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Direct composite resin fillings versus amalgam fillings for permanent posterior teeth (Review)

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[Intervention Review]

Direct composite resin fillings versus amalgam fillings for permanent posterior teeth

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ABSTRACT

Background

Traditionally, amalgam has been used for filling cavities in posterior teeth, and it continues to be the restorative material of choice in some low- and middle-income countries due to its effectiveness and relatively low cost. However, there are concerns over the use of amalgam restorations (fillings) with regard to mercury release in the body and the environmental impact of mercury disposal. Dental composite resin materials are an aesthetic alternative to amalgam, and their mechanical properties have developed sufficiently to make them suitable for restoring posterior teeth. Nevertheless, composite resin materials may have potential for toxicity to human health and the environment.

The United Nations Environment Programme has established the Minamata Convention on Mercury, which is an international treaty that aims "to protect the [sic] human health and the environment from anthropogenic emissions and releases of mercury and mercury compounds". It entered into force in August 2017, and as of February 2021 had been ratified by 127 governments. Ratification involves committing to the adoption of at least two of nine proposed measures to phase down the use of mercury, including amalgam in dentistry. In light of this, we have updated a review originally published in 2014, expanding the scope of the review by undertaking an additional search for harms outcomes. Our review synthesises the results of studies that evaluate the long-term effectiveness and safety of amalgam versus composite resin restorations, and evaluates the level of certainty we can have in that evidence.

Objectives

To examine the effects (i.e. efficacy and safety) of direct composite resin fillings versus amalgam fillings.

Search methods

An information specialist searched five bibliographic databases up to 16 February 2021 and used additional search methods to identify published, unpublished and ongoing studies

Selection criteria

To assess efficacy, we included randomised controlled trials (RCTs) comparing dental composite resin with amalgam restorations in permanent posterior teeth that assessed restoration failure or survival at follow-up of at least three years.

To assess safety, we sought non-randomised studies in addition to RCTs that directly compared composite resin and amalgam restorative materials and measured toxicity, sensitivity, allergy, or injury.

Data collection and analysis

We used standard methodological procedures expected by Cochrane.

Main results

We included a total of eight studies in this updated review, all of which were RCTs. Two studies used a parallel-group design, and six used a split-mouth design. We judged all of the included studies to be at high risk of bias due to lack of blinding and issues related to unit of analysis. We identified one new trial since the previous version of this review (2014), as well as eight additional papers that assessed safety, all of which related to the two parallel-group studies that were already included in the review.

For our primary meta-analyses, we combined data from the two parallel-group trials, which involved 1645 composite restorations and 1365 amalgam restorations in 921 children. We found low-certainty evidence that composite resin restorations had almost double the risk of failure compared to amalgam restorations (risk ratio (RR) 1.89, 95% confidence interval (CI) 1.52 to 2.35; P < 0.001), and were at much higher risk of secondary caries (RR 2.14, 95% CI 1.67 to 2.74; P < 0.001). We found low-certainty evidence that composite resin restorations were not more likely to result in restoration fracture (RR 0.87, 95% CI 0.46 to 1.64; P = 0.66).

Six trials used a split-mouth design. We considered these studies separately, as their reliability was compromised due to poor reporting, unit of analysis errors, and variability in methods and findings. Subgroup analysis showed that the findings were consistent with the results of the parallel-group studies.

Three trials investigated possible harms of dental restorations. Higher urinary mercury levels were reported amongst children with amalgam restorations in two trials, but the levels were lower than what is known to be toxic. Some differences between amalgam and composite resin groups were observed on certain measures of renal, neuropsychological, and psychosocial function, physical development, and postoperative sensitivity; however, no consistent or clinically important harms were found. We considered that the vast number of comparisons made false-positive results likely. There was no evidence of differences between the amalgam and composite resin groups in neurological symptoms, immune function, and urinary porphyrin excretion. The evidence is of very low certainty, with most harms outcomes reported in only one trial.

Authors' conclusions

Low-certainty evidence suggests that composite resin restorations may have almost double the failure rate of amalgam restorations. The risk of restoration fracture does not seem to be higher with composite resin restorations, but there is a much higher risk of developing secondary caries. Very low-certainty evidence suggests that there may be no clinically important differences in the safety profile of amalgam compared with composite resin dental restorations.

This review supports the utility of amalgam restorations, and the results may be particularly useful in parts of the world where amalgam is still the material of choice to restore posterior teeth with proximal caries. Of note, however, is that composite resin materials have undergone important improvements in the years since the trials informing the primary analyses for this review were conducted. The global phase-down of dental amalgam via the Minamata Convention on Mercury is an important consideration when deciding between amalgam and composite resin dental materials. The choice of which dental material to use will depend on shared decision-making between dental providers and patients in the clinic setting, and local directives and protocols.

PLAIN LANGUAGE SUMMARY

Tooth-colored resin fillings compared with amalgam fillings for permanent teeth at the back of the mouth

Review question

This review, carried out within Cochrane Oral Health, describes the effects of tooth-coloured (composite resin) fillings compared with amalgam fillings when placed directly into cavities (holes) in permanent teeth in the back of the mouth.

Background

Traditionally, metal fillings made of a silver-coloured material known as amalgam have been used to treat tooth decay in the back permanent teeth effectively and cheaply; however, due to unhappiness with their metallic look and concerns about the mercury they contain, they are being used less often, particularly in high-income countries. The Minamata Convention on Mercury is a global agreement that has promoted a worldwide reduction in the use of mercury (including amalgam fillings) in order to reduce the impact of mercury on the environment. Tooth-colored fillings made of a composite resin material have been used as an alternative to amalgam fillings. Initially, they were used only in the front teeth, but as their quality has improved, they have been used in permanent teeth at the back of the mouth.

Study characteristics

We searched scientific databases until 16 February 2021 and found eight relevant studies. The studies evaluated 3285 composite fillings and 1955 amalgam fillings; however, it is unclear how many participants received these fillings. The exact age of participants was unclear in some studies, but the studies included both children and adults. The studies took place in the UK, the USA, Portugal, Sweden, the Netherlands, Belgium, Germany, and Turkey.

Participants in six studies received composite and amalgam fillings in different teeth (known as 'split-mouth design'), whilst participants in the other two studies received either composite or amalgam fillings ('parallel-group' design).

Key results

Our main analysis focused on the two parallel-group studies that treated 921 children (aged 6 to 12 years) who had their teeth restored with amalgam (1365) or composite resin (1645) fillings. We found that composite resin fillings were significantly more likely to fail than amalgam fillings when used to fill cavities in permanent teeth at the back of the mouth. Tooth decay after a filling was placed (known as 'secondary caries') occurred more frequently with composite resin compared to amalgam fillings. There was no suggestion of a difference between the materials in the likelihood of filling breaking.

Six of the trials used a 'split-mouth' design, which means that each participant had both types of fillings in different teeth. These studies were less reliable, as they did not explain fully how they conducted the studies, and it was unclear how many people received the fillings. We analysed the split-mouth studies separately from the parallel-group studies, and undertook a statistical approach known as 'subgroup analysis'. This showed that the findings of these studies were compatible with the results from the two parallel-group studies.

Three studies reported negative side effects. Although we found that there were some possible side effects with each material used, this information is unreliable because the study authors carried out so many analyses that 'false positive' results were likely to be found. Overall, it seems that the materials may differ in terms of how safe they are, but the level of the differences identified in the studies may not be important.

To summarise, we found that composite resin fillings may be almost twice as likely to fail compared with amalgam fillings when used for filling permanent teeth at the back of the mouth. Composite fillings do not seem more likely to break, but do seem more likely than amalgam fillings to develop further tooth decay. The current evidence suggests there are no important differences in the safety of amalgam compared with composite resin dental fillings.

Certainty of the evidence

We judge the available evidence to be 'low certainty', which means that the results may change with future research. As the colour of the amalgam and composite resin fillings differed, it would not have been possible to 'blind' those involved in the study from knowing the treatment administered, so there was a high risk of bias in all of the included studies. In addition, the findings were imprecise and sometimes inconsistent, so we cannot be sure that the evidence is reliable.

Implications of the evidence

Overall, the evidence suggests that amalgam restorations are effective, enduring, and safe, while composite resin restorations are more likely to fail and lead to secondary caries. However, the studies in this review were quite old, and composite resin materials have likely improved since the included studies were conducted. Patients and dental providers can discuss together which material they want to use when permanent teeth in the back of the mouth require fillings in the dental clinic. Governments around the world are trying to reduce the use of dental amalgam (according to the Minamata Convention on Mercury), and so each local area will have their own regulations and guidance.

Summary of findings 1. Direct resin composite versus amalgam fillings for permanent or adult posterior teeth

Direct resin composite versus almalgam fillings for permanent or adult posterior teeth

Population: people with permanent or adult posterior teeth
Setting: outpatients
Intervention: composite
Control: amalgam

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of teeth (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Amalgam	Composite				
Failure rate Follow-up: 5 to 7 years	**75 per 1000**	**142 per 1000** (114 to 176)	**RR 1.89** (1.52 to 2.35)	3010 (2 studies)	⊕⊕⊖⊖ **low** [1,2]	Reasons for failure included secondary caries, fracture, restoration loss.
Secondary caries Follow-up: 5 to 7 years	**57 per 1000**	**122 per 1000** (95 to 156)	**RR 2.14** (1.67 to 2.74)	3010 (2 studies)	⊕⊕⊖⊖ **low** [1,3]	
Fracture of restorations Follow-up: 5 to 7 years	**14 per 1000**	**12 per 1000** (6 to 23)	**RR 0.87** (0.46 to 1.64)	3010 (2 studies)	⊕⊕⊖⊖ **low** [1,4]	
Harms Follow-up: 2 weeks to 7 years	See comments			3 studies	⊕⊖⊖⊖ **very low** [1,4,5]	Data were reported for physical development, neurological and psychological effects, neurobehavioural and psychosocial function, kidney function, immune function, urinary mercury, urinary porphyrin excretion, and postoperative sensitivity. Most outcomes were reported in only 1 study. Overall, there was a mixed picture that was not easy to interpret, but did not seem to suggest that either composite resin or amalgam restorations are more likely to lead to clinically important harms.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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).
CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: 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 certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[1]Downgraded one level for performance, detection, and selection bias (unclear allocation concealment).
[2]Downgraded one level for heterogeneity: $I^2 = 87\%$.
[3]Downgraded one level for heterogeneity: $I^2 = 92\%$.
[4]Downgraded one level for imprecision.
[5]Downgraded one level for heterogeneity.

BACKGROUND

Description of the condition

Dental caries (tooth decay) is a dynamic and continuous process composed of cycles of demineralisation of the hard tissue of the teeth followed by cycles of remineralisation. The balance between the two cycles determines the stage of the disease (ICDAS 2011). There is a close relationship between oral health and quality of life; socioeconomic status and home environment have been shown to impact on oral condition (Gomes 2009; Paula 2012). Despite the great accomplishments in oral health obtained globally, caries is still a serious problem, particularly amongst underprivileged groups in low-, middle-, and high-income countries, affecting 60% to 90% of schoolchildren and the vast majority of adults (Costa 2012). It is also the most prevalent oral health problem in several Asian and Latin American countries (WHO 2012).

Modern management of dental caries involves making a diagnosis to determine the person's caries risk status, followed by the application of intervention strategies focused on preventing, arresting, and possibly reversing the caries process to delay restorative treatment until it becomes absolutely necessary (Ferreira Zandona 2012). When the damage on the tooth structure is permanent, the most commonly used treatment involves cleaning the cavity and filling it with a restorative material to restore the shape and function of the tooth.

Primary caries seems to be the most frequent reason for the placement of restorations (fillings), and caries lesions are most commonly found on occlusal surfaces of posterior teeth (Nascimento 2010). Secondary caries is responsible for 60% of all replacement restorations in the typical dental practice, but the association between the type of restoration materials and location of caries and the composition of the microflora has not been found to be statistically significant (Mo 2010).

Description of the intervention

The obturation and filling of occlusal cavities is an issue that has been long studied. The choice of the best material for restoring the anatomical structures that also achieves acceptable resistance to the forces of mastication is still controversial. This review compared dental amalgams and resin composites, the two main categories of dental restorative fillings used in posterior tooth restorations today.

Dental amalgams are metallic alloys. They have been predictable and inexpensive restorative materials for over 150 years. Their use and success rate have been well documented, and they are the most cost-effective materials in posterior teeth restorations. However, they are declining in use in dentistry mainly due to their unaesthetic appearance and concerns about their mercury content (Kelly 2004; Mitchell 2007; Roulet 1997).

Because mercury is a substance that can be toxic to both human health and the environment, the United Nations Environment Programme has established the Minamata Convention on Mercury, which aims "to protect the human health and the environment from anthropogenic emissions and releases of mercury and mercury compounds" (UNEP 2013). The Minamata Convention recommends a phase-down of the use of mercury, including the use of amalgam in dentistry; specifically, parties who have ratified the Convention commit to the adoption of at least two of nine proposed phase-down measures (UNEP 2013). The Convention entered into force internationally on 16 August 2017 (UNEP 2017a), and as of February 2021 had been ratified by 127 governments worldwide (UNEP 2017b).

Dental resin composites were developed in response to demands for tooth-coloured restorations. Dental resin composites are particle-reinforced resins. The field of composite dental restoratives continues to advance, for example, in resin formulation, filler loading and modification, and curing methodologies and mechanisms (Cramer 2011). The indications of resin composites have expanded from anterior teeth to restricted posterior restorations and even to stress-bearing posterior restorations as amalgam substitutes or alternatives (Lutz 1999; Moraschini 2015). Other advantages of dental resin composite restorations include their conservative design and reparability.

How the intervention might work

Dental amalgam and composite resin restorations are still the most commonly used materials for restoring permanent molar and premolar cavities. The choice of amalgam as the preferred material to restore posterior teeth has been gradually replaced by resin composite, which is likely due to a host of factors that include patient and clinician preference (Espelid 2006), cost, environmental and ethical issues, and context (CADTH 2018).

Nevertheless, concerns about the potential toxicity of both dental amalgam and composite resin materials have been raised. For instance, the use of dental amalgam has been restricted or banned in several countries due to its mercury content (Handzel 2017; UNEP 2013; UNEP 2016). Concerns have been raised about the potential toxicity of materials used in some composite resin restorations that may contain derivatives of bisphenol A (BPA), such as "…bisphenol A diglycidyl methacrylate (bis-GMA) especially, but also bisphenol A dimethacrylate (bis-DMA), polycarbonate-modified bis-GMA (PC bis-GMA), ethoxylated bisphenol A glycol dimethacrylate (bis-EMA) and 2,2-bis [(4-methacryloxy polyethoxy) phenyl]propane (bis-MPEPP)]" (Dursun 2016).

When addressing safety concerns of dental amalgam and composite resin restorative materials, it is first important to make the distinction between the restorations themselves and the compounds of which they are composed. Despite concerns about potential health risks from mercury in dental amalgam fillings and BPA (or other toxins) in composite resin restorations, evidence has not been generated to definitively implicate dental amalgam or composite resin restorations as harmful to human health.

A 2018 Canadian cost-consequence analysis comparing amalgam and composite resin restorations of permanent posterior teeth found that, on average, amalgam restorations last longer and cost less (amalgam CAD 171.00 versus composite CAD 219.00; CADTH 2018). Because time to failure, on average, was longer for amalgam restorations, the estimated lifetime cost for amalgam restorations was half that of composite resin restorations (assuming that a failed restoration would be replaced by another of the same size and material). Moreover, crown installation or tooth extraction may occur later in life with amalgam than with composite resin restorations. Whilst composite resin restorations take slightly more time to place, the impact of this on patient or caregiver productivity was found to be minimal. For dental clinics that install amalgam separators to ensure that mercury from the dental amalgam

materials used is not introduced into the environment, additional costs will be incurred.

Why it is important to do this review

This topic was identified as a priority through a comprehensive Cochrane Oral Health prioritisation exercise. It was intended to inform policy and decision-making in light of changes in the use of dental amalgam as a result of the Minamata Convention, as well as to update and expand the assessment of the safety of dental amalgam relative to composite resin. Since adhesive dentistry remains one of the fastest-changing fields (Tanimoto 2015), there is a need to provide a comprehensive update on the effects of dental composite resin materials in comparison with amalgam.

OBJECTIVES

To examine the effects (i.e. efficacy and safety) of direct composite resin fillings versus amalgam fillings.

METHODS

Criteria for considering studies for this review

Types of studies

For the outcome of efficacy, we included randomised controlled trials (RCTs) comparing dental composite resin with dental amalgam restorations in permanent posterior teeth (dating back to 1946). We excluded studies that had less than a three-year follow-up period.

For the outcome of safety, we included RCTs and non-randomised studies that directly compared composite resin and amalgam restorations in people requiring dental caries treatment (dating back to 2007).

Types of participants

For efficacy, participants were people with permanent posterior teeth with dental caries requiring direct restorations that were suitable for treatment with either composite resin or amalgam, or both.

