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Aetiology of Molar Incisor Hypomineralisation – A Systematic Review

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Abstract

Objectives: Molar incisor hypomineralisation (MIH) is a common developmental dental defect of permanent teeth, which can increase the risk of dental caries, infection, and hospitalisation. The aetiology is currently unclear although prenatal or early childhood health factors are suspected. The aim of this systematic review was to assess the strength of evidence linking aetiological factors with MIH.

Methods: A systematic search was conducted using the Medline and Embase electronic databases for studies investigating environmental aetiological factors of MIH. Two reviewers assessed the eligibility of studies. The level of evidence and bias was determined for all eligible studies according to Australian National Health and Medical Research Council guidelines for systematic reviews of aetiology and the Newcastle-Ottawa Scale.

Results: From a total of 2254 studies identified through electronic and hand searching, 28 were eligible for inclusion. Twenty-five of these investigated MIH and three investigated a related condition in primary teeth, Hypomineralised second primary molars (HSPM) and these were analysed separately.

A limited number of studies reported significant associations between MIH and pre- and perinatal factors such as maternal illness and medication use in pregnancy, prematurity and birth complications. Early childhood illness was implicated as an aetiological factor in MIH in several studies, in particular fever, asthma and pneumonia. The studies investigating HSPM revealed an association with maternal alcohol consumption, infantile fever and ethnicity. However, the validity of these findings is impaired by study design, lack of adjustment for confounders, lack of detail and consistency of exposures investigated and poor reporting.

Conclusions: Childhood illness is likely to be associated with MIH. Further prospective studies of the aetiology of MIH/HSPM are needed.

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Introduction

Molar incisor hypomineralisation (MIH) is characterised by demarcated, qualitative defects of enamel of systemic origin affecting one or more first permanent molars with or without incisor involvement (1). More recently, the term hypomineralised second primary molars (HSPM) has been used to describe similar lesions in the second primary molars (2). The affected enamel in both conditions is porous and weak, often leading to rapid breakdown upon eruption and exposure to masticatory forces (3).

The prevalence of MIH has been reported to range from 2.4% to 40.2% (4). From a limited number of studies, the prevalence of HSPM is reported to be 4.9 – 6.9% (2, 5). Both MIH and HSPM are associated with a high burden of disease, due to a range of unique clinical challenges that predispose to treatment failure (6). Given their high prevalence and burden of disease, the cost of these conditions to the general community is substantial.

Based on the distribution and structure of MIH lesions, disruption to ameloblast function during the late maturation stage of amelogenesis is thought to contribute to

qualitative defects that characterise these conditions (7). Since the criteria for MIH were developed, a number of observational studies have tried to determine the associated aetiological factors (8). Although pre-, perinatal or early life illnesses or events have been implicated, the systemic causes have not been identified. There have been two systematic reviews conducted on this topic, both of which reported a lack of evidence to enable any clear conclusion, with lack of standardised outcome measurement being a major limitation (9, 10). The use of alternative criteria such as the modified Developmental Defects of Enamel (mDDE) Index has led to inaccuracies in the determination of the prevalence of the condition because these criteria do not include severe presentations of MIH such as post-eruptive enamel breakdown, atypical restorations and atypical extractions (11). However as there have been a number of recent studies using MIH-specific criteria (8), creating some comparability between studies, an updated systematic review is warranted.

Therefore, the aim of this systematic review was to assess the strength of evidence linking aetiological factors for MIH and HSPM.

Methods

Eligibility criteria

Cohort and case-control studies performed on children that were reported in English were eligible for inclusion in this review. Based on NHMRC levels of evidence, study designs below level III evidence such as cross-sectional studies, case series, case reports, and studies without control groups were excluded (12).

All exposures were eligible for inclusion in the review.

The outcome measure of interest was binary: presence or absence of MIH and/or HSPM for each patient. To this end, studies using MIH/HSPM-specific criteria and any studies that reported on demarcated opacities on the FPM were included. Studies that combined demarcated and diffuse opacities as the outcome measure or that combined teeth other than the FPM, permanent incisors or SPM in the outcome measure were excluded. The severity of MIH/HSPM was not considered in this review.

Search strategy

An electronic search was conducted in February 2015 using the Medline (Ovid and PubMed) and Embase (Ovid) Databases. The search terms were developed with the assistance of an experienced librarian and were sufficiently broad to include studies reporting on MIH under a range of other names (Supplementary Appendix 1 and 2). In addition, hand searching of the reference lists of selected studies and two paediatric dental journals (International Journal of Paediatric Dentistry, European Archives of Paediatric Dentistry) was performed. Unpublished studies were sought by contacting experts in the field and by searching the Proquest Dissertations and Theses global database.

