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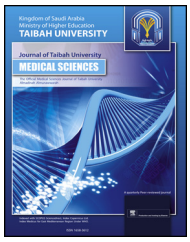

Review Article

Prevalence and risk factors of molar incisor hypomineralization in the Middle East: A systematic review and meta-analysis

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الملخص

أهداف البحث: يعتبر نقص تمعدن المينا في الضرس الرحوي مصدر قلق عالمي متزايد. هنا، نجري مراجعة منهجية وتحليل تلوي لانتشار العوامل / عوامل الخطر المرتبطة بنقص تمعدن المينا في الضرس الرحوي في الشرق الأوسط.

طرق البحث: تضمنت هذه المراجعة المنهجية والتحليل التلوي دراسات على الأطفال الذين يعانون من ضرس دائم واحد على الأقل متأثر بنقص تمعدن المينا في الضرس الرحوي، الذين تتراوح أعمارهم بين 5 و 18 عاما، دون متلازمات أو تشوهات خلقية، ويقيمون في الشرق الأوسط وشملوا المقطعية المستعرضة، وضبط الحالات، أو دراسات الأتراب. تم البحث عن الكلمات الرئيسية المتعلقة ببلدان الشرق الأوسط و نقص تمعدن المينا في الضرس الرحوي بشكل منهجي حتى 10 يناير 2021 في أربع قواعد بيانات: "بيميد، غوغل العلمي، "ساينس دايركت"، و "كوكرين"، وفقا لمعايير الأهلية المحددة. تم استخدام أداة تقييم الجودة من معهد جوانا بريجز لتقييم جميع الدراسات المشمولة. أجريت التحليلات التلوية لتقييم تأثير عوامل الخطر. تم تسجيل بروتوكول الدراسة في "بروسبيرو" (رقم التسجيل: 247391).

النتائج: بعد فحص 4373 وثيقة، تم تضمين 29 دراسة مؤهلة مع ما مجموعه 32636 طفلا من 11 دولة تتراوح أعمارهم بين 7-12 عاما. وتراوحت وتيرة الإبلاغ عن نقص تمعدن المينا في الضرس الرحوي في الشرق الأوسط من 2.3٪ إلى 40.7٪، بمتوسط انتشار 15.05٪. الحمل وأمراض الطفولة المبكرةوالعوامل المتعلقة بالولادة كانت مرتبطة ارتباطا ذو دلالة احصائية مع نقص تمعدن المينا في الضرس الرحوي.

الاستنتاجات: يتماشى متوسط انتشار نقص تمعدن المينا في الضرس الرحوي في الشرق الأوسط مع معدل انتشار نقص تمعدن المينا في الضرس الرحوي العالمي. تعد الأمراض ومضاعفات الولادة من عوامل الخطر التي يمكن السيطرة عليها للوقاية من نقص تمعدن المينا في الضرس الرحوي. كما أظهرت الدراسات المشمولة عدم التجانس العالي في التحليلات التلوية ، هناك حاجة إلى مزيد من الأدلة من الشرق الأوسط لتقييم الانتشار وعوامل الخطر البيئية الأخرى المرتبطة بنقص تمعدن المينا في الضرس الرحوي.

الكلمات المفتاحية: نقص تنسج المينا؛ الشرق الأوسط؛ نقص تمعدن المينا في الضرس الرحوي؛ انتشار؛ عامل الخطر

Abstract

Objectives: Molar incisor hypomineralization (MIH) is a growing global concern. Herein, we conducted a systematic review and meta-analysis of the prevalence and associated factors/risk factors of MIH in the Middle East (ME).

Methods: This systematic review and meta-analysis included studies on children with at least one first permanent molar affected by MIH, aged 5–18 years, without syndromes or congenital anomalies, and residing in the ME and included cross-sectional, case–control, and cohort studies. Keywords related to MIH and ME countries were systematically searched until January 10, 2021 in four databases, PubMed, Google Scholar, Science Direct, and the Cochrane Library, following the specified eligibility criteria. The Joanna Briggs Institute quality assessment tool was used to evaluate all included studies. Meta-analyses were conducted to assess the effect of risk factors. The study protocol was registered on the

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PROSPERO International Prospective Register of Systematic Reviews (Registration No. 247391).

Results: After screening 4,373 documents, 29 eligible studies with a total of 32,636 children aged 7–12 years were included from 11 countries. The frequency of MIH reported in the ME ranged from 2.3% to 40.7%, with a mean prevalence of 15.05%. Pregnancy and early childhood illnesses (odds ratio [OR]: 2.26, 95% confidence interval [CI]: 1.91–2.68; $P < 0.001$) and factors related to delivery (OR: 2.4, 95% CI: 1.55–3.72; $P < 0.001$) were statically significantly associated with MIH.

Conclusion: The mean prevalence of MIH in ME aligns with the global MIH prevalence rate. Illnesses and delivery complications are risk factors that could be controlled to prevent MIH. As included studies showed high heterogeneity in the meta-analyses, further evidence from the ME is needed to assess the prevalence and other associated environmental risk factors for MIH.

Keywords: Enamel hypoplasia; Middle East; Molar incisor hypomineralization; Prevalence; Risk factor

Introduction

Dental clinicians have identified molar incisor hypomineralization (MIH) as a growing concern worldwide. MIH is a developmental dental defect that affects the enamel of one to four first permanent molars, with or without

