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Molar Incisor Hypomineralization (MIH): Etiology, Epidemiology and Global Prevalence – a Narrative Review

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Abstract (Structured)

Background. Molar Incisor Hypomineralization (MIH) is a qualitative developmental defect of dental enamel, primarily affecting one to four first permanent molars and frequently involving permanent incisors. Since its formal recognition by the European Academy of Paediatric Dentistry (EAPD) in 2003, MIH has been increasingly acknowledged as a significant public health concern worldwide, associated with dental hypersensitivity, rapid caries progression, post-eruptive enamel breakdown, and impaired oral health-related quality of life in children.

Aim. The aim of this narrative review was to critically synthesize the current state of knowledge on the etiology and global epidemiology of MIH, with particular emphasis on

prenatal, perinatal, postnatal, genetic, and environmental risk factors, as well as regional and global prevalence data.

Material and methods. A comprehensive literature search was conducted in the PubMed, Scopus, and Web of Science databases, covering publications from 2003 to 2025. The search strategy included the terms: “molar incisor hypomineralization”, “MIH”, “enamel hypomineralization”, “etiology”, “prevalence”, “risk factors”, “amelogenesis”, “genetics”. Studies included original research articles, systematic reviews, meta-analyses, and narrative reviews published in English. Duplicates, conference abstracts, and studies lacking diagnostic criteria for MIH were excluded.

Results. The global pooled prevalence of MIH ranges from approximately 9.4% to 14.2% depending on the meta-analytical approach and diagnostic criteria applied, with significant regional variation – the highest rates reported in South America (up to 18%) and the lowest in Africa (approximately 5–11%). MIH disproportionately affects children aged 6–10 years, with no consistent gender predilection. Etiology is complex and multifactorial, encompassing prenatal factors (maternal illness, medication, fever), perinatal factors (prematurity, hypoxia, cesarean delivery), and postnatal factors (febrile illness, antibiotic use, respiratory infections, systemic diseases). Genetic predisposition is increasingly documented, including variants in amelogenesis-related genes (AMELX, MMP20, FAM83H), immune response genes (TGFBR1, IRF6), vitamin D receptor (VDR) polymorphisms, and xenobiotic detoxification genes. Environmental exposures, particularly to dioxins and bisphenol A, have also been implicated. The estimated heritability of MIH is approximately 20%, underscoring the predominant role of environmental factors acting on a genetically susceptible background.

Conclusions. MIH represents a major, globally distributed enamel developmental disorder of multifactorial etiology. Current evidence supports the concept of gene–environment interaction as the predominant pathogenic mechanism. Standardized epidemiological methodology and prospective longitudinal studies are urgently needed to establish causality, improve early diagnosis, and inform prevention strategies.

Key words: molar incisor hypomineralization, MIH, dental enamel defects, amelogenesis, epidemiology, etiology, prevalence, genetic factors, environmental factors, paediatric dentistry

1. Introduction

Molar Incisor Hypomineralization (MIH) is defined as a qualitative developmental defect of the dental enamel of systemic origin, characterized by demarcated opacities affecting one to four first permanent molars, often accompanied by analogous lesions of the permanent incisors [1, 2]. Clinically, MIH manifests as clearly delineated opacities ranging in colour from white-cream to yellow-brown, reflecting varying degrees of enamel mineral deficit. In more severe forms, post-eruptive breakdown (PEB) of the structurally compromised enamel occurs, exposing dentine and predisposing the affected dentition to accelerated caries development, hypersensitivity, and ultimately premature tooth loss [3, 4].

The condition was formally defined and its diagnostic criteria established by the European Academy of Paediatric Dentistry (EAPD) working group in 2003, following growing clinical concern about the increasing number of children presenting with atypical enamel lesions of systemic rather than local origin [1]. The term MIH replaced earlier, inconsistent nomenclature and provided a unifying framework for both clinical practice and epidemiological research. Since 2003, the scientific output on MIH has expanded dramatically, with hundreds of prevalence studies, etiological investigations, and clinical management trials published worldwide [5].

Pathophysiologically, MIH originates from disruption of ameloblast function during the maturation and mineralization phases of amelogenesis. For first permanent molars and incisors, this critical window spans from approximately the last trimester of pregnancy through the third year of life [6, 7]. Systemic illness, hypoxia, or toxic exposure occurring during this period may interfere with ameloblast activity, leading to incomplete mineral incorporation into the enamel matrix. The enamel produced under these conditions is porous and mechanically fragile — harder to restore, hypersensitive, and prone to rapid breakdown after eruption. Increased protein content and reduced hydroxyapatite give it a characteristic appearance: white-cream opacities in milder cases, deepening to yellow-brown where mineral deficit was more severe [8, 9].