Potentially eligible studies were uploaded onto a reference management system (EndNote X4, The Thompson Corporation, New York, NY, USA) and duplicate records of the same study were then removed. The first stage of study selection was conducted by two reviewers (MS and NK), to eliminate obviously irrelevant studies based on title and abstract. The same reviewers then independently and in duplicate, performed the second stage of study selection after reading through the full reports (Figure 1).

Data extraction was performed by one reviewer (MS) and checked by a second reviewer (KS), with any disagreements resolved by consensus. Subsequently, a total of three amendments were made. Information about study methodology, participant characteristics and findings was entered into a pro-forma spreadsheet. Adjusted (aOR) and unadjusted odds ratios (uOR), *P*-values and 95% Confidence Intervals (CI) were obtained from the studies and if not provided, were calculated where possible using Stata 14 (StataCorp. 2015. *Stata Statistical Software: Release 14*. TX, USA). The Woolf method with a continuity correction delta=0.5 (also known as the Gart method) was applied to calculate these when a group had a cell count of zero (13). The studies on MIH and HSPM were analysed separately. Stratified outcomes, where applicable, were reported separately.

Corresponding authors of 18 of the 28 studies were contacted by email to resolve matters requiring clarification with replies received from 16. The authors of a further four studies could not be contacted.

A meta-analysis was not performed because too few studies had adjusted for confounding.

Level of evidence and risk of bias

The level of evidence was determined using Australian National Health and Medical Research Council (NHMRC) guidelines for reviews of aetiology (12). Risk of bias assessment was conducted in duplicate and independently by two reviewers (MS and NK) using a modified version of the Newcastle-Ottawa Scale (NOS) (Supplementary Appendix 3) (14). Discrepancies were resolved by consensus. The NOS is a star rating system that allocates a maximum of nine stars across three categories – participant selection (four stars), comparability (two stars) and measurement of exposure in case-control studies or outcome in cohort studies (three stars). Studies with fewer than six stars were considered to be at high risk of bias, however no studies were excluded.

Results

The initial search yielded a total of 2254 results, which was ultimately reduced to a total of 28 studies (Figure 1).

Level of evidence and risk of bias

Of the 28 studies, 25 reported on MIH and three on HSPM. Of the studies on MIH, 16 were cohort studies and nine were case-control (Table 1). Four cohort studies (15-18) and one case-control study (19) were prospective. One report (16) included two studies, a prospective cohort (Study 1) and a case-control (Study 2). All prospective studies were linked with existing medical cohorts that had been established for other studies. Overall, three case-control (20-22) and four cohort studies (15, 18, 23, 24) had a high risk of bias, as indicated by the NOS rating system in Table 1. Two of the three studies on HSPM were based on the same cohort, with data collected prospectively (25, 26). The third study was a retrospective cohort study and was based on the same cohort as one of the MIH studies (27, 28).

Measurement of exposures and outcomes

Most studies investigated a broad range of exposures with information about those exposures obtained mostly from parental report through interviews or questionnaires. Only a small number of studies used registries, databases or medical records (22, 24, 29-33). MIH-specific criteria were clearly cited by 13 studies as the tool for identifying participants affected by MIH (17, 23, 24, 27, 29, 30, 32-38). A further seven studies used similar criteria (demarcated opacities and post-eruptive breakdown) without clearly stating inclusion of atypical restorations and/or extractions (15, 16, 18, 21, 31, 39). Two studies added further restrictions to the criteria, with one reporting only on severe demarcated opacities and another including only patients with two or more teeth with demarcated opacities (19, 20). Two studies reported on demarcated opacities only (40, 41) and one study (22) did not explain the index used. All studies on HSPM modified the criteria to apply these to second primary molars with two studies (25, 26) including atypical caries as an additional measure of HSPM. Dental examinations were conducted either in dental clinics or school settings by one to seven examiners. Six studies did not report on the number of examiners nor on training or calibration (15, 16, 20, 22, 39).

