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Aetiology of molar–incisor hypomineralization: a critical review

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Objective. The objective of this study was to assess the strength of evidence for the aetiology of molar–incisor hypomineralization (MIH), often as approximated by demarcated defects.

Method. A systematic search of online medical databases was conducted with assessment of titles, abstracts, and finally full articles for selection purposes. The level and quality of evidence were then assessed for each article according to Australian national guidelines.

Results. Of 1123 articles identified by the database search, 53 were selected for review. These covered a variety of potential aetiological factors, some of which were grouped together for convenience. The level of evidence provided by the majority of papers was low and most did not specifically investigate MIH. There was moderate evidence that polychlorinated biphenyl/dioxin exposure is involved in the aetiology of MIH; weak evidence for the role of nutrition, birth and neonatal factors, and acute or chronic childhood illness/treatment; and very weak evidence to implicate fluoride or breastfeeding.

Conclusion. There is currently insufficient evidence in the literature to establish aetiological factor/s relevant for MIH. Improvements in study design, as well as standardization of diagnostic and examination protocols, would improve the level and strength of evidence.

Introduction

Dental enamel is a unique, highly mineralized tissue of ectodermal origin. It is characterized by a lack of metabolic activity once formed, meaning disturbances during development can manifest as permanent defects in the erupted tooth. Disturbances in the initial matrix secretion phase of amelogenesis will most likely present as quantitative or morphologic defects (hypoplasia), whereas disruptions to the calcification or maturation processes may produce morphologically normal but structurally or qualitatively defective enamel (hypomineralization/hypomaturation). Recently, a particular pattern of enamel defects has been defined in the literature, although several papers have previously described almost identical defects[1–4]; termed 'molar–incisor hypomineralization' (MIH), it refers to demarcated, qualitative defects of enamel of systemic origin, affecting one or more permanent molars [usually the first permanent molars (FPMs)] with or without involvement of the incisor teeth[5]. Although MIH can affect multiple teeth, it is neither chronological in expression such as tetracycline staining or linear enamel hypoplasia, nor does it affect the entire dentition as seen in congenital conditions such as amelogenesis imperfecta, and therefore, appears to be a separate entity. Significant challenges to clinicians are posed by MIH, with contemporary approaches to its restorative management remaining relatively ineffective[6,7].

Although the literature implicates a wide variety of factors in the aetiology of enamel defects, the strength of the scientific evidence is mixed. Further confusion occurs due to a lack of consensus regarding the classification and definition of these defects with the term 'hypoplasia' often used to describe both qualitative and quantitative defects. Alternative terms for enamel defects that appear in the literature are numerous and include: 'mottling'; 'internal enamel hypoplasia'; 'developmental opacities'; 'demarcated, diffuse, or confluent opacities';

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'aplasia'; 'internal and external hypoplasia'; 'pits'; 'grooves'; 'cheese molars'; 'non-fluoride enamel opacities'; 'idiopathic enamel opacities'; and 'opaque spots', making comparisons between studies difficult[8]. In an attempt to standardize the classification of these defects, the descriptive Developmental Defects of Enamel Index (DDE Index) was developed in 1982 by the World Dental Federation (FDI) with subsequent modifications in 1989 and 1992 to improve ease of use (see Appendix S1, Supporting information). The DDE Index, however, is still not used universally nor implemented or reported in a standard fashion.

Similarly, there is no consensus surrounding the definition of the specific condition MIH, or how to record it. For example, it is unclear whether the term MIH is appropriate for cases in which the FPMs are affected but the incisors are not. Using the demarcated opacity category of the DDE Index as a proxy for MIH does allow some inter-study comparisons to be made; however, limitations include: not all demarcated opacities are associated with MIH. Trauma and pulpal infection subsequent to caries in a primary tooth may produce such lesions in the succedaneous tooth. However, as the FPMs do not have a primary predecessor, the presence of such a lesion on an FPM is likely to arise from a different, systemic pathological process; molar teeth affected by MIH have been reported to be susceptible to both post-eruptive breakdown (PEB) and/or rapid caries progression shortly after emerging into the oral cavity. Many studies exclude restored or carious teeth from their assessment which is likely to lead to an under-reporting of MIH, whereas others may classify incorrectly PEB as hypoplasia; severely affected molars sometimes require extraction, often before 10 years of age. Many studies include population samples of children over 10 years old, and few make any attempt to determine the reason for extraction if these teeth are missing – this may also lead to under-reporting of MIH.