For safety, participants were people with dental caries treated with direct dental restorations made of composite resin or amalgam.

Types of interventions

- Intervention: direct dental restorations made from composite resin
- Control: direct dental restorations made from amalgam

Types of outcome measures

We chose outcomes that would allow us to asssess clinical efficacy and safety.

Primary outcomes

- Restoration failure (or survival)
- Harms, including toxicity, sensitivity, allergic reaction, injury

Secondary outcomes

- Reason for failure (according to the evaluation categories of the US Public Health Service (USPHS), which includes colour match, marginal adaptation, anatomical form, and secondary caries (Cvar 2005)), and tooth fracture

Search methods for identification of studies

Electronic searches

Cochrane Oral Health's Information Specialist conducted systematic searches in the following databases for RCTs and controlled clinical trials. There were no language, publication year, or publication status restrictions.

- Cochrane Oral Health Trials Register (searched 16 February 2021) (Appendix 1)
- Cochrane Central Register of Controlled Trials (CENTRAL; 2021, Issue 1) in the Cochrane Library (searched 16 February 2021) (Appendix 2)
- MEDLINE Ovid (1946 to 16 February 2021) (Appendix 3)
- Embase Ovid (1980 to 16 February 2021) (Appendix 4)
- LILACS BIREME Virtual Health Library (Latin American and Caribbean Health Science Information database; from 1982 to 16 February 2021) (Appendix 5)

Review author MM undertook a supplementary search on safety, using strategies she designed for a Canadian Agency for Drugs and Technologies in Health (CADTH) health technology assessment. We searched MEDLINE (1946 to 20 February 2019), Embase (1974 to 20 February 2019), and CENTRAL (January 2019 edition) with one broad search in Ovid (see Appendix 6). We also searched PubMed (1950 to 21 February 2019, see Appendix 6). There was no language restriction, but we restricted studies of the safety of composite resin fillings to 2006 onwards, in accordance with feedback from clinical experts that composite resin materials have developed considerably over recent years, and studies using earlier materials would not be comparable.

Searching other resources

Cochrane Oral Health's Information Specialist searched the following trial registries for ongoing studies:

- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (clinicaltrials.gov; searched 16 February 2021) (Appendix 7);
- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (apps.who.int/trialsearch; searched 16 February 2021) (Appendix 8).

We checked the reference lists of all eligible trials and relevant review articles for additional studies. We contacted the authors of unpublished studies; however, we did not received any replies.

We checked that none of the studies included in this review were retracted due to error or fraud.

For the first version of this review, we contacted the major manufacturers of dental materials (GC and 3M ESPE) in June 2012 to obtain information on published and unpublished studies that may have involved their products. We were informed that no studies comparing resin composite materials and amalgam materials had been carried out. We also contacted Ivoclar Vivident, Kerr, and Dentsply at the same time, but received no reply.

Data collection and analysis

Selection of studies

Two review authors (SK, KS) independently screened the titles and abstracts of all citations using standardised criteria. We retrieved the full text for any titles and abstracts that either review author deemed potentially relevant. The same review authors then independently applied the study selection criteria to each full-text report and compared their selections, resolving all discrepancies through discussion and consensus or by involving a third review author (SM) as necessary. Ongoing discussion amongst review authors occurred during both phases of screening to consider discrepancies and establish consensus on the application of selection criteria. We tabulated excluded studies with our reasons for exclusion (see Characteristics of excluded studies table).

Data extraction and management

The review authors piloted tailored data extraction forms and modified them before use. One review author extracted data from each included study, and a second review author verified the extracted data, with any disagreements resolved through discussion.

We collected the following data from the included reports.

- First author's name, publication year, country, and funding sources
- Study design, analytical approach, and any subgroup analyses of interest
  - for the outcome of efficacy:
    - ☐ number and types of restorations;
    - ☐ a description of the intervention, comparator, and (where reported) the application technique(s) used to place the restoration;
    - ☐ restoration failure rate and reasons for failure (i.e. secondary caries, tooth fracture).
  - for the outcome of safety:
    - ☐ number, age, sex, remote/rural/urban settings, socioeconomic status, and restoration;
    - ☐ types of study participants (where reported);
    - ☐ a description of the intervention, comparator, and (where reported) the numbers of surface areas and/or surface years;
    - ☐ description of outcomes reported, follow-up duration, and study loss to follow-up findings and conclusions regarding the outcomes and subgroups of interest.

Assessment of risk of bias in included studies

Two review authors independently and in duplicate undertook risk of bias assessment for each included study using the Cochrane risk of bias assessment tool (Higgins 2017). We assessed seven domains for each included study: sequence generation (selection bias), allocation sequence concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other potential sources of bias. We assessed risk of bias as 'low', 'high', or 'unclear', with the last category indicating either lack of information or uncertainty over the potential for bias.

After taking into account additional information provided by the authors of some of the included trials, we grouped the studies into the following categories:

- overall low risk of bias (plausible bias unlikely to seriously alter the results);
- overall high risk of bias (plausible bias that weakens confidence in the results), if one or more domains were assessed as at high risk of bias;
- overall unclear risk of bias, if one or more domains were assessed as unclear.

Measures of treatment effect

We considered whether to pool quantitative outcome data separately for the outcomes of efficacy and safety. We considered several factors, including the number of included studies and the amount of between-study clinical and methodological heterogeneity.

We undertook statistical syntheses using Review Manager 5 software (Review Manager 2020), with forest plots presented for summary estimates. We used random-effects meta-analyses unless there were fewer than four studies included in a meta-analysis.

We pooled dichotomous outcomes using risk ratios (RRs) and 95% confidence intervals (CIs). We calculated mean difference (MD) or standardised mean difference (SMD) for continuous data. In the case of studies with a split-mouth design, we aimed to calculate log risk ratio separately for each outcome.

For the safety outcome, we presented the findings narratively by study. We planned to calculate RRs or odds ratios (ORs), converting to a common effect measure to facilitate meta-analysis, if appropriate. For time-to-event data such as restoration failure, we planned to calculate pooled hazard ratios (HRs) and 95% CIs. We planned to meta-analyse continuous data using MD or SMD with corresponding 95% CIs. We intended to pool data on the same outcomes from RCTs and non-randomised studies separately.

Unit of analysis issues

The 2014 review identified a unit of analysis problem in several of the included studies in terms of participants versus restorations. This update aimed to address this issue by undertaking appropriate analyses for each outcome taking into account the units of analysis where possible, following the recommendations in Section 16.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Dealing with missing data

In the case of missing individual data, we analysed only the available data. Where possible, we performed an intention-to-treat (ITT) analysis. In the previous version of this review, we contacted study authors when we required additional information. We addressed the potential impacts of missing data on the findings of the review in the Discussion section.

Assessment of heterogeneity

We aimed to assess statistical heterogeneity using the I^2 statistic (Higgins 2003), which quantifies the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (i.e. chance). We planned to observe heterogeneity

by analysing the point estimates and CIs on the forest plots. We also planned to assess statistical heterogeneity using Cochran's test for heterogeneity and quantified using the I^2 statistic. Based on the *Cochrane Handbook for Systematic Reviews of Interventions*, we considered values of I^2 as follows:

- 0% to 40% might not be important;
- 30% to 60% may represent moderate heterogeneity;
- 50% to 90% may represent substantial heterogeneity; and
- 75% to 100% represents considerable heterogeneity (Deeks 2017).

We considered heterogeneity to be statistically significant if the P value was less than 0.1.

Assessment of reporting biases

Only a proportion of research projects conducted are ultimately published in an indexed journal and become easily identifiable for inclusion in systematic reviews (Easterbrook 1991). Reporting biases arise when the reporting of research findings is influenced by the nature and direction of the findings of the research. We attempted to avoid time lag bias, multiple (duplicate) publication bias, and language bias by conducting a detailed, sensitive search, including searching for ongoing studies. We did not restrict the search by language (other than the search for the safety outcomes), and review authors translated non-English studies.

Data synthesis

We combined RRs for dichotomous data of studies we considered appropriate for inclusion in meta-analysis. We intended to combine the treatment effects from split-mouth trials with those from parallel-group trials where appropriate as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*, Deeks 2017, and in Elbourne 2002; however, this was not possible because of poor reporting. We therefore treated the split-mouth trials as a subgroup so that we could examine the results either in isolation or in combination with the parallel-group studies. This was aimed in particular at providing a broader view and 'bottom-line' to the review question. We used random-effects models where there were more than three studies in any given meta-analysis, and fixed-effect models when combining data from two or three studies. Where meta-analysis was inappropriate, we presented data in Additional tables.

Subgroup analysis and investigation of heterogeneity

Depending on the amount of available data and the degree of observed statistical heterogeneity, we had intended to explore the following potential sources of heterogeneity using subgroup analyses:

- participant age;
- genetic susceptibility to mercury;
- socioeconomic status;
- remote, rural or urban setting;
- developmental/special need;
- numbers of restorations/surface areas/surface years;
- application technique used to place the restoration.

Sensitivity analysis

We had planned to conduct sensitivity analyses (particularly for the question addressing safety) to evaluate the robustness of findings by methodological and statistical factors, including (but not limited to): the impact of varying study risk of bias assessments, alternative study designs (e.g. cohort versus case control), types of analysis (e.g. unadjusted versus adjusted), and effect measures (e.g. RR versus OR).

Summary of findings and assessment of the certainty of the evidence

We have presented a summary of findings table to show the findings of the most important outcomes (Summary of findings 1). We assessed the certainty of the body of evidence by following the GRADE framework with reference to the overall risk of bias of the included studies, directness of the evidence, consistency of the results, precision of the estimates, and risk of publication bias. We categorised the quality of the body of evidence for each of the outcomes as high, moderate, low, or very low.

RESULTS

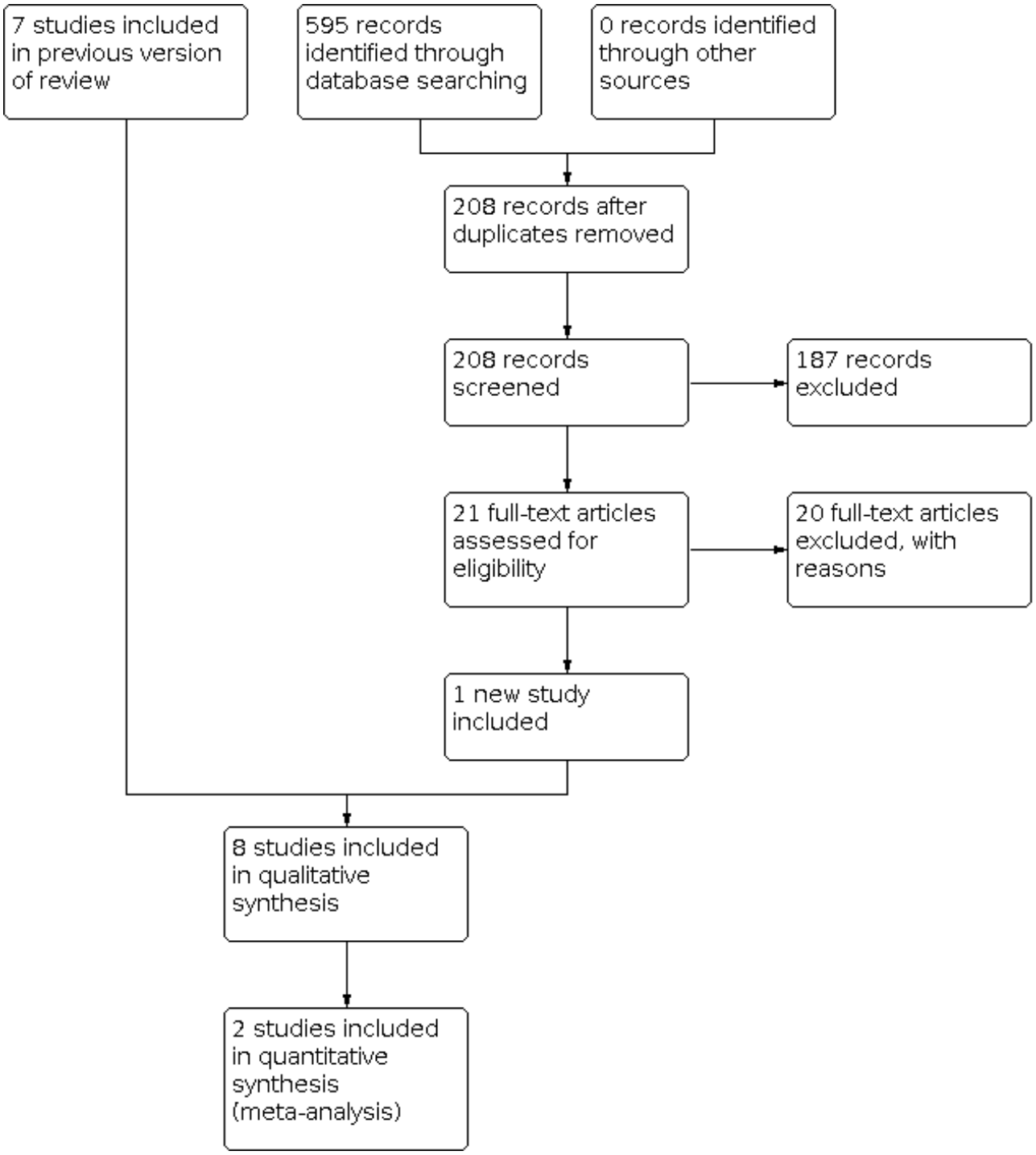
Description of studies

Results of the search

The previous version of this review included seven eligible RCTs reported across 14 articles. Our update identified one additional RCT that addressed both efficacy and safety (Kemaloglu 2016), and our supplementary search identified eight articles addressing safety that related to the two parallel-group RCTs used in our primary analyses (Casa Pia 2007; NECAT 2007).

The updated electronic literature search identified 595 citations, which was reduced to 208 after the removal of duplicates. Twenty-one were potentially relevant and retrieved for full-text scrutiny. Most citations returned by the bibliographic searches were in English, with a small proportion in German, Spanish, and Portuguese (the review author team translated these). We retrieved one report from the grey literature. Of these 21 potentially eligible reports, we found one to be eligible and included it in the review (Kemaloglu 2016). There was complete agreement at the full-text phase of screening (weighted overall Kappa statistic of 1.0). We have presented a PRISMA flow diagram illustrating the results of this search, screening, and selection process in Figure 1 (Moher 2009).

Figure 1. Updated flow diagram 2021



The supplementary search designed to investigate safety identified 6535 citations, 90 of which we considered to be potentially relevant and retrieved for full-text assessment (Appendix 6). We retrieved one report from the grey literature. Of these potentially eligible reports, we found nine to be eligible for inclusion, eight of which related to two RCTs that were already included (Casa Pia 2007; NECAT 2007). The weighted overall Kappa statistic indicated initial agreement at the full-text phase of screening as generating a value of 0.49 (95% CI 0.39 to 0.79), indicating moderate agreement.

Included studies

We included eight RCTs, which were reported in 23 articles. For details on each included study, see Characteristics of included studies.

Design

Two RCTs used a parallel-group design (Casa Pia 2007; NECAT 2007), whilst the other six RCTs used a split-mouth design

(Cunningham 1990; Hendriks 1986; Kemaloglu 2016; Letzel 1989; Norman 1990; Robinson 1988). The split-mouth studies were not conducted, reported, or analysed using methodologically or clinically consistent approaches and did not always clearly report study initiation and end dates.

The two parallel-group RCTs reported data from large studies that were designed to compare amalgam with composite to restore posterior teeth. The Casa Pia Study of Health Effects of Dental Amalgam in Children started in 1996 and followed participants for seven years (Casa Pia 2007). The New England Children's Amalgam Trial (NECAT) was conducted between September 1997 and March 2005 (NECAT 2007).

Casa Pia 2007 and NECAT 2007 were funded by research grants. Three studies were funded by the same dental industry source, ICI (Letzel 1989; Norman 1990; Robinson 1988), whilst the remaining three studies did not state their funding sources (Cunningham 1990; Hendriks 1986; Kemaloglu 2016).

Participants

The two parallel-group trials randomised a total of 1041 participants (Casa Pia 2007 randomised 507; NECAT 2007 randomised 534), and analysed 921 participants. We analysed data from 871 participants in this review. The participants in these two trials were aged six to 12 years at baseline. Follow-up periods were seven and five years, respectively.

The split-mouth trials reported data on 2230 restorations (ranging from 27 to 932 per trial), but did not specify the number of participants recruited or their ages.

Two studies were conducted in the UK (Cunningham 1990; Robinson 1988), one in Portugal (Casa Pia 2007), one in Turkey (Kemaloglu 2016), one in the USA (NECAT 2007), and one multicentre trial was conducted in the USA and Europe (Belgium, Germany, the Netherlands, Sweden, and the UK; Letzel 1989). Two studies did not clearly report their locations (Hendriks 1986; Norman 1990).

Interventions

Participants in the eight included studies received amalgam restoration or composite resin restoration, or both. In NECAT 2007, participants received amalgam, compomer, or composite restoration; data on compomer restorations are not included in this review.