Epidemiological data consistently demonstrate a high global prevalence of MIH, estimated at 9.4–14.2% depending on diagnostic criteria, age group studied, and methodological approach [10, 11]. This places MIH among the most frequent developmental dental anomalies in the permanent dentition of children. Despite its prevalence and clinical impact, the precise etiology of MIH remains insufficiently understood. The condition is

currently regarded as multifactorial, arising from the interaction between genetic predisposition and a range of environmental, systemic, and iatrogenic exposures [12, 13]. Importantly, no single etiological factor has been identified as causally sufficient, and the relative contribution of individual risk factors remains a subject of active investigation [14].

According to generally accepted MIH classification, three principal forms are distinguished. These are based o the severity and progression of dental conditions and consequently determine the appropriate course of further treatment [15].

Tab. 1 MIH classification

Classification	Symptoms
Mild	Changes on the buccal and palatal surfaces of molars (not subjected to masticatory forces). The affected tissues are usually free from caries, no increased sensitivity to external stimuli is observed.
Moderate	Opacities and enamel breakdown on the occlusal surfaces of first permanent molars and incisal edges of incisors. Carious lesions may involve one or two surfaces, but cusp destruction is absent. Increased sensitivity to external stimuli is common. The appearance of teeth and restorations may be either normal or atypical.
Severe	Defects may affect any surface of first permanent molars or incisors. Carious lesions often involve multiple surfaces and may lead to pulpal involvement. Increased sensitivity to external stimuli is frequently present. Teeth and restorations often exhibit an atypical appearance.

The clinical consequences of MIH are significant and multidimensional. Children with MIH experience a higher prevalence of dental caries, greater treatment burden, more frequent restorative failures, compromised anesthetic efficacy during dental procedures, and measurable reductions in oral health-related quality of life [16, 17]. The condition thus constitutes both a paediatric dental and a broader public health challenge, particularly in low- and middle-income countries where access to dental care may be limited [18].

Research Objective. The objective of this narrative review is to synthesize the current evidence on the global epidemiology and multifactorial etiology of MIH, integrating data from systematic reviews, meta-analyses, and original research published between 2003 and 2025.

Research Problems. What is the global and regional prevalence of MIH? What are the established and putative etiological factors? To what extent do genetic predisposition and environmental exposures interact in the pathogenesis of MIH?

Research Hypotheses. MIH is a globally prevalent condition of multifactorial etiology arising from gene–environment interactions during the critical period of amelogenesis in the first years of life.

2. Material and Methods

2.1. Literature Search Strategy

A systematic search of the PubMed/MEDLINE, Scopus, and Web of Science databases was performed in March 2025, without a lower date limit and with an upper limit of March 2025. The following search terms were applied in various combinations: “molar incisor hypomineralization”, “MIH”, “enamel hypomineralization”, “MIH etiology”, “MIH risk factors”, “MIH prevalence”, “MIH epidemiology”, “MIH genetics”, “amelogenesis disruption”, “developmental defects of enamel”, “hypomineralized second primary molars” (HSPM). Boolean operators (AND, OR) were used to combine search terms appropriately.

Reference lists of included systematic reviews and meta-analyses were manually screened to identify additional eligible studies not captured in the electronic search. Where the full text of an article was required for data extraction, it was retrieved directly from the publisher’s database or requested via institutional access.

2.2. Inclusion and Exclusion Criteria

Studies were eligible for inclusion if they involved human participants of any age, reported on the prevalence, incidence, or etiology/risk factors of MIH, applied clearly defined and reproducible diagnostic criteria for MIH preferably consistent with EAPD 2003 or EAPD 2022 criteria, were published in English in peer-reviewed journals, and were original epidemiological studies, systematic reviews, meta-analyses, or high-quality narrative reviews. Studies were excluded if they did not apply explicit diagnostic criteria for MIH, reported exclusively on other developmental defects of enamel (e.g., amelogenesis imperfecta, enamel fluorosis) without separately reporting MIH data, were conference abstracts, letters, or editorials without original data, or reported exclusively on treatment outcomes without etiological or epidemiological data.

2.3. Data Extraction and Quality Assessment

Data were extracted by two independent reviewers using a standardized extraction form, covering: study design, country, year of data collection, sample size, age range of participants, diagnostic criteria used, prevalence of MIH as well as associated risk factors, and key findings. Discrepancies were resolved by consensus. No formal risk of bias assessment was conducted, consistent with the narrative review methodology; however, the quality of the evidence base

is discussed critically in the text. Given the heterogeneous methodology of included studies, a meta-analytical synthesis was not performed; instead, a descriptive synthesis of available data is provided.

