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# Effect of Prevalence and Severity of Molar-Incisor Hypomineralization on Oral Health-Related Quality of Life: A Systematic Review and Meta-Analysis

## Učinak prevalencije i težine molarno-incizalne hipomineralizacije na kvalitetu života povezanu s oralnim zdravljem: sistematizirani pregled i metaanaliza

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### Abstract

**Objectives:** The aim of this systematic review and meta-analysis is to assess the association between the MIH presence as well as the severity and OHRQoL in children. **Material and methods:** Relevant studies were identified in PubMed, Embase, Cochrane and Google Scholar. Studies involving MIH and OHRQoL in children were included. A methodological quality assessment of included studies was performed using the Newcastle-Ottawa Scale (NOS) and its adapted version for cross-sectional studies. Random effects models were used to estimate summary effect measures for the association between MIH presence (presence vs. absence) as well as severity (moderate/severe MIH vs. no MIH) and OHRQoL using generic inverse variance meta-analyses. Tests for heterogeneity, publication bias and sensitivity of results were also performed. **Results:** Out of 1696 identified publications 11 studies reporting on 5,017 children were included in the meta-analysis assessing the impact of MIH presence. There was no statistically significant association between the presence of MIH and lower OHRQoL in affected children (OR = 1.72, 95% CI = 0.99–2.98). Concerning MIH severity and its impact on OHRQoL, a sum of 6 studies were included in the meta-analysis involving a total of 2,595 children. There was a significant association between moderate/severe MIH and lower OHRQoL in affected children (OR = 3.43, 95% CI = 1.69–6.98). **Conclusion:** Moderate/Severe MIH has a significant and clinically relevant negative impact on OHRQoL, and it should therefore be addressed adequately. Future research should also consider the impact of a uniform MIH diagnosis and precise severity criteria.

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### Introduction

The term molar-incisor hypomineralization (MIH), coined in 2001, characterized an enamel defect type. MIH was defined as 'hypomineralization of systemic origin, presenting as demarcated, qualitative defects of enamel of one to four first permanent molars (FPMs) frequently associated with affected incisors (1). A diagnosis predominantly employs the European Academy of Paediatric Dentistry (EAPD) criteria (2), with a 2018 systematic review of 74 studies utilizing these criteria revealing an MIH prevalence of 14.5% (3). Despite the recent significant increase in research relat-

### Uvod

Pojam *hipomineralizacija kutnjaka* (MIH) uveden je 2001., a opisuje vrstu defekta cakline. MIH je definiran kao hipomineralizacija sistemskog podrijetla koja se manifestira kao ograničeni, kvalitativni defekti cakline jednoga do četiriju prvih trajnih kutnjaka, a često su zahvaćeni i sjekutići (1). Dijagnoza se uglavnom temelji na kriterijima Europske akademije dječje stomatologije (EAPD) (2), a sistematizirani pregled 74 istraživanja iz 2018. koji primjenjuje te kriterije otkriva prevalenciju MIH-a od 14,5 % (3). Unatoč značajnom porastu istraživanja u vezi s MIH-om posljednjih

ing to MIH (4,5), its exact etiology remains unclear. MIH has been documented in both permanent and primary teeth (6). In this review, MIH refers to enamel defects diagnosed under the EAPD criteria, encompassing primary and permanent dentition. Clinically, MIH manifests as well-demarcated defects with distinct boundaries from adjacent normal enamel. Variations exist in terms of affected teeth, defect color, size, location, hypersensitivity, and post-eruptive breakdown (PEB) (2,7). This clinical presentation can impact the oral health-related quality of life (OHRQoL) of affected individuals, through functionality and esthetics (8,9).

OHRQoL, is defined as the impact of oral diseases and disorders on aspects of everyday life that a patient or person values, that are of sufficient magnitude, in terms of frequency, severity or duration to affect their experience and perception of their life overall (10). Presently, the evidence concerning the link between MIH and OHRQoL is constrained and at times contradictory, thus necessitating further investigation to elucidate this relationship.

### Aim of the study

The review aims to evaluate the association between MIH regarding its presence as well as its severity and OHRQoL. According to the PECO approach to conduct a systematic review (11), these keywords are concerned: (P)opulation: Children; adolescents; (E)xposure: MIH; (C)ontrol: MIH free; (O)utcome: OHRQoL as measured by validated instruments.

### Material and methods

The review was performed according to the guidelines of the PRISMA statement (12). The review protocol can be accessed via the webpage: <http://www.crd.york.ac.uk/PROSPERO/> (Registration number: CRD42022317411).

#### Literature search

Electronic searches were carried out on 6.4.2022 in the following databases PubMed, EMBASE, Cochrane Central and Google Scholar with no date restrictions. The search strategies were two-pronged, combining the condition (MIH) with the outcome (OHRQoL). Exact search strategies are available in the supplemental file (S1). The search was complemented by reviewing the reference list of all included articles and other reviews on the topic. Experts in the field of MIH were contacted to identify further studies.

#### Eligibility criteria

Only studies, regardless of the study type (observational: cross-sectional, cohort, case-control or interventional), fulfilling the following criteria were included in the systematic review: Studies with a child or adolescent population; Samples involving exclusively participants with a predefined condition were excluded; MIH diagnosis made according to: (EAPD) criteria or its modifications, or as a component of other indices (e.g. DDE index) when the MIH component was extractable independently from other components; OHRQoL estimated using validated questionnaires specific

godina (4, 5), njegova točna etiologija ostaje nejasna. MIH je dokumentiran i na trajnim i na mliječnim zubima (6). U ovom pregledu MIH se odnosi na defekte cakline dijagnostičane prema kriterijima EAPD-a koji obuhvaćaju mliječnu i trajnu denticiju. Klinički se MIH očituje kao ograničeni defekt s jasnim granicama odijeljenim od susjedne normalne cakline. Postoje varijacije kad je riječ o zahvaćenim zubima, boji defekta, veličini, položaju, preosjetljivosti i posteruptivnom urušavanju (2, 7). Ova klinička manifestacija može utjecati na kvalitetu života povezanu s oralnim zdravljem (OHRQoL) zbog narušene funkcije i estetike (8, 9).

OHRQoL se definira kao utjecaj oralnih bolesti i poremećaja na aspekte svakodnevnog života koje pacijent ili osoba cijeni, koji su dovoljne veličine u smislu učestalosti, ozbiljnosti ili trajanja da utječu na njihovo iskustvo i percepciju vlastita života u cjelini (10). Trenutačno su dokazi koji se odnose na veze između MIH-a i OHRQoL-a ograničeni i povremeno kontradiktorni i zato su potrebna dodatna istraživanja kako bi se razjasnio taj odnos.

### Svrha istraživanja

Cilj pregleda bio je procijeniti povezanost MIH-a s obzirom na njegovu prisutnost i težinu i OHRQoL-a. Prema PECO pristupu provođenja sistematiziranog pregleda (11), relevantne su sljedeće ključne riječi: populacija, djeca, adolescenti, ekspozicija, MIH, kontrola, odsutnost MIH-a, ishod, OHRQoL mjeren validiranim instrumentima.

### Materijali i metode

Pregled je proveden prema smjernicama PRISMA-e (12). Njegovu protokolu može se pristupiti na mrežnoj stranici: <http://www.crd.york.ac.uk/PROSPERO/> (registracijski broj: CRD42022317411).

#### Pretraživanje literature

Elektronička pretraživanja provedena su 6. travnja 2022. u sljedećim bazama podataka: PubMed, EMBASE, Cochrane Central i Google Scholar, bez datumskih ograničenja. Strategije pretraživanja bile su dvosmjerne, kombiniralo se stanje (MIH) s ishodom (OHRQoL). Točne strategije pretraživanja dostupne su u dodatnoj datoteci (S1). Pretraživanje je dopunjeno pregledom popisa referencija svih uključenih radova i drugih prikaza o toj temi. Kontaktirani su stručnjaci u području MIH-a da bi se identificirala daljnja istraživanja.

