



# Are Molar-Incisor Hypomineralization and Hypomineralized Second Primary Molars Predictive of Dental Caries?: A Systematic Review

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Eur J Dent 2023;17:7–15.

## Abstract

To estimate the prevalence of dental caries among children affected concomitantly with molar-incisor hypomineralization (MIH) and hypomineralized second primary molars (HSPM).

Electronic databases, including Medline via PubMed, Cochrane Library, Scopus, and Science Direct, were searched. Studies written in English involving children with MIH-HSPM and dental caries were considered eligible. Two reviewers extracted the data according to the PRISMA statement and assessed the bias risk with the Newcastle–Ottawa Scale (NOS) criteria.

Out of 535 studies identified in the initial research, only two articles were included in the present review. A significant association between MIH-HSPM and dental caries in permanent dentition was reported in the two included records (AOR: 3.70;  $p < 0.001$ ). Children with MIH-HSPM expressed significantly higher DMFT and PUFA values than children without MIH-HSPM. However, dmft values did not differ significantly between children with and without HSPM (1.79 [2.4] vs. 1.78 [2.5]; 1.88 [2.73] vs. 1.59 [2.53], respectively).

MIH-HSPM lesions were correlated with a higher prevalence and more severe carious lesions in permanent dentition. However, the results should be interpreted cautiously because the findings were generated by only two studies performed by the same authors. Thus, further well-designed studies are highly recommended.

## Keywords

- ▶ dental enamel hypoplasia
- ▶ tooth
- ▶ deciduous
- ▶ tooth demineralization
- ▶ child
- ▶ prevalence
- ▶ dental caries

## Introduction

Molar incisor hypomineralization (MIH) is usually defined as a qualitative defect of systematic origin with hypomineralization affecting one to four first permanent molars (FPMs), commonly associated with permanent incisors.<sup>1</sup> Hypomineralized second primary molars (HSPM) are MIH-like defects localized in one to four-second primary molars (SPMs).<sup>2</sup>

MIH and HSPM are considered eminent oral health conditions universally affecting children, with a prevalence rate ranging from 2.5% to 40% for MIH and from 0 to 21.8% for HSPM.<sup>3</sup> The diversity of study populations and the shortage of standardization in the investigation protocols can explain this heterogeneity in the findings. Results are still controversial and none of the published research has succeeded to identify clear etiological conditions for MIH and HSPM.

article published online  
September 19, 2022

DOI <https://doi.org/10.1055/s-0042-1749360>.  
ISSN 1305-7456.

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Environmental factors and genetic effects can concomitantly lead to MIH and HSPM occurrence.<sup>4</sup> FPMs and SPMS have a simultaneous period of mineralization as a result risk factors arising during this period could affect those teeth concomitantly.<sup>5</sup> MIH and HSPM association was widely assessed in the literature. A systematic review published in 2018 showed that HSPM was a predictive sign for MIH, with higher MIH prevalence associated with the presence of mild HSPM.<sup>6</sup> MIH and HSPM affected-children are susceptible to expeditious dental caries experience. The porous structure may facilitate the accumulation of bacterial plaque consequently promoting dental caries formation.

Even though the mechanism involved in the hypomineralized teeth hypersensitivity is still ambiguous, Fagrell et al (2008) have reported that the high porosity of hypomineralized teeth widely promotes the penetration of bacteria in the dentinal tubules, causing subclinical pulpal inflammation.<sup>7,8</sup> The discomfort reported by the patients may be spontaneous or caused by thermal or mechanical stimuli.<sup>9</sup> Although a few studies investigated this phenomenon, recent findings have shown that sensitivity is more frequent and intense in severe MIH with post-eruptive enamel breakdown (PEB). This finding is still controversial because of the high frequency of carious lesions involving dentine in severe hypomineralized teeth.<sup>9</sup> MIH-HSPM children rebel tooth brushing because of the discomfort related to hypersensitivity, which can exacerbate caries vulnerability. This is in line with a previous systematic review published in 2017 that showed a high association between MIH and dental caries.<sup>10</sup> Recently, a significant association between HSPM and dental caries has been assessed.<sup>11,12</sup> Therefore, children with HSPM and MIH may be more susceptible to severe carious lesions than non-affected ones.

The present review aimed to determine the prevalence of dental caries among children affected simultaneously with MIH and HSPM.

## Methods

### Protocol and Registration

The present systematic review was designed and conducted following the Preferred Reporting Items for Systematic

Reviews and Meta-Analyses (PRISMA statement) checklist<sup>13</sup> and was recorded in the International Prospective Register of Systematic Reviews (PROSPERO database) under the protocol CRD42020210028.

