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Outcome and comparator choice in Molar Incisor Hypomineralization (MIH) Intervention Studies: A Systematic Review and Social Network Analysis

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Abstract

Introduction: Outcome and comparator choice strongly determine the validity and implementation of clinical trial results. We aimed to assess outcome and comparator choice in intervention studies on Molar Incisor Hypomineralization (MIH) using systematic review and social network analysis (SNA).

Methods: Medline, Embase, Cochrane Central, Google Scholar, opengrey.eu as well as DRKS.de and Clinicaltrials.gov were searched for MIH intervention studies. The search covered the period from 1980-2018. Clinical single-/multi-arm, controlled/uncontrolled studies reporting on the management of MIH were included. Reported outcomes and comparators were extracted and categorized. SNA was used to evaluate comparator choice and the resulting trial networks .

Results: Of the 6575 identified records, 86 were evaluated in full-text and 25 studies (10 randomized controlled trials, 11 prospective and 4 retrospective cohort studies, respectively) were included. In total, 1113 patients with a mean age of 11 years (min/max 6/70 years) were included. Outcomes fell in one of ten different outcome categories: Restoration success, Aesthetic improvement, Pain and hypersensitivity management, Mineral gain, Space management, Anesthesia effectiveness, Preventive success, Efficiency, Quality of life, Periodontal health. Comparators were mainly restorative interventions (12 studies), remineralization (3), treatment of hypersensitivity (3), esthetic interventions (3), and orthodontic interventions (2). A highly clustered comparator network emerged.

Conclusions: MIH intervention studies recorded both clinically- and patient-centered outcomes. COS development should consider these and supplement them with outcomes on, for example, applicability. The high number of compared interventions tested in only few studies and our SNA results implicate that current evidence may not be robust.

Strengths and limitations of this study

- Outcomes and comparators for MIH studies were assessed.
- A systematic review and network analysis was performed.
- Findings of this study will inform core outcomes definition.

Introduction

There is increasing interest into the internal and external validity of clinical studies, as indicated, for example, by their risk of bias [1 2] or their reporting quality [3]. Two aspects which only recently came into the focus but impact on validity are (1) outcome and (2) comparator choice.

So far, most clinical researchers chose the outcomes based on their understanding of what was relevant or not; the involvement of further stakeholders into outcome choice was seldom considered. This impacts on the relevance of study findings and may limit their applicability. Also, researchers usually collected a range of outcomes, without necessarily reporting all of them later on. This may lead to selective reporting and introduce significant bias. The chosen outcomes and outcome measures may further suffer from limited comparability across studies, decreasing the chance to make the best use of clinical studies by synthezing them. Outcome choice is thus relevant for study validity, applicability and relevance, and implementation into practice [4-6].

Comparator choice impacts on the overall usefulness and validity of evidence [7]. Again, usually, most clinical researchers choose the comparators themselves, without necessarily consulting patients or further stakeholders. Comparators relevant to patients, for example, may hence not be evaluated, and certain comparators may be over-proportionally employed [8-10]. The resulting gaps in the evidence may mean important information on possibly useful comparators are unavailable. Also, comparisons against placebo or no intervention (in single arm studies) or less effective options (so called straw men) can lead to overestimation of effectiveness [9-11]. Repeated chain-linked comparisons against less-than-optimal standards was found to significantly distort the totality of evidence [9-11]. Comparator choice is relevant to make clinical research in a specific field useable, applicable, and informative.

The present study assessed outcome and comparator choice in intervention studies on Molar Incisor Hypomineralisation (MIH), a highly prevalent dental developmental disorder with a significant burden for patients and high treatment needs [12].

Given the broad spectrum of clinical presentations, individual needs and available treatment modalities, managing MIH is challenging for most practitioners [13-15]. Assessing the outcome and comparator choice in MIH intervention studies seems warranted. Such assessment is further useful to inform the development of a Core

Outcome Set (COS) for MIH management and prevention studies. COS are a minimum set of outcomes which have been agreed in a systematic consensus process by a diverse group of stakeholders (patients, dentists, researchers etc). COS overcome the problem of a possibly limited relevance of chosen outcomes, the risk of selective reporting and the lack of synthezizability of study findings [16]. A range of COS development initiatives are currently underway in dentistry [17-21].

We aimed to review the outcomes used in MIH interventional studies to inform the development of a COS on MIH. We further aimed to assess the comparators used in these studies and to analyze the resulting study network. This was done using social network analysis (SNA), a method for evaluating the relationships between actors in a network [8] which has been introduced to dentistry recently [22]. As secondary aim, we evaluated if studies clearly indicated their primary outcome, and used a sample size estimation based on this outcome, and if studies were registered before performing them, as should be expected.

Methods

This review was registered on the COMET initiative website [1]. In parts, it builds on a previously published review on MIH management [23].

Search strategy

The following search was adapted for each database:

(((((treatment) OR management) OR prevention) AND molar incisor hypomineralisation) OR molar incisor hypomineralization) OR mih.

Searches were developed and run individually for Medline, Embase, Cochrane Central, Google Scholar, opengrey.eu as well as DRKS and Clinicaltrials.gov and cross references were performed without any language restrictions. The search covered the period from 01.01.1980 to 15.05.2018 (Fig. 1).

Data collection

Inclusion criteria: We included clinical studies in patients diagnosed with MIH. Studies reported on prevention and/or management interventions for MIH teeth. There were no restrictions on setting, time of follow-up, or age.

Selection process: Two authors (FS, KE) screened titles independently and compared their findings. In case of disagreement, titles were included to obtain full-texts. Full-texts were assessed independently after de-duplication. In cases of disagreement, studies were included after consensus was reached through discussion.

Data extraction: The following data was extracted duplicatively and independently by two authors (KE and FS) following calibration using a pilot database:

- Study details (author name, title, journal, year of publication);
- Study characteristics;
    - Study setting (primary or secondary care)
    - Number and age of participants
    - Study type (controlled or uncontrolled, pro- or retrospective)
    - Target condition (MIH lesions on molars, incisors, or both)
    - Number of study arms
    - Interventions compared
    - Follow-up period
    - Outcomes assessed, separated for primary and secondary outcome(s). An outcome was considered a primary outcome if it was stated as such, or where the report clearly focused on one outcome. If no primary outcome was identifiable or multiple outcomes were reported, these were considered secondary outcomes.
    - Outcome measures
- Sample size estimation (reported/not)
- Trial registration (yes/no).

Data synthesis

A list of outcomes was compiled and outcomes with different verbatim terms but similar meanings gathered using a single agreed term. Outcomes were grouped within outcome categories; these were refined through group discussion before all outcomes were categorized using the final agreed terms. The final list of outcome categories

comprised 10 items; Restoration success, Aesthetic improvement, Pain and hypersensitivity management, Mineral gain, Space management, Anesthesia effectiveness, Preventive success, Efficiency, Quality of life and Periodontal health. The use of different outcome categories was analyzed via descriptive statistics. Exemplary outcomes and outcome measures were allocated to one of these outcome categories by discussion and agreement of two authors (KE and FS). Where there was disagreement, consensus was achieved through discussion with all authors.

A list of comparators was compiled and comparators grouped into agreed categories (Table 2). The granularity of these categories allowed to capture specific comparators (like “glass ionomer cement restoration”) while grouping similar comparators in the same category (e.g. different cement brands). Comparator choice was analyzed via SNA. In SNA, nodes (termed ‘vertices’) are formed by comparators, and are connected by edges (comparisons made within the same trial). In a graphical analysis, the node diameter represents the number of comparator arms forming the node and thickness of edges represents the number of direct comparisons. We also color-coded edges for studies on MIH in molars versus incisors. Statistical analysis included the assessment of the degree (average number of comparators per node) and the clustering coefficient (values of one indicate that all possible connections were made, while values of 0, indicate that only the minimum number of connections were made) [24-26]. Graphical analysis was performed using Cytoscape 3.4.0 (National Institute of General Medical Sciences, Bethesda, USA), while for statistical analysis the Python package NetworkX was used.

Patient and Public Involvement

Patients were not involved in this study at this point, but will so in the core outcomes definition.

Results

Included studies

The database search yielded 6575 records; 3117 remained after de-duplication. There were 86 potentially relevant articles and the full texts of all these 86 articles were located (100% retrieval rate); 25 met the inclusion criteria and were incl10uded (Fig. 1).

Characteristics of included trials

Of the 25 included studies, all (100%) were conducted in a secondary care setting (hospital or university). The total numbe11r of participants was 1113; per study a mean of 45 (range 12 – 300) participants were included. Only children (mean age <12 years) were included in 23 included reports (92%). Only one (4%) study reported on adults, too (mean age 33 years). In another publication (4%) it was not possible to determine the age of the participants. There were 8 (32%) one-arm studies, 12 (48%) two-arm studies, 2 (8%) three-arm studies, and 3 (12%) multi-arm studies. Further details on the included studies can be found in Table 1.

Outcome choice

As mentioned, ten outcome categories were deduced from the included studies (Fig. 2). The most frequent specific categories were “Restoration success” and “Pain and hypersensitivity management”; with 12 (35%) and 5 (15%) studies reporting them, respectively. The next most common were “Aesthetic improvement” (4, studies 12%), “Mineral gain” (3 studies, 9%), and “Space management”, “Anesthesia effectiveness” and “Preventive success” (each 2 studies, or 6%). The least common ones were “Quality of life”, “Efficiency” and “Periodontal health” (each only 1 study, or 3%). Outcome categories that have increased in use (from 2000-2009 to 2010-2018) included “Aesthetic improvement”, “Mineral gain”, “Efficiency”, and “Periodontal health”.

Comparator choice

A well connected network of comparators emerged (Fig. 3). Certain comparators were more frequently chosen than others. Comparisons in MIH molars dominated the network. Many studies compared different restorative strategies for MIH molars, normaly composite (with different brands also tested against each other), metal, ceramic or cement restorations. The network graph also highlights that many studies had no comparator, i.e. were single-armed. Hence, the connectivity of the study network is even lower than indicated by the SNA. The median degree was seven,

ranging between 1 and 9. The cluster coefficient was 0.69, indicating that there were "cliques" of comparators present, with comparators being mainly compared within and not across these cliques.

Primary outcome and sample size calculation

Primary outcomes could be identified in 24 (96%) reports (Table 3). Throughout all years (2000 to 2018), "Restoration success" was the most frequently assessed primary outcome (12). In contrast, "Pain and hypersensitivity management" was not measured as a primary outcome in any study between 2000-2009, and in only 3 studies (11%) between 2010 and 2018.

Information on sample size calculation was provided in 4 (16%) reports, all four being published between 2016 and 2018. Of the 4 reports which had a sample size calculation, 2 (50%) related this calculation to the primary outcome.

Trial registration reporting

Only 4 (16%) of all articles reported a trial registration [27]. In the 10 years following the publication of the first CONSORT statement (2001-2010), not a single report included a trial registration. Following the publication of the second CONSORT statement (2011-2018), this increased to 16%.

Discussion

This systematic review assessed outcome and comparator choice in MIH intervention studies, and their change over time. We found that studies recorded a large range of outcomes, especially when considering the limited number of studies overall, and that the diversity of these outcomes is increasing. This is reassuring, and the findings of this review are helpful to develop a COS. We also found that despite the low number of studies available, a large range of different interventions were tested, which led to a highly clustered and not well connected network. This highlights that the current body of evidence on MIH interventions is likely not robust, and may change with more studies coming in (strengthening the network).

The outcomes used in MIH intervention studies focused on two areas; restoration success (measured via the USPHS criteria or similar tools) and pain and hypersensitivity management (measured via scales like the Visual analogue scale or the Schiff Cold Air Sensitivity Scale). Combined, these two areas accounted for 45% of primary outcomes and for 50% of all reported outcomes. However, the use of other outcome categories like quality of life and economic aspects appears to be of growing, reflecting an ongoing shift to patient-centered care (and research) and the increasing relevance of health economics in today's resource-limited healthcare settings. We will, in the next stage of our COS development, suggest these outcomes to be included in the COS on MIH intervention studies, and will seek stakeholder consensus on their inclusion (or not).

We also investigated further outcome-related aspects in the included studies. For example, trial registration, one of the recommendations of the CONSORT statement [28 29], was found in only four studies (and even very recent studies did not commonly report on this). While such registration may be seen as a prerogative of controlled trials, also single-arm prospective trials, for example, should clearly state what is to be investigated using which methods and tools in what population before commencing the study. This does not seem to be the case. Registration would help to reduce selective outcome reporting and could also assit in improving reporting standards (and general methodology) in MIH intervention studies.

Also, of the 25 reports, only 4 studies reported a sample size calculation, and of these, only 2 related this to the primary outcome. Again, while such calculations are mainly demanded for controlled prospective trials, researchers should have a rational basis for calculating the number of participants needed in any study (regardless of its design), be it to ascertain that differences between the interventions can be detected with a planned level of statistical confidence or be it to reduce statistical noise (allowing somewhat firm conclusions). Sample size calculation is a key recommendation in the CONSORT statement, published in 2001 [29] and revised in 2010 [28]. It was promising to find that, since this revision, more publications reported on a sample size calculation (while the overall number of remained low).

Our network analysis indicated a network with limited connectivity, but high clustering. The limited connectivity was grounded in a relatively high number of comparators being tested in only few studies and comparisons. In addition, and not captured by the

SNA, sample sizes were limited (the median was only 33). Clustering indicates the existence of cliques of comparators, with comparisons being conductred mainly within a subgroup of comparators. This decreases the overall information of comparisons across all interventions. Of course, this may be grounded in indications. For example, restorative interventions will usually be compared only against each other, as they will only be applied if non-restorative strategies are not an option. This was also the case here. Moreover, we found clustering along study focus, i.e. the management of molars (focusing largely on hypersensitivity or post-eruptive breakdown) and incisors (often involving interventions to improve the aesthetic appearance).

This study has a number of limitations. First, the effort to improve COS methodology is ongoing, and our review used only one of several available strategies suggested for COS developers. For example, it seems that to reach saturation on outcomes and outcome categories, it may not be necessary to search multiple databases [30], while we did so, also as this review was an update of a previous one and we aimed to apply the same methodology. Second, developing outcome categories and assigning specific verbatim outcomes to these categories is challenging [19], often as outcomes are either inter-related or composites, capturing different outcome categories [31]. While there is no acknowledged MIH outcome classification system, it is clear that alternative classifications may have resulted in changes to the granularity and focus of the results. Third, researchers tend to publish multiple from the same clinical trial [32]. This can be necessary to report on the dataset at different time points, or to report on multiple analyses. However, data is then divided across multiple publications, and linking articles together or with registered protocols can be difficult. We assume to have captured all articles accordingly given the field to be limited. Last, in order to limit selective outcome bias and in the attempt of including the most recent trials, registries were searched in our study, too. This however, has its limitations, since there are often incomplete or unclear registrations, and we were only limitedly able to extract data.

Conclusions

Outcomes reported in interventional trials for the management and prevention of MIH focused on the performance of restorative materials or and the management of pain and hypersensitivity associated with MIH-affected teeth. Outcomes related to oral-

health related quality of life and economics have grown in use and are likely to be important in the future. Patient-reported or patient-centered outcomes were rarely reported. COS development should include these and be supported by new outcomes, e.g. on applicability. The high number of compared interventions tested in only few studies and our SNA results implicate that current evidence may not be robust.

Trial status (Registration):

COMET initiative online http://www.comet-initiative.org/studies/details/1155 [1]

Competing interests

The authors declare no conflict of interest.

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No funding was acquired.

Ethical approval

Not applicable.

Author contributions

The study was conceived by KE and FS. KE and JK analyzed, interpreted the data. KE, P-G J-B and FS wrote the manuscript. All authors read and approved the manuscript.

Transparency declaration

The lead author* affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Table 1. Characteristics of included studies (n = 25). Studies were separated according to target condition (MIH in molars or incisors), and ordered chronologically.

Author	Year	Setting	N part.	Age	Study type	Follow-up (months)	Trial reg.	No. Of Arms	P Cal.
Molars									
Koch and Garcia-Godoy [33]	**2000**	Uni. H	12	6-8	Pro Co	24-60	n	3	n
Lygidakis et al. [34]	**2003**	Uni. H	46	8-10	Pro Co	48	n	1	n
Zagdwon et al. [35]	**2003**	Uni. H	17	6-16	RCT	12-24	n	2	y
Kotsanos et al. [36]	**2005**	Uni. H	72	8	Retro Co	52	n	2	n
Mejare et al. [37]	**2005**	Uni. H	76	6-17	Retro Co	62	n	7	n
Jalevik and Moller [38]	**2007**	Uni. H	27	6-13	Retro Co	44-99	n	1	n
Lygidakis et al. [39]	**2009**	Uni. H	47	6-7	RCT	48	n	2	n
Baroni and Marchionni [40]	**2011**	Uni. H	30	6-9	Pro Co	36	n	1	n
Gaardmand et al. [41]	**2013**	Uni. H	33	8-18	Retro Co	39	n	1	n
Cabasse et al. [42]	**2015**	Uni. H	39	9	Pro Co	n	n	1	n
Fragelli et al. [43]	**2015**	Uni. H	21	6-9	Pro Co	12	n	1	n
Bekes et al. [44]	**2016**	Uni. H	16	8	Pro Co	2	n	2	y
Bakkal et al. [45]	**2017**	Uni. H	38	7-12	RCT	1	n	2	n
de Souza et al. [46]	**2017**	Uni. H	18	6-8	RCT	18	y	2	n
Fragelli et al. [47]	**2017**	Uni. H	21	6-8	RCT	18	n	2	y
Sönmez and Saat [48]	**2017**	Uni. H	42	8-12	RCT	24	n	4	n
Grossi et al. [49]	**2018**	Uni. H	40	7-13	Pro Co	12	y	1	n
Koleventi et al. [50]	**2018**	Uni. H	14	11	Pro Co	6	n	2	n
Pasini et al. [51]	**2018**	Uni. H	40	8-13	Pro Co	4	n/a	2	n/a
Incisors									
Wong and Winter [52]	**2002**	Uni. H	15	n/a	RCT	6	n	1	n
Özgül et al [53]	**2013**	Uni. H	33	7-12	RCT	1	n	6	n
Sheoran et al. [54]	**2014**	Uni. H	25	11-13	RCT	1	n	2	n
Restrepo et al. [55]	**2016**	Uni. H	51	9-12	Pro Co	1	n	2	y
Only Registered									
DRKS00009760	**2016**	Uni. H	40	6-70	RCT	6	y	2	N
DRKS00011882	**2017**	Uni. H	300	7-14	Pro Co	0,5	Y	3	Y

Abbreviations: N of part., number of participants; n/a, not available; Pro Co, prospective cohort; Retro Co, retrospective cohort; RCT, randomized control trial; Uni. H, University hospital; Trial reg., trial registration, P Cal., power calculation; n, no; y, yes

Table 2. Reported outcomes and outcomes measurement instrument within different outcome categories, ordered according to frequency of use in included studies.