Prenatal exposures

As indicated in Figure 2, there was little evidence of an association between the most frequently-investigated prenatal factors and MIH. The association between maternal smoking during pregnancy and MIH was investigated in six studies (16, 17, 19, 36, 38, 40), three of which were prospective (16, 17, 19). All six studies failed to find a significant association. For three of the four studies that performed multiple logistic regression, maternal smoking was not eligible for inclusion in the model due to high *P*-values (low significance) in the simple model (19, 36, 40). No studies examined dose-response effects of smoking. Ten studies assessed the association between maternal illness during pregnancy and MIH, one (19) of which was prospective. Although four studies found a crude (or unadjusted) association (27, 37-39), the only study to perform multiple logistic regression (37) found that once adjusted for confounding, the association was not significant (aOR 1.13, 95% CI 0.84 – 2.12, p=0.221). There was considerable variability in the terms used to describe maternal illness during pregnancy, with some specific to pregnancy-related disease and others reporting more broadly in terms of maternal illness (Table S2). Maternal medication use was investigated in seven studies, six of which were retrospective (19, 23, 27, 34,

38, 40, 41). All studies failed to find an association although multiple logistic regression was not performed in any of the studies. In addition, maternal stress was associated with higher odds of MIH in one study (aOR 3.24, 95% CI 1.33-7.88) but has not been investigated by other studies to enable any comparison (27).

Perinatal exposures

Similarly, there was little evidence of an association between MIH and perinatal factors such as prematurity, low birth weight, caesarean delivery and birth complications (Figure 3). Of the seven studies (19, 27, 36, 38-41) investigating the relationship between caesarean delivery and MIH, one (36), which conducted multiple logistic regression, found a significant positive association. Clarification of the definition of "birth mode" was sought from several authors as this variable was often reported ambiguously under term such as delivery type or normal delivery. Nine studies (19-21, 23, 27, 34, 36, 37, 39) evaluated the association between birth complications and MIH, with one (36) of the two that used a multiple logistic regression model finding higher odds of MIH after adjustment for confounding. Reporting of birth complications varied among studies, with some reporting on specific delivery complications (36) and others combining both complications during delivery and the neonatal period into one variable (27) (Table S5). The relationship between birth weight and MIH was assessed in 10 studies, with three reporting on the association with mean birth weight (20, 29, 40) and a further seven (19, 23, 27, 36-39) specifically evaluating low birth weight. Apart from Ghanim et al (27), who found higher odds of MIH with low birth weight after adjusting for confounding, there was little evidence of an association between MIH and low birth weight. In addition, Brogardh-Roth et al (29) found that per 100g increase in birth weight, the odds of MIH reduced by 0.955 fold (95% CI 0.924-0.987). Despite being investigated widely in 14 studies, only three studies reported an association between prematurity and MIH, with one showing a strongly positive link (29) and the other two (33, 38) reporting prematurity to reduce the risk of MIH. One other study (27) (not tabulated) reported no association with gestational age without any further details and without specifically reporting on premature birth.

Early childhood illness

Illness in early childhood, up to three or four years of age, was widely investigated (Figure 4). In addition to assessing the relationship between a number of specific conditions such as asthma and fever, several retrospective studies evaluated general health or illness in the first three or four years of life. Of these, six (20, 23, 24, 27, 36, 41) reported a crude association, which persisted in the one study that conducted multiple logistic regression (36). There was considerable variability in the definition of general health/illness (Table S8).

Several other studies found associations between specific illnesses and MIH. A number of retrospective studies found an association with higher odds of MIH and early childhood fever, including both studies that adjusted for confounding (27, 37) (Figure 4). In addition to fever, Ghanim et al (27) reported a significant association in cases where fever was combined with other symptoms such as chest and/or ear infections (aOR 3.27, 95% CI 1.09-9.82, p=0.03). Although three retrospective studies (23, 36, 41) found a positive association between MIH and asthma, the one prospective study and another retrospective study that adjusted for confounding did not find such an association (17, 37) (Figure 4). However, Kuhnisch et al. (17) did determine an association (aOR 2.48; 95% CI 1.35-4.56, p<0.05) between respiratory disease and a more severe variant of MIH where incisor involvement was also present. There was variability in how asthma was defined, with some reporting on asthma in the first, first three and first four years of childhood and others combining asthma with other conditions such as allergy (Table S10). In addition to Asthma, Pneumonia is another respiratory condition has been found to increase the odds of MIH in two studies that conducted multiple logistic regression (27, 37) (Table S11). In addition, several other illnesses including measles (37), chicken pox (37, 39), renal disease (24), gastrointestinal disease (37), bronchitis (24), tonsillitis (23, 27), adenoiditis (23) and otitis media (20) have been implicated in the aetiology of MIH, but lack support from other studies.