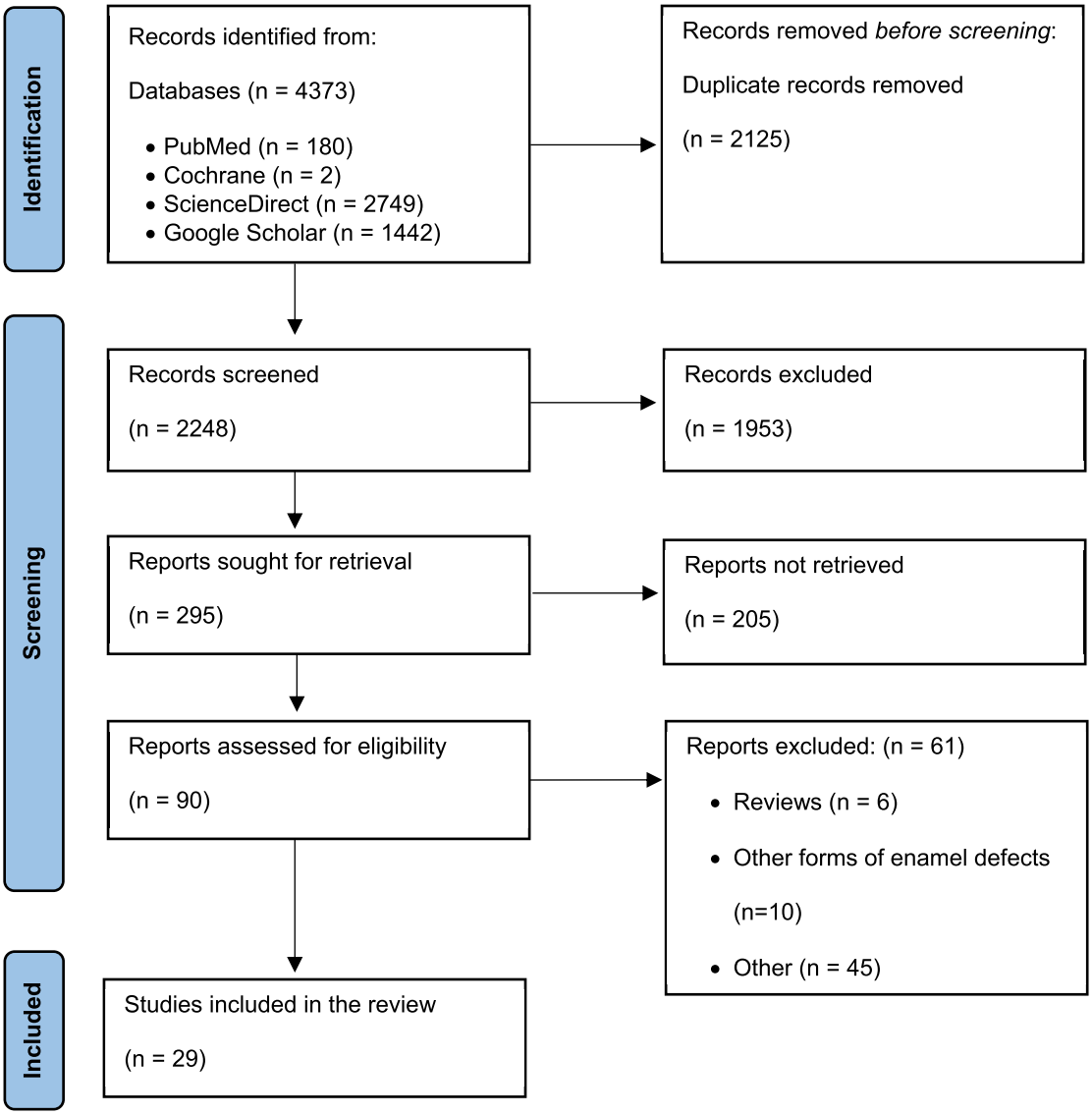

Figure 1: PRISMA chart of the systematic search.

involvement of the anterior incisors.[1] MIH is characterized by hypomineralized, demarcated enamel opacities that appear brownish-yellow to white and creamy, and can be diagnosed after permanent teeth eruption in the oral cavity; however, it must be differentiated from other conditions with similar clinical manifestations.[2]

Several scoring systems can diagnose MIH, including the original developmental defects of the dental enamel index (DDE index), its modified version (mDDE index), and the enamel defects index (EDI index).[3–6] The DDE index records the type (opacity, hypoplasia, and/or discoloration), number, extent (demarcated or diffused), and location (buccal/lingual tooth surface) of the defects in the examined teeth[4]; however, it is time-consuming. This index was later modified to include the measurement of the severity of diffused, demarcated, and hypoplastic defects.[5] The EDI index records basic characteristics of the defects including opacity, hypoplasia, and post-eruptive breakdown and their presence or absence in all identified defects, allowing the evaluation of more details.[6] In 2003, the European Academy of Pediatric Dentistry (EAPD) announced the following diagnostic criteria for MIH: demarcated opacities, post-eruptive enamel breakdown, atypical restoration, extracted molar due to MIH, and unerupted teeth.[3]

The epidemiology of MIH has been the focus of several studies across the globe, with a wide variation in prevalence and associated risk factors being reported. The global prevalence is estimated as 14.2%, with the highest prevalence rate found in South America (18%) and the lowest in Africa (10.9%).[7] The prevalence in Europe varies from 2.4% to 40.2%.[8] Several epidemiological studies have been conducted in Middle Eastern countries, but they have reported varying MIH frequencies. A study in Iraq reported an MIH prevalence rate of 18.6%,[9] whereas studies in Libya and Sudan have reported rates of 2.9% and 20.1%, respectively.[10,11]

The association of MIH with illness during pregnancy, birth prematurity and complications, frequent use of antibiotics, and viral infections, although important, is not well established.[12,13] A systematic review by Silva et al. demonstrated a significant relationship between childhood illness and MIH[14]; genetic links have also been suggested,[15,16] illustrating that the etiology of the disease is multifactorial.

Although several systematic reviews have explored the prevalence and associated factors/risk factors for MIH worldwide, to the best of our knowledge, no such systematic review has been conducted in the Middle East (ME). Such a study could potentially yield interesting results considering the wide genetic admixture present in Middle Eastern societies, where consanguineous marriage is relatively common.[17] Due to the specific environmental risk factors and genetic background of these populations, we hypothesize that the MIH prevalence in Middle Eastern countries may differ from that of other parts of the world. Our research question is: What is the prevalence and risk factors of MIH in the ME?

The PICO for this research is as follows: P: articles discussing MIH in the ME countries, I: prevalence and risk factors, C: those not exposed to the risk factors, O: MIH.

Table 1: Characteristics, frequency, and prevalence of molar incisor hypomineralization in included studies.

Country	Study	City	Data recruitment	Sample design	Diagnostic criteria/tool	Age (years)	Sample size	Prevalence/frequency, N (%)
Egypt	Saber et al. (2018)[21]	Cairo	2014–2015	Hospital-based	Lygidakis et al. (2010) diagnostic criteria + EDI	8–12	1001	23 (2.3)
	Saber et al. (2018)[22]	Cairo	2014–2015	Hospital-based	Ghanim et al. (2015) diagnostic criteria	8–12	1001	23 (2.3)
	Abo Elsoud and Mahfouz (2019)[39]	Suez Canal	–	Non-random sample – multi-school based	EAPD 2003	8–12	1312	131 (9.98)
	Osman et al. (2020)[24]	Cairo	–	Hospital-based	EAPD + Weerheijm (2003) + Mejàre (2009) diagnostic criteria	8–12	1000	142 (14.2)
Iran	Ahmadi et al. (2012)[40]	Zahedan	–	Non-random sample, multischool-based	DDE	7–9	433	55 (12.7)
	1. Ghanim et al. (2014)[41]	Shiraz	–	Multistage sampling design, cluster random sample, multischool-based	EAPD 2003	9–11	810	164 (20.2)
	2. Poureslami et al. (2018)[42]	Kerman	2015–2016	Cluster random sample, multischool-based	EAPD 2003	7–12	779	51 (6.5)
	3. Shojaeepour et al. (2020)[43]	Kerman	–	Cluster random sampling, multi-school-based	EAPD 2003	8–12	2507	129 (5.14)

