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Is There an Association between Asthma and Dental Caries and Molar Incisor Hypomineralisation?

Claudia Flexeder[a] Lamiaa Kabary Hassan[a, b] Marie Standl[a] Holger Schulz[a, c] Jan Kühnisch[b]

[a]Institute of Epidemiology, Helmholtz Zentrum München – German Research Center for Environmental Health, Neuherberg, Germany; [b]Department of Conservative Dentistry and Periodontology, University Hospital, Ludwig-Maximilians-Universität München, Munich, Germany; [c]Comprehensive Pneumology Center Munich (CPC-M), Member of the German Center for Lung Research, Munich, Germany

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Caries · Asthma · Asthma medication · Inhalers · Prevalence · Cohort study · Epidemiology

Abstract
This epidemiological study aimed to compare the caries and molar incisor hypomineralisation (MIH) experience in asthmatic and non-asthmatic adolescents assessed at 10 and 15 years of age. 730 adolescents from ongoing birth cohort studies (GINIplus/LISA) from Munich, Germany, were examined for carious lesions at the age of 10 and 15 years to determine caries experience under inclusion of non-cavitated carious lesions $D_{1-2}T$ and the tooth-related decay-missing-filled index. Furthermore, MIH was scored on all permanent teeth according to the criteria of the European Academy of Paediatric Dentistry. The association between caries and MIH prevalence at the 10-year and 15-year follow-up as well as caries incidence with ever having an asthma diagnosis was analysed using hurdle regression models adjusted for potential confounders. Of the 730 adolescents, 52 and 78 were identified as asthmatics at the 10- and 15-year follow-up, respectively. There were no significant differences in caries prevalence or experience between asthma-free participants and any of the asthma groups (taking metered-dose inhaler (MDI) medication vs. taking no MDI medication). However, a significant positive association was found for asthmatic adolescents who did not take MDI medication with higher MIH/T values (OR = 2.56, 95% CI = 1.03–6.37, p = 0.043) compared to non-asthmatics. In conclusion, asthma did not influence the caries status of adolescents in the present study. Interestingly, a significant association was found between adolescents with asthma who did not take MDI medication and the number of MIH-affected teeth. The association between asthma, medication, and MIH needs further confirmation.

Introduction

Asthma is one of the most common chronic diseases in children and adolescents, and its incidence has steadily increased in recent decades [Smits et al., 2016]. It is now estimated to affect 235 million persons globally [World

Claudia Flexeder and Lamiaa Kabary Hassan contributed equally to this work.

E-Mail karger@karger.com
www.karger.com/cre

Prof. Dr. Jan Kühnisch
Department of Conservative Dentistry and Periodontology
University Hospital, Ludwig Maximilian University of Munich, Goethestrasse 70
DE–80336 Munich (Germany)
E-Mail jkuehn@dent.med.uni-muenchen.de

Health Organization, 2017]. In the Global Asthma Report from 2014, the International Study of Asthma and Allergies in Childhood (ISAAC) stated that 14% of the world's children experienced asthma symptoms in that year and that the burden of asthma was greatest for children and adolescents aged 10–14 years [Global Asthma Network, 2014]. As estimated by the World Health Organization (WHO), asthma is considered among the top five ranked causes for years lost due to disability in 10- to 14-year-olds [World Health Organization, 2012]. While the exact pathomechanisms causing asthma are still unclear, there is a consensus that asthma is an umbrella term for different phenotypes or endotypes, which emerge from various pathophysiological pathways [Smits et al., 2016]. Inhaled asthma medication involves two main categories, β-adrenergic drugs for bronchodilators and anti-inflammatory agents. Mild to severe asthma is typically managed by inhaled β_2-adrenoceptor agonists and increased doses of inhaled glucocorticoids, whereas intermittent asthma is managed with only inhaled β_2-adrenoceptor agonists [Berdel et al., 2006].

Dental caries has also a high prevalence worldwide. Having a multifactorial nature, the risk of developing dental caries is influenced by several factors including physical, biological, behavioural, and lifestyle-related factors [Holst, 2005]. A link between the two diseases (asthma and dental caries) has long been discussed. Some authors proposed that asthma could be a cause for the increased susceptibility of developing carious lesions [Stensson et al., 2010; Wierchola et al., 2006]. Other authors suggested that since asthma medications, mostly applied by metered-dose inhalers (MDI), are acidic in nature and reduce salivary function, they create a favourable environment for cariogenic bacteria [Mazzoleni et al., 2008; Milano et al., 2006; Samec et al., 2013; Santos et al., 2012].