Outcomes

The primary outcome was restoration failure, which all eight included trials reported. Seven trials reported secondary caries (Casa Pia 2007; Cunningham 1990; Hendriks 1986; Kemaloglu 2016; NECAT 2007; Norman 1990; Robinson 1988), whilst two studies reported fracture outcome data (Casa Pia 2007; NECAT 2007).

Three RCTs reported data on harms (Casa Pia 2007; Kemaloglu 2016; NECAT 2007). No studies reported on outcomes of relevance to allergic reaction or injury. Casa Pia 2007 and NECAT 2007 described multiple outcomes relevant to toxicity, whilst Kemaloglu 2016 reported an outcome relevant to sensitivity. See Table 1.

Casa Pia 2007 presented trial results on the effects of mercury on the nervous system and potential damage to the renal system in children. They carried out tests at baseline and at seven years after a filling placement to explore intelligence, nerve conduction velocity, memory, attention, and visuomotor function. To study renal function, they recorded creatinine-adjusted urinary albumin levels at years one, two, three, four, five, six, and seven.

NECAT 2007 focused on the effect of restorations on psychosocial function and physical development in children after five years of follow-up. Study authors measured the effect of restorations on psychosocial function using two validated instruments: Child Behavior Checklist (CBCL) parent report and Behavior Assessment for Children Self Report (BASC-SR). Degree of exposure to restorations was expressed in surface years (SY); however, no direct comparison was made between children in the composite and amalgam arms. The BASC-SR measured emotional symptoms, clinical maladjustment, school maladjustment, personal adjustment, and core syndromes such as anxiety, depression, attitude to school, and interpersonal relations. The CBCL measured competence, total problem behaviours, internalising problems, externalising problems, and core syndromes such as attention problems, withdrawal, anxiety/depression, delinquent behaviours, and aggression. The growth outcomes NECAT 2007 considered were body fat percentage, body mass index (BMI), and height.

Kemaloglu 2016 assessed postoperative sensitivity after restoration placement at two weeks (baseline), six months, one year, and three years using a visual analogue scale completed by participants. The study publication did not report raw data.

We listed all references to studies under the relevant study ID; however, we did not include data from five of the articles assessing harms outcomes, as we judged them to be secondary analyses that did not compare the originally randomised treatment groups (Geier 2011; Geier 2012; Geier 2013; Maserejian 2012; Woods 2013).

Excluded studies

We rejected most records from the updated efficacy search based on title or abstract. We retrieved the full texts of 22 articles and rejected 21 on the basis of ineligible study design (i.e. not randomised or controlled); population (e.g. not dental caries); intervention (e.g. not direct dental restorations); outcome (i.e. not efficacy); or publication (e.g. time frame, type, or availability).

We rejected most records from the safety search based on title or abstract. We retrieved 67 full-text articles for more detailed evaluation and rejected 59 because they evaluated an ineligible population (i.e. secondary analyses not considering originally randomised treatment groups); intervention (i.e. not direct dental restorations); comparison (i.e. no direct comparison of amalgam and composite resin); outcome (i.e. not safety); publication (i.e. not a report of study findings); or time frame (i.e. published prior to 2007).

In the 2014 version of this review, we excluded 43 articles for the following reasons (see Characteristics of excluded studies tables).

- The study design was not randomised or controlled (Allan 1977; Bryant 1994; Busato 1996; Cloyd 1997; Collins 1998; Eames 1974; Fukushima 1988; Hendriks 1985; Johnson 1992; Knibbs 1992; Kopperud 2012; Mjör 1993a; Mjör 1993b; Pieper 1991; Powers

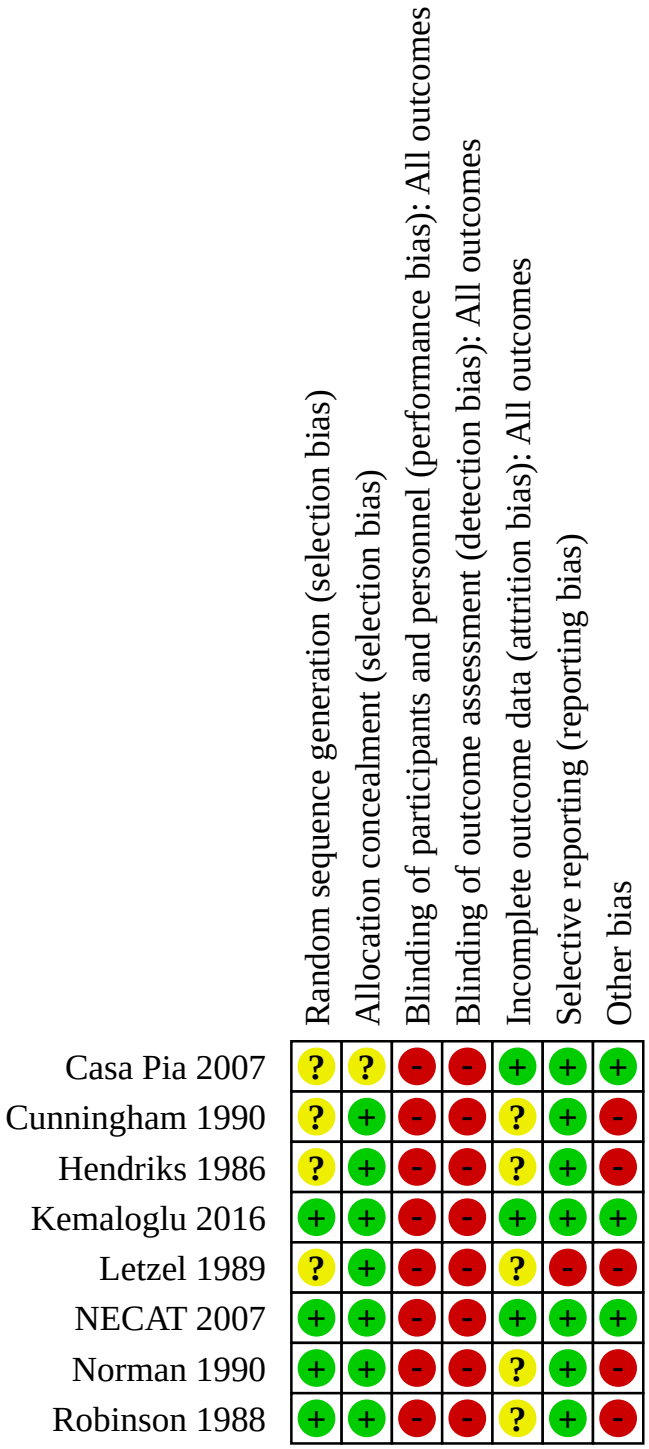
1974; Prati 1988; Rowe 1989; Rytömaa 1984; Samaha 1982; Smales 1992; Tobi 1999; Van Nieuwenhuysen 2003).

- Randomisation was broken (Welbury 1990).
- Follow-up was less than three years (Borgmeijer 1991; Kreulen 1993a; Lambrechts 1984; Leinfelder 1975; Roulet 1977; Walls 1988).
- There was a lack of clarity regarding methodology (comparison between amalgam and composite unclear; not stated if the materials were tested in permanent posterior teeth; lack of clarity on evaluation of longevity and impossibility of obtaining useful data) (Bellinger 2006; Dilley 1990; Kreulen 1993b; Leinfelder 1980; Mair 1998; Mannocci 2005; Nell 1994; Roulet 1978; Shenker 2008; Smales 1992; Wilson 1996).
- We contacted one study author to obtain data for an unpublished trial (Koray), but received no reply.
- We were unable to obtain the full-text article of Solano 1984 for critical appraisal.

Risk of bias in included studies

We judged all of the included studies to be at high risk of bias overall, primarily due to lack of blinding (Figure 2). The main risk of bias for the split-mouth studies was related to failure to take the clustering effect into account in the analysis.

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



Allocation

Random sequence generation

We considered four studies to be at low risk of selection bias (Kemaloglu 2016; NECAT 2007; Norman 1990; Robinson 1988), whilst the other four studies were at unclear risk of bias as there was a lack of detail on the randomisation process (Casa Pia 2007; Cunningham 1990; Hendriks 1986; Letzel 1989).

Allocation concealment

We judged the six split-mouth studies to be at low risk of bias because a lack of allocation concealment would neither make a difference nor introduce bias to a split-mouth study (Cunningham 1990; Hendriks 1986; Kemaloglu 2016; Letzel 1989; Norman 1990; Robinson 1988). We judged NECAT 2007 to be at low risk of bias, as they described an acceptable allocation concealment process. We judged Casa Pia 2007 to be at unclear risk of selection bias because we could not find any explicit description of the allocation concealment process in any of the included articles (including those that the study authors referenced for more details describing methods).

Blinding

We judged all of the included studies to be at high risk of performance bias and detection bias, since the dental restorations look different, and therefore blinding of operators and participants was not possible. Even though some studies indicated that outcome assessment was carried out by evaluators independent of the operators (NECAT 2007; Norman 1990; Robinson 1988), we did not consider this sufficient to minimise detection bias.

Incomplete outcome data

We judged three studies to be at low risk of attrition bias: dropout rates were similar in the intervention and comparator groups in Casa Pia 2007 and NECAT 2007, and the split-mouth study Kemaloglu 2016 evaluated all participants who were assessed at baseline. The other five split-mouth studies reported an overall dropout rate (Cunningham 1990; Hendriks 1986; Letzel 1989; Norman 1990; Robinson 1988); as we were unable to determine whether the dropout rate was differential, we judged the risk of bias to be unclear.

Selective reporting

We judged Letzel 1989 to be at high risk of reporting bias, as it reported all data for composite resin but not for amalgam. All of the other studies presented data for their planned outcomes and were therefore judged to be at low risk of reporting bias.

Other potential sources of bias

We judged three studies as at low risk of bias for this domain as they had no other apparent biases (Casa Pia 2007; Kemaloglu 2016; NECAT 2007).

We assessed five split-mouth studies as being at high risk of other bias due to a unit of analysis error (Cunningham 1990; Hendriks 1986; Letzel 1989; Norman 1990; Robinson 1988). In addition, Letzel 1989 reported that there were notable variations in results across the different centres involved in the trial, but provided no explanation for this.

Effects of interventions

See: **Summary of findings 1** Direct resin composite versus amalgam fillings for permanent or adult posterior teeth

Due to the poor reporting in five split-mouth trials which rendered the reported data unreliable, we decided that the primary analyses should be based on the two parallel-group trials. We undertook a secondary analysis of all included trials.

Failure rate

The parallel-group trials recorded failure rate in the amalgam and composite groups over a period of five years in NECAT 2007 and seven years in Casa Pia 2007. The trials analysed a total of 1365 amalgam restorations and 1645 composite restorations. Our pooled estimate showed that composite restorations had a significantly higher risk of failure than amalgam (risk ratio (RR) 1.89, 95% confidence interval (CI) 1.52 to 2.35; P < 0.001; fixed-effect model; Analysis 1.1). There was indication of heterogeneity (P = 0.005; I^2 = 87%), but, as there were only two studies, this could not be investigated. As the effect estimates for both studies were in the same direction, we decided to present the meta-analysis.

Subgroup analysis of the split-mouth trials found an imprecise result that was inconclusive (RR 1.33, 95% CI 0.84 to 2.11; P = 0.23; random-effects model; analysis not shown). There was no evidence of heterogeneity (P = 0.57; I^2 = 0%). A test for subgroup differences showed no evidence of a significant difference between the parallel-group and split-mouth trials (P = 0.26). The parallel-group and split-mouth trials combined showed more precise results than either alone, and suggested that composite restorations may have a significantly higher risk of failure than amalgam restorations (RR 1.65, 95% CI 1.13 to 2.40, P = 0.009; random-effects model; analysis not shown). There was some evidence of heterogeneity (P = 0.05; I^2 = 52%).

Because the additional split-mouth trial identified in this 2021 update reported zero events of failure in both arms of the study (and described data for only 40 restorations), its incorporation into the subgroup and combined analyses would have had no impact on the original findings (Kemaloglu 2016).

Analysis of subgroups

One study reported failure rates separately in molars and premolars (Casa Pia 2007), but the results were not sufficient to determine whether there was an association between location of the restorations in different teeth and failure rate.

Data were insufficient to consider any of our other planned subgroup or sensitivity analyses.

Reason for restoration failure

Secondary caries

Secondary caries was the most common reason for failure in the included studies. Meta-analysis of the parallel-group studies showed a higher risk of secondary caries in permanent posterior teeth with composite restoration compared with teeth with amalgam restoration (RR 2.14, 95% CI 1.67 to 2.74; P < 0.001; fixed-effect model; Analysis 1.2). There was once again evidence of heterogeneity (P < 0.001; I^2 = 92%), but, as there were only two studies, this could not be investigated. As the effect estimates for

both studies were in the same direction, we decided to present the meta-analysis.

Outcome data from the split-mouth studies alone provided an imprecise result that did not provide evidence of a significant difference in secondary caries when composite restorations were compared with amalgam restorations (RR 1.30, 95% CI 0.34 to 4.97, P = 0.7; random-effects model; analysis not shown). There was no evidence of heterogeneity (P = 0.64; I^2 = 0%). However, a test for subgroup differences showed no evidence of a significant difference between the parallel-group and split-mouth trials (P = 0.58), and combined results of all trials indicated there may be an increased risk of secondary caries with composite restorations compared to amalgam restorations (RR 1.93, 95% CI 0.98 to 3.80; P = 0.06; random-effects model; analysis not shown). There was some evidence of heterogeneity (P = 0.02; I^2 = 64%).

The additional RCT identified in this update reported zero events of secondary caries in both study arms (and described data for only 40 restorations), so its incorporation into the subgroup and combined analyses would have had no impact on the original findings (Kemaloglu 2016).

Fracture of the restoration

Only the two parallel-group trials reported fracture of the restorations (Casa Pia 2007; NECAT 2007). It was not a common reason for failure. There was no evidence of a difference in risk of fracture between the two materials (RR 0.87, 95% CI 0.46 to 1.64, P = 0.66; fixed-effect model; Analysis 1.3). There was no evidence of heterogeneity (P = 0.44; I^2 = 0%).

Harms

Five studies did not assess this outcome. Three studies explored potential harms from toxicity (Casa Pia 2007; NECAT 2007) or sensitivity (Kemaloglu 2016) (see Table 1). We did not find any eligible studies that evaluated allergic reaction or injury. The large number of comparisons carried out by the studies, particularly NECAT 2007, means that false-positive results were likely.

Toxicity

Neuropsychological function

NECAT 2007 reported that there was no difference between composite and amalgam restorations for overall neuropsychological function (see Table 2). Significant differences for some of the subscales were found in both directions, giving inconsistent results. This trial made a large number of comparisons (more than 60). With a 5% level of significance being used for each, we would expect some statistically significant differences to be found by chance, when no true differences exist.

Casa Pia 2007 found no statistically significant differences in measures of memory, attention, visuomotor function, or nerve conduction velocities.

Neurological symptoms

In Casa Pia 2007, neurologists evaluated participants' neurological symptoms (hard signs, soft signs, and positional tremor) annually. They found no statistically significant differences between resin composite and amalgam groups at any time point.

Psychosocial function

NECAT 2007 evaluated psychosocial function in a subset of children using the CBCL (n = 395) and the BASC-SR (n = 426) analyses.

The CBCL has four main composite scores, measured as changes between baseline and five years; there was no difference between groups in the competence or externalising behaviour scores, but the resin composite group had higher scores for total problem behaviour and for internalising behaviour (Table 3). This means adjustment and behaviour were poorer in children with composite fillings after five years' follow-up.

The BASC-SR assessed four global scores and showed no difference between groups for school or clinical maladjustment. The study found a difference between groups in favour of the amalgam group for the other two scores, personal adjustment and emotional symptoms (Table 3).

NECAT 2007 concluded that greater exposure to composite restorations was associated with impaired psychosocial function in children, whereas no adverse psychosocial outcomes were observed with greater amalgam treatment levels.

Physical development

NECAT 2007 assessed physical development in 474 of the 534 children originally randomised. They reported no between-group differences in age-adjusted, mean BMI-for-age Z scores, body fat percentage, or height throughout the five-year study follow-up (Table 4). Additional, exploratory analyses of menarche outcomes in females investigated 113 participants and were restricted to one study site. These analyses indicated that girls in the composite resin group were less likely to have reached menarche during study follow-up compared with those in the amalgam group (48% versus 67%; hazard ratio 0.57, 95% CI 0.35 to 0.95; P = 0.03). Nevertheless, an examination of age at first menarche indicated no statistically significant difference between treatment groups amongst those who had reached first menarche (composite group mean age in years = 12.5 (standard deviation (SD) ± 1.1); amalgam group mean age in years = 12.3 (SD ± 1.0)); mean difference 0.20 (95% CI −0.19 to 0.59).