Iraq	Ghanim et al. (2013)[45]	Mosul	2009–2010	Stratified random sample, multischool-based	EAPD 2003	7–9	823	153 (18.6)
	Noori and Hussein (2014)[29]	Sulaimani	–	Cluster random sample, multischool-based	EAPD 2003	7–9	2347	427 (18.2)
	Salih and Ofi (2015)[30]	Al-Najaf	2014	Non-random sample, school-based	EAPD 2003	7–9	532	105 (19.7)
Jordan	Zawaideh et al. (2011)[31]	Irbid Amman and Al-Karak	2009	Cluster random sample, multistage sampling design, multischool-based	Weerheijm et al. (2003) diagnostic criteria	7–9	3241	570 (17.6)
	Fnaish et al. (2011)[27]	North region	2004–2005	Non-random sample, hospital-based	Demarcated opacities, Post-eruptive defects, Atypical restorations	5–12	3660	120 (3.28)
	Hamdan et al. (2020)[32]	Amman	2015	Simple random sample, multi-school-based	EAPD 2003	8–9	1412	186 (13.17)
Lebanon	Elzein et al. (2020)[33]	North, East, South, Beirut and suburbs	2017–2018	Simple random sample, multischool-based	Ghanim et al. (2015) diagnostic criteria	7–9	659	176 (26.7)
Libya	Fteita et al. (2006)[10]	Benghazi	–	Non-random sample, multischool-based	Modified DDE	7–8.9	378	11 (2.9)
KSA	Allazzam et al. (2014)[11]	Jeddah	2011	Non-random sample, hospital-based	EAPD 2003	8–12	267	23 (8.6)
	Al-Hammad et al. (2018)[23]	Riyadh	2018	Simple random sample, multischool-based	EAPD 2003	8–10	924	376 (40.7)
	Rizk et al. (2018)[34]	Qassim	–	Random sample, multischool-based	EAPD 2003	7–9	411	103 (25.1)
Sudan	Abdalla et al. (2021)[11]	Sudan/Khartoum	2017	Cluster random sample, multischool-based	EAPD 2003	8–11	568	114 (20.1)
Tunisia	Sakly et al. (2020)[35]	Tunis	2017	Random sample, school-based	EAPD 2003	7–12	510	181 (35.4)
Turkey	Kusku et al. (2008)[28]	Istanbul	2007	Non-random sample, hospital-based	Demarcated opacities, Post-eruptive defects, Extensive restorations, Extracted molar due to MIH	7–9	147	22 (14.9)
	4. Sönmez et al. (2013)[36]	Ankara	–	Cluster random sample, multischool-based	Weerheijm et al. (2003) diagnostic criteria	7–12	4018	308 (7.7)
	5. Koruyucu et al. (2018)[8]	Istanbul	–	Cluster random sample, multischool-based	EAPD 2003	8–11	1511	215 (14.2)
	6. Kılınç et al. (2019)[25]	Izmir	2015–2018	Hospital-based	Demarcated opacities, Post-eruptive defects, Extensive restorations, Extracted molar due to MIH	9–10	1237	142 (11.5)
UAE	Hussain et al. (2018)[37]	Dubai	–	Cluster random sample, multi-school-based	EAPD 2003	8–12	369	196 (27.2)
	Ahmad et al. (2019)[38]	Dubai	–	Random sample, multischool-based	EAPD 2003	7–9	779	59 (7.57)

(–): not mentioned, (EAPD): European Academy of Pediatric Dentistry, (EDI): Enamel Defect Index, (DDE): Developmental Enamel Defect.

Table 2: Quality assessment of MIH prevalence studies according to the JBI criteria.

Country	Study	Sample frame	Sample design	Sample size	Study subjects and setting	Sample coverage	Assessment tool	Standardization and reliability	Statistical analysis	Response rate	Total # of yes
Egypt	Saber et al. (2018)[21]	Yes	No	UC	Yes	No	Yes	Yes	Yes	UC	5
	Saber et al. (2018)[22]	Yes	No	UC	Yes	No	Yes	Yes	Yes	UC	5
	Abo Elsoud and Mahfouz (2019)[39]	Yes	No	Yes	UC	Yes	Yes	Yes	UC	UC	5
	Osman et al. (2020)[24]	UC	No	Yes	UC	No	Yes	Yes	Yes	UC	4
Iran	Ahmadi et al. (2012)[40]	Yes	No	UC	UC	Yes	Yes	Yes	Yes	Yes	6
	Ghanim et al. (2014)[41]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
	Poureslami et al. (2018)[42]	Yes	Yes	UC	Yes	Yes	Yes	Yes	Yes	UC	7
	Shojaeepour et al. (2020)[43]	Yes	Yes	Yes	UC	Yes	Yes	Yes	Yes	Yes	8
Iraq	Ghanim et al. (2013)[45]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
	Noori and Hussein (2014)[29]	Yes	Yes	Yes	UC	Yes	Yes	UC	Yes	Yes	7
	Salih and Ofi (2015)[30]	UC	UC	Yes	UC	UC	Yes	UC	Yes	Yes	4
Jordan	Zawaideh et al. (2011)[31]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
	Fnaish et al. (2011)[27]	UC	No	Yes	Yes	No	Yes	Yes	UC	Yes	4
	Hamdan et al. (2020)[32]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Lebanon	Elzein et al. (2020)[33]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	UC	Yes	8
Libya	Fteita et al. (2006)[10]	Yes	No	No	UC	UC	Yes	Yes	Yes	UC	4
KSA	Allazzam et al. (2014)[26]	UC	UC	No	Yes	No	Yes	Yes	Yes	Yes	5
	Al-Hammad et al. (2018)[23]	Yes	Yes	UC	UC	Yes	Yes	Yes	Yes	Yes	7
	Rizk et al. (2018)[34]	Yes	Yes	UC	UC	UC	Yes	Yes	Yes	Yes	6
Sudan	Abdalla et al. (2021)[11]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Tunisia	Sakly et al. (2020)[35]	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	7
Turkey	Kusku et al. (2008)[28]	No	No	No	Yes	No	Yes	Yes	Yes	No	4
	Sönmez et al. (2013)[36]	Yes	Yes	Yes	UC	Yes	Yes	Yes	Yes	Yes	8
	Koruyucu et al. (2018)[8]	Yes	Yes	Yes	UC	Yes	Yes	Yes	Yes	Yes	8
	Kılınç et al. (2019)[25]	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	6
UAE	Hussain et al. (2018)[37]	Yes	Yes	Yes	UC	Yes	Yes	Yes	Yes	Yes	8
	Ahmad et al. (2019)[38]	Yes	Yes	UC	UC	Yes	Yes	Yes	Yes	Yes	7

UC (Unclear).

We conducted a systematic review and evaluated the literature to report the prevalence, frequency, and possible associated/risk factors for MIH in the ME.

Materials and Methods

Study registration and protocol

The study protocol was registered on the PROSPERO International Prospective Register of Systematic Reviews (Registration No. 247391). The following countries were considered Middle Eastern[18]: Kingdom of Saudi Arabia (KSA), Kuwait, Bahrain, Qatar, United Arab Emirates (UAE), Oman, Yemen, Palestine, Syria, Jordan, Lebanon, Iraq, Iran, Turkey, Cyprus, Egypt, Libya, Tunisia, Algeria, Morocco, Sudan, and Mauritania. Hence, studies from these countries were included in our review.

Three independent trained reviewers searched for selected keywords according to indexed terms in Medical Subject Headings related to MIH and Middle Eastern countries in four main databases: PubMed, Google Scholar, Science Direct, and the Cochrane Library. The strategy adopted to conduct the literature search on these databases is detailed in the Supplementary Material. The search was not restricted by date or language of publication. Gray literature was searched using the Gray Literature Report.[19] The literature search was updated until January 10, 2021. The reporting of the results was in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement checklist and its extension for Abstracts. The search phases were identified and presented using the PRISMA 2020 flow diagram (Figure 1).