Early childhood medication (not tabulated)

Of the studies evaluating the association between antibiotic use and MIH, in two retrospective studies (27, 41) a significant association with antibiotic use in the first year of life was reported. Although Allazam et al (23) reported an association between antibiotic use any time in early childhood and MIH (uOR 5.91, 95% CI 1.85-

18.86), Pitiphat et al (36) found that this association did not remain significant when adjusted for confounding (uOR 2.5, 95% CI 1.2-5.2, aORs not provided). Both Laisi (31) (in a prospective study, uOR 2.06, 95% CI 1.01-4.17) and Whatling and Fearne (39) (retrospective study, uOR 5.22, 95% CI 1.11-5.89) reported a strong association with the use of amoxicillin. However, Arrow (40) did not find such an association when the data was stratified according to consumption at 0-1 years and 1-3 years. Souza et al (38) reported a significant association when amoxicillin was combined with other antibiotics, albeit only in rural locations (uOR 1.92, 95% CI 1.02-3.62). They did not assess the association with amoxicillin alone. Ghanim et al (27) reported that the type of antibiotic did not demonstrate an association although there was no further information provided in this regard.

In a study using a Danish medication prescription database, Wogelius et al (33) found that although anti-asthma medication was not associated with MIH (uOR 0.82, 95% CI 0.39-1.65), there may be an association with a subset of cases involving post-eruptive breakdown (uOR 2.42, 95% CI 0.70-7.43). Using drug histories, Loli et al (22) reported an association with aerosol therapy for respiratory diseases (uOR 3.19 95% CI 1.72 – 5.9). In neither study was it possible to control for the illness itself, implying that asthma medication may actually be a proxy measure of disease. In the only other study to assess the relationship with asthma medication Arrow failed to find an association (uOR 1.17, 95% CI 0.51-2.26) (40).

Breastfeeding (not tabulated)

In 1996, Finnish researchers suggested an association between breastfeeding and MIH as part of a study investigating the adverse effects of dioxins (16). The same group subsequently published studies showing that an association no longer existed, attributing this to reduction in the levels of dioxin pollution (18). All but one of the more recent studies, including both prospective and retrospective studies, have also failed to find any significant association. The only exception is a Swedish case-control study but as multiple regression was not conducted the association may be due to confounding by other factors (19).

Hypomineralised second primary molars

As only three reports (25, 26, 28) (two of which were from the same study) investigating the aetiology of HSPM were available, there is considerably less evidence regarding its aetiology than for MIH (Table 1). However, because both studies have relatively low risk of bias and adjust for confounding and because one is prospective in nature (25, 26), the findings are relatively robust. The Dutch studies conducted by Elfrink et al indicated that while maternal antibiotic use during pregnancy is unlikely to be associated with HSPM, maternal alcohol intake may be (25, 26). In addition, Dutch ethnicity and fever in the first year of life were associated with HSPM. Ghanim et al reported possible associations with a large number of factors, with perinatal factors and neonatal illness being most common, followed by prenatal factors (28).

Discussion

Observational studies provide the only means of assessing the association between suspected aetiological factors and MIH in the population, because randomisation is impossible. However, the absence of randomisation means that confounders may mask the true relationship between a factor and MIH. In the present review, three different tools for assessing risk of bias of individual studies were trialled, including the NHMRC quality criteria, the Scottish Intercollegiate Guidelines Network critical appraisal checklist and NOS (14, 42, 43). Consistent with the findings of Deekes et al, the latter was found to be the most appropriate for the subject (44). Modification of the ratings for some items was required to suit the nature of the research question. Although demonstration that the outcome was not present at the start of the study is an item for the NOS in cohort studies, this is not appropriate in studies of MIH where the presence or absence of the disease can only be confirmed on eruption of the teeth, many years after the exposure. As such, this category was removed. In addition, the rating system for ascertainment of exposure was changed to two stars for secure records and one star for ascertainment through questionnaire, interview (self-report) or medical record. Similarly, the rating system for ascertainment of exposure was changed for case-control studies so that a star was allocated not just for exposures from secure records but also questionnaires, interviews and medical records. Finally, because this review examined the role of many aetiological factors, it was not possible to identify a main confounder and a secondary confounder for rating of comparability. Accordingly, the scoring was changed to provide two stars for

controlling for confounding using multiple logistic regression and one star for adjusting for at least one potential confounder, including matching cases and controls for factors such as age and gender. The NOS bias score moves away from providing a single bias score for each study, but instead should be considered in the context of each of the criteria. This minimises the chance that a study with a major flaw in one aspect could be judged to be low bias because it performs well in all other aspects of the assessment criteria. Despite clear guidelines for reporting of observational studies, many studies, including several recently published, were let down by poor reporting, in particular regarding non-participation and loss to follow-up, blinding and power calculations (45).