Outcome category	Outcome examples	Exemplary outcome measures
Restoration success	Clinical performance Restoration quality Survival of tooth and restoration	Modified US Public Health Service (USPHS) criteria Modified atraumatic restorative treatment (ART) criteria Radiographic evaluation (Bitewings) Number of reinterventions Survival rate
Pain and hypersensitivity management	Response to stimulus	Schiff Cold Air Sensitivity Scale (SCASS) Questionnaires
Aesthetic improvement	Aesthetic improvement	Questionnaires Clinical photography
Mineral gain	Mineral gain	Laserfluorescence readings Scanning electron microscope (SEM)/ Energy Dispersive X-ray Spectrometry (EDX) Quantitative Light-Induced Fluorescence (QLF)
Space management	Space closure after extraction Need of orthodontic intervention	Amount of spontaneous space closure
Anesthesia effectivness	Anesthesia technique Need for local anesthesia	Presence of pain during treatment
Preventive success	Clinical performance Sealant quality Ability to prevent caries and enamel breakdown	Success/ Modified US Public Health Service (USPHS) criteria
Efficiency	Costs of treatment	Placement time Used materials Laboratory costs
Quality of life	Oral health-related quality of life (OHRQoL)	Self-administered oral health related quality of life (OHRQoL) questionnaires (COHIP G-19, CPQ 8-10, CPQ 11-14)
Periodontal health	Presence of gingivitis and periodontitis Oral hygiene Subgingival microbiota	Gingival index (GI) Pocket depth (PD) Turesky plaque index Checkerboard DNA-DNA hybridization

Table 3. Primary and secondary outcomes reported in each study.

Author (year)	Restoration success	Pain and hypersensitivity management	Aesthetic improvement	Mineral gain	Space management	Anesthesia effectivness	Preventive success	Efficiency	Quality of life	Periodontal health
Koch and Garcia-Godoy (2000) [33]	x									
Wong and Winter (2002) [52]			x							
Lygidakis et al. (2003) [34]	x	♦					♦			
Zagdwon et al. (2003) [35]	x							♦		
Kotsanos et al. (2005) [36]	x				♦					
Mejare et al. (2005) [37]	x				♦					
Jalevik and Moller (2007) [38]					x					
Lygidakis et al. (2009) [39]	x									
Baroni and Marchionni (2011) [40]				x						
Gaardmand et al. (2013) [41]	x									
Özgül et al (2013) [53]		x								
Sheoran et al. (2014) [54]			x							
Cabasse et al. (2015) [42]						x				
Fragelli et al. (2015) [43]	x									
Bekes et al. (2016) [44]		x								
DRKS00009760 (2016)			x							
Restrepo et al. (2016) [55]				x						
Bakkal et al. (2017) [45]				x						
de Souza et al. (2017) [46]	x									
DRKS00011882 (2017)									x	
Fragelli et al. (2017) [47]	x						x			
Sönmez and Saat (2017) [48]	x		♦							
Grossi et al. (2018) [49]	x	♦				♦				
Koleventi et al. (2018) [50]										x
Pasini et al. (2018) [51]		x								

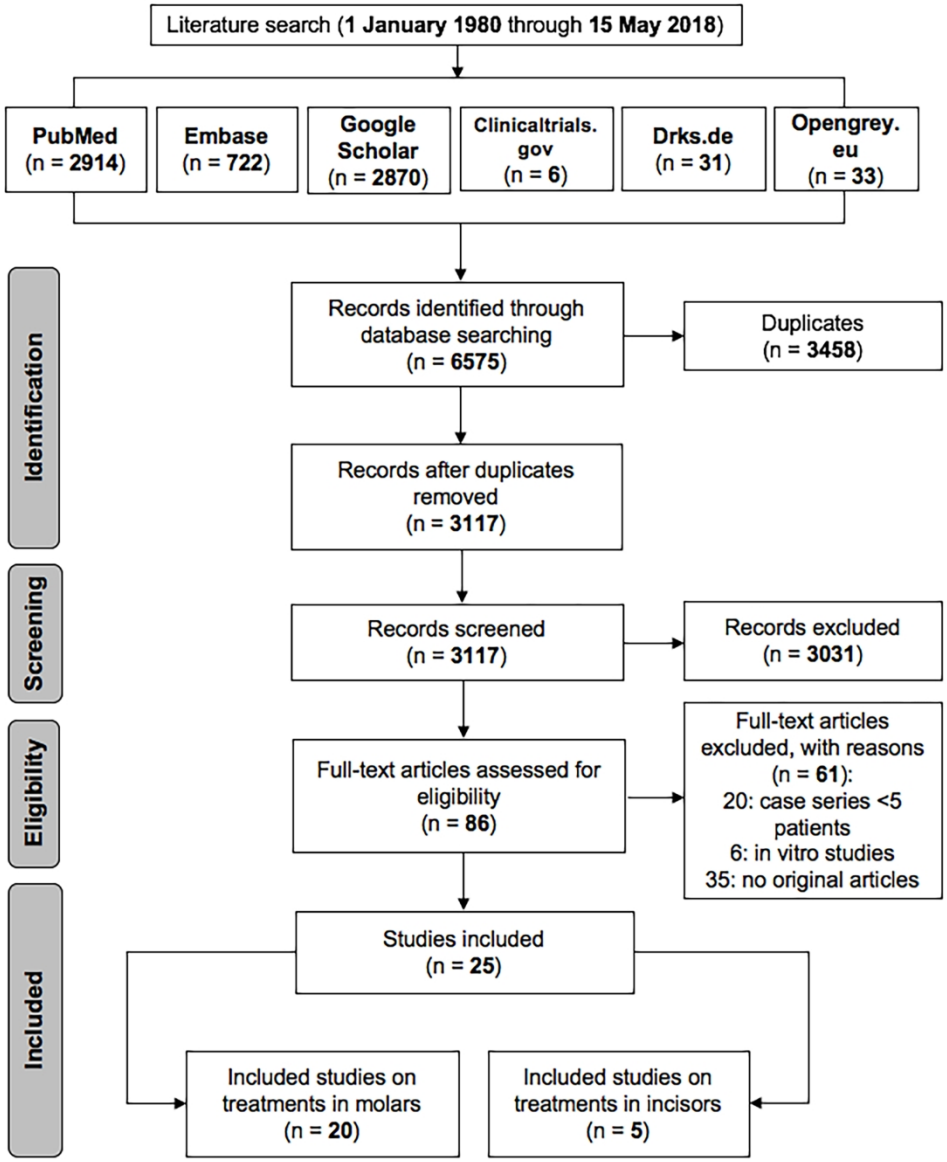
x, primary outcome; ♦, secondary outcome

Figure legends:

Figure 1. Flow chart of the search.

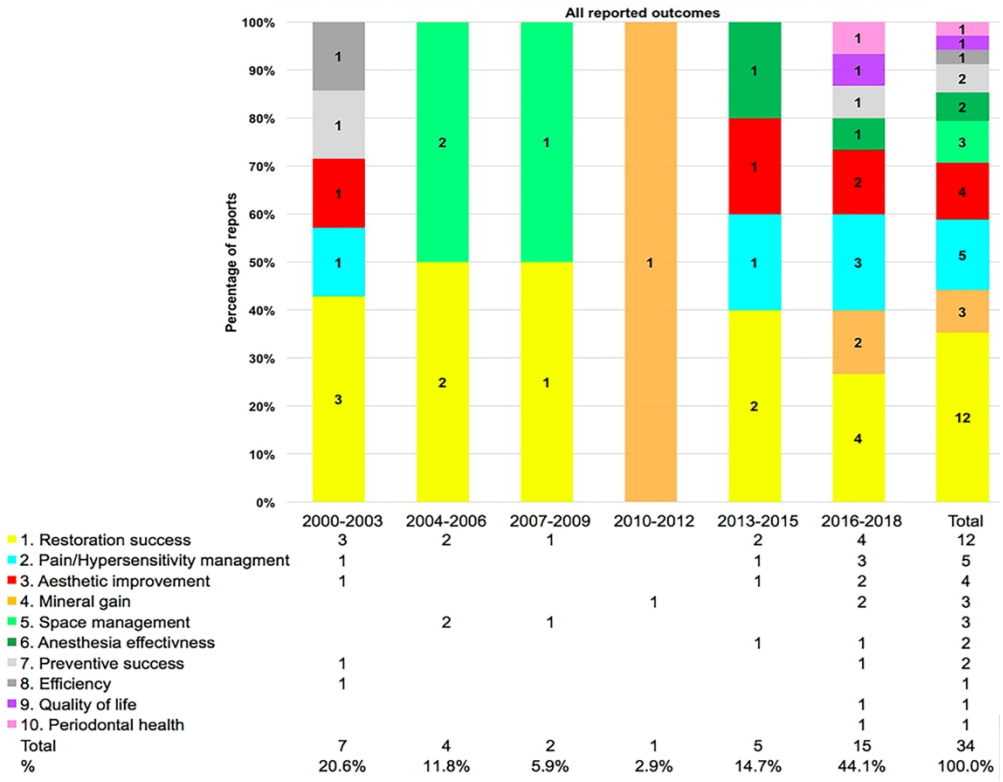
Figure 2. Reported outcomes for MIH intervention studies over time. N number of studies using this outcome in the specific period.

Figure 3. Networks of different comparisons. Different comparators (nodes) were compared directly with each other (edges, colored according to target condition; pink: MIH lesions in incisors, violet: MIH lesions in molars). The node diameter represents the number of studies involving this comparator, the thickness of the edge the number of direct comparisons between two comparators. Certain comparators were not connected to the main network.



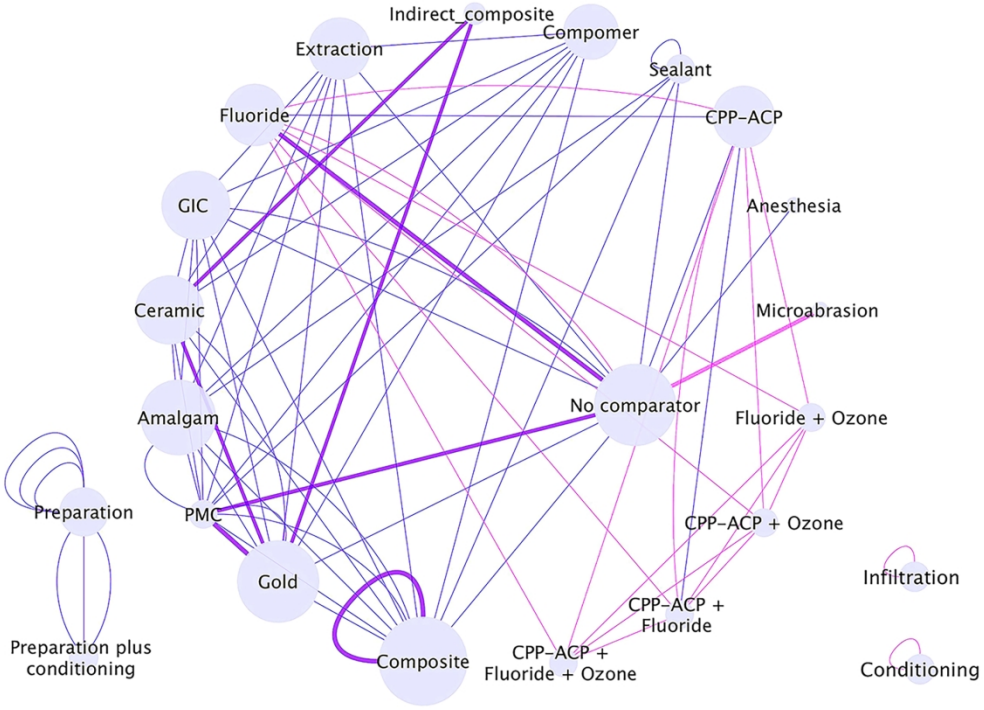
Flow chart of the search.

238x282mm (300 x 300 DPI)



Reported outcomes for MIH intervention studies over time. N number of studies using this outcome in the specific period.

360x280mm (300 x 300 DPI)



Networks of different comparisons. Different comparators (nodes) were compared directly with each other (edges, colored according to target condition; pink: MIH lesions in incisors, violet: MIH lesions in molars). The node diameter represents the number of studies involving this comparator, the thickness of the edge the number of direct comparisons between two comparators. Certain comparators were not connected to the main network.

209x152mm (300 x 300 DPI)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4-6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4-5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5-6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	-
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	-
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	-
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	-
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8-10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	-
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	11

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Outcome and comparator choice in Molar Incisor Hypomineralization (MIH) Intervention Studies: A Systematic Review and Social Network Analysis

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Keywords:	Systematic review, Molar incisor hypomineralization, core outcome set, MIH, prevention, management

Outcome and comparator choice in Molar Incisor Hypomineralization (MIH) Intervention Studies: A Systematic Review and Social Network Analysis

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Keywords

Systematic review, molar incisor hypomineralization, core outcome set, outcomes, MIH, prevention, management, intervention

Tables: 3

Figures: 4

Abstract

Objectives: Outcome and comparator choice strongly determine the validity and implementation of clinical trial results. We aimed to assess outcome and comparator choice in intervention studies on Molar Incisor Hypomineralization (MIH) using systematic review and social network analysis (SNA).

Design and data sources: Medline, Embase, Cochrane Central, Google Scholar, opengrey.eu as well as DRKS.de and Clinicaltrials.gov were searched for MIH intervention studies. The search covered the period from 1980-2019.

Eligibility criteria: Clinical single-/multi-arm, controlled/uncontrolled studies reporting on the management of MIH were included. Reported outcomes and comparators were extracted and categorized. SNA was used to evaluate comparator choice and the resulting trial networks.

Data extraction: Of the 7979 identified records, 100 were evaluated in full-text and 35 studies (17 randomized controlled trials, 14 prospective and 4 retrospective cohort studies) were included.

Results: In total, 2124 patients with a mean age of 11 years (min/max 6/70 years) were included. Outcomes fell in one of 11 different outcome categories: Restoration success, Aesthetic improvement, Pain/ hypersensitivity/ discomfort, Mineral gain, Space management, Anesthesia effectiveness, Preventive success, Efficiency, Quality of life, Gingival and periodontal health and Patient satisfaction. Comparators were mainly restorative interventions (17 studies), remineralization (3), treatment of hypersensitivity (10), esthetic interventions (5), and orthodontic interventions (3). Two highly clustered comparator networks emerged; many interventions were not robustly linked to these networks.

Conclusions: MIH intervention studies recorded both clinically- and patient-centered outcomes. Core Outcome Set (COS) development should consider these and supplement them with outcomes on, for example, applicability. The high number of compared interventions tested in only few studies and our SNA results implicate that the current evidence may not be robust.

Strengths and limitations of this study

- Molar incisor hypomineralization (MIH) is a frequent condition. No core outcome set on MIH exists.
- Outcomes and comparators for MIH studies were assessed using a systematic review.
- A network analysis was performed to evaluate the robustness of comparisons.
- The findings of this study will aid in core outcomes definition.
- The available body of evidence is limited and likely not robust.

Introduction

There is increasing interest into the internal and external validity of clinical studies, as indicated, for example, by their risk of bias [1 2] or their reporting quality [3]. Two aspects which only recently came into the focus, but impact on validity are (1) outcome and (2) comparator choice.

So far, most clinical researchers chose the outcomes based on their understanding of what was relevant or not; the involvement of further stakeholders into outcome choice was seldom considered. This impacts on the relevance of study findings and may limit their applicability. Also, researchers usually collected a range of outcomes, without necessarily reporting all of them later on (selective reporting); mainly as data on outcomes with unwanted findings (which may nevertheless be relevant) can be omitted. The chosen outcomes and outcome measures may further suffer from limited comparability across studies, decreasing the chance to make the best use of clinical studies by synthesizing them. Outcome choice is thus relevant for study validity, applicability, and relevance, and implementation into practice [4-6].

Comparator choice impacts on the overall usefulness and validity of evidence [7]. Again, usually, most clinical researchers choose the comparators themselves, without necessarily consulting patients or further stakeholders such as insurers, regulators etc. Comparators relevant to patients, for example, may hence not be evaluated, and certain comparators may be over-proportionally employed [8-10]. The resulting gaps in the evidence may mean important informations on possibly useful comparators are unavailable. Also, comparisons against placebo or no intervention (in single arm studies) or less effective options (so called straw men) can lead to overestimation of effectiveness [9-11]. Repeated chain-linked comparisons against less-than-optimal standards was found to significantly distort the totality of evidence [9-11]. Comparator choice is relevant to make clinical research in a specific field useable, applicable, and informative.

The present study assessed outcome and comparator choice in intervention studies on Molar Incisor Hypomineralisation (MIH), a highly prevalent dental developmental disorder with a significant burden for patients and high treatment needs [12]. MIH is characterized by demarcated creamy-white, yellowish-brown or brown lesions with or without posteruptive enamel breakdown and hypersensitivity, affecting the permanent

molars with or without additional affection of the incisors [13-15]. The severity of the lesions, the symptomatology of the affected tooth as well as the patient's dental age, caries risk and expectations need to be considered in the management of MIH [15]. Dentists oftentimes need to employ different treatment strategies when dealing with MIH patients, including restoring cavities, alleviating pain or improving aesthetics [16], [17]. Given the broad spectrum of clinical presentations, individual needs and available treatment modalities, managing MIH is challenging for most practitioners [13-15].

Assessing the outcome and comparator choice in MIH intervention studies seems warranted. Such assessment is further useful to inform the development of a Core Outcome Set (COS) for MIH management and prevention studies. COS are a minimum set of outcomes which have been agreed in a systematic consensus process by a diverse group of stakeholders (patients, dentists, researchers, insurance companies etc). COS overcome the problem of a possibly limited relevance of chosen outcomes, the risk of selective reporting and the lack of synthesizability of study findings [18]. A range of COS development initiatives are currently underway in dentistry [19-23].

We aimed to review the outcomes used in MIH intervention studies to inform the development of a COS on MIH. We further aimed to assess the comparators used in these studies and to analyze the resulting study network. This was done using social network analysis (SNA), a method for evaluating the relationships between actors in a network [8], which has been introduced to dentistry recently [24]. As secondary aim, we evaluated if studies clearly indicated their primary outcome, if studies used a sample size estimation based on this outcome, and if studies were registered a priori, as should be expected.

Methods

This review was registered on the Core Outcome Measures in Effectiveness Trials (COMET) initiative website [1]. In parts, it builds on a previously published review on MIH management [25].

Search strategy

The following search was adapted for each database:

(treatment OR management OR prevention) AND (molar incisor hypomineralisation OR molar incisor hypomineralization OR mih).

Searches were developed and run individually for Medline, Embase, Cochrane Central, Google Scholar, opengrey.eu as well as DRKS and Clinicaltrials.gov and cross references were performed without any language restrictions. The search covered the period from 01.01.1980 to 03.04.2019 (Fig. 1).

Data collection

Inclusion criteria: We included all types of clinical studies (retrospective or prospective, controlled trials or cohort studies) in patients diagnosed with MIH. Note that studies conducted before 2001 on the condition will not have employed the term “MIH”, and may have been missed by our search. This, however, was accepted, as without a clear case definition, other conditions may have be captured by these studies too, without being able to separate conditions post hoc. Studies reported on prevention and/or management interventions for MIH teeth. There were no restrictions on setting, time of follow-up, or patients’ age. Case reports or case series with a sample size of < 10 participants were excluded. No language restriction was set; studies in languages other than English, German or Arabic (if present) were translated by native speakers. Selection process: Two authors (FS, KE) screened titles independently and compared their findings. In case of disagreement, titles were included to obtain full-texts. Full-texts were assessed independently after de-duplication. In cases of disagreement, studies were included after consensus was reached through discussion.