Despite the fact that there is a considerable amount of literature on the effect of asthma on dental caries, the results seem to be conflicting [e.g., Arafa et al., 2017; Chuang et al., 2018]. In a recent meta-analysis, which included 18 studies, Alavaikko et al. [2011] confirmed the association between asthma and dental caries and assessed that asthma increased the risk of caries by the factor two. However, Maupomé et al. [2010] argued that a meta-analysis of the published literature was not viable due to the heterogeneity of the variables, measurements, and statistical approaches. In a review of 27 studies, Maupomé et al. [2010] claimed that there is no strong evidence for a causal relation between caries and asthma. Both author groups agree on the fact that the majority of studies performed so far are small case-control studies and that a need for longitudinal cohort studies is evident [Alavaikko et al., 2011; Maupomé et al., 2010].

Besides caries, respiratory diseases including asthma have been suggested to be associated with the development of molar incisor hypomineralisation (MIH). However, previous literature shows that asthma was regarded as a risk factor for the development of MIH in the first few years of life only [Allazzam et al., 2014; de Lima et al., 2015; Kühnisch et al., 2014b; Tourino et al., 2016]. To examine whether asthma could also pose a risk for the development of MIH during childhood, this study examines the association between asthma and MIH up to the age of adolescence.

In our longitudinal study, we aimed to assess the association between asthma and asthma medication during childhood and adolescence and the occurrence of caries or MIH, assessed on all permanent teeth, at the age of 10 and 15 years. Our null hypothesis was that there is no association between asthma, MDI use, and caries or MIH development.

Material and Methods

Study Population

The study population consisted of the ongoing GINIplus (German Infant Nutritional Intervention plus environmental and genetic influences on allergy development) and LISA (Influence of Lifestyle-Related Factors on the Immune System and the Development of Allergies in Childhood) birth cohort studies. Healthy full-term new-borns were recruited from obstetric clinics within four German cities (Munich, Leipzig, Wesel, and Bad Honnef). The present analysis is restricted to participants from the Munich study centre, who participated in the dental examination at the 10- and 15-year follow-up examinations. In GINIplus, infants with a family history of atopic diseases, i.e., at least one parent and/or sibling having reported hay fever, allergic rhinitis, allergic conjunctivitis, atopic eczema, or physician-diagnosed asthma, were allocated to the interventional study arm investigating the effect of different hydrolysed formulas for allergy prevention in the first year of life [Berg et al., 2010]. All children without a family history of allergic diseases and children whose parents did not give consent for the intervention were allocated to the non-interventional arm. In LISA, the participants were not pre-selected based on a family history of allergic diseases [Heinrich et al., 2012]. A detailed description of the GINIplus and LISA studies has been published elsewhere [Berg et al., 2010; Heinrich et al., 2012; Heitmüller et al., 2013; Kühnisch et al., 2014a].

Dental Examination

Prior to the dental examination, the participants brushed their teeth. The standardised examination equipment included a dental mirror, a blunt CPI probe (CP-11.5B6, Hu-Friedy, Chicago, IL, USA), and a halogen lamp (Ri-Magic, Rudolf Riester GmbH, Jung-

ingen, Germany). Each child was investigated at the designated appointment by one calibrated dentist.

The caries status was determined as tooth-related decay-missing-filled (DMF) index for the permanent dentition (D_{3-4}MFT) using WHO standard methodology. A D_{3-4} lesion was recorded when the surface had an unmistakable cavity, undermined enamel, or a detectably softened floor or wall [World Health Organization, 1997]. Non-cavitated caries lesions (D_{1-2}T) were recorded on a tooth-related level according to the ICDAS/UniViSS criteria [Kühnisch et al., 2009; Kühnisch et al., 2011; Pitts et al., 2013]. First visible signs, established caries lesions, and microcavities without dentin exposure were classified as non-cavitated caries lesion. In case of multiple findings, the DMF index, non-cavitated caries lesions, and sealants were recorded separately.

In addition, teeth with demarcated opacities, enamel breakdown of the hypomineralised enamel, and atypical restorations were diagnosed according to the criteria of the European Academy of Paediatric Dentistry (EAPD) [Lygidakis et al., 2010] on all permanent teeth [Kühnisch et al., 2014a; Lygidakis et al., 2010]. Hypomineralised lesions with a diameter of <1 mm were not recorded [Lygidakis et al., 2010]. Other enamel defects, e.g., hypoplasia, fluorosis (diffuse opacities), amelogenesis imperfect, and dentinogenesis imperfecta were clearly distinguished from MIH and were not recorded. MIH-associated defects were not scored on the DMF index.

