Systematic Review
Pediatric Dentistry

Do patients with molar incisor hypomineralization have more dental anxiety and behavior management problems? A systematic review with meta-analysis

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Abstract: This systematic review evaluated the available evidence on whether children with molar incisor hypomineralization (MIH) have more dental fear and anxiety (DFA) and dental behavior management problems (DBMPs) than those without MIH (Prospero CDR42020203851). Unrestricted searches were performed in PubMed, Scopus, Web of Science, Lilacs, BBO, Embase, Cochrane Library, APA PsycINFO, Open Grey, and Google Scholar. Observational studies evaluating DFA and/or DBMPs in patients with and without MIH were eligible. Reviews, case reports, interventional studies, and those based on questionnaires to dentists were excluded. The methodological quality assessment was based on the Newcastle-Ottawa Scale. Random-effects meta-analyses were conducted to synthesize data on DFA. The certainty of evidence was performed according to GRADE. Seven studies that evaluated a total of 3,805 patients were included. All of them presented methodological issues, mainly in the comparability domain. Most studies observed no significant difference in DFA between children with and without MIH. The meta-analysis did not show a significant effect of MIH on the standardized units for the DFA scores (SMD = 0.03; 95%CI: -0.06–0.12; p = 0.53; I^2 = 0%). Synthesis including only the results for severe cases of MIH also did not show a significant effect of the condition on DFA scores (MD = 8.68; 95%CI: -8.64–26.00; p = 0.33; I^2 = 93%). Two articles found DBMPs were significantly more frequent in patients with MIH. The overall certainty of evidence was very low for both outcomes assessed. The current evidence suggests no difference in DFA between children with and without MIH; DBMPs are more common in patients with MIH. This information should be viewed with caution because of the very low quality evidence obtained.

Keywords: Dental Enamel Hypoplasia; Dental Anxiety; Behavior.

Introduction

The terms dental fear and dental anxiety represent different progressive degrees of the same psychological condition and have been used indistinctly in scientific literature.[1] The term dental fear and anxiety

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(DFA) is used to describe strong negative emotions associated with dental treatment among children and adolescents.[2] Dental behavior management problems (DBMPs), defined as uncooperative and disruptive behaviors resulting in delay of treatment or making it impossible,[3] are more frequently observed in patients with DFA.[4,5]

DFA is a problem frequently faced by pediatric dentists, interfering with the management and dental treatment of children.[6,7] Anxious patients usually delay dental treatment and routinely miss the appointments, which can lead to worsening of oral health and the need for more complex procedures.[6]

The reason why patients develop DFA is still unclear. Some factors may be related to its presence, such as previous experience with dental caries and dental pain.[8-11] However, a recent study has not found any association between dental caries and dental fear,[12] while another study has found that dental anxiety was influenced by previous experiences with dental caries in the primary dentition.[13] The presence of MIH did not seem to increase DFA, but it had a negative impact on the quality of life of children and adolescents.[14]

DBPMs have posed a constant challenge to pediatric dentists. Failure to handle a child with disruptive behavior may compromise dental treatment. To avoid this problem, it is useful to identify children at risk for DBMPs in order to develop an appropriate management strategy. Previous unpleasant dental or medical experience and awareness of existing dental problems are factors that usually cause a negative impact on children's behavior. Conversely, an appropriate approach to these children, shorter appointments, and less complex procedures favor a better behavior in the dental chair.[4,5]

Molar incisor hypomineralization (MIH) is a qualitative defect that causes the affected enamel to be more porous and fragile, tending to fracture under masticatory forces and to expose the underlying dentin.[15] Children with MIH usually complain about tooth hypersensitivity, tend to avoid toothbrushing, which predisposes to bacterial plaque accumulation and contributes to the development of dental caries.[16]

Patients with MIH are usually reluctant to open their mouths and react intensively to air jet even when it is used only for dental examination.[17] The treatment can be painful as it is more difficult to obtain an effective anesthesia due to a chronic inflammation of the pulp cells.[18] Furthermore, the altered prismatic morphology of hypomineralized enamel impairs bonding and can lead to loss of fillings.[19] Molars severely affected by MIH often show extensive disintegration and need complex restorative treatment.[20] Consequently, children with MIH usually receive more dental treatment than do unaffected children.[21] Thus, it has been advocated that affected children may be at risk for DFA and DBMPs.[17] However, the literature on this subject is controversial.

The knowledge on whether the presence of MIH increases DFA and DBPMs is clinically relevant. Patients with MIH might need a special plan of dental care, focused on a comfortable and calm environment and shorter appointments. Thus, the aim of the present study was to summarize the current available evidence on MIH and the presence of DFA and DBPMs through a systematic review.

Methodology

The purpose of this systematic review was to assess the available evidence on whether children with MIH have more DFA and DBMPs than children without MIH. Its protocol was registered on Prospero (CDR42020203851) and it complied with the PRISMA 2020 statement (http://prisma-statement.org/).

Eligibility criteria

According to the PECO strategy (Population, Exposure, Comparison, and Outcome),[22] observational studies (cohort, cross-sectional, and case-control studies) that evaluated children and adolescents (P) with MIH (E) compared with individuals without MIH (C), regarding DFA and DBPMs (O), were eligible.

Literature reviews, *in vitro* studies, case reports, intervention studies, opinion articles, letters to the editor, and theses were not included. Studies based on questionnaires applied to dentists and studies that evaluated patients with special needs or any problem that could interfere with the assessed outcomes were also excluded.