The aims of this review were to assess the strength of evidence regarding the aetiology of MIH and to make recommendations for future research. Although acknowledging the limitations identified earlier, the term 'demarcated defects' has been chosen as the outcome of interest where MIH-specific criteria were not used.

Method

A systematic search of Medline, Embase, and the Cochrane Library online databases was performed for articles related to the aetiology of defective enamel. Non-English language, animal studies, and articles published prior to 1989 were excluded. The following search string (given in Medline Ovid format) was utilized with alterations made as appropriate for the different database requirements: (i) tooth abnormalities/; (ii) dental enamel hypoplasia/; (iii) tooth discoloration/; (iv) dental enamel/; (v) molar/; (vi) tooth calcification/; (vii) (enamel adj2 defect$).mp. [mp = title, original title, abstract, name of substance word, subject heading word]; (viii) (enamel adj2 hypo$).mp. [mp = title, original title, abstract, name of substance word, subject heading word]; (ix) (MIH or 'molar incisor hypominerali#ation' or 'molar incisor hypo-minerali#ation').mp. [mp = title, original title, abstract, name of substance word, subject heading word]; (x) idiopathic enamel.mp. [mp = title, original title, abstract, name of substance word, subject heading word]; (xi) 'cheese molar$'.mp. [mp = title, original title, abstract, name of substance word, subject heading word]; (xii) enamel opacit$.mp. [mp = title, original title, abstract, name of substance word, subject heading word]; (xiii) or/1–12; (xiv) limit 13 to (English language and 'aetiology (optimized)' and 'all child (0 to 18 years)'); (xv) tooth abnormalities/et, ab; (xvi) dental enamel hypoplasia/et, ab; (xvii) tooth discoloration/et, ab; (xviii) molar/ab; (xix) dental enamel/ab; (xx) tooth calcification/ab; (xxi) *tooth abnormalities/et, ab or *dental enamel hypoplasia/et, ab or *tooth discoloration/et, ab or *molar/ab or *dental enamel/ab or *tooth calcification/ab; (xxii) limit 21 to (English language and 'all child (0 to 18 years)'); (xxiii) 14 or 22; (xxiv) *tooth abnormalities/or *dental enamel hypoplasia/or *tooth discoloration/or *dental enamel/or *molar/or *tooth calcification/or 7 or 8 or 9 or 10 or 11 or 12; (xxv) limit 24 to (English language and 'aetiology (optimized)' and 'all child (0 to 18 years)'); and (xxvi) 22 or 25 27. 23 not 26.

Results were downloaded into EndNote X (The Thomson Corporation, New York, NY, USA), and two reviewers (F.C. and D.M.)

reviewed the titles and abstracts independently excluding case studies/reports, studies on skeletal remains, studies *exclusively* concerning fluorosis, true hypoplasia, inherited conditions or prevalence, articles which did not report original data, and duplicates not automatically picked up by EndNote. If there was any uncertainty, the article progressed to the next review round. Subsequently, the reviewer lists were combined and further studies excluded by mutual agreement between the two reviewers after which the complete articles were assessed. If assessment of the FPMs did not form part of the examination, studies were excluded; however, those examining the primary dentition only were not excluded as lesions typical of MIH have been described, particularly affecting the second molars, in the primary dentition[9]. Any disagreements were settled by consulting a third reviewer (N.K.). Rankings of I to IV and A to C, respectively, for level and quality of evidence were assigned to each article based on National Health and Medical Research Council of Australia criteria (see Appendix S2, Supporting information)[10–12]. A random 10% sample of papers was reassessed by the reviewers to determine variability; any differences were discussed and a consensus was reached for the ranking of that paper.