#### Kriterij prihvatljivosti

U sistematizirani pregled uključena su samo istraživanja, bez obzira na vrstu (opservacijsko: presječno, kohortno, slučaj-kontrola ili intervencijsko), koja ispunjavaju sljedeće kriterije: istraživanja s populacijom djece ili adolescenata; isključeni su uzorci koji uključuju isključivo sudionike s unaprijed definiranim stanjem; dijagnoza MIH-a postavljena je prema (EAPD) kriterijima ili njegovim modifikacijama, ili kao komponenta drugih indeksa (npr., DDE indeks) kada se komponenta MIH-a mogla izdvojiti neovisno o drugim komponentama; OHRQoL je procijenjen korištenjem validi-

for children; Only studies with a control group free of MIH were included; Only studies with a sample size > 20 were included; Letters to the editor or conference abstracts were excluded; Language restrictions were set to English, German and French.

### Study selection

After duplicates removal, two reviewers (AA and RH) independently screened the titles and abstracts of studies to examine the eligibility of retrieved references in accordance with above-mentioned inclusion criteria. Full-text copies of relevant references were then obtained. Both reviewers then independently assessed the full texts of potential studies for eligibility, and reasons for exclusion were recorded. In both stages, disagreements were also resolved by the decision of a third independent reviewer (JS). For multiple studies reporting on the same population, only the latest studies were included.

### Data extraction

Data extraction was performed by two reviewers independently and in duplicate (AA, RH). A spreadsheet was used for data entry. Due to various MIH severity classifications available (13,14) and the different classifications used in the underlying literature (table 1), mild MIH was defined as MIH TNI 1 or demarcated opacities, while moderate/severe MIH was defined as the other forms of MIH including post-eruptive breakdown (PEB) and/or hypersensitivity.

### Data synthesis

Outcomes of different OHRQoL instruments were combined for this systematic review in line with previous studies (15,16). One study (17) presented the results in more than two defined subgroups (mild MIH, severe MIH, no MIH). The mild and severe subgroups were combined in meta-analyses involving the MIH presence. In the following study (18) CPQ 8-10 and CPQ 11-14 were used, however the latter was only undertaken by 6 participants. Their results were excluded. Another study did not present the results on the overall OHRQoL but presented the results per domain (19). In this case, the OR (95% CI) was calculated per domain. Afterwards, all OR (95% CI) were pooled with a fixed-effects meta-analysis, and the number of events per subgroup was recalculated proportional to the sample size of the study. One study (20) reported the perception of MIH impact on the OHRQoL, using the Parental-Caregivers Perception Questionnaire (P-CPQ) and the child perception questionnaire (CPQ). Only the CPQ scores were extracted to prevent double reporting. In one study (21) mean and SD were not available per subgroup; subsequently the authors were contacted and missing data were obtained.

All included studies used instruments indicating better OHRQoL with a lower score, except for one study (22) using Child Oral Health Impact Profile (COHIP). The absolute mean differences were used for comparability purposes during estimation of respective standardized mean difference (SMD). In the study (23) standard deviations (SD) were not provided and were estimated using the methods described in the Cochrane Handbook (24). One study (25) did not

ranih upitnika specifičnih za djecu; uključena su samo istraživanja s kontrolnom skupinom bez MIH-a; uključena su samo istraživanja s veličinom uzorka > 20; pisma uredniku ili sažetci konferencija bili su isključeni; jezična ograničenja postavljena su na engleski, njemački i francuski.

### Odabir istraživanja

Nakon uklanjanja duplikata dvaju recenzenta (A. A. i R. H.) neovisno su pregledali naslove i sažetke istraživanja kako bi ispitali prihvatljivost dohvaćenih referencija u skladu s gore navedenim kriterijima uključivanja. Zatim su prikupljeni cjeloviti tekstovi relevantnih referencija. Nakon toga su oba recenzenta odvojeno ocjenjivala prihvatljivost cjelovitih tekstova potencijalnih istraživanja, a razlozi za isključenje su zabilježeni. U obje faze nesuglasice su riješene odlukom trećega neovisnog recenzenta (J. S.). Između više istraživanja koja su izvještavala o istoj populaciji, uključena su samo najnovija.

### Vađenje podataka

Vađenje podataka obavila su neovisno dva recenzenta (A. A., R. H.). Za unos podataka korištena je proračunska tablica. Zbog različitih dostupnih klasifikacija težine MIH-a (13, 14) i različitih klasifikacija korištenih u osnovnoj literaturi (tablica 1.), blagi MIH definiran je kao MIH TNI 1 ili ograničena zamućenja, a umjereni/teški MIH definiran je kao drugi oblici MIH-a, uključujući posteruptivno urušavanje (PEB) i/ili preosjetljivost.

### Sinteza podataka

Ishodi različitih OHRQoL instrumenata kombinirani su za ovaj sistematizirani pregled u skladu s dosadašnjim istraživanjima (15, 16). U jednom istraživanju (17) predstavljeni su rezultati u više od dviju definiranih podskupina (blagi MIH, teški MIH, odsutnost MIH-a). Blage i teške podskupine kombinirane su u metaanalizama koje uključuju prisutnost MIH-a. U sljedećem istraživanju (18) korišteni su CPQ 8-10 i CPQ 11-14, ali ovo drugo obuhvatilo je samo 6 sudionika. Njihovi rezultati su izuzeti. U drugom istraživanju nema rezultata o ukupnom OHRQoL-u, ali su zabilježeni rezultati po domeni (19). U ovom slučaju OR (95 % IP) je izračunat po domeni. Nakon toga svi su OR-i (95 % IP) združeni s metaanalizom fiksnih učinaka, a broj događaja po podskupini ponovno je izračunat proporcionalno veličini uzorka. U jednom istraživanju (20) autori su izvijestili o percepciji utjecaja MIH-a na OHRQoL koristeći se upitnikom percepcije roditelja i skrbnika (P-CPQ) i upitnikom percepcije djeteta (CPQ). Izdvojeni su samo rezultati CPQ-a kako bi se spriječilo dvostruko izvještavanje. U jednom istraživanju (21) srednja vrijednost i SD nisu bili dostupni po podskupini te se naknadno kontaktiralo s autorima i dobiveni su podatci koji su nedostajali.

U svim uključenim istraživanjima korišteni su instrumenti koji pokazuju bolji OHRQoL s nižim rezultatom, osim jednoga (22) koje se koristilo Profilom utjecaja na oralno zdravlje djeteta (COHIP). Apsolutne srednje razlike korištene su u svrhu usporedivosti tijekom procjene odgovarajuće standardizirane srednje razlike (SMD). U istraživanju (23) nisu navedene standardne devijacije (SD) pa su procijenjene s pomoću meto-

allow for the MIH severity classification and was excluded from the respective analysis. Another study (26) presented the OHRQoL results according to the MIH treatment need index (MIH-TNI). Therefore, for the purpose of inclusion in meta-analyses involving MIH severity, the (MIH-TNI 2, MIH-TNI 3 and MIH-TNI 4) subgroups were combined. Likewise, in another study (23) MIH patients in the moderate severity and high severity categories were also combined for inclusion in the same analysis.

### Quality assessment

Two reviewers (AA, RH) independently assessed the methodological quality assessment of the included studies The Newcastle-Ottawa Scale (NOS) for case-control, cohort studies (27) as well as the adapted version for cross-sectional studies (28) were used for the purpose of methodological quality. Disagreements were resolved by the decision of a third independent reviewer (JS).