Immune function

A subset of children were invited to take part in a substudy of NECAT 2007 to measure immune function. The substudy analysed data from 59 of 257 children (31 in the composite resin group, 35 in the amalgam group). The paper reported that the characteristics of children in the substudy were similar to those of the overall study population; it is not entirely clear if they were selected randomly. No significant difference was found between groups at any time point for total white cell counts, T cell, B cell, neutrophil, and monocyte responsiveness.

Renal effects

Both Casa Pia 2007 and NECAT 2007 measured kidney function and reported this outcome in one article relating to each study. NECAT 2007 included 490 children in the primary analyses and found no difference in biomarker levels or prevalence of high biomarker values. NECAT 2007 reported that the composite group had lower odds of microalbuminuria (MA) at years 3 or 5 (repeat-measures logistic regression analysis; number with MA/number analysed, year 3: composite resin group = 15/148 (9.5%), amalgam

group = 18/135 (13%); number with MA/number analysed, year 5: composite resin group = 18/186 (9.7%), amalgam group = 30/193 (16%); P = 0.03). The study authors suggest that this finding may be due to chance or confounding and required corroboration, since albuminuria is common in the general population, including children, and can result from everyday exposures like extreme physical exertion or infections causing fever. Casa Pia 2007 reported microalbuminuria in yearly age cohorts and found no difference between the treatment groups (Table 5), nor did they did find any evidence for differences between resin composite and amalgam restorations for any other renal biomarkers.

Urinary mercury

NECAT 2007 found a significantly higher level of mean urinary mercury in children in the amalgam group at five-year follow-up (0.9 µg/g creatinine; range 0.1 to 5.7 µg/g creatinine), as compared with children in the composite group (0.6 µg/g creatinine; range 0.1 to 2.9 µg/g creatinine; P < 0.001; 95% CIs not reported). In Casa Pia 2007, urinary mercury levels were reported as a primary outcome of interest. Children in both treatment groups had comparable urinary mercury levels at baseline: 1.5 µg/L (SD ± 1.2; range 0.1 to 7.7) for amalgam and 1.4 µg/L (SD ± 1.1; range 0.0 to 8.6) for composite resin. Urinary mercury levels became significantly higher in children assigned to amalgam through years 2 to 6, with a peak level of 3.2 µg/L in year 2 postintervention (P < 0.001; 95% CIs not reported); levels for the composite resin group were only reported graphically. We were unable to pool data due to poor reporting in both studies.

By follow-up year 7, urinary mercury in the amalgam group had dropped to around baseline level (reported narratively and graphically only), and there was no evidence of a difference between groups, which suggests that urinary mercury excretion reduces over time in those with dental amalgam restorations.

Casa Pia 2007 found no significant group differences in creatinine-adjusted urinary albumin over the seven years of follow-up. A re-analysis of the data published in 2011, based on amalgam size and years of exposure, found a significant association between amalgam and the porphyrin biomarkers for mercury-related enzyme blockage, which suggests that amalgams are a significant contributor to mercury body burden. A further investigation of a subgroup of children with genotyping assays demonstrated a genetic susceptibility to the adverse neurobehavioural effects of mercury exposure in children, predominantly in boys.

Urinary porphyrin excretion

Another report generated from Casa Pia 2007 presented the urinary porphyrin excretion in 479 children (i.e. all those for whom porphyrin data were available). No statistically significant differences were found in any of the primary analyses comparing the randomised treatment groups, nor in a series of subgroup analyses (i.e. by age, race, and sex). Trial authors noted that although they observed "incipient increases" in a subgroup analysis of eight- and nine-year-old participants, these were much lower than the level at which renal function is likely to be affected.

Sensitivity

Postoperative sensitivity

Kemaloglu 2016 found a between-group difference at three years in favour of composite resin restorations (P < 0.05), but we did not consider this to be a clinically important difference. There was no difference between groups at the earlier time points.

DISCUSSION

Summary of main results

We identified eight RCTs assessing the efficacy of amalgam versus resin composite fillings, and have presented a summary of our findings in Summary of findings 1. We judged the certainty of the evidence to be low due to high risk of bias, inconsistency, or imprecision in the results. Our primary analysis of two parallel-group trials suggests that restoration failure and secondary caries may be almost twice as likely with composite restorations compared to amalgam restorations. We added the data from split-mouth studies and conducted a subgroup analysis, which showed that the split-mouth study results were consistent with our primary findings. The evidence suggests that there may be no difference in fracture rates between amalgam and composite restorations.

Both parallel-group trials assessed potential harms related to toxicity, and one split-mouth trial evaluated postoperative sensitivity. It is possible that differences were identified due to the large number of comparisons undertaken at 0.05 level of significance, which could make false-positive results more likely. The evidence was mixed, and a clear pattern did not emerge. In terms of toxicity, two trials reported that urinary mercury excretion was lower in the composite resin compared to the amalgam group up to five- or six-year follow-up. At seven-year follow-up, one trial did not find a difference between groups, suggesting that mercury exposure from dental amalgam restorations may attenuate over time. Moreover, the levels identified were not toxic. Some differences between amalgam and composite resin groups were observed on certain measures of renal, neuropsychological and psychosocial function, physical development, and postoperative sensitivity; however, no consistent or clinically important harms were found. There was no evidence of differences between the amalgam and composite resin groups in neurological symptoms, immune function, and urinary porphyrin excretion. In terms of sensitivity, postoperative sensitivity to cold was higher for people with amalgam restorations than those with resin composite restorations at three years. The trial authors did not comment on the clinical significance of this, but did discuss whether variability in bonding materials may have played a role in the postoperative sensitivity findings.

Overall, there were some differences noted between composite and amalgam fillings with respect to other potential harms, but we judged these as unlikely to be of any clinical importance. The evidence is of very low certainty, with most harms outcomes reported in only one trial.

Overall completeness and applicability of evidence

The eight included studies were RCTs that compared resin composite restorations with amalgam restorations in permanent posterior teeth, with follow-up periods ranging between three and seven years. We reported results for failure rate, secondary caries, fracture of restorations, and adverse effects in this review. The event of a failure is reported rather than the 'non-event' of survival.

Only three trials reported on adverse effects associated with either amalgam or composite restorations, and the generalisability of the findings from these trials to populations other than healthy

children (e.g. children or adults with potentially mercury-sensitive health conditions such as chronic kidney disease) is unclear. There is recent research exploring genetic susceptibility to the adverse neurological effects of mercury exposure in children, with effects manifested predominantly amongst boys. It is acknowledged that a comprehensive systematic review of adverse events would include observational studies, which were not part of this review.

The dental material industry is continuously evolving and improving the products that clinicians use. All but one of the included studies were conducted more than 10 years ago. Some of the materials used in the studies included in this review may no longer be in use or may have been replaced by products with better mechanical properties and better resistance to wear, shrinkage, and fracture. In this respect, the results of this review may not be a true reflection of the quality of restorations that are currently in use.

Quality of the evidence

We assessed the evidence on effectiveness as low certainty due to high risk of bias (lack of blinding) and inconsistency, and the harms data provide only very low certainty evidence. Differences in oral hygiene may have contributed to the inconsistency observed in failure rate and secondary caries outcomes owing to age differences of participants in the two trials (mean ages 7.9 and 10.2 years). Inconsistency may have also resulted from the difference in adhesives used for composite restoration in the studies. The trial that found an association between composite restoration and impaired psychosocial function reported that participants received additional composite restoration in cases where any anterior teeth needed restoration. This may have amplified the effects of composite restoration on psychosocial function.

Potential biases in the review process

There were unit of analysis issues with all of the included studies, as even the parallel-group studies had more than one filling per person, and the data were analysed without taking the clustering into account. This meant that the confidence intervals for the effect estimates were smaller than they should be; however, this effect will be very small. The effect for the split-mouth studies is unknown, as there is a lack of clarity in their reporting, which is why we did not include them in the primary analysis.

Agreements and disagreements with other studies or reviews

The results obtained in the process of the current systematic review are consistent with the conclusions of the systematic review performed by the Canadian Agency of Drugs and Technologies in Health (CADTH 2018), which presented safety, efficacy, and cost-effectiveness, although the duration of follow-up in the two studies presenting efficacy data was inadequate to permit inclusion of these studies in our review. A scoping review carried out in 2020 found both composite resin and amalgam materials were widely recommended for restorative treatment of early childhood carious lesions (Correa-Faria 2020). A systematic review conducted in 2020 identified one RCT, which showed that class II composite restorations may have a higher risk of failure compared with amalgam restorations (Splieth 2020).

AUTHORS' CONCLUSIONS

Implications for practice

Low-certainty evidence suggests that fillings made of resin composite lead to higher failure rates and secondary caries risk than amalgam restorations. The international commitment to reducing mercury will increasingly restrict the use of amalgam fillings, but there are still many parts of the world where it is the material of choice for the restoration of posterior teeth with proximal caries. Safety data is very limited for both types of filling material, but very low-certainty evidence suggests there may be no clinically important differences in the safety profile of composite resin and amalgam dental restorations.

Implications for research

This review suggests that there are higher failure rates with resin composite than with amalgam restorations. However, the included studies are from 2007, and composite dental restorative materials have advanced considerably in the last 10 years. Since the proposed discontinuation of amalgam use depends on quality improvement of non-mercury-based alternative restorative materials (BDA 2013), there is a need for new research to demonstrate long-term effectiveness and safety of the latest improved composite materials, techniques, and instruments for placing them. If split-mouth trial design is to be used in future studies, data should be analysed and reported appropriately, taking into account the clustering of sites within participants (Lesaffre 2009).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Casa Pia 2007

Study characteristics	
Methods	Study design: parallel-group RCT Conducted in: Lisbon, Portugal Number of centres: 1 at Lisbon Faculty of Dental Medicine Recruitment period: started in 1996 Funding source: National Institute of Dental & Craniofacial Research
Participants	Inclusion criteria: children born from 1986 through 1989. At least 1 carious lesion in a permanent posterior tooth. Urinary mercury concentration < 10 µg/L. Blood lead concentration of < 15 µg/dL. An IQ score at least 67 on Comprehensive Test of Nonverbal Intelligence Exclusion criteria: prior exposure to dental amalgam, interference health condition Age: 8 to 12 years Caries risk status: unclear Location of teeth filled: 1545 permanent molars and 203 premolars

Casa Pia 2007 *(Continued)*

	Type of cavity filled: 879 Class I restorations and 869 Class II restorations Number randomised: 507 children Number evaluated: 472 children
Interventions	Comparison: composite vs amalgam Group A: 233 children received 892 composite restorations Group B: 239 children received 856 amalgam restorations Type of moisture control: restorations were placed using rubber dam isolation whenever possible. Duration of follow-up: 7 years
Outcomes	• Failure rate, estimated at 7 years • Secondary caries, estimated at 7 years • Fracture of restoration, estimated at 7 years • Adverse sentinel health events • Neurobehavioural assessment of memory, attention concentration, and motor/visuomotor domains, as well as nerve conduction velocities, estimated at year 1, 2, 3, 4, 5, 6, and 7
Notes	Sample size calculation: selected to ensure adequate power for detecting 2 potential scenarios The first scenario was a small but near-uniform effect of 0.3 SD for the 3 neurobehavioural outcomes, and half of that (0.15 SD) for the nerve conduction outcome. The effect size of 0.3 SD represents a shift that would cause the proportion of abnormally low values in a normally distributed population to increase from 2.5% to 5.0%, thus doubling the proportion classified as abnormally low. For the second scenario, a potential effect in only 1 of the 4 outcomes was of interest, so an effect size of 0.5 SD in the nerve conduction outcome was used, with no effects in the others. A sample size of 400 (200 in each group) through 5 years of follow-up provided adequate power (97%) to detect both scenarios.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Children were randomly assigned to 1 of the 2 treatment groups, but study authors did not explain the method of randomisation.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported. Blinding was not possible due to the clinical characteristics of the interventions.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Restorative procedures were standardised, and dentists were calibrated before starting the trial, but there is no indication that assessors were blinded or different from the operators.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Of 507 children initially randomised, 19 had no dental exam after baseline, and 16 had no restoration to posterior teeth at baseline. None of the children who had fillings placed were lost to follow-up, and all of them were analysed in the group that they had been allocated to by randomisation. 472 children (93%) were followed up for 1 year.

Casa Pia 2007 *(Continued)*

Selective reporting (reporting bias)	Low risk	Expected outcomes reported.
Other bias	Low risk	No other bias apparent.

Cunningham 1990

Study characteristics	
Methods	Study design: RCT, split-mouth design Conducted in: Liverpool, UK Number of centres: 3 dentists, 1 based at Liverpool Dental Hospital, 2 general practitioners Recruitment period: not reported Funding source: unclear
Participants	Inclusion criteria: teeth requiring the treatment of Class I and Class II carious lesions Exclusion criteria: unclear Age: not reported Caries risk status: unclear Location of teeth filled: not reported Type of cavity filled: O: 83 cavities, MO: 140 cavities, DO: 164 cavities, MOD: 122 cavities Number randomised: 605 cavities (Class I or Class II lesions) were randomly assigned to be restored with 2 different amalgams and 3 different composites Number evaluated: 509 restorations
Interventions	Comparison: composite vs amalgam Group A: 309 composite restorations Group B: 200 amalgam restorations Type of moisture control: unclear Duration of follow-up: 3 years
Outcomes	• Failures and fractures of the restorations, estimated at year 3 • Contact points, estimated at 6, 12, 24, and 36 months • Gingival inflammation, estimated at 6, 12, 24, and 36 months • Marginal stain and caries, estimated at year 3 • Color match, estimated at year 3
Notes	Sample size calculation: unclear

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Cunningham 1990 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Teeth were randomly assigned to treatment groups, but study authors did not explain the method of randomisation used to generate the allocation sequence.
Allocation concealment (selection bias)	Low risk	There was no information regarding the method used to conceal the allocation sequence; however, due to the study design (split-mouth), a lack of allocation concealment was unlikely to introduce bias.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported. Blinding was not possible due to the clinical characteristics of the interventions.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding was not possible due to the clinical characteristics of the interventions.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Of the original 605 restorations, 509 could be examined at 3 years, and the losses were reported to have been evenly distributed across the trial arms, though numbers per group were not explicitly given. Follow-up 84.1%
Selective reporting (reporting bias)	Low risk	All data were well reported.
Other bias	High risk	Unit of analysis error - the total number of participants was not indicated in the paper. There were 5 materials under consideration, and each tooth was randomised to 1 of them, but the number of restorations per participant is not clear.

Hendriks 1986

Study characteristics	
Methods	Study design: RCT, split-mouth design Conducted in: unclear Number of centres: 3 operators Recruitment period: unclear Funding source: unclear
Participants	Inclusion criteria: not reported Exclusion criteria: not reported Age: adults Caries risk status: unclear Location of teeth filled: 108 permanent molars and 124 premolars Type of cavity filled: not reported Number randomised: 242 cavities Number evaluated: 232 cavities

Hendriks 1986 *(Continued)*

Interventions	Comparison: composite vs amalgam Group A: 174 composite restorations Group B: 58 amalgam restorations Type of moisture control: rubber dam Duration of follow-up: 3 years
Outcomes	Failures of restorations estimated at year 3
Notes	Sample size calculation: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The 4 materials within each series were distributed at random over the teeth selected for restoration, and the participants were assigned at random to 1 of 3 operators. Study authors did not describe the method of randomisation.
Allocation concealment (selection bias)	Low risk	Information in the paper regarding allocation concealment was unclear; however, due to the design of the study (split-mouth), a lack of allocation concealment was unlikely to introduce bias.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported. Blinding was not possible due to the clinical characteristics of the interventions.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding was not possible due to the clinical characteristics of the interventions.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The 3-year retrieval percentage of both the participants and restorations was 96%; however, dropout rate was not reported by trial arm.
Selective reporting (reporting bias)	Low risk	All data were well reported.
Other bias	High risk	Unit of analysis error - number of restorations per participant not reported

Kemaloglu 2016

Study characteristics

Methods	Study design: RCT Quote: "The study was conducted according to the ethical standards stated in the Helsinki Declaration and approved by the Institutional Review Board/Ethics Committee of Ege University."
Participants	20 people in need of at least 2 posterior restorations Inclusion criteria: teeth asymptomatic, occlusal and adjacent teeth in contact, cavity sizes exceeding the 1/3 of the faciolingual distance between cuso tips

Kemaloglu 2016 *(Continued)*

	Exclusion criteria: with < 20 teeth, poor oral hygiene, bruxism, periodontitis, a history of allergic reactions to any of the materials used
Interventions	Composite restorations Bonded amalgam restorations 50 restorations (2 in each participant) placed by 2 dentists who practised the technique before the first restoration (5 people did not return for 2-week appointment)
Outcomes	Performance of restoration measured using modified US Public Health Service criteria for retention, marginal adaptation, anatomic form, surface texture, and secondary caries. Postoperative sensitivity (response to cold) using VAS Measured at baseline (2 weeks), 6 months, 1 year, and 3 years
Notes	Trial authors concluded that posterior resin composite can be used even in large cavities.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomization of the restorations was obtained by flipping a coin to choose the first teeth to be restored by the resin composite."
Allocation concealment (selection bias)	Low risk	Split-mouth study
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding was not possible, as the interventions looked different.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Two examiners who were not involved in the placement of the restorations evaluated the restorations after 2 weeks (baseline), 6 months, 1 and 3 years. In case of disagreement, the examiners reevaluated the restorations until they reached a consensus." Quote: "Postoperative sensitivity evaluation was blindly conducted by trained examiner after 2 weeks (baseline), 6 months, 1 and 3 years." The study attempted to reduce bias, but as the restorations looked different, blinding was not possible.
Incomplete outcome data (attrition bias) All outcomes	Low risk	5 people did not return for baseline assessment at 2 weeks, but those who embarked on the study completed it.
Selective reporting (reporting bias)	Low risk	Outcomes were reported as planned.
Other bias	Low risk	None noted.