Before the study, a three-day theoretical and practical calibration training focussed on scoring of cavitated lesions, non-cavitated caries lesions, sealants, and MIH was undertaken with the examiners (Y.M., I.M., and K.R.) by an experienced dentist and epidemiologist (J.K.). A more detailed description of the calibration training is given elsewhere [Heitmüller et al., 2013; Kühnisch et al., 2018].

Definition of Asthma and Confounding Variables

Yearly information on physician-diagnosed asthma was collected from self-administered questionnaires which were filled in by the parents. The questionnaires were completed at 6, 12, 18, and 24 months and at 4, 6, 10, and 15 years of age in the LISA study and at 1, 2, 3, 4, 6, 10, and 15 years in the GINIplus study. Based on the information on yearly asthma diagnosis, two binary exposure variables for ever having an asthma diagnosis were defined starting from the age of 3 up to 10 and 15 years, respectively. Information on asthma diagnosis before the age of 3 years was not taken into account as symptoms such as wheezing and cough are very common in the first years of life, and performing reproducible lung function tests is not possible for most young children. Thus, it might be difficult to diagnose asthma with certainty at this age range [Berdel et al., 2006; Global Initiative for Asthma, 2017]. Information on asthma medication intake during the last 24 months before the follow-up at 6 years and the last 12 months before the follow-up at 10 and 15 years was obtained from the questionnaires. We focused on inhaled asthma therapy by MDI, i.e., short- and long-acting β_2-adrenoceptor agonists, cromoglicate, and corticosteroids.

The set of covariates or potential confounders considered for adjustment were characteristics such as sex, age, BMI at age 10 and 15 years, respectively, parental atopy, and study. Study was either GINIplus observation arm, GINIplus intervention arm, or LISA. Parental atopy was defined as either mother or father reported to have hay fever, allergic rhinitis, allergic conjunctivitis, atopic eczema, or physician-diagnosed asthma. Furthermore, other lifestyle factors were considered such as maternal smoking during pregnancy (yes vs. no), breastfeeding habits (>4 months, 1–4 months, and no exclusive breastfeeding), parental education level defined as the highest level achieved either by mother or father (low for <10 years, medium for 10 years, high for >10 years), and adolescent smoking at 15 years (yes vs. no).

Statistical Analysis

The descriptive statistical analysis revealed the prevalence of caries at the 10-year and 15-year follow-up and caries incidence in the 5-year period between the two follow-ups. Moreover, prevalence rates of MIH were analysed for the two follow-ups. The analysis of the caries data included the determination of prevalence rates according to different cut-offs (i.e., $D_{1-2} = 0$, $D_{3-4}MF = 0$, and $D_{1-4}MF = 0$). For the statistical analysis of the MIH data, the measurement of the distribution pattern for each study participant was included. Adolescents with at least one MIH in the permanent dentition were categorised to group MIH/1, while those without any demarcated opacities were scored as free of MIH. Adolescents with at least one affected first permanent molar were grouped as MIH/2 [Lygidakis et al., 2010], and those with hypomineralisation on their first permanent molars and incisors as MIH/3 [Kühnisch et al., 2014b]. Prevalence rates were estimated according to the definitions. Furthermore, mean values and standard deviations for each entity, caries (i.e., D_{1-2}/T and D_{3-4}MF/T) and MIH (i.e., for the affected permanent teeth (MIH/T)), were calculated.

For the explorative statistical analysis, asthma was categorised into three groups: healthy controls which were defined as reference group, asthmatics who did not use any MDI, and asthmatics who took MDI medications. All numbers are reported for the 10-year and 15-year follow-up, respectively. Since the population had a low caries risk, the DMF index showed a positively skewed distribution with a large stack of zero counts for those adolescents without caries experience. To account for this zero-inflated distribution, a specific statistical analysis method, the hurdle regression model [Preisser et al., 2012], was used. This two-part model was used to analyse the association between the oral health parameters as a continuous outcome variable and the asthma variable as a predictor with three groups. The first part of this model used logistic regression for the probability of a non-zero count, which refers to caries or MIH prevalence. Odds ratios (OR) were calculated. The second part of the model used Poisson regression for the mean count among the subjects with a non-zero count, which refers to caries or MIH severity. Relative risks were determined [Hofstetter et al., 2016]. In the basic model, the set of potential confounders considered for adjustment included characteristics like sex, age, BMI at 10 years and 15 years, respectively, and study. In the fully adjusted model, other lifestyle factors were considered as potential confounders such as maternal smoking during pregnancy, breastfeeding habits, parental education level, adolescent smoking at age 15 years only, and parental atopy. A statistical comparison was considered significant if the two-sided p value was <0.05. All analyses were performed using the statistical software R 3.3.2 [R Core Team, 2017]. Poisson hurdle regression models were used, as implemented in the R package "pscl" [Jackman, 2017; Zeileis et al., 2008].