### Present Research Question

The review question was “Are children affected concomitantly with MIH and HSPM at high risk for developing dental caries?” This question was based on the Population, Intervention, Comparators, Outcomes, and Study design (PICOS) format, resulting in the following (► **Table 1**):

-P: the population was: children older than 6 years, in mixed dentition with MIH-HSPM and dental caries were included in the present review.

-I: The intervention: we searched for the type of association between Molar incisor hypomineralization, hypomineralized second primary molars, and dental caries.

C: the comparators: were the control groups of the studies.

O: The main outcome or endpoint of interest was the prevalence of carious lesions in MIH-HSPM children.

S: The study design: observational studies.

### Inclusion and Exclusion Criteria

Inclusion and Exclusion criteria are summarized in ► **Table 1**. Studies that pooled children affected with MIH, HSPM, and dental caries were included in the present systematic review:

-Studies that included children in mixed dentition, reported the prevalence of dental caries in children affected with both MIH and HSPM.

-Studies that assessed the outcomes of dental caries using the DMFT (decayed, missing, and filled teeth) index as described by the World Health Organization (WHO); the International Caries Detection and Assessment System (ICDAS II) or Pulp, ulceration, fistula, abscess (PUFA/pufa) index.

-Studies that evaluated the outcomes of MIH and HSPM using the European Academy of Pediatric Dentistry (EAPD) index or the Modified Index of Developmental Defects of Enamel.

**Table 1** The PICOS format illustrating the review question:

|              |   |
|--------------|---|
| Population   | Children older than 6 years, in mixed dentition, <u>with MIH-HSPM and dental caries were included in the present review.</u><br><u>Children aged under 6 years or older than 12 years were excluded.</u>  |
| Intervention | <u>Type of association between molar incisor hypomineralization, hypomineralized second primary molars and dental caries.</u><br>Publications that assessed only MIH and dental caries or studies interested in HSPM and dental caries without MIH assessment were excluded.          |
| Comparators  | The control groups of the studies   |
| Outcomes     | The main outcome or endpoint of interest was the prevalence of carious lesions in MIH-HSPM children.  |
| Study design | Observational studies were included.<br>Case reports, narrative studies (dissertations), literature reviews, meta-analyses, systematic reviews, clinical practice guidelines, theses, chapters of textbooks or textbooks, brief communications, and annals of congress were excluded. |

The following publications were excluded:

- Publications that assessed only MIH and dental caries or studies interested in HSPM and dental caries without MIH assessment.
- Studies that involved children aged under 6 years or older than 12 years, studies that did not answer the review question, and studies written in a language other than English.
- Case reports, narrative studies (dissertations), literature reviews, meta-analyses, systematic reviews, clinical practice guidelines, theses, chapters of textbooks or textbooks, brief communications, and annals of congress.

### Information Sources and Search Strategy

Two authors (B.S.M. and C.F.) used four online databases: Medline via PubMed, Cochrane Library, Scopus, and Science Direct to identify pertinent studies. The two authors reviewed the gray literature using an advanced Google search. The first 50 PDFs derived were screened for eligibility to identify additional studies. The search was limited to studies published in English without restrictions on publication year. The initial search for articles was performed on January 20, 2021, and a subsequent search was conducted on December 01, 2021.

The reference sections of full-text records were also hand-screened by the two authors to identify further eligible publications.

A selection of search terms, Medical Subject Heading terms (MeSH), and keywords were established and adapted for each database. Only terms related to MIH, HSPM, and dental caries were used to identify eligible studies. The set of keywords used during the search is given in ►Table 2.

### Study Selection

Zotero 5.0.59 software was used to manage bibliographies, citations, and duplicates. Three-stage publications' selection was managed by the two authors. First, to eliminate obviously irrelevant references, only the titles of studies were considered for eligibility by the authors. Second, the authors excluded irrelevant studies based on their abstract.

The ultimate stage was based on a full-text assessment of the remaining articles from the second stage. The reference sections of the included studies assessed for eligibility were manually searched to identify supplemental records by the two authors. Disaccords were resolved by a senior author (F. M.) and a discussion between the three reviewers (M.B.S., F. C., and F.M.).

### Outcome Variables

In the present systematic review, the authors considered the prevalence of carious lesions in MIH-HSPM children as the main outcome and the severity of dental caries in those children as the secondary outcome, for a direct assessment of the caries susceptibility among MIH-HSPM affected children.