Letzel 1989

Study characteristics

Letzel 1989 *(Continued)*

Methods	Study design: multicentre RCT, split-mouth design Conducted in: Liverpool (UK), London (UK), Manchester (UK), North Carolina (USA), Indianapolis (USA), South Illinois (USA), Philadelphia (USA), Gothenburg (Sweden), Nijmegen (Netherlands), Leuven (Belgium), Louvain (Belgium), Bonn (Germany) Number of centres: 12 Recruitment period: not reported Funding source: ICI Dental (Imperial Chemical Industries), Macclesfield, UK
Participants	Inclusion criteria: adults with teeth requiring posterior Class I or II restorations. Sound tooth or a sound restored tooth in proximal contact with each of the teeth were included. Exclusion criteria: people who may have been unable to return for 5 years or who required special management, extensive restorative care, or cuspal replacement. Teeth requiring Class II restorations that had no proximal contact. Pairs of opposing teeth Age: adults, age not reported Caries risk status: unclear Location of teeth filled: posterior teeth Type of cavity filled: Class I and II restorations Number randomised: 447 adults, 1164 cavities Number evaluated: 338 adults, 693 cavities
Interventions	Comparison: composite vs amalgam Group A: 461 composite restorations Group B: 232 amalgam restorations Type of moisture control: unclear Duration of follow-up: 5 years
Outcomes	Primary outcome: failure In order to trace the causes of failure in each case, reasons for failure were classified according to a system described by Letzel and colleagues in 1988. This system was designed for an evaluation of the influence of experimental variables and operators on the survival rate of restorations included in controlled clinical trials of dental amalgams. The system distinguishes between 3 types of restoration failure: • Type 1: failures directly related to the restoration (i.e. the material and the way it is manipulated into a restoration); • Type 2: failures related to the restorative process (i.e. the result of the decision-making process of the operator); • Type 3: failures caused by external factors.
Notes	Sample size calculation: not reported 12 centres were involved in the trial, but data from 10 centres were used in the review because these centres complied with the condition of fully reviewing the restorations after at least 4 years.
Risk of bias	

Letzel 1989 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The study authors declared that randomisation was done in 5 centres, but do not state if the sequence generation had been at random in the other centres.
Allocation concealment (selection bias)	Low risk	Information in the paper regarding allocation concealment was unclear; however, due to the design of the study (split-mouth), a lack of allocation concealment was unlikely to introduce bias.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported. Blinding was not possible due to the clinical characteristics of the interventions.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding was not possible due to the clinical characteristics of the interventions.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Follow-up at 4 years was 76% for composite restorations. Dropout rate for amalgam was not clearly reported.
Selective reporting (reporting bias)	High risk	Data seemed to be well reported for composite, but only partially reported for amalgam, in particular follow-up data.
Other bias	High risk	There were variations in practice and dropout rate amongst the centres, and the reason for these variations was not clearly explained. Unit of analysis error - number of restorations reported but not number of restorations per participant

NECAT 2007

Study characteristics	
Methods	Study design: parallel-group RCT Conducted in: USA Number of centres: 5 community centres in Boston and Maine, USA Recruitment period: 1997 to 2005 Funding source: unclear
Participants	Inclusion criteria: children fluent in English Had ≥ 2 posterior teeth with dental caries. Primary and permanent teeth Exclusion criteria: had known prior or existing amalgam restorations. Had a physician-diagnosed psychological behavioural, neurologic, immunosuppressive, or renal disorder Age: 6 to 10 years Caries risk status: not reported Location of teeth filled: posterior teeth Type of cavity filled: Class I and Class II restorations

NECAT 2007 *(Continued)*

	Number randomised: 534 children Number evaluated: 449 children
Interventions	Comparison: composite vs amalgam Group A: 753 composite restorations Group B: 509 amalgam restorations Type of moisture control/tooth isolation: rubber dam Duration of follow-up: 5 years. Evaluation every 6 months
Outcomes	Rate of replacement and repair of the restorations, psychosocial function (5-year follow-up), physical development (5-year follow-up)
Notes	Sample size calculation: not reported. Only data from permanent teeth were used in the review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was stratified by geographic location (Boston/Cambridge vs Farmington) and number of teeth with caries (2 to 4 versus 5 or more), using randomly permuted blocks within each of the 4 strata..."
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was stratified...using randomly permuted blocks within each of the four strata to achieve balance...Assignment was made via telephone, using software and encrypted files at New England Research Institutes by staff personnel not involved in data collection."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and dentists could not be blinded to treatment assignment due to the clinical characteristics of the interventions.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding was not possible for efficacy outcomes due to the clinical characteristics of the interventions. Quote: "Participants and dentists could not be blinded to treatment assignment, but all individuals who collected outcome data (e.g., neuropsychological tests) or analyzed specimens (e.g., for mercury) were blinded to children's treatment assignments" (Bellinger and colleagues 2007)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up at 3 years was 84%, and losses were similar in both groups.
Selective reporting (reporting bias)	Low risk	All data were well reported.
Other bias	Low risk	No other apparent biases

Norman 1990

Study characteristics

Norman 1990 *(Continued)*

Methods	Study design: RCT, split-mouth design Conducted in: unclear Number of centres: 1 Recruitment period: not reported Funding source: ICI (Imperial Chemical Industries), Macclesfield, UK
Participants	Inclusion criteria: individuals in need of posterior Class I and II restorations. Maximum of 4 restorations was allowed. Selection of the teeth required that there be a sound tooth or a sound restored tooth in proximal contact to the restoration. At least a portion of the restoration was required to be in contact with an opposite tooth or restoration. Exclusion criteria: not reported Age: 28 to 40 years Caries risk status: not reported Location of teeth filled: molars and premolars Type of cavity filled: Class I and II restorations Number randomised: 62 participants, 160 restorations Number evaluated: 123 restorations
Interventions	Comparison: composite vs amalgam Group A: 80 Occlusin composite. Light-cured, highly filled hybrid posterior composite resin Group B: 43 Dispersalloy amalgam Type of moisture control: rubber dam was used to isolate the teeth Duration of follow-up: 5 years
Outcomes	Primary outcomes: failure and recurrent caries Secondary outcomes: wear, marginal adaptation, anatomic form, interproximal contacts
Notes	Sample size calculation: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	All restorations were placed by following a random selection chart for composite resins and amalgam.
Allocation concealment (selection bias)	Low risk	There was no information regarding the method used to conceal the allocation sequence; however, due to the design of the study (split-mouth), a lack of allocation concealment was unlikely to introduce bias.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported. Blinding was not possible due to the clinical characteristics of the interventions.

Norman 1990 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding was not possible due to the clinical characteristics of the interventions.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Follow-up at 5 years was 80.6%; however, dropout rate was not reported by trial arm.
Selective reporting (reporting bias)	Low risk	All data were well reported.
Other bias	High risk	Unit of analysis error - number of restorations reported but not number of participants

Robinson 1988

Study characteristics	
Methods	Study design: RCT, split-mouth design Conducted in: Guy's Hospital, London, UK Number of centres: 1 Recruitment period: not clear Funding source: ICI Dental, Macclesfield, UK
Participants	Inclusion criteria: adults who required O and proximo-O restorations in vital premolars and molars Exclusion criteria: mental and physical disabilities likely to prevent continued co-operation, people who would not be available for the long-term follow-up visits over the 5 years, and restorations requiring cuspal replacement Age: 19 to 66 years Caries risk status: not reported Location of teeth filled: molars and premolars Type of cavity filled: Class I and II restorations Number randomised: 58 participants, 98 composites and 27 amalgams Number evaluated: 90 restorations
Interventions	Comparison: composite vs amalgam Group A: 70 Occlusin composite Group B: 20 Aristaloy amalgam Type of moisture control/tooth isolation used: rubber dam isolation in 82.4% of cases Duration of follow-up: 3 years
Outcomes	Failure rate in terms of the following criteria: gingival condition, interproximal contacts, colour match, anatomic form, surface roughness

Robinson 1988 *(Continued)*

Notes	Sample size calculation: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were allocated to receive composite or amalgam restoration in the ratio 3:1 from a randomised table.
Allocation concealment (selection bias)	Low risk	There was no information regarding the method used to conceal the allocation sequence; however, due to the design of the study (split-mouth), a lack of allocation concealment was unlikely to introduce bias.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported. Blinding was not possible due to the clinical characteristics of the interventions.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding was not possible due to the clinical characteristics of the interventions.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Follow-up at 36 months was 78.4%, but it was unclear whether dropout was balanced between trial arms.
Selective reporting (reporting bias)	Low risk	All data were well reported.
Other bias	High risk	Unit of analysis error - number of restorations reported but not number of participants

DO: distal and occlusal; **IQ:** intelligence quotient; **MO:** mesial and occlusal; **MOD:** mesial, occlusal, and distal; **O:** occlusal; **RCT:** randomised controlled trial; **SD:** standard deviation; **VAS:** visual analogue scale

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Allan 1977	Non-RCT. Retrospective analysis of dental records
Bellinger 2006	This article reports data from the New England Children's Amalgam Trial. As the data for permanent and temporary dentition were not informed separately, it was not possible to extract the data for permanent posterior teeth.
Borgmeijer 1991	Insufficient follow-up and incomplete data
Bryant 1994	Not an RCT. No randomisation
Busato 1996	Not an RCT. No randomisation
Cloyd 1997	Not an RCT. No randomisation
Collins 1998	Not an RCT. No randomisation

Study	Reason for exclusion
Dilley 1990	Did not evaluate longevity correctly
Eames 1974	Not an RCT. No randomisation
Fukushima 1988	Not an RCT. No randomisation
Hendriks 1985	Not an RCT. No randomisation
Johnson 1992	Not an RCT. No randomisation
Knibbs 1992	Not an RCT. No randomisation
Kopperud 2012	Not an RCT
Koray	Unpublished. Study author did not respond to request for data.
Kreulen 1993a	No long-term follow-up. No caries and fracture reporting
Kreulen 1993b	Intervention did not correspond with the aims of this review.
Lambrechts 1984	Follow-up 18 months
Leinfelder 1975	Follow-up 24 months
Leinfelder 1980	As the study considered anterior and posterior restorations, it is not possible to be certain that the failures occurred in Class I and II restorations.
Mair 1995	No data could be extracted.
Mair 1998	No data could be extracted.
Mannocci 2005	Intervention did not correspond with the aims of this review.
Mjör 1993a	Not an RCT. No randomisation
Mjör 1993b	Not an RCT
Nell 1994	Intervention did not correspond with the aims of this review.
Pieper 1991	Not an RCT. Retrospective study
Powers 1974	Not an RCT. No randomisation
Prati 1988	Not an RCT. No randomisation
Roulet 1977	Follow-up 12 months
Roulet 1978	Same data as Roulet 1977
Rowe 1989	Not an RCT. No randomisation
Rytömaa 1984	Not an RCT. No randomisation
Samaha 1982	Not an RCT. No randomisation

Study	Reason for exclusion
Shenker 2008	This article reported data from the New England Children's Amalgam Trial. As the data for permanent and temporary dentition were not informed separately, it was not possible to extract the data for permanent posterior teeth.
Smales 1991	Not an RCT. No randomisation
Smales 1992	Intervention did not correspond with the aims of this review.
Solano 1984	Study data were unpublished (master's dissertation) and could not be found for critical appraisal.
Tobi 1999	Randomised at tooth level, but only partially analysed and reported
Van Nieuwenhuysen 2003	Not an RCT. No randomisation
Walls 1988	Follow-up 24 months
Welbury 1990	Randomisation broken by ignoring it in 20/150 pairs of teeth.
Wilson 1996	Did not compare amalgam versus composite

RCT: randomised controlled trial

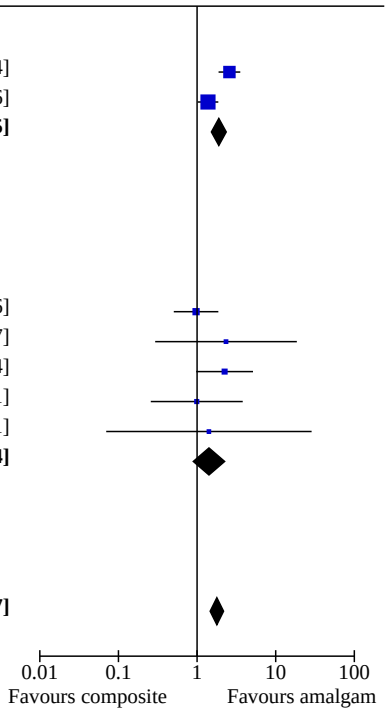
DATA AND ANALYSES

Comparison 1. Composite resin fillings versus amalgam fillings

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Failure rate	7	5200	Risk Ratio (M-H, Fixed, 95% CI)	1.78 [1.47, 2.17]
1.1.1 Failure rate - parallel-group studies	2	3010	Risk Ratio (M-H, Fixed, 95% CI)	1.89 [1.52, 2.35]
1.1.2 Failure rate - split-mouth studies	5	2190	Risk Ratio (M-H, Fixed, 95% CI)	1.42 [0.90, 2.24]
1.2 Secondary caries	6	4036	Risk Ratio (M-H, Fixed, 95% CI)	2.11 [1.66, 2.69]
1.2.1 Secondary caries - parallel-group studies	2	3010	Risk Ratio (M-H, Fixed, 95% CI)	2.14 [1.67, 2.74]
1.2.2 Secondary caries - split-mouth studies	4	1026	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [0.43, 5.21]
1.3 Fracture of restorations	2	3010	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.46, 1.64]

Analysis 1.1. Comparison 1: Composite resin fillings versus amalgam fillings, Outcome 1: Failure rate

Study or Subgroup	Composite Events	Composite Total	Amalgam Events	Amalgam Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Failure rate - parallel-group studies						
Casa Pia 2007 (1)	129	892	48	856	33.2%	2.58 [1.88 , 3.54]
NECAT 2007	112	753	55	509	44.5%	1.38 [1.02 , 1.86]
Subtotal (95% CI)		**1645**		**1365**	**77.7%**	**1.89 [1.52 , 2.35]**
Total events:	241		103			
Heterogeneity: Chi² = 7.89, df = 1 (P = 0.005); I² = 87%						
Test for overall effect: Z = 5.76 (P < 0.00001)						
1.1.2 Failure rate - split-mouth studies						
Cunningham 1990	21	309	14	200	11.5%	0.97 [0.51 , 1.86]
Hendriks 1986	7	174	1	58	1.0%	2.33 [0.29 , 18.57]
Letzel 1989	54	932	6	232	6.5%	2.24 [0.98 , 5.14]
Norman 1990	6	107	3	53	2.7%	0.99 [0.26 , 3.81]
Robinson 1988	2	98	0	27	0.5%	1.41 [0.07 , 28.61]
Subtotal (95% CI)		**1620**		**570**	**22.3%**	**1.42 [0.90 , 2.24]**
Total events:	90		24			
Heterogeneity: Chi² = 2.95, df = 4 (P = 0.57); I² = 0%						
Test for overall effect: Z = 1.49 (P = 0.14)						
Total (95% CI)		**3265**		**1935**	**100.0%**	**1.78 [1.47 , 2.17]**
Total events:	331		127			
Heterogeneity: Chi² = 12.44, df = 6 (P = 0.05); I² = 52%						
Test for overall effect: Z = 5.80 (P < 0.00001)						
Test for subgroup differences: Chi² = 1.25, df = 1 (P = 0.26), I² = 19.7%						

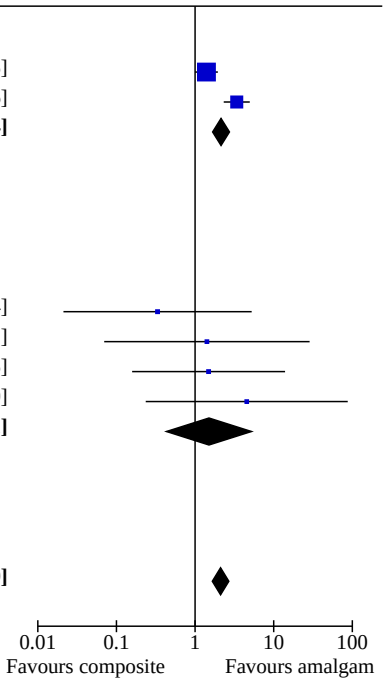


Footnotes

(1) Fixed-effect model displayed as primary result is for parallel group subgroup

