

On Oral Health in Young People with Asthma

Malin Stensson

Department of Cariology
Institute of Odontology at Sahlgrenska Academy
University of Gothenburg



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To Fredrik, Hilda and Ella

I think we're going to the moon because it's in the nature of the human being to face challenges. It's by the nature of his deep inner soul... we're required to do these things just as salmon swim upstream.

Neil Armstrong

Abstract

On Oral Health in Young People with Asthma

Malin Stensson, Department of Cariology, Institute of Odontology, Sahlgrenska Academy, University of Gothenburg, Box 450, SE-405 30 Gothenburg, Sweden. Email: malin.stensson@hhj.hj.se

Objective. The aim of this thesis was to investigate the oral health of young individuals with and without asthma. **Material.** In Study I, a group of 3- (n=66) and 6-year-old children (n=61) with asthma and two healthy control groups (n=62 and n=55 respectively) participated. In Study II, 3-year-old children with asthma (n=64) and a healthy control group (n=50) were followed from 3 to 6 years of age. In Study III, adolescents with severe and long-term asthma (n=20) and a healthy control group (n=20) were included. In Study IV, young adults with long-term asthma (n=20) and a healthy control group (n=20) participated. **Methods.** A clinical examination was performed and the prevalence of caries, gingival inflammation, plaque and the numbers of mutans streptococci and lactobacilli in saliva were determined. In Study II, the caries increment between 3 and 6 years of age was investigated. A radiographic examination was conducted in all the studies, apart from in the 3-year-old children. The participants or their parents were interviewed regarding various oral health-related factors. To assess the caries risk, a computer program, the “Cariogram”, was used. In Studies III and IV, the salivary secretion rate and plaque pH, after a sucrose rinse for up to 40 min at two approximal sites, were measured. In Study IV, gingival crevicular fluid, periodontal pockets and the plaque formation rate were determined. **Results.** In Study I, the mean \pm SD dfs in the 3-year-olds with asthma was 1.4 ± 3.2 compared with 0.5 ± 1.2 in the control group ($p < 0.05$). The corresponding figures for the 6-year-olds were 2.5 ± 3.9 and 1.8 ± 2.8 (NS). The 3-year-old children with asthma had more gingival bleeding than the healthy controls ($p < 0.05$). Children with asthma reported a higher consumption of sugar-containing drinks and were more frequently mouth breathers than the control groups ($p < 0.05$). Children with asthma and an immigrant background had a higher mean dfs than children with an immigrant background in the control group. In the follow-up study (Study II), the increment of initial caries was higher for children with asthma compared with the control group ($p < 0.05$). At both 3 and 6 years of age, asthmatic children were more frequently mouth breathers than their controls (only statistically significant in the 6-year-olds). In Study III, the mean \pm SD DFS was 4.9 ± 5.5 in adolescents with asthma compared with 1.4 ± 2.3 in the control group ($p < 0.01$). The Cariogram data in the control group showed that 75% had a “chance of avoiding caries” compared with 54% in the asthma group ($p < 0.01$). A lower initial and final pH in plaque was found in the asthma groups (only statistically significant in Study III). More gingival inflammation ($p < 0.05$), more frequent mouth breathing (NS) and a lower salivary secretion rate were found in the adolescents and young adults with asthma compared with the control groups ($p < 0.05$). The mean \pm SD DFS was 8.6 ± 10.6 in the young adult asthma group compared with 4.0 ± 5.2 in the controls (NS). **Conclusions.** The results of this thesis indicate that young individuals with asthma have a higher caries prevalence, more gingival inflammation and are more frequently mouth breathers compared with healthy individuals of the same age. In younger children with asthma, a higher intake of sugary drinks was more common and, in the older age group (adolescents and young adults), a lower salivary secretion rate and plaque pH were found in the asthma groups compared with the control groups.

Key words: Adolescents, Asthma, Caries, Cariogram, Gingival bleeding, Mouth breathing, Oral health, Plaque-pH, Saliva secretion

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Paper I-IV

Original papers

The thesis is based on the following papers, which are referred to by their Roman numerals in the text:

- I. Stensson M, Wendt L-K, Koch G, Oldaeus G, Birkhed D. Oral health in pre-school children with asthma. *Int J Paediatr Dent* 2008;18:243-250.
- II. Stensson M, Wendt L-K, Koch G, Nilsson M, Oldaeus G, Birkhed D. Oral health in pre-school children with asthma – followed from 3 to 6 years. *Int J Paediatr Dent* 2010;20:165-172.
- III. Stensson M, Wendt L-K, Koch G, Oldaeus G, Lingström P, Birkhed D. Caries-related factors and plaque-pH response in adolescents with long-term asthma. *Caries Res*, accepted for publication.
- IV. Stensson M, Wendt L-K, Koch G, Oldaeus G, Ramberg P, Birkhed D. Oral health in young adults with long-term, controlled asthma. *Acta Odontol Scand*, accepted for publication.

Abbreviations and definitions

The following terminology has been used in this thesis:

GINA	Global Initiative for Asthma
ISAAC	International Study of Asthma and Allergies in Childhood
defs	decayed, extracted, filled tooth surfaces in primary teeth
DMFS	Decayed, Missed, Filled tooth Surfaces in permanent teeth
i	initial caries
m	manifest caries
a	approximal
SD	Standard Deviation
NS	Not statistical Significant

Introduction

In this thesis, the oral health of individuals with asthma at different ages from childhood to young adulthood was investigated. Since asthma and caries are two of the most prevalent diseases in the world, affecting people of all ages^{1,2}, it is a matter of interest to investigate whether there are any association between these two diseases.

Dental caries

Dental caries is a process involving an interaction between cariogenic microorganisms, diet and host³. This interaction may affect any tooth surface in the oral cavity and lead to the destruction of the teeth, due to changes in the pathological shift in the oral biofilm. These changes cause demineralisation of the tooth structure. During the first stage, caries is defined as *initial caries*, verified as a loss of mineral in the enamel giving a chalky appearance but without any cavitation. If the surface loss progresses into the dentine, *manifest caries* appears⁴.

A substantial decline in caries prevalence has been reported during the last century⁵, but, in spite of this, dental caries is one of the most common diseases and a public health problem² and there are still individuals and populations that show a high caries prevalence^{6,7}. In Sweden, the past few decades, the decrease in caries prevalence in young children has changed to a tendency towards stagnation⁸. In a report by The National Board of Health and Welfare from 2008⁹, 95% of Swedish 3-year-olds were caries free. The corresponding figures for 6-year-olds was 74%, for 12-year-olds 61% and for 19-year-olds 30%. The mean DFT was 0.9 in Swedish 12- year-olds and 2.8 in the 19-year-olds. Only teeth with manifest, not initial caries were registered in this report. As a result, the national reports do not always give the total picture of the caries situation and the outcome is often underestimated^{10,11}. This problem is revealed when comparing different studies. In studies investigating caries prevalence in young Swedish individuals, the majority of caries lesions in these individuals were initial lesions^{12,11,13}.

Caries-related factors

Caries development is influenced by environmental and hereditary factors. Frequent intakes of fermentable carbohydrates, poor oral hygiene, impaired salivary flow rate and low salivary buffer capacity, contributing to caries development. The metabolic activity in the oral biofilm (dental plaque), including lactobacilli and mutans streptococci, is also of great importance^{14,15}.

Dietary habits

The relationship between caries and fermentable carbohydrates, especially sugar, is well-documented¹⁶. Nowadays, this relationship is not so evident due to more frequent exposure to fluorides. However, in individuals with a frequent intake of sugary products, in combination with poor oral hygiene, the result is a high rate of caries development^{17,18}. Frequent sugar intake during the first year of life is a risk factor for caries development in pre-school children¹⁹.

Tooth-brushing habits

Optimal oral hygiene is important for caries prevalence²⁰. If good oral hygiene habits are established in early childhood, this behaviour is often also maintained later in life²¹. A Swedish study by Hugoson et al.²² reports that the frequency of tooth brushing has increased since the 1970s, and, in 2003, about 73-93% of individuals between 3 and 80 years of age brushed their teeth at least twice a day.

Fluoride toothpaste

One explanation for the decline in caries prevalence during the last few decades could be the regular use of fluoride toothpaste²³. This regular exposure to fluoride inhibits the demineralisation of the enamel and stimulates the remineralisation of the tooth surface²⁴. In a review article from 2009²⁵, it was concluded that the daily use of fluoride toothpaste has a significant caries-preventive effect in children.