Data extraction: The following data was extracted duplicatively and independently by two authors (KE and FS) following calibration using a pilot database:

- Study details (author name, title, journal, year of publication);
- Study characteristics;
    - Study setting (primary or secondary care)
    - Number and age of participants
    - Study type (controlled or uncontrolled, pro- or retrospective)
    - Target condition (MIH lesions on molars, incisors, or both)
    - Number of study arms

- Interventions compared
- Follow-up period
- Outcomes assessed, separated for primary and secondary outcome(s). An outcome was considered a primary outcome if it was stated as such, or where the report clearly focused on one outcome. If no primary outcome was identifiable or multiple outcomes were reported, these were considered secondary outcomes.
- Outcome measures

- Sample size estimation (yes/no)
- Trial registration (yes/no).

Data synthesis

A list of outcomes was compiled and outcomes with different verbatim terms but similar meanings gathered using a single agreed term. Outcomes were grouped with in outcome categories; these were refined through group discussion before all outcomes were categorized using the final agreed terms. The final list of outcome categories comprised 11 items; Restoration success, Aesthetic improvement, Pain and hypersensitivity management, Mineral gain, Space management, Anesthesia effectiveness, Preventive success, Efficiency, Quality of life, Gingival and Periodontal health, and Patient satisfaction. The use of different outcome categories was analyzed via descriptive statistics. Exemplary outcomes and outcome measures were allocated to one of these outcome categories by discussion and agreement of two authors (KE and FS). Where there was disagreement, consensus was achieved through discussion with all authors.

A list of comparators was compiled and comparators were grouped into agreed categories. The granularity of these categories allowed to capture specific comparators (like “glass ionomer cement restoration”) while grouping similar comparators in the same category (e.g. different cement brands). Comparator choice was analyzed via SNA. In SNA, nodes (termed ‘vertices’) are formed by comparators, and are connected by edges (comparisons made within the same trial). In a graphical analysis, the node diameter represents the number of comparator arms forming the node and thickness of edges represents the number of direct comparisons. We

performed separate analyses (and graphic representations) for studies on MIH in molars versus incisors. Statistical analysis included the assessment of the degree (average number of comparators per node) and the clustering coefficient (values of one indicate that all possible connections were made, while values of 0 indicate that only the minimum number of connections were made) [26-28]. Statistical analysis was only performed for the main network in each sub-analysis (molars; incisors). The Python package NetworkX was used.

Patient and public involvement

Patients were not involved in this study at this point, but will be during the core outcomes definition.

Results

Included studies

The database search yielded 7979 records; 4106 remained after de-duplication. There were 100 potentially relevant articles and the full texts of all these 100 articles were located (100% retrieval rate); 35 met the inclusion criteria and were included (Fig. 1).

Characteristics of included trials

Of the 35 included studies, all (100%) were conducted in a secondary care setting (hospital or university). The total number of participants was 2124; per study a mean of 60 (range 12 – 300) participants were included. Only children (mean age < 12 years) were included in 33 included reports (94%). Only one (3%) study reported on adults (mean age 33 years). In two other publications (6%) it was not possible to determine the age of the participants. There were 10 (29%) one-arm studies, 18 (51%) two-arm studies, 3 (9%) three-arm studies, and 4 (11%) multi-arm studies. Further details on the included studies can be found in Table 1.

Outcome choice

In total, 11 outcome categories were deduced from the included studies (Fig. 2, Table 2). The most frequent specific categories were “Restoration success” and “Pain/ discomfort/ hypersensitivity”; with 17 (49%) and 12 (34%) studies reporting them, respectively. The next most common were “Quality of life” and “Efficiency” (each 5 studies, 14%); “Aesthetic improvement” and “Preventive success” (4 studies, 11%); “Mineral gain”, “Space management” and “Anesthesia effectiveness” (each 3 studies, 9%). The least common ones were “Patient satisfaction” and “Gingival and periodontal health” (each 2 studies, or 6%). Outcome categories that have increased in use (from 2000-2009 to 2010-2018) included “Aesthetic improvement”, “Mineral gain”, “Efficiency”, and “Gingival and periodontal health”.

Findings for molars

For molars, 10 outcome categories were identified from the included studies. Those were: “Restoration success” with a total of 17/28 studies reporting on it (15/17 as primary outcome and 2/17 as secondary outcome); “Pain/discomfort/hypersensitivity” with a total of 12/28 studies reporting on it (4/12 as primary outcome and 8/11 as secondary outcome); “Quality of life” with a total of 5/28 studies reporting on it (2/5 as primary outcome and 3/5 as secondary outcome); “Efficiency” with a total of 5/28 studies reporting on it (1/5 as primary outcome and 4/5 as secondary outcome); “Preventive success” with a total of 4/28 studies reporting on it (3/4 as primary outcome and 1/4 as secondary outcome); “Anesthesia effectiveness” with a total of 3/28 studies reporting on it (2/3 as primary outcome and 1/3 as secondary outcome); “Space management” with a total of 3/28 studies reporting on it (1/3 as primary outcome and 2/3 as secondary outcome); “Mineral gain” with a total of 2/28 studies reporting on it (all as primary outcome); “Gingival and periodontal health” with a total of 2/28 studies reporting on it (1/2 as primary outcome and 1/2 as secondary outcome); “Patient satisfaction” with a total of 2/28 studies reporting on it (all as secondary outcome).

Findings for incisors

For incisors, only four outcome categories were identified from the included studies. Those were: “Aesthetic improvement” with a total of 4/7 studies reporting on it (all as primary outcome); “Pain/discomfort/hypersensitivity” with a total of 1/7 study reporting on it (as primary outcome); “Quality of life” with a total of 1/7 study reporting on it (as primary outcome); “Mineral gain” with a total of 1/7 study reporting on it (as primary outcome).

Comparator choice

Two separate analyses on comparator choice were performed; one for studies on molars and one on incisors. In both groups, a loosely connected main network and a number of further, unconnected networks or comparators were present, indicating poor connectivity between comparators (Figs. 3 and 4). Certain comparators were more frequently chosen than others.

In molars (Fig. 3), many studies compared different restorative strategies, for example composite (with different brands also tested against each other), metal, ceramic or cement restorations. Further comparisons, non-connected to this main (restorative) network, involved caries preventive interventions, management of hypersensitivity, and cavity preparation and condition techniques. The mean degree of the main, restorative network was 5.9, with a density of 0.49. The cluster coefficient (which ranges from 0 – no clustering – to 1 – maximum clustering) was 0.76, indicating that there was significant clustering, with certain comparators being compared with each other (in “cliques”), while other possible comparisons (against comparators outside of these cliques) not having been made.

In incisors (Fig. 4), a main network, comparing different remineralization strategies, emerged, with two further networks and two further, non-connnected comparators on aesthetic management of MIH. The mean degree of the main (remineralization) network was 5, with a density of 1.0. The cluster coefficient was 1.0, indicating that there were “cliques” of comparators present, with comparators being mainly compared within and not across these cliques.

Primary outcome and sample size calculation

Primary outcomes could be identified in all 35 (100%) reports (Table 3). Throughout all years (2000 to 2019), "Restoration success" was the most frequently assessed primary outcome (17/35). Information on sample size calculation was provided in 7 (20%) reports, all but one being published between 2016 and 2019. Of these 7 reports, 5 (71%) related this calculation to the primary outcome.

Trial registration reporting

Only 10 (29%) of all articles reported a trial registration [29]. In the 10 years following the publication of the first CONSORT statement (2001-2010), not a single report included a trial registration. Following the publication of the second CONSORT statement (2011-2019), this increased to 29%.

Discussion

This systematic review assessed outcome and comparator choice in MIH intervention studies, and their change over time. We found that studies recorded a large range of outcomes, especially when considering the limited number of studies overall, and that the diversity of these outcomes is increasing. This is reassuring, and the findings of this review are helpful to develop a COS. We also found that despite the low number of studies available, a large range of different interventions were tested, which led to the occurrence of segregated networks. Resulting from this clustering and the fact that most interventions were not well compared against alternatives, the current body of evidence on MIH interventions is likely not robust.

The outcomes used in MIH intervention studies focused on two main areas; restoration success (measured via the USPHS criteria or similar tools) and pain/ discomfort/ hypersensitivity (measured via scales like the Visual analogue scale or the Schiff Cold Air Sensitivity Scale). Combined, these two areas accounted for the majority of primary and all reported outcomes. Both, restoring MIH teeth and managing pain can be assumed to be the major difficulties dentists face when treating MIH. Research has shown that MIH-affected children receive and need more dental treatment compared to unaffected children [30-35]. Also already restored MIH-molars remain within short re-

treatment cycles [30]. The porous nature of MIH enamel and the presence of post eruptive enamel breakdown leads to the presence of hypersensitivity and pain, which are often the patients' chief complaint and affect their quality of life. It also increases the risk of dental fear and anxiety [15 36-38]. Overall, the focus on how to best restore these teeth and alleviate pain seems justified.

Nevertheless the use of other outcome categories like quality of life or efficiency appears to be growing, reflecting an ongoing shift to patient-centered care (and research) and the increasing relevance of health economics in today's resource-limited healthcare settings. We will, in the next stage of our COS development, suggest these outcomes to be included in the COS on MIH intervention studies, and will seek stakeholder consensus on their inclusion (or not).

We also investigated further outcome-related aspects in the included studies. For example, trial registration, one of the recommendations of the CONSORT statement [39 40], was found in only 10 studies (and even very recent studies did not commonly report on this). While such registration may be seen as a prerogative of controlled trials, also single-arm prospective trials should clearly state what is to be investigated using which methods and tools in what population before commencing the study. This does not seem to be the case. Registration would help to reduce selective outcome reporting and could also assist in improving reporting standards (and general methodology) in MIH intervention studies.

Also, of the 35 reports, only 7 studies reported a sample size calculation, and of these, only 5 related this to the primary outcome. Again, while such calculations are mainly demanded for controlled prospective trials, researchers should have a rational basis for calculating the number of participants needed in any study (regardless of its design), be it to ascertain that differences between the interventions can be detected with a planned level of statistical confidence or be it to reduce statistical noise (allowing somewhat firm conclusions). Sample size calculation is a key recommendation in the CONSORT statement, published in 2001 [40] and revised in 2010 [39]. It was promising to find that, since this revision, more publications reported on a sample size calculation (while the overall number remained low).

Our network analysis found that most comparisons in MIH trials included few, favoured comparators; many possible comparisons were never made, and some comparators were not at all compared against alternatives. Moreover, and understandable,

comparators focusing on specific indications (managing pain, restoring cavities, improving aesthetics) were connected within, not between these indications. Overall, the information emerging from such poorly connected networks with regards to the relative efficacy of the interventions (answering the question of which intervention is most suited for a specific therapeutic goal) is likely not robust. The small sample sizes in most studies further add to the limited robustness of the existing evidence. Overall, the relatively "young" field of MIH research has so far not accrued sufficiently robust data which allows strong recommendations for clinicians.

This study has a number of limitations. First, the effort to improve COS methodology is ongoing, and our review used only one of several available strategies suggested for COS developers. For example, it seems that to reach saturation on outcomes and outcome categories, it may not be necessary to search multiple databases [41], while we did so, also as this review was an update of a previous one and we aimed to apply the same methodology. Second, developing outcome categories and assigning specific verbatim outcomes to these categories is challenging [21], often as outcomes are either inter-related or composites, capturing different outcome categories [42]. While there is no acknowledged MIH outcome classification system, it is clear that alternative classifications may have resulted in changes to the granularity and focus of the results. Third, researchers tend to publish multiple reports from the same clinical trial [43]. This can be necessary to report on the dataset at different time points, or to report on multiple analyses. Data is then divided and spread across multiple publications, which makes linking or summarizing these articles very difficult. We assume to have captured all articles given the field being limited. Last, in order to limit selective outcome bias and in the attempt of including the most recent trials, registries were searched in our study, too. This however, has its limitations, since there are often incomplete or unclear registrations, and we were only limitedly able to extract data.

Conclusions

Outcomes reported in interventional trials for the management and prevention of MIH focused on the performance of restorative materials or and the management of pain and hypersensitivity associated with MIH-affected teeth. Outcomes related to oral-health related quality of life and economics have grown in use and are likely to be

important in the future. Patient-reported or patient-centered outcomes were rarely reported. COS development should include these and may supplement them with new outcomes, e.g. on applicability. The high number of compared interventions tested in only few studies and our SNA results implicate that current evidence may not be robust.

Trial status (Registration):

COMET initiative online http://www.comet-initiative.org/studies/details/1155 [1]

Competing interests

The authors declare no conflict of interest.

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Ethical approval

Not applicable.

Author contributions

The study was conceived by KE and FS. KE and JK analyzed, interpreted the data. KE, P-G J-B and FS wrote the manuscript. All authors read and approved the manuscript.

Transparency declaration

The lead author* affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Data availability statement

All data relevant to the study are included in the article or uploaded as supplementary information.

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69. Hasmun N, Lawson J, Vettore MV, et al. Change in Oral Health-Related Quality of Life Following Minimally Invasive Aesthetic Treatment for Children with Molar Incisor Hypomineralisation: A Prospective Study. *Dentistry journal* 2018;6(4) doi: 10.3390/dj6040061 [published Online First: 2018/11/06]

Table 1. Characteristics of included studies (n=35). Studies were separated according to target condition (MIH in molars or incisors), and ordered chronologically.

Author	Year	Setting	N part.	Age	Study type	Follow-up (months)	Trial reg.	No. of Arms	P cal.
Molars									
Koch and Garcia-Godoy [44]	**2000**	Uni. H	12	6-8	Pro Co	24-60	n	3	n
Lygidakis et al. [45]	**2003**	Uni. H	46	8-10	Pro Co	48	n	1	n
Zagdwon et al. [46]	**2003**	Uni. H	17	6-16	RCT	12-24	n	2	y
Kotsanos et al. [32]	**2005**	Uni. H	72	8	Retro Co	52	n	4	n
Mejare et al. [33]	**2005**	Uni. H	76	6-17	Retro Co	62	n	7	n
Jalevik and Moller [47]	**2007**	Uni. H	27	6-13	Retro Co	44-99	n	1	n
Lygidakis et al. [48]	**2009**	Uni. H	47	6-7	RCT	48	n	2	n
Baroni and Marchionni [49]	**2011**	Uni. H	30	6-9	Pro Co	36	n	1	n
Gaardmand et al. [50]	**2013**	Uni. H	33	8-18	Retro Co	39	n	1	n
Cabasse et al. [51]	**2015**	Uni. H	39	9	Pro Co	n	n	1	n
Fragelli et al. [52]	**2015**	Uni. H	21	6-9	Pro Co	12	n	1	n
Bekes et al. [53]	**2016**	Uni. H	16	8	Pro Co	2	n	2	y
Bakkal et al. [54]	**2017**	Uni. H	38	7-12	RCT	1	n	2	n
de Souza et al. [55]	**2017**	Uni. H	18	6-8	RCT	18	y	2	n
Fragelli et al. [56]	**2017**	Uni. H	21	6-8	RCT	18	n	2	y
Sönmez and Saat [57]	**2017**	Uni. H	42	8-12	RCT	24	n	4	n
Dixit and Joshi [58]	**2018**	Uni. H	32	8-14	RCT	n/a	n	2	y
Folayan et al. [59]	**2018**	Uni. H	73	8-16	Pro Co	n/a	n	2	n
Grossi et al. [60]	**2018**	Uni. H	40	7-13	Pro Co	12	y	1	n
Koleventi et al. [61]	**2018**	Uni. H	14	11	Pro Co	6	n	2	n
Pasini et al. [62]	**2018**	Uni. H	40	8-13	Pro Co	4	n/a	2	n/a
Dhareula et al. [63]	**2019**	Uni. H	30	8-13	RCT	36	y	2	y
Incisors									
Wong and Winter [64]	**2002**	Uni. H	15	n/a	RCT	6	n	1	n
Özgül et al [65]	**2013**	Uni. H	33	7-12	RCT	1	n	6	n
Sheoran et al. [66]	**2014**	Uni. H	25	11-13	RCT	1	n	2	n

Restrepo et al. [67]	**2016**	Uni. H	51	9-12	Pro Co	1	n	2	y
Bhandari et al. [68]	**2018**	Uni. H	n/a	7-16	Pro Co	6	n	1	n
Hasmun et al. [69]	**2018**	Uni. H	111	7-16	Pro Co	n/a	n	1	y
Only Registered									
DRKS00009760	**2016**	Uni. H	40	6-70	RCT	6	y	2	n
DRKS00011882	**2017**	Uni. H	300	7-14	Pro Co	0,5	y	3	n/a
NCT03614819	**2018**	Uni. H	122	6-10	RCT	24	y	2	n/a
NCT03760497	**2018**	Uni. H	300	6-10	RCT	24	y	3	n/a
NCT03826810	**2019**	Uni. H	48	n/a	RCT	12	y	2	n/a
NCT03870958	**2019**	Uni. H	195	6-9	RCT	36	y	2	n/a
NCT03862014	**2019**	Uni. H	100	6-10	RCT	24	y	2	n/a

Abbreviations: N of part., number of participants; n/a, not available; Pro Co, prospective cohort; Retro Co, retrospective cohort; RCT, randomized control trial; Uni. H, University hospital; Trial reg., trial registration, P cal., power calculation; n, no; y, yes

Table 2. Reported outcome category, outcome examples and outcomes measures, ordered according to the frequency of use in included studies.

Outcome category	Outcome examples	Exemplary outcome measures
Restoration success	Clinical performance Restoration quality Survival of tooth and restoration	Modified US Public Health Service (USPHS) criteria Modified atraumatic restorative treatment (ART) criteria Radiographic evaluation (Bitewings) Number of reinterventions Survival rate
Pain/ discomfort/ hypersensitivity	Response to stimulus Pain during and after dental treatment/ intervention	Schiff Cold Air Sensitivity Scale (SCASS) Questionnaires Modified behavior pain scale Visual Analogue Scale (VAS)
Aesthetic improvement	Aesthetic improvement	Questionnaires Clinical photography
Mineral gain	Mineral gain	Laserfluorescence readings Scanning electron microscope (SEM)/ Energy Dispersive X-ray Spectrometry (EDX) Quantitative Light-Induced Fluorescence (QLF)
Space management	Space closure after extraction Need of orthodontic intervention	Amount of spontaneous space closure
Anesthesia effectiveness	Anesthesia technique Need for local anesthesia	Presence of pain during treatment Pain efficacy scale
Preventive success	Clinical performance Sealant quality Ability to prevent caries and enamel breakdown	Success/ Modified US Public Health Service (USPHS) criteria
Efficiency	Costs of treatment	Placement time Used materials Laboratory costs
Quality of life	Oral health-related quality of life (OHRQoL)	Self-administered oral health related quality of life (OHRQoL) questionnaires (COHIP G-19, CPQ 8-10, CPQ 11-14)
Gingival and periodontal health	Presence of gingivitis and periodontitis Oral hygiene Subgingival microbiota	Gingival index (GI) Pocket depth (PD) Turesky plaque index Checkerboard DNA-DNA hybridization
Patient satisfaction	Patient satisfaction with treatment	Visual Analogue Scale (VAS) Questionnaires

Table 3. Primary and secondary outcomes reported in each study.