Analysis 1.2. Comparison 1: Composite resin fillings versus amalgam fillings, Outcome 2: Secondary caries

Study or Subgroup	Composite Events	Composite Total	Amalgam Events	Amalgam Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 Secondary caries - parallel-group studies						
NECAT 2007 (1)	95	753	46	509	59.8%	1.40 [1.00 , 1.95]
Casa Pia 2007	113	892	32	856	35.6%	3.39 [2.31 , 4.96]
Subtotal (95% CI)		**1645**		**1365**	**95.4%**	**2.14 [1.67 , 2.74]**
Total events:	208		78			
Heterogeneity: Chi² = 11.88, df = 1 (P = 0.0006); I² = 92%						
Test for overall effect: Z = 6.06 (P < 0.00001)						
1.2.2 Secondary caries - split-mouth studies						
Hendriks 1986	1	174	1	58	1.6%	0.33 [0.02 , 5.24]
Robinson 1988	2	98	0	27	0.8%	1.41 [0.07 , 28.61]
Norman 1990	3	107	1	53	1.5%	1.49 [0.16 , 13.95]
Cunningham 1990	3	309	0	200	0.7%	4.54 [0.24 , 87.40]
Subtotal (95% CI)		**688**		**338**	**4.6%**	**1.50 [0.43 , 5.21]**
Total events:	9		2			
Heterogeneity: Chi² = 1.68, df = 3 (P = 0.64); I² = 0%						
Test for overall effect: Z = 0.64 (P = 0.52)						
Total (95% CI)		**2333**		**1703**	**100.0%**	**2.11 [1.66 , 2.69]**
Total events:	217		80			
Heterogeneity: Chi² = 13.97, df = 5 (P = 0.02); I² = 64%						
Test for overall effect: Z = 6.07 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.30, df = 1 (P = 0.58), I² = 0%						

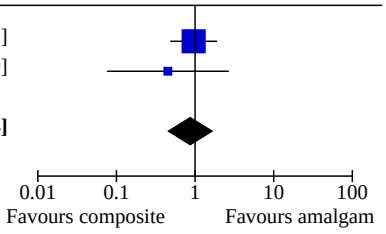


Footnotes

(1) Fixed-effect model displayed as primary result is for parallel group subgroup

Analysis 1.3. Comparison 1: Composite resin fillings versus amalgam fillings, Outcome 3: Fracture of restorations

Study or Subgroup	Composite Events	Composite Total	Amalgam Events	Amalgam Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Casa Pia 2007	16	892	16	856	82.0%	0.96 [0.48 , 1.91]
NECAT 2007	2	753	3	509	18.0%	0.45 [0.08 , 2.69]
Total (95% CI)		**1645**		**1365**	**100.0%**	**0.87 [0.46 , 1.64]**
Total events:	18		19			
Heterogeneity: Chi² = 0.60, df = 1 (P = 0.44); I² = 0%						
Test for overall effect: Z = 0.44 (P = 0.66)						
Test for subgroup differences: Not applicable						



ADDITIONAL TABLES

Table 1. Harms

Study	Report	Type of harm	Outcome
NECAT 2007	Bellinger 2007	Toxicity	Neuropsychological function
			Urinary mercury

Table 1. Harms *(Continued)*

	Bellinger 2008		Psychosocial status
	Shenker 2008		Immune function
	Barregard 2008		Renal effects
	Maserejian 2012		Physical development
Casa Pia 2007	Lauterbach 2008		Neurological symptoms
	DeRouen 2006		Neurobehavioural effects
	Woods 2007		Urinary mercury
	Woods 2008		Renal effects
	Woods 2009		Urinary porphyrin excretion
Kemaloglu 2016		Sensitivity	Postoperative sensitivity

Table 2. Neuropsychological function

Memory									
Method of measurement - RAVLT memory test									
	Resin composite			Amalgam					
	n	Mean	SD	n	Mean	SD	MD	95% CI	P value
At 7 years	176	9.73	2.79	172	9.65	2.86	0.08	−0.51, 0.68	0.79
Method of measurement - WRAML visual memory (1) WMS-III reproductions delayed (2)									
	Resin composite			Amalgam					
	n	Mean	SD	n	Mean	SD	MD	95% CI	P value
At 7 years (2)	176	32.98	6.24	172	33.02	6.24	−0.03	−1.35, 1.28	0.96
Method of measurement - WRAML visual learning (1) WMS-III reproductions immediate (2)									
	Resin composite			Amalgam					
	n	Mean	SD	n	Mean	SD	MD	95% CI	P value
At 7 years (2)	176	35.79	3.68	172	35.15	4.47	0.64	−0.22, 1.50	0.15
Method of measurement - RAVLT total learning test									
	Resin composite			Amalgam					
	n	Mean	SD	n	Mean	SD	MD	95% CI	P value
At 7 years	176	47.36	9.48	172	46.06	9.09	1.30	−0.65, 3.25	0.19
Attention/concentration									
Method of measurement - coding (1) WAIS-III digit symbol (2)									
	Resin composite			Amalgam					

Table 2. Neuropsychological function *(Continued)*

	n	Mean	SD	n	Mean	SD	MD	95% CI	P value
At 7 years (2)	176	9.45	2.98	172	9.45	2.86	0.00	−0.61, 0.61	1.00
Method of measurement - symbol search (1) WAIS-III symbol search (2)									
	Resin composite			Amalgam					
	n	Mean	SD	n	Mean	SD	MD	95% CI	P value
At 7 years (2)	176	9.40	2.85	172	9.77	3.08	−0.37	−0.99, 0.25	0.25
Method of measurement - digit span (1) WAIS-III digit span (2)									
	Resin composite			Amalgam					
	n	Mean	SD	n	Mean	SD	MD	95% CI	P value
At 7 years (2)	176	7.64	2.17	172	7.70	2.21	−0.06	−0.52, 0.40	0.80
Method of measurement - finger windows (1) WAIS-III spatial span (2)									
	Resin composite			Amalgam					
	n	Mean	SD	n	Mean	SD	MD	95% CI	P value
At 7 years (2)	176	9.03	2.96	172	9.34	2.99	−0.31	−0.94, 0.32	0.33
Method of measurement - trial A, seconds (1) adult trial A, seconds (2)									
	Resin composite			Amalgam					
	n	Mean	SD	n	Mean	SD	MD	95% CI	P value
At 7 years (2)	176	28.94	12.06	172	28.72	11.26	0.22	−2.23, 2.67	0.86
Method of measurement - trial B, seconds (1) adult trial B, seconds (2)									
	Resin composite			Amalgam					
	n	Mean	SD	n	Mean	SD	MD	95% CI	P value

Table 2. Neuropsychological function *(Continued)*

At 7 years (2)	176	63.84	25.5	172	65.34	25.07	−1.50	−6.81, 3.81	0.58
Method of measurement - Stroop word									
	Resin composite			Amalgam					
	n	Mean	SD	n	Mean	SD	MD	95% CI	P value
At 7 years	176	41.7	8.09	172	41.41	8.04	0.29	−1.40, 1.98	0.74
Method of measurement - Stroop colour									
	Resin composite			Amalgam					
	n	Mean	SD	n	Mean	SD	MD	95% CI	P value
At 7 years	176	41.59	8.16	172	42.67	8.14	−1.08	−2.79, 0.63	0.22
Method of measurement - Stroop colour-word									
	Resin composite			Amalgam					
	n	Mean	SD	n	Mean	SD	MD	95% CI	P value
At 7 years	176	46.99	9.71	172	48.42	9.41	−1.43	−3.44, 0.58	0.16
Visuomotor									
Method of measurement - WRAVMA matching (1) WASI matrices (2)									
	Resin composite			Amalgam					
	n	Mean	SD	n	Mean	SD	MD	95% CI	P value
At 7 years (2)	176	24.44	5.33	172	24.83	5.02	−0.39	−1.48, 0.70	0.48
Method of measurement - WRAVMA pegs (dominant)									
	Resin composite			Amalgam					
	n	Mean	SD	n	Mean	SD	MD	95% CI	P value

Table 2. Neuropsychological function *(Continued)*

At 7 years	176	119.38	15.83	172	119.01	15.55	0.37	−2.93, 3.67	0.83
Method of measurement - WRAVMA pegs (non-dominant)									
	Resin composite			Amalgam					
	n	Mean	SD	n	Mean	SD	MD	95% CI	P value
At 7 years	176	119.38	15.83	172	119.01	15.55	0.37	−2.93, 3.67	0.83
Method of measurement - standard reaction time									
	Resin composite			Amalgam					
	n	Mean	SD	n	Mean	SD	MD	95% CI	P value
At 7 years	176	0.76	0.14	172	0.77	0.15	−0.01	−0.04, 0.02	0.52
Method of measurement - finger tapping (dominant)									
	Resin composite			Amalgam					
	n	Mean	SD	n	Mean	SD	MD	95% CI	P value
At 7 years	176	50.5	6.56	172	50.51	6.56	−0.01	−1.39, 1.37	0.99
Method of measurement - finger tapping (non-dominant)									
	Resin composite			Amalgam					
	n	Mean	SD	n	Mean	SD	MD	95% CI	P value
At 7 years	176	44.49	6.33	172	44.48	6.34	0.01	1.32, 1.34	0.99
Nerve conduction velocity									
Method of measurement - tibial, m/s									
	Resin composite			Amalgam					
	n	Mean	SD	n	Mean	SD	MD	95% CI	P value

Table 2. Neuropsychological function *(Continued)*

At 7 years	140	50.15	5.09	140	50.78	5.07	−0.63	−1.82, 0.56	0.30
Method of measurement - ulnar, m/s									
	Resin composite			Amalgam					
	n	Mean	SD	n	Mean	SD	MD	95% CI	P value
At 7 years	140	57.58	6.52	140	59.26	6.41	−1.68	−3.19, 0.17	0.03
Intelligence									
Method of measurement - CTONI									
	Resin composite			Amalgam					
	n	Mean	SD	n	Mean	SD	MD	95% CI	P value
At 7 years	176	81	12	173	81	12	0.00	−2.52, 2.52	1.00
Method of measurement - WASI									
	Resin composite			Amalgam					
	n	Mean	SD	n	Mean	SD	MD	95% CI	P value
At 7 years	176	92	13	173	94	14	−2.00	−4.84, 0.84	0.17

CI: confidence interval; **CTONI:** Comprehensive Test of Non-Verbal Intelligence; **MD:** mean difference; **RAVLT:** Rey Auditory Verbal Learning Test; **SD:** standard deviation; **WAIS-III:** Wechsler Adult Intelligence Scale - Third Edition; **WASI:** Wechsler Abbreviated Scale of Intelligence; **WMS-III:** Wechsler Memory Scale - Third Edition; **WRAML:** Wide Range Assessment of Memory and Learning; **WRAVMA:** Wide Range Assessment of Visual Motor Abilities

Table 3. Psychosocial function

	Composite (permanent/posterior occlusal SY)	Amalgam (permanent/posterior occlusal SY)	Composite versus amalgam
	Mean (SE)	**Mean (SE)**	**P value**
BASC-SR Composite Score[a], adjusted mean			
Emotional symptoms index[b]	46.3 (0.6)	44.6 (0.6)	0.05
Clinical maladjustment	45.7 (0.6)	44.0 (0.6)	0.08
School maladjustment	50.4 (0.7)	50.8 (0.8)	0.29
Personal adjustment	51.3 (0.6)	53.3 (0.6)	0.005
CBCL Change Score, adjusted mean			
Competence	−0.9 (0.6)	0.8 (0.6)	0.13
Total problem behaviours	−2.1 (0.7)	−3.3 (0.7)	0.007
Internalising problems	−2.1 (0.6)	−3.8 (0.6)	0.03
Externalising problems	−1.5 (0.8)	−1.8 (0.6)	0.06

BASC-SR: Behavior Assessment for Children Self Report; **CBCL:** Child Behavior Checklist parent report; **SE:** standard error; **SY:** surface years
[a]BASC-SR scores reported in the table above reflect the scores of children aged 6 to 10 years. However, the BASC-SR was developed for children ≥ 8 years. Change in BASC-SR was therefore assessed amongst children aged ≥ 8 years as a subgroup.
[b]Higher score is worse for school adjustment, clinical maladjustment, and emotional symptoms index; a lower score is worse for personal adjustment.

Table 4. Physical development

	Composite	Amalgam	Composite versus amalgam	
	5-year change (SE)	**5-year change (SE)**	**β (SE)**	**P value**
Growth outcome in girls				
Body fat percentage	8.8 (0.7)	7.7 (0.8)	0.05 (0.83)	0.95
BMI-for-age z-score	0.36 (0.06)	0.21 (0.07)	0.08 (0.12)	0.49
Height	30.7 (0.5)	31.2 (0.5)	0.77 (1.18)	0.51
Growth outcome in boys				
Body fat percentage	4.9 (0.9)	5.7 (0.9)	0.57 (0.82)	0.49
BMI-for-age z-score	0.13 (0.08)	0.25 (0.07)	−0.21 (0.23)	0.36
Height	34.4 (0.6)	33.5 (0.6)	0.48 (0.83)	0.56

BMI: body mass index; **SE:** standard error

Table 5. Kidney function

Creatinine-adjusted urinary albumin levels				
	Composite		Amalgam	
	Mean	95% CI	Mean	95% CI
Year 1	7.4	4.2 to 12.5	7.7	3.1 to 11.5
Year 2	9.4	5.3 to 16.1	8.6	5.5 to 13.4
Year 3	9.9	6.8 to 16.7	9.0	5.5 to 17.9
Year 4	9.25	5.8 to 20.8	8.7	5.6 to 14.5
Year 5	8.2	5.1 to 14.3	8.0	5.4 to 12.5
Year 6	7.5	4.8 to 14.3	7.3	4.8 to 14.0
Year 7	6.8	4.4 to 13.7	6.5	4.3 to 12.3

CI: confidence interval

APPENDICES

Appendix 1. Cochrane Oral Health Trials Register search strategy

Cochrane Oral Health's Trials Register is available via the Cochrane Register of Studies. For information on how the register is compiled, see https://oralhealth.cochrane.org/trials

From October 2013, searches of Cochrane Oral Health's Trials Register were conducted using the Cochrane Register of Studies and the search strategy below:

#1 ((tooth or teeth or molar* or bicuspid* or "Class I" or "Class II"):ti,ab) AND (INREGISTER)
#2 ((fill* or restor*):ti,ab) AND (INREGISTER)
#3 (#1 and #2) AND (INREGISTER)
#4 (amalgam*:ti,ab) AND (INREGISTER)
#5 ((resin* and composite*):ti,ab) AND (INREGISTER)
#6 (("bisphenol A-Glycidyl methacrylate" or compomer* or Bis-GMA):ti,ab) AND (INREGISTER)
#7 (("enamel bond*" or (concise and resin*) or (white and sealant*) or "conclude resin*" or Adaptic or Delton or Epoxylite-9075 or (Kerr and seal*) or Nuva-seal or Panavia or Retroplast or Silux):ti,ab) AND (INREGISTER)
#8 (#5 or #6 or #7) AND (INREGISTER)
#9 (#3 and #4 and #8) AND (INREGISTER)

In May 2012, a search of the Cochrane Oral Health Group's Trials Register was conducted using the Procite software and the search strategy below:

(((tooth or teeth or molar* or bicuspid* or "Class I" or "Class II") and (fill* or restor*)) and (amalgam and ((resin* and composite*) or "bisphenol A-Glycidyl methacrylate" or compomer* or Bis-GMA or "enamel bond*" or (concise and resin*) or (white and sealant*) or "conclude resin*" or Adaptic or Delton or Expoylite-9075 or (Kerr and seal*) or Nuva-seal or Panavia or Retroplast or Silux)))

Appendix 2. Cochrane Central Register of Controlled Clinical Trials (CENTRAL) search strategy

#1 MeSH descriptor Dental Restoration, Permanent explode all trees
#2 MeSH descriptor Dental Restoration, Temporary explode all trees
#3 ((tooth in All Text or teeth in All Text or molar* in All Text or bicuspid* in All Text or "Class I" in All Text or "Class II" in All Text) and (restor* in All Text or fill* in All Text))

#4 (#1 or #2 or #3)
#5 MeSH descriptor Dental amalgam this term only
#6 amalgam* in Title, Abstract or Keywords
#7 (#5 or #6)
#8 MeSH descriptor Composite resins explode all trees
#9 ((resin* in Title, Abstract or Keywords near/3 composite* in Title, Abstract or Keywords) or "bisphenol A-Glycidyl methacrylate" in Title, Abstract or Keywords or compomer* in Title, Abstract or Keywords or Bis-GMA in Title, Abstract or Keywords)
#10 ("enamel bond*" in Title, Abstract or Keywords or (concise in Title, Abstract or Keywords near/3 resin* in Title, Abstract or Keywords) or (white in Title, Abstract or Keywords near/3 sealant* in Title, Abstract or Keywords) or "conclude resin*" in Title, Abstract or Keywords or Adaptic in Title, Abstract or Keywords or Delton in Title, Abstract or Keywords or Epoxylite-9075 in Title, Abstract or Keywords or (Kerr in Title, Abstract or Keywords near/5 seal* in Title, Abstract or Keywords) or Nuva-seal in Title, Abstract or Keywords or Panavia in Title, Abstract or Keywords or Retroplast in Title, Abstract or Keywords or Silux in Title, Abstract or Keywords)
#11 (#8 or #9 or #10)
#12 (#4 and #7 and #11)