2.4. AI Utilization

Artificial intelligence tools (Claude, Anthropic) were used for two specific purposes in the preparation of this manuscript: assistance in the organization and synthesis of extracted literature data during the review process, and refinement of the academic English language of the manuscript to ensure clarity, consistency, and adherence to scientific writing standards. All AI tools were used strictly as assistive instruments under full human supervision. The final interpretation of all results, clinical conclusions, and scientific judgments were made exclusively by the human authors. AI tools served solely to enhance efficiency in data organization and linguistic refinement, without replacing human expertise in the analytical or interpretive process.

3. Results

3.1. Global and Regional Epidemiology of MIH

Since the formalization of MIH diagnostic criteria by the EAPD in 2003, a substantial body of epidemiological literature has accumulated. Large-scale meta-analyses have consistently demonstrated that MIH is a globally prevalent condition, affecting a clinically significant proportion of children in all world regions. However, reported prevalence rates vary considerably across studies, reflecting differences in diagnostic criteria, examiner calibration, age groups examined, and methodological quality [10, 11, 19].

The most comprehensive meta-analysis of global MIH prevalence, reported by Zhao et al. (2018), included 70 studies encompassing 89,520 individuals and 10,823 cases of MIH, yielding a pooled global prevalence of 14.2% (95% CI: 12.6–15.8%) [10]. In this analysis, South America reported the highest regional prevalence (18.0%; 95% CI: 13.8–22.2%), while Africa reported the lowest (10.9%; 95% CI: 4.2–17.6%). Importantly, the prevalence was higher among children aged 10 years or younger (15.1%; 95% CI: 12.1–18.2%) compared to older children (12.1%; 95% CI: 8.0–16.3%), consistent with the hypothesis that MIH lesions may be partially masked by wear, caries, or restorations in older dentitions.

The systematic review and meta-analysis of Schwendicke et al. (2018), based on 99 studies covering 113,144 participants from 43 countries, estimated a pooled prevalence of 13.1% (95% CI: 11.8–14.5%), and calculated that this translates to approximately 717 million incident cases and 1.25 billion prevalent cases of MIH globally, underscoring the immense

public health burden of this condition [18]. Crucially, this analysis demonstrated that the burden of MIH is disproportionately concentrated in low- and middle-income countries, where access to dental care is limited and the consequences of MIH-associated caries and tooth loss are most severe.

A more recent literature review covering studies published between 1987 and July 2023, which specifically included only studies with sample sizes exceeding 1,000 children and using EAPD 2003 classification, reported an overall global MIH prevalence of 9.4% based on 80 studies and 179,800 examined children [19]. In this analysis, regional prevalence was highest in the Americas (17.7%), followed by Asia (10.7%), with Europe (7.3%) and Africa (4.9%) reporting lower rates. The variation between this estimate and those of Zhao et al. and Schwendicke et al. is attributable to methodological differences, including the restriction to larger studies and variation in the age ranges included.

A meta-analysis of epidemiological trends published by Sluka et al. (2024), covering studies from 2000 to 2020, found that global MIH prevalence did not demonstrate a statistically significant increase over the studied period, contradicting the widespread clinical impression of a rising prevalence [20]. However, the heterogeneity of study designs, diagnostic criteria, and age groups precluded definitive conclusions. The authors emphasized that meaningful trend analysis requires prospective, longitudinal, population-based studies with consistent methodology. A 2025 systematic review and meta-analysis further estimated global MIH prevalence at approximately 12.8%, confirming stability of estimates across the past decade when methodologically comparable studies are compared [21].

In Europe, MIH prevalence studies have yielded variable results. A large Swiss study covering over 30,000 schoolchildren reported a prevalence of approximately 8.8% [22]. A recent cross-sectional study in the Basel-Landschaft region of Switzerland reported 10.8% [23]. Studies from Germany, Italy, the United Kingdom, and Scandinavia have generally reported prevalences in the range of 5–15% [24, 25]. In Central and Eastern Europe, data remain limited, though a Polish pilot study in Silesian children estimated a prevalence of 15.4% [26]. Gender analyses across multiple meta-analyses have consistently found no statistically significant difference in MIH prevalence between males and females [10, 11].

Globally, the first permanent lower molar is the most frequently affected tooth in MIH. Incisor involvement, when present, predominantly affects the upper central incisors. An association between MIH and hypomineralized second primary molars (HSPM) has been documented, with HSPM representing a predictive marker for subsequent MIH development in the permanent dentition. A meta-analysis by McCarra et al. (2022) estimated HSPM

prevalence at approximately 7.6% globally [27]. The relationship between HSPM and MIH is clinically important, as detection of HSPM may facilitate earlier identification of at-risk children and prompt preventive intervention.