Salivary factors

Saliva plays an important role in maintaining oral health. Saliva has several caries-prevention functions, such as antimicrobial systems, buffer capacity, content of calcium, inorganic phosphate and pH-increasing substances. However, one of the most important functions when it comes to preventing caries is the flushing and neutralising effect of the saliva²⁶. An impaired saliva secretion rate may be a side-effect of medication²⁷ and occur more often in older individuals, but has also been found in younger adults²⁸. Studies investigating the saliva secretion rate in young individuals are contradictory. This differences may be explained by the difficulty involved in measuring the saliva secretion rate in young children and the fact that the salivary glands do not appear to be fully developed until the age of 15²⁹⁻³¹.

Demographic factors

Two important demographic risk factors in relation to caries are low socio-economic status and immigrant background. According to some researchers, this risk factors may have an indirect effect on oral health^{32,33}. Children with this background often have a higher consumption of sugary products and poorer oral hygiene compared with children without this background^{6,8,32,33}. In the Scandinavian countries, several studies have reported an association between high caries prevalence and immigrant background in children living in a areas with low socio-economic status^{6,8,32-34}.

Previous caries prevalence

Another important risk factor for caries development is past caries experience. Several studies have reported that caries experience in the primary teeth is strongly associated to caries development in the permanent dentition^{35,36}. This is in accordance with two systemic reviews^{37,38}, that confirmed past caries experience as one of the most significant predictor of future caries development in young individuals.

Microbiological factors

Mutans streptococci colonise the tooth surfaces and are the major pathogens of the development of dental caries. The cariogenic potential of these microorganisms is related to their acidogenic and aciduric properties and their ability to adhere to the tooth surface and to other bacteria³⁹.

Mutans streptococci are mainly associated with the initiation of the caries lesion compared with the highly acidogenic lactobacilli, which are more common in the caries lesions that have progressed into the dentine. In addition, high levels of lactobacilli indicate the high consumption of fermentable carbohydrates⁴⁰.

Dental plaque and gingival inflammation

In 1965, Løe et al.⁴¹ demonstrated that the accumulation of a microbial biofilm, also known as dental plaque, on healthy gingiva results in gingival inflammation. The gingival inflammation is reversible if good oral health measures are instituted, but, if untreated, it may lead to irreversible inflammatory disease in the periodontal tissues^{41,42}. Plaque-induced gingival inflammation occurs both in children and adults^{42,43}, but during adolescent a decline follows to gradually rise throughout adult life⁴⁴.

Dental erosion

Dental erosion may be defined as the “loss of dental hard tissue by a chemical process that does not involve bacteria”⁴⁵. It is more frequent in young children and adolescents due to their higher consumption of soft drinks compared with older individuals⁴⁶. The majority of the teeth with signs of erosions are the lower first molars and the buccal and palatal surfaces of maxillary anterior teeth^{47,48}. Both extrinsic and intrinsic factors are associated with dental erosion. The intake of acidic food and drinks, medical drugs and vomiting are an example of such factors. In a systematic review from 2008, a strong association between gastro-oesophageal reflux and dental erosion was found⁴⁹. Drinking and eating habits-, are also important factors in the development of dental erosions^{50,51}.

Mouth breathing

Mouth breathing is an oral habit that can be defined as consistently using the mouth, rather than the nose, as the pathway of air during respiration⁵². Factors that contribute to mouth breathing may be enlarged adenoids and tonsils, and swelling of the mucous membranes in the nasal airways due to allergy and asthma disease⁵³. In children, a correlation has been found between mouth breathing and both caries and gingival inflammation⁵²⁻⁵⁷. This inflammation is often located in the labial gingiva in the anterior region of the upper jaw-,

and may be associated with inadequate upper lip coverage⁵⁴. This reduces the protective effect of the saliva and may cause gingival inflammation^{56,57}

Risk assessment of caries

As caries is a multifactorial disease and affects individuals in different ways, it is interesting to identify risk individuals. The Cariogram is a computer-based program with a graphical image illustrating the caries risk profiles in individuals⁵⁸ (see Figure 1). It is a predictive model and makes it possible to identify the impact of individual risk factors. Longitudinal studies have evaluated the Cariogram and found that the model appeared to predict caries increment in both children and older individuals⁵⁹⁻⁶¹. When using the Cariogram the individuals are first examined clinically and relevant data for caries are collected. The factors are caries-related bacteria, diet, susceptibility (fluoride exposure, salivary secretion and salivary buffer capacity) and circumstances (caries experience and related diseases). The program presents its results as a pie chart, where "bacteria" appears as a red sector, "diet" as a dark-blue sector, "susceptibility" as a light-blue sector and "circumstances" as a yellow sector, see the example in Figure 1.

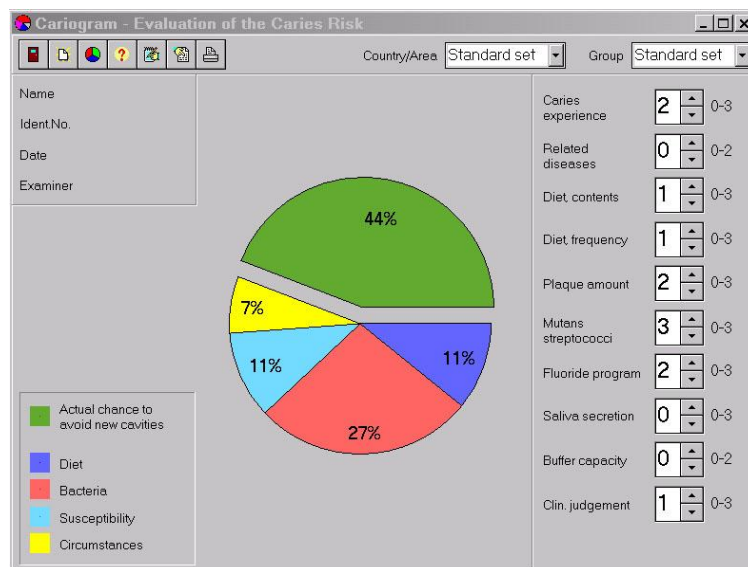


Figure 1. An example of a Cariogram showing an individual with a 44% "chance of avoiding new cavities" (courtesy Dr Gunnel. Hänsel-Petersson).

Asthma

Asthma is one of the most common chronic diseases throughout the world and is a serious global health problem that affect people of all ages. When uncontrolled, asthma can affect daily life, and is sometimes fatal. Asthma is a disorder defined by its clinical, physiological and pathological characteristics. The definition according to the Global Initiative for Asthma (GINA)⁶² is as follows.

“Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread, but variable, airflow obstruction within the lung that is often reversible either spontaneously or with treatment.”

The aetiology of asthma is not fully understood, but several factors have an impact on the development and prognosis. The risk factors for asthma can be divided into host factors (genetic factors, gender, obesity) and environmental factors (allergens, infections, occupational sensitisers, tobacco smoke, outdoor/ indoor air pollution, diet). The mechanisms whereby these factors influence the development of asthma are complex⁶³.

Host factors

Asthma has a heritable component and multiple genes may be involved in the pathogenesis of asthma^{64,65}. In young children, male gender and premature birth is a risk factor. However, as children get older, the difference between the gender narrows, and by adulthood asthma is more common in women than in men. Mediators such as leptin associated with obesity may affect airway function and increase the development of asthma disease⁶².

Environmental factors

The specific role of indoor and outdoor allergens has not been fully unravelled, but they are well known for causing asthma exacerbations. Respiratory infections in early childhood have been associated with the development of asthma⁶⁶ and exposure to tobacco smoke affects children both prenatally and after birth⁶².

The role of outdoor and indoor pollution remains unclear. Some diets (soy protein, processed foods) have been reported to increase asthma symptoms^{67,68}.

Clinical diagnosis of asthma

In young children repeated episodes of breathlessness, wheezing, cough and chest tightness in combination with a viral infection are suggestive of asthma. From five years of age measuring the airflow limitation, in particular the measurement of forced expiratory volume in one second (FEV₁) can be performed by spirometry. The demonstration of the reversibility of FEV₁ is one of the most important tool to confirming an asthma diagnosis. Because there is a strong association between asthma and allergy, especially in schoolchildren, allergy testing is important, either with a skin prick test or by the determination of specific Immunoglobulin E in serum, which can help to identify asthma disease^{69,70}.

Classification of asthma

The classification of asthma in these four studies (I-IV) is based on the classification of the severity of asthma symptoms in the Swedish guidelines on the management of asthma (Swedish Paediatric Society, Section of Paediatric Allergy)⁷¹. This classification is based on the guidelines of the Global Initiative for Asthma (GINA)⁶² and is presented in Table 1.

