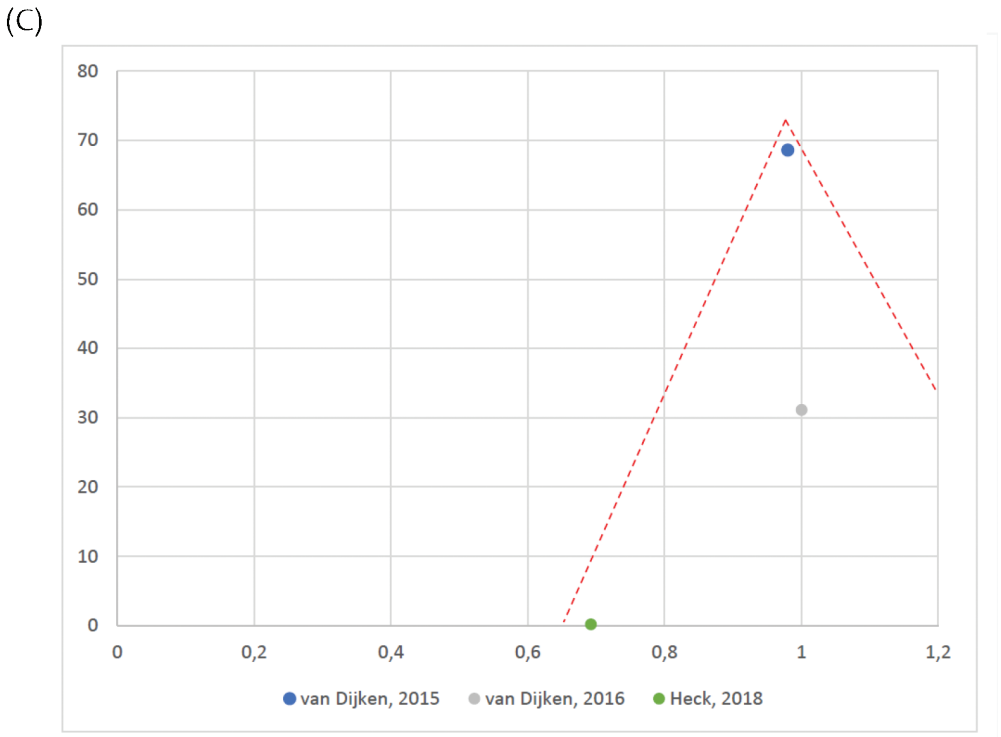


Fig. 3 (**A**) Marginal discoloration funnel plot; (**B**) marginal adaptation funnel plot; (**C**) secondary carries funnel plot

The most difficult criterion to deal with was the dropout at follow-up, in particular, studies by Balkaya et al[22] and Heck et al[16] reported a dropout of 22.94% at 2 years and 41.67% at 10 years, without specification of causes. Loss of this amount could affect the power of the study and therefore could make difficult drawing consistent conclusions.

However, the overall rating of all criteria included for assessing bias intra-studies assigned good quality rate to all trials, and therefore, they were all considered for statistical analysis.

A further aspect deserving to be considered is the duration of experimental studies based on up-to-date knowledge, the annual failure rate of conservative restorations is ranged between 1 and 3%,[31,32] and the secondary caries are the most frequent causes accountable for this.[33,34]

This estimate is not in agreement with data reported in trials assessed for this study in which 0 cases of secondary caries are reported in 1- and 2-year follow-up works. For this reason, these RCTs were not included in the meta-analysis. With this in mind, it seems to be advisable to extend the duration of the follow-up period regarding secondary caries to empower scientific and statistical findings.

About inter-studies bias, no differences of inclusion criteria and dental elements considered were found and the viscosity of materials and cupping layer technique do not seem accountable for low results, even if the two studies by Van Dijken et al[17,24] used a cupping layer performed with traditional composite over the bulk-fill restoration.

Differences inter-studies seem to be more strongly attributable to the classification of restorations (Black's classification) and adhesive systems used.

