Supplementary Table 1. PRISMA 2020 Checklist.

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	p.1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	p. 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	p.3-4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	p. 4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	p. 5-6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	p. 5-6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	p.5-6,S.fig.2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	p.7; Fig.1
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	p. 5-7
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	p. 5-6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	p. 5-6
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	p. 6-7
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	p. 7
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	p. 7
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	p. 7
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	p. 7
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	p. 7
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	p. 7
Reporting bias	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	p. 7

Section and Topic	Item #	Checklist item	Location where item is reported
assessment			
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	p. 7
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	p. 7; Fig. 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	p. 7
Study characteristics	17	Cite each included study and present its characteristics.	
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	p. 8-9
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	p. 9-11
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	p. 8
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	p. 8
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	p. 8
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	p. 8-11
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	p. 9-11
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	p. 11
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	p. 12-15
	23b	Discuss any limitations of the evidence included in the review.	p. 12-15
	23c	Discuss any limitations of the review processes used.	p. 16-17
	23d	Discuss implications of the results for practice, policy, and future research.	p. 17-18
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	p. 2, 5
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	p. 2, 5
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	p. 19
Competing interests	26	Declare any competing interests of review authors.	p. 19
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

Supplementary Table S2. Search strategies (search performed on 08.07.2024).

Database	Search strategy
PubMed	((molar AND hypominerali*) OR (MIH) OR (hypominerali*) OR (demarcated AND opacities) OR (developmental AND opacit*) OR (white AND opaque AND enamel) OR (enamel AND opacit*) OR (enamel AND defect) OR (developmental AND dental AND defects) OR (calcification AND molar))AND((cpp-acp) OR (casein phosphopeptide-amorphous calcium phosphate) OR (GC tooth mousse) OR (recaldent) OR (MI paste plus) OR (MI varnish) OR (tooth mousse plus) OR (arginine) OR (Arg) OR (xylitol) OR (Remin Pro) OR (bioactive glass) OR (BAG) OR (sodium calcium phosphosilicate) OR (Novamin) OR (tricalcium phosphate) OR (TCP) OR (fluoride) OR (sodium monofluorophosphate) OR (calcium sucrose phosphate) OR (TiF4 varnish) OR (Duraphat) OR (nano hydroxyapatite) OR (NAOCL) OR (sodium hypochlorite) OR (silver diamine fluoride))
Embase	(('molar'/exp OR molar) AND hypominerali* OR 'mih'/exp OR mih OR hypominerali* OR (demarcated AND opacities) OR (developmental AND opacit*) OR (('white'/exp OR white) AND opaque AND ('enamel'/exp OR enamel)) OR (('enamel'/exp OR enamel) AND opacit*) OR (('enamel'/exp OR enamel) AND defect) OR (developmental AND ('dental'/exp OR dental) AND defects) OR (('calcification'/exp OR calcification) AND ('molar'/exp OR molar))) AND ('cpp acp' OR 'casein phosphopeptide-amorphous calcium phosphate' OR (('casein'/exp OR casein) AND 'phosphopeptide amorphous' AND ('calcium'/exp OR calcium) AND ('phosphate'/exp OR phosphate)) OR 'gc tooth mousse' OR (gc AND ('tooth'/exp OR tooth) AND mousse) OR recaldent OR 'mi paste plus' OR (mi AND ('paste'/exp OR paste) AND ('plus'/exp OR plus)) OR 'mi varnish' OR (mi AND ('varnish'/exp OR varnish)) OR 'tooth mousse plus' OR (('tooth'/exp OR tooth) AND mousse AND ('plus'/exp OR plus)) OR 'arginine'/exp OR arginine OR 'arg'/exp OR arg OR 'xylitol'/exp OR xylitol OR 'remin pro' OR (remin AND pro) OR 'bioactive glass'/exp OR 'bioactive glass' OR (('bioactive'/exp OR bioactive) AND ('glass'/exp OR glass)) OR 'bag'/exp OR bag OR 'sodium calcium phosphosilicate' OR (('sodium'/exp OR sodium) AND ('calcium'/exp OR calcium) AND phosphosilicate) OR 'novamin'/exp OR novamin OR 'tricalcium phosphate'/exp OR 'tricalcium phosphate' OR (tricalcium AND ('phosphate'/exp OR phosphate)) OR 'tcp'/exp OR tcp OR 'fluoride'/exp OR fluoride OR 'sodium monofluorophosphate'/exp OR 'sodium monofluorophosphate' OR (('sodium'/exp OR sodium) AND ('monofluorophosphate'/exp OR monofluorophosphate)) OR 'calcium sucrose phosphate' OR (('calcium'/exp OR calcium) AND ('sucrose'/exp OR sucrose) AND ('phosphate'/exp OR phosphate)) OR 'tif4 varnish' OR (tif4 AND ('varnish'/exp OR varnish)) OR 'duraphat'/exp OR duraphat OR 'nano hydroxyapatite'/exp OR 'nano hydroxyapatite' OR (('nano'/exp OR nano) AND ('hydroxyapatite'/exp OR hydroxyapatite)) OR naocl OR 'sodium hypochlorite'/exp OR 'sodium hypochlorite' OR (('sodium'/exp OR sodium) AND ('hypochlorite'/exp OR hypochlorite)) OR 'silver diamine fluoride'/exp OR 'silver diamine fluoride' OR (('silver'/exp OR silver) AND ('diamine'/exp OR diamine) AND ('fluoride'/exp OR fluoride)))