3.2. Pathophysiological Background: Amelogenesis and Its Vulnerability

A thorough understanding of MIH etiology requires consideration of the developmental timeline of enamel formation for the affected teeth. Amelogenesis – the process of enamel development – proceeds through sequential stages: secretory, transitional, maturation, and post-maturation. The first permanent molars and permanent incisors undergo their critical mineralization and maturation phases from approximately the 28th week of intrauterine life through the third year of postnatal life, with the greatest vulnerability concentrated in the perinatal period and the first two to three years after birth [6, 7].

During the maturation stage of amelogenesis, ameloblasts perform a complex series of functions, including the active transport of calcium and phosphate ions into the enamel matrix, the secretion and reabsorption of matrix proteins, and the regulation of pH within the enamel space through bicarbonate transport [8, 28]. Hydroxyapatite crystallization during maturation liberates protons, which must be neutralized by bicarbonate to permit sustained crystal growth. Disruption of ameloblast function at this stage, whether by hypoxia, systemic inflammation, medication exposure, or toxic insult, may impair calcium transport, bicarbonate secretion, or protease activity (particularly that of matrix metalloproteinase-20 and kallikrein-4), resulting in incomplete mineral incorporation into the enamel matrix [9, 28].

The histological hallmark of MIH-affected enamel is reduced mineral density with increased porosity and elevated protein content compared to normal enamel. Scanning electron microscopy and X-ray fluorescence analyses have demonstrated that MIH enamel contains proportionally more organic material and water, with correspondingly reduced hydroxyapatite content. The colour of MIH opacities, ranging from white-cream (mild mineral deficit) to yellow-brown (severe mineral deficit with iron incorporation), reflects the degree and duration of ameloblast impairment [8, 9]. The structural weakness of MIH-affected enamel makes it susceptible to PEB under masticatory forces, particularly in first permanent molars that are subject to high occlusal loading shortly after eruption.

3.3. Prenatal Etiological Factors

Prenatal factors that may influence amelogenesis include maternal systemic illnesses, medication use during pregnancy, nutritional deficiencies, and perinatal complications. The evidence for purely prenatal associations with MIH is, however, less consistent than for

postnatal factors, reflecting the earlier developmental window and the greater challenge of retrospective exposure ascertainment.

A comprehensive systematic review and meta-analysis by Butera et al. (2023), which evaluated 40 publications and applied PRISMA criteria and the Newcastle-Ottawa scale for quality assessment, found that a history of maternal illness during pregnancy was significantly associated with MIH development in offspring (OR: 4.03; 95% CI: 1.33–12.16; p = 0.01) [29]. Similarly, low birth weight, which may reflect intrauterine growth restriction or premature delivery, both indicative of a compromised intrauterine environment, was significantly associated with MIH (OR: 1.23; 95% CI: 1.10–1.38; p = 0.0005) [29].

The systematic review of Garot et al. (2021), which is among the most methodologically rigorous analyses of MIH etiology to date and included 64 studies in qualitative synthesis and 45 in quantitative meta-analysis, found that evidence for prenatal etiological factors was largely inconclusive, with the exception of non-specific maternal illnesses during pregnancy [30]. The authors cautioned that heterogeneous study designs, retrospective exposure ascertainment by parental questionnaire, and poor control for confounding severely limited conclusions about prenatal causality. Specific conditions investigated but not consistently confirmed include maternal urinary tract infections, gestational diabetes, pre-eclampsia, thyroid disorders, and antibiotic use during pregnancy [31].

Nutritional factors during pregnancy, particularly vitamin D status, have attracted increasing research attention. Vitamin D is a critical regulator of calcium and phosphate metabolism, and its role in amelogenesis is supported by both experimental and clinical evidence. Animal studies have demonstrated that vitamin D deficiency during enamel formation produces enamel defects histologically similar to MIH. However, human epidemiological data are conflicting: while some studies suggest an association between reduced maternal or early childhood vitamin D levels and MIH, a prospective cohort study by Van der Tas et al. found no significant relationship between vitamin D concentrations measured at fetal, neonatal, or early childhood stages and the development of MIH by age six [32, 39].

The role of environmental toxins with prenatal exposure, particularly polychlorinated biphenyls (PCBs) and dioxins, has been investigated in several studies. Dioxins are lipophilic compounds that accumulate in breast milk and may reach the developing enamel organ through maternal transfer. Animal experimental models have demonstrated that dioxin exposure impairs ameloblast function and produces enamel defects resembling MIH [33, 40]. Epidemiological support for this mechanism in humans comes from ecological analyses

correlating MIH prevalence with environmental pollution levels, though direct causal evidence remains limited.