In particular, the choice of including restorations of different classes deserves to be deeply considered. Class II restorations are more exposed to the risk of microleakage due to interdental plaque; however, on the other hand, the difficulty to assess carious lesions in distal and mesial walls is too closely linked to clinical experience and diagnostic tools.[35] In this systematic review, trials by Heck et al[16] and Van Dijken[17,24] evaluated both class II and class I restorations, probably slightly affecting effect and weight of studies in meta-analysis.

To solve this bias, it would be useful to include in the analysis trials where only one kind of restoration is evaluated and the assessment of secondary carious lesions is carried out by mean of diagnostic instrumental tools.

The different adhesive systems used could represent a confounder in the meta-analysis procedure; literature, indeed, reports different clinical performances related to different generations of adhesive systems, influenced by clinical steps and chemical formulation.[14,36]

The last-one generation simplified systems are more exposed to failures, particularly due to the mix of etching, priming and bonding phases[14] with subsequent different behaviors, due to different properties and interaction between tissues and materials.[37] This aspect could be responsible for differences highlighted in the present study, indeed results presented by Heck et al[16] showed a lower RR for three outcomes compared to those from other researchers and this could be accountable to the fact that Heck et al[16] used 1-step adhesives in the study group and 2-step adhesive in the control group.

In trials analyzed, different adhesive systems were used by different authors, for example, Van Dijken et al[17,24] and

Balkaya et al[22,23] used all-in-one adhesives and Alkurdi et al,[18] Colak et al,[19] and Yazici et al[20] used etch and rinse systems.

With regard to this, it would be advisable for bolstering its quality that a review of literature takes into consideration trials in which the same adhesive system is used for conservative restorations assessed.

Further analyses of subgroups performed in this meta-analysis showed the possibility that results could be affected by the poor follow-up period of the most studies in addition to the different adhesive systems.

Authors decided to include also the studies mentioning the use of cupping layers in bulk-fill restorations. Conventionally, manufactures of bulk-fill resins advice to use cupping layers in restoring teeth (especially in case of flowable resins); this aspect, in our opinion, seemed to represent a routinely operative step in several bulk-fill restorations and, because of this, a plausible influence of the microleakage outcomes in daily dental practice.

The design of the study is a further matter to consider when a review with meta-analysis is carried out, it is true also for the present work. Literature reports different designs such as in vitro and in vivo study. During the search performed for this review, most of the studies resulted were in vitro studies. This design of studies allows obtaining results close to clinical condition if they follow strict steps.[38-40] In particular, studies aiming to evaluate microleakage of conservative restorations require peculiar phases: collecting and storing of the dental sample, performing restorations following procedures, thermocycling to mimic real clinical behavior of that, dyeing microleakage, and observing defects.[41] Certainly, these are fundamental phases for all protocols; however, they can differ among different studies. A typical example is represented by thermocycling phase that could be performed both by a laboratory instrument (thermocycler) and by mean of water thanks at different temperatures. These differences, together with the possibility to perform a variable number of cycles at different timeframes, show that there is no unique protocol with consequent differences between in vitro studies.

These aspects are contributory factors in increasing risk of bias, for this reason only in vivo studies were included in this meta-analysis with the further advantage to have real clinical conditions.

Our results showed statistically significant differences regarding the three variables evaluated between direct restorations performed using bulk-fill composite resin and those performed with traditional composite resins. Specifically, bulk-fill composites restorations were found to have 5.1% of decreased risk of marginal discoloration and 1.4% of secondary caries, whereas showed 6.5% of increased risk of incorrect marginal adaptation.

Unfortunately, this meta-analysis could not provide strong evidences about the class of composites most responsible for microleakage because of different results obtained from analysis and further trials with extended follow-ups and strict protocols are advisable to obtain evidence-based results and avoid as much as possible risk of bias inter-studies.

However, findings are surely useful for clinicians that could identify bulk-fill composites as reliable and effective materials for direct restorations. Moreover, their properties allow to speed up the chair-side process without undermining clinical success overtime.

We might assume that bulk-fill resins are not a therapeutic balance, but a good solution for directly rehabilitating, further they enable decreasing operative time, as literature greatly reports,[42,43] not affecting clinical results.

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Conflict of Interest
None declared.

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