Appendix 3. MEDLINE Ovid search strategy

1. Dental restorations, permanent/
2. Dental restorations, temporary/
3. ((tooth or teeth or molar$ or bicuspid$ or "Class I" or "Class II") and (restor$ or fill$)).ti,ab.
4. or/1-3
5. Dental amalgam/
6. amalgam$.ti,ab.
7. or/5-6
8. exp Composite resins/
9. ((resin$ adj3 composite$) or "bisphenol A-Glycidyl methacrylate" or compomer$ or Bis-GMA).ti,ab.
10. ("enamel bond$" or (concise adj3 resin$) or (white adj3 sealant$) or "conclude resin$" or Adaptic or Delton or Epoxylite-9075 or (Kerr adj5 seal$) or Nuva-seal or Panavia or Retroplast or Silux).ti,ab.
11. or/8-10
12. 4 and 7 and 11

Appendix 4. Embase Ovid search strategy

1. Tooth filling/
2. ((tooth or teeth or molar$ or bicuspid$ or "Class I" or "Class II") and (restor$ or fill$)).ti,ab.
3. 1 or 2
4. Dental alloy/
5. amalgam$.ti,ab.
6. or/4-5
7. exp Resin/
8. ((resin$ adj3 composite$) or "bisphenol A-Glycidyl methacrylate" or compomer$ or Bis-GMA).ti,ab.
9. ("enamel bond$" or (concise adj3 resin$) or (white adj3 sealant$) or "conclude resin$" or Adaptic or Delton or Epoxylite-9075 or (Kerr adj5 seal$) or Nuva-seal or Panavia or Retroplast or Silux).ti,ab.
10. or/7-9
11. 3 and 6 and 10

Appendix 5. LILACS BIREME Virtual Health Library search strategy

(Mh dental restorations, permanent or Mh dental restorations, temporary or (tooth or teeth or diente$ or dente$ or molar$ or premolar $ or bicuspid$ or "Class I" or "Class II") and (restor$ or restaura$ or fill$)) [Words] and (Mh Dental amalgam or amalgam$) AND (Mh Composite resins or (resin$ and composite$) or (resin$ and compuesta$) or (resin$ and composta$) or "bisphenol A-Glycidyl methacrylate" or compomer$ or Bis-GMA or "enamel bond$" or (concise$ and resin$) or (white and sealant$) or "conclude resin$" or Adaptic or Delton or Epoxylite-9075 or (Kerr and seal$) or Nuva-seal or Panavia or Retroplat or Silux or Compómeros or Compômeros) [Words]

Appendix 6. Supplementary searches

Efficacy search conducted on 26 June 2017, with monthly updates to 1 February 2019

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials May 2017, Embase 1974 to 2017 June 23, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to present

#	Searches
1	exp Dental restoration, permanent/
2	Dental restoration, temporary/
3	((tooth or teeth or molar$ or bicuspid$ or "Class I" or "Class II") and (restor$ or fill$)).ti,ab,kf.
4	or/1-3
5	Dental amalgam/
6	amalgam$.ti,ab,kf.
7	or/5-6
8	exp Composite resins/
9	((resin$ adj3 composite$) or "bisphenol A-Glycidyl methacrylate" or compomer$ or Bis-GMA).ti,ab,kf.
10	(enamel bond$ or (concise adj3 resin$) or (white adj3 sealant$) or conclude resin$ or Adaptic or Delton or Epoxylite-9075 or (Kerr adj5 seal$) or Nuva-seal or Panavia or Retroplast or Silux).ti,ab,kf.
11	or/8-10
12	4 and 7 and 11
13	12 use ppez
14	exp Dental Restoration, Permanent/
15	exp Dental Restoration, Temporary/
16	((tooth or teeth or molar$ or bicuspid$ or "Class I" or "Class II") and (restor$ or fill$)).af.
17	or/14-16
18	Dental amalgam/
19	amalgam$.ti,ab,kw.
20	or/18-19
21	exp Composite resins/
22	((resin$ adj3 composite$) or "bisphenol A-Glycidyl methacrylate" or compomer$ or Bis-GMA).ti,ab,kw.
23	(enamel bond$ or (concise adj3 resin$) or (white adj3 sealant$) or conclude resin$ or Adaptic or Delton or Epoxylite-9075 or (Kerr adj5 seal$) or Nuva-seal or Panavia or Retroplast or Keywords or Silux).ti,ab,kw.
24	or/21-23
25	17 and 20 and 24

(Continued)

26	25 use cctr
27	Tooth filling/
28	((tooth or teeth or molar$ or bicuspid$ or "Class I" or "Class II") and (restor$ or fill$)).ti,ab,kw.
29	or/27-28
30	exp Dental alloy/
31	amalgam$.ti,ab,kw.
32	or/30-31
33	exp Resin/
34	((resin$ adj3 composite$) or "bisphenol A-Glycidyl methacrylate" or compomer$ or Bis-GMA).ti,ab,kw.
35	(enamel bond$ or (concise adj3 resin$) or (white adj3 sealant$) or conclude resin$ or Adaptic or Delton or Epoxylite-9075 or (Kerr adj5 seal$) or Nuva-seal or Panavia or Retroplast or Silux).ti,ab,kw.
36	or/33-35
37	29 and 32 and 36
38	37 use oemezd
39	13 or 26 or 38
40	limit 39 to yr="2012 -Current"
41	remove duplicates from 40

Safety search, last conducted on 20 February 2019

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** January 2019**, Embase** 1974 to 2019 February 20**, Ovid MEDLINE(R) ALL** 1946 to February 20, 2019
Search Strategy:

#	Searches
1	Dental amalgam/
2	(exp Dental Restoration, Permanent/ or Dental Restoration, Temporary/ or Dental Materials/tu or exp Dental caries/th) and (Silver/ or Mercury/ or (amalgam or amalgams or silver or mercury).ti,ab,kf,kw.)
3	((silver or mercury) and (dental or dentist* or tooth or teeth or filling* or premolar* or molar* or bicuspid* or incisor* or cuspid*)).ti,ab,kf,kw.

(Continued)

4	(amalgam or amalgams).ti,ab,kf,kw. and (Silver/ or Mercury/ or (dental or dentist* or tooth or teeth or silver or mercury or filling* or restor* or premolar* or molar* or bicuspid* or incisor* or cuspid*).ti,ab,kf,kw.)
5	(amalgam or amalgams).ti. and (dentist* or dental or oral biology or oral bioscience* or oral health or oral research or endodont* or oral science or caries research or oral medical or dentaire or stomatolog*).jw.
6	or/1-5
7	6 use medall
8	6 use cctr
9	Dental amalgam/
10	Dental alloy/ and Amalgam/
11	(Dental restoration/ or Dental Material/ or Tooth Filling/ or exp Dental Caries/th) and (Silver/ or Mercury/ or (amalgam or amalgams or silver or mercury).ti,ab,kw.)
12	((silver or mercury) and (dental or dentist* or tooth or teeth or filling* or premolar* or molar* or bicuspid* or incisor* or cuspid*)).ti,ab,kw.
13	(amalgam/ or (amalgam or amalgams).ti,ab,kw.) and (Silver/ or Mercury/ or (dental or dentist* or tooth or teeth or silver or mercury or filling* or restor* or molar* or bicuspid* or incisor* or cuspid*).ti,ab,kw.)
14	(amalgam or amalgams).ti. and (dentist* or dental or oral biology or oral bioscience* or oral health or oral research or endodont* or oral science or caries research or oral medical or dentaire or stomatolog*).jx.
15	or/9-14
16	15 use oemezd
17	(conference review or conference abstract).pt.
18	16 not 17
19	7 or 8 or 18
20	exp safety/
21	equipment safety/
22	exp equipment failure/
23	consumer product safety/
24	"product recalls and withdrawals"/
25	medical device recalls/
26	"safety-based medical device withdrawals"/
27	product surveillance, postmarketing/

(Continued)

28	postmarketing surveillance/
29	clinical trial, phase iv.pt.
30	phase 4 clinical trial/
31	clinical trials, phase iv as topic/
32	"phase 4 clinical trial (topic)"/
33	exp postoperative complications/
34	exp postoperative complication/
35	exp intraoperative complications/
36	peroperative complication/
37	exp side effect/
38	"side effects (treatment)"/
39	exp adverse drug reaction/
40	exp drug safety/
41	exp "drug toxicity and intoxication"/
42	exp "drug-related side effects and adverse reactions"/
43	exp drug-induced liver injury/
44	exp drug hypersensitivity/
45	drug recalls/
46	drug recall/
47	safety-based drug withdrawals/
48	abnormalities, drug-induced/
49	exp "side effects (drug)"/
50	(hazard* or defect* or misuse* or failure* or malfunction* or error*).ti,kf,kw.
51	(safe* or adverse* or undesirable or harm* or injurious or risk or risks or reaction* or complication* or poison*).ti,kf,kw.
52	(side effect* or safety or unsafe).ti,ab,kf,kw.
53	((adverse or undesirable or harm* or toxic or injurious or serious or fatal) adj3 (effect* or reaction* or event* or outcome* or incident*)).ab.
54	((drug or chemically) adj induced).ti,ab,kf,kw.

(Continued)

55	(toxic or toxicit* or toxologic* or intoxication or noxious or tolerability or teratogen*).ti,ab,kf,kw.
56	(warning* or recall* or withdrawn* or withdrawal*).ti,kf,kw.
57	(death or deaths or fatal or fatality or fatalities).ti,kf,kw.
58	exp environmental exposure/
59	or/20-58
60	19 and 59
61	Dental amalgam/ae, ct, po, to
62	exp Dental Restoration, Permanent/ or Dental Restoration, Temporary/ or Dental Materials/ or exp Dental caries/th or Dental amalgam/ or (amalgam or amalgams or dental or dentist* or tooth or teeth or filling* or premolar* or molar* or bicuspid* or incisor* or cuspid*).ti,ab,kf,kw.
63	Silver/ae, ct, to or Mercury/ae, to, bl or exp Mercury poisoning/ or exp Mercury poisoning, nervous system/
64	62 and 63
65	exp Dental Restoration, Permanent/ae, ct, mo or Dental Restoration, Temporary/ae, ct or Dental Materials/ae, co, ct, po, to
66	Dental amalgam/ or Silver/ or Mercury/ or (amalgam or amalgams or silver or mercury).ti,ab,kf,kw.
67	65 and 66
68	61 or 64 or 67
69	68 use medall
70	68 use cctr
71	Dental amalgam/ae, ct, to
72	Dental alloy/am, ae, to and amalgam/am, ae, to
73	Dental restoration/ or Dental Material/ or Tooth Filling/ or exp Dental Caries/th or Dental alloy/ or dental amalgam/ or (amalgam or amalgams or dental or dentist* or tooth or teeth or filling* or premolar* or molar* or bicuspid* or incisor* or cuspid*).ti,ab,kw.
74	Silver/ae, to or Mercury/ae, to or Mercurialism/
75	73 and 74
76	amalgam/am, ae, to and (dental or dentist* or tooth or teeth or silver or mercury or filling* or restor* or molar* or bicuspid* or incisor* or cuspid*).ti,ab,kw.
77	Dental procedure/ae or Dental Material/am, ae, to
78	Amalgam/ or Dental amalgam/ or (amalgam or amalgams or silver or mercury).ti,ab,kw.
79	77 and 78

(Continued)

80	71 or 72 or 75 or 76 or 79
81	80 use oemezd
82	81 not 17
83	69 or 70 or 82
84	60 or 83
85	exp Composite Resins/
86	(exp Dental Restoration, Permanent/ or Dental Restoration, Temporary/ or Dental Materials/tu or exp Dental caries/th) and composite*.ti,ab,kf,kw.
87	(composite* adj3 (resin* or restor* or filling* or dental or dentist* or conventional or microfilled or macrofilled or hybrid or flowable or packable or nanofilled or direct or indirect or small particle* or condensable or bonded or non-bonded or nonbonded)).ti,ab,kf,kw.
88	(composite* adj3 (poly-acid or polyacid or polyacrylate or polyacrylic or acrylic)).ti,ab,kf,kw.
89	((resin or resins) adj3 (filled or unfilled or synthetic* or dental or restor*)).ti,ab,kf,kw.
90	((tooth-colored or tooth-coloured) adj3 (filling* or restor*)).ti,ab,kf,kw.
91	(White adj3 filling*).ti,ab,kf,kw.
92	exp Dental Restoration, Permanent/ or Dental Restoration, Temporary/ or Dental Materials/tu or exp Dental caries/th or (composite* or resin or resins).ti,ab,kf,kw.
93	Bisphenol A-Glycidyl Methacrylate/ or (alumino silicate polyacrylic acid or "bisphenol A-Glycidyl methacrylate" or Bis-GMA or BisGMA or triethylene glycol dimethacrylate or urethane dimethacrylate*).ti,ab,kf,kw.
94	92 and 93
95	Compomer*.ti,ab,kf,kw.
96	composite*.ti. and (dentist* or dental or oral biology or oral bioscience* or oral health or oral research or endodont* or oral science or caries research or oral medical or dentaire or stomatolog*).jw.
97	or/85-91,94-96
98	97 use medall
99	97 use cctr
100	exp Resin/ and composit*.ti,ab,kw.
101	(Dental restoration/ or Dental Material/ or Tooth Filling/ or exp Dental Caries/th) and composite*.ti,ab,kw.
102	(composite* adj3 (resin* or restor* or filling* or dental or dentist* or conventional or microfilled or macrofilled or hybrid or flowable or packable or nanofilled or direct or indirect or small particle* or condensable or bonded or non-bonded or nonbonded)).ti,ab,kw.

(Continued)

103	(composite* adj3 (poly-acid or polyacid or polyacrylate or polyacrylic or acrylic)).ti,ab,kw.
104	((resin or resins) adj3 (filled or unfilled or synthetic* or dental or restor*)).ti,ab,kw.
105	((Tooth-colored or tooth-coloured) adj3 (filling* or restor*)).ti,ab,kw.
106	(White adj3 filling*).ti,ab,kw.
107	Dental restoration/ or Dental Material/ or Tooth Filling/ or exp Dental Caries/th or (composite* or resin or resins).ti,ab,kw.
108	"bisphenol A bis(2 hydroxypropyl) ether dimethacrylate"/ or (alumino silicate polyacrylic acid or "bisphenol A-Glycidyl methacrylate" or Bis-GMA or BisGMA or triethylene glycol dimethacrylate or urethane dimethacrylate*).ti,ab,kw.
109	107 and 108
110	Compomer*.ti,ab,kw.
111	composite*.ti. and (dentist* or dental or oral biology or oral bioscience* or oral health or oral research or endodont* or oral science or caries research or oral medical or dentaire or stomatolog*).jx.
112	or/100-106,109-111
113	112 use oemezd
114	113 not 17
115	98 or 99 or 114
116	59 and 115
117	exp Composite Resins/ae, ct, to
118	exp Dental Restoration, Permanent/ae, ct, mo or Dental Restoration, Temporary/ae, ct or Dental Materials/ae, co, ct, po, to
119	Composite resins/ or (composite* or resin or resins).ti,ab,kf,kw.
120	118 and 119
121	exp Dental Restoration, Permanent/ae, ct, mo or Dental Restoration, Temporary/ae, ct or Dental Materials/ae, ct, co, po, to
122	("bisphenol A-Glycidyl methacrylate" or Bis-GMA or BisGMA).ti,ab,kf,kw.
123	121 and 122
124	117 or 120 or 123
125	124 use medall
126	125 use cctr
127	exp Resin/am, ae, to and composit*.ti,ab,kw.