3.4. Perinatal Etiological Factors

Perinatal factors, those occurring around the time of birth, represent some of the best-documented risk determinants for MIH. The pathogenic mechanism linking perinatal complications to MIH is thought to involve systemic hypoxia, which impairs oxidative phosphorylation in metabolically active ameloblasts and thereby disrupts calcium transport and matrix protein processing during the critical maturation phase of first permanent molar enamel development [6, 30].

The meta-analysis of Garot et al. (2021) identified two perinatal factors with statistically significant associations with MIH: prematurity (OR: 1.45; 95% CI: 1.24–1.70; p = 0.0002) and caesarean delivery (OR: 1.45; 95% CI: 1.09–1.93; p = 0.01) [30]. Caesarean delivery, in the context of this literature, likely serves as a proxy for obstetric complications associated with perinatal hypoxia rather than representing an independent causal factor. Children who experienced documented perinatal hypoxia were found to be substantially more likely to develop MIH than their normoxic counterparts, consistent with the central role of hypoxic injury to ameloblasts during this developmental window [30].

A Romanian cross-sectional study by Gherghina et al. (2024), conducted on 57 children from mixed dentition aged 6–11 years, identified additional perinatal risk factors including prolonged labour, medication use at birth, and early postnatal medication, with the mean age of MIH-affected mothers significantly higher than controls (35.56 years versus 29.36 years; p = 0.0001) [34]. The finding that advanced maternal age is associated with MIH warrants further investigation, as it may reflect a proxy for various obstetric complications or epigenetic changes.

Low birth weight, regardless of the mechanism of delivery, represents an established MIH risk factor in multiple studies, with a pooled OR of 1.23 in the meta-analysis of Butera et al. (2023) [29]. Prematurity and low birth weight frequently co-occur, compounding hypoxic and nutritional insults to the developing enamel organ during a period of maximum vulnerability.

3.5. Postnatal Etiological Factors

Postnatal factors represent the most consistently documented category of MIH risk determinants in the literature. The postnatal etiological window extends from birth to approximately the third year of life, corresponding to the completion of maturation-stage amelogenesis in first permanent molars and incisors. During this period, systemic illnesses,

febrile episodes, antibiotic exposure, and various environmental and nutritional factors may impair ameloblast function.

The meta-analysis of Garot et al. (2021) identified a broad range of postnatal systemic illnesses as significant MIH risk factors, including measles, urinary tract infections, otitis media, gastric disorders, bronchitis, kidney disease, pneumonia, and asthma [30]. A recurring theme across these associations is the systemic inflammatory response and febrile episodes that accompany these conditions. High fever impairs protein synthesis and cellular metabolism, potentially including the enzymatic and transport functions of ameloblasts. The OR for febrile illness in early childhood was 1.48 (95% CI: 1.18–1.84; p = 0.0005) in the meta-analysis of Butera et al. (2023) [29].

Antibiotic exposure in early childhood is among the most frequently reported MIH risk factors. The meta-analysis of Butera et al. (2023) found a pooled OR of 1.76 (95% CI: 1.31–2.37; p = 0.0002) for antibiotic use and MIH [29]. The mechanistic explanation is not fully established: antibiotics may act directly as ameloblast toxins (as proposed for tetracyclines and some macrolides), or they may serve as a proxy for the systemic infections that necessitate their use [14, 29]. The interpretation is further complicated by the high co-occurrence of febrile illness and antibiotic prescription in clinical practice.

Specific systemic diseases have been associated with elevated MIH risk. A study by Kuklik et al. found that celiac disease, characterized by malabsorption of nutrients including calcium, phosphorus, and vitamin D, increased the risk of MIH by 4.75-fold [32]. This finding supports the hypothesis that nutritional deficiencies during enamel maturation may be a pathway through which systemic diseases influence MIH risk. HIV infection and its treatment with protease inhibitors has also been linked to elevated MIH prevalence in affected children, likely reflecting both the immunological effects of the virus and the direct and indirect effects of antiretroviral therapy on enamel-forming cells [32].

From a clinical standpoint, respiratory disorders represent a particularly relevant MIH risk factor. Asthma and recurrent upper respiratory tract infections were identified as significant contributors in multiple independent studies [30, 35]. The proposed mechanism involves intermittent hypoxia secondary to airway obstruction, combined with systemic inflammation and, in asthmatic children, repeated beta-2 agonist use. In everyday practice, many children with MIH present with a history of recurrent chest infections or ENT problems in infancy — a pattern that aligns well with experimental data. Altner et al. (2024) studied 100 Austrian children with MIH and 100 age-matched controls, confirming a statistically

significant association with childhood respiratory illness; ENT disorders were among the most frequently cited conditions in the affected group [31].