Overall, there are three major problems with the studies of MIH. The first is the lack of adjustment for confounding. Since randomisation is impossible, the ability of confounders to exaggerate or diminish the importance of some factors is a recognised flaw of observational studies. This is generally overcome through various statistical methods, most commonly multiple regression, which are almost mandatory in such studies. However, a large number of studies in this review made no attempt to adjust for potential confounders. Even where some form of adjusting was performed, this was reported poorly with confounders often not listed nor explained, and unadjusted and adjusted *P*-values not provided. Ideally, selection of confounders should be based on existing evidence and the plausibility of a putative association with both the exposure of interest and the outcome, in this case, MIH.

The retrospective nature of most studies is another major problem with studies of MIH. As most are case-control or retrospective cohort studies, the level of evidence for the findings in this review is low. As discussed previously by Alaluusua (2010), retrospective studies rely on parent recall, often many years after the event (9). There is strong evidence to indicate that mothers accurately recall perinatal factors such as gestational age, birth weight and mode of delivery, even many years after the events (46). However, some aspects of maternal health during pregnancy, recall of breastfeeding duration, child illness and medication use is less likely to be reliable (47, 48). A number of studies cited the difficulty in obtaining medical records and even these, unless kept in a standardised way, may lack the consistency and detail needed. There are many barriers to conducting prospective studies, including cost,

loss to follow-up, and non-participation. As such, using existing medical cohorts provides a practical means of conducting prospective studies. Nevertheless, the compatibility of such cohorts, and specifically their inclusion and exclusion criteria, with a study of MIH needs to be considered to ensure that all or at least most relevant exposures are included. These problems could be overcome with closer collaboration between oral and medical research and early engagement in both the planning and implementation of birth cohorts.

Finally, the lack of detail and consistency with the exposures investigated limits comparisons between studies. Further, it is likely that the study participants, often the mothers completing questionnaires regarding exposure to various environmental factors, were also given similarly basic details about the exposures and so the accuracy of their responses are questionable. This may be partly due to the large number of exposures assessed in many studies, however in order to ensure the accuracy of the data collected, clear definitions of exposures investigated are recommended.

In addition to the limitations of the studies included in this review, the exclusion of studies written in languages other than English may have resulted in important findings being omitted. Despite the limitations of the present review, there appears to be considerable evidence for an association between early childhood illness and MIH. Further prospective studies are needed to investigate the role of medications, and whether the relationship changes with the type, number and severity of illnesses. A number of biological mechanisms for the association have been suggested, and are supported by laboratory and animal studies. Ameloblast function is highly sensitive to changes in their surrounding environment, including changes induced by systemic illness (49). The mechanism for how such factors lead to the specific changes in ameloblasts that then result in MIH is still unclear although several possibilities have been suggested. Recent *in vitro* rat studies show that pre-natal exposure to endocrine disrupting chemicals (EDCs) can result in MIH-like lesions (50). The authors suggest that EDCs may increase expression of enamel proteins, reduce expression of the kallikrein 4 gene and lead to the accumulation of albumin, which hampers crystal growth. However, there are no observational studies investigating this link. Altered expression of genes important in enamel formation has also been suggested as the link

between fever and enamel defects (51). Alternatively, the aetiology may relate to a metabolic disturbance such as described in rat studies showing that acidic conditions (a result of both localised inflammation and hypoxia) can prevent crystal growth due to the build-up of hydrogen ions (52). Another possible mechanism may be morphological alterations in ameloblasts that then lead to changes in enamel prism structure, although the lesions in MIH are more complex (49). Further laboratory studies regarding the protein composition, structure and ultrastructure of hypomineralised enamel will compliment observational studies in establishing a clear pathogenesis for MIH. Further to this, genetic predisposition and epigenetic influences are also likely to play a part in the putative multifactorial aetiology of the condition, and further investigations of these factors are also needed.

Conclusion

Prenatal and perinatal factors are infrequently associated with MIH. However, despite a lack of prospective studies, early childhood illness (in particular fever) appear to be associated with MIH. Further prospective studies that adjust for confounding based on biological principles, as well as genetic and epigenetic studies are needed because the aetiology is likely to be multifactorial.

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Figure legends

Figure 1: PRISMA Flow Chart

Figure 2: Forest plot of the association between prenatal factors and MIH. A meta-analysis was not conducted as too few studies adjusted for confounding. *Adjusted odds ratio. N/A= odds ratio not provided and could not be calculated

Figure 3: Forest plot of the association between perinatal factors and MIH. A meta-analysis was not conducted as too few studies adjusted for confounding. *Adjusted odds ratio. N/A= odds ratio not provided and could not be calculated

Figure 4: Forest plot of the association between childhood factors and MIH. A meta-analysis was not conducted as too few studies adjusted for confounding. *Adjusted odds ratio. N/A= odds ratio not provided and could not be calculated