Search

A systematic literature search was performed in MEDLINE/PubMed, Scopus/Elsevier, Web of Science/Clarivate LILACS/VHL, BBO/VHL, Embase/Elsevier, Cochrane Library/Wiley, and APA PsycoINFO databases until March, 2021. Searches in the Open Grey and Google Scholar databases were also performed to assess the gray literature. No restrictions on language or year of publication were imposed to the searches. If any article written in any language other than English, Portuguese, or Spanish was retrieved, a professional translator service would be hired. Reference lists of each selected article were checked manually to find eligible studies not captured by the main search. Expert authors were contacted by e-mail in order to find unpublished or ongoing studies. Alerts were set in all databases to retrieve newly published articles.

The search strategies were created using MeSH terms, entry and free terms in English combined with the Boolean operators AND / OR. The search strategy was firstly developed for PubMed, but adapted for each database. Terms in Portuguese were added to the search strategies for the VHL platform. All these procedures were supervised by an expert librarian (D.F.M.). The search strategies used in each database are provided in Table 1.

Selection of studies

All the identified records were imported into the EndNote Web software (Thomson Reuters, New York, USA) and duplicates were removed. Titles and abstracts were read by two independent researchers (P.P.G.R. and R.C.J.) to determine the eligibility of the studies. Full articles were retrieved and examined when title and abstract did not provide enough information for a definitive decision. The screened lists of each researcher (P.P.G.R. and R.C.J.) were compared and disagreements were resolved by a third author (V.M.S.).

Data extraction

Two independent reviewers (P.P.G.R. and R.C.J.) extracted the data from the selected studies using an Excel spreadsheet (Microsoft 10). From each study, the following data were extracted: details of the studies (author, year of publication, country, and study design); sample characteristics (number of participants, sex, age), criterion used for the diagnosis of MIH; outcome assessed (DFA, DBPMs); evaluation methods (what instruments were used to measure DFA and DBMPs and who answered them); and results (frequencies of events, prevalence, mean SD, and median). An e-mail was sent to the corresponding author when additional data not found in the articles were necessary.

Quality appraisal

The quality assessment of the selected studies was conducted by two authors separately (PPGR and RCJ) using Newcastle-Ottawa Quality Assessment Scales (NOS).[23] Questions and disagreements were answered and solved by a third author (VMS). For cohort and case-control studies, NOS allocates a maximum of nine stars divided into three criteria: selection of the sample (4 stars), comparability (two stars), and outcome/exposure (three stars). For cross-sectional studies, an adapted version of NOS was used,[24] with the allocation of a maximum of 10 stars, assigning five stars to selection of the sample.

Representativeness of the population and recruitment of exposed/not exposed patients from the same population were the main factors considered in the quality assessment of sample selection. Assessment of exposure was considered appropriate by trained and calibrated examiners when the diagnosis of hypomineralization was based on specific indices for MIH[25,26] or developmental defects of enamel.[27] In the comparability domain, the presence of dental caries was considered the most important factor to be controlled and the additional factor was the age range of the sample. Description of independent evaluation of MIH and DFA and/or DBPMs performed by two different examiners was required to regard the assessment of the outcome as independent and blind.

Synthesis methods

Initially, the extracted data were synthesized qualitatively. Demographic characteristics of the samples, outcomes assessed (DFA or DBPMs), and the corresponding assessment methods were evaluated to identify clinical/methodological heterogeneity across the studies. A critical interpretation of the data

Table 1. Electronic databases and research strategies.