Eligibility criteria

This systematic review included studies conducted on children with at least one first permanent molar affected by MIH, aged 5–18 years, with no syndromes or congenital anomalies, and residing in the ME. Studies with cross-sectional, case–control, or cohort design were included.

The search strategy excluded studies conducted on individuals older than 18 years of age; with other forms of enamel hypomineralization, syndromes, or congenital anomalies; or living in a country not stated in the above-mentioned list. Pilot studies, systematic or other reviews, case reports, and unpublished studies (e.g., unpublished theses) were also excluded.

Data extraction

Three investigators independently searched the literature. All identified studies were uploaded to EndNote X9 (Clarivate Analytics, PA, USA), and duplicates were removed. Three independent researchers selected eligible studies for further assessment and extracted the data according to the above-mentioned inclusion criteria. The titles were screened initially, followed by abstract screening. Then full texts of articles that needed further clarification and

Table 3: Quality assessment of MIH associated factor/risk factor studies according to the JBI criteria.

Study	Group comparability	Matched cases/controls	Similar identification criteria	Reliable and valid exposure measurement	Similar measurements for Cases/controls	Confounding factors identification	Confounding factors management	Reliable and valid outcome assessment	Meaningful exposure period	Statistical analysis	Total # of yes
Ahmadi et al. (2012)[40]	Yes	No	Yes	Yes	Yes	No	No	Yes	UC	Yes	6
Allazzam et al. (2014)[26]	Yes	No	Yes	No	Yes	No	No	No	UC	Yes	4
Elzein et al. (2021)[44]	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	UC	Yes	8
Ghanim et al. (2013)[45]	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	UC	Yes	8
Kılınç et al. (2019)[25]	Yes	No	Yes	UC	Yes	No	No	No	UC	Yes	4
Koruyucu et al. (2018)[8]	Yes	No	Yes	No	Yes	Yes	Yes	Yes	UC	Yes	7
Sönmez et al. (2013)[36]	Yes	No	Yes	UC	Yes	Yes	Yes	Yes	UC	Yes	7

UC (Unclear).

Table 4: Associated factors/risk factors of MIH (postnatal).

Study	Prenatal and perinatal factors											Postnatal factors		
	Number of pregnancies	Exposure to medications	Pregnancy illnesses	Maternal stress	Ultrasonic scans	Maternal consumption of canned food	Mode of delivery	Low birth weight	Preterm labor	Birth complications	Baby incubator	Length of breastfeeding	Meds during breastfeeding	Antibiotic intake
Ahmadi et al. (2012)[40]	–	–	Yes	–	–	–	Yes	–	Yes	Yes	–	Yes	–	Yes
Allazzam et al. (2014)[26]	–	No	No	–	–	–	No	No	No	No	–	No	No	Yes
Elzein et al. (2020)[33]	No	–	No	–	–	Yes	No	–	No	No	No	No	No	Yes
Ghanim et al. (2013)[45]	Yes	No	Yes	Yes	Yes	–	–	Yes	–	Yes	Yes	Yes	–	No
Kılınç et al. (2019)[25]	–	–	–	–	–	–	–	Yes	Yes	–	–	–	–	–
Koruyucu et al. (2018)[8]	–	–	Yes	–	–	–	–	No	Yes	–	–	Yes	–	–
Sönmez et al. (2013)[36]	–	–	No	–	–	–	–	No	Yes	No	–	No	–	–

selected eligible studies were retrieved. The reference lists of the included studies were hand searched. The researchers were blinded to each other's decisions. In case of any disagreement or conflict in opinion, a discussion with two expert reviewers was conducted to reach a consensus.

The following data were extracted: year of publication, date of data collection, country, sample design, MIH diagnostic criteria/tool used, age group, sample size, frequency and prevalence of MIH, and associated factors/risk factors related to MIH. The prevalence and frequency reported by the studies were analyzed, and all data were recorded as tables using an Excel spreadsheet and Word document. To determine the prevalence of MIH in Middle Eastern countries, the mean MIH prevalence reported in the included studies was calculated.

Quality assessment

All included eligible studies were critically appraised by three independent researchers using a standardized tool, namely the Joanna Briggs Institute (JBI) critical appraisal tool. Depending on the design of the study, quality was assessed as a judgment (yes, no, unclear, not applicable) through questions using two JBI critical appraisal tools: the JBI prevalence critical appraisal tool and the JBI critical appraisal checklist for case–control studies.[20] The highest scores for the JBI prevalence critical appraisal tool were 9 and 10 for case–control studies. For prevalence studies, we considered studies with a score of $\leq$3 as low quality, 4–6 as moderate quality, and $\geq$7 as high quality. Additionally, for risk factor studies, we considered studies with a score of $\leq$4 as low quality, 5–7 as moderate quality, and $\geq$8 as high quality. The degree of agreement between the authors' judgment was assessed using the Kappa score, which was 0.875 for the prevalence and 0.7 for risk factor studies.

Meta-analyses

Quantitative synthesis was conducted to assess the association between the different reported environmental risk factors and MIH. A meta-analysis requires at least two studies. RevMan software (version 5; 1, Nordic Cochrane Centre, Cochrane collaboration, 2001) was used to perform the meta-analyses. A statistically significant P-value was set at 0.05. Random-effect models were used in case of significant heterogeneity ($P > 0.05$). The possibility of small study effect was assessed visually through funnel plots. Egger's test was used to evaluate publication bias. The significance level was set at 0.05.

Results

The initial search retrieved 4373 studies. After removing duplicates (n = 2125), the remaining records (n = 2248) were screened for exclusion by title. The records (n = 1953) were excluded to reach a sum of articles (n = 295) screened for exclusion by abstract. A total collection of records (n = 205) was then excluded, and the remaining studies (n = 90) were assessed for eligibility. Among these, 61 were excluded for the following reasons: review articles (n = 6); evaluated other forms of enamel defects (n = 10); or other reasons, for example, studies investigating hypomineralization in primary teeth or conducted outside the ME (n = 45). Twenty-nine studies were included (Figure 1). While most (n = 22) studies only discussed MIH prevalence, a few (n = 2) investigated only the associated factors/risk factors of MIH. Five studies discussed both. The distribution of studies varied among the Middle Eastern countries. The highest number of studies conducted in a specific country was four (Egypt, Iran, Iraq, and Turkey) followed by three (Jordan and KSA). Two studies were conducted in both Lebanon and the United Arab Emirates, whereas only one study each was conducted in Libya, Sudan, and Tunisia. Half of the Middle Eastern countries included in our search did not conduct studies on MIH prevalence and associated factors/risk factors. All studies were published between 2006 and 2021. The highest number of studies, six each, was published in 2018 and 2020.