Results

A total of 1123 articles were identified by the database search from which 53 were selected according to the criteria. The methodology and results of these articles were analysed. Studies were generally cross-sectional, cohort, or case-control designs, and none were randomized controlled trials. Details of the studies and the critical appraisals are presented in Appendix S3, Supporting information. Intra- and inter-reviewer agreement was complete (kappa = 1) for assessment of the level of evidence, but only moderate (kappa = 0.56) for quality of evidence. Preliminary review of the 53 selected studies identified a variety of factors implicated in the aetiology of developmental defects of enamel. These factors can be subdivided into five categories: infant exposure to dioxins and biphenols, perinatal events, exposure to fluoride, childhood illness, and specific chronic diseases. Consequently, the results of this review will be presented in the form of five hypotheses and their supporting evidence.

*That exposure to environmental contaminants such as polychlorinated biphenyls (PCBs) and polychlorinated dibenzo-*p*-dioxins/dibenzofurans (dioxins) is a risk factor for MIH (Table 1)*

Exposure to PCBs and dioxins has been reported as a potential cause of enamel defects with breast milk postulated as a source. Overall, there was moderate evidence that PCB/dioxin exposure is associated with enamel defects, but very weak evidence that breastfeeding in and of itself is an aetiological factor. Of the four studies investigating PCB/dioxin exposure, three reported a significant association with enamel defects[13–15], whereas the fourth was methodologically compromised, in that the

Table 1. Summary of papers concerning the aetiological role of environmental contaminants and breastfeeding.

Study[citation number]	Design	Level of evidence	Quality of evidence
Jan *et al*. 2007[13]	Cohort	III-2	B1
Jan and Vrbic 2000[14]	Cohort	III-2	B1
Alaluusua *et al*. 1996[15]	Cohort	II	B1
Wang *et al*. 2003[16]	Cohort	II	C
Alaluusua *et al*. 1996 (two studies presented in one paper)[3]	Cohort and case-control	III-2 & III-3	B1
Jalevik *et al*. 2001[17]	Cross-sectional	IV	B1
Dietrich *et al*. 2003[18]	Case control	III-3	B2
Li *et al*. 1995[20]	Cohort	III-2	B2
Beentjes *et al*. 2002[19]	Case control	III-3	B2
Lunardelli and Peres 2006[21]	Case control	III-3	B2
Agarwal *et al*. 2003[22]	Cohort	II	C
Rugg-Gunn *et al*. 1998[23]	Cohort	III-2	B1

Table 2. Summary of papers concerning the aetiological role of birth complications, maternal factors, and nutrition.

Study[citation number]	Design	Level of evidence	Quality of evidence
Dietrich *et al*. 2003[18]	Case control	III-3	B2
Rugg-Gunn *et al*. 1997[24]	Cohort	III-2	B1
Aine *et al*. 2000[25]	Cohort	III-2	B2
Drummond *et al*. 1992[26]	Cohort	III-2	B2
Fadavi *et al*. 1992[27]	Cohort	III-2	C
Lai *et al*. 1997[28]	Cohort	III-2	B2
Seow 1996[29]	Cohort	III-2	B1
Naidoo *et al*. 2005[30]	Cohort	III-2	C
Agarwal *et al*. 2003[22]	Cohort	II	C
Fearne *et al*. 1990[31]	Cohort	II	B2
Chaves *et al*. 2007[32]	Cohort	II	B1
Lunardelli and Peres 2006[21]	Case control	III-3	B2
Beentjes *et al*. 2002[19]	Case control	III-3	B2
Martinez *et al*. 2002[33]	Cross-sectional	IV	C

authors' definition of 'hypoplasia' was absent, and statistical analysis combined these lesions with other 'developmental defects' including fusion and impaction, and therefore, was of little value to the current review[16].

Only one study reported a significant increase in the prevalence of defects in association with longer breastfeeding; however, dioxin levels were not determined[3]. These authors also conducted a prospective cohort study in the same country in which both breastfeeding duration and dioxin exposure were assessed, and reported that dioxin levels but not duration of breastfeeding were significantly related to enamel defects[15]. Therefore, it seems reasonable to suggest the results of the former paper may reflect the relationship between dioxin dose and breastfeeding duration rather than the influence of breastfeeding duration on defects. The relationship between contaminant levels in children and duration of breastfeeding is supported by the results of Wang *et al.*[16], and the relationship between contaminant levels in children and defects in a recent retrospective cohort study[13]. Three other studies undertaken in western European populations reported no significant relationship between breastfeeding and enamel defects[17–19].