### Data Collection Process

A spreadsheet (Excel 2013, Microsoft), performed based on the Cochrane Handbook for systematic reviews checklist,

was used to extract data. The data extraction was conducted independently by the two reviewers (M.B.S. and F.C.) and any disagreements were discussed until a consensus was reached.

The following items were summarized: publication details (author name, year of publication, and country), study characteristics (study design, sample size, and sample age), examination conditions, diagnostic criteria, the prevalence of MIH, HSPM, dental caries, and the association between MIH, HSPM, and dental caries.

### Quality Assessment

The quality assessment of the included studies was performed independently by the two authors using an adapted form of the Newcastle Ottawa cohort scale for cross-sectional studies.<sup>14</sup> This scale includes seven items with ten stars assigned over three categories: selection (maximum 5 stars), comparability (maximum 2 stars), and evaluation of outcome (maximum 3 stars).

A study was estimated as high quality if the total mark was ranging seven or higher. To assess the risk of bias, the authors determined methodological cut-off points: the primary confounder (the letter "a" under comparability) was attributed to dental caries in the primary dentition, as it has a pertinent effect on the etiology of carious lesions in the permanent teeth. Further possible confounders (letter "b" under "comparability") were attributed to further risk factors related to caries formation in permanent teeth, for instance, socioeconomic status and age. Concerning the outcome rating (item 1 under outcome) the independent blind assessment was represented by the estimation of dental caries, MIH, and HSPM by distinct examiners.<sup>10</sup> It was difficult for an examiner to assess the outcome (carious lesions) without perceiving the exposures (MIH, HSPM). Finally, the statistical test (item, "2" under outcome) measured the association using confidence intervals and the probability level (*p*-value).

## Results

### Study Selection

A total of 535 eligible articles were selected: 218 from PubMed, 108 from Cochrane Library, 117 from Scopus, 90 from Science Direct and two publications were added from a manual search. After removing 252 duplicates, titles, and abstracts of 283 studies were screened in the first phase and 236 articles were excluded based on the selection criteria. The references of the 47 remaining articles were screened to find out further records.

After reading the full text of the selected 47 records, only two articles were included in the present review for qualitative synthesis. The PRISMA flow diagram summarizing the search method and the article selection process is shown in ►Fig. 1.

### Study Characteristics

The descriptive characteristics and results of the two articles are summarized in ►Table 3. The included publications were published between 2018 and 2019 and were performed in

**Table 2** Keywords used to develop the search strategies

| Database         | Search strategy  | Results |
|------------------|--|---------|
| PubMed           | -"Dental Enamel Hypoplasia"[Mesh] AND "Tooth, Deciduous"[Mesh] AND "Tooth Demineralization"[Mesh] AND "Child"[Mesh] AND "prevalence"[Mesh].<br>- ("Molar"[Mesh] OR "Incisor"[Mesh]) AND "Dental Enamel Hypoplasia"[Mesh] AND "Tooth Demineralization"[Mesh] AND "Child"[Mesh] AND "prevalence"[Mesh].<br>-Dental Enamel Hypoplasia"[Mesh]) AND "Tooth, Deciduous"[Mesh] AND "Prevalence"[Mesh] AND "Child"[Mesh] AND "prevalence"[Mesh].<br>- "Dental Enamel Hypoplasia"[Mesh]) AND "Tooth, Deciduous"[Mesh] AND "Tooth Demineralization"[Mesh] AND "Child"[Mesh] AND "Dental Caries"[Mesh] AND "prevalence"[Mesh].<br>- ("Molar"[Mesh] OR "Incisor"[Mesh]) AND "Dental Enamel Hypoplasia"[Mesh] AND "Tooth Demineralization"[Mesh] AND "Child"[Mesh] AND "Dental Caries"[Mesh] AND "prevalence"[Mesh].<br>-Dental Enamel Hypoplasia"[Mesh] AND "Tooth, Deciduous"[Mesh] AND "Prevalence"[Mesh] AND "Child"[Mesh] AND "Dental Caries"[Mesh]. | 218     |
| Scopus           | -("Molar incisor hypomineralization" OR "Dental enamel hypoplasia" OR "MIH") AND ("Hypomineralized second primary molars" OR "Deciduous molar hypomineralization" OR "HSPM") AND "prevalence."<br>-("Molar incisor hypomineralization" OR "Dental enamel hypoplasia" OR "MIH") AND ("Hypomineralized second primary molars" OR "Deciduous molar hypomineralization" OR "HSPM") AND "Dental caries" AND "prevalence"<br>-("Molar incisor hypomineralization" OR "Dental enamel hypoplasia" OR "MIH") AND "Dental caries" AND "prevalence."<br>-("Hypomineralized second primary molars" OR "Deciduous molar hypomineralization" OR "HSPM") AND "Dental caries" AND "prevalence."  | 117     |
| Science Direct   | -("Molar incisor hypomineralization" OR "Dental enamel hypoplasia" OR "MIH") AND ("Hypomineralized second primary molars" OR "Deciduous molar hypomineralisation" OR "HSPM") AND "prevalence."<br>-("Molar incisor hypomineralization" OR "Dental enamel hypoplasia" OR "MIH") AND ("Hypomineralized second primary molars" OR "Deciduous molar hypomineralization" OR "HSPM") AND "Dental caries" AND "prevalence." -("Molar incisor hypomineralization" OR "Dental enamel hypoplasia" OR "MIH") AND "Dental caries" AND "prevalence."<br>-("Hypomineralized second primary molars" OR "Deciduous molar hypomineralization" OR "HSPM") AND "Dental caries" AND "prevalence."  | 90      |
| Cochrane Library | #1Molar incisor hypomineralization<br>#2dental enamel hypoplasia<br>#3MIH<br>#4Hypomineralised second primary molars<br>#5Deciduous molar hypomineralization<br>#6HSPM<br>#7prevalence #8 #1 OR #2 OR #3 AND #4 OR #5 OR 6 AND #7<br>#9Dental caries<br>#10 #8 AND #9<br>#11 #1 OR #2 OR #3 AND #7 AND #9<br>#12 #4 OR #5 OR #6 AND #7 AND #9  | 108     |