MEDLINE (PubMed)	#1 (dental enamel hypoplasia[MeSH Terms]) OR (dental enamel hypoplasia[Title/Abstract]) OR (enamel defect*[Title/Abstract]) OR (enamel opacit*[Title/Abstract]) OR (enamel hypoplas*[Title/Abstract]) OR (molar incisor hypomineralization[Title/Abstract]) OR (MIH[Title/Abstract]) OR (molar incisor[Title/Abstract]) OR (hypomineral*[Title/Abstract]) OR (cheese molar[Title/Abstract]) OR (demarcated opacit*[Title/Abstract]) OR (demarcated defect*[Title/Abstract]) #2 (Anxiety[MeSH Terms]) OR (anxiety disorder[MeSH Terms]) OR (dental anxiety[MeSH Terms]) OR (fear[MeSH Terms]) OR (behavior[MeSH Terms]) OR (Anxiety[Title/Abstract]) OR (Anxiety disorder[Title/Abstract]) OR (dental anxiety[Title/Abstract]) OR (fear[Title/Abstract]) OR (dental fear[Title/Abstract]) OR (odontophobia*[Title/Abstract]) OR (behavio*[Title/Abstract]) OR (phobia dental[Title/Abstract]) OR (Anxieties Dental[Title/Abstract]) #1 AND #2
Elsevier (Scopus)	#1 TITLE-ABS-KEY ("dental enamel hypoplasia" OR "enamel defect" OR "enamel defects" OR "enamel opacity" OR "enamel opacities" OR "enamel hypoplasia" OR "enamel hypoplasias" OR "molar incisor hypomineralization" OR mih OR "molar incisor" OR hypomineral* OR "cheese molar" OR "demarcated opacity" OR "demarcated opacities" OR "demarcated defect" OR "demarcated defects") #2 TITLE-ABS-KEY (Anxiety OR "Anxiety disorder" OR "dental anxiety" OR fear OR "dental fear" OR odontophobia* OR behavio* OR "phobia dental" OR "Anxieties dental") #1 AND #2
Clarivate (Web of Science)	#1 TS=("dental enamel hypoplasia" OR "enamel defect" OR "enamel defects" OR "enamel opacity" OR "enamel opacities" OR "enamel hypoplasia" OR "enamel hypoplasias" OR "enamel hypoplastic" OR "molar incisor hypomineralization" OR mih OR "molar incisor" OR hypomineralization OR hypomineralisation OR Hypomineralized OR "cheese molar" OR "demarcated opacity" OR "demarcated opacities" OR "demarcated defects" OR "demarcated defect") #2 TS=(Anxiety OR "Anxiety disorder" OR "dental anxiety" OR fear OR "dental fear" OR odontophobia* OR behavio* OR "phobia dental" OR "Anxieties dental") #1 AND #2
Elsevier (Embase)	#1 'enamel hypoplasia'/exp OR 'enamel hypoplasia':ab,ti OR 'enamel defect*': ab,ti OR 'enamel opacit*: ab,ti OR 'enamel hypoplas*: ab,ti OR 'molar incisor hypomineralization': ab,ti OR 'mih': ab,ti OR 'molar incisor': ab,ti OR 'cheese molar': ab,ti OR 'demarcated opacit*': ab,ti OR 'demarcated defect*: ab,ti #2 'ansiety"/exp OR 'anxiety disorder'/exp OR 'dental anxiety'/exp OR 'fear'/exp OR 'behavior"/exp OR anxiety:ab,ti OR 'anxiety disorder':ab,ti OR fear:ab,ti OR behavior:ab,ti OR 'dental anxiety": ab,ti OR 'dental phobia':ab,ti OR 'phobia dental':ab,ti OR 'anxiet* dental':ab,ti #1 AND #2
Lilacs (BBO/VHL)	#1 tw:((mh:(dental enamel hypoplasia)) OR (mh:(hipoplasia do esmalte dentário)) OR (tw:("dental enamel hypoplasia")) OR (tw:("hipoplasia do esmalte dentário")) OR (tw:("enamel defect")) OR (tw:("defeito de esmalte")) (tw:("enamel defects")) OR (tw:("defeitos de esmalte")) OR (tw:("enamel opacity")) OR (tw:("opacidade de esmalte")) OR (tw:("enamel opacities")) OR (tw:("opacides de esmalte")) OR (tw:("enamel hypoplasia")) OR (tw:("hipoplasia de esmalte")) (tw:("enamel hypoplasias")) OR (tw:("hipoplasias de esmalte")) (tw:("enamel hypoplastic")) OR (tw:("esmalte hipoplastico")) OR (tw:("molar incisor hypomineralization")) OR (tw:("hipomineralização molar incisivo")) OR (tw:(mih)) OR (tw:(hmi)) OR (tw:("molar incisor")) OR (tw:("molar incisivo")) OR (tw:(hypomineralization)) OR (tw:(hipomineralização)) OR (tw:(hypomineralisation)) OR (tw:(hipomineralização)) OR (tw:(hypomineralized)) OR (tw:(hipomineralizado)) OR (tw:("cheese molar")) OR (tw:("molar de queijo")) OR (tw:("cheese molars")) OR (tw:("molares de queijo")) OR (tw:("demarcated opacity")) OR (tw:("opacidade demarcada")) OR (tw:("demarcated opacities)") OR (tw:("opacidades demarcadas")) OR (tw:("demarcated defect")) OR (tw:("defeito demarcado")) OR (tw:("demarcated defects")) OR (tw:("defeitos demarcados"))) #2 tw:((mh:(anxiety)) OR (mh:(ansiedade)) OR (mh:(desordens de ansiedade)) OR (mh:(anxiety disorders)) OR (mh:(dental anxiety)) OR (mh:(ansiedade dental)) OR (mh:(fear)) OR (mh:(medo)) OR (mh:(behavior)) OR (mh:(comportamento)) OR (tw:(anxiety)) OR (tw:(ansiedade)) OR (tw:("anxiety disorder")) OR (tw:("desordem de ansiedade")) OR (tw:("dental anxiety")) OR (tw:("ansiedade dental")) OR (tw:(fear)) OR (tw:(medo)) OR (tw:(comportamento)) OR (tw:(behavior)) OR (tw:(odontophobia)) OR (tw:(odontofobia)) OR (tw:("phobia dental")) OR (tw:("fobia dentaria")) OR (tw:("anxieties dental")) OR (tw:("ansiedade dentaria")) OR (tw:("phobia dental")) OR (tw:("fobia dental"))) #1 AND #2