In contrast, studies of developing nation populations reported breastfeeding had a protective effect against enamel defects[20–22]. This suggests that nutrition may be a more relevant factor and is supported by Rugg-Gunn *et al*. who reported a significant positive association between defects and malnutrition and, in turn, between malnutrition and early cessation of breast/bottle feeding[23].

That pre-, peri-, and neonatal problems increase the prevalence of MIH (Table 2)

It appears malnutrition and health problems during pregnancy, birth, and the neonatal period contribute to a higher incidence of enamel defects in the primary dentition; however, the specific aetiological factor/s responsible have not been identified and may prove difficult to isolate due to the coexisting or closely related nature of many of these putative aetiological factors. Given that lesions typical of MIH have been reported in the second primary molars, separate data for these teeth would have been useful in the current review. Because this was not the case, we must acknowledge the influence of non-systemic factors (e.g. trauma to anterior teeth from intubation) on the significance of results reported. The role of these factors in the aetiology of defects in the permanent dentition remains unclear at this stage.

The lack of consistency in outcome measure, examiner calibration, and blinding of assessment limits the strength of the evidence, and data analysis is complicated by the strong associations between many of the variables; for example, premature infants are likely to have low birth weight; premature and low-birth-weight infants are more likely to require intubation and have health problems than full-term babies. Most studies failed to address these confounding factors in their data analysis.

Table 3. Summary of papers concerning the aetiological role of fluoride.

Study[citation number]	Design	Level of evidence	Quality of evidence
Rugg-Gunn *et al*. 1997[24]	Cohort	III-2	B1
Angellilo *et al*. 1990[44]	Cohort	III-2	B2
Clarkson and O'Mullane 1992[34]	Cohort	III-2	B2
de Liefde and Herbison 1989[35]	Cohort	III-2	B1
Downer *et al*. 1994[36]	Cross-sectional	IV	B1
Ekanayake and van der Hoek 2003[37]	Cohort	III-2	B2
Hiller *et al*. 1998[38]	Cohort	III-2	B1
Mackay and Thomson 2005[40]	Cross-sectional	IV	B1
Milsom and Mitropoulos 1990[41]	Cohort	III-2	B1
Nunn *et al*. 1994[43]	Cohort	III-2	C
Koch 2003[42]	Cohort	III-2	B2
Balmer *et al*. 2005[39]	Cohort	III-2	B2

Most papers were retrospective cohort studies (7/14, 50%)[24–30], and although there were three prospective cohort studies, one was of little value methodologically and all examined primary teeth only[22,31,32]. This was the case for the majority of studies[21,22,26–28,31,32]; therefore, caution must be taken when extrapolating the findings to the permanent dentition. Although reporting significantly more defects in the permanent dentition of a cohort of premature babies, Aine *et al*. could not establish a significant relationship with any individual potential aetiological factor. This was in contrast to the authors' analysis of the primary dentition in which prematurity, duration of intubation, and parenteral nutrition were reported as statistically significantly associated with the presence of defects[25]. Neither the study by Aine *et al*. nor that of Seow used the DDE Index; using an 'opacity' category instead, which included diffuse as well as demarcated lesions, limiting their value to the current review[29]. A case-control study of MIH reported no significant differences between MIH and unaffected populations in terms of birth weight, problems during pregnancy, birth or the neonatal period; however, the sample size was small and relied on retrospective data[19]. Two studies were of low quality with poor methodological design and no statistical analyses[30,33].

Two large population-based studies are reviewed in this section as they included, as a component of the larger study, analysis of the influence of malnutrition and neonatal, perinatal, and early childhood health problems on enamel defects in permanent teeth[18,24]. Malnutrition was reported as being associated with the prevalence of defects with statistical significance in the former study; however, no details were reported regarding the sample size of this analysis subgroup. In the latter study, the sample consisted of only 31 affected and 31 control subjects out of the 2408 participating in the study, and there were no significant relationships reported between any of the neonatal or perinatal problems and enamel defects.