Table 1: The classification of asthma according to the Swedish guidelines on the management of asthma⁷¹

Mild asthma
Exacerbations are rare and symptoms at night uncommon (\leq once a month). No use of inhaled steroids and only intermittent use of short-acting β_2 -agonists
Moderate asthma
Exacerbations are more frequent and symptoms at night more common (2–3 times a month). Periodic use of inhaled steroids in low to moderate doses (\leq 400 $\mu\text{g}/\text{day}$) in combination with short-acting β_2 -agonists
Severe asthma
Exacerbations weekly and regular use of 100-400 $\mu\text{g}/\text{day}$ of inhaled steroids in combination with long-acting β_2 -agonists or leukotriene receptor antagonists
Very severe asthma
Exacerbations weekly and symptoms every day. Regular use of 400-800 $\mu\text{g}/\text{day}$ of inhaled steroids in combination with long-acting β_2 -agonists or leukotriene receptor antagonists

Prevalence of asthma

The prevalence of asthma differ between countries and has increased in some countries, while it has stabilised in others. According to the International Study of Asthma and Allergies in Childhood (ISAAC), the highest prevalence in children (6-7 and 13-14 years old) was found in Ireland and the United Kingdom, while the lowest asthma rates for both ages were found in Albania⁷². In Sweden, asthma has become one of the most common conditions during childhood, and among school-children and adolescents, about 10% are affected by asthma symptoms, while the figure for children under the age of 2 is as high as 20%⁷⁰.

Asthma medication

The goal of asthma treatment is to achieve and maintain clinical control of the disease. The main treatment can be classified as inhalation of controllers or relievers. Inhaled medication is available as a metered-dose inhaler or as dry-powder inhalers.

In small children a metered-dose inhaler with a spacer is more common. Controllers are medications known as glucocorticosteroids, which are taken every day on a long-term basis and have an anti-inflammatory effect. Relievers are medication that quickly reverses bronchoconstriction and relieves its symptoms. The most common relievers are short-acting or long-acting inhaled β_2 -agonists. If glucocorticosteroids fail to achieve control of asthma, the addition of a long-acting inhaled β_2 -agonist or anti-inflammatory montelukast may be needed⁷⁰.

Asthma and oral health

Chronic diseases are sometimes mentioned as a risk factor for the oral health in children⁷³. Mc Derra et al.⁷⁴ reported that the parents of children with asthma may overindulge their children with frequent consumption of sweets and sugary drinks, and this consumption may contribute to the development of caries. Apart from this, it is difficult to judge whether the increased risk for caries in individuals with asthma is caused by the disease itself or by the medical treatment.

During the last 20 years, several studies have investigated the oral health of asthmatics and the results are somewhat conflicting. The relationship between asthma and oral health has been summarised in two literature reviews by Maupomé et al.⁷⁵ and Thomas et al.⁷⁶. In the review by Maupomé et al. the association between asthma and caries was studied, and 29 articles, the majority from Scandinavian countries, North America and Asia, published between 1979 and 2010, were included. The authors found no strong evidence that there exist a causal link between caries and asthma. The studies with a large number of participants showed a negative or even inverse association between caries and asthma disease⁷⁵. In the other review by Thomas et al. the relationship between asthma and caries, dental erosion, periodontal diseases and oral candidiasis was studied. The authors found that asthmatic patients may run a higher risk of developing dental diseases⁷⁶.

In Table 2, English-language reports from 1979 to 2010 on the association between asthma and caries, asthma and gingival inflammation/plaque, and asthma and saliva secretion, are presented. Most of the studies found a correlation between asthma and caries, asthma and gingival inflammation, plaque and asthma and a low salivary rate and asthma in both children and adults, whereas some have found no such relationship (see Table 2).

To summarise, most of the studies have been conducted in children and adolescents and few studies have focused on adult populations with asthma (see Table 2). Possible reasons for the different results may be that most studies have a cross-sectional design, small samples and differences in study populations, including incoherent age groups, or differences in terms of medication and the severity of the asthma disease. However, the majority of studies investigating the oral health of individuals with asthma indicate that asthmatics run an increased risk of oral diseases, especially caries. There is therefore, a need for well-controlled studies, with homogeneous study groups of asthmatics in different ages.

Wogelius et al.⁷⁷ studied the caries prevalence in 5- to 7-year-old Danish children (n=926) with prescribed asthma drugs. They found no increase in the risk of dental caries in the primary dentition, while the risk were increased in newly erupted molars. In a study from 1999 in the USA⁷⁸, patient records from asthmatic children from 2 to 13 years of age were examined and a higher caries prevalence was found in the asthmatic children in both the primary and the permanent dentition compared with healthy controls. This is in line with the findings in the studies by Ersin et al.⁷⁹ and Milano et al.⁸⁰ which reported a positive correlation between caries prevalence and frequency of asthma medication and duration of the asthma disease. This is in contrast to Eloit et al.⁷² who revealed that neither the period nor the severity of the asthma had a significant influence on the risk of caries in asthmatic children.

One explanation for the higher caries prevalence in asthmatics may be a reduced saliva flow rate^{79,82-86}. Ryberg et al.⁸² found an impaired level of total protein, amylase, hexosamine, peroxidase, lysozyme, secretory IgA and potassium after inhalation with β_2 -agonists in the saliva of asthmatic individuals. In another study, Ryberg et al.⁸⁷ also observed that the impaired gland function is caused by the medication and not by the asthma disease. This is in agreement with the findings in experimental studies in rats, where the administration of β -agonists causes hypertrophy and hyperplasia of the salivary glands^{88,89}. The decreased saliva flow rate may be related to higher counts of mutans streptococci and or lactobacilli^{79,83,90}.

A reduced saliva secretion rate and a change in saliva composition may not only contribute to an increased risk of caries, they may also increase the risk of dental erosions in asthmatics^{74,91,92}. Furthermore, it has been shown that the inhalation of corticosteroids and β_2 -agonists may result in substantial pH-drops in plaque and saliva below the critical value of 5.7 for enamel demineralisation^{79,93}. O'Sullivan et al.⁹⁴ reported that the majority of the dry-powder inhalers have a lower pH than the metered-dose inhalers. To help the asthma patients tolerate the taste of the drugs, some of the medication also contains lactose as a carrier vehicle. Low pH, titratable acidity and the potentially cariogenic lactose-based dry-powder form may increase the risk of erosions and caries in asthmatics. This is in line with some studies^{95,91}, but conflicting to others⁹⁶. Tootla et al.⁹⁶ investigated the demineralising potential of asthma inhalers in subsurface enamel and they found no significant acidogenic/cariogenic effect from asthma inhalers. Another explanation for dental erosions in asthmatics may be gastro-oesophageal reflux disease⁹⁷. However, in studies in children with dental erosions and asthma, no high frequency of reflux has been found⁹⁸. This is in agreement with the findings of Dugmore and Rock⁹⁸, who concluded that it is unlikely that problems with reflux disease have any significant influence on tooth erosions in asthmatics.

Mc Derra et al.⁷⁴ found a higher intake of sugary drinks, although it was not statistically significant, in children with asthma compared with healthy individuals. The higher intake of sugary drinks could be due to more frequent mouth breathing, which is common in asthmatics⁹⁹. A relationship between mouth breathing and dentofacial anomalies in asthmatics such as more dental crossbite, overbite and overjet in asthmatic children has been found⁹⁹⁻¹⁰¹. The possible effect of the asthma disease on the periodontal status has been discussed in several studies^{74,82,84,85,102-105}. The higher frequency of mouth breathing, as well as various immunological factors in asthmatics has been linked to more gingival inflammation in both children and adults with asthma^{74,106,105}. In a study from Finland, asthmatic children had more gingival inflammation, pronounced in the upper front region¹⁰². A higher concentration of IgE in gingival tissue which can cause periodontal destruction, has been found in patients with asthma¹⁰⁷. Individuals with asthma often suffer from birch pollen allergy and more gingival inflammation in asthmatics with allergy has been observed during the pollen season when compared with the off-season¹⁰⁸. It has also been reported in some studies that children with asthma have more plaque and calculus compared with children without asthma^{74,109}.

The higher levels of calculus in asthmatics compared with non-asthmatics may be explained by increased levels of calcium and phosphorus in submaxillary and parotid saliva¹⁰⁹.

However, this is in contrast to Ryberg et al.⁸³, who reported decreased levels of calcium in stimulated parotid saliva.

Table 2. Summary of studies on the association between asthma and oral health determinants. The positive relation are marked in bold.