### Statistical analysis

Statistical analyses were performed in Review Manager 5.4.1 (29). All analyses were performed with a dichotomous independent variable, either the MIH presence (MIH vs. no MIH) or MIH severity (moderate/severe MIH vs. No MIH).

Both meta-analyses were performed using random effect models. In order to achieve the consistency of results, continuous outcomes with their respective confidence intervals were transformed using the methods described in (24,30).

Statistical heterogeneity was assessed by using  $Chi^2$  and  $I^2$  tests and sensitivity analyses were performed to test the robustness of the summary estimates.

### Publication bias

To investigate possible non-reporting bias (e.g. publication bias) and small study effects, funnel plots were prepared and visually examined for signs of asymmetry.

## Results

### Search results

A total of 1,696 references were identified in the initial search. A flow-chart illustrating the review process and the number of studies that were excluded at each review stage is shown in Figure 1. The 19 excluded studies following full-text assessment are listed with the respective exclusion reason(s) in the supplementary file (S3).

#### *Characteristics of included studies*

12 articles remained after the review process. Of these 11 were included in the meta-analyses and 1 study (31) was narratively summarized (S2), as assessment of continuous data indicated they were skewed. Details on the included studies are summarized in table 1.

da opisanih u Cochraneovu priručniku (Cochrane Handbook) (24). Jedno istraživanje (25) nije omogućilo klasifikaciju težine MIH-a i bilo je isključeno iz odgovarajuće analize. U drugom istraživanju (26) rezultati OHRQoL-a bili su prema indeksu potrebe za liječenjem MIH-a (MIH – TNI). Stoga, u svrhu uključivanja u metaanalize koje uključuju ozbiljnost MIH-a, podskupine (MIH-TNI 2, MIH-TNI 3 i MIH-TNI 4) su kombinirane. Isto tako, u drugom istraživanju (23) pacijenti s MIH-om u kategorijama srednje i visoke težine također su kombinirani za uključivanje u istu analizu.

### Procjena kvalitete

Dva recenzenta (A. A., R. H.) neovisno su procijenila metodološku kvalitetu uključenih istraživanja. Ljestvica Newcastle-Ottawa (NOS) za slučaj-kontrolu, kohortna istraživanja (27) te prilagođena verzija za presječna istraživanja (28) korišteni su u svrhu metodološke kvalitete. Nesuglasice su riješene odlukom trećega neovisnog recenzenta (J. S.).

### Statistička analiza

Statističke analize provedene su u Review Manageru 5.4.1 (29). Sve analize provedene su s dihotomnom nezavisnom varijablom - i prisutnost MIH-a (MIH nasuprot odsutnosti MIH-a) i ozbiljnost MIH-a (umjereni/teški MIH nasuprot odsutnosti MIH-a).

Obje metaanalize provedene su korištenjem modela slučajnih učinaka. Kako bi se postigla dosljednost rezultata, kontinuirani ishodi s odgovarajućim intervalima pouzdanosti transformirani su s pomoću metoda opisanih u literaturi, (24, 30).

Statistička heterogenost procijenjena je korištenjem testova  $Chi^2$  i  $I^2$ , a analize osjetljivosti provedene su da bi se testirala robusnost sažetih procjena.

### Pristranost objave

Da bi se istražila moguća pristranost neprijavlivanja (npr., pristranost objave) i mali učinci istraživanja, pripremljeni su dijagrami lijevka i vizualno ispitani na znakove asimetrije.

## Rezultati

### Rezultati pretraživanja

U početnoj pretrazi identificirano je ukupno 1696 referencija. Dijagram koji ilustrira postupak pregleda i broj istraživanja isključenih u svakoj fazi pregleda nalazi se na slici 1. Ukupno 19 istraživanja koja su isključena poslije procjene cjelovitoga teksta navedeno je s odgovarajućim razlozima isključenja u dodatnoj datoteci (S3).

#### *Karakteristike uključenih istraživanja*

Nakon recenzije preostalo je 12 radova. Od njih je 11 uključeno u metaanalizu, a jedno je (31) narativno sažeto (S2) jer je procjena kontinuiranih podataka pokazala da su bili iskrivljeni. Pojednostosti o uključenim istraživanjima sažete su u tablici 1.



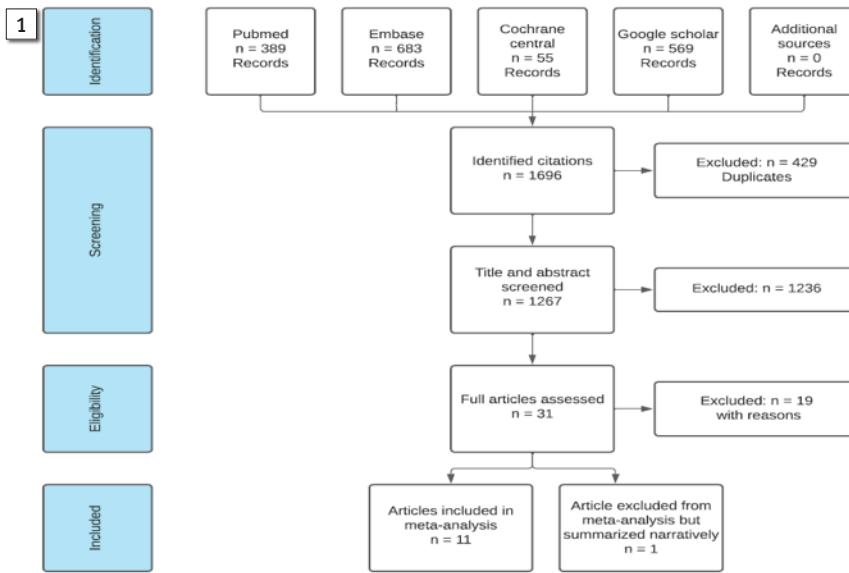


Figure 1 Flow-chart of the study selection for this systematic review and meta-analysis

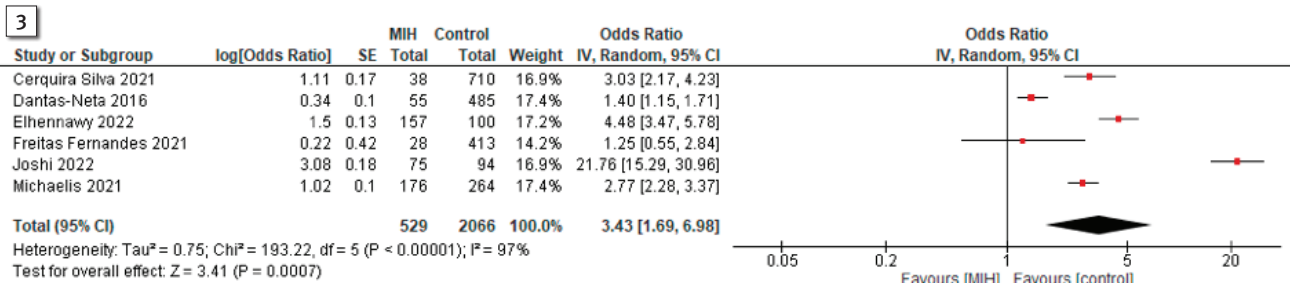
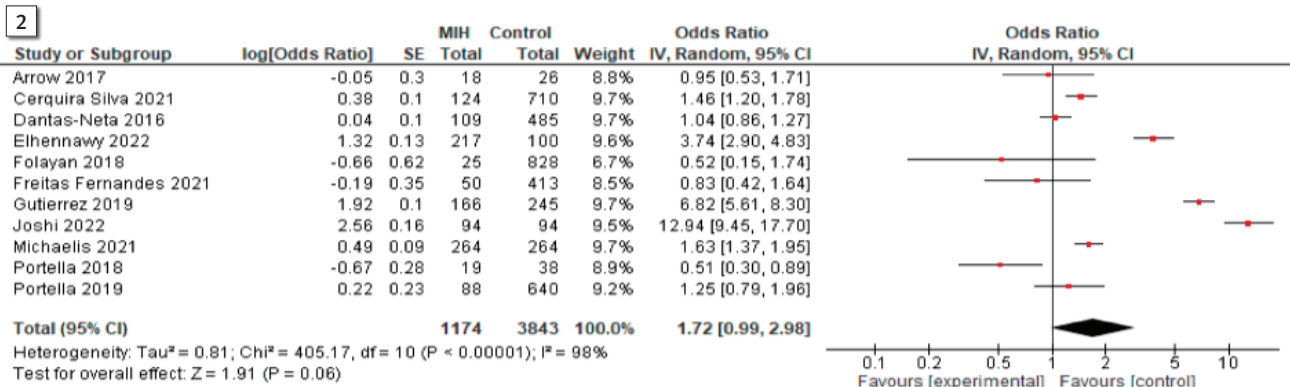
Slika 1. Dijagram odabira istraživanja za ovaj sistematizirani pregled i metaanalizu