That fluoride is a risk factor for MIH (Table 3)

Noting that studies reporting solely on fluorosis were excluded from this review, the studies that were analysed provided strong evidence that fluoride exposure is related to *diffuse* defects of enamel. The evidence, however, is weak for its involvement in the aetiology of demarcated defects distinct from these fluorotic lesions and more typical of MIH. Again, there were wide variations in the methodological quality of the studies with common areas of concern being: lack of control for or non-quantified alternative sources of fluoride, examination conditions, teeth examined, and blinding of examiners. The vast majority of the studies (11/12, 92%) report no association between the prevalence of demarcated defects and fluoride exposure[24,34–43], but the strength of evidence for each study is weak. In some instances, statistical analysis is either not conducted or not reported[39,42,43]. The only study that presented data suggesting a significant difference in the prevalence of demarcated defects with respect to water fluoridation levels reported that diffuse defects were the

Table 4. Summary of papers concerning the aetiological role of childhood illness.

Study[citation number]	Design	Level of evidence	Quality of evidence
Jalevik *et al*. 2001[17]	Cross-sectional	IV	B1
Rugg-Gunn *et al*. 1998[23]	Cohort	III-2	B1
van Amerongen and Kreulen 1995[1]	Cross-sectional	IV	C
Tapias-Ledesma *et al*. 2003[45]	Case control	III-3	B2
Beentjes *et al*. 2002[19]	Case control	III-3	B2

'discriminating factor' between fluoride exposure level groups[44].

That common childhood illnesses increase the prevalence of MIH (Table 4)

This group of studies concerns common or general childhood health problems; chronic diseases and medical conditions will be discussed subsequently. According to the published literature, there is no clear evidence for the role of childhood illness and treatment in the aetiology of enamel defects. Respiratory problems[1,17,19,23,45] and otitis media[17,19] are the most consistently implicated, although other conditions and medications have been reported to be significantly related to dental defects in isolated studies[17,19,45]. The majority of authors acknowledge the possible confusion between, and confounding influence of, the effect of the disease itself as opposed to the effect of any treatment on dental development, a problem which may prove insurmountable as ethical considerations are likely to prevent a definitive prospective study from being established.

An example of the complexity of this issue can be seen in a recent case-control study in which a lower prevalence of enamel defects was found in FPMs in children who reported a higher intake of mucolytics[45]. This suggests putatively that it is untreated respiratory problems that may pose a risk to the developing tooth. In the same study, however, medical treatment involving macrolides was reportedly associated with a higher prevalence of defects. Interestingly, intake of amoxicillin, often considered an aetiological factor[46], was not found to have an association with enamel defects. It should be noted that the data in this study were analysed on a per-year basis, and the numbers for each factor assessed were not described, so it is possible that very small sample sizes affected the results of the statistical analysis. Recurrent or multiple illnesses may contribute to enamel defect formation. One study showed that frequency of paediatric care and greater number of episodes of urinary tract infection were both associated with MIH[45], whereas another reported that children with MIH were ill more frequently[19]. The latter was an MIH-specific case-control study and also reported a tendency for MIH-affected children to suffer from a greater variety of illnesses, although otitis media, pneumonia, and high fever were implicated particularly.

A significant limitation of many studies is the reliance on retrospective parental recall for medical information. Even accessing medical records can be unreliable as they vary in quality, possibly omit information regarding minor complaints, and almost certainly lack a record of any treatments which were either not advised by the doctor (e.g. giving antibiotics left over from another family members' treatment) or for which the doctor was not consulted (i.e. over-the-counter medications).

Additionally, the level of evidence is low for childhood illness as two papers were cross-sectional studies, one did not include any statistical analysis[1,17], another case-control study did not match the control population to the case population[45], and although yet another study used a cohort design; the cohorts were selected on the basis of socioeconomic status as medical issues were not the primary focus[23].

That the prevalence of MIH is significantly higher in medically compromised populations (Table 5)

A variety of medical conditions such as coeliac disease, cystic fibrosis, and renal disease have been studied in relation to enamel defects,

Table 5. Summary of papers concerning the aetiological role of medical conditions.