MIH prevalence

All prevalence studies had a cross-sectional design. Table 1 summarizes MIH characteristics, frequency, and

Postnatal factors														
Allergy	Asthma	Tonsillitis	Bronchitis	Pneumonia	Urinary tract infection	Otitis media	Chicken pox/Measles	Rubella	High fever	Renal Disorders	GIT problems	Jaundice	Hypocalcemia	Maternal consumption of canned food
Yes	Yes	–	–	–	No	Yes	–	–	No	Yes	–	–	–	–
No	Yes	Yes	–	–	No	No	No	–	Yes	No	No	No	–	–
No	No	–	–	No	–	Yes	–	–	Yes	No	–	–	–	Yes
–	Yes	Yes	–	Yes	No	–	No	–	Yes	–	Yes	No	Yes	–
–	Yes	–	Yes	–	–	–	–	–	Yes	–	–	–	–	–
–	Yes	No	Yes	No	No	–	Yes	No	Yes	Yes	Yes	–	–	–
–	No	No	No	Yes	No	No	Yes	No	Yes	–	Yes	–	–	–

(Yes): Significant relationship, (No): No significant relationship, (–): Not mentioned.

prevalence. The countries were arranged alphabetically; under each country, the studies were arranged in ascending order from the earliest to the most recently published.

The mean prevalence of MIH in the ME was 15%. The reported frequencies ranged from 2.3% in Egypt to 40.7% in KSA.[21–23] Seven studies were hospital-based, reporting the frequency rather than the prevalence of MIH.[21,22,24–28] The remaining studies were population-representative and multischool-based,[8–11,23,29–43] with the exception of two studies conducted in a single school setting[30,35] (Table 1).

All studies were conducted on a mixed dentition age group with the participants' ages ranging from 7 to 12 years. The single exception was a study that included participants as young as 5 years old.[27] The sample size, description of the study subjects, and settings differed. Twelve studies did not report the date of data collection.[8,10,24,29,34,36–41,43] The MIH diagnostic criteria used in these studies also varied. While 17 studies used the EAPD (2003) diagnostic criteria, 3 referred to other assessment tools such as the DDE index, mDDE index, and EDI. Six studies used the diagnostic criteria developed by Weerheijm et al., Mejare, Lygidakis et al., and Ghanim et al.,[21,22,24,31,33,36] whereas three developed their own assessment criteria for the diagnosis of MIH.[25,27,28] All studies used a single assessment tool, except for two that were conducted using a combination of diagnostic tools[21,24] (Table 1).

Quality assessment

Tables 2 and 3 summarize the constructive critical appraisal of the studies included in this review. The assessment tool was built in to evaluate the way the studies were conducted in relation to their design, the findings, and proper statistical management.[20] Among the MIH prevalence studies (Table 2), 15 were rated as being high quality, of which 5 received the highest score (total = 9).[9,11,31,32,41] The remaining 12 studies were rated as being moderate quality. The areas of shortcomings varied, with limitations in the description of study subjects and setting. A standard assessment tool was used in all studies except for one, wherein its use was unclear.[27]

Table 3 presents the critical appraisal tool used for studies evaluating associated factors/risk factors. Varying quality was reported in these studies. While two of them were high quality,[44,45] two were low quality,[25,26] and the remaining three were moderate quality.[8,36,40] Generally, all studies lacked proper matching between cases and controls in terms of sex distribution, socioeconomic status, and other factors. Three studies did not report the confounding factors that may have been encountered or mentioned how they were managed.[25,26,40] It was unclear whether the exposure period to the risk factors was meaningful in all of the studies included in this review.

MIH-associated factors/risk factors

MIH-associated factors/risk factors were discussed in seven studies.[8,25,26,36,44,45] All associated factors/risk factors studies had a case–control design and were observational in nature. The studies were conducted to investigate a wide range of exposures via parental interviews or questionnaires designed to determine the possible association of several exposures with the occurrence of MIH. Nevertheless, none of the studies investigated whether genetic factors were related to MIH, or were clinical trials or cohort-based investigations.

Prenatal- and postnatal-associated factors/risk factors (Table 4, Figures 2,3)

The association between illness during pregnancy and MIH was investigated in six studies, three of which found no significant association.[26,36,44] Postnatal-associated factors/risk factors varied considerably in their association with MIH . High fever was the only factor with a significant association with MIH in all studies except one.[40] Similarly, frequent antibiotic use was assessed in four studies[26,40,44,45]; all found a significant association, with one exception.[45]

Viral infections were investigated in four studies, and the results varied. While chicken pox and measles were significantly associated with MIH in two studies,[8,36] this was not the case in the other two studies.[26,45] Rubella was only evaluated in two studies; no significant association with MIH was reported.[8,36]

Sönmez et al.[36] found that otitis media, tonsillitis, and bronchitis were not significantly associated with MIH. By contrast, Ahmadi et al.[40] and Elzain et al.[33] reported that otitis media had a significant association with MIH. Ghanim et al.[45] and Allazam et al.[26] reported that tonsillitis was significantly associated with MIH. Additionally, Koruyucu et al.[8] and Kılınç et al.[25] found that bronchitis had a significant association with MIH. The results of pneumonia as an associated factor/risk factor varied among the four studies,[8,36,44,45] two of which failed to find an association.[8,44] Urinary tract infection (UTI) was assessed in five studies, and none reported any significant association with MIH.[8,26,36,40,45]

Asthma was also investigated as an associated factor/risk factor in all seven studies, two of which reported that it was not significantly associated with MIH.[36,44] Among the three studies that assessed the association of allergy with MIH,[26,40,44] only one study found a significant association.[40]

Hypocalcemia and maternal consumption of canned food were only assessed by one study each; Ghanim et al.[45] investigated the former while Elzein et al.[33] investigated the latter. Both studies found a significant association between the assessed factor and MIH. Medications taken during breastfeeding and jaundice were each evaluated in two studies, and revealed no significant association with MIH.[26,44,45]

Gastrointestinal tract (GIT) problems were investigated in four studies,[8,26,36,45] all of which reported significant associations with MIH, except one.[26] Renal disorders were evaluated in four studies,[8,26,40,44] two of which showed a significant association with MIH[8,40] (Table 2).

The meta-analysis showed a statistically significant increase in odds ratio (OR) and total overall effect of illness and an association with MIH (OR: 2.26 and 95% confidence interval [CI]: 1.91−2.68; $P < 0.001$). Pregnancy illness (OR: 2.19; $P = 0.0001$), asthma (OR: 3.55; $P = 0.002$), tonsillitis (OR: 2.23; $P = 0.01$), pneumonia (OR: 2.69; $P = 0.01$), UTI (OR: 1.62; $P = 0.005$), chickenpox or measles (OR: 2.37; $P = 0.01$), fever (OR: 2.00; $P < 0.001$), renal disorder (OR: 11.85; $P = 0.03$), and GIT (OR: 3.02; $P = 0.0004$) showed a statistically significant increase in OR and an association with MIH. Although child medication showed increased OR, the relationship was not statistically significant (OR: 3.03; $P = 0.115$). Other factors such as maternal stress during pregnancy, frequent exposure to ultrasonic scans, and maternal consumption of canned food were reported only once and thus not included in the meta-analyses. After the P value was adjusted for multiple comparisons using Benferroni correction, the significance level was set to $P = 0.0033$. Bronchitis, UTI, otitis media, rubella, and jaundice were still significant after the adjustment.