First author, Country; year	N	Study design	Age	Asthma drugs	Caries	Gingival inflammation / plaque	Low salivary rate
Hyppä T ¹⁰² , Finland; 1979	A:30 C:30	Case-control	10–12	Cromoglycate Corticosteroids	Negative	Positive ¹	Negative
Hyppä T ¹⁰³ , Finland; 1981	A:20 C:20	Cross-sectional	20–58	No information		Positive	Negative
Storhaug K ¹¹⁰ , Norway; 1985	A:47 C:386	Cross-sectional	1–6	No information	Positive		
Bjerkeborn, B ¹¹¹ , Sweden; 1987	A:61 C:55	Cross-sectional	5–18	β ₂ -agonists Theophyllines Corticosteroids Cromoglycate	Negative	Negative	Positive ²
Ryberg M ⁹⁰ , Sweden; 1987	A:24 C:24	Cross-sectional	10–20	β ₂ -agonists	Positive		Negative
Ryberg M ⁸³ , Sweden; 1991	A:21 C:21	Follow-up	14–24	β ₂ -agonists	Positive		Positive
Arnrup K ¹¹¹ , Sweden; 1993	A:25 C:244	Cross-sectional	0–19	No information	Positive		
McDerra EJ ⁷⁴ , Great Britain; 1998	A:100 C:149	Case-control	4–16	Current use of inhalers	Positive	Positive	
Kankaala TM ¹¹² , Finland; 1998	A:51 C:102	Follow-up, Case-control	>3	Corticosteroids β ₂ -agonists	Positive		
Laurikainen K ⁸⁴ , Finland; 1998	A:37 C:35	Cross-sectional	25–50	Corticosteroids β ₂ -agonists	Negative	Positive ¹	Positive
Lenander-Lumikari M ⁸⁵ , Finland; 1998	A:26 C:33	Cross-sectional	25–50	Corticosteroids β ₂ -agonists		Positive ¹	Positive
Milano M ⁷⁸ , USA; 1999	A:179 C:165	Case-control	2–13	Continuous use of asthma-drugs	Positive		
Shulman JG ¹¹³ , USA; 2001	A:1129 C:5809	Case-control	4–16	Corticosteroids β ₂ -agonists	Negative		
Meldrum AM ¹¹⁴ , New Zealand; 2001	A:92 C:206	Follow-up Cohort	14–24	Antiasthmatic drugs	Negative		

First Author, Country; Year	N	Study design	Age	Asthma drugs	Caries	Gingival inflammation / plaque	Low salivary rate
Reddy DK ¹¹⁵ , India; 2003	A:205	Cross-sectional	3–18	Inhalers	Positive		
Shulman JG ¹¹⁶ , USA; 2003	A:253 C:1358	Case-control	13–17	Antiasthmatic drugs Antihistamines Corticosteroids	Negative	Negative	
Eloot A.K ⁸¹ , Belgium; 2004	A:140	Cross-sectional	3–17	Corticosteroids β_2 -agonists	Negative	Negative	
Wogelius A ⁷⁷ , Denmark; 2004	A:1496 C:3424	Cohort	5–7	Corticosteroid β_2 -agonists	Positive ³		
Ersin NK ⁷⁹ , Turkey; 2006	A:106 C:100	Cross-sectional	6–19	Corticosteroids β_2 -agonists Leukotriene ant	Positive	Negative ⁴	Positive
Bimstein E ¹¹⁷ , USA; 2006	A:50 C:114 ⁵	Case-series	85.5 month ⁶	Treatment for asthma	Positive	Positive	
Milano M ⁸⁰ , USA; 2006	A:156	Case-series	4–14	Corticosteroids β_2 -agonists	Positive		
Wierchola B ¹¹⁸ , Poland; 2006	A:326 C:326	Case-control	3–15	Corticosteroids β_2 -agonists	Mainly positive		
Khalilzadeh S ¹¹⁹ , Iran; 2007	A:45 C:46	Case-control	5–15	Corticosteroids β_2 -agonists	Positive		
Sag C ⁸⁶ , Turkey; 2007	A:15 ⁷	Single-blind clinical study	7-17	Corticosteroid Long-acting β_2 -agonists	Not measured	Positive	Positive
Shashikiran ND ¹⁰⁴ , India; 2007	A:105 C:106	1-year follow-up	6–14	Salbutamol inhalers	Positive	Positive	
Mazzoleni M ¹²⁰ , Italy; 2008	A:30 C:30	Case-control	6–12	Corticosteroids Short-acting β_2 -agonists	Positive		
Metha A ¹²¹ , India; 2009	A:80 C:80	Case-control	11–25	Corticosteroids β_2 -agonists	Positive		
Metha A ¹⁰⁵ , India; 2009	A:80 C:80	Case-control	11–25	Corticosteroids β_2 -agonists		Positive	
Anjomshoaa I ¹¹⁶ , USA; 2009	A:48 ⁹	Cross-sectional	17–84	No information	Positive		

¹More gingival inflammation, no differences in plaque

²In children of the young ages with severe asthma

³Increased risk of caries in newly erupted permanent molars

⁴Only plaque indices were measured

⁵Mean age in months

⁶Children with other diseases

⁷Only individuals with asthma before and after treatment with asthma medication

⁸Increased plaque index, no differences in gingival inflammation

⁹Dental data from 318 patients, including 48 with asthma

Aims

This thesis focuses on the oral health of asthmatics and consists of four papers with participants with and without asthma, aged from 3 to 24 years. The specific aims were:

- to study the oral health and its determinants in one group of 3-year-old children and one group of 6-year-old children with asthma, with special reference to asthma, severity, period of exposure to medication and mouth breathing (Paper I),
- to compare caries incidence and caries-associated factors in children followed from 3 to 6 years of age with and without asthma and to investigate whether factors connected with the asthma disease trigger caries development (Paper II),
- to compare caries prevalence and various caries-related factors in a group of adolescents with long-term severe asthma with a matched healthy control group (Paper III), and
- to compare oral health in a group of young adults with long-term asthma with a matched healthy control group and to investigate whether there was any association between asthma and caries and asthma and periodontal factors (Paper IV).

Material and Methods

All the data in this thesis are based on three cross-sectional studies (Papers I, III and IV) and one follow-up study (Paper II). All the studies were performed in the Municipality of Jönköping, a medium-sized city, located in the south of Sweden, with about 126 000 inhabitants. A summary of design and study populations is presented in Figure 2.

Study design

Paper I

This study had a cross-sectional design with clinical examinations and interviews on oral health and its determinants in a group of 3- and 6-year-old children with and without asthma. The data was collected in 2004-2005.

Paper II

This study had a longitudinal follow-up design with clinical examinations and interviews on oral health, its determinants and caries increment in a group of 3-year-olds with and without asthma followed to 6 years of age. The data was collected in 2004-2008.

Paper III

This study had a cross-sectional design with clinical examinations and interviews on oral health, including the Cariogram and plaque-pH, in a group of adolescents (12-16 years of age) with and without asthma. The data was collected in 2008.

Paper IV

This study had a cross-sectional design with clinical examinations and interviews on oral health, including plaque-pH, plaque formation rate, measurement of gingival inflammation and gingival crevicular fluid in a group of young adults (18-24 years of age) with and without asthma. The data was collected in 2009.