Environmental exposures in the postnatal period have also been investigated as MIH risk factors. Dioxins and polychlorinated biphenyls present in breast milk may transfer to the infant during lactation, with studies suggesting that longer breastfeeding duration may paradoxically be associated with elevated MIH risk in heavily polluted regions [33, 40]. Bisphenol A (BPA), a plasticizer present in food containers and dental materials, has been shown in animal models to produce enamel lesions histologically similar to MIH. The elevated prevalence of MIH in urban compared to rural children, observed in several epidemiological studies, has been attributed to higher environmental toxic load in industrialized settings [40].

3.6. Genetic Factors and Heritability of MIH

Genetic contributions to MIH have received growing attention over the past decade. Twin studies, family-based analyses, and genome-wide association studies (GWAS) consistently indicate a heritable component, though the estimated heritability is approximately 20% — a relatively modest figure that underscores the dominant role of environmental exposures [36]. Put differently, genetic makeup appears to determine how vulnerable a child is to exogenous insults rather than causing MIH directly.

A systematic review by Muñoz et al. (2024) evaluated 16 studies examining the association between genetic variants and MIH or HSPM, identifying significant associations between MIH and single nucleotide polymorphisms (SNPs) in multiple gene categories: amelogenesis-related genes, immune response genes, xenobiotic detoxification genes, aquaporin genes, and ion transport genes [36]. The study demonstrated that interactions between amelogenesis and immune response gene variants, rather than single-gene effects, may be particularly important in MIH susceptibility, suggesting epistatic genetic architecture.

Key amelogenesis-related genetic associations with MIH include SNPs in the MMP20 gene (encoding matrix metalloproteinase-20, the principal protease responsible for enamel matrix protein removal during maturation). A study by Hocevar et al. identified a significant association between the rs2245803 polymorphism in MMP20 and MIH development, with homozygous carriers of the risk allele demonstrating increased susceptibility [36]. The FAM83H gene, mutations in which cause autosomal dominant hypocalcified amelogenesis imperfecta, has also been implicated in MIH susceptibility. Gene expression analyses in buccal epithelial cells from MIH patients have demonstrated altered expression of AMELX, AMBN, ENAM, TUFT1, FAM83H, and MMP20 compared to controls [32].

Immune response gene polymorphisms have emerged as another important MIH genetic determinant. Bussaneli et al. identified a significant association between the rs10733708 polymorphism in the TGFBR1 gene (encoding transforming growth factor-beta receptor type I) and severe MIH, and demonstrated gene–gene interactions between TGFBR1 and amelogenesis-related genes including AMELX [36]. This finding is pathophysiologically plausible, as TGF-β signaling regulates ameloblast differentiation and function, and dysregulation of this pathway may impair enamel maturation.

Polymorphisms in the vitamin D receptor (VDR) gene have been associated with MIH in a population-based study by Kühnisch et al. (2020), which examined 731 schoolchildren in Brazil. The study found that the VDR rs739837 and rs2228570 polymorphisms were associated with more severe MIH affecting incisors, providing a molecular mechanism through which individual variation in vitamin D response may modulate MIH susceptibility [37]. Aquaporin gene variants, relevant to water channel activity in ameloblasts and potentially to ion transport during enamel mineralization, have also been associated with MIH [36].

Gene-environment interaction in MIH was explicitly demonstrated by Bezamat et al. (2021), who analysed salivary samples from 1,065 children across four cohorts and genotyped for nine SNPs [41]. A significant interaction between genetic variants in the TGFA gene and environmental/medical exposures, including medication use after age three, was identified in one cohort, though not replicated across all cohorts, highlighting the geographic and environmental specificity of gene–environment interactions. The study underlines the current paradigm that MIH arises at the intersection of genetic vulnerability and environmental insult.

SNPs associated with xenobiotic detoxification pathways, particularly those involved in dioxin and aromatic hydrocarbon metabolism, have also been linked to MIH susceptibility, providing a molecular explanation for why exposure to environmental pollutants may differentially affect enamel development depending on an individual's genetic background [36]. Epigenomic analyses using nanopore sequencing technology have recently begun to explore the role of epigenetic modifications (particularly DNA methylation in amelogenesis-related genes) in MIH, with preliminary results suggesting that epigenetic dysregulation may constitute an additional mechanism linking early-life environmental exposures to lasting enamel developmental outcomes [32].