There was statistically significantly high heterogeneity between the included studies in the meta-analyses. After excluding the two studies with small numbers of MIH cases,[26,40] the heterogeneity (I^2) dropped to zero in four of the postnatal risk factors (pregnancy illness, rubella,

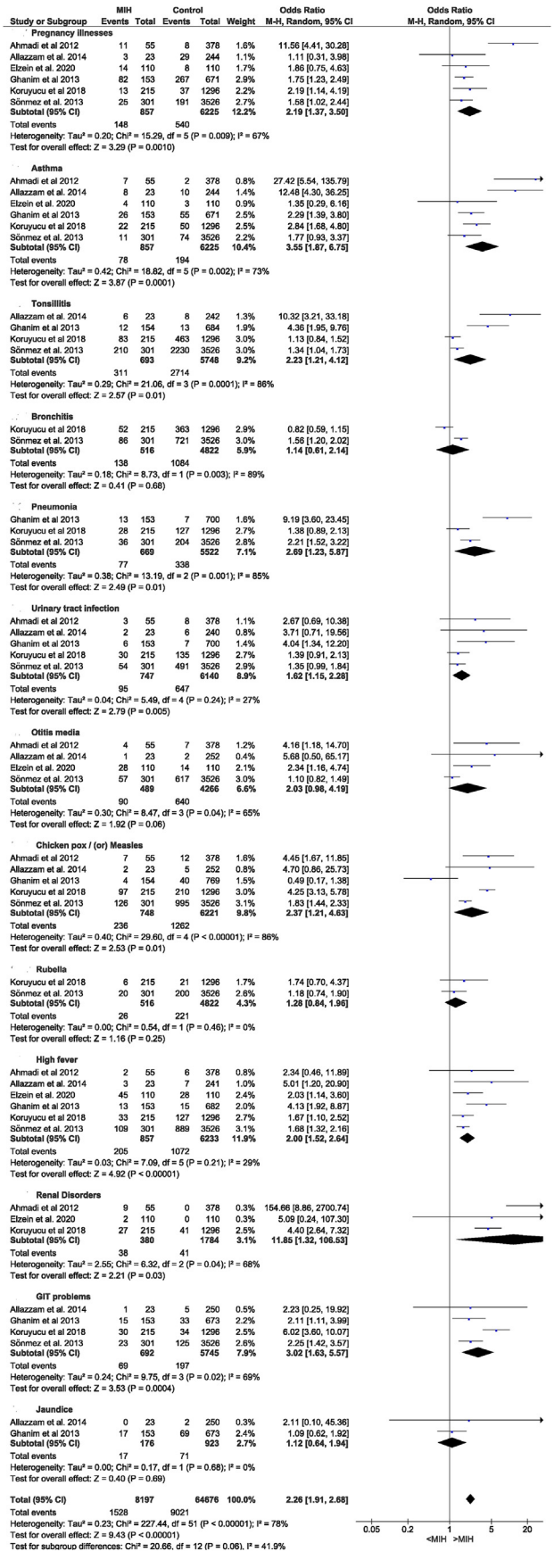

Figure 2: Meta-analysis for the association between maternal and childhood illnesses and MIH.

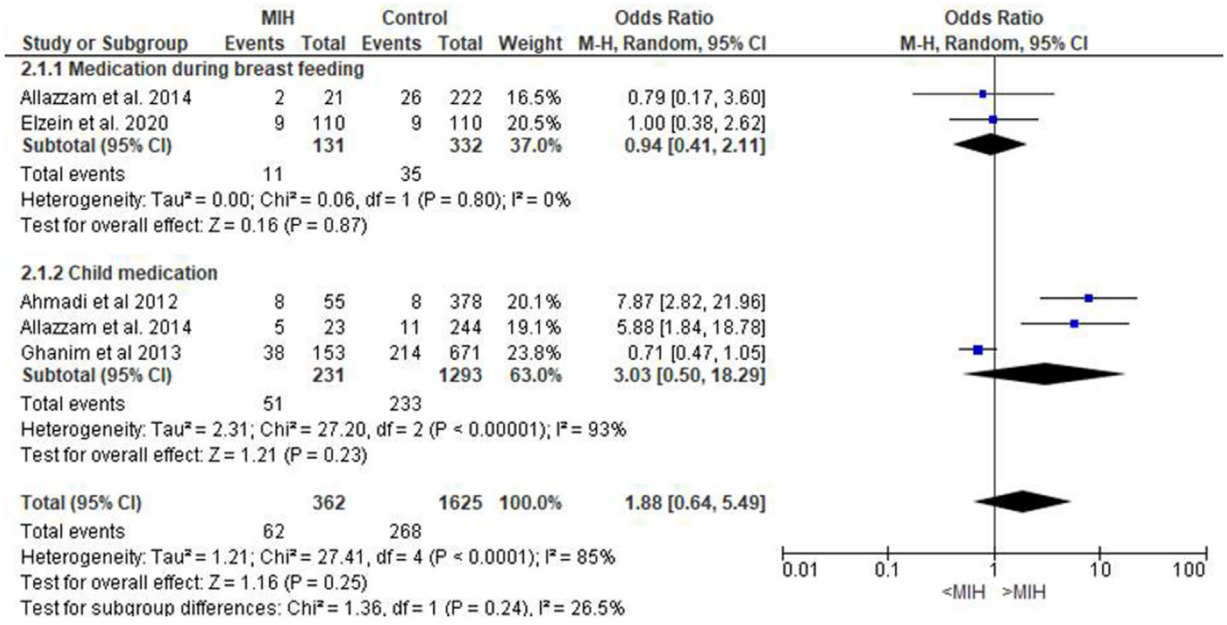

Figure 3: Meta-analysis for the association between medication exposure and MIH in children.

tonsillitis, and asthma) in the meta-analyses; however, the relationship remained significant ($P < 0.05$) (Supplementary Fig. 1).

Perinatal-associated factors/risk factors (Table 4, Figure 4)

Preterm labor was the only associated factor investigated in most of the risk factor studies, four of which reported a significant association with MIH.[8,25,36,40] The association between low birth weight and MIH varied between studies, while two investigations reported a significant relationship.[25,46] The mode of delivery had a significant association with MIH in only one study.[40] Lastly, the evidence for birth complication as an associated factor/risk factor for MIH varied among the studies; this association was assessed in five investigations, three of which[26,36,44] failed to report a significant association (Table 2).

The meta-analysis showed a significant total overall effect and increase OR of perinatal factors and MIH (OR: 2.40 and 95% CI: 1.55−3.34; $P < 0.001$). Mode of delivery (OR: 1.79; $P = 0.03$), premature labor (OR: 2.26; $P = 0.01$), and birth complication (OR: 2.24; $P = 0.03$) showed a statistically significant increase in OR and an association with MIH. Although incubator use and low birth weight showed increased OR for MIH, the relationship was not statistically significant (OR: 2.69, $P = 0.15$ and OR: 2.80, $P = 0.13$, respectively). Table 5 summarizes the meta-analysis outcomes.