Continue

Continuation

Wiley (Cochrane Library)	#1 "dental enamel hypoplasia" OR enamel defect* OR enamel opacit* OR enamel hypoplas* OR "molar incisor hypomineralization" OR mih OR "molar incisor" OR hypomineral* OR "cheese molar" OR demarcated opacit* OR demarcated defect* #2 MeSH descriptor: [Dental Enamel Hypoplasia] explode all trees #3 MeSH descriptor: [Anxiety] explode all trees #4 MeSH descriptor: [Anxiety Disorders] explode all trees #5 MeSH descriptor: [Dental Anxiety] explode all trees #6 MeSH descriptor: [Fear] explode all trees #7 MeSH descriptor: [Behaviorism] explode all trees #8 Ansiety OR "Anxiety disorder" OR "dental anxiety" OR fear OR "dental fear" OR odontophobia* OR "phobia dental" OR "anxieties dental" OR behavio* #9 #3 OR #4 OR #5 OR #6 OR #8 #10 #3 OR #4 OR #5 OR #6 OR #7 OR #8 #11 #1 OR #2 #12 #11 AND #10
PsycINFO (Google Scholar	((Any Field: ("dental enamel hypoplasia")) *OR* (Any Field: (enamel defect*)) *OR* (Any Field: (enamel opacity*)) *OR* (Any Field: (enamel hypoplas*)) *OR* (Any Field: ("molar incisor hypomineralization")) *OR* (Any Field: (MIH)) *OR* (Any Field: (molar incisor)) *OR* (Any Field: (hypomineral*)) *OR* (Any Field: ("cheese molar")) *AND* (Any Field: (demarcated opacit*)) *AND* (Any Field: (demarcated defect*))) *AND* ((Any Field: (Anxiety)) *OR* (Any Field: (Anxiety disorder)) *OR* (Any Field: ("dental anxiety")) *OR* (Any Field: (fear)) *OR* (Any Field: ("dental fear")) *OR* (Any Field :(odontophobia*)) *OR* (Any Field: (behavior)) *OR* (Any Field: ("phobia dental")) *OR* (Any Field: ("Anxieties Dental)) *AND* Publication Type: Journal #1 "molar incisor hypomineralization" OR MIH OR "demarcated opacity" #2 Anxiety OR "Anxiety disorder" OR "dental anxiety" OR fear OR "dental fear" OR odontophobia* OR behavio* OR "phobia dental" OR "Anxieties dental" #1 AND #2
Open Grey	#1 ("dental enamel hypoplasia" OR "enamel defect*" OR "enamel opacit*" OR "enamel hypoplas*" OR "molar incisor hypomineralization" OR mih OR "molar incisor" OR hypomineral* OR "cheese molar*" OR "demarcated opacit*" OR "demarcated defect*") #2 (Anxiety OR "Anxiety disorder" OR "dental anxiety" OR fear OR "dental fear" OR odontophobia* OR behavio* OR "phobia dental" OR "Anxieties dental")

was carried out to combine results and conclusions. Random-effects meta-analyses were performed to calculate the mean differences (MD) or standardized mean differences (SMD) and corresponding 95% confidence interval (95% CI) of DFA scores between groups with and without MIH. Studies that reported their results as dichotomous data were not included in the quantitative synthesis. Subgroup analyses were performed to explore the variables 'severity of condition', 'age of samples' and 'diagnostic criteria for MIH' as potential sources of heterogeneity. Sensitivity tests were performed to assess the robustness of the analyses. The I^2 index was calculated to assess statistical heterogeneity. All analyses were performed using Review Manager 5.4 software.

Certainty of the evidence

The GRADEpro tool[28] was used to rate the certainty of evidence, considering the following items for analysis: risk of bias, inconsistency, indirectness, imprecision, suspicion of publication bias, presence of large effect, dose-effect gradient,

and plausible confounders.[28,29] Since no meta-analysis was performed for DBPMs, all the judgments were adapted to qualify the evidence synthesized narratively for this outcome.[30]

Results

Selection of studies

Searches in the databases retrieved 1,411 studies. After removal of duplicates, 520 studies remained, and 12 studies were additionally retrieved from alerts (from March to August 2021). After reading titles and abstracts, 518 reports were excluded for not meeting the inclusion criteria. Thirteen articles were read in full and seven of them were excluded. No eligible study was found through manual search in the reference lists of the included articles. Two records were found in OpenGrey, but both were excluded after reading the title/abstract. From the first 100 matches from Google Scholar, two reports were considered eligible, but only one was selected after reading. Finally, seven studies were included in this review.[2,13,17,31-34] The flowchart of the literature search, according to the Prisma 2020 Statement,[22] is presented in Figure 1.

Characteristics of the studies

Regarding the data on DFA, all the included studies were considered to be cross-sectional because the participants were selected according to exposure (MIH), and the outcome (DFA) was assessed at a specific point in time. Two studies had been conducted in Sweden,[17,31] one in Australia,[32] two in Brazil,[12,13] one in Greece,[34] and one in Turkey.[33] The samples of the studies varied widely in size, from 44 to 2,335 participants, and in age, from 8 to 18 years. All sample studies included male and female participants. Two articles resulted from one study that assessed the same sample in two different periods at an interval of 10 years.[17,31] DFA was assessed at two specific points in time, when children were 8 years old [17] and later when they were 18 years old,[31] characterizing cross-sectional data. Concerning DBMPs, the data were retrieved retrospectively from the dental records over the previous six years[17] and 10 years,[31] characterizing longitudinal data.

In two studies,[13,34] MIH was diagnosed using the criteria proposed by EAPD.[25] Three studies[17,31,32] used the DDE criteria,[27] in which the presence of demarcated opacities was regarded as MIH. One study[12] used a newly validated criterion for MIH proposed by Ghanin et al.[26] Another study[33] did not mention which criterion was used for MIH diagnosis.