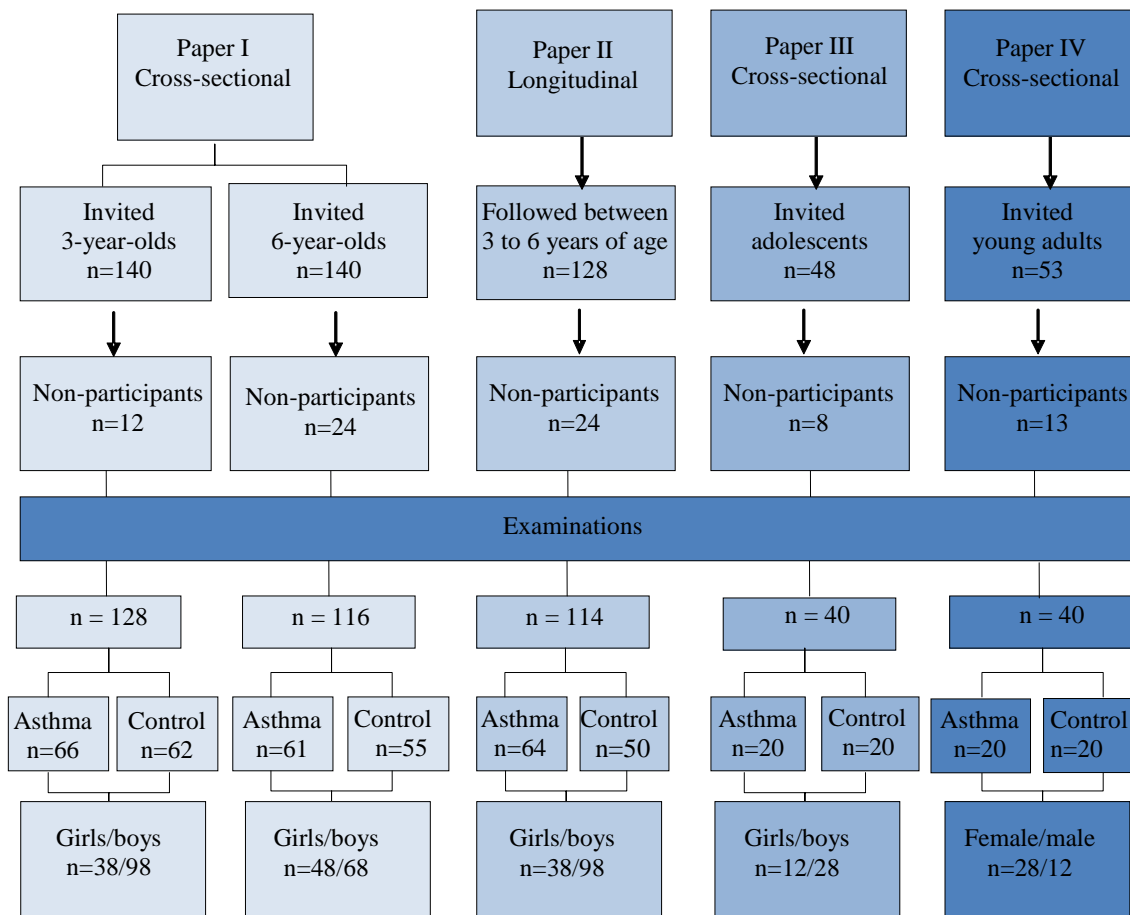


Figure 2. Flow chart of the design and the study populations.

Study populations

Study I

Children with asthma were selected from the Department of Paediatrics at the County Hospital, Ryhov, and from three child welfare centres in the Municipality of Jönköping. The inclusion criteria for the asthmatics were asthma diagnosed by a physician and medical treatment during the last year. The study population consisted of two different age groups. One of the groups, children with asthma, was born between April 2001 and January 2002 and living in the selected area. The other study group consisted of 6-year-old children with asthma born between April 1998 and April 1999 and living in the same area (n=61). Two age- and gender-matched control groups (3 years, n=62, 6 years, n=55) were randomly selected from the County Council's register of persons in Jönköping and consisted of children without a diagnosis of asthma (status was confirmed by the parents). The mean ages of the children at the time of the dental examinations were 3 years (± 2 months) and 6 years (± 2 months). Children with asthma were divided into 3 subgroups according to the debut of the disease: 1) < 1 year of age, 2) 1-2 years of age and 3) > 2 years of age respectively. According to the length of exposure to asthma drugs, the 6-year-olds were divided into four groups: exposed for 1) < 2 years, 2) 2-3 years, 3) > 3-5 years and children exposed for 4) > 5 years. According to the regularity of inhaled steroid medication, the asthmatic children were divided into 2 groups: 1) intermittent use in periods of ≥ 1 time/day and 2) regular daily use ≥ 1 time/day.

Study II

Children with asthma were selected from the same area as in Study I. The inclusion criteria for the asthmatics were asthma diagnosed by a physician and medical treatment at 3 years of age. The study population consisted of children with asthma (n=64), born between April 2001 and January 2002 and residing in the Municipality of Jönköping. These children were examined at 3 and 6 years of age. An age- and gender-matched control group (n=55) was randomly selected from the County Council's register of persons in Jönköping and consisted of children without a diagnosis of asthma (status was confirmed by the parents). The ages of the children at the time of the dental examinations were 3 years (± 2 months) and 6 years (± 2 months). Children with asthma were divided into the same subgroups as in Study I.

Study III

Adolescents with asthma (n=20) were selected from the same area as the children in Studies I and II. The inclusion criteria for the asthma group were asthma diagnosed by a physician and medical treatment for severe or very severe asthma for a minimum of four years. A gender- and age-matched healthy friend, a “social twin”, without a diagnosis of asthma served as a control subject for each of the asthmatic adolescents (n=20). The mean age was 14.0 ± 1.3 years in the asthmatic adolescents and 14.3 ± 1.4 years in the control group. The asthma group was divided into two subgroups according to the debut of the disease: 1) < 5 years of age and 2) ≥ 5 years of age. Furthermore, with respect to the length of exposure to asthma drugs, they were divided into two subgroups: exposed for 1) < 9 years and 2) ≥ 9 years.

Study IV

The young adults with asthma were living in the city of Jönköping and receiving treatment at one of the primary health care centres in the city. The inclusion criteria were asthma diagnosed by a physician and medical treatment for asthma for a minimum of four years and medical treatment consisting of a prescribed combination of inhaled long-acting β_2 -agonists and glucocorticosteroids during the last 2 years. The study population comprised young adults between 18 and 24 years of age with long-term, controlled asthma (n=20). A gender- and age-matched healthy friend, a “social twin”, without a diagnosis of asthma served as a control subject for each of the asthmatic adolescents (n=20). The mean age in years was 21.6 ± 2.3 in the asthma group and 21.7 ± 2.0 in the control group. The asthma group was divided into the same subgroups as in Study III.

Classification of asthma

In Study I, II and III, a senior paediatrician divided the asthmatic children into 4 groups (*mild, moderate, severe and very severe*), according to the classification of severity of asthma symptoms in the Swedish guidelines on the management of asthma (Swedish Paediatric Society, Section of Paediatric Allergy)⁷¹ based on definitions according to the Global Initiative for Health (GINA)⁶¹ guidelines (Table 1). In Study IV, the young adults with asthma had asthma diagnosed by a physician for a minimum of four years and a prescribed combination of inhaled long-acting β_2 agonists and glucocorticosteroids during the last two years. The participants in this asthma group therefore represent a group of individuals with *moderate asthma*.

Non-participants

The number of non-participants is presented in Fig. 2. The main reasons for drop-outs in all four studies were moving out of the area or unwillingness to participate. In Study I, one child in the 6-year-old control group was being treated at a specialist clinic of paediatric dentistry and was therefore excluded. In the same study, two 6-year-old children (one with asthma and one control) were excluded because of other chronic diseases. In Study II, one child in the control group had developed asthma during the follow-up period and was therefore excluded. In the two studies with adolescents (Study III) and young adults (Study IV), the reasons for not taking part in the study in some cases was that they were tired of medical care that had lasted for several years of their life. As a result, the individuals in the control group were selected by the participants in the asthma group (a friend) and no drop-outs in the control groups occurred.

Examination procedures

An overview of examination procedures used in the four studies is presented in Table 3. All the participants were examined clinically and interviewed by one and the same examiner (MS). Before the start and during the studies, the examiner was calibrated repeatedly to an experienced dentist (LKW) in terms of diagnostic criteria. The radiographic bitewings were analysed by these two authors, where one of the examiners was not aware of the group to which the participant belonged. In the event of disagreement, the findings from the radiographs were discussed until consensus was reached. Each examination took 30-60 minutes and was performed with a mirror and probe and under optimal light conditions. The participants were instructed not to eat or drink for two hours preceding the saliva sampling. In Studies III and IV, the participants were examined twice and were instructed not to clean their teeth for 3 days and not to eat or drink anything for two hours before the second examination, including the measurement of pH in dental plaque.

Table 3. Examinations in Study I, II, III and IV

	I	II	III	IV
Caries	X	X	X	X
Radiographs	X ¹	X	X	X
Plaque	X	X	X	
Plaque formation rate				X
Gingival inflammation	X	X	X	X
Gingival crevicular fluid				X
Saliva				
Microorganisms	X	X	X	X
Secretion rate			X	X
Plaque-pH			X	X
Dental erosion				X
Cariogram			X	
Interview	X	X	X	X

¹ Only in the 6-year-olds

Clinical caries examination

In all four papers, both initial and manifest caries lesions were diagnosed. Initial caries was defined as “a demineralised surface with a chalky appearance” and manifest caries as “the minimal level that could be verified as cavities by gentle probing”⁴. The methods were almost identical in Study I and Study II. In order to avoid interference with exfoliated teeth, initial and manifest caries were only diagnosed on primary molars and canines in the 6-year-old group (Study I). In Study II, the caries increment between 3 and 6 years was only recorded in canines and molars. In Study III and Study IV, all permanent tooth surfaces were examined.

Radiographical examination

Two posterior bitewings were taken in the 6-year-old children (Study I and II) and four bitewing radiographs were taken in the adolescents and young adults (Study III and IV). Initial proximal caries was defined as “a caries lesion in the enamel that has not reached the enamel–dentine junction or a lesion that reaches or penetrates the enamel-dentine junction but does not appear to extend into the dentine”. Manifest proximal caries was defined as “a caries lesion that clearly extends into the dentine”³⁶. In Study IV, the level of the alveolar bone loss was recorded, defined as 2 mm or more from the cement-enamel junction to the bone crest

Plaque, gingival status and periodontal pockets

Study I

The presence of visible plaque was recorded after drying the teeth with air as “visible” or “no visible” plaque, according to Plaque Indices 2 and 3 according to Silness and Løe¹²⁴. Plaque was registered buccally on primary upper incisors in the 3-year-olds, and on all surfaces in primary canines and molars in the 6-year-olds.