4. Discussion

Taken together, the evidence reviewed here confirms that MIH is common — more common than many clinicians appreciate — and that understanding why it develops remains an open question. Epidemiological, histological, experimental, and molecular data all point toward the same conclusion: MIH is the product of genetic susceptibility meeting environmental opportunity, with the critical window concentrated around birth and the first years of life.

Prevalence data from major meta-analyses converge on a figure of roughly 9.4–14.2% globally [10, 11, 18, 19], which places MIH firmly in the category of public health problems requiring systematic attention. The consistently higher rates seen in South America compared to Africa are interesting, though the African data are sparse and should be interpreted cautiously. Regional differences likely reflect some combination of socioeconomic conditions, environmental exposures, and genetic background — though disentangling these influences is not straightforward. The absence of a gender effect, consistently replicated across meta-analyses, stands out when compared with many other developmental conditions. The most plausible interpretation is that the environmental and inflammatory triggers driving MIH act similarly on male and female ameloblasts during the relevant developmental window [10].

Many paediatric dentists report seeing more MIH than they did a decade ago. Whether this reflects a genuine rise in incidence or better case detection is genuinely uncertain. Sluka et al. (2024) found no statistically significant trend in MIH prevalence over two decades, but heterogeneous methodology across studies makes this conclusion tentative rather than definitive [20]. Increased awareness of the condition since the EAPD's 2003 definition almost certainly accounts for some of the apparent rise — dentists who know what to look for find more of it. Whether environmental changes are also contributing remains an open question.

The breadth of postnatal risk factors — febrile illness, antibiotics, respiratory disease, gastrointestinal disease, renal disease, celiac disease, HIV — can seem difficult to reconcile at first glance. In clinical practice, however, a unifying pattern becomes apparent: any significant illness in the first three years of life, especially when accompanied by fever or hypoxia, can disrupt ameloblast function. This shared mechanism explains why so many apparently unrelated conditions converge on the same phenotype. The timing of MIH lesions within a child's dentition often mirrors the timing of documented illness episodes, lending credibility to this interpretation [12, 14].

Evidence for genetic contributions — SNPs in MMP20, FAM83H, AMELX, TGFBR1, IRF6, VDR, and xenobiotic detoxification genes — has shifted the conceptual framing of MIH away from a purely environmental model [36, 37, 38]. This is an important shift, but it should not be overstated. With heritability at around 20%, genetics predisposes rather than determines. Environmental exposure still drives the majority of cases. What the genetic data add is an explanation for why two children raised in similar conditions may have very different outcomes — one developing severe MIH, the other unaffected. Bezamat et al. (2021) demonstrated gene–environment interactions empirically, showing that the impact of medication exposure on MIH risk differed depending on genotype [41], which fits this model well.

Environmental exposures, particularly to dioxins, PCBs, and BPA, represent a relatively underexplored but potentially important category of MIH risk factors. The demonstration in animal models that these compounds produce enamel lesions similar to MIH, combined with the ecologically observed higher prevalence of MIH in urban relative to rural children, motivates further epidemiological investigation of environmental toxic load as a MIH risk factor [33, 40]. This is particularly relevant in Central and Eastern European contexts where industrial pollution remains a concern [26].

The evidence base supporting the current review has several notable limitations that should be acknowledged. Perhaps the most consequential is the near-universal reliance on retrospective parental questionnaires for exposure data, which introduces substantial recall bias. Parents asked years later about illnesses during their child's first year of life cannot be expected to reconstruct an accurate timeline, and this uncertainty inevitably limits causal inference. Beyond this, prevalence estimates across studies are difficult to compare because diagnostic criteria, age groups, and examiner calibration vary considerably. Most available studies are cross-sectional, meaning we can observe associations but cannot establish that exposures preceded the outcome. Geographic coverage is also uneven — data from sub-Saharan Africa, Central Asia, and Central Europe remain sparse. Finally, the genetic literature is still maturing; many reported associations have not been independently replicated, and replication is the cornerstone of genetic epidemiology.

Looking ahead, the field's most pressing need is longitudinal data. Cross-sectional studies can identify associations; they cannot establish causality or timing. Prospective birth cohort studies with biological sample collection — enabling objective rather than retrospective exposure ascertainment — would transform what is currently a literature full of associations into one capable of supporting causal conclusions. Alongside this, the field needs

standardized diagnostic criteria and examiner calibration protocols applied consistently across studies, without which cross-study comparisons remain unreliable. Genetic research requires large-scale GWAS with independent replication cohorts; the current genetic literature contains many promising signals but few replicated findings. Epigenomic approaches — examining methylation changes in amelogenesis genes linked to early-life exposures — represent a genuinely novel direction. And studies from underrepresented regions, particularly sub-Saharan Africa and Central Asia, are needed before the global picture can be considered complete.