Study[citation number]	Design	Level of evidence	Quality of evidence
Aguirre *et al*. 1997[47]	Cohort	III-2	B1
Aine *et al*. 1990[48]	Cohort	III-2	B2
Aine *et al*. 1992[49]	Cohort	III-2	B1
Farmakis *et al*. 2005[50]	Cohort	III-2	B2
Maki *et al*. 1991[51]	Cohort	III-2	B2
Priovolou *et al*. 2004[52]	Cohort	III-2	B2
Wierink *et al*. 2007[53]	Cohort	III-2	B1
Rasmusson and Eriksson 2001[54]	Cohort	III-2	B2
Mariani *et al*. 1994[55]	Cohort	III-2	B1
Erturul *et al*. 2003[57]	Cohort	III-2	C
Nunn *et al*. 2000[58]	Case series	IV	B2
Azevedo *et al*. 2006[59]	Cohort	III-2	B2
Narang *et al*. 2003[60]	Cohort	III-2	C
Alpaslan *et al*. 1999[61]	Cohort	III-2	C
Hallett *et al*. 1992[62]	Cohort	III-2	B2
Dahllof *et al*. 1989[63]	Cohort	III-2	B2
De Coster *et al*. 2002[64]	Cohort	III-2	B2
Kotilainen *et al*. 1995[65]	Cohort	III-2	C

but many investigated hypoplasia exclusively and were excluded from this review. Overall, it appears that children with chronic medical conditions, and/or undergoing their treatment, have a higher prevalence of enamel defects, but the quality of studies is such that the evidence is weak, particularly with regard to MIH. The quality of evidence would improve if studies used standard methodologies and indices. Furthermore, finding an appropriate comparison control group is challenging and rarely reported. Including groups to serve as positive controls, that is, those with similar symptoms but not the disease itself, or those who have been exposed to similar treatment (e.g. antibiotics) for other reasons, as well as unaffected individuals might also be valuable for comparative analysis.

The most commonly reported condition associated with enamel defects is coeliac disease (nine studies)[47–55]. These studies often used a different, coeliac-specific index – the Aine Index[56] (see Appendix S1, Supporting information). Although this index does have a non-specific category into which MIH lesions would likely fall, there is no breakdown into diffuse/demarcated lesion types. Regardless of the index used, all of these studies reported that developmental defects of enamel were more common in individuals with coeliac disease, with specific defects consistently found in those studies using the Aine Index. No significant differences in non-specific defect prevalence were reported[47,54], but many studies either did not present these data[51] or did not conduct any analysis[48,49,53].

The remaining studies are more difficult to compare because they: deal with a range of conditions including renal disease[57,58], cystic fibrosis[59,60], lymphoma[61], congenital cardiac defects[62], cleft lip/palate[63], Marfan syndrome[64], and Silver Russell syndrome[65]; generally have poorer methodologies; often do not use a standard index; and fail to give adequate details on how defects were classified. All authors reported more defects in the test population, although for permanent teeth only in one study[59] and primary teeth only in another[62]; however, the strength of this evidence is very weak.

Discussion

Until MIH is a universally recognized condition with an accepted definition and standard diagnostic criteria, any investigation into its aetiology will be compromised to some extent. Although some components of the DDE Index can be used as a proxy, there are limitations. A modified DDE Index has been developed in an attempt to ameliorate this situation (see Appendix S1, Supporting information)[66]. Under this index, demarcated lesions are further subdivided into mild, moderate, and severe categories with the latter including teeth displaying PEB or an existing restoration. In the course of this review, it was noted that several studies specifically excluded carious or restored teeth which is likely to lead to the underestimation of the prevalence of MIH, and therefore, compromise subsequent statistical analysis. Similarly, it would seem prudent to account for any missing FPMs because affected teeth can be so severely compromised as to require extraction at an early age[67,68]. An MIH-specific index was used in a paper by Jasulaityte *et al*. in 2007 which attempted to account for PEB and extracted teeth (see Appendix S1, Supporting information)[69]. The lack of consistency in the use of the term hypoplasia hindered this review. The term 'hypoplasia' literally refers to a *quantitative*

developmental defect, and any studies that both defined it as such and did not include any opacity data were excluded. However, hypoplasia is also commonly and incorrectly used to describe *qualitative* defects. As a result, several studies, despite the poor quality of evidence they offered, could not be excluded from the review, as the true nature of the defect/s was not known.