Figure 2 Forest plot and summary measure of the association between MIH presence and OHRQoL

Slika 2. Dijagram i sažeta mjera povezanosti između prisutnosti MIH-a i OHRQoL-a

Figure 3 Forest plot and summary measure of the association between moderate/severe MIH and OHRQoL

Slika 3. Dijagram i sažetak mjerenja povezanosti između umjerenoga/teškoga MIH-a i OHRQoL-a



Quality assessment

The methodological quality of the included studies was rated by the NOS for case-control, cohort studies as well as the adapted version for cross-sectional studies. Scores ranged from 4 to 9 points. The scores of each individual study are shown in supplementary file (S4).

Meta-analysis

MIH presence and OHRQoL

When comparing children with (n=1174) and without (n=3843) MIH, no statistically significant association was observed between the presence of MIH and low OHRQoL (OR=1.72, 95% CI=0.99–2.98) (Fig. 2). Statistical heterogeneity was present ( $\chi^2 = 405.17, p < 0.00001$ ). The  $I^2 = 98\%$  indicates considerable heterogeneity between the different studies (24).

Procjena kvalitete

Metodološku kvalitetu uključenih istraživanja ocijenio je NOS za slučaj-kontrolu, kohortna istraživanja i prilagođenu verziju za presječna istraživanja. Rezultati su se kretali od 4 do 9 bodova. Bodovi svakoga istraživanja nalaze se u dodatnoj datoteci (S4).

Metaanaliza

Prisutnost MIH-a i OHRQoL

Uspoređujući djecu s MIH-om (n = 1174) i bez njega (n = 3843), nije uočena statistički značajna povezanost između prisutnosti MIH-a i niskoga OHRQoL-a (OR = 1,72, 95 % CI = 0,99 – 2,98) (slika 2.). Zabilježena je statistička heterogenost ( $\chi^2 = 405,17, p < 0,00001$ ).  $I^2 = 98\%$  što upućuje na značajnu heterogenost između različitih istraživanja (24).

**Table 1** Summary of the study characteristics of the included studies for this systematic review and meta-analysis on MIH and OHRQoL  
**Tablica 1.** Sažetak karakteristika istraživanja uključenih u ovaj sistematizirani pregled i metaanalizu MIH-a i OHRQoL-a

Author, Year	Ref. number	Country	Study design	Sample size	Age in years	MIH	Participants inclusion and exclusion criteria	Severity criteria	MIH N	Severe MIH N (Presentation other than demarcated Opacity)	Without MIH N	OHRQoL
Arrow 2017	(32)	Australia	cohort	91	Mean = 14.7	DDE	None, this is a follow-up study of a sample of children selected according to geographic location, before the eruption of permanent dentition <ul style="list-style-type: none"> <li>All first permanent molars fully erupted</li> <li>Children not undergoing orthodontic treatment with fixed appliances at the time of evaluation</li> <li>Children with special care needs who lacked cooperation or were unable to answer the questions were excluded</li> </ul>	None	18	-	70	CPQ11-14
Freitas Fernandes 2021	(20)	Brazil	cross-sectional	463	11-14	EAPD	<ul style="list-style-type: none"> <li>All first permanent molars fully erupted</li> <li>Children not undergoing orthodontic treatment with fixed appliances at the time of evaluation</li> <li>Children with special care needs who lacked cooperation or were unable to answer the questions were excluded</li> </ul>	<ul style="list-style-type: none"> <li>Mild: Demarcated opacities</li> <li>Severe: Fracture/ Atypical restoration/ Atypical caries/ Tooth loss due to MIH</li> </ul>	50	28	413	CPQ11-14
Folayan 2018	(33)	Nigeria	cross-sectional	853	6-16	EAPD	<ul style="list-style-type: none"> <li>Participants with special care needs were excluded</li> </ul>	None	25	-	828	C-OIDP
Gutiérrez 2019	(25)	Mexico	cross-sectional	411	8-10	EAPD	<ul style="list-style-type: none"> <li>At least one first permanent molar erupted</li> <li>Children with orthodontic attachments that prevented the examination of the tooth surface were excluded</li> </ul>	<ul style="list-style-type: none"> <li>Mild: 1 white or creamy demarcated opacity affecting less than 1/3 of the tooth surface</li> <li>Moderate/severe: Any other defect (e.g. Brown opacity)</li> </ul>	166	-	245	CPQ8-10
Porcella 2019	(19)	Brazil	cross-sectional	728	8	EAPD	<ul style="list-style-type: none"> <li>All first permanent molars fully erupted</li> <li>Children not undergoing orthodontic treatment with fixed appliances at the time of evaluation</li> <li>Children without a history of orthodontic treatment</li> <li>Absence of other types of enamel defects</li> </ul>	<ul style="list-style-type: none"> <li>Mild: Demarcated opacity</li> <li>Severe: Fracture/ Atypical restoration/ Tooth loss due to MIH</li> </ul>	88	25	640	CPQ 8-10
Porcella 2018	(18)	Brazil	case-control	93	Mean = 8.5	EAPD	<ul style="list-style-type: none"> <li>All first permanent molars fully erupted</li> <li>Children not undergoing orthodontic treatment with fixed appliances at the time of evaluation</li> <li>Absence of other types of enamel defects</li> </ul>	<ul style="list-style-type: none"> <li>Mild: Demarcated opacity</li> <li>Severe: Fracture/ Atypical restoration/ Tooth loss due to MIH</li> </ul>	21	-	42	CPQ8-10
Cerqueira Silva 2021	(17)	Brazil	cross-sectional	834	5	EAPD	<ul style="list-style-type: none"> <li>All four second primary molars erupted</li> <li>Children not undergoing orthodontic treatment with fixed appliances at the time of evaluation</li> <li>Children with special care needs or syndromes who lacked cooperation were excluded</li> <li>Children without amelogenesis imperfecta</li> </ul>	<ul style="list-style-type: none"> <li>Mild: Demarcated opacity</li> <li>Severe: Fracture/ Atypical caries/ Atypical restoration/ Tooth loss due to MIH</li> </ul>	124	38	710	ECOHIS
Michaels 2021	(23)	Germany	cross-sectional	528	7-10	EAPD	<ul style="list-style-type: none"> <li>Children were included if they had at least one tooth affected by caries or MIH</li> <li>Children were excluded if presented with both caries and MIH</li> </ul>	<ul style="list-style-type: none"> <li>Based on Manthu-Maju and Wright criteria, each MIH affected tooth was assigned a score from 1-3.</li> <li>By adding all the risk points acquired through each affected tooth, the patients are divided in one of three severity categories</li> </ul>	264	176	264	CPQ8-10
Elhennawy 2022	(22)	Germany	cross-sectional	317	7-14	EAPD	<ul style="list-style-type: none"> <li>To be included in the MIH group: <ul style="list-style-type: none"> <li>children had to have at least one MIH affected untreated first permanent molar with more than 1/3 of its clinical crown erupted</li> <li>To be included in the control group: <ul style="list-style-type: none"> <li>Children had to attend dental clinic for a routine check-up without acute problems</li> <li>Children were excluded if they could not speak/write german</li> </ul> </li> </ul> </li> <li>All permanent first molars and permanent incisors fully erupted</li> <li>Children presenting with other types of enamel defects were excluded</li> <li>Children undergoing orthodontic treatment with fixed appliances were excluded</li> </ul>	<ul style="list-style-type: none"> <li>Mild: demarcated opacities</li> <li>Severe: post-eruptive breakdown</li> </ul>	217	157	100	COHIP-G19
Dancas-Neta 2016	(21)	Brazil	cross-sectional	594	11-14	EAPD	<ul style="list-style-type: none"> <li>All permanent first molars fully erupted</li> <li>Children were excluded if they could not speak german</li> <li>Children presenting with other types of enamel defects were excluded</li> <li>Children with systemic compromise were excluded</li> <li>Children with severe malocclusions/ undergoing orthodontic treatment were excluded</li> <li>Children with enamel developmental defects other than MIH were excluded.</li> </ul>	<ul style="list-style-type: none"> <li>Mild: demarcated opacities</li> <li>Moderate/ Severe: Fracture/ Atypical restoration/ Tooth loss due to MIH</li> </ul>	109	55	485	CPQ11-14
Joshi 2022	(26)	Germany	cross-sectional	188	8-10	EAPD	<ul style="list-style-type: none"> <li>All first permanent molars fully erupted</li> <li>Children were excluded if they could not speak german</li> <li>Children presenting with other types of enamel defects were excluded</li> <li>Children with systemic compromise were excluded</li> <li>Children with severe malocclusions/ undergoing orthodontic treatment were excluded</li> <li>Children with enamel developmental defects other than MIH were excluded.</li> </ul>	MIH-TNI	94	57	94	CPQ8-10