Chile<sup>15</sup> and Australia.<sup>16</sup> The two included articles were cross-sectional in design and were conducted in primary schools amongst children aged between 6 and 12 years.

**Assessment of Risk of Bias**

Using the adapted form of the Newcastle Ottawa cohort scale for cross-sectional studies, the two included studies were rated as high-quality studies (► **Table 4**). The record conducted by Gambetta-Tessini et al in 2019 scored 9 stars and the study conducted by the same authors in 2019 had a score of 7 stars.<sup>15,16</sup>

**Main Outcomes**

MIH and HSPM outcomes were assessed by the two authors using the modified EAPD protocol. The outcomes of MIH and HSPM were represented by prevalence and percentages.

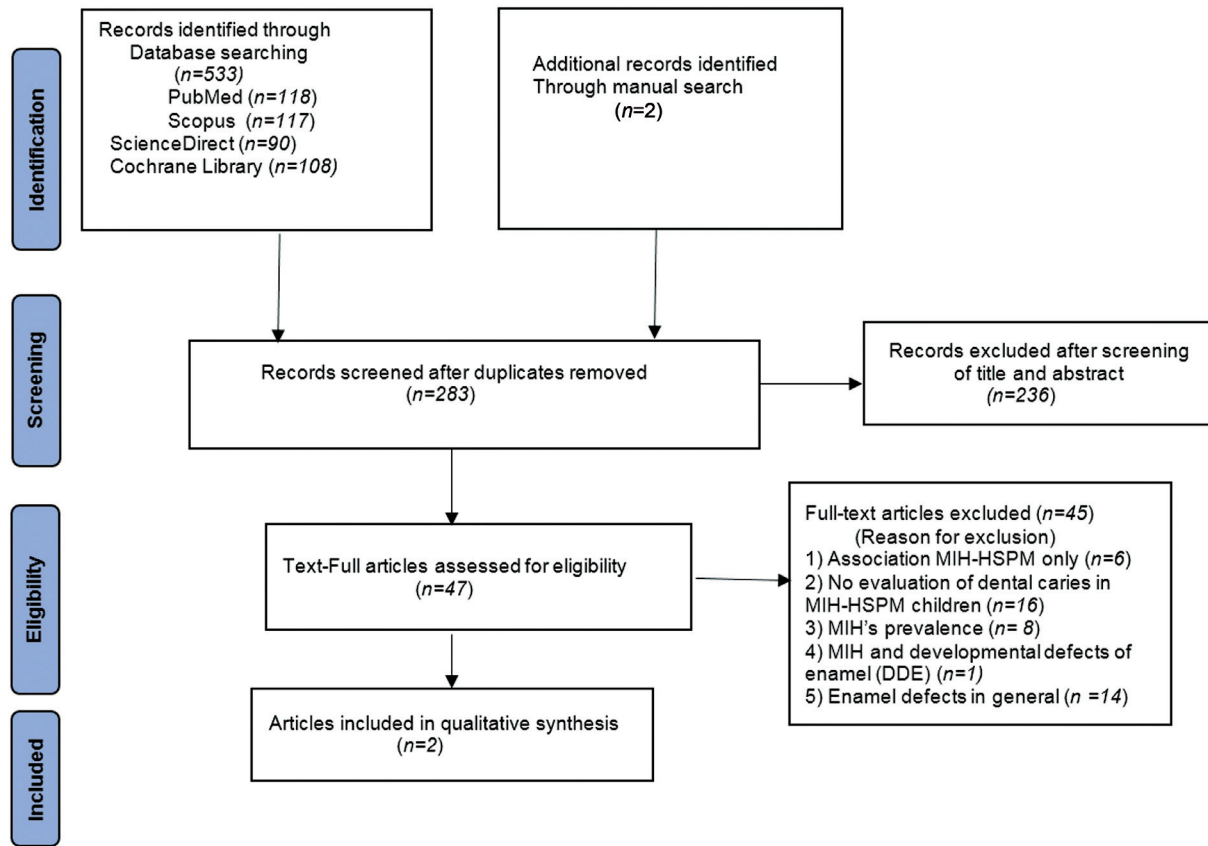
Carious lesions were recorded according to the criterion settled by the WHO,<sup>17</sup> the ICDAS II scoring criteria,<sup>18</sup> and PUFA/pufa.<sup>16</sup>