Author (year)	Restoration success	Pain/ discomfort/ hypersensitivity	Aesthetic improvement	Mineral gain	Space management	Anesthesia effectivness	Preventive success	Efficiency	Quality of life	Gingival and periodontal health	Patient satisfaction
Koch and Garcia-Godoy (2000) [44]	x										
Wong and Winter (2002) [64]			x								
Lygidakis et al. (2003) [45]	x	♦					♦				
Zagdwon et al. (2003) [46]	x							♦			
Kotsanos et al. (2005) [32]	x				♦						
Mejare et al. (2005) [33]	x				♦						
Jalevik and Moller (2007) [47]					x						
Lygidakis et al. (2009) [48]	x										
Baroni and Marchionni (2011) [49]				x							
Gaardmand et al. (2013) [50]	x										
Özgül et al (2013) [65]		x									
Sheoran et al. (2014) [66]			x								
Cabasse et al. (2015) [51]						x					
Fragelli et al. (2015) [52]	x										
Bekes et al. (2016) [53]		x									
DRKS00009760 (2016)			x								
Restrepo et al. (2016) [67]				x							
Bakkal et al. (2017) [54]				x							
de Souza et al. (2017) [55]	x										
DRKS00011882 (2017)									x		
Fragelli et al. (2017) [56]	x						♦				
Sönmez and Saat (2017) [57]	x	♦									
Bhandari et al. (2018) [68]			x								
Dixit and Joshi (2018) [58]		♦				x		♦			
Folayan et al. (2018) [59]								x			
Grossi et al. (2018) [60]	x	♦				♦					
Hasmun et al. (2018) [69]									x		

Koleventi et al. (2018) [61]						x	
Pasini et al. (2018) [62]		x					
NCT03614819 (2018)	♦	♦	x	♦	♦		♦
NCT03760497 (2018)	x	♦			♦		♦
Dhareula et al. (2019) [63]	x	♦				♦	
NCT03826810 (2019)	♦	x					
NCT03870958 (2019)		♦	x	♦	♦		
NCT03862014 (2019)	x						

x, primary outcome; ♦, secondary outcome

Figure legends:

Figure 1. Flow chart of the search.

Figure 2. Reported outcomes for MIH intervention studies over time. N number of studies using this outcome in the specific period.

Figure 3. Networks of comparisons made in molars. Different comparators (nodes) were compared directly with each other. The node diameter represents the number of studies involving this comparator, moreover the number of studies is added between brackets in each node, the thickness of the edge represents the number of direct comparisons between two comparators. Certain comparators were not connected to the main network. Abbreviations: PMC, preformed metal crowns; GIC, glass ionomer cement; ART, atraumatic restorative treatment; aPDT, low-intensity laser and photodynamic Therapy; SDF, silver diamine Fluoride; ARR, atraumatic resin restoration; CPP-ACP; casein phosphopeptide-amorphous calcium phosphate; SEA, self-etching adhesive; TEA; total-etch adhesive; HCL; hydrochloric acid; NaOCl, sodium hypochlorite.

Figure 4. Networks of comparisons made in incisors. Different comparators (nodes) were compared directly with each other. The node diameter represents the number of studies involving this comparator, moreover the number of studies is added between brackets in each node, the thickness of the edge the number of direct comparisons between two comparators. Certain comparators were not connected to the main network. Abbreviations: CPP-ACP; casein phosphopeptide-amorphous calcium phosphate; HCL; hydrochloric acid showing studies on MIH-affected molars, while B) studies on MIH-affected incisors.

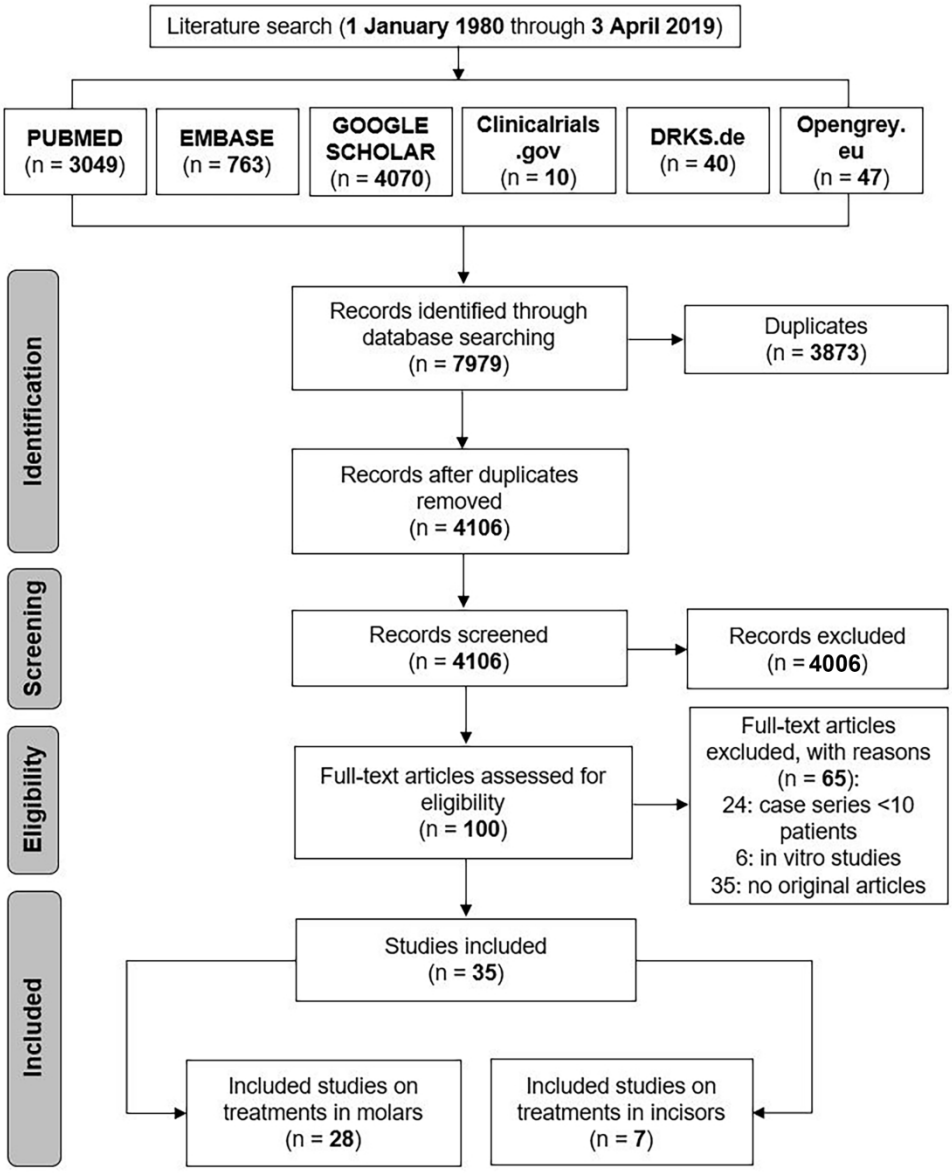

Figure 1. Flow chart of the search.

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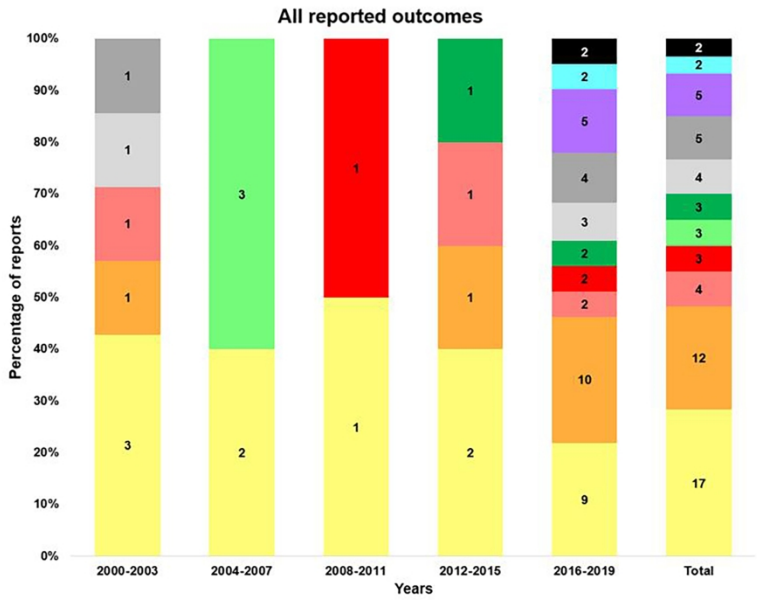

	2000-2003	2004-2007	2008-2011	2012-2015	2016-2019	Total
1. Restoration success	3	2	1	2	9	17
2. Pain/discomfort/hypersensitivity	1			1	10	12
3. Aesthetic improvement	1			1	2	4
4. Mineral gain			1		2	3
5. Space management		3				3
6. Anesthesia effectivness				1	2	3
7. Preventive success	1				3	4
8. Efficiency	1				4	5
9. Quality of life					5	5
10. Gingival and Periodontal health					2	2
11. Patient satisfaction					2	2
Total	7	5	2	5	41	60
%	11.67%	8.33%	3%	8.33%	68.33%	100.00%

Figure 2. Reported outcomes for MIH intervention studies over time. N number of studies using this outcome in the specific period.

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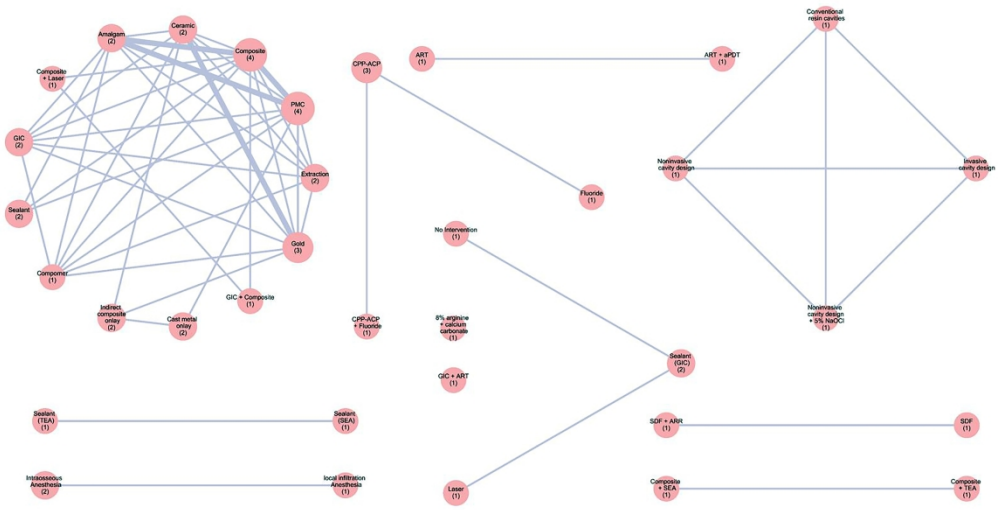

Figure 3. Networks of comparisons made in molars. Different comparators (nodes) were compared directly with each other. The node diameter represents the number of studies involving this comparator, moreover the number of studies is added between brackets in each node, the thickness of the edge represents the number of direct comparisons between two comparators. Certain comparators were not connected to the main network. Abbreviations: PMC, preformed metal crowns; GIC, glass ionomer cement; ART, atraumatic restorative treatment; aPDT, low-intensity laser and photodynamic Therapy; SDF, silver diamine Fluoride; ARR, atraumatic resin restoration; CPP-ACP; casein phosphopeptide-amorphous calcium phosphate; SEA, self-etching adhesive; TEA; total-etch adhesive; HCL; hydrochloric acid; NaOCl, sodium hypochlorite.

417x218mm (300 x 300 DPI)

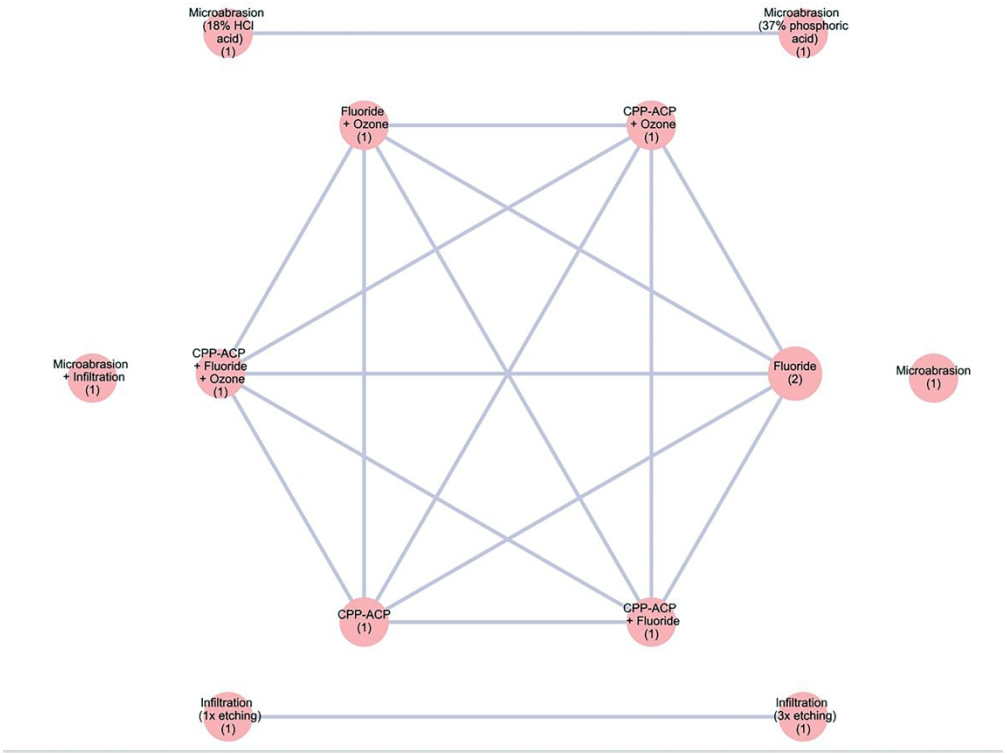

Figure 4. Networks of comparisons made in incisors. Different comparators (nodes) were compared directly with each other. The node diameter represents the number of studies involving this comparator, moreover the number of studies is added between brackets in each node, the thickness of the edge the number of direct comparisons between two comparators. Certain comparators were not connected to the main network. Abbreviations: CPP-ACP; casein phosphopeptide-amorphous calcium phosphate; HCL; hydrochloric acid showing studies on MIH-affected molars, while B) studies on MIH-affected incisors.

312x234mm (300 x 300 DPI)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4-6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4-5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5-6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	-
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	-
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	-
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	-
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8-10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	-
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	11

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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Outcome and comparator choice in Molar Incisor Hypomineralization (MIH) Intervention Studies: A Systematic Review and Social Network Analysis

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Keywords:	Systematic review, Molar incisor hypomineralization, core outcome set, MIH, prevention, management

Outcome and comparator choice in Molar Incisor Hypomineralization (MIH) Intervention Studies: A Systematic Review and Social Network Analysis

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Keywords

Systematic review, molar incisor hypomineralization, core outcome set, outcomes, MIH, prevention, management, intervention

Tables: 3

Figures: 4

Abstract

Objectives: Outcome and comparator choice strongly determine the validity and implementation of clinical trial results. We aimed to assess outcome and comparator choice in intervention studies on Molar Incisor Hypomineralization (MIH) using systematic review and social network analysis (SNA).

Design and data sources: Medline, Embase, Cochrane Central, Google Scholar, opengrey.eu as well as DRKS.de and Clinicaltrials.gov were searched for MIH intervention studies. The search covered the period from 1980-2019.

Eligibility criteria: Clinical single-/multi-arm, controlled/uncontrolled studies reporting on the management of MIH were included. Reported outcomes and comparators were extracted and categorized. SNA was used to evaluate comparator choice and the resulting trial networks.

Data extraction: Of the 7979 identified records, 100 were evaluated in full-text and 35 studies (17 randomized controlled trials, 14 prospective and 4 retrospective cohort studies) were included.

Results: In total, 2124 patients with a mean age of 11 years (min/max 6/70 years) were included. Outcomes fell in one of 11 different outcome categories: Restoration success, Aesthetic improvement, Pain/ hypersensitivity/ discomfort, Mineral gain, Space management, Anesthesia effectiveness, Preventive success, Efficiency, Quality of life, Gingival and periodontal health, and Patient satisfaction. Comparators were mainly restorative interventions (17 studies), remineralization (3), treatment of hypersensitivity (10), aesthetic interventions (5), and orthodontic interventions (3). Two highly clustered comparator networks emerged; many interventions were not robustly linked to these networks.

Conclusions: MIH intervention studies recorded both clinically- and patient-centered outcomes. Core Outcome Set (COS) development should consider these and supplement them with outcomes on, for example, applicability. The high number of compared interventions tested in only few studies and our SNA results implicate that the current evidence may not be robust.

Strengths and limitations of this study

- Molar incisor hypomineralization (MIH) is a frequent condition. No core outcome set on MIH exists.
- Outcomes and comparators for MIH studies were assessed using a systematic review.
- A network analysis was performed to evaluate the robustness of comparisons.
- The findings of this study will aid in core outcomes definition.
- The available body of evidence is limited and likely not robust.

Introduction

There is increasing interest in the internal and external validity of clinical studies, as indicated, for example, by their risk of bias [1 2] or their reporting quality [3]. Two aspects that only recently came into the focus, but have an impact on the validity are (1) outcome and (2) comparator choice.

So far, most clinical researchers chose the outcomes based on their understanding of what was relevant or not; the involvement of further stakeholders into outcome choice was seldom considered. This impacts on the relevance of study findings and may limit their applicability. Also, researchers usually collected a range of outcomes, without necessarily reporting all of them later on (selective reporting); mainly as data on outcomes with unwanted findings (which may nevertheless be relevant) can be omitted. The chosen outcomes and outcome measures may further suffer from limited comparability across studies, decreasing the chance to make the best use of clinical studies by synthesizing them. Outcome choice is thus relevant for study validity, applicability, and relevance, and implementation into practice [4-6].

Comparator choice impacts on the overall usefulness and validity of evidence [7]. Again, usually, most clinical researchers choose the comparators themselves, without necessarily consulting patients or further stakeholders such as insurers, regulators, etc. Comparators relevant to patients, for example, may hence not be evaluated, while other comparators may be over-proportionally employed [8-10]. The resulting gaps in the evidence may mean important data on possibly useful comparators are unavailable. Also, comparisons against placebo or no intervention (in single arm studies) or less effective options (so-called straw men) can lead to overestimation of effectiveness [9-11]. Repeated chain-linked comparisons against less-than-optimal standards were found to significantly distort the totality of evidence [9-11]. Comparator choice is relevant to make clinical research in a specific field useable, applicable, and informative.

The present study assessed outcome and comparator choice in intervention studies on Molar Incisor Hypomineralisation (MIH), a highly prevalent dental developmental disorder with a significant burden for patients and high treatment needs [12]. MIH is characterized by demarcated creamy-white, yellowish-brown or brown lesions with or without posteruptive enamel breakdown and hypersensitivity, affecting the permanent molars with or without additional affection of the incisors [13-15]. The severity of the

lesions, the symptomatology of the affected tooth as well as the patient's dental age, caries risk and expectations need to be considered in the management of MIH [15]. Dentists often need to employ different treatment strategies when dealing with MIH patients, including restoring cavities, alleviating pain or improving aesthetics [16], [17]. Given the broad spectrum of clinical presentations, individual needs and available treatment modalities, managing MIH is challenging for most practitioners [13-15].

