

# Developmental defects of enamel among Slovenian asthmatic children



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## Abstract

**Aim** Asthma is a chronic lung disease characterised by reversible airway obstruction, inflammation of the airway, and increased responsiveness of the airways to stimuli. It is a growing global health problem, and its prevalence is high among children. The results from studies evaluating the effect of asthma on the prevalence of developmental defects of enamel (DDE) are inconclusive. Study Design: The objective of this cross-sectional study aimed to investigate the influence of childhood asthma on the prevalence of DDE and study some general and asthmatic factors on the prevalence of DDE. The study population consisted of children aged 2–17 years ( $n = 138$ ) under treatment for asthma who had used anti-asthmatic medications for at least one year; 140 controls were their healthy siblings. For studying different factors on DDE, 308 asthmatic children were added to the cohort thus forming a group of 446 asthmatic children.

**Methods** Developmental defects of enamel were determined with the DDE index. All primary and permanent teeth were evaluated. Questionnaires completed by parents and data from the patients' medical records provided information on various confounding factors.

**Results** In primary teeth, no statistically significant differences were found. In permanent teeth, demarcated opacities and total DDE were statistically significantly higher among asthmatic children compared to healthy siblings. Among asthmatic children ( $n = 446$ ), no statistically significant difference in the prevalence of DDE was found among gender, fluoride exposure history, parents' education, and asthmatic factors like the duration of medication use, use of metered-dose or dry-powder inhaled form, use of additional antihistamines or leukotriene antagonist.

**Conclusion** The results showed that asthmatic children have a higher prevalence of DDE on permanent teeth compared to their healthy siblings. The DDE in asthmatic children are more related to the asthma disease instead of its treatment. Asthmatic children need a unique dental approach to prevent further loss of dental substance.

**KEYWORDS** Asthma; Developmental defects of enamel; MIH; Children; Teeth.

## Introduction

Asthma is a chronic lung disease characterised by reversible airway obstruction, inflammation of the airway, and increased responsiveness of the airways to stimuli. It is a significant

public health problem, while its prevalence is increasing in developed countries, especially among children [Reddel et al., 2015]. The treatment of asthma starts with avoidance of trigger stimuli, while symptom control with anti-asthmatic medicines is the main component of most asthma treatments. Pharmacological management of chronic childhood asthma involves two main categories of drugs: bronchodilators and anti-inflammatory agents. Children with mild asthma are often managed only with inhaled  $\beta_2$ -agonist bronchodilators. Inhaled glucocorticoids are effective anti-inflammatory agents recommended for children with moderate to severe asthma [Thomas et al., 2010].

Some studies have reported that asthmatic children have a higher prevalence of dental caries and erosion compared to healthy children [Wierchola et al., 2006; Samec et al., 2013; Harrington et al., 2016], while some lack this correlation [Eloot et al., 2004; Tootla et al., 2005]. A few studies present that asthmatic children have a higher prevalence of developmental defects of enamel (DDE) [Guergolette et al., 2009; Wogelius et al., 2010; Mastora et al., 2017].

In both dentitions, DDE are frequent findings. Defects of enamel are classified as enamel hypoplasia or enamel hypomineralisation, which can be presented as abnormal enamel translucency. The formation of enamel occurs in three stages. The stage where the production of proteins involved in amelogenesis happens is called matrix formation. The stage in which mineral content is acquired and the proteins are removed is calcification. The stage in which the enamel is calcified and the remaining proteins are removed, is maturation. Disorders in the matrix formation stage evoke enamel hypoplasia, while disorders in the stage of calcification or maturation cause hypomineralisation [Jälevik, 2001; Caruso et al., 2016].

The aetiology of DDE includes genetic, chemical, or systemic factors. Genetic DDEs are found as amelogenesis imperfecta or as part of a generalised disease (hypoparathyroidism, epidermolysis bullosa, chromosomal anomalies). Fluoride and chlortetracycline are well-recognized chemical factors. Systemic factors include malnutrition, metabolic disturbances, infectious diseases, respiratory diseases, but most often, the causes are unknown [Jälevik et al., 2001]. Epidemiological studies in children with systemic diseases studying DDEs provide essential data for the public health system. They identify possible aetiological factors and identify groups that merit unique preventive treatments.