(Continued)

128	Dental procedure/ae or Dental Material/am, ae, to
129	exp Resin/ or (composite* or resin or resins).ti,ab,kw.
130	128 and 129
131	Dental procedure/ae or Dental Material/am, ae, to
132	("bisphenol A-Glycidyl methacrylate" or Bis-GMA or BisGMA).ti,ab,kw.
133	131 and 132
134	127 or 130 or 133
135	134 use oemezd
136	135 not 17
137	125 or 126 or 136
138	116 or 137
139	84 or 138
140	limit 139 to yr="2016 -Current"
141	remove duplicates from 140

PubMed search, conducted 21 February 2019

Clinical efficacy

Recent queries

Search	Add to builder	Query	Items found	Time
#11	Add	Search **#9 AND #10**	3	08:41:24
#10	Add	Search **publisher[sb] OR 2019/02/17:2019/02/21[edat]**	546179	08:41:16
#9	Add	Search **#3 AND #4 AND #8**	1807	08:40:37
#8	Add	Search **#5 OR #6 OR #7**	30990	08:39:48
#7	Add	Search **enamel bond*[tiab] OR (concise[tiab] AND resin*[tiab]) OR (white[tiab] AND sealant*[tiab]) OR conclude resin*[tiab] OR Adaptic[tiab] OR Delton[tiab] OR Epoxylite-9075 OR (Kerr[tiab] AND seal*[tiab]) OR Nuva-seal[tiab] OR Panavia[tiab] OR Retroplast[tiab] OR Silux[tiab]**	6715	08:39:36

(Continued)

#6	Add	Search **(resin*[tiab] AND composite*[tiab]) OR "bisphenol A-Glycidyl methacrylate"[tiab] OR compomer*[tiab] OR Bis-GMA[tiab]**	17337	08:39:29
#5	Add	Search **Composite resins[mh]**	24218	08:39:22
#4	Add	Search **Dental amalgam[mh] OR amalgam*[tiab]**	13020	08:39:10
#3	Add	Search **#1 OR #2**	50119	08:39:00
#2	Add	Search **(tooth[tiab] OR teeth[tiab] OR molar*[tiab] OR bicuspid*[tiab] OR "Class I"[tiab] OR "Class II"[tiab]) AND (restor*[tiab] OR fill*[tiab])**	33949	08:38:48
#1	Add	Search **Dental restoration, permanent[mh] OR Dental restoration, temporary[mh]**	24862	08:36:41

Safety

Search	Add to builder	Query	Items found	Time
#45	Add	Search **#43 AND #44**	123	10:52:29
#44	Add	Search **publisher[sb] OR 2019/02/17:2019/02/21[edat]**	546179	10:52:15
#43	Add	Search **#27 OR #42**	8682	10:51:44
#42	Add	Search **#35 OR #41**	2162	10:51:24
#41	Add	Search **#36 OR #38 OR #40**	858	10:50:07
#40	Add	Search **#32 AND #39**	76	10:49:15
#39	Add	Search **"bisphenol A-Glycidyl methacrylate"[tiab] OR Bis-GMA[tiab] OR BisGMA[tiab]**	1221	10:49:00
#32	Add	Search **Dental Restoration, Permanent[mh]/adverse effects OR Dental Restoration, Permanent[mh]/contraindications OR Dental Restoration, Permanent[mh]/mortality OR Dental Restoration, Temporary[mh]/adverse effects OR Dental Restoration, Temporary[mh]/contraindications OR Dental Materials[mh]/adverse effects OR Dental Materials[mh]/complications OR Dental Materials[mh]/contraindications OR Dental Materials[mh]/poisoning OR Dental Materials[mh]/toxicity**	2570	10:48:53
#38	Add	Search **#32 AND #37**	857	10:48:45

(Continued)

#37	Add	Search **Composite resins[mh] OR composite*[tiab] OR resin[tiab] OR resins[tiab]**	192063	10:48:30
#36	Add	Search **Composite Resins[mh]/adverse effects OR Composite Resins[mh]/contraindications OR Composite Resins[mh]/toxicity**	476	10:48:15
#35	Add	Search **#28 OR #31 OR #34**	1400	10:47:18
#34	Add	Search **#32 AND #33**	536	10:46:55
#33	Add	Search **Dental amalgam[mh] OR Silver[mh] OR Mercury[mh] OR amalgam[tiab] OR amalgams[tiab] OR silver[tiab] OR mercury[tiab]**	116392	10:46:08
#31	Add	Search **#29 AND #30**	986	10:39:36
#30	Add	Search **Silver[mh]/adverse effects OR Silver[mh]/contraindications OR Silver[mh]/toxicity OR Mercury[mh]/adverse effects OR Mercury[mh]/toxicity OR Mercury[mh]/blood OR Mercury poisoning[mh] OR Mercury poisoning, nervous system[mh]**	8327	10:39:26
#29	Add	Search **Dental Restoration, Permanent[mh] OR Dental Restoration, Temporary[mh] OR Dental Materials[mh]/therapeutic use OR Dental Materials[mh]/therapy OR Dental caries[mh]/therapy OR Dental amalgam[mh] OR amalgam[tiab] OR amalgams[tiab] OR dental[tiab] OR dentist*[tiab] OR tooth[tiab] OR teeth[tiab] OR filling*[tiab] OR premolar*[tiab] OR molar*[tiab] OR bicuspid*[tiab] OR incisor*[tiab] OR cuspid*[tiab]**	508967	10:39:18
#28	Add	Search **Dental amalgam[mh]/adverse effects OR Dental amalgam[mh]/contraindications OR Dental amalgam[mh]/poisoning OR Dental amalgam[mh]/toxicity**	392	10:39:10
#27	Add	Search **#18 AND #26**	7588	10:38:47
#26	Add	Search **#19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25**	3573266	10:38:34
#25	Add	Search **warning*[ti] OR recall*[ti] OR withdrawn[ti] OR withdrawal*[ti] OR death[ti] OR deaths[ti] OR fatal[ti] OR fatality[ti] OR fatalities[ti]**	185785	10:37:31
#24	Add	Search **toxic[tiab] OR toxicit*[tiab] OR toxologic*[tiab] OR intoxication[tiab] OR noxious[tiab] OR tolerability[tiab] OR teratogen*[tiab] OR Poison*[tiab]**	699502	10:37:25
#23	Add	Search **(adverse[tiab] OR undesirable[tiab] OR harm*[tiab] OR toxic[tiab] OR injurious[tiab] OR serious[tiab] OR fatal[tiab]) AND (effec-**	767293	10:37:18

(Continued)

		t*[tiab] OR reaction*[tiab] OR event*[tiab] OR outcome*[tiab] OR incident*[tiab])		
#22	Add	Search **side effect[tiab] OR safety[tiab] OR unsafe[tiab]**	484394	10:37:09
#21	Add	Search **Hazard*[ti] OR defect*[ti] OR misuse*[ti] OR failure*[ti] OR malfunction*[ti] OR error*[ti] OR safe*[ti] OR adverse[ti] OR undesirable[ti] OR harm*[ti] OR injurious[ti] OR risk[ti] OR risks[ti] OR reaction*[ti] OR complication*[ti] OR poison*[ti]**	1320653	10:37:01
#20	Add	Search **"Drug-related side effects and adverse reactions"[mh] OR Drug-Induced Liver Injury, Chronic[mh] OR drug hypersensitivity[mh] OR drug recalls[mh] OR safety-based drug withdrawals[mh] OR abnormalities, drug-induced[mh] OR environmental exposure[mh]**	398050	10:36:55
#19	Add	Search **Safety[mh] OR Equipment Safety[mh] OR Equipment Failure[mh] OR Consumer Product Safety[mh:noexp] OR "Product Recalls and Withdrawals"[mh:noexp] OR Medical Device Recalls[mh] OR Safety-Based Medical Device Withdrawals[mh] OR Product Surveillance, Postmarketing[mh:noexp] OR Clinical Trial, Phase IV[pt] OR Clinical Trials, Phase IV as Topic[mh] OR Postoperative Complications[mh] OR Intraoperative Complications[mh]**	692020	10:36:48
#18	Add	Search **#5 OR #17**	64969	10:35:58
#17	Add	Search **#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #15 OR #16**	54639	10:35:24
#16	Add	Search **Compomer*[tiab]**	801	10:33:49
#15	Add	Search **#13 AND #14**	4228	10:33:43
#14	Add	Search **Bisphenol A-Glycidyl Methacrylate[mh] OR alumino silicate polyacrylic acid[tiab] OR "bisphenol A-Glycidyl methacrylate"[tiab] OR Bis-GMA[tiab] OR BisGMA[tiab] OR triethylene glycol dimethacrylate[tiab] OR urethane dimethacrylate*[tiab]**	5131	10:33:29
#13	Add	Search **Dental Restoration, Permanent[mh] OR Dental Restoration, Temporary[mh] OR Dental Materials[mh:noexp]/therapy OR Dental Materials[mh:noexp]/therapeutic use OR Dental caries[mh]/therapy OR composite*[tiab] OR resin[tiab] OR resins[tiab]**	209804	10:33:23
#12	Add	Search **White[tiab] AND filling*[tiab]**	752	10:33:15
#11	Add	Search **(tooth-colored[tiab] OR tooth-coloured[tiab]) AND (filling*[tiab] OR restor*[tiab])**	546	10:33:08

(Continued)

#10	Add	Search **(resin[tiab] OR resins[tiab]) AND (filled[tiab] OR unfilled[tiab] OR synthetic*[tiab] OR dental[tiab] OR restor*[tiab])**	19427	10:33:03
#9	Add	Search **composite*[tiab] AND (poly-acid[tiab] OR polyacid[tiab] OR polyacrylate[tiab] OR poly-acrylic[tiab] OR acrylic[tiab])**	1809	10:32:55
#8	Add	Search **composite*[tiab] AND (resin*[tiab] OR restor*[tiab] OR filling*[tiab] OR dental[tiab] OR dentist*[tiab] OR conventional[tiab] OR microfilled[tiab] OR macrofilled[tiab] OR hybrid[tiab] OR flowable[tiab] OR packable[tiab] OR nanofilled[tiab] OR direct[tiab] OR indirect[tiab] OR small particle*[tiab] OR condensable[tiab] OR bonded[tiab] OR non-bonded[tiab] OR nonbonded[tiab])**	36165	10:32:48
#7	Add	Search **(Dental Restoration, Permanent[mh] OR Dental Restoration, Temporary[mh] OR Dental Materials[mh:noexp]/therapy OR Dental Materials[mh:noexp]/therapeutic use OR Dental caries[mh]/therapy) AND composite*[tiab]**	1569	10:32:40
#6	Add	Search **Composite Resins[mh]**	24218	10:32:32
#5	Add	Search **#1 OR #2 OR #3 OR #4**	13439	10:32:16
#4	Add	Search **(amalgam[tiab] OR amalgams[tiab]) AND (Silver[mh] OR Mercury[mh] OR dental[tiab] OR dentist*[tiab] OR tooth[tiab] OR teeth[tiab] OR silver[tiab] OR mercury[tiab] OR filling*[tiab] OR restor*[tiab] OR premolar*[tiab] OR molar*[tiab] OR bicuspid*[tiab] OR incisor*[tiab] OR cuspid*[tiab])**	7208	10:31:50
#3	Add	Search **(silver[tiab] OR mercury[tiab]) AND (dental[tiab] OR dentist*[tiab] OR tooth[tiab] OR teeth[tiab] OR filling*[tiab] OR premolar*[tiab] OR molar*[tiab] OR bicuspid*[tiab] OR incisor*[tiab] OR cuspid*[tiab])**	4949	10:31:44
#2	Add	Search **(Dental Restoration, Permanent[mh] OR Dental Restoration, Temporary[mh] OR Dental Materials[mh:noexp]/therapy OR Dental Materials[mh:noexp]/therapeutic use OR Dental caries[mh]/therapy) AND (Silver[mh] OR Mercury[mh] OR amalgam[tiab] OR amalgams[tiab] OR silver[tiab] OR mercury[tiab])**	894	10:31:37
#1	Add	Search **Dental amalgam[mh]**	8299	10:31:30

Appendix 7. ClinicalTrials.gov search strategy

Expert search interface:

amalgam AND (resin OR "bisphenol A-Glycidyl methacrylate" OR compomer* OR Bis-GMA OR "enamel bond*" OR "white sealant*" OR Adaptic OR Delton OR Epoxylite-9075 OR Kerr OR Nuva-seal OR Panavia OR Retroplast OR Silux)

Appendix 8. WHO ICTRP search strategy

amalgam AND resin OR amalgam AND "bisphenol A-Glycidyl methacrylate" OR amalgam AND compomer* OR amalgam AND Bis-GMA OR amalgam AND "enamel bond*" OR amalgam AND "white sealant*" OR amalgam AND Adaptic OR amalgam AND Delton OR amalgam AND Epoxylite-9075 OR amalgam AND Kerr OR amalgam AND Nuva-seal OR amalgam AND Panavia OR amalgam AND Retroplast OR amalgam AND Silux

WHAT'S NEW

Date	Event	Description
6 August 2021	New citation required but conclusions have not changed	Conclusions remain the same after the addition of one new efficacy trial and eight new papers assessing safety (drawn from the two parallel-group trials already included in the review).
16 February 2021	New search has been performed	Search modified and updated to 16 February 2021. Additional searches undertaken for the outcome of harms. New review authors added and author order changed.

HISTORY

Protocol first published: Issue 1, 2006
Review first published: Issue 3, 2014

Date	Event	Description
21 May 2014	Amended	Conclusions edited to reflect received feedback.

CONTRIBUTIONS OF AUTHORS

Conceiving the review: María Graciela Rasines Alcaraz (GR), Patrick Roger Schmidlin (PRS)
Co-ordinating the review: GR
Leading the 2021 update: Sara D Khangura (SDK)
Revising the methods for update: SDK, Kelsey Seal (KS), Monika Mierzwinski-Urban (MMU), Helen V Worthington (HW)
Developing search strategy: Dell Davis (DD), MMU
Handsearching of relevant journals: GR
Retrieve from literature references list: GR
Contacting authors: GR
Obtaining and screening data on unpublished studies: Analia Veitz-Keenan (AVK), Philipp Sahrmann (PS), PRS, GR, SDK, KS
Screening search results: AVK, GR, SDK, KS, HW
Screening retrieved papers against inclusion criteria: PS, PRS, SDK, KS
Appraising risk of bias in studies: AVK, PS, PRS, GR, SDK, KS
Extracting data from studies: HW, AVK, PS, PRS, GR, SDK, KS
Entering data into Review Manager 5: GR, HW
Analyses of data: HW, GR, SDK, SMM
Interpretation of data: HW, AVK, PS, PRS, GR, SDK, SMM
Writing the review: HW, AVK, PS, PRS, GR, SDK, ZIE

DECLARATIONS OF INTEREST

Helen V Worthington: none known. I am an Editor (and former Co-ordinating Editor) with Cochrane Oral Health.
Sara D Khangura: none known. I was employed by CADTH when working on the review.
Kelsey Seal: none known. I was employed by CADTH when working on the review.
Monika Mierzwinski-Urban: none known. I was employed by CADTH when working on the review.
Analia Veitz-Keenan: none known.
Philipp Sahrmann: none known

Patrick Roger Schmidlin: none known
Dell Davis: none known
Zipporah Iheozor-Ejiofor: none known. I was employed by Cochrane Oral Health when working on the review.
María Graciela Rasines Alcaraz: none known

SOURCES OF SUPPORT

Internal sources

- Canadian Agency for Drugs and Technologies in Health (CADTH), Canada

  Several members of the author team were employed by CADTH when they worked on this review update.

External sources

- Cochrane Oral Health Group Global Alliance, UK

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- National Institute for Health Research (NIHR), UK

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Differences between the original review and this update

- We updated the Background section.
- We expanded the scope of the review to search specifically for data on harms.
- Typograpical errors in abstract corrected.

Differences between protocol and the original review

- The participant inclusion criterion in the protocol was originally restricted to adults and adolescents. However, we considered tooth type (permanent posterior teeth) as a more important criterion than age group, therefore we included studies on children. We only reported data on permanent posterior teeth in this review.
- We modified the title slightly.
- We could not analyse participant satisfaction, as none of the randomised controlled trials provided data for this variable.
- Partial reporting precluded a calculation of cost-effectiveness.
- In the protocol, survival rate was listed as the primary outcome; however, this review lists failure rate as primary outcome. Failure rate is reported in this review as a proxy for survival rate.
- We had planned to assess potential reporting biases (including publication bias, time lag bias, multiple (duplicate) publication bias, and language bias) by constructing a funnel plot; however, this was not possible as we had fewer than 10 studies.
- Only dichotomous data were available.
- The review used random-effects models, unless there were fewer than four studies, in which case we used fixed-effect models; this was the general policy for Cochrane Oral Health. Our protocol had stated random-effects models only.
- We did not find sufficient data to conduct any of the subgroup or sensitivity analyses we had planned.

NOTES

This is an update of Rasines Alcaraz MG, Veitz-Keenan A, Sahrmann P, Schmidlin PR, Davis D, Iheozor-Ejiofor Z. Direct composite resin fillings versus amalgam fillings for permanent or adult posterior teeth. Cochrane Database of Systematic Reviews 2014, Issue 3. Art. No.: CD005620. DOI: 10.1002/14651858.CD005620.pub2

INDEX TERMS

Medical Subject Headings (MeSH)

Acrylic Resins [adverse effects] [*therapeutic use]; Composite Resins [adverse effects] [*therapeutic use]; Dental Amalgam [adverse effects] [*therapeutic use]; Dental Caries [*therapy]; Dental Restoration Failure; Dental Restoration, Permanent [adverse effects] [*methods]; *Dentition, Permanent; Molar; Polyurethanes [adverse effects] [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Child; Humans