Regarding the association between MIH, HSPM, and its impact on dental caries, statistical tests were used represented by *p-value* and adjusted odds ratio (AOR) in the included records (► **Table 3**).

As shown in ► **Table 3**, the two pooled articles found a positive association between MIH/HSPM and dental caries.<sup>15,16</sup>

It was principally represented by a high AOR: 3.70 and  $p < 0.001$ .<sup>15,16</sup>

The authors found a higher prevalence of dental caries in MIH/HSPM children compared with non-affected ones. This was represented by a higher DMFT mean (SD) expressed by those affected children compared with those who were not



**Fig. 1** PRISMA flow diagram showing systematic review process. This figure described the process of systematic search throughout different online databases to seek eligible studies. Only two articles were included finally.

affected, and the values ranged from 1.08 (1.86) to 1.28 (1.7).<sup>15,16</sup>

The dmft mean (SD) ranged from 1.79 (2.4) to 1.88 (2.73) in demarcated hypomineralized lesions-affected children.<sup>15,16</sup> However, the authors stated that dmft did not differ significantly between those infants with and without hypomineralized primary teeth.<sup>15,16</sup>

PUFA mean values were 0.02 (s.d.=0.15)<sup>16</sup> and 0.18 (s.d.=0.5)<sup>15</sup> among affected children compared with 0<sup>16</sup> and 0.01 (s.d.=0.1)<sup>15</sup> among non-affected children.

Concerning pufa mean values, Gambetta-Tessini et al in 2019 found similar results in both hypomineralized and defect-free teeth, values were 0.24 (s.d.=0.6) and 0.27 (s.d.=0.8) respectively. In the second study, pufa were slightly higher in MIH-HSPM affected group compared with non-affected ones, values were 0.26 (s.d.=0.78) and 0.18 (s.d.=0.97) respectively.

The prevalence of hypomineralized teeth with severe carious lesions was 14.6% compared with 2.2% of defect-free teeth.<sup>15</sup> The second study<sup>16</sup> reported that 9.3% of demarcated hypomineralized lesions were diagnosed with severe carious lesions compared with 1.9% of unaffected teeth.

Therefore, the two publications showed that MIH-HSPM defects increased the severity of the carious lesions as a high OR (2.17) and a significant *p*-value (< 0.001) were reported.<sup>15,16</sup>

## Discussion

The present review aimed to determine the effect of MIH/HSPM lesions on the dental caries experience. MIH may be considered one of the risk factors for dental caries. Therefore, children with hypomineralized teeth may need regular monitoring to prevent dental caries extension.

The sample size of the included studies ranged from 327 to 577 children, which was in line with the literature that recommended a standardized evaluation of MIH/HSPM prevalence using a sufficiently explicit sample involving a minimum of 300 candidates.<sup>19</sup>

The age of candidates in this review ranged from 6 to 12 years. It has been recommended to evaluate MIH at 8 years of age when all molars and incisors have barely erupted<sup>10</sup> restricting the risk of enamel defects concealment by carious cavities or restorations.