Although asthma affects all age groups, with a global prevalence of up to 20% of children aged 6–7 [Lai et al.,

Permanent teeth	Asthmatic children N = 138 n (%)	Healthy siblings N = 140 n (%)	P value (Chi-square)
Demarcated opacity	24 (17.4)	10 (7.1)	0.009*
Absent demarcated opacity	114 (82.6)	130 (92.9)	
Diffuse opacity	3 (2.2)	2 (1.4)	0.640
Absent diffuse opacity	135 (97.8)	138 (98.6)	
Hypoplastic enamel defects	1 (0.7)	0 (0)	0.313
Absent hypoplastic enamel defects	137 (99.3)	140 (0)	
Total developmental enamel defects	27 (19.6)	12 (8.6)	0.008*
Absent developmental enamel defects	111 (80.4)	128 (91.4)	

\*P value <0.05 Test  $\chi^2$

TABLE 1 Prevalence of DDE in permanent teeth among asthmatic children and healthy siblings (n=278).

Tooth	Asthmatic children n (%)	Healthy siblings n (%)	Total n (%)
18	0 (0)	0 (0)	0 (0)
17	0 (0)	0 (0)	0 (0)
16	1 (0.7)	0 (0)	1 (0.4)
15	0 (0)	0 (0)	0 (0)
14	0 (0)	0 (0)	0 (0)
13	1 (0.7)	0 (0)	1 (0.4)
12	6 (4.3)	2 (1.4)	8 (2.9)
11	7 (5.1)	4 (2.9)	11 (4.0)
21	12 (8.7)	5 (3.6)	17 (6.1)
22	5 (3.6)	2 (1.4)	7 (2.5)
23	1 (0.7)	0 (0)	1 (0.4)
24	0 (0)	0 (0)	0 (0)
25	0 (0)	1 (0.7)	1 (0.4)
26	2 (1.4)	0 (0)	2 (0.7)
27	0 (0)	0 (0)	0 (0)
28	0 (0)	0 (0)	0 (0)
38	0 (0)	0 (0)	0 (0)
37	0 (0)	0 (0)	0 (0)
36	1 (0.7)	2 (1.4)	3 (1.1)
35	0 (0)	0 (0)	0 (0)
34	0 (0)	1 (0.7)	1 (0.4)
33	1 (0.7)	0 (0)	1 (0.4)
32	0 (0)	1 (0.7)	1 (0.4)
31	2 (1.4)	2 (1.4)	4 (1.4)
41	3 (2.2)	1 (0.7)	4 (1.4)
42	2 (1.4)	1 (0.7)	3 (1.1)
43	2 (1.4)	0 (0)	2 (0.7)
44	0 (0)	0 (0)	0 (0)
45	1 (0.7)	0 (0)	1 (0.4)
46	0 (0)	1 (0.7)	1 (0.4)
47	0 (0)	0 (0)	0 (0)
48	0 (0)	0 (0)	0 (0)
SUM	47 (0.011)	23 (0.005)	70 (0.078)

\*Mann-Whitney U-test

TABLE 2. Frequencies of DDE among single permanent teeth (n = 278).

2009], studies on asthma and dental enamel defects are still missing.

Due to a lack of studies, we decided to conduct a new study with healthy siblings as a control group, which definitively adds to the results' weight. In our study, we also included different general and asthmatic factors that could interfere with the DDE.

### Materials and methods

The study population consisted of children aged 2–17 years under treatment for chronic bronchial asthma at the University Children's Hospital, Ljubljana, Slovenia. The degree of asthma was not detected. The study protocol was approved by the ethics committee at the Ministry of Health in Slovenia (No.165/07/09) and was in accordance with the Helsinki Declaration of 1975, as revised in 2000. All the parents gave written informed consent for inclusion in this study. Children having additional diseases such as heart diseases, gastroesophageal reflux, chromosomal abnormalities, infectious diseases, eating disorders, and frequent vomiting were excluded from the study. To be included in the study, patients must have used anti-asthmatic medications daily for at least one year and had physician-diagnosed asthma and those who had a healthy sibling made up the patient/control cohort, which consisted of 278 children (138 asthmatic children and 140 non asthmatic siblings as controls). For studying different factors on DDE, 308 asthmatic children without controls were added to the cohort, forming a group of 446 asthmatic children.

Dental examinations were carried out at the University Dental Clinic in a dental chair under artificial light by two calibrated dentists using a standard dental mirror and rounded dental probe. The dental examiners were blinded to children with and without asthma. Children had their teeth cleaned before the examination. Radiography was not used in this study. Developmental enamel defects were determined by the DDE index (Developmental Defects of Enamel) [1982]. We used eight codes: 0 = healthy tooth surface, 1 = demarcated opacity, 2 = diffuse opacity, 3 = hypoplastic, 4 = other defects, 5 = demarcated and diffuse opacity, 6 = demarcated and hypoplastic, 7 = diffuse and hypoplastic, 8 = demarcated, diffuse and hypoplastic dental surface. All primary and permanent teeth were included in the clinical examination.