Table 1: Level of evidence and risk of bias of included studies

Figure 1: PRISMA Flow Chart

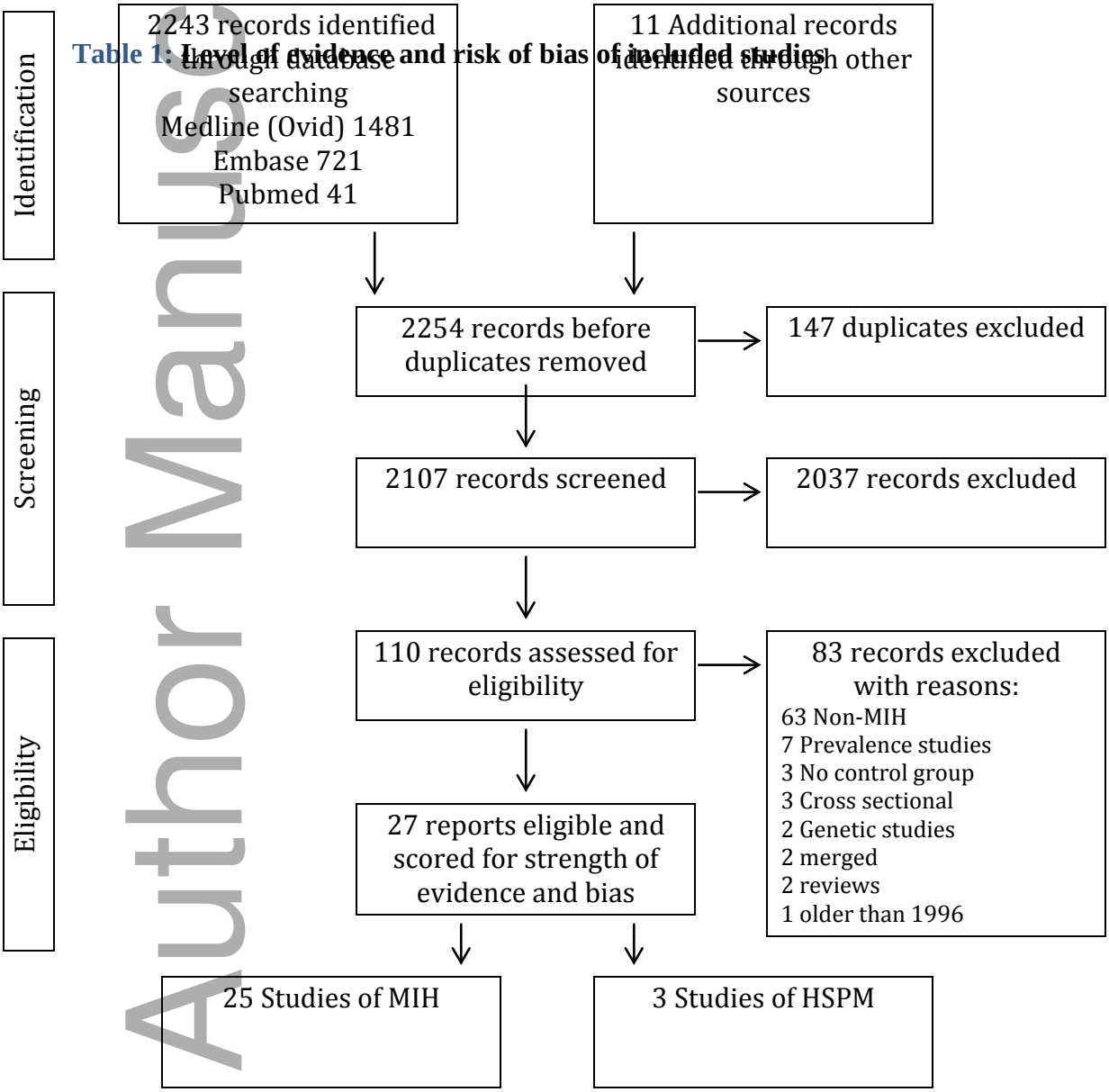
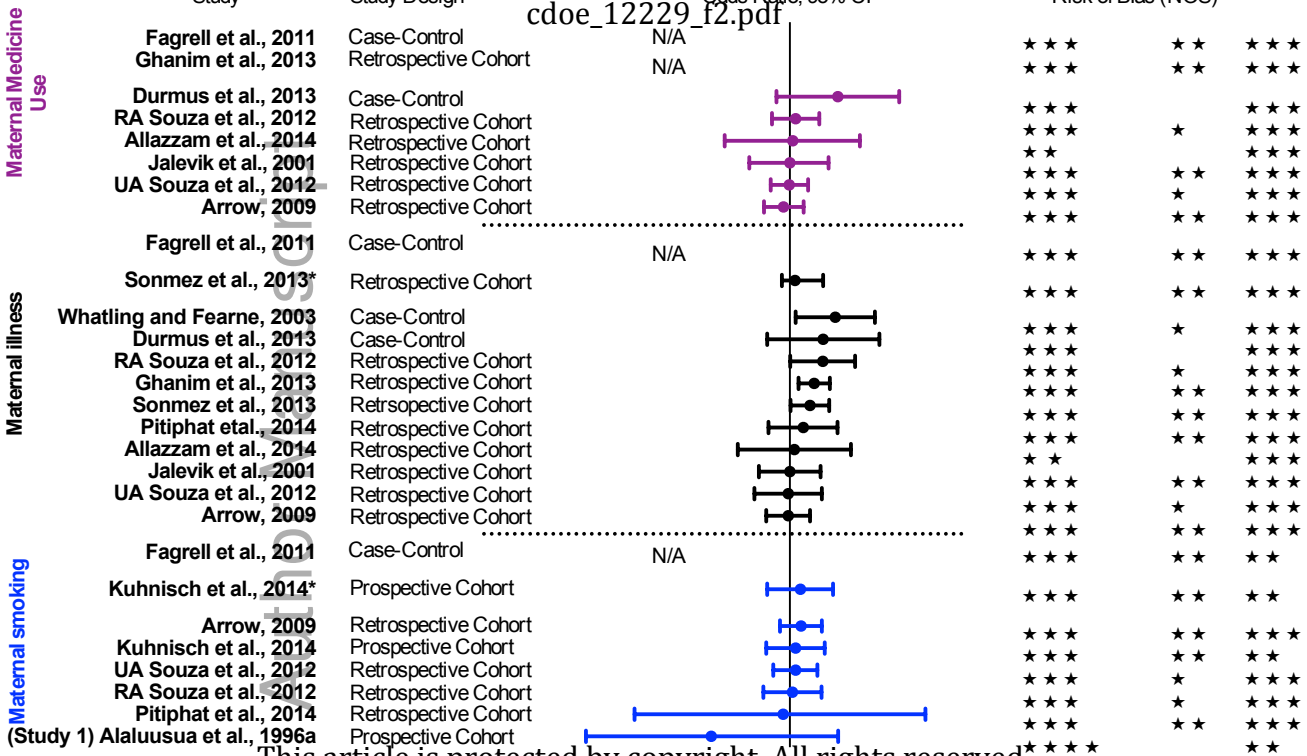