For HSPM, the age of 5 years could be convenient for detecting enamel defects because most SPMs fully erupt at this stage and HSPM are distinctly perceptible. Also, at this age children are relatively more cooperative allowing proper oral examinations. The non-difference in dmft values between children with or without hypomineralized teeth and the similar pufa values in the study of Gambetta Tessini et al in 2018 can be related to the advanced sample age.<sup>15,16</sup> Currently, between 6 and 12 years, SPMs are highly exposed

**Table 3** Characteristics of the included studies

| Study   | Study design    | Sample characteristics                                     | Examination Conditions   | Diagnostic criteria for MIH/HSPM | Diagnostic criteria for dental caries                | MIH prevalence | HSPM prevalence | MIH-HSPM association       | Caries prevalence   | Association MIH/ HSPM and dental caries | Main outcomes   |
|---|-----------------|--|--|----------------------------------|--|----------------|-----------------|----------------------------|---|---|---|
| K.Gambetta-Tessini et al. 2018/ <sup>16</sup> Australia | Cross-sectional | 327 children<br>Males: 173<br>Females: 154<br>6-12 (years) | Two Catholic schools and Nine public schools/<br>Teeth dried/ External light source + disposable examination Kits. | Modified EAPD protocol           | DMFT/dmft index<br>ICDAS II index<br>PUFA/pufa index | 14.7% (48/327) | 8% (26/327)     | OR: 2.90<br>p-value: 0.02  | MIH/HSPM:<br>DMFT mean (s.d.): 1.08 (1.86)<br>dmft mean (s.d.): 1.88 (2.73)<br>PUFA mean (s.d.): 0.02 (0.15)<br>pufa mean (s.d.): 0.26 (0.78)<br><br>MIH/HSPM free:<br>DMFT mean (s.d.): 0.53 (1.29)<br>dmft mean (s.d.): 1.59 (2.53)<br>PUFA mean (s.d.): 0<br>pufa mean (s.d.): 0.18 (0.97)   | AOR: 2.17<br>p-value < 0.001            | -MIH-HSPM children had a higher prevalence and more severe dental caries compared with non-affected ones.<br>-Significant association between MIH and HSPM. |
| K.Gambetta-Tessini et al. 2019/ <sup>15</sup> Chile     | Cross-sectional | 577 children<br>Males: 285<br>Females: 292<br>6-12 (years) | Three schools: public, sub-sidised and private/ teeth brushed and dried/ Artificial light.                         | Modified EAPD protocol           | DMFT/dmft index<br>ICDAS II index<br>PUFA/pufa index | 15.8% (91/577) | 5% (29/577)     | AOR: 3.7<br>p-value: 0.001 | MIH/HSPM:<br>DMFT mean (s.d.): 1.28 (1.7)<br>dmft mean (s.d.): 1.79 (2.4)<br>ICDAS II > 0: 89 (6.8)<br>PUFA mean (s.d.): 0.18 (0.5)<br>pufa mean (s.d.): 0.24 (0.6)<br>PUFA + pufa prevalence: 24.1%<br><br>MIH/HSPM free:<br>DMFT mean (s.d.): 0.76 (1.4)<br>dmft mean (s.d.): 1.78 (2.5)<br>ICDAS II > 0: 1222 (93.2)<br>PUFA mean (s.d.): 0.27 (0.8)<br>pufa mean (s.d.): 0.27 (0.8) | AOR: 3.70<br>p-value < 0.001            | -Positive association between:<br>-MIH-HSPM, and dental caries prevalence and severity.<br>-MIH and HSPM.   |

Abbreviations: AOR, adjusted odds ratio; DHL, demarcated hypomineralized lesions; dmft, decayed missing due to caries and filled teeth in primary teeth; DMFT, decayed missing due to caries and filled teeth in the permanent teeth; HSPM, hypomineralized second primary molars; ICDAS II, international caries detection and assessment system II; MIH, molar incisor hypomineralization; OR, odds ratio; P, p-Value; PUFA, pulp ulceration fistula abscess teeth in primary teeth; SD/sd, standard deviation



**Table 4** Quality assessment using the Newcastle-Ottawa Scale adapted for cross-sectional studies

| Author<br>Year<br>Country                               | Study<br>Design          | Selection<br>1 2 3 4 | Comparability<br>5a 5b | Outcomes<br>6 7 | Total          |
|---|--------------------------|----------------------|------------------------|-----------------|----------------|
| Gambetta-Tessini et al<br>2018/ Australia <sup>16</sup> | Cross-sectional<br>Study | *****                | **                     | **              | 9 High quality |
| Gambetta-Tessini et al<br>2019/ Chile <sup>15</sup>     | Cross-sectional<br>Study | ***                  | **                     | **              | 7 High quality |

