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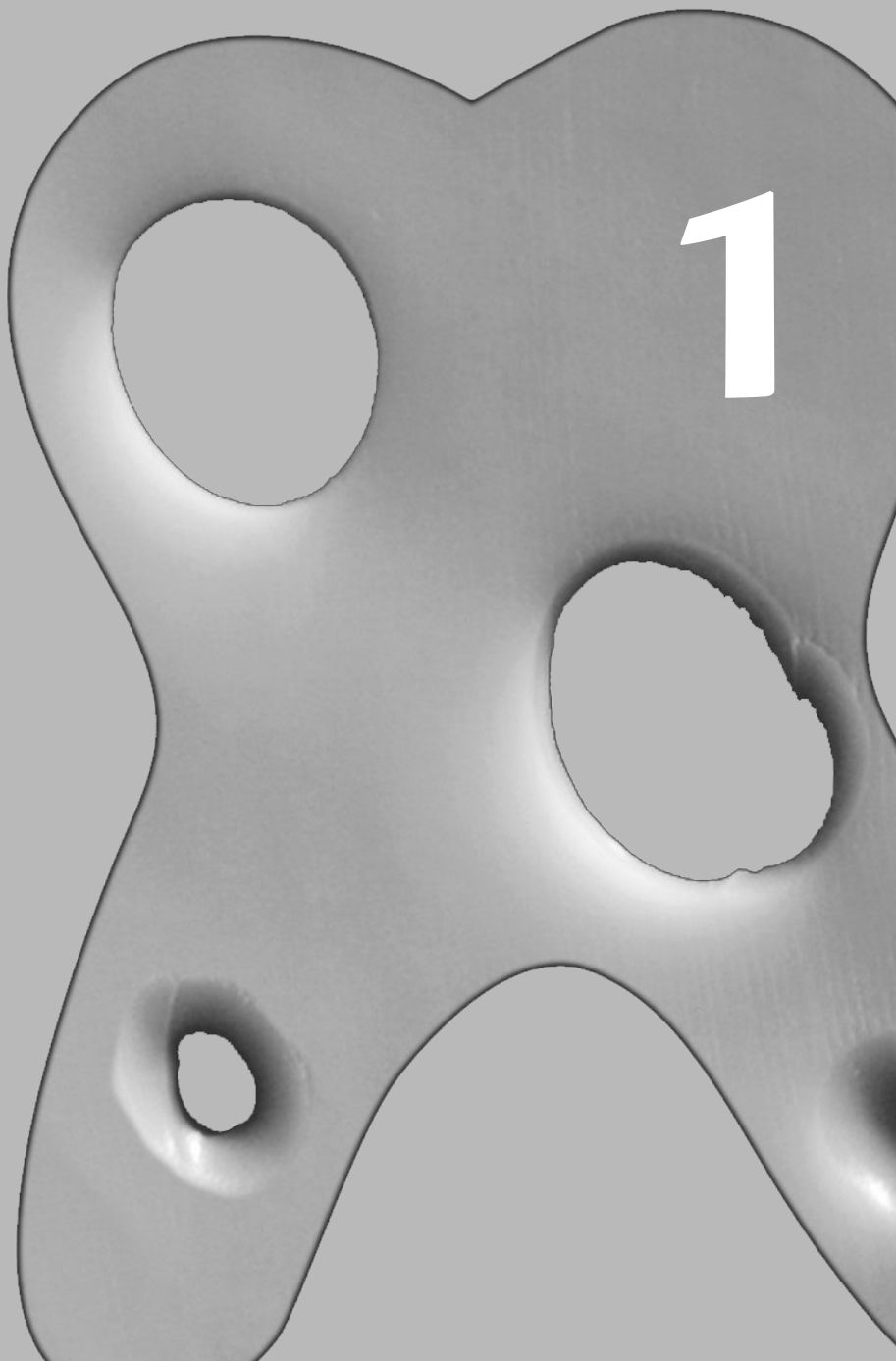
Introduction and research questions