Evaluation of small study effects

The funnel plots for studies assessing the relationship between illness and MIH (Supplementary Fig. 2) and those assessing the relationship between perinatal factors and MIH do not have the shape of the funnel (Supplementary Figs. 3 and 4). Egger's test for regression intercept gave $P = 0.415$ for maternal illness, $P = 0.243$ for child asthma, $P = 0.988$ for chickenpox/measles, $P = 0.076$ for high fever, $P = 0.489$ for renal disorders, $P = 0.879$ for GIT, $P = 0.067$ for otitis media, and $P = 0.115$ for child medication, indicating no evidence of publication bias for the above variables (Table 5).

Discussion

This systematic review discussed the prevalence and associated factors/risk factors of MIH in Middle Eastern countries. The prevalence rate ranged from 2.3% (in Egypt)[21,22] to 40.7% (in KSA).[23] Our hypothesis was rejected as we found that the overall mean MIH prevalence in the ME was 15%, similar to the global MIH prevalence rate (14.2%).[7]

Two studies conducted in Egypt by Saber et al.[21,22] using different diagnostic tools showed low MIH prevalence. Although fluoride levels in the Nile River range between 0.113 and 0.452 mg/L, considered as low according to the World Health Organization guidelines,[48] there is no association between the prevalence of MIH and fluoride levels in drinking water.[47] Another potential explanation could be the hospital-based study design. Abo ElSaoud and Mahfouz conducted a population-based study in the Suez Canal region and reported a higher prevalence (9.98%); the quality of this study was rated as moderate.[39] Therefore, we recommend further population-based studies in this particular case.

Al-Hammad et al.[23] reported the highest prevalence rate among all included studies (40.7%), although the study population was restricted to individuals aged 8−10 years. Quality-related factors such as the examiners' calibration, reliability, reproducibility tests, and cleaning of index teeth before examination were satisfied in this study, providing additional strength to its results.

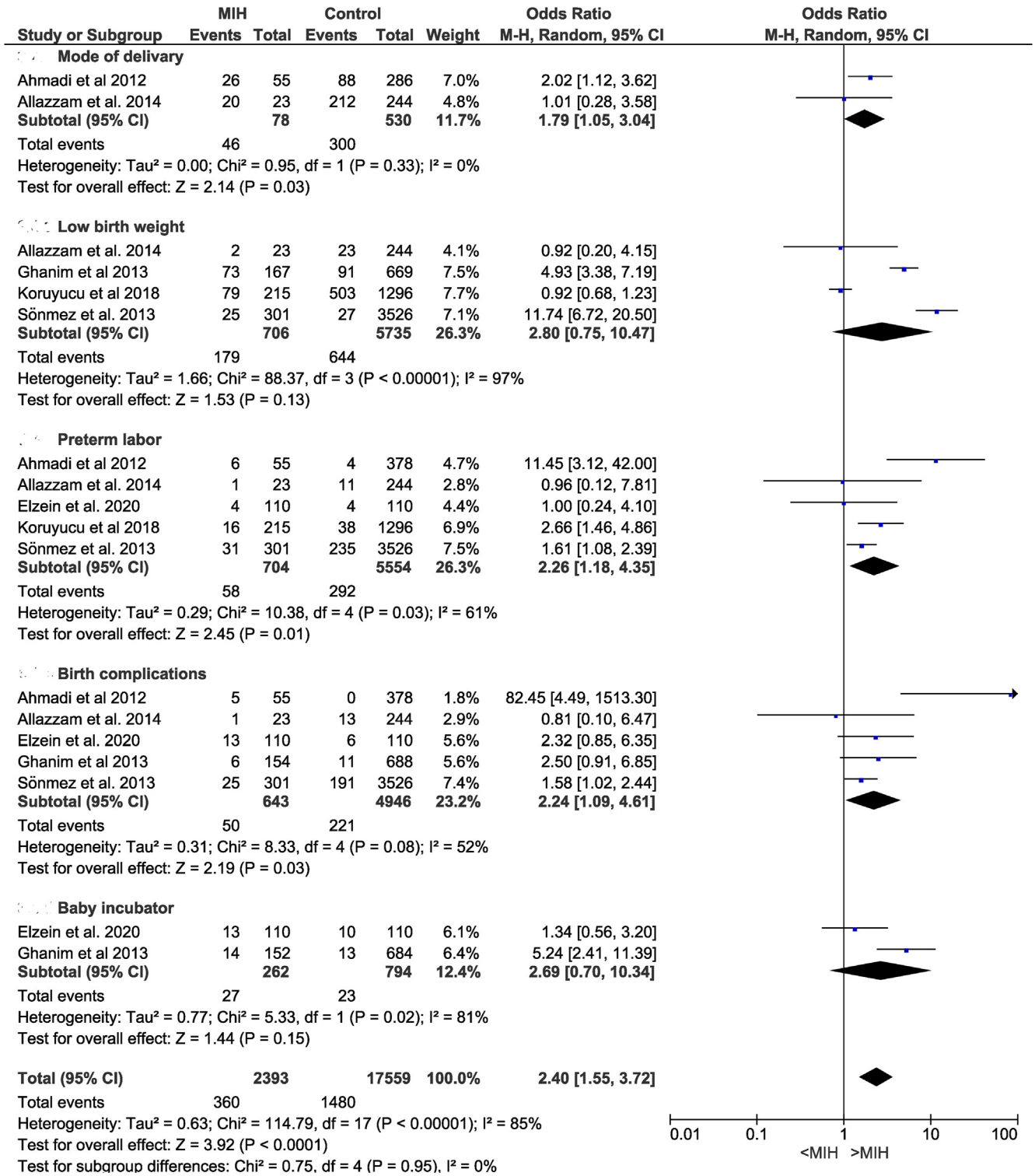

Figure 4: Meta-analysis for the association between perinatal factors and MIH in children.

The MIH diagnostic criteria enunciated by the EAPD in 2003 were used in most studies included herein[50]; however, some developed their own diagnostic tools. The criteria used in the different studies were nevertheless comparable, except for minor differences; therefore, this cannot explain the reported variations in prevalence rates. Teeth were dried in five studies at the time of examination,[9,25,31,32,41] against the EAPD recommendations. Five studies did not clearly state cleaning the teeth before examination.[21,27,38,42,43] Since examining teeth without cleaning food debris and plaque accumulation might mask enamel defects, this could ultimately lead to the underestimation of MIH, and the prevalence reported on these studies was low.

Table 5: Summary of meta-analysis outcome.

Subgroup Analysis	Cases	Controls	OR (95% CI)	Heterogeneity I2	Egger's Test[a]
Pregnancy illnesses	857	6225	2.19 (1.37, 3.50)	67%	P = 0.4154
Asthma	857	6225	3.55 (1.87, 6.75)	73%	P = 0.3476
Tonsillitis	693	5748	2.23 (1.21, 4.12)	86%	P = 0.0435
Bronchitis	516	4822	1.14 (0.61, 2.14)	89%	P < 0.0001
Pneumonia	669	5522	2.69 (1.23, 5.87)	85%	P = 0.3173
Urinary tract infection	747	6140	1.62 (1.15, 2.28)	27%	P = 0.0224
Otitis media	489	4266	2.03 (0.98, 4.19)	65%	P < 0.0001
Chicken pox/(or) Measles	748	6221	2.37 (1.21, 4.63)	86%	P = 0.9880
Rubella	516	4822	1.28 (0.84, 1.96)	0%	P < 0.0001
High fever	857	6233	2.00 (1.52, 2.64)	29%	P = 0.0760
Renal disorder	380	1784	11.85 (1.32, 106.53)	68%	P = 0.4894
GIT	692	5745	3.02 (1.63, 5.57)	69%	P = 0.8796
Jaundice	176	923	1.12 (0.64, 1.94)	0%	P < 0.0001
Medication during breast feeding	131	332	0.94 (0.41, 2.11)	0%	P < 0.0001
Child medication	231	1293	3.03 (0.50, 18.29)	93%	P = 0.1153

[a] Egger's test for a regression intercept gave a $P > 0.05$, indicating no evidence of publication bias.