Study II

The presence of visible plaque was recorded after drying the teeth with air as “visible” or “no visible” plaque, according to the same indices as in Study I. Plaque was registered on all surfaces in primary canines and molars.

Study III

The plaque index was recorded as “visible” or “not visible” plaque according to Ainamo and Bay¹²⁵ in all permanent teeth. The indices were calculated by adding the surfaces with plaque divided by the number of examined surfaces, expressed as percent.

Study IV

In each individual, the right or left quadrant was randomly selected in the upper and lower jaw, with a total of 14 teeth (7 in the upper and 7 in the lower jaw). The plaque formation rate was recorded after 3 days without toothbrushing and proximal cleaning. The plaque index was recorded according to Turesky’s modification of the Quigley Hein Index; grade 1-5¹²⁶ after disclosing the plaque with Erythrosin[®] (Rondell Red; Nordenta, Enköping, Sweden). Periodontal pockets (≥ 4 mm) were measured.

Gingival inflammation

Study I

Gingival inflammation was diagnosed after gentle probing as “bleeding” or “no bleeding” according to Løe and Silness¹²⁷ on all primary tooth surfaces in the 3-year-old children and in all canines and primary molars in the 6-year-olds.

Study II

Gingival inflammation was diagnosed after gentle probing as “bleeding” or “no bleeding” according to the same indices as in Study I in all primary canines and molars in the 3- and 6-year-old children.

Study III

Gingival inflammation was diagnosed after gentle probing, according to the indices of Ainamo and Bay¹²⁵ as “bleeding” or no “bleeding” on all permanent tooth surfaces. The indices were calculated by adding the surfaces with gingival bleeding divided by the number of examined surfaces, expressed as percent.

Study IV

Gingival inflammation was diagnosed after gentle probing corresponding to indices 0 and 3 according to Løe and Silness¹²⁷ on the same tooth surfaces as those selected for the plaque formation rate.

Gingival crevicular fluid

In Study IV, gingival crevicular fluid was collected at the mesio-buccal sites on 16, 24, 33 and 41 using a standard filter paper (Periopaper, Oraflow Inc., NY, USA). The sites were isolated with cotton rolls and air dried. The paper strip was placed gently in the crevice and left in place for 30 seconds. The amount of fluid absorbed by the paper was measured using the Periotron 8000 model 2 (Oraflow Inc.) and was calibrated against different volumes of distilled water to obtain a standard curve.

Dental erosions

In Study IV, erosions were diagnosed on all buccal, lingual and occlusal tooth surfaces, according to Johansson et al.¹²⁸.

1 = smoothed enamel, developmental structures have totally or partially vanished. Enamel surface is shiny, matt, irregular, “melted”, rounded or flat, macro-morphology generally intact.

2 = enamel surface as described in Grade 1 but with macro-morphology clearly changed, faceting or concavity formation within the enamel, no dentinal exposure.

3 = enamel surface as described for Grades 1 and 2 but with macro-morphology greatly changed (close to dentinal exposure of large surfaces) or dentine surface exposed by $\leq 1/3$.

4 = enamel surface as described for Grades 1, 2 and 3 and with dentine surface exposed by $> 1/3$ or pulp visible through the dentine.

Saliva sampling

In Studies III and IV, a paraffin-stimulated whole saliva sample was collected. Both non-stimulated and paraffin-stimulated whole saliva were collected for 5 min and the secretion rate was expressed as ml/min. One millilitre of stimulated saliva was transferred into a vial with 1 ml of pre-reduced transport fluid and sent to the Department of Cariology in Göteborg. The sample was dispersed on a Whirlimixer for 30 seconds and serially diluted in 0.05 M phosphate buffer (pH 7.3). 25- μ l portions were plated in duplicate on mitis salivarius with bacitracin agar for the growth of mutans streptococci and in Rogosa Selective Lactobacilli agar for the growth of lactobacilli. The Rogosa agar plates were incubated aerobically at 37°C for 3 days. The mitis salivarius agar plates were incubated in candle jars at 37°C for 2 days. The number of colony-forming units of mutans streptococci was counted on the mitis salivarius bacitracin agar and identified by their characteristic colony morphology. All colony-forming units in Rogosa agar were considered to be lactobacilli. The number of colony-forming units was transformed to logarithms prior to the statistical analysis. The buffer capacity of paraffin-stimulated whole saliva was estimated by using the Dentobuff[®] Strip test (Orion Diagnostica, Espoo, Finland) and expressed as high (blue), medium (green) or low (yellow), according to the manufacturer's instructions.

Plaque-pH measurements

In Study III and IV, plaque-pH was measured at baseline and at seven time points (1, 3, 5, 10, 20, 30, and 40 min) after a rinsing with 10 ml of a 10% sucrose solution for 1 min. pH was measured with the microtouch method¹²⁹ in two approximal tooth spaces in the upper jaw (regio 16/15 and 13/12). An iridium microelectrode, with a diameter of 0.1 mm and a tip with a 2 mm long loop (Beetrode model MEPH3L, WP. Instruments Inc., New Haven, Conn., USA), was used.

The electrode was connected to an Orion SA 720 pH/ISE meter (Orion Research Inc., Boston, Mass., USA). A reference electrode (MERE1, W.P. Instruments Inc.) was used. A salt bridge was created in KCl between the reference electrode and one of the subject's fingers. The electrodes were calibrated prior to the reading of each value according to Scheie et al.¹³⁰.

Interview

In all four studies, a semi-structured interview, using standardised forms, was conducted (Appendices I and II). The participants or the parent/care-giver of the child was interviewed about prior and current medication, mode of administration and duration of asthma medication, immigrant background (defined as at least one parent born outside the Nordic countries), tooth brushing habits, use of fluorides, mouth breathing during the last year, and dietary habits (drinking during the night and number of daily intakes of caries risk products). The intake frequency of each risk product was calculated according to Wendt and Birkhed¹⁹.

Cariogram

In Study III, a special PC-based computer program (Cariogram) was used to assess the caries risk⁵⁸. The risk was expressed as the "chance of avoiding caries" (in %) for each individual. The adolescents were divided into five subgroups according to the Cariogram: 1) 0-20% (high caries risk), 2) 21-40%, 3) 41-60%, 4) 61-80% and 5) 81-100% (low caries risk). In the Cariogram, the following nine parameters of relevance to caries were entered into the program: 1) caries experience, 2) related diseases, 3) diet content, 4) diet frequency, 5) plaque amount, 6) mutans streptococci, 7) fluoride programme, 8) saliva secretion and 9) saliva buffering capacity. To avoid confounding factors, the Cariogram parameter called "related diseases or condition associated with caries" was excluded from the calculation.

Statistical methods

The data were analysed using the Statistical Package for the Social Sciences (SPSS) version 13.0, 16.0 and 17.0 software program (SPSS Inc., Chicago, IL, USA) (Study I-IV). In Study II, SAS software version. 9.1.3 (Copyright, SAS Institute Inc., Cary, NC, USA), Statistica ver. 8, Copyright Stat Soft, Inc. (2008) and SPSS version. 16.0 (SPSS Inc., Chicago, IL, USA) were used.

Fisher's exact test was used to test the association between caries as an independent variable with categorical dependent variables and Mann-Whitney U test was used for continuous dependent variables. In Study I and II, multivariate logistic regression analyses were performed to explore the effects on caries (as a dependent variable) with variables of relevance to oral health (explanatory variables), such as dietary habits, and the presence of plaque, bleeding on probing (gingivitis) and mouth breathing, as well as the asthma disease, the debut of the disease and the period of exposure to medication. In Study II, the uni and multivariate analyses of def were coded as at different levels (0, 1, 2, 3, and 4). To decide if whether a variable should be included in the multivariate analyses, a significance level of $p < 0.2$ was set. In all the analyses, the results for some continuous variables are presented as mean \pm SD and the level of statistical significance was set at $p < 0.05$.