Table 1. Characterisation of the participants (n = 730 adolescents) from the GINIplus and LISA cohorts

GINIplus study	
Intervention arm	284 (38.9)
Observation arm	165 (22.6)
Total	449 (61.5)
LISA study	281 (38.5)
Male sex	364 (49.9)
Age, years	
At 10-year follow-up	10.2±0.2
At 15-year follow-up	15.2±0.3
Body mass index, kg/m²	
At 10-year follow-up	17.0±2.2
At 15-year follow-up	20.7±3.1
Parental education	
Low (<10 years)	23 (3.2)
Medium (10 years)	125 (17.1)
High (>10 years)	548 (75.1)
Missing	34 (4.7)
Prevalence of asthma at 10-year follow-up	
Yes	
No MDI	12 (1.6)
MDI	40 (5.5)
Total	52 (7.1)
No	678 (92.9)
Prevalence of asthma at 15-year follow-up	
Yes	
No MDI	21 (2.9)
MDI	57 (7.8)
Total	78 (10.7)
No	652 (89.3)
Adolescent smoking at 15 years	
Yes	70 (9.6)
No	624 (85.5)
Missing	36 (4.9)
Breastfeeding	
>4 months	391 (53.6)
1–4 months	194 (26.6)
Never	101 (13.8)
Missing	44 (6.0)
Maternal smoking during pregnancy	
Yes	69 (9.5)
No	648 (88.8)
Missing	13 (1.7)
Parental atopy	
Yes	500 (68.5)
No	218 (29.9)
Missing	12 (1.6)

Values are n (%) or mean ± SD.

Results

Complete information on physician-diagnosed asthma and caries prevalence and incidence was available for 730 participants. The study population characteristics are shown in Table 1. At the 10-year follow-up, 7.1% of the population (52 individuals) were considered asthmatics using the previously mentioned criteria, this rate increased to 10.7% (78 subjects) at the 15-year follow-up. Out of the 52 asthmatic participants at age 10 years, 12 adolescents (23%) did not take MDIs, while at age 15 years 21 (27%) of the 78 asthmatic adolescents did not take MDIs.

The overall measurements of caries and MIH prevalence and experience at the 10-year and 15-year follow-up are summarized in Tables 2 and 3. At age 15 years, 63.7% of all adolescents had no obvious caries in the permanent dentition ($D_{3-4}MF = 0$). After inclusion of non-cavitated caries lesions ($D_{1-4}MF = 0$), the percentage of caries-free adolescents fell to 21.0% (Table 2). Mean caries experience for the overall study population was 0.9 (SD = 1.7) $D_{3-4}MF/T$. Additionally, a mean of 4.3 (SD = 5.3) D_{1-2}/T was determined (Table 3). When considering the definition by the EAPD (MIH/2), 13.8% of the adolescents were diagnosed with MIH (Table 2). A mean of 1.3 (SD = 2.4) teeth were affected by any demarcated opacities, enamel breakdown, or atypical restoration (Table 3).

The prevalence rate of caries for the asthmatics at the 10-year follow-up was higher than that for the non-asthmatics (Table 2). 38.5% of the 10-year-old asthmatics were caries-free, while 46.6% of the non-asthmatics were caries-free. This relation was reversed at the age of 15 years. Asthmatics showed a lower prevalence of non-cavitated and cavitated caries lesions than non-asthmatics. Only 20.6% of the non-asthmatics were caries-free compared to 24.4% of the asthmatics at the 15-year follow-up (Table 2).