All included studies[12,13,17,31-34] assessed the association between MIH and DFA and two of them also assessed the association with DBMPs.[17,31] The assessment instruments varied widely. One study[32] used the Modified Child Dental Anxiety Scale – Face ($MCDAS_f$)[35] answered by children. One study[13] used the Dental Anxiety Question (DAQ),[36] which contained a single-item question "Do you think that your child is afraid of going to the dentist?" with four possible answers ("no (1)", "a little (2)", "yes, he/she is afraid (3)," and "yes, he/she is very afraid (4)"), responded by parents or guardians. Five studies assessed DFA through the Children's Fear Survey Schedule – Dental Subscale (CFSS-DS),[37] a multi-item self-report scale composed of 15 items, and each can be given five different scores ranging from "not afraid at all (1)" to "very much afraid (5). This instrument was answered by parents[17] in one study and by adolescents[32] in another study. In two studies, children answered the dental subscale.[12,32] In the other study, it was unclear who answered the questions.[34] Two studies also assessed the presence of DBMPs through dental records with disruptive behavior resulting in delay of treatment or rendering treatment impossible.[17,31]

The studies used different approaches to classify or measure DFA. Four studies used cut-off points to dichotomize the data. Jalevik[17] and Laureano[12] reported CFSS-DS scores ≥ 38 as presence of DFA. Menoncin[13] considered DAQ scores ≥ 2 as presence of DFA. Özükoç[33] used different cut-off points, rating CFSS-DS scores between 15 and 25 as no dental fear, 26 to 32 as mild dental fear, and 33 to 38 as moderate dental fear. Fear, however, can be kept under control, or fear is borderline and score ≥ 39 indicates severe dental fear. Three studies compared the mean score obtained through the instruments between the groups with and without MIH.[31-34] The data extraction is presented in Table 2.

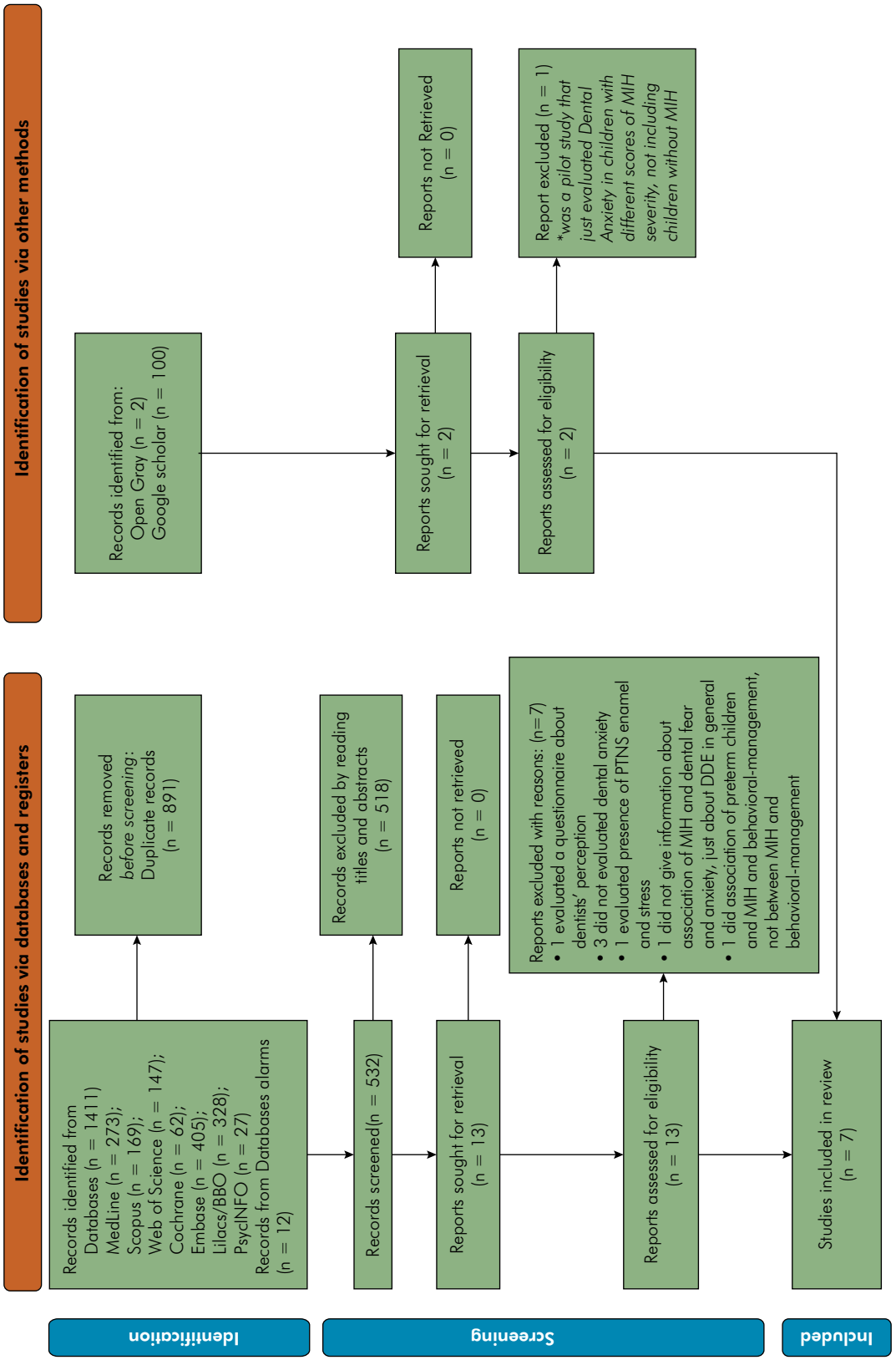

Figure 1. Flowchart of the searches and selection of studies according to PRISMA 2020.

Table 2. Data extraction from the included studies.