5. Conclusions

MIH affects an estimated 9.4–14.2% of children worldwide — a figure that places it among the most frequent developmental dental anomalies of the permanent dentition. Prevalence varies substantially by region, and the burden falls disproportionately on low- and middle-income countries where access to restorative care is limited and the consequences of post-eruptive breakdown are therefore more severe.

The etiology of MIH is multifactorial and incompletely understood. What the evidence supports is a model in which genetically susceptible individuals encounter, during the critical perinatal period and first three years of life, systemic or environmental insults that impair ameloblast function. The list of documented risk factors is broad: prenatal maternal illness; perinatal complications including prematurity, low birth weight, hypoxia, and caesarean delivery; postnatal febrile illnesses, antibiotic exposure, respiratory and gastrointestinal disease; specific systemic conditions such as celiac disease and HIV; and environmental toxins including dioxins and bisphenol A. The breadth of this list is itself informative — it suggests that the ameloblast is sensitive to many forms of systemic disruption, rather than to one specific insult.

Genetic factors account for approximately 20% of phenotypic variance and modulate individual susceptibility through polymorphisms in amelogenesis-related genes (MMP20, FAM83H, AMELX), immune response genes (TGFBR1, IRF6), vitamin D receptor genes, aquaporin genes, and xenobiotic detoxification pathway genes. Gene–environment interactions appear central to MIH pathogenesis, though much of the genetic evidence still awaits replication.

Despite real progress since the condition was formally defined in 2003, the causal picture remains incomplete. The associations are well-documented; the mechanisms linking them to enamel defects are less certain; and the interventions that might reduce MIH incidence are

still largely theoretical. Closing these gaps will require the kind of longitudinal, prospective research that has so far been largely absent from the field. The clinical significance of MIH — its impact on children's quality of life, treatment burden, and dental anxiety — provides ample justification for that investment.

The relationship between MIH and dental caries is one of the most clinically consequential aspects of this condition. Multiple cross-sectional studies and systematic reviews have demonstrated a significant association between MIH and elevated caries experience. A systematic review by Americano et al. (2017) confirmed this association across diverse populations, with children diagnosed with MIH demonstrating consistently higher DMFT (Decayed, Missing, Filled Teeth) scores than MIH-free controls [13]. The mechanisms driving this association are multiple and reinforcing. MIH enamel is porous and structurally weak, providing ready access for bacterial colonization. Post-eruptive breakdown creates irregular surfaces that trap plaque. Hypersensitivity — which in clinical practice can be severe enough to make toothbrushing genuinely painful for affected children — further compromises oral hygiene compliance. The elevated protein content of hypomineralized enamel may additionally serve as a substrate for cariogenic bacteria [9, 16]. From a management perspective, this combination is demanding: adhesion of conventional resin-based materials to hypomineralized enamel is unpredictable, and achieving adequate local anaesthesia in these hypersensitive teeth is a well-recognized challenge that often requires modified anaesthetic protocols.

One clinical observation that helps interpret MIH etiologically is the asymmetric distribution of lesion severity across affected teeth. In daily practice, it is common to encounter a child in whom one molar is severely hypomineralized while another is only mildly affected, or where incisors are spared entirely. This asymmetry points toward episodic, temporally discrete insults — rather than a prolonged or continuous process — as the principal pathogenic mechanism. Each tooth passes through its critical maturation phase at a slightly different time, so an illness episode lasting a few weeks may affect one tooth heavily while leaving another largely intact [6, 7]. This interpretation is consistent with the concentration of MIH risk in the perinatal period and the first years of life, during which discrete events such as fever, infection, or hypoxia can differentially affect teeth at different stages of mineralization.

The etiological evidence has practical implications for prevention, even in the absence of a single modifiable cause. Several interventions that are already recommended for other reasons may incidentally reduce MIH risk. Improved antenatal care — reducing preterm birth,

perinatal hypoxia, and intrauterine growth restriction — addresses what is probably the highest-risk etiological window. Adequate vitamin D and calcium nutrition during pregnancy and infancy, already a public health priority for bone development, is biologically plausible as a protective factor for enamel mineralization. Restricting antibiotic use in early childhood to genuine clinical indications, in line with antimicrobial stewardship, reduces exposure to a documented MIH risk factor and has obvious independent benefits. From a dental perspective, targeted screening of high-risk children — ex-premature infants, those with chronic respiratory disease, those with a history of severe or prolonged febrile illness in infancy — could allow earlier MIH diagnosis and preventive intervention before post-eruptive breakdown occurs [2, 3, 13].

Disclosure

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