Questionnaires completed by parents and data from the patients' medical records provided information on demographics, medical history, medication usage, dietary history, oral hygiene habits, fluoride exposure, and for asthmatic children also type, dose, frequency, length and mode of medicine application. For the glucocorticoid dose, we used the dose the children had been using for the previous six months.

### Statistical method

The Chi-square test was used to test the distribution of subjects between groups for categorical independent variables, and the Mann-Whitney U-tests were used to test the association between enamel defects as a dependent variable with independent variables.

	DDE absent n (%)	DDE present n (%)	*P-value
<b>Gender</b>			
Male	216 (80.0)	54 (20.0)	0.583
Female	137 (77.8)	39 (22.2)	
<b>Fluoride exposure history</b>			
Use of fluoride pills	136 (75.1)	45 (24.9)	0.085
No fluoride pills use	217 (81.9)	48 (18.1)	
<b>Parents' education</b>			
Elementary school or profession school or Secondary school	246 (78.1)	69 (21.9)	0.396
High school or University or postgraduate studies	107 (81.7)	24 (18.3)	
<b>Asthmatic factors</b>			
The duration of medication use (1–3 years)	140 (82.4)	30 (17.6)	0.191
The duration of medication use (> 3 years)	213 (77.2)	63 (22.8)	
Medicines use in metered-dose inhaled form	251 (80.7)	60 (19.3)	0.172
Medicines use in dry powder-inhaled form	82 (74.5)	28 (25.5)	
Use of additional leukotriene antagonists	60 (72.3)	23 (27.7)	0.088
No additional leukotriene antagonists	293 (80.7)	70 (19.3)	
Use of antihistamines	17 (80.8)	7 (29.2)	0.303
No antihistamines use	336 (79.6)	86 (20.4)	
*P-value <0.05 Test $\chi^2$			

**TABLE 3** Proportions of DDE in permanent teeth of asthmatic children (n = 446) with regard to gender, fluoride exposure history, parents' education and asthmatic factors (duration of medication use, use of metered-dose or dry-powder inhaled form, use of additional antihistamines or leukotriene antagonist).

The data were analysed using the SPSS 25.0 statistical software package for Windows (SPSS Inc., Chicago, USA). The level of statistical significance was set at  $P \leq 0.05$ .

## Results

We included 278 children (mean age  $9.14 \pm 3.56$  years) in the study. There was no statistically significant difference between asthmatic children and healthy siblings concerning fluoride intake, dietary habits, oral hygiene, dental visits, and parents' education.

The mean length of anti-asthmatic medication use in the 138 asthmatic children was  $5.46 \pm 3.32$  years; 31.9% of asthmatic children used medicines from one year to 3 years, 68.1% used them for more than four years; 75.2% of asthmatic children used medicines in metered-dose inhaled form, while 24.8% used them in dry powder-inhaled form. All asthmatic children used glucocorticoid daily and bronchodilator as circumstances required. Of the asthmatic children (n=446), 18.8% used additional leukotriene antagonists, and 5.1% used antihistamines. After medicine application, 76.8% of asthmatic children rinsed their mouths with water. 65.9% of children used inhalers with a spacer.

In primary teeth, DDE were more frequent in the posterior segment (2.0%), and diffuse opacities were the most frequent lesions. In comparison to permanent teeth, DDE appeared less frequently. In primary teeth, we found no statistically significant differences in DDE prevalence among asthmatic children and healthy siblings.

The prevalence of DDE in permanent teeth among asthmatic children and healthy siblings are presented in Table 1. The most frequent DDEs were demarcated opacities, followed by diffuse opacities and hypoplastic enamel defects. The prevalence of demarcated opacities and total DDE were statistically significantly higher among asthmatic children compared to healthy siblings.

The distribution of DDE in permanent teeth is presented in Table 2. In a group of asthmatic children and healthy siblings' upper left central incisor most frequently had DDE.

Proportions of DDE in permanent teeth in asthmatic children

(n=446) are presented in Table 3. No statistically significant difference was found among gender, fluoride exposure history, parents' education and asthmatic factors like the duration of medication use, use of metered-dose or dry-powder inhaled form, use of additional antihistamines or leukotriene antagonist.