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INTRODUCTION

Diseases of the dentition, such as dental caries and enamel malformations, are among the most common chronic illnesses worldwide (1, 2). Caries generally cause oral discomfort and pain and influence a child's ability to eat, do schoolwork and sleep (2). The prevalence of caries in children in the Netherlands, as in other developed countries, has declined since 1975 (4). Although it had stabilised, the prevalence of caries is now slightly increasing (5). Paediatric dentists warned about the increasing number of children who need extensive dental treatment, which received renewed attention, even in the national newspapers, in 2011. Because the incidence of caries has been declining, the emphasis of research has been more on predicting caries (6) and other dental problems, such as developmental enamel defects. Developmental enamel defects are not uncommon, both in the primary and permanent dentitions, and can be divided into hypomineralisation and hypoplasia (7, 8). Enamel hypoplasia is a quantitative defect of the enamel, and enamel hypomineralisation is a qualitative defect of the enamel identified visually as an alteration in the translucency of the enamel, with a clear border, variable in degree, and a white, yellow or brown colour. It has also been termed a demarcated opacity (7, 9). The first permanent molars with hypomineralisations are often associated with affected permanent upper incisors and, more rarely, lower incisors (10). Therefore, the name Molar Incisor Hypomineralisation (MIH) is currently used (10-12). In the primary dentition, hypomineralisations are also found in the second primary molars, a process known as Deciduous Molar Hypomineralisation (DMH).

History

Among the earliest authors publishing on hypomineralisations in the permanent dentition were Koch et al. (13) who reported its prevalence in Swedish children in various birth cohorts. This observation led to work by many researchers, who between them collectively defined the name, definition and scoring criteria of hypomineralisations (9, 10).

Many different names have been used for Molar Incisor Hypomineralisation (MIH): hypomineralised first permanent molars, non-fluoride hypomineralisation, idiopathic enamel hypomineralisation, non-endemic mottling of enamel and cheese molars (10).

Experts of the European Academy of Paediatric Dentistry (EAPD) developed diagnostic criteria for MIH in 2003, and these criteria were updated in 2009 (9, 14). These criteria (see Table 1.1) should be interpreted in the same way in all future research on MIH and DMH to improve the comparability of results. In this thesis, we used the MIH criteria and recommendations for DMH but made some modifications: the definition of DMH only involves the second primary molar, and atypical caries were added because many cavities are not restored in the primary dentition.

Table 1.1: Criteria for the diagnosis of MIH and DMH

Mild: • Opacity: A defect that changes the translucency of the enamel, variable in degree. The defective enamel is of normal thickness with a smooth surface and can be white, yellow or brown in colour. The demarcated opacity is not caused by caries, ingestion of excess fluoride during tooth development or amelogenesis imperfecta, etc. *Severe:* • Posteruptive enamel loss: A defect that indicates surface enamel loss after the eruption of the tooth, e.g., hypomineralisation-related attrition. Enamel loss due to erosion was excluded, and/or • Atypical caries: The size and form of the caries lesion do not match the present caries distribution in the child's mouth, and/or • Atypical restoration: The size and form of the restoration do not match the present caries distribution in the child's mouth, and/or • Atypical extraction: The absence of a molar that does not fit with the dental development and caries pattern of the child.

The association between DMH and MIH is only speculated on in the literature (9). We performed a large prospective cohort study to evaluate this association.

Prevalence

In many countries, researchers have established the prevalence of MIH in healthy children. The reported prevalence varies between 2.4% and 40.2% (14). A comparison of the various studies proved difficult due to differences in patient selection (at random or not, age of the children), different scoring criteria ((modified) Developmental Defects of Enamel ((m)DDE) index, EAPD criteria or other criteria) and differences in the examination circumstances (clinically or by photographs, in a dental chair or in a classroom, etc.) (3, 15, 16).