The caries incidence rates for the 52 asthmatics were calculated for the 5-year period between the two follow-ups. 32.7% of the asthmatic adolescents developed obvious caries lesions in comparison to 30.4% of the non-asthmatics. The frequency rate of the non-cavitated lesions was comparable between the two groups, 57.7% for the asthmatic group and 55.2% for the non-asthmatics. The increase in non-cavitated caries lesions for the asthmatic group ($\Delta D_{1-2}/T = 3.4$) turned out to be of equal magnitude to that for the non-asthmatic group ($\Delta D_{1-2}/T = 3.3$). Similarly, when using the DMF index, the non-asthmatic group recorded $\Delta D_{3-4}MF/T =$

Table 2. Caries and molar incisor hypomineralisation prevalence (given in *n*/%) in asthmatics and non-asthmatics at the 10- and 15-year follow-up

	Non-asthmatics		Asthmatics		All adolescents	
10-year follow-up						
Participants	678/92.9		52/7.1		730	
D_{1-2} = 0 vs. D_{1-2} >0	350/51.6	328/48.4	25/48.1	27/51.9	375/51.4	355/48.6
D_{3-4}MF = 0 vs. D_{3-4}MF >0	580/85.5	98/14.5	41/78.8	11/21.2	621/85.1	109/14.9
D_{1-4}MF = 0 vs. D_{1-4}MF >0	316/46.6	362/53.4	20/38.5	32/61.5	336/46.0	394/54.0
MIH/1 = 0 vs. MIH/1 = 1	466/68.7	212/31.3	33/63.5	19/36.5	499/68.4	231/31.6
MIH/2 = 0 vs. MIH/2 = 1	586/86.4	92/13.6	46/88.5	6/11.5	632/86.6	98/13.4
MIH/3 = 0 vs. MIH/3 = 1	614/90.6	64/9.4	47/90.4	5/9.6	661/90.5	69/9.5
15-year follow-up						
Participants	652/89.3		78/10.7		730	
D_{1-2} = 0 vs. D_{1-2} >0	171/26.2	481/73.8	25/32.1	53/67.9	196/26.8	534/73.2
D_{3-4}MF = 0 vs. D_{3-4}MF >0	419/64.3	233/35.7	46/59.0	32/41.0	465/63.7	265/36.3
D_{1-4}MF = 0 vs. D_{1-4}MF >0	134/20.6	518/79.4	19/24.4	59/75.6	153/21.0	577/79.0
MIH/1 = 0 vs. MIH/1 = 1	409/62.7	243/37.3	47/60.3	31/39.7	456/62.5	274/37.5
MIH/2 = 0 vs. MIH/2 = 1	559/85.7	93/14.3	70/89.7	8/10.3	629/86.2	101/13.8
MIH/3 = 0 vs. MIH/3 = 1	591/90.6	61/9.4	72/92.3	6/7.7	663/90.8	67/9.2

Table 3. Caries and molar incisor hypomineralisation experience (given in means ± SD) in asthmatics and non-asthmatics at the 10- and 15-year follow-up

	Non-asthmatics	Asthmatics	All adolescents
10-year follow-up			
Participants, *n*	678	52	730
D_{1-2}/T	1.1±1.5	1.2±1.5	1.1±1.5
D_{3-4}MF/T	0.3±0.8	0.4±0.8	0.3±0.8
D_{3-4}/T	0.02±0.1	0.02±0.1	0.02±0.1
M_{3-4}/T	0.0±0.0	0.0±0.0	0.0±0.0
F_{3-4}/T	0.2±0.7	0.3±0.8	0.2±0.7
MIH/T	0.8±1.5	0.7±1.2	0.8±1.5
15-year follow-up			
Participants, *n*	652	78	730
D_{1-2}/T	4.3±5.3	4.2±5.4	4.3±5.3
D_{3-4}MF/T	0.9±1.7	1.0±1.7	0.9±1.7
D_{3-4}/T	0.1±0.6	0.1±0.4	0.1±0.6
M_{3-4}/T	0.0±0.0	0.0±0.0	0.0±0.0
F_{3-4}/T	0.8±1.5	0.9±1.7	0.8±1.6
MIH/T	1.3±2.5	1.3±2.0	1.3±2.4

0.7, while the asthmatic group had a mean value of ΔD_{3-4}MF/T = 0.8.

The prevalence of MIH differed according to the used index teeth which represent different phenotypes (Table 2). At least one hypomineralised tooth (MIH/1) was observed in 37.5% (*n* = 274) of all subjects at age 15. Considering the EAPD definition (MIH/2), 13.8% (*n* = 101) of all participants were found to be affected by MIH. The MIH/3 group consisted of 9.2% (*n* = 67) of the overall population and showed MIH lesions in incisors and first permanent molars. The asthmatics showed comparable mean values of MIH/T to the non-asthmatics at the 10-year follow-up (0.7 vs. 0.8), while for the 15-year follow-up, we also noticed similar mean values for MIH/T for the asthmatic group (1.3) compared to the non-asthmatics (1.3) (Table 3).