### MIH severity and OHRQoL

Children with moderate/severe MIH (n=529) are 3.43 times more likely to have an impact on OHRQoL compared to those without MIH (n=2066) (OR=3.43, 95 % CI = 1.69–6.98) (Fig. 3). Statistical heterogeneity was present ( $X^2= 193.22$ ,  $P = 0.0008$ ) and was interpreted as considerable ( $I^2 = 97 %$ )

### Publication bias

Visual examination of funnel plots for both meta-analyses provided no indication for bias. The funnel plots for both meta-analyses are presented in the supplemental file (S5).

### Sensitivity analysis

In the first meta-analysis concerned with MIH presence, differences in significance appeared for summary estimates when each of the following studies (18,20,32,33) were omitted. On the other hand, for the MIH severity meta-analysis, none of them led to significant changes in the summary when omitted. Summary estimates, following the omission of one study results consecutively from both meta-analyses, are presented in the supplemental file (S6).

## Discussion

This review identified a total of 11 studies reporting on 5,017 children, of which (n=1,174) presented with MIH, which were included in the meta-analysis assessing the impact of MIH presence. Concerning MIH severity and its impact on OHRQoL, a total 6 studies were included in the meta-analysis involving a total of 2,595 children, of whom (n=529) presented with moderate/severe MIH.

In the first meta-analysis, the association between MIH presence and low OHRQoL was examined. The results indicated a lack of statistically significant association (OR=1.72, 95% CI=0.99–2.98), though a noticeable trend was observed. Conversely, the second meta-analysis explored the relationship between moderate/severe MIH presence and OHRQoL, revealing a statistically significant association (OR=3.43, 95% CI=1.69–6.98).

A separate systematic review (34) also explored the impact of MIH on children's OHRQoL, though without quantitative analysis. It suggested that irrespective of MIH severity, there was a connection with impaired OHRQoL. This contrasts with the findings of the current review, where a significant association was only established with moderate/severe MIH cases.

The results of the present review should be interpreted under consideration of multiple factors, especially the criteria used for MIH diagnosis as well as severity determination throughout the included studies. Owing to the inherent items of the EAPD criteria for MIH diagnosis coupled with the predominant cross-sectional study design of included studies (n = 9), a positive MIH diagnosis does not necessarily differentiate between treated and untreated MIH affected children, a result of atypical restorations being a diagnostic criterion for MIH. Only one included study (22) using EAPD criteria explicitly excluded treated MIH patients. This inability to differentiate might underestimate the impact of

### Težina MIH-a i OHRQoL

Djeca s umjerenim/teškim MIH-om (n = 529) imaju 3,43 puta veću vjerojatnost utjecaja na OHRQoL u usporedbi s onom bez MIH-a (n = 2066) (OR = 3,43, 95 % IP = 1,69 – 6,98) (slika 3.). Zabilježena je statistička heterogenost ( $X^2= 193,22$ ,  $P = 0,0008$ ) i protumačena je kao značajna ( $I^2 = 97 %$ ).

### Priistranost publikacije

Vizualna analiza dijagrama lijevka za obje metaanalize nije dala naznake priistranosti. Dijagrami lijevka za obje metaanalize nalaze se u dodatnoj datoteci (S5).

### Analiza osjetljivosti

U prvoj metaanalizi koja se bavila prisutnošću MIH-a, pojavile su se razlike u značajnosti za sažete procjene kada je svako od sljedećih istraživanja (18, 20, 32, 33) izostavljeno. S druge strane, za metaanalizu težine MIH-a, nijedno od njih nije potaknulo značajne promjene u sažetku kada je izostavljeno. Sažete procjene, poslije izostavljanja rezultata jednog istraživanja uzastopno iz obje metaanalize, nalaze se u dodatnoj datoteci (S6).

## Rasprava

U ovom pregledu identificirano je ukupno 11 istraživanja koja su izvještavala o 5017 djece, od kojih (n = 1 174) s MIH-om, koja su bila uključena u metaanalizu koja procjenjuje utjecaj prisutnosti MIH-a. Što se tiče težine MIH-a i njegova utjecaja na OHRQoL, u metaanalizu je uključeno ukupno 6 istraživanja s 2595 djece, od kojih (n = 529) ima umjereni/teški MIH.

U prvoj metaanalizi ispitana je povezanost između prisutnosti MIH-a i niskog OHRQoL-a. Rezultati su pokazali nedostatak statistički značajne povezanosti (OR = 1,72, 95 % IP = 0,99 – 2,98), iako je uočen zamjetni trend. Nasuprot tomu, druga metaanaliza istraživala je odnos između umjerenoga/teškoga MIH-a i OHRQoL-a, otkrivajući statistički značajnu povezanost (OR = 3,43, 95 % IP = 1,69 – 6,98).

Zasebni sistematizirani pregled (34) također je istraživao utjecaj MIH-a na OHRQoL djece, iako bez kvantitativne analize. Sugerirao je da, bez obzira na ozbiljnost MIH-a, postoji povezanost s narušavanjem OHRQoL-a. To je u suprotnosti s nalazima u ovom pregledu u kojemu je značajna povezanost utvrđena samo kod slučajeva s umjerenim/teškim MIH-om.

Rezultate ovog pregleda treba tumačiti uzimajući u obzir više čimbenika, posebno kriterije koji se koriste za dijagnozu MIH-a te određivanje težine u uključenim istraživanjima. Zbog inherentnih stavki EAPD kriterija za dijagnozu MIH-a zajedno s dominantnim dizajnom presječnih istraživanja (n = 9), pozitivna dijagnoza MIH-a ne pravi nužno razliku između liječene i neliječene djece s MIH-om. Samo je jedno uključeno istraživanje (22) koje se koristilo kriterijima EAPD-a izričito isključilo liječene pacijente s MIH-om. Ta nemogućnost razlikovanja mogla bi podcijeniti utjecaj MIH-a na OHRQoL pogođene djece jer bi djeca s kontroliranim MIH-om mogla imati bolji OHRQoL u usporedbi s onima s neliječanim MIH-om.