Author (Year), Country	Description of the study design by authors	Sample / Groups	Age (years)	Diagnostic criterion	Outcome	Instrument	Main results	Conclusions/ Comments by the authors	Critical appraisal
Laureano et al. (2020), Brazil	Cross-sectional	n = 466 G1 (with MIH) = 56 G2 (no MIH) = 410	8–10	Ghanin 2019	DFA	CFSS-DS answered by patients	G1 = 27% have DFA G2 = 20.9 % have DFA PR (95% CI) G1 = 1.27 (0.89 - 1.82) G2 = 1	*"MIH was not associated with dental fear."*	The sample was relatively large and was representative of the population. MIH was not signficantly associated with DFA.
Özükoç (2019), Turkey	Cross-sectional	n = 112 G1 (with MIH) = 58 mild MIH = 26 moderate MIH = 19 severe MIH = 13 G2 (no MIH) = 54	8–12	Not mentioned	DFA	CFSS-DS answered by patients	G1 mild = 24.7 (SD 13.3) G1 moderate = 26.3 (SD 15.2) G1 severe = 41.5 (SD 14.5) G2 = 23.5 (SD 12.3)	*"The study showed that there is actually a relationship between the severity of MIH and DFA, and DFA increases as MIH also increases."*	Sample is not representative and is relatively small. The criteria used for the assessment of exposure were not described.
Menocin et al. (2018), Brazil	Cross-sectional	n = 731 G1 (with MIH) = 88 G2 (no MIH) = 643	8	EAPD	DFA	DAQ answered by parents	G1: 64.8% (57/ 88) G2: 54.1% (348/ 643)	*"Although the prevalence of DFA was higher among schoolchildren with MIH, the association between these two conditions was not significant."*	The study had a representative sample and confounding factors (caries experience and age) were controlled for.
Arrow (2017), Australia	Cohort	n = 88 G1 (Demarc. Opac.) = 18 G2 (no Enamel Defects) = 26 G3 (Diffuse Opac.) = 44	14.7 (13.7–15.8) SD = 0.3	DDE	DFA	MCDASf answered by patients	Overall mean = 20.6 (SD = 7.5) G1: 18.9 (SD = 7.1) G2: 21.0 (SD = 8.2) G3: 20.2 (SD = 6.8)	No significant association between the presence of enamel defects and DFA. .	Data related to DFA and enamel defects were cross-sectional. We assume that demarcated opacities are MIH, but the diagnosis did not follow specific criteria for MIH. Confounding factors were controlled. Caries experience was considered in the analysis and age range was narrow. The sample was relatively small.
Kosma et al. (2016), Greece	Cross-sectional	n = 2335 G1 (with MIH) = 498 G2 (no MIH) = 1837	8 (n = 1179) 14 (n = 1156)	EAPD	DFA	CFSS-DS answered by patients	G1: mean = 26.5 (SD 9.6) G2: mean = 26.2 (SD 9.9)	*"No statistically significant difference was found between the mean CFSS-DS score in children with and without MIH."*	Study with representative sample. Age was controlled for in the selection of participants. Caries experience was not controlled for.

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Jalevik & Klingberg (2012), Sweden	Case-control	n = 67 G1 (severe MIH) = 30 G2 (no MIH) = 37	18	DDE	DFA	CFSS-DS answered by patients	G1: mean = 22.0 (SD 6.2); CFSS-DS > 29 = 13.3% (4/30). G2: mean = 21.7 (SD 5.8); CFSS-DS > 29 = 16.2% (6/37).	*"DBMPs were still more common in patients with severe MIH, whereas DFA did not differ between patients with severe MIH and controls."*	As the participants were selected by the exposure (MIH) and not by the outcome (DFA), we assume that the study followed a cross-sectional design. The sample was representative, but relatively small. All the children were included in the cohort with 8-year-olds followed up to the age of 18 years. DFA was assessed at a specific point in time. Data on DBMPs were retrieved retrospectively from dental records. Age was controlled for in the sample selection. Caries experience was not controlled for in the analysis.
					DBMPs	Notes in the dental records	G1: 20% 6/30 G2: 2.7% 1/37		
Jalevik & Klingberg (2002), Sweden	Case-control	n = 73 G1 (severe MIH) = 32 G2 (no MIH) = 41	7-8 y	DDE	DFA	CFSS-DS answered by parents	G1: mean = 23.3 (SD 7.5); CFSS-DS > 29 = 25% (8/32). G2: mean = 20.8 (SD 5.4); CFSS-DS > 29 = 4.9% (2/41).	*"There were more children in the MIH-group than in the control group who had high levels of DFA (CFSS-DS scores ≥ 29) and DBMPs."*	As the participants were selected by the exposure (MIH) and not by the outcome (DFA), we assume that the study followed a cross-sectional design. Age of the participants was controlled for, but dental caries was not considered as a confounding factor. The sample was representative, but relatively small. Data on DBMPs were retrieved retrospectively from dental records.
					DBMPs	Notes in the dental records	G1: 46.9% (15/32) G2: 2.4% (1/41)		

CFSS-DS: Children's fear survey schedule - dental subscale; DAQ: Dental anxiety question; DBMP: Dental behaviour management problems; DDE: Developmental defects of enamel; DFA: Dental fear and anxiety; G1: Group with MIH; G2: Group without MIH; MCDASf: Modified child dental anxiety scale - faces version; MIH : Molar incisor hypomineralization.