To address the major aim of this study, the dental parameters were analysed in relation to the presence of asthma and the use of MDIs using Poisson hurdle regression models (Tables 4–6). Table 4 shows the results of the regression models using cross-sectional data. There was no significant difference noticed, neither in the prevalence of non-cavitated (D_{1-2}/T) nor in the prevalence of cavitated caries lesions (D_{3-4}MF/T) at the 10-year or the 15-year follow-up (Table 4). In addition, no significant influence of asthma on caries incidence (ΔD_{1-2}/T and ΔD_{3-4}MF/T) was determined (Table 5). Similarly, in the fully adjusted model including additional possible confounders, no association between asthma and dental caries was observed. The results were consistent among the asthmatics independent of the use of MDIs (Tables 4 and 5).

The present study showed no significant association between asthma and the different MIH categories at the 10-year follow-up (Table 6). However, at the 15-year follow-up, significantly higher MIH/T values (OR = 2.56, 95% CI = 1.03–6.37, $p = 0.043$) were observed in the asthmatics who were not taking MDI in the fully adjusted models.

Table 4. Poisson hurdle regression models to analyse the association between asthma and caries in 730 adolescents at the 10- and 15-year follow-up

Model	Caries prevalence		Caries severity	
	OR (CI)	*p* value	RR (CI)	*p* value
10-year follow-up				
D_{1-2}/T				
1/Hurdle				
No MDI	1.01 (0.31–3.24)	0.990	0.71 (0.33–1.52)	0.377
MDI	1.09 (0.57–2.09)	0.793	0.93 (0.64–1.34)	0.691
2/Hurdle				
No MDI	1.11 (0.35–3.58)	0.859	0.75 (0.35–1.64)	0.477
MDI	1.13 (0.57–2.25)	0.732	0.89 (0.59–1.34)	0.582
$D_{3-4}MF/T$				
1/Hurdle				
No MDI	2.10 (0.54–8.09)	0.283	0.80 (0.16–4.04)	0.784
MDI	1.36 (0.60–3.10)	0.457	0.89 (0.33–2.36)	0.813
2/Hurdle				
No MDI	2.00 (0.51–7.86)	0.320	0.98 (0.19–5.07)	0.977
MDI	1.12 (0.44–2.83)	0.811	1.18 (0.39–3.57)	0.764
15-year follow-up				
D_{1-2}/T				
1/Hurdle				
No MDI	0.72 (0.28–1.85)	0.494	0.98 (0.58–1.67)	0.945
MDI	0.76 (0.42–1.38)	0.363	1.02 (0.73–1.42)	0.911
2/Hurdle				
No MDI	0.82 (0.31–2.17)	0.696	0.99 (0.57–1.73)	0.979
MDI	0.81 (0.42–1.54)	0.517	1.05 (0.72–1.51)	0.808
$D_{3-4}MF/T$				
1/Hurdle				
No MDI	1.08 (0.44–2.68)	0.865	0.70 (0.30–1.67)	0.427
MDI	1.25 (0.72–2.19)	0.427	0.92 (0.57–1.48)	0.721
2/Hurdle				
No MDI	1.03 (0.41–2.62)	0.950	0.76 (0.34–1.71)	0.504
MDI	1.10 (0.59–2.03)	0.762	1.15 (0.71–1.86)	0.559

The reference group are the non-asthmatics. Model 1 is adjusted for study, sex, age, and body mass index. Model 2 has the same adjustments as Model 1 plus socio-economic factors and other lifestyle factors (parental education, smoking during pregnancy, parental atopy, breastfeeding habits, and adolescent smoking at 15 years).

Hurdle, Poisson hurdle model; OR, odds ratio; CI, confidence interval; RR, relative risk; MDI, metered-dose inhalers.