Note: Selection 1: Representativeness of the sample; Selection 2: Sample size; Selection 4: Ascertainment of the exposure; comparability: Comparability of subjects in different outcome groups based on the study design or analysis. Confounding factors are controlled; Outcome 1: Assessment of the outcome; Outcome 2: Statistical test

to prolonged environmental risk factors exacerbating the defect severity into PEB and carious lesions. The probability of confusing PEB arising from hypomineralization as the main cause in teeth with severe dental caries exists due to the relatively advanced age. This may underestimate the true number of teeth with PEB because of hypomineralization as a primary outcome. Also, restorations may conceal primary hypomineralization and even the common absence of those teeth at this age group may explain this HSPM underestimation. Owen et al find similar results and reported that HSPM presence did not predispose those children to greater caries risk; the authors explained their findings by the overall low caries prevalence in their study resulting in a limited number of HSPM with cavitated lesions.<sup>20</sup> Thus, the current results reporting HSPM prevalence and its association with dental caries should be interpreted cautiously. However, many authors reported a positive association between HSPM and dental caries among samples of similar age, e.g., 7-to-9-year-old children.<sup>11,12</sup>

In the present review, the two included studies<sup>15,16</sup> showed that children with MIH and HSPM express a higher dental caries prevalence in permanent dentition. This was mainly represented by a higher DMFT index and a significant *p*-value less than 0.05. It is well known that porosity and poor mechanical resistance have been increased by enamel hypomineralization, especially in the case of PEB.<sup>21</sup> Thus, hypomineralized lesions facilitate bacterial plaque agglomeration and increase dental cavities development.

Teeth with severe hypomineralized defects present, hypersensitivity that results in tooth brushing avoidance. Thus, children are more susceptible to dental caries, especially in cases of poor oral health, high sugar consumption, and low salivary buffer capacity.<sup>1,15,21</sup>

In addition, the association between MIH, HSPM and dental caries can be explained by common etiological factors. In fact, Vieira and Kup. (2016) in their systematic review have demonstrated that a genetic mutation may occur during dental enamel formation, causing disturbances in the maturation stages of enamel.<sup>22</sup> These disturbances mostly affect the first permanent molars and incisors and may consequently lead to the MIH occurrence. SPMs, permanent canines, and premolars may also be involved. Other genetic variations, in any of the above 100 genes expressed over late enamel formation, can explain the involvement of further teeth.

Genetic factors contribute likely to dental caries etiology.<sup>23</sup> Mutations in genes such as dentine sialophosphoprotein mutation lead to abnormal proteins or decrease the load of these proteins in immature teeth. Therefore, inadequate mineralization arises and possibly affects both bacterial adherence and resistance of enamel to an acid pH; so, the vulnerability of tooth surfaces to carious lesions is increased.<sup>23</sup>

Some authors have suggested that mutations in kallikrein-related peptidase 4 (KLK4) gene expression is implicated in more porous and weak enamel formation, leading to hypomineralization and caries. This can be explained by the fact that KLK4 secretes enamel matrix protein.<sup>22,23</sup> Variations in genes, which produce enamel mineralization, may increase the susceptibility to MIH, HSPM, and dental caries simultaneously. However, environmental factors play a significant role in the etiology of dental caries (e.g., sugar consumption, poor oral health, oral bacteria and malocclusions),<sup>24,25</sup> MIH and HSPM (e.g., health during pregnancy, delivery complications, birth weight, childhood illness).<sup>26,27</sup> Therefore, additional studies in various populations are required to determine the part of both environmental and genetic factors in those dental issues. Thus, susceptible patients could be identified earlier in the future.<sup>28</sup>

The present review demonstrated also that not only the caries prevalence but also the severity of the carious lesions can be significantly associated with the enamel hypomineralization. A high odds ratio was reported in the study conducted by Gambetta-Tessini et al in 2019 and the prevalence of MIH/HSPM affected teeth with severe carious lesions was 14.6% compared with 2.2% of the non-affected ones.<sup>15</sup> This may be related to the rapid carious lesions progress in the case of hypomineralized enamel because of its overly altered and delicate structure. However, other factors like poor oral hygiene and access constraints to oral care can be implicated in caries severity.<sup>16</sup> In addition, a higher PUFA experience was reported in MIH-HSPM affected groups. Children affected with hypomineralized lesions such as MIH and HSPM present in most cases pulp involvement requiring endodontic treatment.<sup>29,30</sup>

The two included studies<sup>15,16</sup> reported that hypomineralized lesions were correlated with a higher dental caries severity, especially amongst children from low socioeconomic status. This was in line with recent publications which illustrated a significant association between MIH, dental

caries risk, and socioeconomic factors.<sup>31</sup> In fact, families from low SES express unfavorable oral hygiene and restricted access to both preventive measures and restorative treatment. Leading caries to progress more rapidly into severe lesions. Therefore, health authorities should provide and facilitate dental services access to disadvantaged families through preventive oral health companies and programs.