Hypomineralization caused by MIH might be misdiagnosed as other enamel defects.[2,49,50] Proper study design of investigations evaluating the prevalence of MIH should consider this important point in the inclusion and exclusion criteria. In our review, almost half of the studies clearly stated the presence of other forms of enamel hypomineralization as an exclusion criterion. Six studies did not clearly state the exclusion criteria, while eight did not explicitly state the exclusion of children undergoing orthodontic treatment. This may have led to MIH overestimation.[11,27,31,32,34–36,40]

The optimal age for MIH assessment is 8–11 years. All permanent first molars and central incisors are present in the oral cavity by 8 years of age. Therefore, it is easier to observe the initial state of enamel defects and a shorter time is available for caries development. Beyond 11 years of age, the extent of MIH can be severe enough to require tooth extraction, which may negatively affect the examination and result in incomplete recording of MIH prevalence. We suggest that assessing MIH from 9 years of age would be more precise as the lateral incisors will be included in the examination process, as seen in the studies by Ghanim et al.[41] and Kılınç et al.[25] One study by Fnaish et al.[27] investigating MIH and other dental anomalies included children as young as 5 years old. Subsequently, MIH prevalence was underestimated.

Associated factors/risk factors for MIH were divided into three categories: prenatal, perinatal, and postnatal. In our study, all postnatal factors were directly related to the child, with two exceptions (medication intake during breastfeeding and maternal consumption of canned food). Breastfeeding was addressed in six studies,[8,26,36,40,44,45] three of which failed to significantly associate it with MIH.[26,36,44] Ghanim et al., and Ahmadi et al. found significant associations but in opposite directions.[40,45] According to Ghanim et al.,[46] MIH was more prevalent in children who were breastfed for less than 2 years, suggesting that extended breastfeeding offers a protective role against MIH. According to Ahmadi et al.,[40] MIH was more prevalent in children breastfed for longer periods, while the authors offered the transmission of the mother's malnourishment and vitamin D deficiency to the child as a potential explanation. These findings were in line with those of Alaluusua et al.[51]

With the exception of Ahmadi et al.,[40] high fever had a significant association with MIH in all included studies. This finding was in line with several previous studies.[52–54] MIH was also associated with more episodes of upper respiratory tract infections. Hypoventilation and low oxygen levels associated with upper respiratory tract infections can impair the matrix protein structure.[55–57] Corticosteroids therapy suppresses osteoclast formation and leads to improper bone formation. A similar effect may extend to ameloblasts, leading to improper enamel formation.[58,59] High fever and birth prematurity affect the enamel matrix and can degenerate enamel prisms, which in turn are associated with MIH development.[60,61] These findings are in line with those reported by Silve et al.,[14] who assessed the global etiology of MIH and reported a significant relationship between early childhood illness and MIH.

The consumption of canned food and drinks had a significant association with MIH during pregnancy and breastfeeding in a study by Elzain et al.[44] The authors theorized that this association was related to the harmful effect of canned food and the presence of bisphenol A (BPA), an endocrine-disrupting chemical widely utilized in plastics and epoxy resins.[62] BPA can cross the placental barrier or transfer through breast milk and adversely affect the child.[63,64]

The association between MIH and the antibiotic intake was investigated in four studies, three of which reported significant associations.[45] Antibiotic intake during amelogenesis may cause structural changes in ameloblasts, ultimately leading to enamel matrix reduction.[65]

Maternal stress was evaluated in a single study and found to be significantly associated with MIH,[45] but no proper definition of stress or explanation for the association was provided.

Only five studies fulfilled all the JBI criteria.[9,11,31,32,41] Approximately one-quarter of the studies were hospital-based, reporting the frequency rather than the

prevalence of MIH. Although the authors clarified in their aims that they exclusively evaluated the frequency of MIH, the titles of the studies were frequently misleading.

According to Elfrink et al.,[66] a random sample of at least 300 is preferred for prevalence studies. In our review, four studies did not report the sample size calculation or provided an explanation for it.[10,26,28,35] Two of these studies had a sample size of less than 300; therefore, the results may represent the frequency rather than the prevalence of MIH, despite their stated aim.[26,28]

This review had some limitations. The number of studies included was small, and most were cross-sectional, which provides a low level of evidence regarding associated factors/risk factors. Although different methods and diagnostic tools were used, most studies used EAPD 2003, and the remaining ones used a tool with only minor differences.

Further studies with large samples representative of the overall population and performed in conjunction with national oral health surveys are needed to better determine the prevalence and risk factors of MIH in the ME. Moreover, based on the quality and heterogeneity between studies shown in the meta-analysis, observational, longitudinal cohort studies that take advantage of medical records availability and memory recall are needed to determine possible etiological factors of MIH. None of the studies focused on potential genetic associations. Finally, the overall prevalence and risk factors for MIH in the ME remain unclear due to the lack of quality data. More countries in the ME should be encouraged to report epidemiological data on MIH to fill this gap in knowledge.

Conclusion

1. The mean MIH prevalence in the ME is 15%, which is comparable with the global MIH prevalence rate. Therefore, based on the limited data available at present, our original hypothesis that MIH prevalence in Middle Eastern countries may differ from that of other parts of the world was not validated.
2. Maternal and early childhood illness are associated with MIH.
3. Delivery complications and mode are associated with MIH.
4. Evidence for the association of MIH with genetics is lacking in the literature from ME countries; thus, further investigation is warranted.
5. Better-designed studies with large samples representative of the overall population and longitudinal cohorts are needed to assess the prevalence and risk factors for MIH in the ME and to overcome the heterogeneity found in this meta-analysis.
6. More countries in the ME should conduct national oral health surveys.

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Conflict of interest

The authors have no conflict of interest to declare.

Ethical approval

Due to the nature of the study, no ethical approval was needed because data from previous published studies in which informed consent was obtained by the primary investigators were retrieved and analyzed.

Author contributions

STB: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Writing – Original Draft, Writing - Review & Editing, Visualization and Project administration. HAA: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Writing – Original Draft, Writing - Review & Editing and Visualization. MTQ: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Writing – Original Draft, Writing - Review & Editing and Visualization. HJS: Conceptualization, Methodology, Validation, Formal analysis, Writing - Review & Editing, Visualization and Supervision. NMF: Conceptualization, Methodology, Validation, Formal analysis, Writing - Review & Editing, Visualization and Supervision. All authors critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jtumed.2022.12.011.

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