In addition to differences in diagnostic indices, the teeth and surfaces to which the index is applied vary between studies making any inter-study comparisons almost impossible. Many studies of enamel defects, both aetiological and epidemiological, do not include all of the teeth involved in MIH, particularly the upper FPMs. Permanent, primary, and mixed dentitions are all represented in the reviewed articles; furthermore, some studies recorded data from as few as one surface of four teeth through to all visible surfaces of all teeth present. Anecdotally, it is the molars that are the most problematic for patients and clinicians alike, and the fact that incisors are often apparently unaffected is one point of contention regarding the definition, and indeed name, of MIH. Confounding factors may be introduced by the inclusion of incisor teeth as the consequences of trauma and infection are common causes of demarcated enamel defects. However, for accurate information regarding MIH, all FPMs and permanent incisors should be included in the outcome assessment. Similarly, it is important to establish a standard protocol that addresses the issue of lesion size and multiple lesions on a single tooth or surface. This review has identified studies that have recorded all defects present, some that only recorded the most severe defect, and, most commonly, studies that fail to give any such details.

Protocols for the clinical examination varied across these studies, with some assessing lesions on dry teeth, some wet, and others both. Significantly, more lesions were identified on dry than wet teeth[70,71]. The detection of carious lesions is associated with similar issues particularly for non-cavitated lesions for which examinations should be in a dental chair under good light on clean, dry teeth[72]. Other examination variables included pre-examination cleaning procedures and differences in lighting conditions. Many studies failed to specify details of these variables or provide information on examiner blinding and calibration. Reporting of data was similarly variable with many studies not breaking down results across the three main categories of defects in the DDE Index. In particular, diffuse and demarcated lesions were often combined to form an 'opacity' group. Such results are difficult to interpret in relation to MIH.

One of the most challenging aspects of the search for a better understanding of MIH is the likely complexity of its pathogenesis. Basic scientific research is increasingly demonstrating that ameloblasts are highly susceptible to relatively minor changes in their environment; for example, increases in temperature[73], hypocalcaemia[74], and pH levels[75] can all disrupt the normal process of amelogenesis, and that the susceptibility to environmental conditions can be influenced by genetics[76–78]. Therefore, any maternal or childhood illness, or exposure to medications, environmental contaminants, etc. that may cause a change to the environment in which the ameloblasts are functioning can putatively contribute to the development of defective enamel. It is likely that many factors acting simultaneously (as in the preterm, low birth weight, respiratorily compromised neonate) or sequentially (as in the child with otitis media with associated fever subsequently treated with antibiotics) contribute to the development of MIH. The putative multifactorial nature of the aetiology may go some way to explain the variation in distribution of the lesions seen clinically as the exact timing, nature, and/or specific combination of the insult/s may determine the clinical presentation.

Conclusion

According to the available evidence in relation to MIH or similar enamel defects, exposure to PCBs/dioxins does appear to be a risk factor for developing MIH-like defects and is worthy of further investigation. Increased duration of breast-feeding, however, does not itself increase the prevalence of MIH, and indeed, may in fact reduce enamel defects. Pre-, peri-, and neonatal problems increase the prevalence of developmental dental defects in general, particularly in the primary dentition; however, a substantial amount of further evidence is required to establish their role in the aetiology of MIH. There is some

evidence to link early childhood malnutrition to an increased prevalence of enamel defects, but further research is required to confirm any direct relationship. Fluoride exposure is unlikely to be a risk factor for MIH. Common childhood illnesses and/or their treatment do appear to increase the prevalence of MIH, but again further work will be required to clarify the specific cause/s of this observed effect. The prevalence of dental defects is significantly higher in medically compromised populations; however, improvements in study design are needed to strengthen the evidence, particularly with regard to MIH. It is also likely that, in addition to the environmental exposures so far identified, genetic susceptibility may play a role in the aetiology of this challenging disorder. Long-term prospective epidemiological studies that use clearly defined clinical protocols and indices, and include the collection of comprehensive environmental and genetic information are required.

What this paper adds

- This paper provides an analysis and summary of aetiological information regarding MIH published in the last 18 years.
- Current evidence for the aetiology of MIH is weak, and strategies are suggested to improve the strength of future research.

Why this paper is important to paediatric dentists

- Paediatric dentists are highly likely to encounter children with MIH in their clinical practice.
- Knowledge regarding aetiological factors assists identification of children potentially at risk for MIH.

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Supporting information

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Appendix S1. Developmental defects of enamel indices.

Appendix S2. Criteria for assessing level and quality of evidence.

Appendix S3. Studies included in review (in alphabetical order).

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