MIH on affected children's OHRQoL, as children with managed MIH might have better OHRQoL compared to counterparts with untreated MIH.

The current review's limitations include the predominance of cross-sectional studies, which hampers causal inference. However, two identified studies (35,36) addressed the impact of MIH treatment on OHRQoL, using a prospective clinical trial design evaluating the OHRQoL in children before and after treatment. An improvement in the OHRQoL post-treatment is shown. The exact reasons for the exclusion of both studies from this review can be found in the supplementary material (S3).

Regarding MIH severity, among the 6 studies included in the meta-analysis, only 2 (23,26) allowed classification of patients as Moderate/Severe MIH patients in the presence of hypersensitivity when MIH presented only as demarcated opacities. This suggests possible underestimation of the association between severe MIH and impaired OHRQoL.

Furthermore, clinical heterogeneity was judged to be considerable between the included studies (Table 1). In one study (17) the impact of HSPM rather than MIH impact was evaluated. However, HSPM diagnosis was made according to the modified EAPD criteria (37) which were identical to MIH diagnostic criteria in this index. Nonetheless, the performed sensitivity analysis where the study results in question were omitted from the summary odds ratios for both meta-analyses resulted in no change in significance of the reported outcomes (S6).

The strength of this review, however, lies in the comprehensive search strategy that included a search of 4 electronic databases, and a review of reference lists of other reviews in the field and reference lists of all included trials. Despite such a comprehensive search, it is still possible that this review missed some potentially eligible studies. Furthermore, contacting authors concerning missing information led to more complete and robust results. From a methodological perspective, a significant strength of the present review lies in the statistical analysis, which allowed the combination of continuous and dichotomous results presented in the different included studies, thus allowing for more robust results.

## Conclusion

No general significant but at tendency to an association between MIH presence and low OHRQoL in affected children was found, as possible inclusion of previously dentally managed MIH participants may have played a role in this outcome. Still, a statistically significant association between moderate/severe MIH and lower OHRQoL exists highlighting that especially children with more severe forms of MIH need clinical attention.

## Conflict of interest

The authors declare no conflicts of interest with respect to the authorship and/or publication of this article.

Ograničenja ovog pregleda jesu prevlast presječnih istraživanja, što otežava uzročno zaključivanje. Međutim, dva identificirana istraživanja (35, 36) bavila su se utjecajem liječenja MIH-a na OHRQoL, koristeći se prospektivnim dizajnom kliničkog istraživanja koji je procjenjivao OHRQoL u djece prije i poslije liječenja. Istaknuto je poboljšanje OHRQoL-a poslije liječenja. Točni razlozi za isključenje obaju istraživanja iz ovog pregleda mogu se pronaći u dopunskom materijalu (S3).

Što se tiče ozbiljnosti MIH-a, među 6 istraživanja uključenih u metaanalizu samo su 2 (23, 26) dopuštala klasifikaciju pacijenata kao bolesnika s umjerenim/teškim MIH-om u prisutnosti preosjetljivosti kada se MIH manifestirao samo kao ograničeno zamućenje. To upućuje na moguće podcjenjivanje povezanosti između teškoga MIH-a i narušenoga OHRQoL-a.

Nadalje, ocijenjeno je da je klinička heterogenost značajna između uključenih istraživanja (tablica 1.). U jednom istraživanju (17) procijenjen je utjecaj HSPM-a, a ne MIH-a. No dijagnoza HSPM-a postavljena je prema modificiranim kriterijima EAPD-a (37) koji su u ovom indeksu bili identični dijagnostičkim kriterijima MIH-a. Bez obzira na to, provedena analiza osjetljivosti u kojoj su predmetni rezultati istraživanja izostavljeni iz sažetih omjera za obje metaanalize, nije rezultirala promjenom značajnosti prijavljenih ishoda (S 6).

No snaga ovog pregleda je u sveobuhvatnoj strategiji pretraživanja koja je uključivala 4 elektroničke baze podataka te pregled popisa referencija drugih pregleda na terenu i popisa referencija svih uključenih istraživanja. Unatoč tako opsežnom pretraživanju, moguće je da su u ovom pregledu izostavljena neka potencijalno prihvatljiva istraživanja. Nadalje, kontaktiranje autora u vezi s informacijama koje su nedostajale omogućilo je potpunije i robusnije rezultate. Iz metodološke perspektive, velika snaga ovog pregleda je u statističkoj analizi koja je omogućila kombinaciju kontinuiranih i dihotomnih rezultata prikazanih u različitim uključenim istraživanjima, čime su omogućeni robusniji rezultati.

## Zaključak

Nije pronađena opća značajna razlika, ali postojala je tendencija povezanosti između prisutnosti MIH-a i niskoga OHRQoL-a kod pogođene djece, s obzirom na to da je moguće uključivanje sudionika s MIH-om koji su prije toga liječeni možda imalo ulogu u ovom ishodu. Ipak, postoji statistički značajna povezanost između umjerenoga/teškoga MIH-a i nižeg OHRQoL-a, te se ističe da djeca s težim oblicima MIH-a trebaju kliničku skrb.

## Sukob interesa

Autori nisu bili u sukobu interesa.



**Author's contribution:** A.A.: Conceptualization, Investigation, Formal analysis, Writing - Original Draft; R. H. - Validation, Investigation, Visualization, Writing - Original Draft; U.S. - Conceptualization, Writing - Review & Editing, Supervision; C.H.S - Conceptualization, Writing - Review & Editing, Supervision; J.S. - Project administration, Conceptualization, Supervision, Methodology, Writing - Review & Editing. All authors gave their final approval and agree to be accountable for all aspects of the work.

**Doprinos autora:** A. A. – konceptualizacija, istraživanje, formalna analiza, pisanje teksta - izvorni nacrt; R. H. – provjera valjanosti, istraživanje, vizualizacija, pisanje teksta - izvorni nacrt; U. S. – konceptualizacija, pisanje teksta, pregled i uređivanje, nadzor; C. H. S. – konceptualizacija, pisanje teksta, pregled i uređivanje, nadzor; J. S. – administracija projekta, konceptualizacija, nadzor, metodologija, pisanje teksta, pregled i uređivanje. Svi autori dali su konačno odobrenje i suglasni su da odgovaraju za sve aspekte rada.

### Sažetak

**Svrha istraživanja:** Cilj ovog sistematiziranog pregleda i metaanalize bio je procijeniti povezanost između MIH-a i OHRQoL-a u djece. **Materijali i metode:** Pronađena su relevantna istraživanja u bazama PubMed, Embase, Cochrane i Google Scholar. Uključena su istraživanja koja su obrađivala MIH i OHRQoL u djece. Metodološka procjena kvalitete tih istraživanja obavljena je s pomoću ljestvice Newcastle-Ottawa (NOS) i njezine prilagodene verzije za presječne studije. Za procjenu sažetih mjera učinka za povezanost između prisutnosti MIH-a (prisutnost prema povezanosti) upotrijebljeni su modeli slučajnih učinaka, a za težinu (umjereni/teški MIH prema odsutnosti MIH-a) i OHRQoL upotrijebljena je generička metaanaliza inverzne varijance. Obavljeni su i testovi heterogenosti, pristranosti objave i osjetljivosti rezultata. **Rezultati:** Od 1696 identificiranih časopisa, u metaanalizu procjene utjecaja prisutnosti MIH-a uključeno je 11 istraživanja koja su izvještavala o 5017 djece. Nije bilo statistički značajne povezanosti između prisutnosti MIH-a i nižega OHRQoL-a u pogodne djece (OR = 1,72, 95 % IP = 0,99–2,98). Kad je riječ o težini MIH-a i njegova utjecaja na OHRQoL, zbroj od 6 istraživanja uključen je u metaanalizu koja obuhvaća ukupno 2595 djece. Postojala je značajna povezanost između umjerenoga/teškoga MIH-a i nižega OHRQoL-a u pogodne djece (OR = 3,43, 95 % IP = 1,69 – 6,98).