Ethical considerations

The study protocols for the four studies follow the ethical rules for research, with the general ethical principles (*respect for persons, justice and beneficence*) described in the Helsinki Declaration¹²⁴. All the studies were approved by the Ethics Committee at the University of Linköping, Sweden. In research that includes humans, it is important to consider the ethical principle of "respect for persons" (*autonomy*). The participating children and adolescents (Studies I, II and III) are young individuals with impaired or diminished autonomy, which requires that they are dependent on adults. Informed consent for the children to participate was therefore obtained from the parents or care-givers for the children aged < 16 years. The written information letter to all participants (one information letter to the child and one to the parent) included the purpose of the study, information about the clinical examinations, the fact that participation in the study was voluntary and that all the data would be treated confidentially. Information was also given about the examination being free of charge and that all participants would be taking part in the same examination procedure, no matter whether they belonged to the asthma or the control group (*justice*). Radiographic examinations were performed on 6-year-olds, adolescents and young adults. A radiographic examination was excluded if the participant had recently (6 months) had a radiographic examination. The investigator was obliged to inform the participant's ordinary dentist if oral diseases were found during the examinations, based on an obligation to maximise benefits and minimise harm (*beneficence*).

Results

Caries

There was a general trend in all four studies for asthmatics to have a higher caries prevalence than individuals without asthma (Table 4).

Study I

The mean dfs in the 3-year-olds with asthma was 1.4 ± 3.2 compared with 0.5 ± 1.2 in the control group ($p < 0.05$). The corresponding figures for the 6-year-olds were 2.5 ± 3.9 and 1.8 ± 2.8 (NS). Nine percent of the 3-year-old children with asthma had six or more caries lesions, compared with none in the control group, and in the 6-year-old children with asthma, 10% had nine or more caries lesions, compared with 2% of the children in the control group.

Study II

During the follow-up period, the number of children with caries increased from 29% to 61% in the asthma group and from 16% to 36% in the control group ($p < 0.05$). Seventeen percent of the 6-year old children with asthma had six or more lesions compared with 8% in the control group ($p < 0.05$). Of these children, only asthmatics ($n=3$) have had manifest proximal caries lesions in their molars at 3 years of age. The caries increment from 3 to 6 years of age is presented in Table 5.

Study III

The approximal and total DFS were statistically significantly higher in the asthma group ($p < 0.01$). Only one participant with asthma was caries free compared with 13 in the control group. In the asthma group, 6 individuals had ≥ 6 caries lesions compared with only 1 in the control group ($p < 0.05$). No adolescent in the control group had ≥ 9 caries lesions compared with 6 in the asthma group ($p < 0.01$).

Study IV

In the young adults, the prevalence of initial approximal caries lesions was statistically significant higher in the asthma group than in the control group ($p < 0.01$). In the asthma group, 7 individuals had ≥ 9 caries lesions compared with 3 in the control group (NS).

Table 4. Mean value of tooth surfaces with initial caries (d_i/D_i), manifest caries (d_{mfs}/D_{mFS}) and total caries prevalence (D_{i+mFS}/d_{i+mfs}) in the asthma and control groups in Study I, II, III and IV.

Study	Group	Initial caries (d_i/D_i)	Manifest caries + filled surfaces (d_{mfs}/D_{mFS})	Total (d_{i+mfs} or D_{i+mFS})	p-value
I	Asthma 3 yrs	0.8±1.6	0.6±2.6	1.4±3.2	<0.05
	Control 3 yrs	0.4±1.0	0.1±0.4	0.5±1.1	
	Asthma 6 yrs ¹	1.2±1.9	1.3±3.0	2.5±3.9	
	Control 6 yrs ¹	0.9±1.7	0.9±2.0	1.8±2.8	
II	Asthma 3 yrs ¹	0.2±0.5	0.1±0.5	0.3±0.9	<0.05
	Control 3 yrs ¹	0.04±0.3	0.0±0.0	0.04±0.3	
	Asthma 6 yrs ¹	1.5±1.8	1.3±3.4	2.8±4.4	
	Control 6 yrs ¹	0.7±1.7	1.1±3.2	1.8±3.7	
III	Asthma	3.5±4.9	1.4±1.4	4.9±5.5	<0.05
	Control	0.7±1.4	0.7±1.4	1.4±2.3	
IV	Asthma	6.0±8.1	2.7±3.7	8.6±10.6	
	Control	1.3±2.0	2.8±5.1	4.0±5.2	

¹Only primary molars and canines

Table 5. Mean caries increment \pm SD (initial and manifest caries in primary molars and canines) between 3 and 6 years of age in the asthma and control group.

Lesions	Asthma	Control	p-value
Initial	1.3±1.7	0.7±1.6	<0.05
Manifest	1.2±3.2	1.1±3.2	
Total	2.5±3.5	1.8±3.7	

Plaque, gingival status and periodontal pockets

Study I

No difference was found in the presence of plaque between children with asthma and the control groups. Fourteen percent of the 3-year-olds and 16% of the 6-year-olds with asthma had bleeding gingivitis compared with no 3-year-old child and 9% of the 6-year-olds in the control group. This difference was only statistically significant for the 3-year-olds ($p<0.01$).

Study II

No difference was found in the presence of plaque between children with asthma and the control group. At both 3 and 6 years of age, more children with asthma had bleeding gingivitis compared with children in the control group, although this was only statistically significant when the children were 3-years old ($p<0.01$).

Study III

The mean plaque index was 6.4 ± 8.1 in the asthma group and 7.8 ± 5.8 in the control group (NS). The mean number of tooth surfaces exhibiting gingival bleeding was $5.5\pm 5.4\%$ in the asthma group compared with $0.7\pm 1.6\%$ in the control group ($p<0.01$). Surfaces with gingival inflammation were mainly located buccally on the upper incisors in the asthma group.

Study IV

There were no differences between the asthma and control group when it came to the plaque formation rate, i.e. 2.2 ± 0.4 vs. 2.0 ± 0.8 . The mean gingival index in the asthma group was 1.8 ± 0.4 while it was 1.3 ± 0.8 in the control group ($p=0.03$). Surfaces with gingival inflammation were mainly located buccally on the upper incisors in the asthma group. No difference was found between the two groups in terms of the mean volume of gingival crevicular fluid. In young adults with asthma and allergy ($n=15$), a higher mean volume of gingival crevicular fluid was found compared with asthmatics without allergy ($n=5$, NS). Nor were any statistically significant differences found between the two groups in terms of the number of periodontal pockets and alveolar bone loss.

Dental erosion

In the young adults, dental erosions were mild (Grade 1) in most cases both in the asthma and in the control group. Individuals with erosions on the occlusal tooth surfaces, (cuspal cuppings) were more frequent in the asthma group (n=15) compared with the control group (n=8; NS). In 9 individuals in the asthma group, ≥ 4 surfaces with dental erosions in the palatal anterior tooth surfaces in the maxillary jaw was found compared to 4 individuals in the control group (NS).

Salivary and microbiological factors

In the adolescents and the young adults, a lower stimulated saliva flow rate was found for the asthma groups compared with their controls ($p < 0.05$). No statistically significant difference was found in the number of colony forming units of mutans streptococci and lactobacilli between the asthma and control groups, nor was any difference found between the groups in terms of buffer capacity. In the adolescents, the mean stimulated saliva flow rate was 1.6 ± 0.7 compared with 2.4 ± 1.0 in the control group ($p < 0.05$). The corresponding figures for the young adults were 2.0 ± 0.6 and 2.8 ± 1.1 ($p < 0.01$).

Plaque-pH measurements

The mean pH curves and the area under the curve (AUC) at two approximal sites (16/15 and 13/12) in Study III and IV are shown in Fig. 3 and Table 6. Adolescents and young adults with asthma had a lower initial pH and the control groups and showed a faster pH recovery back to resting pH compared with the asthma groups. However, the difference was only statistically significant in the adolescents.

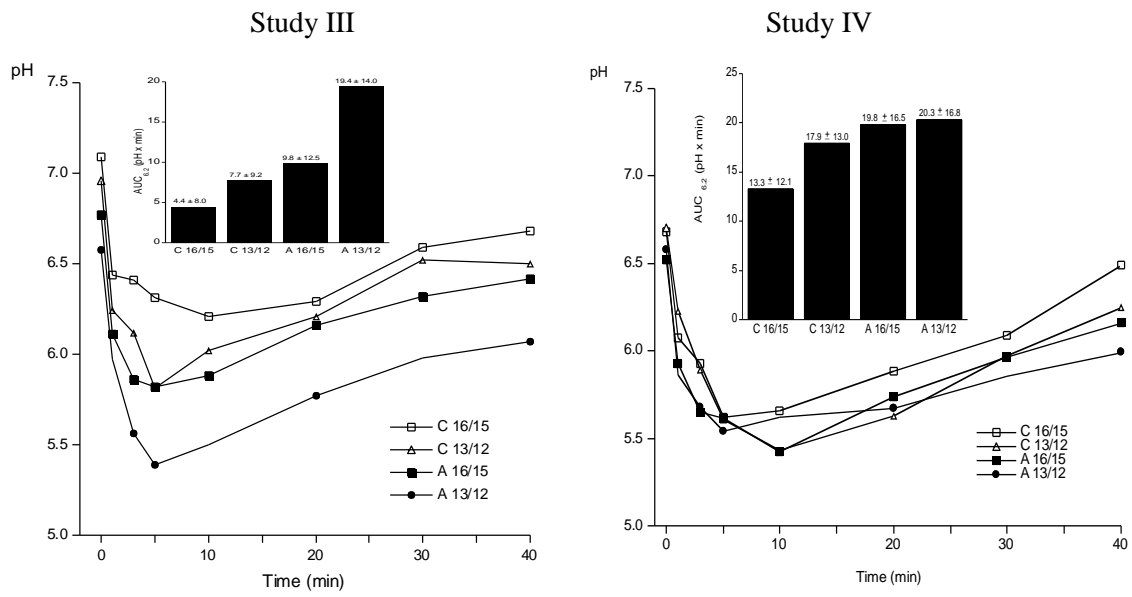


Figure 3. Changes in plaque-pH in two approximal tooth areas (16/15 and 13/12) after a mouthrinse with 10 ml of a 10% sucrose solution for 1 min in individuals with asthma (A) and without asthma (C). The corresponding data for the area under the curve below pH 6.2 ($AUC_{6.2}$) for the two groups and two sites are also shown, $n=20$ per group.