Assessing the outcome and comparator choice in MIH intervention studies seems warranted. Such an assessment is further useful to inform the development of a Core Outcome Set (COS) for MIH management and prevention studies. COS are a minimum set of outcomes that have been agreed in a systematic consensus process by a diverse group of stakeholders (patients, dentists, researchers, insurance companies, etc). COS overcome the problem of a possibly limited relevance of chosen outcomes, the risk of selective reporting and the lack of synthesizability of study findings [18]. A range of COS development initiatives is currently underway in dentistry [19-23].

We aimed to review the outcomes used in MIH intervention studies to inform the development of a COS on MIH. We further aimed to assess the comparators used in these studies and to analyze the resulting study network. This was done using social network analysis (SNA), a method for evaluating the relationships between factors in a network [8], which has been introduced to dentistry recently [24]. As secondary aim, we evaluated if studies clearly indicated their primary outcome, if studies used a sample size estimation based on this outcome, and if studies were registered a priori, as should be expected.

Methods

This review was registered on the Core Outcome Measures in Effectiveness Trials (COMET) initiative website [1]. In parts, it builds on a previously published review on MIH management [25].

Search strategy

The following search was adapted for each database:

(treatment OR management OR prevention) AND (molar incisor hypomineralisation OR molar incisor hypomineralization OR mih).

Searches were developed and run individually for Medline, Embase, Cochrane Central, Google Scholar, opengrey.eu as well as DRKS and Clinicaltrials.gov and cross references were performed without any language restrictions. The search covered the period from 01.01.1980 to 03.04.2019 (Fig. 1).

Data collection

Inclusion criteria: We included all types of clinical studies (retrospective or prospective, controlled trials or cohort studies) in patients diagnosed with MIH. Note that studies conducted before 2001 on the condition will not have employed the term “MIH”, and may have been missed by our search. This, however, was accepted, as without a clear case definition, other conditions may have been captured by these studies too, without being able to separate conditions post hoc. Studies reported on prevention and/or management interventions for MIH teeth. There were no restrictions on setting, time of follow-up, or patients’ age. Case reports or case series with a sample size of < 10 participants were excluded. No language restriction was set; studies in languages other than English, German or Arabic (if present) were translated by native speakers. Selection process: Two authors (FS, KE) screened titles independently and compared their findings. In case of disagreement, titles were included to obtain full-texts. Full-texts were assessed independently after de-duplication. In cases of disagreement, studies were included after consensus was reached through discussion.

Data extraction: The following data was extracted duplicatively and independently by two authors (KE and FS) following calibration using a pilot database:

- Study details (author name, title, journal, year of publication);
- Study characteristics;
    - Study setting (primary or secondary care)
    - Number and age of participants
    - Study type (controlled or uncontrolled, pro- or retrospective)
    - Target condition (MIH lesions on molars, incisors, or both)
    - Number of study arms
    - Interventions compared

- Follow-up period
- Outcomes assessed, separated for primary and secondary outcome(s). An outcome was considered a primary outcome if it was stated as such, or where the report clearly focused on one outcome. If no primary outcome was identifiable or multiple outcomes were reported, these were considered secondary outcomes.
- Outcome measures

- Sample size estimation (yes/no)
- Trial registration (yes/no).

Data synthesis

A list of outcomes was compiled and outcomes with different verbatim terms but similar meanings gathered using a single agreed term. Outcomes were grouped within outcome categories; these were refined through group discussion before all outcomes were categorized using the final agreed terms. The final list of outcome categories comprised 11 items; Restoration success, Aesthetic improvement, Pain and hypersensitivity management, Mineral gain, Space management, Anesthesia effectiveness, Preventive success, Efficiency, Quality of life, Gingival and Periodontal health, and Patient satisfaction. The use of different outcome categories was analyzed via descriptive statistics. Exemplary outcomes and outcome measures were allocated to one of these outcome categories by discussion and agreement of two authors (KE and FS). Where there was disagreement, a consensus was achieved through discussion with all authors.

A list of comparators was compiled and comparators were grouped into agreed categories. The granularity of these categories allowed to capture specific comparators (like “glass ionomer cement restoration”) while grouping similar comparators in the same category (e.g. different cement brands). Comparator choice was analyzed via SNA. In SNA, nodes (termed ‘vertices’) are formed by comparators and are connected by edges (comparisons made within the same trial). In a graphical analysis, the node diameter represents the number of comparator arms forming the node and thickness of edges represents the number of direct comparisons. We performed separate analyses (and graphic representations) for studies on MIH in

molars versus incisors. Statistical analysis included the assessment of the degree (average number of comparators per node) and the clustering coefficient (values of one indicate that all possible connections were made, while values of 0 indicate that only the minimum number of connections were made) [26-28]. Statistical analysis was only performed for the main network in each sub-analysis (molars; incisors). The Python package NetworkX was used.

Patient and public involvement

Patients were not involved in this study at this point but will be during the core outcomes definition.

Results

Included studies

The database search yielded 7979 records; 4106 remained after de-duplication. There were 100 potentially relevant articles and the full texts of all these 100 articles were located (100% retrieval rate); 35 met the inclusion criteria and were included (Fig. 1).

Characteristics of included trials

Of the 35 included studies, all (100%) were conducted in a secondary care setting (hospital or university). The total number of participants was 2124; per study, a mean of 60 (range 12 – 300) participants were included. Only children (mean age < 12 years) were included in 33 included reports (94%). Only one (3%) study reported on adults (mean age 33 years). In two other publications (6%) it was not possible to determine the age of the participants. There were 10 (29%) one-arm studies, 18 (51%) two-arm studies, 3 (9%) three-arm studies, and 4 (11%) multi-arm studies. Further details on the included studies can be found in Table 1.

Outcome choice

In total, 11 outcome categories were deduced from the included studies (Fig. 2, Table 2). The most frequent specific categories were “Restoration success” and “Pain/

discomfort/ hypersensitivity"; with 17 (49%) and 12 (34%) studies reporting them, respectively. The next most common were "Quality of life" and "Efficiency" (each 5 studies, 14%); "Aesthetic improvement" and "Preventive success" (4 studies, 11%); "Mineral gain", "Space management" and "Anesthesia effectiveness" (each 3 studies, 9%). The least common ones were "Patient satisfaction" and "Gingival and periodontal health" (each 2 studies, or 6%). Outcome categories that have increased in use (from 2000-2009 to 2010-2018) included "Aesthetic improvement", "Mineral gain", "Efficiency", and "Gingival and periodontal health".

Findings for molars

For molars, 10 outcome categories were identified from the included studies. Those were: "Restoration success" with a total of 17/28 studies reporting on it (15/17 as primary outcome and 2/17 as secondary outcome); "Pain/discomfort/hypersensitivity" with a total of 12/28 studies reporting on it (4/12 as primary outcome and 8/11 as secondary outcome); "Quality of life" with a total of 5/28 studies reporting on it (2/5 as primary outcome and 3/5 as secondary outcome); "Efficiency" with a total of 5/28 studies reporting on it (1/5 as primary outcome and 4/5 as secondary outcome); "Preventive success" with a total of 4/28 studies reporting on it (3/4 as primary outcome and 1/4 as secondary outcome); "Anesthesia effectiveness" with a total of 3/28 studies reporting on it (2/3 as primary outcome and 1/3 as secondary outcome); "Space management" with a total of 3/28 studies reporting on it (1/3 as primary outcome and 2/3 as secondary outcome); "Mineral gain" with a total of 2/28 studies reporting on it (all as primary outcome); "Gingival and periodontal health" with a total of 2/28 studies reporting on it (1/2 as primary outcome and 1/2 as secondary outcome); "Patient satisfaction" with a total of 2/28 studies reporting on it (all as secondary outcome).

Findings for incisors

For incisors, only four outcome categories were identified from the included studies. Those were: "Aesthetic improvement" with a total of 4/7 studies reporting on it (all as primary outcome); "Pain/discomfort/hypersensitivity" with a total of 1/7 study reporting

on it (as primary outcome); “Quality of life” with a total of 1/7 study reporting on it (as primary outcome); “Mineral gain” with a total of 1/7 study reporting on it (as primary outcome).

Comparator choice

Two separate analyses on comparator choice were performed; one for studies on molars and one on incisors. In both groups, a loosely connected main network and several further, unconnected networks or comparators were present, indicating poor connectivity between comparators (Figs. 3 and 4). Certain comparators were more frequently chosen than others.

In molars (Fig. 3), many studies compared different restorative strategies, for example, composite (with different brands also tested against each other), metal, ceramic or cement restorations. Further comparisons, non-connected to this main (restorative) network, involved caries preventive interventions, management of hypersensitivity, and cavity preparation and condition techniques. The mean degree of the main, restorative network was 5.9, with a density of 0.49. The cluster coefficient (which ranges from 0 – no clustering – to 1 – maximum clustering) was 0.76, indicating that there was significant clustering, with certain comparators being compared with each other (in “cliques”), while other possible comparisons (against comparators outside of these cliques) not having been made.

In incisors (Fig. 4), a main network, comparing different remineralization strategies, emerged, with two further networks and two further, non-connnected comparators on aesthetic management of MIH. The mean degree of the main (remineralization) network was 5, with a density of 1.0. The cluster coefficient was 1.0, indicating that there were “cliques” of comparators present, with comparators being mainly compared within and not across these cliques.

Primary outcome and sample size calculation

Primary outcomes could be identified in all 35 (100%) reports (Table 3). Throughout all years (2000 to 2019), “Restoration success” was the most frequently assessed

primary outcome (17/35). Information on sample size calculation was provided in 7 (20%) reports, all but one being published between 2016 and 2019. Of these 7 reports, 5 (71%) related this calculation to the primary outcome.

Trial registration reporting

Only 10 (29%) of all articles reported a trial registration [29]. In the 10 years following the publication of the first CONSORT statement (2001-2010), not a single report included a trial registration. Following the publication of the second CONSORT statement (2011-2019), this increased to 29%.

Discussion

This systematic review assessed outcome and comparator choice in MIH intervention studies, and their change over time. We found that studies recorded a large range of outcomes, especially when considering the limited number of studies overall, and that the diversity of these outcomes is increasing. This is reassuring, and the findings of this review are helpful to develop a COS. We also found that despite the low number of studies available, a large range of different interventions was tested, which led to the occurrence of segregated networks. Resulting from this clustering and the fact that most interventions were not well compared against alternatives, the current body of evidence on MIH interventions is likely not robust.

The outcomes used in MIH intervention studies focused on two main areas; restoration success (measured via the USPHS criteria or similar tools) and pain/ discomfort/ hypersensitivity (measured via scales like the Visual analog scale or the Schiff Cold Air Sensitivity Scale). Combined, these two areas accounted for the majority of primary and all reported outcomes. Both restoring MIH teeth and managing pain can be assumed to be the major difficulties dentists face when treating MIH. Research has shown that MIH-affected children receive and need more dental treatment compared to unaffected children [30-35]. Also already restored MIH-molars remain within short re-treatment cycles [30]. The porous nature of MIH enamel and the presence of post eruptive enamel breakdown leads to the presence of hypersensitivity and pain, which are often the patients' chief complaints and affect their quality of life. They also

increase the risk of dental fear and anxiety [15 36-38]. Overall, the focus on how to best restore these teeth and alleviate pain seems justified.

Nevertheless, the use of other outcome categories like quality of life or efficiency appears to be growing, reflecting an ongoing shift to patient-centered care (and research) and the increasing relevance of health economics in today's resource-limited healthcare settings. We will, in the next stage of our COS development, suggest these outcomes to be included in the COS on MIH intervention studies, and will seek stakeholder consensus on their inclusion (or not).

We also investigated further outcome-related aspects in the included studies. For example, trial registration, one of the recommendations of the CONSORT statement [39 40], was found in only 10 studies (and even very recent studies did not commonly report on this). While such registration may be seen as a prerogative of controlled trials, also single-arm prospective trials should clearly state what is to be investigated using which methods and tools in what population before commencing the study. This does not seem to be the case. Registration would help to reduce selective outcome reporting and could also assist in improving reporting standards (and general methodology) in MIH intervention studies.

Also, of the 35 reports, only 7 studies reported a sample size calculation, and of these, only 5 related this to the primary outcome. Again, while such calculations are mainly demanded for controlled prospective trials, researchers should have a rational basis for calculating the number of participants needed in any study (regardless of its design), be it to ascertain that differences between the interventions can be detected with a planned level of statistical confidence or be it to reduce statistical noise (allowing somewhat firm conclusions). Sample size calculation is a key recommendation in the CONSORT statement, published in 2001 [40] and revised in 2010 [39]. It was promising to find that, since this revision, more publications reported on a sample size calculation (while the overall number remained low).

Our network analysis found that most comparisons in MIH trials included few, favored comparators; many possible comparisons were never made, and some comparators were not at all compared against alternatives. Moreover, and understandable, comparators focusing on specific indications (managing pain, restoring cavities, improving aesthetics) were connected within, not between these indications. Overall, the information emerging from such poorly connected networks with regards to the

relative efficacy of the interventions (answering the question of which intervention is most suited for a specific therapeutic goal) is likely not robust. The small sample sizes in most studies further add to the limited robustness of the existing evidence. Overall, the relatively "young" field of MIH research has so far not accrued sufficiently robust data which allows strong recommendations for clinicians.

This study has a number of limitations. First, the effort to improve COS methodology is ongoing, and our review used only one of several available strategies suggested for COS developers. For example, it seems that to reach saturation on outcomes and outcome categories, it may not be necessary to search multiple databases [41], while we did so, also as this review was an update of a previous one and we aimed to apply the same methodology. Second, developing outcome categories and assigning specific verbatim outcomes to these categories is challenging [21], often as outcomes are either inter-related or composites, capturing different outcome categories [42]. While there is no acknowledged MIH outcome classification system, it is clear that alternative classifications may have resulted in changes to the granularity and focus of the results. Third, researchers tend to publish multiple reports from the same clinical trial [43]. This can be necessary to report on the dataset at different time points or to report on multiple analyses. Data is then divided and spread across multiple publications, which makes linking or summarizing these articles very difficult. We assume to have captured all articles given that the field is limited. Last, in order to limit selective outcome bias and in the attempt of including the most recent trials, registries were searched in our study, too. This, however, has its limitations, since there are often incomplete or unclear registrations, and we were only limitedly able to extract data.

Conclusions

Outcomes reported in interventional trials for the management and prevention of MIH focused on the performance of restorative materials or and the management of pain and hypersensitivity associated with MIH-affected teeth. Outcomes related to oral-health related quality of life and economics have grown in use and are likely to be important in the future. Patient-reported or patient-centered outcomes were rarely reported. COS development should include these and may supplement them with new outcomes, e.g. on applicability. The high number of compared interventions tested in

only a few studies and our SNA results implicate that current evidence may not be robust.

Trial status (Registration):

COMET initiative online http://www.comet-initiative.org/studies/details/1155 [1]

Competing interests

None declared

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Ethical approval

Not applicable.

Author contributions

The study was conceived by KE and FS. KE and JK analyzed, interpreted the data. KE, P-G J-B and FS wrote the manuscript. All authors read and approved the manuscript.

Transparency declaration

The lead author* affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Data availability statement

All data relevant to the study are included in the article or uploaded as supplementary information.

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Table 1. Characteristics of included studies (n=35). Studies were separated according to target condition (MIH in molars or incisors), and ordered chronologically.

Author	Year	Setting	N part.	Age	Study type	Follow-up (months)	Trial reg.	No. of Arms	P cal.
Molars									
Koch and Garcia-Godoy [44]	**2000**	Uni. H	12	6-8	Pro Co	24-60	n	3	n
Lygidakis et al. [45]	**2003**	Uni. H	46	8-10	Pro Co	48	n	1	n
Zagdwon et al. [46]	**2003**	Uni. H	17	6-16	RCT	12-24	n	2	y
Kotsanos et al. [32]	**2005**	Uni. H	72	8	Retro Co	52	n	4	n
Mejare et al. [33]	**2005**	Uni. H	76	6-17	Retro Co	62	n	7	n
Jalevik and Moller [47]	**2007**	Uni. H	27	6-13	Retro Co	44-99	n	1	n
Lygidakis et al. [48]	**2009**	Uni. H	47	6-7	RCT	48	n	2	n
Baroni and Marchionni [49]	**2011**	Uni. H	30	6-9	Pro Co	36	n	1	n
Gaardmand et al. [50]	**2013**	Uni. H	33	8-18	Retro Co	39	n	1	n
Cabasse et al. [51]	**2015**	Uni. H	39	9	Pro Co	n	n	1	n
Fragelli et al. [52]	**2015**	Uni. H	21	6-9	Pro Co	12	n	1	n
Bekes et al. [53]	**2016**	Uni. H	16	8	Pro Co	2	n	2	y
Bakkal et al. [54]	**2017**	Uni. H	38	7-12	RCT	1	n	2	n
de Souza et al. [55]	**2017**	Uni. H	18	6-8	RCT	18	y	2	n
Fragelli et al. [56]	**2017**	Uni. H	21	6-8	RCT	18	n	2	y
Sönmez and Saat [57]	**2017**	Uni. H	42	8-12	RCT	24	n	4	n
Dixit and Joshi [58]	**2018**	Uni. H	32	8-14	RCT	n/a	n	2	y
Folayan et al. [59]	**2018**	Uni. H	73	8-16	Pro Co	n/a	n	2	n
Grossi et al. [60]	**2018**	Uni. H	40	7-13	Pro Co	12	y	1	n
Koleventi et al. [61]	**2018**	Uni. H	14	11	Pro Co	6	n	2	n
Pasini et al. [62]	**2018**	Uni. H	40	8-13	Pro Co	4	n	2	n/a
Dhareula et al. [63]	**2019**	Uni. H	30	8-13	RCT	36	y	2	y
Incisors									
Wong and Winter [64]	**2002**	Uni. H	15	n/a	RCT	6	n	1	n
Özgül et al [65]	**2013**	Uni. H	33	7-12	RCT	1	n	6	n
Sheoran et al. [66]	**2014**	Uni. H	25	11-13	RCT	1	n	2	n
Restrepo et al. [67]	**2016**	Uni. H	51	9-12	Pro Co	1	n	2	y
Bhandari et al. [68]	**2018**	Uni. H	n/a	7-16	Pro Co	6	n	1	n
Hasmun et al. [69]	**2018**	Uni. H	111	7-16	Pro Co	n/a	n	1	y

Only Registered									
DRKS00009760	**2016**	Uni. H	40	6-70	RCT	6	y	2	n
DRKS00011882	**2017**	Uni. H	300	7-14	Pro Co	0,5	y	3	n/a
NCT03614819	**2018**	Uni. H	122	6-10	RCT	24	y	2	n/a
NCT03760497	**2018**	Uni. H	300	6-10	RCT	24	y	3	n/a
NCT03826810	**2019**	Uni. H	48	n/a	RCT	12	y	2	n/a
NCT03870958	**2019**	Uni. H	195	6-9	RCT	36	y	2	n/a
NCT03862014	**2019**	Uni. H	100	6-10	RCT	24	y	2	n/a

Abbreviations: N of part., number of participants; n/a, not available; Pro Co, prospective cohort; Retro Co, retrospective cohort; RCT, randomized control trial; Uni. H, University hospital; Trial reg., trial registration, P cal., power calculation; n, no; y, yes

Table 2. Reported outcome category, outcome examples and outcomes measures, ordered according to the frequency of use in included studies.