In the Netherlands, the most recently reported prevalence of MIH is 14.3% (17). The prevalence differs from country to country and changes per birth-year. In the study of Koch et al. (13), the prevalence varied between the different birth-years from 6.3% to 15.4%, with a high prevalence peak in children born in 1970. The prevalence of MIH in the Netherlands also differed between the various cohorts in the TJZ (Tandheelkundige verzorging Jeugdige Ziekenfondsverzekerden) study: 9.7% in the study from 1999 and 14.3% in the study from 2003 (17, 18). Data on the prevalence of DMH were lacking. In the recent TJZ studies, second primary molars were also investigated for DMH, and we established the prevalence of DMH in the Netherlands.

Enamel hypomineralisation

Enamel is the hardest tissue in the human body, but its formation can be disturbed rather easily (1). Disturbances in enamel formation leave a permanent mark in the tooth. These disturbances can be inherited (e.g., amelogenesis imperfecta), acquired (e.g., induced by chemicals such as in fluorosis) or idiopathic (e.g., DMH and MIH). DMH and MIH are probably caused by a disturbance in the initial calcification and/or during the maturation phase of the enamel, causing demarcated opacities (10, 19, 20). In MIH molars, these opacities contain more carbon and less calcium and

phosphate (21, 22). Although the mineral composition of the enamel has not yet been investigated in DMH, the same results can be expected as for MIH. The vulnerability of teeth with DMH or MIH can be explained by the lower mineral content or other mineral composition of the enamel. The colour of the demarcated opacity in MIH molars (white, yellow or brown) was reported to be associated with the mineral density of the enamel (23). Opacities in MIH molars contained 3- to 21-fold more protein than normal enamel (20, 23), and brown opacities in particular contained more protein (20). The mineral content of the enamel is reflected in the mechanical properties of the enamel (20, 24). In MIH molars, the enamel density in the hypomineralised areas is lower than in sound areas (19). Little is known about the mineral content and density in DMH molars. Studies used the micro-computer tomography (microCT) technique to determine mineral content in MIH molars. MicroCT, a miniaturised version of the whole body CT scan, is a non-destructive x-ray absorption microscopic technique for the 3D visualisation of teeth. It can also perform quantitative measurements of the mineral content (19). In the permanent dentition, MIH molars showed a 19-20% reduction of mineral concentration in the affected enamel, the hypomineralised enamel had a mineral concentration gradient opposite that of normal enamel and the hypomineralised areas were distributed randomly throughout the MIH molars, with only the cervical region being less affected.
No studies on the mineral concentration in hypomineralised areas of DMH molars have been performed yet. Therefore, we performed a microCT study to compare DMH molars with sound second primary molars.

Relationship with caries

Caries can affect each tooth and surface, with a preference for pits, fissures and proximal surfaces (6, 25). Caries at other, less vulnerable, sites could be a sign of severe caries (6). Caries patterns can also be associated with aetiology (26). In early childhood caries (ECC), when the causative factor is a sweet(ened) liquid diet, especially at night, the primary teeth are affected following the eruption sequence, and the mandibular incisors are affected last (27). Not all caries lesions, however, follow the eruption sequence. Many investigators have tried to find a pattern for predicting caries (6, 28), which becomes more important when caries prevalence in the population is declining (6).
The second primary molars were reported to be more often affected by caries than the first primary molars (6, 29-31). The second primary molars erupt 10-12 months after the first primary molars at the age of 24-30 months (32, 33), leading to the assumption that the first primary molars have a greater prevalence of caries due to a longer presence in the oral cavity.
Both MIH and hypoplasia in the primary dentition influence caries prevalence in children (10, 34, 35). DMH could be an explanation for the differences in caries prevalence between the first and second primary molars (34, 35). Important in interpreting this hypothesis is that DMH had not been investigated as a putative caries-influencing factor previously, like we did now.

Determinants and associated factors

Tooth development, although genetically controlled, is reported to be sensitive to disturbances from the environment (3). Because enamel is not remodelled like bone, disturbances acquired during its development leave a permanent record in the tooth (36).