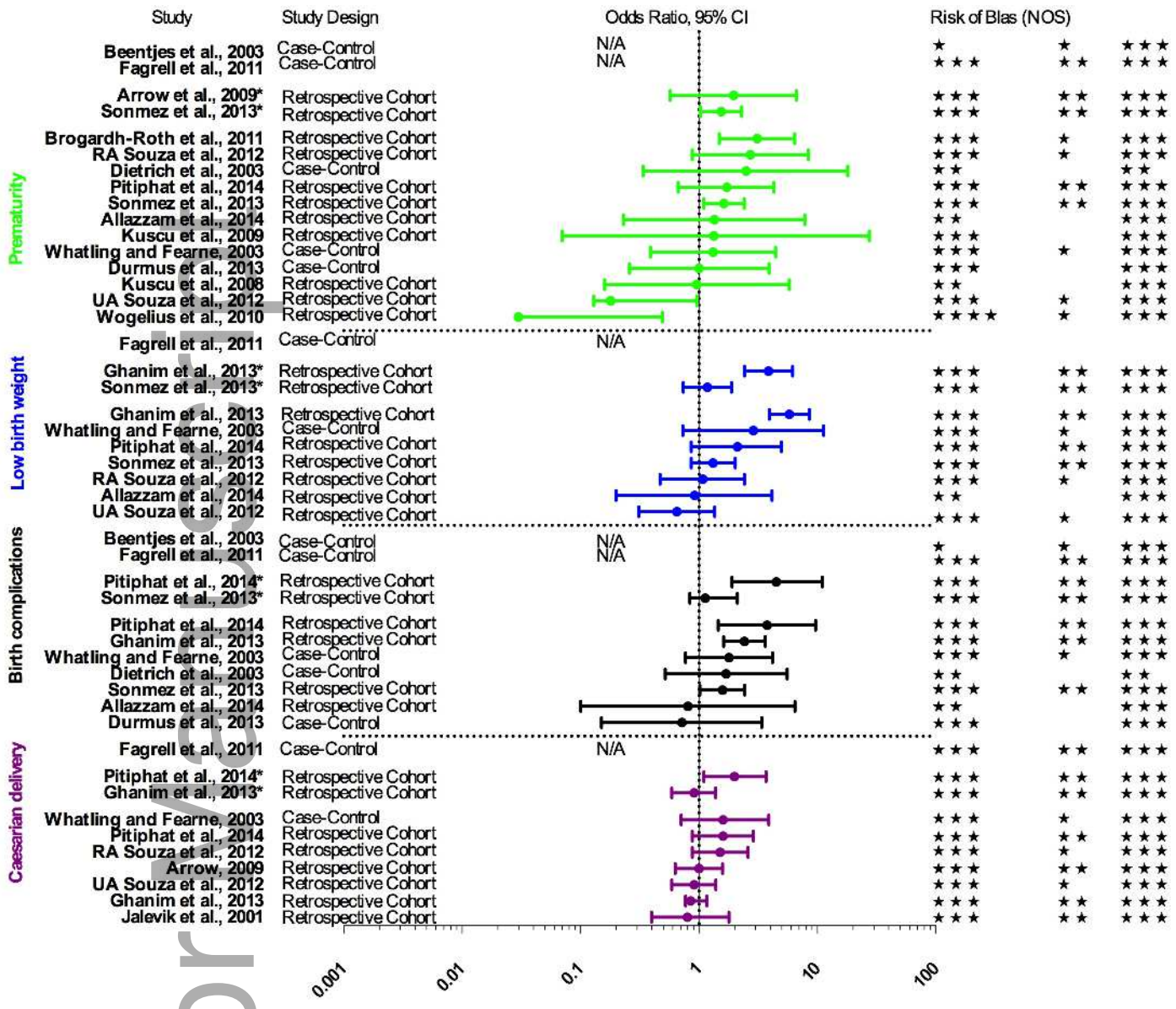
Table 1: Level of evidence and risk of bias of included studies