Table 5. Poisson hurdle regression models to analyse the association between asthma and incidence rate of caries in 730 adolescents between the 10- and 15-year follow-up

Model	Caries prevalence		Caries severity	
	OR (CI)	*p* value	RR (CI)	*p* value
$\Delta D_{1-2}/T$				
1/Hurdle				
No MDI	2.51 (0.64–9.85)	0.187	0.75 (0.38–1.46)	0.395
MDI	0.96 (0.49–1.90)	0.908	0.87 (0.56–1.35)	0.541
2/Hurdle				
No MDI	2.85 (0.71–11.46)	0.140	0.84 (0.42–1.69)	0.629
MDI	1.04 (0.50–2.14)	0.918	0.97 (0.60–1.56)	0.897
$\Delta D_{3-4}MF/T$				
1/Hurdle				
No MDI	1.43 (0.43–4.76)	0.560	1.14 (0.39–3.29)	0.813
MDI	0.90 (0.44–1.84)	0.768	0.90 (0.43–1.89)	0.787
2/Hurdle				
No MDI	1.64 (0.49–5.50)	0.421	1.28 (0.48–3.39)	0.621
MDI	0.84 (0.39–1.82)	0.657	1.15 (0.54–2.41)	0.720

The reference group are the non-asthmatics. Model 1 is adjusted for study, sex, age, and body mass index. Model 2 has the same adjustments as Model 1 plus socio-economic factors and other lifestyle factors (parental education, smoking during pregnancy, parental atopy, and breastfeeding habits).

Hurdle, Poisson hurdle model; OR, odds ratio; CI, confidence interval; RR, relative risk; MDI, metered-dose inhalers.

Discussion

The aim of the present study was to examine the association between asthma and dental caries or MIH under inclusion of inhaled asthma therapy using MDIs in a population-based sample of adolescents. The major finding was that adolescents suffering from asthma did not show any significant difference in caries incidence nor prevalence compared to healthy controls independent of MDI medication (Tables 4 and 5). The results appear to be well supported by previous reports and coincide with the findings of the review by Maupomé et al. [2010] that large cohort studies are more likely to find no association than case-control studies. Contrary to previous literature [Samec et al., 2013; Santos et al., 2012], in our study, asthma medication seemed to have no effect on dental caries. However, this is in line with reports of other recently published studies [Alaki et al., 2013; Brigic et al., 2015].

There are only a few cohort studies that have examined the association between asthma and caries in adolescents [Meldrum et al., 2001; Wogelius et al., 2004]. The study by Meldrum et al. [2001], with a comparable study design to the present study, also found no apparent association between dental caries and asthma. Another cohort study, by Wogelius et al. [2004], found no association in the primary dentition, while for the permanent teeth, asthmatics who took both inhaled β-antagonists and corticosteroids, seemed to have a higher caries susceptibility. However, the age of the participants was between 5 and 7 years, which means they did not have a fully erupted permanent dentition, unlike the participants in the present study and the study by Meldrum et al. [2001]. The increase in the prevalence of MIH from 10 years (31.6%) to 15 years (37.5%) in this study may be related to the fact that the permanent dentition has fully erupted at the age of 15 years so that more teeth can be assessed compared to age 10 years.

Table 6. Poisson hurdle regression models to analyse the association between asthma and molar incisor hypomineralisation (MIH) in 730 adolescents at the 10- and 15-year follow-up

	MIH prevalence		MIH severity	
	OR (CI)	*p* value	RR (CI)	*p* value
10-year follow-up				
MIH/T				
1/Hurdle				
No MDI	3.27 (0.99–10.79)	0.052	0.67 (0.25–1.78)	0.421
MDI	0.91 (0.44–1.85)	0.786	0.65 (0.30–1.41)	0.273
2/Hurdle				
No MDI	2.98 (0.90–9.85)	0.073	0.67 (0.27–1.68)	**0.389**
MDI	0.80 (0.37–1.74)	0.571	0.80 (0.38–1.71)	0.573
15-year follow-up				
MIH/T				
1/Hurdle				
No MDI	2.59 (1.05–6.38)	**0.039**	0.90 (0.46–1.74)	0.751
MDI	0.82 (0.46–1.46)	0.494	0.92 (0.53–1.59)	0.753
2/Hurdle				
No MDI	2.56 (1.03–6.37)	**0.043**	0.87 (0.46–1.65)	0.677
MDI	0.77 (0.41–1.45)	0.421	0.94 (0.53–1.65)	0.828

The reference group are the non-asthmatics. Model 1 is adjusted for study, sex, age, and body mass index. Model 2 has the same adjustments as Model 1 plus socio-economic factors and other lifestyle factors (parental education, smoking during pregnancy, parental atopy, breastfeeding habits, and adolescent smoking at 15 years).

Boldface indicates significance.

Hurdle, Poisson hurdle model; OR, odds ratio; CI, confidence interval; RR, relative risk; MDI, metered-dose inhalers.