Methodological quality assessment

The quality assessment according to NOS[23] criteria is presented in Table 3. All the included studies presented methodological issues.[12,13,17,31-34] In the selection domain, although all the seven studies recruited exposed and not exposed patients from the same population, in two of them[32,33] the sample was not considered representative of the population, and in four of them the sample was relatively small.[17,31-33] Only in three studies, exposure was diagnosed according to a specific criterion proposed for MIH.[12,13,34] In one study,[33] the criteria to define exposure was not clearly explained. Comparability was the most affected domain because five out of seven studies[12,17,31,33,34] did not control for caries experience as a confounding factor. Regarding the outcome domain, it was not possible to assure that the assessment of the outcome, both DFA and DBMPs, was independent or blind in any of the studies.

Results of individual studies and syntheses

The results of the seven included studies are shown in Table 1. Overall, most of the studies observed no significant difference in DFA between children with and without MIH.[12,13,31,32,34] The meta-analysis did not show a significant effect of MIH on the standardized units for the DFA scores (SMD = 0.03; 95%CI: -0.06–0.12; p = 0.53; I^2 = 0%; Figure 2). Subgroup analyses evidenced no influence of 'severity of MIH', 'age of samples', and 'diagnostic criteria for MIH' on this result. Similarly, sensitivity tests alternating the different reported results according to the MIH severity described by Özükoç[31] or different follow-up periods, as reported by Jalevic and Klingberg,[17,31] did not alter the significance or direction of the estimated effect. Three studies (two evaluating the same sample in different time periods) considered the severity of MIH in the analysis[17,31,33] and only one of them observed significantly higher scores of DFA for MIH children when only the severe cases were considered[31] The meta-analysis including only the results for severe cases of MIH[31,33] also did not show a significant effect of the condition on DFA scores (MD = 8.68; 95%CI: -8.64–26.00; p = 0.33; I^2 = 93%). The studies that evaluated DFA as a dichotomous outcome were considered methodologically heterogeneous, given that in one of them,[12] the data were collected from children and in the other one[13] from the parents; therefore, these data were not combined in a meta-analysis. Only two studies considered caries experience as a potential confounding factor in the analysis.[13,32]

Two articles[17,31] were obtained from one study that evaluated DBMPs in the same sample at an interval of 10 years. In the first article,[17] the patients

Table 3. Risk of bias of included studies (Newcastle-Ottawa).

Authors (year)	Newcastle-Ottawa Scale				
	Country	Selection (max 5*/4*)	Comparability (max 2*)	Outcome (max 3*)	Total
Dental fear and anxiety					
Laureano et al. (2020)	Brazil	*****	*	**	8*/10
Özükoç et al. (2019)	Turkey	*	*	**	4*/10
Menocin et al. (2018)	Brazil	*****	**	**	9*/10
Arrow (2017)	Australia	**	**	**	6*/9
Kosma et al. (2016)	Greece	*****	*	**	8*/10
Jalevik and Klingberg (2012)	Sweden	***	*	**	6*/9
Jalevik and Klingberg (2002)	Sweden	***	*	**	6*/9
Dental behavior management problem					
Jalevik and Klingberg (2012)	Sweden	**	*	**	5*/9
Jalevik and Klingberg (2002)	Sweden	**	*	**	5*/9

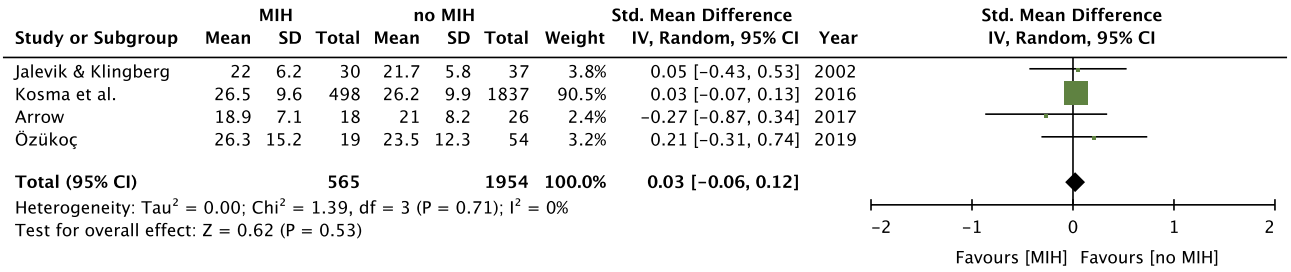

Figure 2. Random-effects meta-analysis on the effect of MIH on DFA scores.

were aged 7 to 8 years and DBMPs were significantly more frequent in children with MIH, according to notes retrieved from their dental records. For the second article,[31] the presence of disruptive behavior was checked in the dental records over the previous 10 years and DBMPs were still significantly more frequent in MIH patients.

Certainty of the evidence

The overall certainty of the evidence was very low for both outcomes assessed. All the observational studies presented methodological limitations that could have altered the reported results and seriously affected the evidence. Furthermore, we consider that the indirectness item was also affected because several studies did not use a specific method for the diagnosis of the exposure of interest (MIH). The number of subjects evaluated in relation to DBMPs was insufficient to have conclusive evidence on the matter, thus affecting the imprecision item. The publication bias was considered unsuspected. Because the evidence presented limitations affecting its validity, no item was considered to increase the certainty of the evidence.

Discussion

Patients affected by severe MIH usually need more dental treatment and experience more dental pain and discomfort on repeated occasions than those without it. A longitudinal study suggested these patients are more likely to have DFA and DBMPs.[17] Based on that, possible association between the presence of MIH and DFA or DBMPs has been widely cited in the literature. Recently, new studies have found divergent results. The present systematic review was built upon this divergence.