Dental development starts with the formation of the dental lamina from the ectodermal epithelium. Tooth development follows the bud, cap and bell stages, generating the shape of the tooth. The cells from the dental lamina differentiate into, among others, ameloblasts and dentinoblasts (37). Dentin and enamel formation occur simultaneously along a line that will develop into the dentino-enamel junction (1) (see Figure 1.1 and 1.2). Amelogenesis is a slow developmental process that can be divided into the following steps: secretory stage, transitional stage and maturation stage (3).

At the secretory stage, the enamel matrix is formed in large amounts. The ameloblasts secrete enamel proteins, and enamel crystals grow in length, resulting in a thickening of the enamel layer (1, 3).

At a certain point, the secretory ameloblasts undergo a transition (transitional stage), and the maturation of the enamel will start. During the maturation stage, the enamel layer hardens. The crystals stop their growth in length and start to grow in width and thickness, which results in a mineralised tissue with more than 95% mineral content (1, 3). After the maturation stage, the ameloblasts degenerate with the other layers of the enamel-epithelium during tooth eruption (37).

The development of the second primary molars occurs somewhat earlier than the development of the first permanent molars and permanent incisors, but the periods of their development overlap (32, 33) and the maturation of the permanent molar is slower (38). If a risk factor occurs during this overlapping period, a hypomineralisation might occur in the primary and permanent dentition (39). Because the second primary molars erupt 4 years earlier in life than the first permanent molars, DMH might be a clinically useful predictor for MIH.

A number of recent studies on MIH focused on the possible determinants (3, 15, 16). Numerous determinants have been identified in the literature, but the conclusions of these different studies have been contradictory (3, 15, 16, 40).

Commonly mentioned determinants for MIH are summarised in Table 1.2.

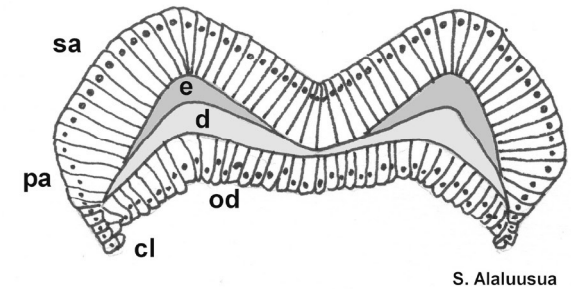

Figure 1.1: Schematic picture of a developing molar.
The cells of the cervical loop (cl) proliferate and develop into presecretory ameloblasts (pa) and further into secretory ameloblasts (sa). After odontoblasts (od) have deposited a small predentine layer, secretion of the enamel matrix can start. Secretory ameloblasts have deposited the protein rich enamel matrix, which contains only small quantities of minerals, in the cusp tips.
e: enamel; d: dentine (and predentine) (3).

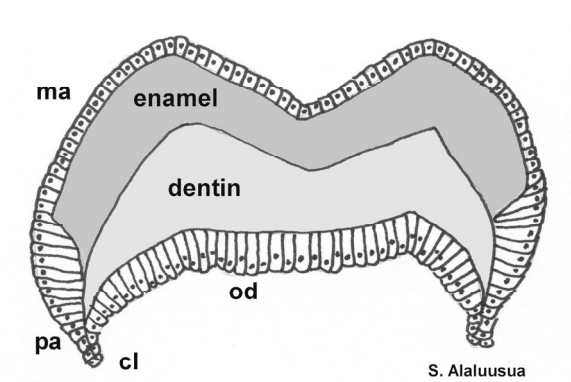

Figure 1.2: Schematic picture of a developing molar.
In the occlusal half of the tooth, the ameloblasts are at the maturation stage. The enamel matrix is resorbed by the ameloblasts (ma) and the massive mineralisation of the enamel is carried out. More cervically, ameloblasts are at a short, so-called transitional stage before entering the maturation stage (transitional-stage ameloblasts). In the most cervical part of the crown, the secretion of the enamel matrix is still on going by secretory ameloblasts. Apoptotic cell death of the ameloblasts begins at the transitional stage and peaks at the maturation stage. Most ameloblasts die before the tooth erupts into the oral cavity.
pa: presecretory ameloblasts; cl: cervical loop; od: odontoblasts (3).
(Courtesy: S. Alaluusua, Helsinki, Finland).