Uniquely, this is the first cohort study that examines the association between asthma and non-cavitated carious lesions, which are considered an important dental health variable, as they are an early and sensitive disease marker [Kühnisch et al., 2009; Kühnisch et al., 2011; Pitts, 2009]. The fact that only the DMF index was measured may have underestimated caries prevalence and experience in previous studies. The present findings show that caries (54%, 79%) and MIH (31.6%, 37.5%) are prevalent conditions in adolescents from Munich, Germany, examined at 10 and 15 years of age, respectively (Tables 2 and 3). It should be emphasized that all dental health variables are documented based on an accurate clinical examination with good intra- and inter-examiner reliability [Kühnisch et al., 2018].

To our knowledge, this is the first study to investigate the association between MIH and asthma in a longitudinal population-based study of children and adolescents. A recent systematic review by Silva et al. [2016] demonstrated that during infancy, asthma may act as a risk factor for the development of MIH [Allazzam et al., 2014; Kühnisch et al., 2014b; Silva et al., 2016; Tourino et al., 2016]. Whilst the aetiology of MIH is still unclear [Silva et al., 2016], the present study did not show that asthma or the intake of MDIs had an effect on the prevalence of MIH at the 10-year follow-up. The borderline significant effect determined in MIH/T (OR = 2.56, 95%CI = 1.03–6.37, $p = 0.043$) at the 15-year follow-up could be explained by the low number of asthmatics who were not taking any MDIs in our sample (Table 1). This is supported by the wide confidence interval (Table 6). Therefore, the results should not be overvalued and indicate the need for further research.

As respiratory diseases during childhood could have an effect on MIH [Kühnisch et al., 2014b], sensitivity analyses were conducted in a subpopulation. Information on antibiotic use and tertian fever during the first 2 years of life as well as doctor-diagnosed pneumonia during the first 5 years of life was available in the LISA study and used as additional confounding variables. The results show that the association between asthma and MIH did not change after further adjustment (data not shown).

The longitudinal design of our study and the long-term follow-up until 15 years of a large study population should be understood as a strength. It allows the analysis at two time points, which increases the validity of the results. The statistical approach used in the present study (Tables 4–6) included the hurdle regression model according to the latest recommendation for epidemiological studies as the included indices frequently showed a strongly positive skewed distribution with a large peak of zeros [Hofstetter et al., 2016]. Furthermore, the availability of a broad range of caries and MIH parameters assessed on all permanent teeth on a population-based level should be mentioned as another strength of the present study.

An aspect that should be regarded carefully is the sample size. Whilst the population size of the cohort was large, it consisted mostly of healthy adolescents. At the 10-year follow-up, only 52 (7.1%) study participants were classified to have physician-diagnosed asthma of whom only 12 did not take any MDI medication. However, the lifetime prevalence of asthma in our study is higher than that reported in a recent Germany-wide study of the Robert Koch Institute [Schmitz et al., 2014]. Furthermore, the definition of asthma is based on parental reports of a doctor diagnosis for each year up to 15 years of age, but there was no clinical ascertainment of the parentally reported diagnosis. Moreover, the definition of asthma cannot reflect the complexity of the disease, since the classification according to different phenotypes of the disease is lacking. Von Bülow et al. [2015]

reported that poor asthma control was associated with a low socio-economic status. Poor asthma control was defined as a high exacerbation rate and high use of inhalers [Von Bülow et al., 2015] suggestive of an increased risk of dental caries [Alavaikko et al., 2011]. The present cohort originates from a high socio-economic background, and most parents in the sample are highly educated (Table 1), which reflects the metropolitan area of Munich with a relatively high quality of life, high cost of living, and low unemployment. Although detailed information on the frequency of MDI medication is not available, it can be assumed that the asthmatic participants had their asthma well controlled.

In conclusion, the present study indicates that there is no association between asthma and dental caries in adolescents. An increased odd of borderline significance was found for MIH/T in asthmatics without MDI medication at the age of 15, but future longitudinal studies are needed to confirm this finding.

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Statement of Ethics

Written informed consent for study participation was obtained from the participants' families as well as from the participants themselves. The study was approved by the Ethics Committee of the Bavarian Board of Physicians (10-year follow-up: No. 05100 for GINIplus and No. 07098 for LISA, 15-year follow-up: No. 10090 for GINIplus and No. 12067 for LISA).

Disclosure Statement

The authors declare no potential conflicts of interest with respect to the authorship and publication of this article.

Author Contributions

J.K., M.S., and H.S. designed the study. L.K.H. conducted the statistical analyses and wrote the initial draft. C.F. contributed to the statistical analysis and revised the manuscript. All authors contributed to the acquisition and interpretation of data and approved the final version.

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