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**MeSH pojmovi:** hipomineralizacija kutnjaka; kvaliteta života; dijete  
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## Supplement S1

### Search strategies

#### PubMed:

“Dental Enamel Hypoplasia”[Mesh] OR MIH[tiab] OR “molar incisor hypomineralization”[tiab] OR “molar incisor hypomineralisation”[tiab] OR “incisor molar hypomineralization”[tiab] OR “incisor molar hypomineralisation”[tiab] OR “molar hypomineralization”[tiab] OR “molar hypomineralisation”[tiab] OR “hypomineralized molar\*”[tiab] OR “hypomineralised molar\*”[tiab] OR “incisor hypomineralization”[tiab] OR “incisor hypomineralisation”[tiab] OR “deciduous molar hypomineralization”[tiab] OR “deciduous molar hypomineralisation”[tiab] OR “hypomineralized second primary molar\*”[tiab] OR “hypomineralised second primary molar\*”[tiab] OR “enamel defect\*”[tiab] OR “developmental defects of enamel”[tiab] OR “developmental defect of enamel”[tiab] OR “enamel developmental defect\*”[tiab] OR “dental enamel”[tiab] OR “tooth demineralization”[tiab] OR “tooth demineralisation”[tiab] OR “enamel hypoplasia”[tiab] OR “Tooth Abnormalit\*”[tiab] OR “Incisor opacit\*”[tiab] OR “Dental Enamel Hypoplasia”[tiab]

AND

“Quality of Life”[Mesh] OR OHRQoL[tiab] OR QoL[tiab] OR HRQL[tiab] OR HRQoL[tiab] OR OHRQL[tiab] OR “patient reported outcome\*”[tiab] OR “perception\*”[tiab] OR “Oral Health”[tiab] OR “Psychosocial impact\*”[tiab] OR “Life Quality”[tiab] OR “Health-Related”[tiab] OR “Quality Of Life”[tiab] OR “Health Related Quality Of Life”[tiab]

#### Embase:

(‘tooth malformation’/exp OR mih:ab,ti,kw OR ‘molar incisor hypomineralization’:ab,ti,kw OR ‘incisor molar hypomineralization’:ab,ti,kw OR ‘molar hypomineralization’:ab,ti,kw OR ‘hypomineralized molar\*’:ab,ti,kw OR ‘incisor hypomineralization’:ab,ti,kw OR ‘deciduous molar hypomineralization’:ab,ti,kw OR ‘hypomineralized second primary molar\*’:ab,ti,kw OR ‘enamel defect\*’:ab,ti,kw OR ‘developmental defect\* of enamel’:ab,ti,kw OR ‘enamel developmental defect\*’:ab,ti,kw OR ‘dental enamel’:ab,ti,kw OR ‘tooth demineralization’:ab,ti,kw OR ‘enamel hypoplasia’:ab,ti,kw OR ‘tooth abnormalit\*’:ab,ti,kw OR ‘incisor opacit\*’:ab,ti,kw OR ‘dental enamel hypoplasia’:ab,ti,kw)

AND (‘quality of life’/exp OR OHRQoL:ab,ti,kw OR qol:ab,ti,kw OR hrql:ab,ti,kw OR hrqol:ab,ti,kw OR ohrql:ab,ti,kw OR ‘patient reported outcome\*’:ab,ti,kw OR ‘perception\*’:ab,ti,kw OR ‘oral health’:ab,ti,kw OR ‘psychosocial impact\*’:ab,ti,kw OR ‘life quality’:ab,ti,kw OR ‘health related’:ab,ti,kw OR ‘quality of life’:ab,ti,kw OR ‘health related quality of life’:ab,ti,kw)

#### Cochrane central:

([mh “Dental Enamel Hypoplasia”] OR MIH:ti,ab,kw OR “molar incisor hypomineralization”:ti,ab,kw OR “incisor molar hypomineralization”:ti,ab,kw OR “molar hypomineralization”:ti,ab,kw OR “hypomineralized molar\*”:ti,ab,kw OR “incisor hypomineralization”:ti,ab,kw OR “deciduous molar hypomineralization”:ti,ab,kw OR “hypomineralized second primary molar\*”:ti,ab,kw OR “enamel defect\*”:ti,ab,kw OR “developmental defects of enamel”:ti,ab,kw OR “developmental defect of enamel”:ti,ab,kw OR “enamel developmental defect\*”:ti,ab,kw OR “dental enamel”:ti,ab,kw OR “tooth demineralization”:ti,ab,kw OR “enamel hypoplasia”:ti,ab,kw OR “Tooth Abnormalit\*”:ti,ab,kw OR “Incisor opacit\*”:ti,ab,kw OR “Dental Enamel Hypoplasia”:ti,ab,kw) AND ([mh “Quality of Life”] OR OHRQoL:ti,ab,kw OR QoL:ti,ab,kw OR HRQL:ti,ab,kw OR HRQoL:ti,ab,kw OR OHRQL:ti,ab,kw OR “patient reported outcome\*”:ti,ab,kw OR “perception\*”:ti,ab,kw OR “Oral Health”:ti,ab,kw OR “Psychosocial impact\*”:ti,ab,kw OR “Life Quality”:ti,ab,kw OR “Health-Related”:ti,ab,kw OR “Quality Of Life”:ti,ab,kw OR “Health Related Quality Of Life”:ti,ab,kw)

#### Google Scholar:

“molar incisor hypomineralisation” AND “Quality of Life”

## Supplement S2

Narrative review of study not included in meta-analyses

Study	Country	Study design	Sample size	Age in years	n(%) participants with MIH	OHRQoL instrument	Summary of results
Velandia et al. 2018 (1)	Colombia	case-control	88	8-10	88	CPQ 8-10	MIH is associated with a worst OHRQoL in children

This study was conducted in Bucaramanga. Age of participants varied between 7-10 years old ( $8.6 \pm 1.2$  years). 88 children were selected by convenience sampling and were divided equally into a case group (with MIH) and a control group (without MIH). Diagnosis of MIH was carried out using the EAPD criteria, whereas the severity of MIH was evaluated using the criteria of Mathu Muju and Wright. The Oral Health Related Quality of Life was measured using the CPQ 8-10, which consists of 25 questions divided in 4 domains, where the lower scores indicate a better OHRQoL.

Furthermore, a questionnaire filled by the parents/caregivers was used to collect socio-demographic information. A statistically significant difference was found in the average CPQ 8-10 scores between the MIH group ( $17.4 \pm 14.1$ ) and the control group ( $4.3 \pm 4.1$ ), indicating a negative impact of MIH on OHRQoL in children. These results are in agreement with a study done in Mexico that used the same questionnaire (Gutierrez TV et al.). On the other hand, (Arrow et al. 2017, Freitas Fernandes et al. 2021) found no association of enamel defects in first permanent molars on OHRQoL. Even though in this study no statistically significant difference was found regarding the severity of MIH, severe MIH was associated with greater negative impact on OHRQoL than mild MIH in another study (Elhennawy et al. 2021). Although female participants with MIH in this study showed higher CPQ 8-10 scores than males, which comes in line with other studies (Dantas-Neta et al. 2016), this difference was not of significance. On the other hand, a statistically significant difference regarding socioeconomic status and type of social security was found among participants with and without MIH.