Table 1.2: Determinants for Molar Incisor Hypomineralisation (MIH), overview from the literature.

Determinants of Molar Incisor Hypomineralisation (MIH)	Nutrition	Medical problems	Medical problems	Premature birth	Oxygen shortage	Nutritrion	Breastfeeding	Childhood diseases	Medication	Environmental pollution (dioxins)
Reference	prenatal		perinatal			postnatal				
Aine et al., 2000 (39)				+		+				
Alaluusua et al., 1996a (41)							+			
Alaluusua et al., 1996b (42)										+
Alaluusua et al., 2004 (43)										+
Van Amerongen& Kreulen, 1995 (44)			+		+			+		
Beentjes et al., 2002 (8)				-	-			+		
Fagrell et al., 2011 (15)		-		-		+	+	-	-	
Holtta et al., 2001 (45)										+
Jalevik&Noren, 2000 (7)		-	-					-		
Jalevik et al., 2001 (46)		-	-				-	+	+	
Jontell&Linde, 1986 (47)	+					+				
Kuscu et al., 2008 (48)								+		
Kuscu et al., 2009 (49)										-
Laisi et al., 2008 (50)										+
Laisi et al., 2009 (51)									+	
Lygidakis et al., 2008 (52)		±		+				+		
Salmela et al., 2011 (53)										+
Whatling&Fearne, 2008 (54)		+	-	-			-	+	+	
Wogelius et al., 2010 (55)									+	
Crombie et al., 2009 (16) (review)	±	±		±		+	±	+	+	+
Alaluusua, 2010 (3) (review)		+	+	+	-	+	+	+	+	+

- no influence
± possible influence
+ influence

Identifying the cause of MIH is still difficult. Several possible reasons for this difficulty have been reported:
- The cause of MIH is multifactorial and/or a threshold level needs to have been reached before enamel defects are caused or become apparent (3, 8, 12, 16).
- Most studies on the determinants are retrospective, giving biased data. Parents are unable to remember health and nutritional details after approximately 8 years (3, 15, 16).
- The study populations were small and selected (3, 15, 16).

Compared with hypomineralisation defects in the permanent dentition, very little has been written on hypomineralisation defects in the primary dentition. The few articles on this topic have stated that in the primary dentition, the second primary molar is the tooth most often affected by hypomineralisation (56-59). Possible determinants have only been hypothesised about. The same determinants are expected as for MIH molars, although occurring somewhat earlier in life (perinatal instead of postnatal) (39, 57, 60, 61). The developmental period of the first permanent molars and second primary molars have some overlap, but the second primary molars start to develop earlier and quicker. Pre- and perinatal factors do not seem to have much influence on MIH, but they may be determinants for DMH. To study these factors, information during pregnancy and early life needs to be collected prospectively in a large cohort of children. In the Generation R study, a population-based prospective cohort study following pregnant women and their children from foetal life until young adulthood in Rotterdam, the Netherlands, determinants for DMH were studied.

Aims

The overall aim of this thesis was to describe and provide more insight into Deciduous Molar Hypomineralisation (DMH), including its prevalence, enamel mineral content, pre-, peri- and postnatal determinants and associations with Molar Incisor Hypomineralisation (MIH) and caries.

Prevalence

The aim of this study was to report on the prevalence of Deciduous Molar Hypomineralisation (DMH) in 5-year-old Dutch children.

Validity and reliability of intra-oral photographs

The aims of this study were (i) to assess whether intra-oral photographs could be used to score caries and hypomineralisation on primary molars (using the adapted Molar Incisor Hypomineralisation (MIH) criteria) and (ii) to assess the reliability and validity of these scores in 3- to 7-year-old Dutch children by comparing them with direct clinical scorings.