Reference	Country	Number of participants	Newcastle- Ottawa Scale		
			Selection	Comparability	Outcome
MIH - Prospective Cohort Studies					

Study 1, Alaluusua et al., 1996a (16)	Finland	102	★★★★		★★
Alaluusua et al., 1996b (15)	Finland	97	★★★		★★
Kuhnisch et al, 2014 (17)	Germany	692	★★★	★★	★★
Laisi et al., 2008 (18)	Finland	167	★★★		★★
MIH - Retrospective cohort studies					
Allazzam et al., 2014 (23)	Saudi Arabia	267	★★		★★★
Arrow, 2009 (40)	Australia	550	★★★	★★	★★★
Brogardh-Roth et al., 2011 (29)	Sweden	164	★★★	★	★★★
Ghanim et al., 2013 (27)	Iraq	832	★★★	★★	★★★
Jalevik et al., 2001 (41)	Sweden	516	★★★	★★	★★★
Kuscu et al., 2009 (30)	Turkey	153	★★★		★★★
Kuscu et al., 2008 (24)	Turkey	147	★★		★★★
Laisi et al., 2009 (31)	Finland	141	★★★		★★★
Pitiphat et al., 2014 (36)	Thailand	282	★★★	★★	★★★
Sonmez et al., 2013 (37)	Turkey	3827	★★★	★★	★★★
Souza et al., 2012 (38)	Brazil	903	★★★	★	★★★

Wogelius et al., 2010 (33)	Denmark	647	★★★★	★	★★★
MIH – Case-Control Studies					
Study 2, Alaluusua et al., 1996a (16)	Finland	40 cases 40 controls	★★★	★	★★★
Beentjes et al., 2002 (20)	Holland	24 cases 21 controls	★	★	★★★
Dietrich et al., 2003 (21)	Germany	31 cases 31 controls	★★		★★
Durmus et al., 2013 (34)	Turkey	54 cases 53 controls	★★★		★★★
Fagrell et al., 2011 (19)	Sweden	224 cases 253 controls	★★★	★★	★★★
Loli et al., 2015 (22)	Italy	91 cases 91 controls	★	★	★★★
Lygidakis et al., 2008 (32)	Greece	360 cases 360 controls	★★★	★	★★★
Muratbegovic et al., 2007 (35)	Bosnia and Herzegovina	34 cases 41 controls	★★★		★★★
Whatling and Fearne, 2008 (39)	UK	57 cases 52 controls	★★★	★	★★★
HSPM – Prospective cohort studies					
Elfrink et al., 2013 (25)	Holland	6690	★★★★	★★	★★★
Elfrink et al., 2014 (26)	Holland	6690	★★★	★★	★★★
HSPM - Retrospective cohort studies					
Ghanim et al., 2012 (28)	Iraq	691	★★★	★★	★★★





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