Outcome category	Outcome examples	Exemplary outcome measures
Restoration success	Clinical performance Restoration quality Survival of tooth and restoration	Modified US Public Health Service (USPHS) criteria Modified atraumatic restorative treatment (ART) criteria Radiographic evaluation (Bitewings) Number of reinterventions Survival rate
Pain/ discomfort/ hypersensitivity	Response to stimulus Pain during and after dental treatment/ intervention	Schiff Cold Air Sensitivity Scale (SCASS) Questionnaires Modified behavior pain scale Visual Analogue Scale (VAS)
Aesthetic improvement	Aesthetic improvement	Questionnaires Clinical photography
Mineral gain	Mineral gain	Laserfluorescence readings Scanning electron microscope (SEM)/ Energy Dispersive X-ray Spectrometry (EDX) Quantitative Light-Induced Fluorescence (QLF)
Space management	Space closure after extraction Need of orthodontic intervention	Amount of spontaneous space closure
Anesthesia effectiveness	Anesthesia technique Need for local anesthesia	Presence of pain during treatment Pain efficacy scale
Preventive success	Clinical performance Sealant quality Ability to prevent caries and enamel breakdown	Success/ Modified US Public Health Service (USPHS) criteria
Efficiency	Costs of treatment	Placement time Used materials Laboratory costs
Quality of life	Oral health-related quality of life (OHRQoL)	Self-administered oral health related quality of life (OHRQoL) questionnaires (COHIP G-19, CPQ 8-10, CPQ 11-14)
Gingival and periodontal health	Presence of gingivitis and periodontitis Oral hygiene Subgingival microbiota	Gingival index (GI) Pocket depth (PD) Turesky plaque index Checkerboard DNA-DNA hybridization
Patient satisfaction	Patient satisfaction with treatment	Visual Analogue Scale (VAS) Questionnaires

Table 3. Primary and secondary outcomes reported in each study.

Author (year)	Restoration success	Pain/ discomfort/ hypersensitivity	Aesthetic improvement	Mineral gain	Space management	Anesthesia effectiveness	Preventive success	Efficiency	Quality of life	Gingival and periodontal health	Patient satisfaction
Koch and Garcia-Godoy (2000) [44]	x										
Wong and Winter (2002) [64]			x								
Lygidakis et al. (2003) [45]	x	♦					♦				
Zagdwon et al. (2003) [46]	x							♦			
Kotsanos et al. (2005) [32]	x				♦						
Mejare et al. (2005) [33]	x				♦						
Jalevik and Moller (2007) [47]					x						
Lygidakis et al. (2009) [48]	x										
Baroni and Marchionni (2011) [49]				x							
Gaardmand et al. (2013) [50]	x										
Özgül et al (2013) [65]		x									
Sheoran et al. (2014) [66]			x								
Cabasse et al. (2015) [51]						x					
Fragelli et al. (2015) [52]	x										
Bekes et al. (2016) [53]		x									
DRKS00009760 (2016)			x								
Restrepo et al. (2016) [67]				x							
Bakkal et al. (2017) [54]				x							
de Souza et al. (2017) [55]	x										
DRKS00011882 (2017)									x		
Fragelli et al. (2017) [56]	x						♦				
Sönmez and Saat (2017) [57]	x	♦									
Bhandari et al. (2018) [68]			x								
Dixit and Joshi (2018) [58]		♦				x		♦			
Folayan et al. (2018) [59]								x			
Grossi et al. (2018) [60]	x	♦				♦					
Hasmun et al. (2018) [69]									x		

Koleventi et al. (2018) [61]						x	
Pasini et al. (2018) [62]		x					
NCT03614819 (2018)	♦	♦	x	♦	♦		♦
NCT03760497 (2018)	x	♦			♦		♦
Dhareula et al. (2019) [63]	x	♦				♦	
NCT03826810 (2019)	♦	x					
NCT03870958 (2019)		♦	x	♦	♦		
NCT03862014 (2019)	x						

x, primary outcome; ♦, secondary outcome

Figure legends:

Figure 1. Flow chart of the search.

Figure 2. Reported outcomes for MIH intervention studies over time. N number of studies using this outcome in a specific period.

Figure 3. Networks of comparisons made in molars. Different comparators (nodes) were compared directly with each other. The node diameter represents the number of studies involving this comparator, moreover, the number of studies is added between brackets in each node, the thickness of the edge represents the number of direct comparisons between two comparators. Certain comparators were not connected to the main network. Abbreviations: PMC, preformed metal crowns; GIC, glass ionomer cement; ART, atraumatic restorative treatment; aPDT, low-intensity laser and photodynamic Therapy; SDF, silver diamine Fluoride; ARR, atraumatic resin restoration; CPP-ACP; casein phosphopeptide-amorphous calcium phosphate; SEA, self-etching adhesive; TEA; total-etch adhesive; HCL; hydrochloric acid; NaOCl, sodium hypochlorite.

Figure 4. Networks of comparisons made in incisors. Different comparators (nodes) were compared directly with each other. The node diameter represents the number of studies involving this comparator, moreover, the number of studies is added between brackets in each node, the thickness of the edge the number of direct comparisons between two comparators. Certain comparators were not connected to the main network. Abbreviations: CPP-ACP; casein phosphopeptide-amorphous calcium phosphate; HCl;hydrochloric acid.

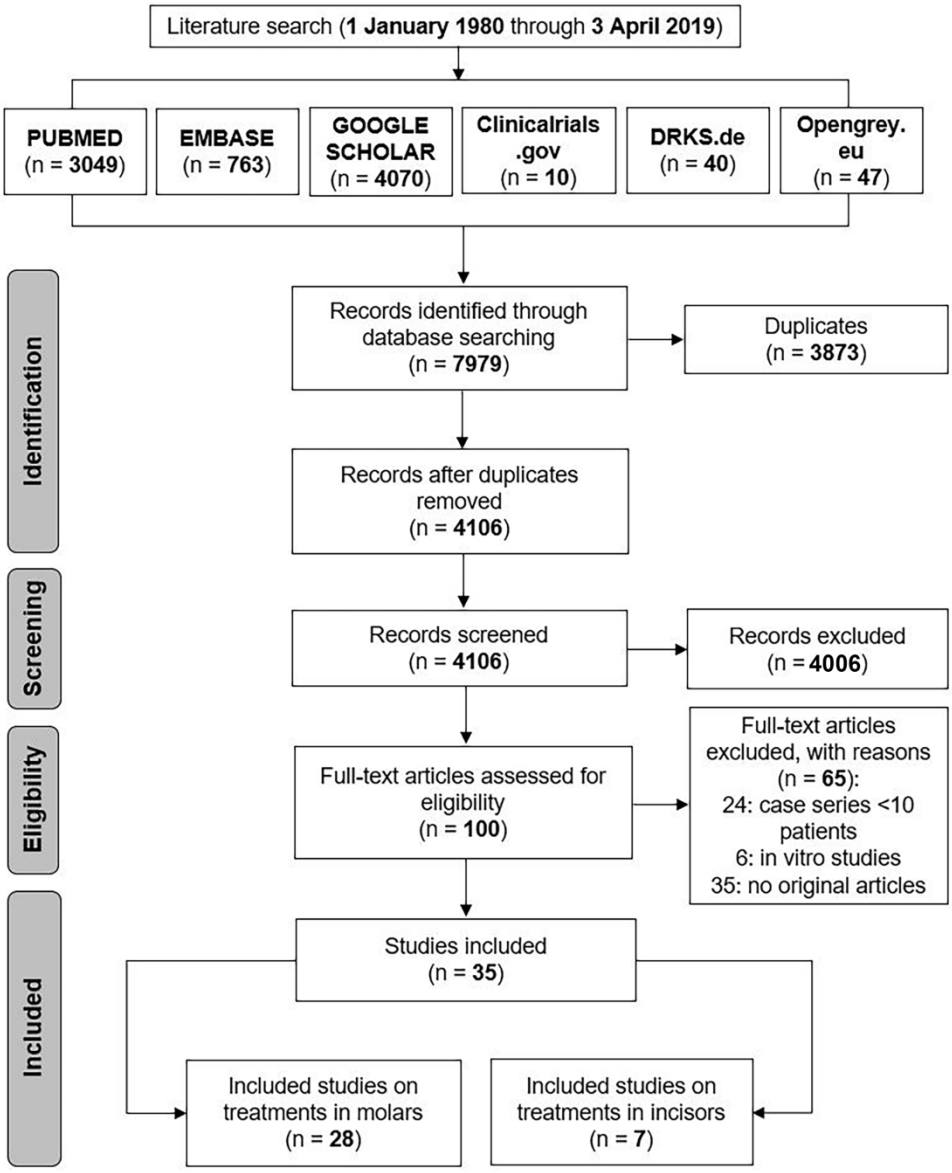

Figure 1. Flow chart of the search.

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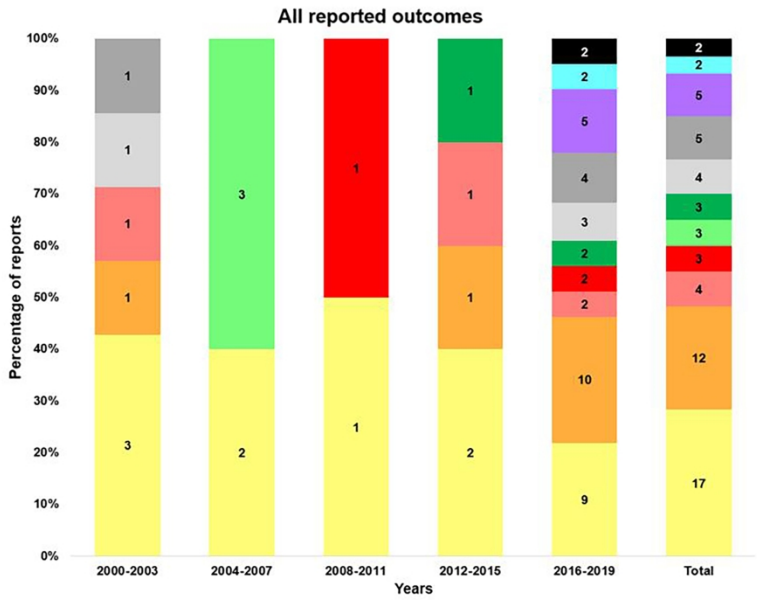

	2000-2003	2004-2007	2008-2011	2012-2015	2016-2019	Total
1. Restoration success	3	2	1	2	9	17
2. Pain/discomfort/hypersensitivity	1			1	10	12
3. Aesthetic improvement	1			1	2	4
4. Mineral gain			1		2	3
5. Space management		3				3
6. Anesthesia effectivness				1	2	3
7. Preventive success	1				3	4
8. Efficiency	1				4	5
9. Quality of life					5	5
10. Gingival and Periodontal health					2	2
11. Patient satisfaction					2	2
Total	7	5	2	5	41	60
%	11.67%	8.33%	3%	8.33%	68.33%	100.00%

Figure 2. Reported outcomes for MIH intervention studies over time. N number of studies using this outcome in the specific period.

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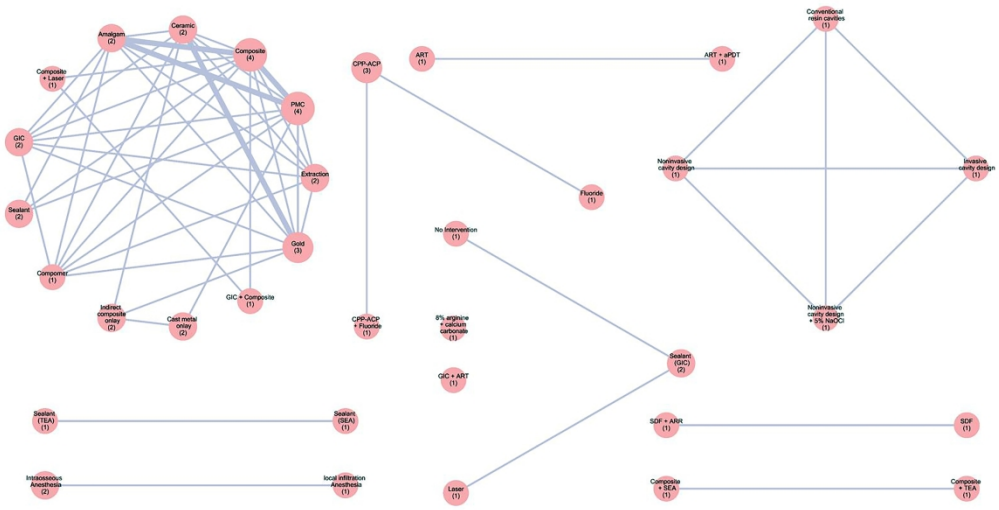

Figure 3. Networks of comparisons made in molars. Different comparators (nodes) were compared directly with each other. The node diameter represents the number of studies involving this comparator, moreover the number of studies is added between brackets in each node, the thickness of the edge represents the number of direct comparisons between two comparators. Certain comparators were not connected to the main network. Abbreviations: PMC, preformed metal crowns; GIC, glass ionomer cement; ART, atraumatic restorative treatment; aPDT, low-intensity laser and photodynamic Therapy; SDF, silver diamine Fluoride; ARR, atraumatic resin restoration; CPP-ACP; casein phosphopeptide-amorphous calcium phosphate; SEA, self-etching adhesive; TEA; total-etch adhesive; HCL; hydrochloric acid; NaOCl, sodium hypochlorite.

417x218mm (300 x 300 DPI)

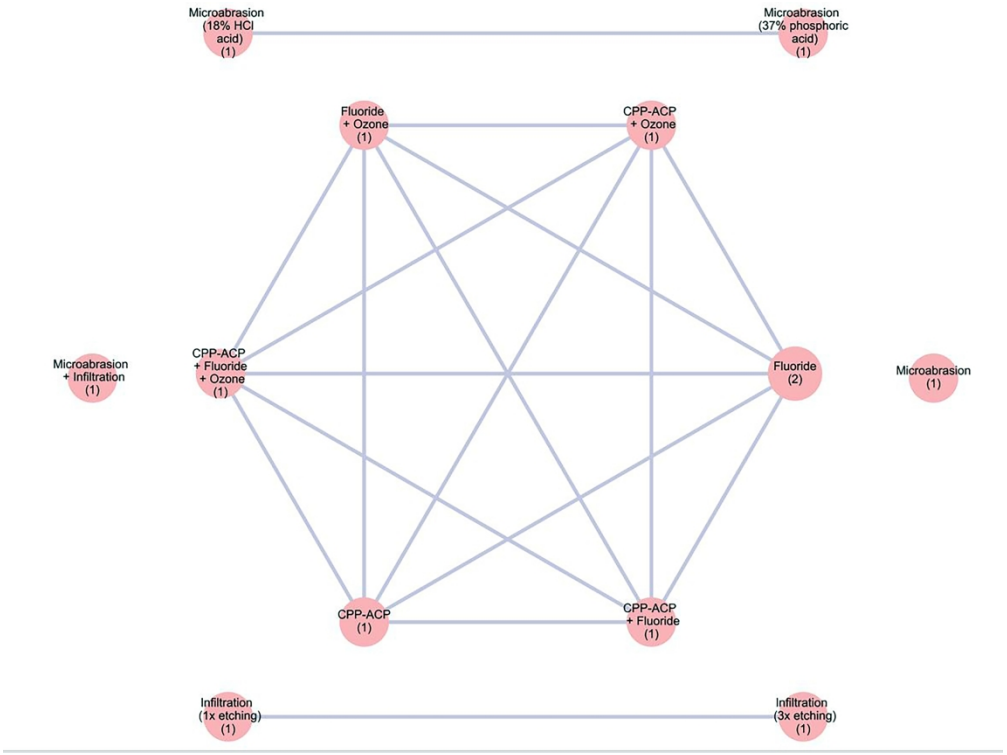

Figure 4. Networks of comparisons made in incisors. Different comparators (nodes) were compared directly with each other. The node diameter represents the number of studies involving this comparator, moreover the number of studies is added between brackets in each node, the thickness of the edge the number of direct comparisons between two comparators. Certain comparators were not connected to the main network. Abbreviations: CPP-ACP; casein phosphopeptide-amorphous calcium phosphate; HCL; hydrochloric acid showing studies on MIH-affected molars, while B) studies on MIH-affected incisors.

312x234mm (300 x 300 DPI)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4-6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4-5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5-6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	-
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	-
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	-
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	-
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8-10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	-
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	11

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Outcome and comparator choice in Molar Incisor Hypomineralization (MIH) Intervention Studies: A Systematic Review and Social Network Analysis

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Keywords:	Systematic review, Molar incisor hypomineralization, core outcome set, MIH, prevention, management

Outcome and comparator choice in Molar Incisor Hypomineralization (MIH) Intervention Studies: A Systematic Review and Social Network Analysis

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Keywords

Systematic review, molar incisor hypomineralization, core outcome set, outcomes, MIH, prevention, management, intervention

Tables: 3

Figures: 4

Abstract

Objectives: Outcome and comparator choice strongly determine the validity and implementation of clinical trial results. We aimed to assess outcome and comparator choice in intervention studies on Molar Incisor Hypomineralization (MIH) using systematic review and social network analysis (SNA).

Design and data sources: Medline, Embase, Cochrane Central, Google Scholar, opengrey.eu as well as DRKS.de and Clinicaltrials.gov were searched for MIH intervention studies. The search covered the period from 1980-2019.

Eligibility criteria: Clinical single-/multi-arm, controlled/uncontrolled studies reporting on the management of MIH were included. Reported outcomes and comparators were extracted and categorized. SNA was used to evaluate comparator choice and the resulting trial networks.

Data extraction: Of the 7979 identified records, 100 were evaluated in full-text and 35 studies (17 randomized controlled trials, 14 prospective and 4 retrospective cohort studies) were included.

Results: In total, 2124 patients with a mean age of 11 years (min/max 6/70 years) were included. Outcomes fell in one of 11 different outcome categories: Restoration success, Aesthetic improvement, Pain/ hypersensitivity/ discomfort, Mineral gain, Space management, Anesthesia effectiveness, Preventive success, Efficiency, Quality of life, Gingival and periodontal health, and Patient satisfaction. Comparators were mainly restorative interventions (17 studies), remineralization (3), treatment of hypersensitivity (10), aesthetic interventions (5), and orthodontic interventions (3). Two highly clustered comparator networks emerged; many interventions were not robustly linked to these networks.

Conclusions: MIH intervention studies recorded both clinically- and patient-centered outcomes. Core Outcome Set (COS) development should consider these and supplement them with outcomes on, for example, applicability. The high number of compared interventions tested in only few studies and our SNA results implicate that the current evidence may not be robust.

Strengths and limitations of this study

- Molar incisor hypomineralization (MIH) is a frequent condition. No core outcome set on MIH exists.
- Outcomes and comparators for MIH studies were assessed using a systematic review.
- A network analysis was performed to evaluate the robustness of comparisons.
- The findings of this study will aid in core outcomes definition.
- The available body of evidence is limited and likely not robust.