## Discussion

This cross-sectional study among 2–17-year-old Slovene children showed a statistically significantly higher prevalence of total and demarcated DDE in permanent teeth among asthmatic children compared to their healthy siblings. The results of our study are in accordance with other studies [Jalevik et al., 2001; Guergolette et al., 2009; Mastora et al., 2017]. In Greek 6–12-year old asthmatic children, 34.3% had DDE present compared to only 8.6% DDE present in the control group [Mastora et al., 2017]. The prevalence of DDEs was also higher among Brazilian pediatric patients with asthma [Guergolette et al., 2009]. There was also a statistically significant positive correlation between asthma and the presence of demarcated opacities in the first permanent molars in a group of 8-year-old Swedish children [Jalevik et al., 2001]. However, since several influencing factors were studied, the authors estimated that results should be interpreted with caution, while there were only a few children with asthma present in the study. Our study's association between asthma and DDEs appears firmer, since only asthmatic children with severe asthma were included, and controls were healthy siblings. The agreement was also partially found with a study of 6–8-year-old Danish children, where an increased risk in asthmatic children was found only with severe demarcated opacities [Wogelius et al., 2010].

On the contrary, some studies have shown no connection between asthma and enamel defects [Rezende et al., 2019]. They found that more (53.2%) asthmatic children had DDE than controls (46.8%), which was not statistically significant. Lack of significance could be due to fewer asthmatic children (n = 112) examined and randomly selected controls compared to our study.

The total prevalence of DDE in asthmatic children (19.6%) was more than double compared to healthy siblings. In Slovenia, a similar study found the prevalence of DDE to be 14.4% among 6-to-11-year old children [Grošelj and Jan, 2013]. Asthmatic children prevalence of DDEs in our study is in the middle of the global prevalence of Molar Incisor Hypomineralisation (MIH), ranging from 0.5% to 40.2%, according to different studies [Mast et al., 2013; Giuca et al., 2020]. MIH is defined as demarcated, qualitative developmental defects of systemic origin of the enamel of one or more first permanent molar with or without involvement of the incisors [Weerheijm, 2003]. In our study, we also found incisors and molars to be the teeth most frequently affected by DDEs.

The pathogenesis of DDEs is multifactorial, where a genetic component, prenatal, perinatal, and postnatal exposures, play a role [Silva et al., 2016]. Demarcated opacities in permanent teeth are commonly caused by local trauma and infection during tooth development. Since asthmatic children in primary teeth have dental caries more frequently [Samec et al., 2013], we cannot exclude DDEs on permanent teeth are not caused by pulpal and periapical infections in the anterior sector. It is estimated that many health problems before five years of age can modulate the ameloblast activity and cause irreversible enamel changes; asthma is no exception [Jälevik and Norén, 2000]. Asthma as a disease could interfere with the ameloblast activity by oxygen deprivation, or ameloblast activity could be interfered by asthmatic medication (glucocorticoids or bronchodilators). Osteoblast formation and activity are suppressed by corticosteroid therapy [Rehman and Lane, 2003]. A similar effect could be possible on ameloblasts; only the changes would be permanent since the enamel tissue is less dynamic than bone.

In the second part of the study, we analysed the influence of different factors on the prevalence of DDE, asthmatic factors like the duration of medication use, use of metered-dose or dry-powder inhaled form, use of additional antihistamines or leukotriene antagonist did not influence the prevalence of DDE. No connection between asthma treatment and the prevalence of DDEs was also found in similar studies [Wogelius et al., 2010; Mastora et al., 2017].

Asthmatic patients have episodes of oxygen deprivation, which affects ameloblasts that are overly sensitive to oxygen supply [Jälevik and Norén, 2000]. Guergolette et al. [2009] showed that if asthma symptoms occurred before the age of three, DDE appeared more frequently. Since we found no connections between asthma treatment and DDE, we conclude that the DDE is probably more related to the asthma disease than its treatment, although it is difficult to distinguish between the two factors regarding the aetiology of DDE [Guergolette et al., 2009; Mastora et al., 2017].

Fluoride exposure did not statistically significantly influence the prevalence of DDE among asthmatic children in our study. Also, the p-value was low. Results are in accordance with other studies that also found that the prevalence of DDE was higher in the areas where fluoride exposure was increased [Balmer et al., 2005].

## Conclusion

Regardless of the aetiological factor, asthmatic children have DDEs more frequently, and paediatric dentists should consider asthmatic children to be at higher risk for DDE. Since

dental caries is also more frequent among asthmatic children, dental practitioners must be prudent in distinguishing between DDE and demineralised non-cavitated carious lesions. With appropriate prevention and care, we should aim for these lesions not to become cavitated carious lesions.

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