Relationship between Deciduous Molar Hypomineralisation (DMH) and caries
The aims of this study were (i) to look for a difference in caries prevalence between the surfaces of the first and second primary molars and (ii) to investigate determinants both directly and indirectly associated with caries in second primary molars.

Mineral density in Deciduous Molar Hypomineralisation (DMH)
The aim of this study was to determine the mineral (hydroxyapatite) density of sound and opaque areas in DMH molars and healthy teeth.

Determinants and associated factors of Deciduous Molar Hypomineralisation (DMH)
The aim of this study was to examine the possible determinants of DMH in a prospective cohort study in the prenatal period and the first year of life of the children. The association between antibiotics and asthma medication used during pregnancy with DMH was also studied.

Relationship between Deciduous Molar Hypomineralisation (DMH) and Molar Incisor Hypomineralisation (MIH)
The aim of this study was to determine the association between DMH in the second primary molars and MIH in the first permanent molars.

Some overlap between chapters can be seen because the chapters are based on separate publications on the same topic. The chapters are not arranged chronologically for editorial reasons.

Study populations

Dental practices
For the study on the validity of the intra-oral camera, a convenience sample of 62 children (aged 2.92-7.17 years, mean 4.96 years [SD±1.27]; 38.7% girls) visiting the dental practice of one of the investigators between November 2007 and February 2008 was asked to participate. All invited children participated in the study. The accompanying parent gave consent for taking the intra-oral photographs.
Children from the same dental practices were asked to donate their extracted second primary molars for the study on the mineral content of DMH molars.

TJZ study
As part of a Dutch standardised epidemiological survey (Tandheelkundige verzorging Jeugdige Ziekenfondsverzekerden (TJZ); dental care for children insured by Health Insurance Funds), the dentition of 5-year-old children were examined every six years. The children were living in Gouda, Alphen aan de Rijn, ´s Hertogenbosch or Breda, and their parents received a letter about

the investigation and were asked to give permission for the participation of their child in the investigation. The parents of these children were insured by Health Insurance Funds, under which approximately 60% of the Dutch population was insured. Professional oral care for children was included in this insurance plan (4). The dental examination was performed by calibrated dentists in a dental van. Ethical approval was given for this study. All teeth were examined using the dmfs score.

The second primary molars of 5-year-olds were evaluated for DMH by visual examination, using criteria adapted from the EAPD criteria for diagnosing MIH in the permanent dentition (9). During the calibration sessions, the examiners were trained in diagnosing DMH molars.

Table 1.3: Participants in the TJZ study.

Year	1999	2005
Children invited	692	974
Permission	540 (78%)	495 (51%)
Clinically examined	435 (63%)	386 (38%)
2nd primary molars examined	-	1517
DMH children	-	19 (4,9%)
DMH molars	-	55 (3,6%)

Generation R study

The Generation R study is a population-based prospective cohort study from foetal life until young adulthood. It has previously been described in detail (62, 63).

The cohort included 9778 mothers and their children living in Rotterdam, the Netherlands. Enrolment of mothers was aimed at early pregnancy (gestational age <18 weeks) but was possible until the birth of the child. All children were born between April 2002 and January 2006 and formed a prenatally enrolled birth-cohort. Sixty-one percent of all the eligible children in the study area, participated in this study (63). The study was approved by the Medical Ethics Committee of the Erasmus Medical Centre, Rotterdam. Written informed consent was obtained from all participants.

For the postnatal phase of the study, 7893 children were available (63). Most mothers (51.0%) and children were of Dutch origin (54.8%).

Measurements during pregnancy included questionnaires, foetal ultrasounds and physical examinations. From pharmacy reports, data on medication use of the mother during pregnancy is got.

Birth parameters, like birth weight and length, were measured at time of birth. Many other data on both mother and child were collected by means of regular questionnaires.