Due to the convenience sampling in this study and including participants from only a public educational institution, that doesn't include all socio-economical levels, the results found could not be generalized. Furthermore, many confounding variables were not taken into consideration in the analyses.

## Supplement S3

Excluded articles after full text assessment with reasons

Reference	Article title	Reason for exclusion
(2)	Assessing the prevalence of molar-incisor hypomineralization and its effects on oral health-related quality of life in children aged 8-12 years in the city of Kerman, Iran	No control group
(3)	Changes in oral health-related quality of life after treatment of hypersensitive molar incisor hypomineralization-affected molars with a sealing	No control group
(4)	Child oral health-related quality of life (COHQoL), enamel defects of the first permanent molars and caries experience among children in Western Australia	MIH not extractable as it is divided into incisors and molars, in addition a more recent study is available
(5)	Dental caries, but not malocclusion or developmental defects, negatively impacts preschoolers' quality of life	MIH not extractable
(6)	Developmental enamel defects and their impact on child oral health-related quality of life	MIH not extractable
(7)	Enamel development defects and oral symptoms: A hierarchical approach	Not the full questionnaire results were reported
(8)	Hat die Molaren-Inzisiven-Hypomineralisation einen Einfluss auf die mundgesundheitsbezogene Lebensqualität betroffener Kinder?	No control group
(9)	Health and oral health-related quality of life of children and adolescents with chronic kidney disease: a cross-sectional study	MIH not extractable and kidney disease
(10)	Impact of Developmental enamel defects on quality of life in 5-year-old children	MIH not extractable
(11)	Influence of customized therapy for molar incisor hypomineralization on children's oral hygiene and quality of life	No validated QoL instrument
(12)	Molar-incisor hypomineralization: parent's and children's impact perceptions on the oral health-related quality of life	no control group
(13)	Oral health-related quality of life among Brazilian preschool children	MIH not extractable
(14)	Oral health-related quality of life of 11- and 12-year-old public school children in Rio de Janeiro	MIH not extractable
(15)	Oral health-related quality-of-life among children in Swedish dental care: The impact from malocclusions or orthodontic treatment need	MIH not extractable
(16)	Oral health-related quality-of-life in Swedish children before and after dental treatment under general anesthesia	MIH not extractable

(17)	Prevalence of self-reported dental pain and associated factors among eight- to ten-year-old Brazilian schoolchildren	MIH not extractable
(18)	The clinical efficacy of orthodontic treatment and implant restoration in the treatment of malocclusion with dentition defects and their impact on patients' quality of life	MIH not extractable
(19)	The influence of oral health conditions, socioeconomic status and home environment factors on schoolchildren's self-perception of quality of life	MIH not extractable
(20)	Treatment of Severe Caries and Molar Incisor Hypomineralization and Its Influence on Oral Health-Related Quality of Life in Children: A Comparative Study	Only severe caries hence not comparable with other control groups and only severe MIH hence not comparable with other studies

### Supplement S4

Methodological quality assessment of the studies included in the meta-analysis

#### Option 1

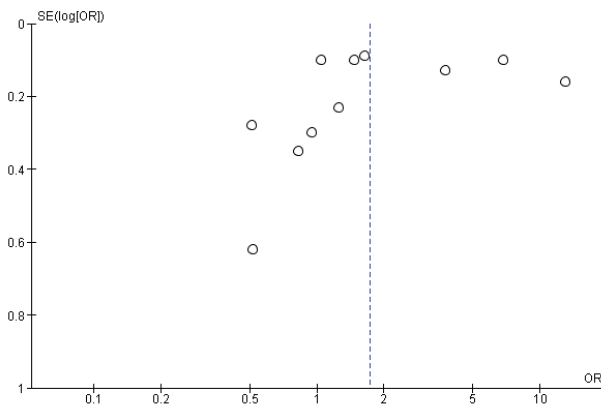
Study	Study design	Newcastle–Ottawa scale (NOS) adapted for cross-sectional studies		
		Selection (max 5 stars)	Comparability (max 2 stars)	Outcome (max 3 stars)
(21)	Cross-sectional	*****	**	**
(22)	Cross-sectional	*****	*	***
(23)	Cross-sectional	****	**	**
(24)	Cross-sectional	***	*	**
(25)	Cross-sectional	****	**	**
(26)	Cross-sectional	****	*	**
(27)	Cross-sectional	****	*	**
(28)	Cross-sectional	*****	*	*
(29)	Cross-sectional	***	*	**
(1)	Cross-sectional	**		*
Study	Study Design	Newcastle–Ottawa scale (NOS) for cohort studies		
		Selection (max 4 stars)	Comparability (max 2 stars)	Outcome (max 3 stars)
(30)	Cohort	***		**
Study	Study Design	Newcastle–Ottawa scale (NOS) for cohort studies		
		Selection (max 4 stars)	Comparability (max 2 stars)	Outcome (max 3 stars)
(31)	Case control	**	**	

Each star refers to a positive answer in the Newcastle-Ottawa Quality Assessment Form.

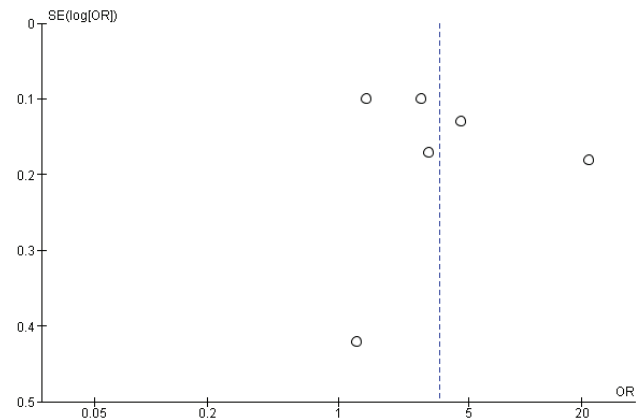


## Supplement S5

## Funnel plots



Funnel plot for the evaluation of publication bias for studies evaluating the association of MIH presence and OHRQoL



Funnel plot for the evaluation of publication bias for studies evaluating the association of severe MIH and OHRQoL

## Supplement S6

## Sensitivity analysis

Meta-analysis	Study omitted	OR (95% CI)	P value
MIH presence	Arrow, 2017 (30)	1.82 (1.02 - 3.25)	0.04
	Cerqueira Silva et al. 2021(21)	1.73 (0.92 - 3.25)	0.09
	Dantas-Neta et al. 2016 (28)	1.81 (1.00 - 3.26)	0.05
	Elhennawy et al. 2022 (26)	1.57 (0.86 - 2.89)	0.14
	Folayan et al. 2018 (23)	1.87 (1.06 - 3.31)	0.03
	Freitas Fernandes et al. 2021(22)	1.84 (1.03 - 3.28)	0.04
	Gutiérrez et al. 2019 (24)	1.50 (0.89 - 2.51)	0.13
	Joshi et al. 2022 (27)	1.41 (0.85 - 2.33)	0.19
	Michaelis et al. 2021 (29)	1.71 (0.89 - 3.26)	0.11
	Portella et al. 2018 (31)	1.94 (1.10 - 3.42)	0.02
Portella et al. 2019 (25)	1.77 (0.98 - 3.19)	0.06	
MIH severity	Cerqueira Silva et al. 2021(21)	3.51 (1.50 - 8.18)	0.004
	Dantas-Neta et al. 2016 (28)	4.15 (1.98 - 8.74)	0.0002
	Elhennawy et al. 2022 (26)	3.23 (1.36 - 7.71)	0.008
	Freitas Fernandes et al. 2021 (22)	4.06 (1.88 - 8.77)	0.0004
	Joshi et al. 2022 (27)	2.42 (1.51 - 3.87)	0.0002
	Michaelis et al. 2021 (29)	3.56 [1.36 - 9.34]	0.01

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