Introduction

There is increasing interest in the internal and external validity of clinical studies, as indicated, for example, by their risk of bias [1 2] or their reporting quality [3]. Two aspects that only recently came into the focus, but have an impact on the validity are (1) outcome and (2) comparator choice.

So far, most clinical researchers chose the outcomes based on their understanding of what was relevant or not; the involvement of further stakeholders into outcome choice was seldom considered. This impacts on the relevance of study findings and may limit their applicability. Also, researchers usually collected a range of outcomes, without necessarily reporting all of them later on (selective reporting); mainly as data on outcomes with unwanted findings (which may nevertheless be relevant) can be omitted. The chosen outcomes and outcome measures may further suffer from limited comparability across studies, decreasing the chance to make the best use of clinical studies by synthesizing them. Outcome choice is thus relevant for study validity, applicability, and relevance, and implementation into practice [4-6].

Comparator choice impacts on the overall usefulness and validity of evidence [7]. Again, usually, most clinical researchers choose the comparators themselves, without necessarily consulting patients or further stakeholders such as insurers, regulators, etc. Comparators relevant to patients, for example, may hence not be evaluated, while other comparators may be over-proportionally employed [8-10]. The resulting gaps in the evidence may mean important data on possibly useful comparators are unavailable. Also, comparisons against placebo or no intervention (in single arm studies) or less effective options (so-called straw men) can lead to overestimation of effectiveness [9-11]. Repeated chain-linked comparisons against less-than-optimal standards were found to significantly distort the totality of evidence [9-11]. Comparator choice is relevant to make clinical research in a specific field useable, applicable, and informative.

The present study assessed outcome and comparator choice in intervention studies on Molar Incisor Hypomineralisation (MIH), a highly prevalent dental developmental disorder with a significant burden for patients and high treatment needs [12]. MIH is characterized by demarcated creamy-white, yellowish-brown or brown lesions with or without posteruptive enamel breakdown and hypersensitivity, affecting the permanent molars with or without additional affection of the incisors [13-15]. The severity of the

lesions, the symptomatology of the affected tooth as well as the patient's dental age, caries risk and expectations need to be considered in the management of MIH [15]. Dentists often need to employ different treatment strategies when dealing with MIH patients, including restoring cavities, alleviating pain or improving aesthetics [16], [17]. Given the broad spectrum of clinical presentations, individual needs and available treatment modalities, managing MIH is challenging for most practitioners [13-15].

Assessing the outcome and comparator choice in MIH intervention studies seems warranted. Such an assessment is further useful to inform the development of a Core Outcome Set (COS) for MIH management and prevention studies. COS are a minimum set of outcomes that have been agreed in a systematic consensus process by a diverse group of stakeholders (patients, dentists, researchers, insurance companies, etc). COS overcome the problem of a possibly limited relevance of chosen outcomes, the risk of selective reporting and the lack of synthesizability of study findings [18]. A range of COS development initiatives is currently underway in dentistry [19-23].

We aimed to review the outcomes used in MIH intervention studies to inform the development of a COS on MIH. We further aimed to assess the comparators used in these studies and to analyze the resulting study network. This was done using social network analysis (SNA), a method for evaluating the relationships between factors in a network [8], which has been introduced to dentistry recently [24]. As secondary aim, we evaluated if studies clearly indicated their primary outcome, if studies used a sample size estimation based on this outcome, and if studies were registered a priori, as should be expected.

Methods

This review was registered on the Core Outcome Measures in Effectiveness Trials (COMET) initiative website [1]. In parts, it builds on a previously published review on MIH management [25].

Search strategy

The following search was adapted for each database:

(treatment OR management OR prevention) AND (molar incisor hypomineralisation OR molar incisor hypomineralization OR mih).

Searches were developed and run individually for Medline, Embase, Cochrane Central, Google Scholar, opengrey.eu as well as DRKS and Clinicaltrials.gov and cross references were performed without any language restrictions (online supplementary appendix 1). The search covered the period from 01.01.1980 to 03.04.2019 (Fig. 1).

Data collection

Inclusion criteria: We included all types of clinical studies (retrospective or prospective, controlled trials or cohort studies) in patients diagnosed with MIH. Note that studies conducted before 2001 on the condition will not have employed the term “MIH”, and may have been missed by our search. This, however, was accepted, as without a clear case definition, other conditions may have been captured by these studies too, without being able to separate conditions post hoc. Studies reported on prevention and/or management interventions for MIH teeth. There were no restrictions on setting, time of follow-up, or patients’ age. Case reports or case series with a sample size of < 10 participants were excluded. No language restriction was set; studies in languages other than English, German or Arabic (if present) were translated by native speakers. Selection process: Two authors (FS, KE) screened titles independently and compared their findings. In case of disagreement, titles were included to obtain full-texts. Full-texts were assessed independently after de-duplication. In cases of disagreement, studies were included after consensus was reached through discussion.

Data extraction: The following data was extracted duplicatively and independently by two authors (KE and FS) following calibration using a pilot database:

- Study details (author name, title, journal, year of publication);
- Study characteristics;
    - Study setting (primary or secondary care)
    - Number and age of participants
    - Study type (controlled or uncontrolled, pro- or retrospective)
    - Target condition (MIH lesions on molars, incisors, or both)
    - Number of study arms

- Interventions compared
- Follow-up period
- Outcomes assessed, separated for primary and secondary outcome(s). An outcome was considered a primary outcome if it was stated as such, or where the report clearly focused on one outcome. If no primary outcome was identifiable or multiple outcomes were reported, these were considered secondary outcomes.
- Outcome measures

- Sample size estimation (yes/no)
- Trial registration (yes/no).

Data synthesis

A list of outcomes was compiled and outcomes with different verbatim terms but similar meanings gathered using a single agreed term. Outcomes were grouped within outcome categories; these were refined through group discussion before all outcomes were categorized using the final agreed terms. The final list of outcome categories comprised 11 items; Restoration success, Aesthetic improvement, Pain and hypersensitivity management, Mineral gain, Space management, Anesthesia effectiveness, Preventive success, Efficiency, Quality of life, Gingival and Periodontal health, and Patient satisfaction. The use of different outcome categories was analyzed via descriptive statistics. Exemplary outcomes and outcome measures were allocated to one of these outcome categories by discussion and agreement of two authors (KE and FS). Where there was disagreement, a consensus was achieved through discussion with all authors.

A list of comparators was compiled and comparators were grouped into agreed categories. The granularity of these categories allowed to capture specific comparators (like “glass ionomer cement restoration”) while grouping similar comparators in the same category (e.g. different cement brands). Comparator choice was analyzed via SNA. In SNA, nodes (termed ‘vertices’) are formed by comparators and are connected by edges (comparisons made within the same trial). In a graphical analysis, the node diameter represents the number of comparator arms forming the node and thickness of edges represents the number of direct comparisons. We

performed separate analyses (and graphic representations) for studies on MIH in molars versus incisors. Statistical analysis included the assessment of the degree (average number of comparators per node) and the clustering coefficient (values of one indicate that all possible connections were made, while values of 0 indicate that only the minimum number of connections were made) [26-28]. Statistical analysis was only performed for the main network in each sub-analysis (molars; incisors). The Python package NetworkX was used.

Patient and public involvement

Patients were not involved in this study at this point but will be during the core outcomes definition.

Results

Included studies

The database search yielded 7979 records; 4106 remained after de-duplication. There were 100 potentially relevant articles and the full texts of all these 100 articles were located (100% retrieval rate); 35 met the inclusion criteria and were included (Fig. 1).

Characteristics of included trials

Of the 35 included studies, all (100%) were conducted in a secondary care setting (hospital or university). The total number of participants was 2124; per study, a mean of 60 (range 12 – 300) participants were included. Only children (mean age < 12 years) were included in 33 included reports (94%). Only one (3%) study reported on adults (mean age 33 years). In two other publications (6%) it was not possible to determine the age of the participants. There were 10 (29%) one-arm studies, 18 (51%) two-arm studies, 3 (9%) three-arm studies, and 4 (11%) multi-arm studies. Further details on the included studies can be found in Table 1.

Outcome choice

In total, 11 outcome categories were deduced from the included studies (Fig. 2, Table 2). The most frequent specific categories were “Restoration success” and “Pain/ discomfort/ hypersensitivity”; with 17 (49%) and 12 (34%) studies reporting them, respectively. The next most common were “Quality of life” and “Efficiency” (each 5 studies, 14%); “Aesthetic improvement” and “Preventive success” (4 studies, 11%); “Mineral gain”, “Space management” and “Anesthesia effectiveness” (each 3 studies, 9%). The least common ones were “Patient satisfaction” and “Gingival and periodontal health” (each 2 studies, or 6%). Outcome categories that have increased in use (from 2000-2009 to 2010-2018) included “Aesthetic improvement”, “Mineral gain”, “Efficiency”, and “Gingival and periodontal health”.

Findings for molars

For molars, 10 outcome categories were identified from the included studies. Those were: “Restoration success” with a total of 17/28 studies reporting on it (15/17 as primary outcome and 2/17 as secondary outcome); “Pain/discomfort/hypersensitivity” with a total of 12/28 studies reporting on it (4/12 as primary outcome and 8/11 as secondary outcome); “Quality of life” with a total of 5/28 studies reporting on it (2/5 as primary outcome and 3/5 as secondary outcome); “Efficiency” with a total of 5/28 studies reporting on it (1/5 as primary outcome and 4/5 as secondary outcome); “Preventive success” with a total of 4/28 studies reporting on it (3/4 as primary outcome and 1/4 as secondary outcome); “Anesthesia effectiveness” with a total of 3/28 studies reporting on it (2/3 as primary outcome and 1/3 as secondary outcome); “Space management” with a total of 3/28 studies reporting on it (1/3 as primary outcome and 2/3 as secondary outcome); “Mineral gain” with a total of 2/28 studies reporting on it (all as primary outcome); “Gingival and periodontal health” with a total of 2/28 studies reporting on it (1/2 as primary outcome and 1/2 as secondary outcome); “Patient satisfaction” with a total of 2/28 studies reporting on it (all as secondary outcome).

Findings for incisors

For incisors, only four outcome categories were identified from the included studies. Those were: “Aesthetic improvement” with a total of 4/7 studies reporting on it (all as primary outcome); “Pain/discomfort/hypersensitivity” with a total of 1/7 study reporting on it (as primary outcome); “Quality of life” with a total of 1/7 study reporting on it (as primary outcome); “Mineral gain” with a total of 1/7 study reporting on it (as primary outcome).

Comparator choice

Two separate analyses on comparator choice were performed; one for studies on molars and one on incisors. In both groups, a loosely connected main network and several further, unconnected networks or comparators were present, indicating poor connectivity between comparators (Figs. 3 and 4). Certain comparators were more frequently chosen than others.

In molars (Fig. 3), many studies compared different restorative strategies, for example, composite (with different brands also tested against each other), metal, ceramic or cement restorations. Further comparisons, non-connected to this main (restorative) network, involved caries preventive interventions, management of hypersensitivity, and cavity preparation and condition techniques. The mean degree of the main, restorative network was 5.9, with a density of 0.49. The cluster coefficient (which ranges from 0 – no clustering – to 1 – maximum clustering) was 0.76, indicating that there was significant clustering, with certain comparators being compared with each other (in “cliques”), while other possible comparisons (against comparators outside of these cliques) not having been made.

In incisors (Fig. 4), a main network, comparing different remineralization strategies, emerged, with two further networks and two further, non-connnected comparators on aesthetic management of MIH. The mean degree of the main (remineralization) network was 5, with a density of 1.0. The cluster coefficient was 1.0, indicating that there were “cliques” of comparators present, with comparators being mainly compared within and not across these cliques.

Primary outcome and sample size calculation

Primary outcomes could be identified in all 35 (100%) reports (Table 3). Throughout all years (2000 to 2019), "Restoration success" was the most frequently assessed primary outcome (17/35). Information on sample size calculation was provided in 7 (20%) reports, all but one being published between 2016 and 2019. Of these 7 reports, 5 (71%) related this calculation to the primary outcome.

Trial registration reporting

Only 10 (29%) of all articles reported a trial registration [29]. In the 10 years following the publication of the first CONSORT statement (2001-2010), not a single report included a trial registration. Following the publication of the second CONSORT statement (2011-2019), this increased to 29%.

Discussion

This systematic review assessed outcome and comparator choice in MIH intervention studies, and their change over time. We found that studies recorded a large range of outcomes, especially when considering the limited number of studies overall, and that the diversity of these outcomes is increasing. This is reassuring, and the findings of this review are helpful to develop a COS. We also found that despite the low number of studies available, a large range of different interventions was tested, which led to the occurrence of segregated networks. Resulting from this clustering and the fact that most interventions were not well compared against alternatives, the current body of evidence on MIH interventions is likely not robust.

The outcomes used in MIH intervention studies focused on two main areas; restoration success (measured via the USPHS criteria or similar tools) and pain/ discomfort/ hypersensitivity (measured via scales like the Visual analog scale or the Schiff Cold Air Sensitivity Scale). Combined, these two areas accounted for the majority of primary and all reported outcomes. Both restoring MIH teeth and managing pain can be assumed to be the major difficulties dentists face when treating MIH. Research has shown that MIH-affected children receive and need more dental treatment compared to unaffected children [30-35]. Also already restored MIH-molars remain within short re-

treatment cycles [30]. The porous nature of MIH enamel and the presence of post eruptive enamel breakdown leads to the presence of hypersensitivity and pain, which are often the patients' chief complaints and affect their quality of life. They also increase the risk of dental fear and anxiety [15 36-38]. Overall, the focus on how to best restore these teeth and alleviate pain seems justified.

Nevertheless, the use of other outcome categories like quality of life or efficiency appears to be growing, reflecting an ongoing shift to patient-centered care (and research) and the increasing relevance of health economics in today's resource-limited healthcare settings. We will, in the next stage of our COS development, suggest these outcomes to be included in the COS on MIH intervention studies, and will seek stakeholder consensus on their inclusion (or not).

We also investigated further outcome-related aspects in the included studies. For example, trial registration, one of the recommendations of the CONSORT statement [39 40], was found in only 10 studies (and even very recent studies did not commonly report on this). While such registration may be seen as a prerogative of controlled trials, also single-arm prospective trials should clearly state what is to be investigated using which methods and tools in what population before commencing the study. This does not seem to be the case. Registration would help to reduce selective outcome reporting and could also assist in improving reporting standards (and general methodology) in MIH intervention studies.

Also, of the 35 reports, only 7 studies reported a sample size calculation, and of these, only 5 related this to the primary outcome. Again, while such calculations are mainly demanded for controlled prospective trials, researchers should have a rational basis for calculating the number of participants needed in any study (regardless of its design), be it to ascertain that differences between the interventions can be detected with a planned level of statistical confidence or be it to reduce statistical noise (allowing somewhat firm conclusions). Sample size calculation is a key recommendation in the CONSORT statement, published in 2001 [40] and revised in 2010 [39]. It was promising to find that, since this revision, more publications reported on a sample size calculation (while the overall number remained low).

Our network analysis found that most comparisons in MIH trials included few, favored comparators; many possible comparisons were never made, and some comparators were not at all compared against alternatives. Moreover, and understandable,

comparators focusing on specific indications (managing pain, restoring cavities, improving aesthetics) were connected within, not between these indications. Overall, the information emerging from such poorly connected networks with regards to the relative efficacy of the interventions (answering the question of which intervention is most suited for a specific therapeutic goal) is likely not robust. The small sample sizes in most studies further add to the limited robustness of the existing evidence. Overall, the relatively "young" field of MIH research has so far not accrued sufficiently robust data which allows strong recommendations for clinicians.

This study has a number of limitations. First, the effort to improve COS methodology is ongoing, and our review used only one of several available strategies suggested for COS developers. For example, it seems that to reach saturation on outcomes and outcome categories, it may not be necessary to search multiple databases [41], while we did so, also as this review was an update of a previous one and we aimed to apply the same methodology. Second, developing outcome categories and assigning specific verbatim outcomes to these categories is challenging [21], often as outcomes are either inter-related or composites, capturing different outcome categories [42]. While there is no acknowledged MIH outcome classification system, it is clear that alternative classifications may have resulted in changes to the granularity and focus of the results. Third, researchers tend to publish multiple reports from the same clinical trial [43]. This can be necessary to report on the dataset at different time points or to report on multiple analyses. Data is then divided and spread across multiple publications, which makes linking or summarizing these articles very difficult. We assume to have captured all articles given that the field is limited. Last, in order to limit selective outcome bias and in the attempt of including the most recent trials, registries were searched in our study, too. This, however, has its limitations, since there are often incomplete or unclear registrations, and we were only limitedly able to extract data.

Conclusions

Outcomes reported in interventional trials for the management and prevention of MIH focused on the performance of restorative materials or and the management of pain and hypersensitivity associated with MIH-affected teeth. Outcomes related to oral-health related quality of life and economics have grown in use and are likely to be

important in the future. Patient-reported or patient-centered outcomes were rarely reported. COS development should include these and may supplement them with new outcomes, e.g. on applicability. The high number of compared interventions tested in only a few studies and our SNA results implicate that current evidence may not be robust.

Trial status (Registration):

COMET initiative online http://www.comet-initiative.org/studies/details/1155 [1]

Competing interests

None declared

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Ethical approval

Not applicable.

Author contributions

The study was conceived by KE and FS. KE and JK analyzed, interpreted the data. KE, P-G J-B and FS wrote the manuscript. All authors read and approved the manuscript.

Transparency declaration

The lead author* affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Data availability statement

All data relevant to the study are included in the article or uploaded as supplementary information.

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Table 1. Characteristics of included studies (n=35). Studies were separated according to target condition (MIH in molars or incisors), and ordered chronologically.