In addition, the two pooled publications reported that HSPM represents a predictive sign for MIH. This was mainly illustrated by high odds ratios and significant *p*-value. Those findings agreed with a previous systematic review and meta-analysis.<sup>6</sup> Actually, the crown calcification of SPMs begins on the 18th week *in utero* and lasts for 1 year after childbirth, while for the first permanent molars the crown mineralization starts at the end of the third gestational trimester and persists for three years after childbirth.<sup>32</sup>

Therefore, the second deciduous molars and the first permanent molars can be concomitantly affected by the risk factors acting during the simultaneous terms of mineralization. As a result, primary and permanent dentition may undergo hypomineralization defects.<sup>5</sup>

Regarding the quality assessment, an adapted form of the Newcastle Ottawa Scale for cross-sectional studies was used as all records included in this review are cross-sectional in design. The authors predetermined methodologically appropriate cut-off points for the evaluation. To eliminate the probability of subjectiveness, the scores were granted when there was adequate information, and the reviewers were familiarized with the NOS.

Commonly, assessments are esteemed blinded if the examiner assesses outcomes without realizing the presence or not of the exposure. In the present studies, it was difficult for the examiner to evaluate caries (outcome) without seeing MIH (exposure). Therefore, we reviewed blind assessment as performed when MIH and dental caries were evaluated by two distinct examiners.<sup>10</sup> None of the studies followed this condition; consequently, the risk of bias can arise restricting the validity of the current surveys.

Potential confounders such as age, gender, region, sample size, and socioeconomic status were considered in the two studies. This may also occasion biased findings.<sup>15,16</sup>

Although all pooled studies were recorded as high quality using the NOS scale, we can identify some limitations related to those surveys, e.g., differences in diagnostic criteria compared with other studies, especially, that the index which was used by the authors is recently employed in the literature. Although it has been known as a valid diagnostic index,<sup>33</sup> Lopes et al have reported that the use of alternative classification, other than the EAPD criterion, generates a reduction in MIH prevalence.<sup>34</sup> Thus, a standardization of the employed index is recommended to reduce heterogeneity in MIH/HSPM findings.<sup>34</sup> As explained earlier outcomes about HSPM prevalence and association with dental caries need cautious interpretation as in literature the optimal age for HSPM assessment is 5 years.

Concerning the current systematic review, we cannot neglect some restrictions, e.g., the same authors conducted the two included studies. This did not influence their char-

acteristics as they had been conducted separately and displayed different populations, countries, and outcomes. However, biased results may occur. Also, few studies have been interested in the effect of MIH and HSPM on carious lesions experience, so the results need cautious interpretation. Thus, pertinently future studies are particularly necessary to issue further confirmation about this topic.

## Conclusion and Recommendations

To the best of our knowledge, the present systematic review is the first report aiming to assess the caries experience among MIH-HSPM affected children. Those infants present a higher prevalence and more severe carious lesions in permanent dentition.

Although in this review, dental caries experience does not differ between children with or without HSPM, clinicians should give more intention and regular follow-up at more frequent intervals for children with hypomineralized primary teeth as they may have a risk to develop dental caries, poor oral hygiene, and MIH in permanent dentition. Therefore, prevention should be performed directly after hypomineralized teeth eruption. Dietary advice, fluoride toothpaste with a minimum of 1450 ppm (ppm), and professional application of resin-based fissure sealants for intact hypomineralized molars should be programmed for MIH affected children to minimize caries risk and tooth hypersensitivity.<sup>35</sup>

Dentists must receive ongoing training on this topical issue. In addition, there is a need to perform well-designed studies in different populations to assess the part of both environmental and genetic factors in the etiology of MIH, HSPM, and dental caries. As follows, susceptible patients can be identified earlier in the future.

### Availability of Data and Materials

All data generated and analyzed and related to this work are included in this published article.

### Authors' contributions

M.B.S. and F.C.: conceived the idea, collected the data, wrote the article; M.B.S., F.C.: collected the data; M.B.S., F.C., and F.M.: analyzed the data; F.M., A.B. and H.G.: provided comprehensive judgment and assisted in editing the final version of the manuscript. All authors reviewed the manuscript.

### Funding

None.

### Conflict of Interest

None declared.

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