At age 5 to 6, the children were invited for a check-up visit at the Sophia's Children's Hospital, Erasmus Medical Centre. From March 2008 until January 2012, 6690 children visited the Erasmus Medical Centre. As a part of this visit, intra-oral photographs of their teeth were taken.

In Figure 1.3 a flow diagram of the participants of the Generation R study is shown.

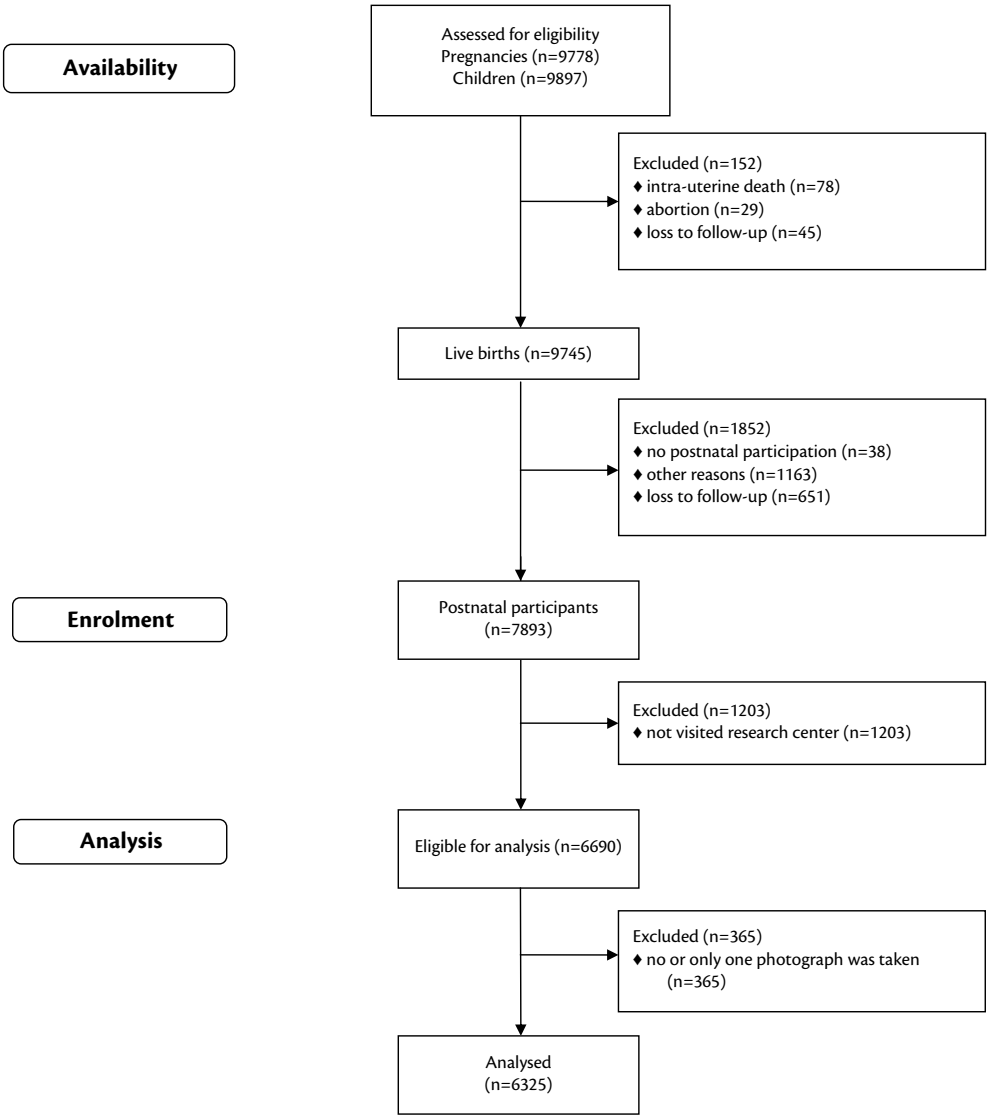

Figure 1.3: Flow diagram participants Generation R study

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