Author	Year	Setting	N part.	Age	Study type	Follow-up (months)	Trial reg.	No. of Arms	P cal.
Molars									
Koch and Garcia-Godoy [44]	**2000**	Uni. H	12	6-8	Pro Co	24-60	n	3	n
Lygidakis et al. [45]	**2003**	Uni. H	46	8-10	Pro Co	48	n	1	n
Zagdwon et al. [46]	**2003**	Uni. H	17	6-16	RCT	12-24	n	2	y
Kotsanos et al. [32]	**2005**	Uni. H	72	8	Retro Co	52	n	4	n
Mejare et al. [33]	**2005**	Uni. H	76	6-17	Retro Co	62	n	7	n
Jalevik and Moller [47]	**2007**	Uni. H	27	6-13	Retro Co	44-99	n	1	n
Lygidakis et al. [48]	**2009**	Uni. H	47	6-7	RCT	48	n	2	n
Baroni and Marchionni [49]	**2011**	Uni. H	30	6-9	Pro Co	36	n	1	n
Gaardmand et al. [50]	**2013**	Uni. H	33	8-18	Retro Co	39	n	1	n
Cabasse et al. [51]	**2015**	Uni. H	39	9	Pro Co	n	n	1	n
Fragelli et al. [52]	**2015**	Uni. H	21	6-9	Pro Co	12	n	1	n
Bekes et al. [53]	**2016**	Uni. H	16	8	Pro Co	2	n	2	y
Bakkal et al. [54]	**2017**	Uni. H	38	7-12	RCT	1	n	2	n
de Souza et al. [55]	**2017**	Uni. H	18	6-8	RCT	18	y	2	n
Fragelli et al. [56]	**2017**	Uni. H	21	6-8	RCT	18	n	2	y
Sönmez and Saat [57]	**2017**	Uni. H	42	8-12	RCT	24	n	4	n
Dixit and Joshi [58]	**2018**	Uni. H	32	8-14	RCT	n/a	n	2	y
Folayan et al. [59]	**2018**	Uni. H	73	8-16	Pro Co	n/a	n	2	n
Grossi et al. [60]	**2018**	Uni. H	40	7-13	Pro Co	12	y	1	n
Koleventi et al. [61]	**2018**	Uni. H	14	11	Pro Co	6	n	2	n
Pasini et al. [62]	**2018**	Uni. H	40	8-13	Pro Co	4	n	2	n/a
Dhareula et al. [63]	**2019**	Uni. H	30	8-13	RCT	36	y	2	y
Incisors									
Wong and Winter [64]	**2002**	Uni. H	15	n/a	RCT	6	n	1	n
Özgül et al [65]	**2013**	Uni. H	33	7-12	RCT	1	n	6	n
Sheoran et al. [66]	**2014**	Uni. H	25	11-13	RCT	1	n	2	n
Restrepo et al. [67]	**2016**	Uni. H	51	9-12	Pro Co	1	n	2	y
Bhandari et al. [68]	**2018**	Uni. H	n/a	7-16	Pro Co	6	n	1	n
Hasmun et al. [69]	**2018**	Uni. H	111	7-16	Pro Co	n/a	n	1	y

Only Registered									
DRKS00009760	**2016**	Uni. H	40	6-70	RCT	6	y	2	n
DRKS00011882	**2017**	Uni. H	300	7-14	Pro Co	0,5	y	3	n/a
NCT03614819	**2018**	Uni. H	122	6-10	RCT	24	y	2	n/a
NCT03760497	**2018**	Uni. H	300	6-10	RCT	24	y	3	n/a
NCT03826810	**2019**	Uni. H	48	n/a	RCT	12	y	2	n/a
NCT03870958	**2019**	Uni. H	195	6-9	RCT	36	y	2	n/a
NCT03862014	**2019**	Uni. H	100	6-10	RCT	24	y	2	n/a

Abbreviations: N of part., number of participants; n/a, not available; Pro Co, prospective cohort; Retro Co, retrospective cohort; RCT, randomized control trial; Uni. H, University hospital; Trial reg., trial registration, P cal., power calculation; n, no; y, yes

Table 2. Reported outcome category, outcome examples and outcomes measures, ordered according to the frequency of use in included studies.

Outcome category	Outcome examples	Exemplary outcome measures
Restoration success	Clinical performance Restoration quality Survival of tooth and restoration	Modified US Public Health Service (USPHS) criteria Modified atraumatic restorative treatment (ART) criteria Radiographic evaluation (Bitewings) Number of reinterventions Survival rate
Pain/ discomfort/ hypersensitivity	Response to stimulus Pain during and after dental treatment/ intervention	Schiff Cold Air Sensitivity Scale (SCASS) Questionnaires Modified behavior pain scale Visual Analogue Scale (VAS)
Aesthetic improvement	Aesthetic improvement	Questionnaires Clinical photography
Mineral gain	Mineral gain	Laserfluorescence readings Scanning electron microscope (SEM)/ Energy Dispersive X-ray Spectrometry (EDX) Quantitative Light-Induced Fluorescence (QLF)
Space management	Space closure after extraction Need of orthodontic intervention	Amount of spontaneous space closure
Anesthesia effectiveness	Anesthesia technique Need for local anesthesia	Presence of pain during treatment Pain efficacy scale
Preventive success	Clinical performance Sealant quality Ability to prevent caries and enamel breakdown	Success/ Modified US Public Health Service (USPHS) criteria
Efficiency	Costs of treatment	Placement time Used materials Laboratory costs
Quality of life	Oral health-related quality of life (OHRQoL)	Self-administered oral health related quality of life (OHRQoL) questionnaires (COHIP G-19, CPQ 8-10, CPQ 11-14)
Gingival and periodontal health	Presence of gingivitis and periodontitis Oral hygiene Subgingival microbiota	Gingival index (GI) Pocket depth (PD) Turesky plaque index Checkerboard DNA-DNA hybridization
Patient satisfaction	Patient satisfaction with treatment	Visual Analogue Scale (VAS) Questionnaires

Table 3. Primary and secondary outcomes reported in each study.

Author (year)	Restoration success	Pain/ discomfort/ hypersensitivity	Aesthetic improvement	Mineral gain	Space management	Anesthesia effectiveness	Preventive success	Efficiency	Quality of life	Gingival and periodontal health	Patient satisfaction
Koch and Garcia-Godoy (2000) [44]	x										
Wong and Winter (2002) [64]			x								
Lygidakis et al. (2003) [45]	x	♦					♦				
Zagdwon et al. (2003) [46]	x							♦			
Kotsanos et al. (2005) [32]	x				♦						
Mejare et al. (2005) [33]	x				♦						
Jalevik and Moller (2007) [47]					x						
Lygidakis et al. (2009) [48]	x										
Baroni and Marchionni (2011) [49]				x							
Gaardmand et al. (2013) [50]	x										
Özgül et al (2013) [65]		x									
Sheoran et al. (2014) [66]			x								
Cabasse et al. (2015) [51]						x					
Fragelli et al. (2015) [52]	x										
Bekes et al. (2016) [53]		x									
DRKS00009760 (2016)			x								
Restrepo et al. (2016) [67]				x							
Bakkal et al. (2017) [54]				x							
de Souza et al. (2017) [55]	x										
DRKS00011882 (2017)									x		
Fragelli et al. (2017) [56]	x						♦				
Sönmez and Saat (2017) [57]	x	♦									
Bhandari et al. (2018) [68]			x								
Dixit and Joshi (2018) [58]		♦				x		♦			
Folayan et al. (2018) [59]								x			
Grossi et al. (2018) [60]	x	♦				♦					
Hasmun et al. (2018) [69]									x		

Koleventi et al. (2018) [61]						x	
Pasini et al. (2018) [62]		x					
NCT03614819 (2018)	♦	♦	x	♦	♦		♦
NCT03760497 (2018)	x	♦			♦		♦
Dhareula et al. (2019) [63]	x	♦				♦	
NCT03826810 (2019)	♦	x					
NCT03870958 (2019)		♦	x	♦	♦		
NCT03862014 (2019)	x						

x, primary outcome; ♦, secondary outcome

Figure legends:

Figure 1. Flow chart of the search.

Figure 2. Reported outcomes for MIH intervention studies over time. N number of studies using this outcome in a specific period.

Figure 3. Networks of comparisons made in molars. Different comparators (nodes) were compared directly with each other. The node diameter represents the number of studies involving this comparator, moreover, the number of studies is added between brackets in each node, the thickness of the edge represents the number of direct comparisons between two comparators. Certain comparators were not connected to the main network. Abbreviations: PMC, preformed metal crowns; GIC, glass ionomer cement; ART, atraumatic restorative treatment; aPDT, low-intensity laser and photodynamic Therapy; SDF, silver diamine Fluoride; ARR, atraumatic resin restoration; CPP-ACP; casein phosphopeptide-amorphous calcium phosphate; SEA, self-etching adhesive; TEA; total-etch adhesive; HCL; hydrochloric acid; NaOCl, sodium hypochlorite.

Figure 4. Networks of comparisons made in incisors. Different comparators (nodes) were compared directly with each other. The node diameter represents the number of studies involving this comparator, moreover, the number of studies is added between brackets in each node, the thickness of the edge the number of direct comparisons between two comparators. Certain comparators were not connected to the main network. Abbreviations: CPP-ACP; casein phosphopeptide-amorphous calcium phosphate; HCl;hydrochloric acid.

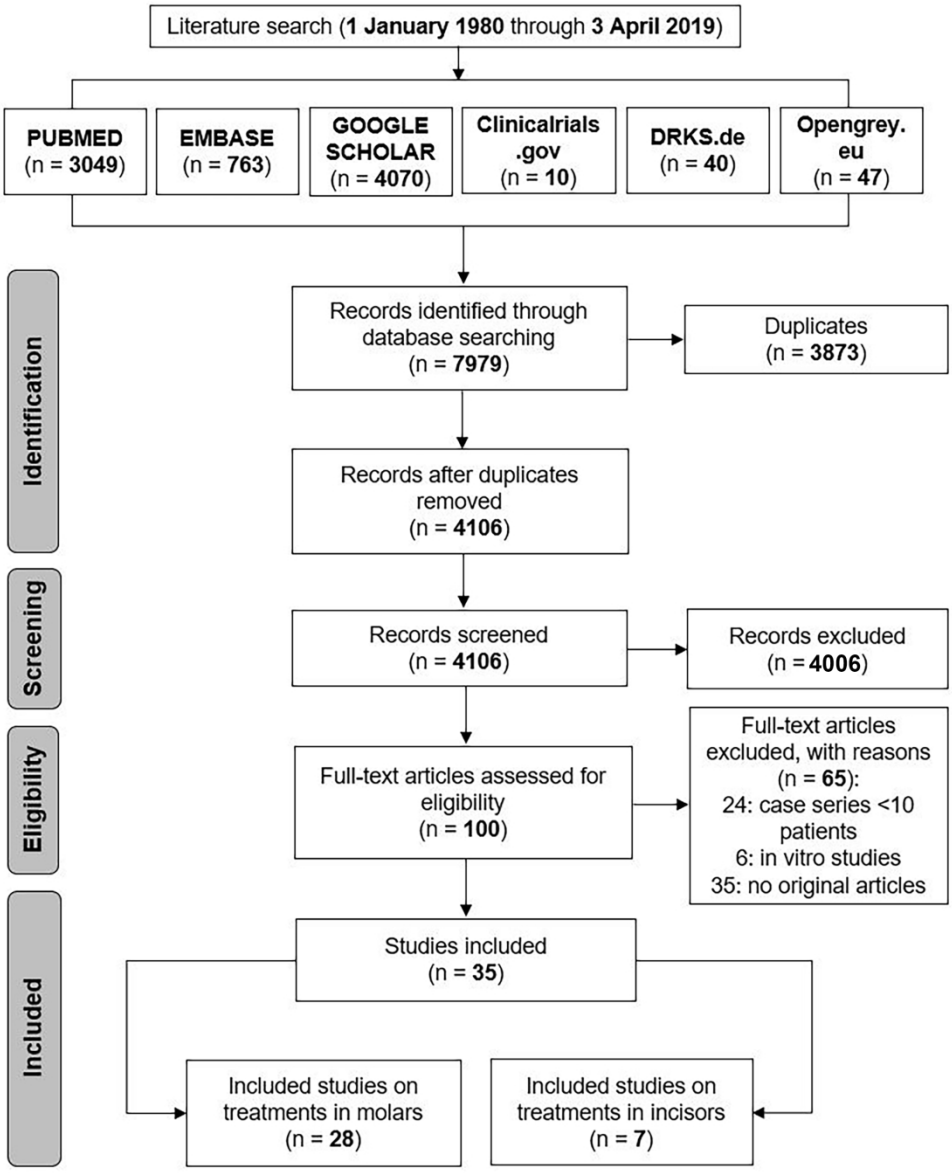

Figure 1. Flow chart of the search.

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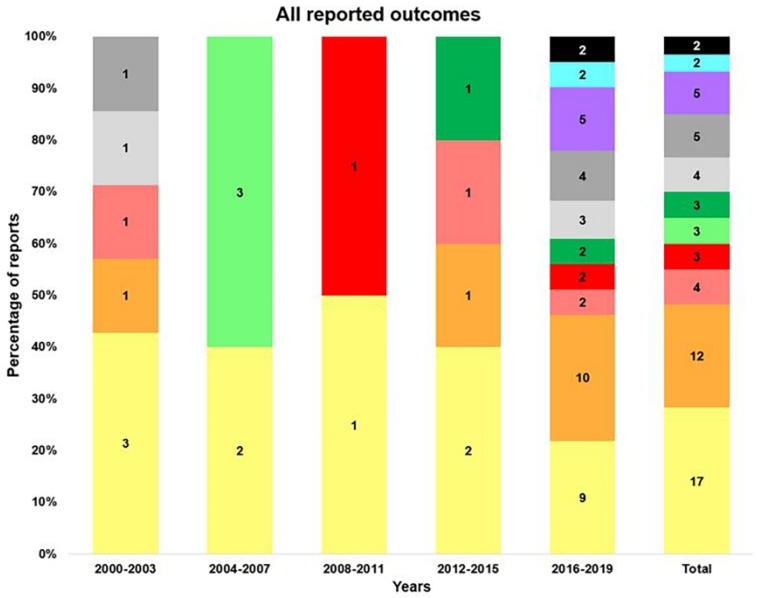

	2000-2003	2004-2007	2008-2011	2012-2015	2016-2019	Total
1. Restoration success	3	2	1	2	9	17
2. Pain/discomfort/hypersensitivity	1			1	10	12
3. Aesthetic improvement	1			1	2	4
4. Mineral gain			1		2	3
5. Space management		3				3
6. Anesthesia effectivness				1	2	3
7. Preventive success	1				3	4
8. Efficiency	1				4	5
9. Quality of life					5	5
10. Gingival and Periodontal health					2	2
11. Patient satisfaction					2	2
Total	7	5	2	5	41	60
%	11.67%	8.33%	3%	8.33%	68.33%	100.00%

Figure 2. Reported outcomes for MIH intervention studies over time. N number of studies using this outcome in the specific period.

264x244mm (300 x 300 DPI)

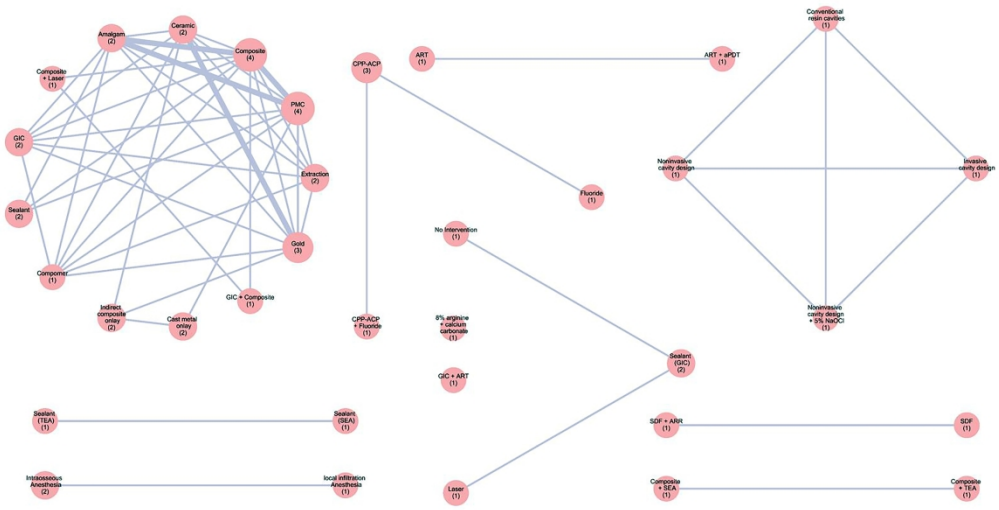

Figure 3. Networks of comparisons made in molars. Different comparators (nodes) were compared directly with each other. The node diameter represents the number of studies involving this comparator, moreover the number of studies is added between brackets in each node, the thickness of the edge represents the number of direct comparisons between two comparators. Certain comparators were not connected to the main network. Abbreviations: PMC, preformed metal crowns; GIC, glass ionomer cement; ART, atraumatic restorative treatment; aPDT, low-intensity laser and photodynamic Therapy; SDF, silver diamine Fluoride; ARR, atraumatic resin restoration; CPP-ACP; casein phosphopeptide-amorphous calcium phosphate; SEA, self-etching adhesive; TEA; total-etch adhesive; HCL; hydrochloric acid; NaOCl, sodium hypochlorite.

417x218mm (300 x 300 DPI)

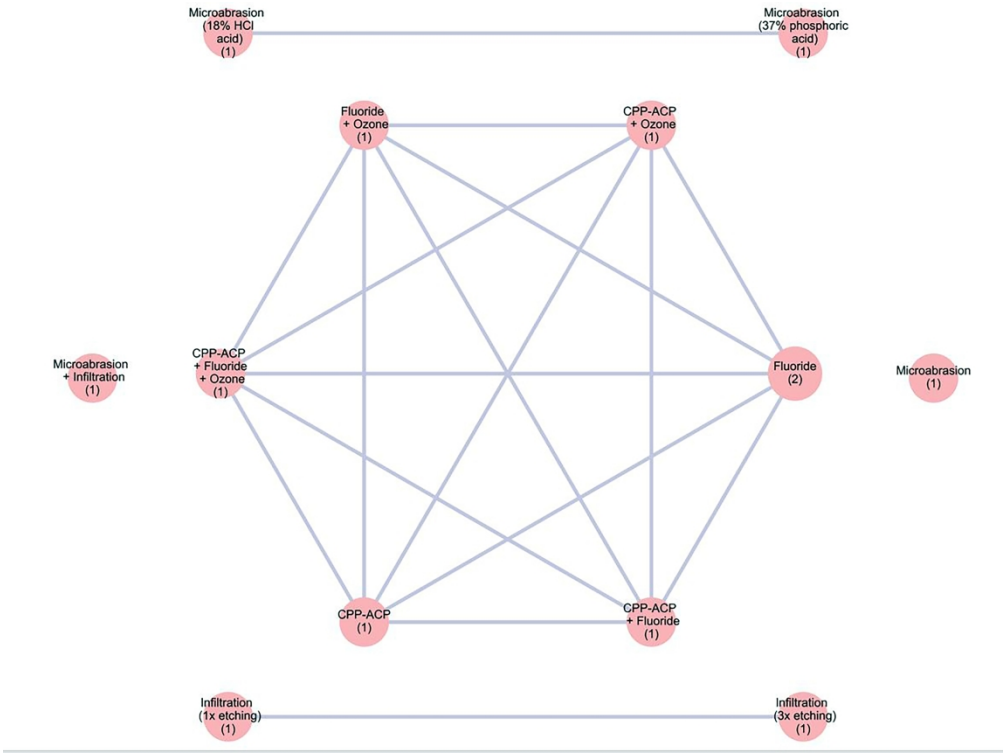

Figure 4. Networks of comparisons made in incisors. Different comparators (nodes) were compared directly with each other. The node diameter represents the number of studies involving this comparator, moreover the number of studies is added between brackets in each node, the thickness of the edge the number of direct comparisons between two comparators. Certain comparators were not connected to the main network. Abbreviations: CPP-ACP; casein phosphopeptide-amorphous calcium phosphate; HCL; hydrochloric acid showing studies on MIH-affected molars, while B) studies on MIH-affected incisors.

312x234mm (300 x 300 DPI)

Appendix 1

Database:

Medline (PUBMED)

Search period:

01.01.1980 to 03.04.2019

Search strategy (keywords):

(((((treatment) OR management) OR prevention) AND molar incisor hypomineralisation) OR molar incisor hypomineralization) OR mih

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4-6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4-5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5-6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	-
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	-
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	-
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	-
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8-10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	-
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	11

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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