Most studies included in this review did not observe a significant association between MIH and DFA.[12,13,31,32,34] When similar studies were combined in a meta-analysis, a significant effect of MIH was not observed on the standardized units for the DFA scores. The etiology of DFA might be complex and multifactorial and might differ between individuals from different cultural and social environments, but previous experience with caries and dental pain have been consistently mentioned as relevant factors associated with increased DFA.[4,8-10] In this context, it might be somehow expected that children with MIH present increased DFA when compared with children without MIH, given that it is significantly associated with increased caries indices and higher frequency of restorative procedures.[16,38] One study observed an increased DFA only in the group with severe MIH.[33] However, the meta-analysis assessing the results of both studies on severe cases of MIH[31,33] did not show a significant effect of the condition on DFA scores. Further studies should consider the severity of MIH because critical aspects such as treatment need, dental pain, or discomfort may not differ between mild and severe MIH.

Age is another factor that plays a critical role, as it has been shown that DFA tends to decrease over time, being less frequent in older children.[2,4] For this reason, in the present review, age was an additional confounding factor considered in the quality assessment of the studies. Interestingly, the study that evaluated DFA in the same sample at the ages of 7 to 8 years[17] and later at 18 years[31] observed a significant increase in DFA in MIH

children only at the ages of 7 to 8 years. On the other hand, based on the subgroup analyses performed in quantitative syntheses, it should be mentioned that the results were consistent, regardless of the age of the participants.

The presence of DBMPs was evaluated in this review as a secondary outcome. Out of the seven included articles, only two[17,31] presented data about this outcome assessed in the same sample at a 10-year interval. In both reports, DBMPs were more common in patients with MIH. However, as the data on this outcome were based on notes in the dental records, they might be inaccurate. An appropriate assessment of children's behavior is important to support dental treatment planning, achieving efficiency and improving patients' behaviors.[39] Further studies on the association between DBMPs and MIH through a validated rating scale for behavior evaluation would be desirable to obtain more consistent results.

There is a pool of multi-item and single-item scales to assess DFA in children and adolescents. In the present review, the instruments used to assess DFA and the type of respondents varied widely. Moreover, while some of the studies analyzed the data on DFA as continuous variables,[17,31-34] other studies used cut-off points to categorize those children and adolescents according to the presence or absence of DFA.[12,13]

All the studies included in the present review had methodological limitations. External validity was affected because most of the studies did not have a representative sample or were based on relatively small samples.[17,31-33] Additionally, most of the data were cross-sectional, and then it was not possible to establish a cause-effect relationship between MIH and DFA. In the two reports that assessed DBMPs, using the same sample,[17,32] it was not possible to guarantee that DBMPs (outcome) had not been present prior to MIH (exposure).

Comparability was a major concern. Caries experience and age were considered the most relevant confounding factors in this review. However, only two studies[13,32] controlled for both. The presence of dental caries was considered the most important confounding factor because children with dental caries tend to have more pain, more dental treatment needs, and are more susceptible to DFA.[8,40,41] However, only two studies controlled for caries in the multivariate analysis testing the association between MIH and DFA.[13,32] The age of the participants was considered an additional confounding factor that should be controlled for, given that the first permanent molars erupt around the age of 6 years. MIH molars may fracture due to masticatory efforts over time.[42,43] The older the children, the longer the tooth will be under masticatory forces, tending to fracture, increasing severity, and possibly causing pain, which eventually might result in more DFA. However, studies that evaluated DFA in children without MIH observed that it tends to decrease with age.[4]

A well-trained dentist experienced in dealing with children's behavior management might be able to reduce DFA and DBMPs in patients, even if they are exposed to repetitive treatments. Therefore, such possibility is a relevant aspect to be considered in this discussion. Preferably, future studies should standardize the way dentists approach these children or should take into consideration the experience and professional qualification background of these dentists.

It should be mentioned that although the results of the syntheses represent the current state of the evidence, they are not conclusive. It is important to emphasize that the results of the meta-analyses should be viewed with caution as they are based on a limited number of studies with methodological issues. In addition, some degree of bias could exist as it was not possible to include all studies in the quantitative synthesis as some reported different measures of effect and were methodologically heterogeneous. This, along with other reasons, resulted in the very low quality of the total body of evidence for both outcomes assessed. Firstly, because all the included studies followed an observational design, which by itself provides a low quality of evidence. Secondly, all studies had methodological limitations that could have influenced the results and seriously affected the evidence. The indirectness item was also affected because three studies[17,31,32] evaluated the presence of MIH (exposure of interest) using the

DDE index, which is not specific to MIH, and another study[33] did not even mention the criterion used for the diagnosis of MIH. Therefore, the certainty of the evidence was rated down due to the following parameters: study design, methodological issues, risk of bias, and indirectness. Regarding the DBMP outcome, it was not possible to conduct a meta-analysis. The certainty of the evidence was judged following guidelines proposed for cases in which there is no single summary measure of effect.[30] For DBMPs, the evidence was rated down due to the study design, methodological issues, risk of bias, indirectness, and imprecision.

Conclusion

Based on this systematic review, the evidence suggests that there is no difference in DFA between patients with and without MIH. The two studies reporting on DBMPs observed that behavioral problems were more frequent among children with MIH. These results must be interpreted with caution due to the very low certainty of the evidence. Further studies on the severity of MIH, using validated rating scales for behavior evaluation and controlling for important confounding factors for DFA would be desirable to obtain more consistent results.

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