Database	Search strategy
Cochrane Central Register of Controlled Trials (CENTRAL)	((molar AND hypominerali*) OR (MIH) OR (hypominerali*) OR (demarcated AND opacities) OR (developmental AND opacit*) OR (white AND opaque AND enamel) OR (enamel AND opacit*) OR (enamel AND defect) OR (developmental AND dental AND defects) OR (calcification AND molar)) AND ((cpp-acp) OR (casein phosphopeptide-amorphous calcium phosphate) OR (GC tooth mousse) OR (recaldent) OR (MI paste plus) OR (MI varnish) OR (tooth mousse plus) OR (arginine) OR (Arg) OR (xylitol) OR (Remin Pro) OR (bioactive glass) OR (BAG) OR (sodium calcium phosphosilicate) OR (Novamin) OR (tricalcium phosphate) OR (TCP) OR (fluoride) OR (sodium monofluorophosphate) OR (calcium sucrose phosphate) OR (TiF4 varnish) OR (Duraphat) OR (nano hydroxyapatite) OR (NAOCL) OR (sodium hypochlorite) OR (silver diamine fluoride))

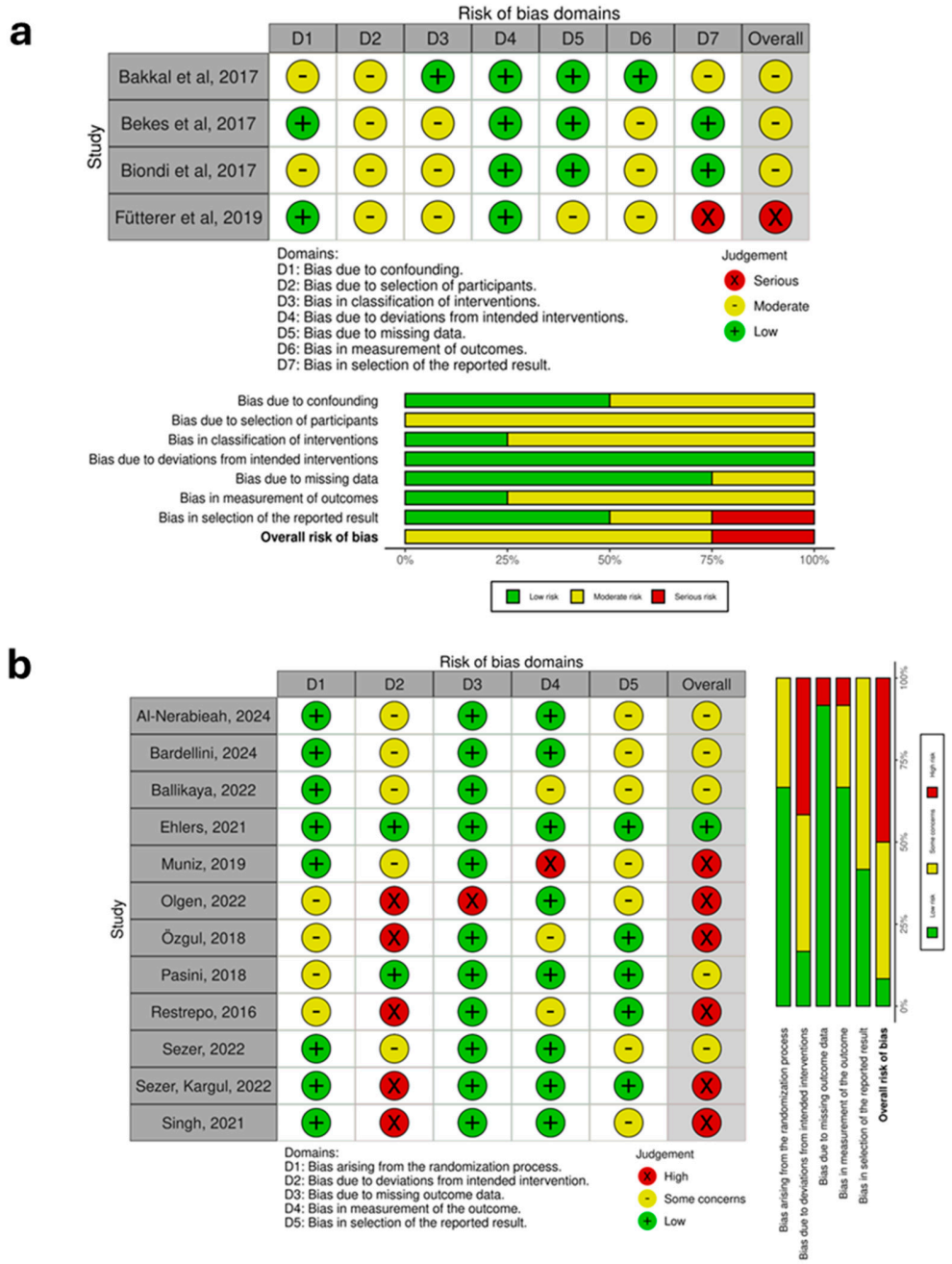
Supplementary Table S3. Description of severity level according to the EAPD criteria (described by Lygidakis et.al, 2022).

Severity level	Signs and symptoms
Mild	Demarcated enamel opacities without enamel breakdown Induced sensitivity to external stimuli e.g., air/water but not brushing Mild aesthetic concerns on discoloration of the incisors
Severe	Demarcated enamel opacities with breakdown and caries Spontaneous and persistent hypersensitivity affecting function e.g., brushing, mastication Strong aesthetic concerns that may have socio-psychological impact

Supplementary Table S4. List of excluded studies during full text-selection.

Author, year	Reasons for exclusion
Amaechi et.al, 2022	Randomized in-situ study.
Cardoso-Martins et. al, 2022$_a$	In-vitro study.
Cardoso-Martins et.al, 2022$_b$	In-vitro study.
Gatón-Hernandéz et.al, 2020	Restorative approach used.
Mendonca et.al, 2022	Protocol for RCT.
Nogueira et.al, 2021	Study not reporting hypersensitivity/remineralization outcomes.

Supplementary Figure S1. Risk of bias of the included in the study.



Supplementary Figure S2. Different agents used for hypersensitivity in MIH lesions.