Table 6. Initial pH, final pH, minimum-pH for individuals with and without asthma. Mean values \pm SD for two approximal sites (13/12 and 16/15) are shown.

	pH-value	Asthma	Control	p-value
Study III	Site 13/12			
	Initial pH (0 min)	6.6 \pm 0.5	7.0 \pm 0.3	<0.01
	Final pH (40 min)	6.1 \pm 0.6	6.5 \pm 0.5	<0.01
	Minimum pH	5.2 \pm 0.4	5.6 \pm 0.4	<0.01
	Maximum decrease	1.4 \pm 0.6	1.4 \pm 0.5	
	Site 16/15			
	Initial pH (0 min)	6.7 \pm 0.6	7.0 \pm 0.3	<0.05
	Final pH	6.4 \pm 0.5	6.7 \pm 0.5	<0.05
Minimum pH	5.5 \pm 0.5	5.9 \pm 0.6	<0.01	
Maximum decrease	1.2 \pm 0.5	1.1 \pm 0.5		
Study IV	Site 13/12			
	Initial pH (0 min)	6.6 \pm 0.5	6.7 \pm 0.3	
	Final pH (40 min)	6.0 \pm 0.7	6.2 \pm 0.5	
	Minimum pH	5.2 \pm 0.4	5.6 \pm 0.4	
	Maximum decrease	1.4 \pm 0.4	1.1 \pm 0.4	
	Site 16/15			
	Initial pH (0 min)	6.5 \pm 0.5	6.6 \pm 0.4	
	Final pH	6.2 \pm 0.6	6.5 \pm 0.5	
Minimum pH	5.3 \pm 0.6	5.5 \pm 0.9		
Maximum decrease	1.2 \pm 0.5	1.1 \pm 0.3		

Interview

There was no statistically significant difference in the frequency of toothbrushing habits between individuals with and without asthma and all the participants used fluoridated dentifrice. The number of individuals reporting frequent mouth breathing was statistically significantly higher in the asthma groups than in the control groups (Study I, II and IV). In 3-year-old children and adolescents with asthma, mouth breathing was associated with a higher mean dfs/DFS. However, the difference was only statistically significant in the 3-year-olds. Children and adolescents with asthma consumed sugary drinks more frequently than the control groups, although the difference between the two groups was only statistically significant in the 3-year-olds. At 3 years of age, the mean defs in children with asthma and an immigrant background was statistically significantly higher than in children with an immigrant background in the control group. The prevalence of allergy was higher in the asthma groups than in the control groups at all ages and it was most pronounced in the adolescents, where 19 of 20 individuals with asthma had some form of allergy.

Cariogram

The mean “chance of avoiding caries” was statistically significantly lower in adolescents with asthma ($54\pm 21\%$) compared with adolescents in the control group ($75\pm 20\%$) ($p < 0.05$). In the low risk group (81-100% “chance of avoiding caries”), 10% of the individuals belonged to the asthma group compared with 55% in the control group ($p < 0.01$). The Cariogram factors contributing to the higher risk profiles for the asthmatics were: susceptibility (light-blue sector, including; intake of fluoride, saliva secretion, saliva buffer capacity) and diet (the dark-blue sector, see Fig. 1).

Multiple logistic regression analyses

In the regression analyses, variables that indicate an increased risk of caries were intake of sugary drinks > 1 times/day, immigrant status (Study I), plaque, mouth breathing (Study I and II) and early caries experience (Study II).

Characteristics of children with asthma

Study I

The majority of the children had mild to moderate asthma. The most common mode of administration of the asthma drugs in the 3-year-olds was inhalation by a metered-dose inhaler. In the 6-year-olds inhalation using a dry-powder inhaler was more common. The mean dfs was 2.6 ± 5.5 for 3-year-old children who medicated regularly compared with 1.2 ± 1.9 for the 3-year-olds that medicated intermittently with steroids (NS). The corresponding figures for the 6-year-olds were 3.0 ± 5.0 compared with 2.0 ± 3.0 (NS). There was a tendency for participants with severe asthma to have a higher caries prevalence than participants with mild and moderate asthma, although the difference was not significant. There was no statistically significant difference in mean dfs and exposure time to the disease.

Study II

Of the children with asthma at 3 years of age, 63% had no medication at 6 years of age. The majority of the children had mild to moderate asthma. One child that had very severe asthma at 3 years of age was in remission from diagnosed mild asthma at 6 years of age. The administration of asthma drugs was almost identical to that of the 6-year-old group in Study I. No association between caries and the exposure and length of the medication or the severity of the disease was found in the asthma group.

Study III

All adolescents had severe or very severe asthma and they all used a dry-powder inhaler. The adolescents with asthma with a prescribed combination of inhaled long-acting β_2 -agonists and glucocorticosteroids had a mean DFS of 5.2 ± 6.0 compared with 3.8 ± 3.7 for adolescents medicated with inhaled steroids and short-acting β_2 -agonists separately (NS).

Study IV

The young adults had moderate asthma and inhalation by dry-powder inhaler had been used by all the participants for at least 4 years. There was no statistically significant difference in mean DFS in asthmatics with a debut of the disease before 5 years of age ($n=13$) compared with those with a debut at the age of 5 years or older ($n=7$). Asthmatics with a duration of asthma disease of < 9 years ($n=4$) compared with asthmatics with a duration of > 9 years ($n=16$) had a mean DFS of 4.2 ± 5.8 and 9.7 ± 11.4 , respectively (NS). No differences in mean

DFS were found between the two different asthma medication subgroups. Individuals with both asthma and allergy had a mean DFS of 9.0 ± 11.1 compared with 7.8 ± 10.5 in asthmatics without allergy (NS).

Discussion

The present studies have revealed differences in caries prevalence between individuals with and without asthma. Furthermore, at all ages, larger numbers of participants with six or more caries lesions belonged to the asthma groups compared with the control groups. Both asthma and caries are complex conditions and the epidemiology of these diseases has changed dramatically in recent decades. The prevalence of asthma has increased, while the prevalence of caries, on the other hand, has declined in most industrialised countries.

During the 1990s, the medical treatment for asthma changed and the regular use of inhaled bronchodilators has declined and been replaced by the early introduction of preventive therapy involving inhaled corticosteroids⁷⁰. Nowadays, this approach is internationally approved in asthma management⁶³. Comparing studies performed in the 20th century with studies performed today, including participants using a combination of corticosteroids and β_2 -agonists, is therefore complicated. The ideal method for research investigating the oral health of individuals with asthma may be longitudinal studies with study groups including asthmatic individuals with and without medication. This is not possible for ethical reasons, but it would perhaps answer the question of whether asthma medication affects oral health. One strength of the present study is that all the participants had a physician-diagnosed asthma disease and almost all the asthmatics were being medicated with both β_2 -agonists and corticosteroids. Furthermore, all the individuals with asthma in the selected geographical areas were invited to participate. The groups were therefore homogeneous. In the two studies comprising adolescents and young adults, the number of participants was small, but the groups were well balanced with respect to both the duration of the disease and the length of medication (10 years). These well-controlled asthma groups differ from other studies with study groups with a shorter duration of the disease and differences in severity^{74,105,121}.

The clinical examination and the semi-structured interview were not performed in a blind manner, which may bias the results. However, the X-rays in the radiographic examination in all the papers were analysed by a person who did not know whether the participant belonged to either the asthma or the control group. One factor that could influence the statistical outcome of these studies is the skewed distribution of caries prevalence, while the large standard deviation, which results in difficulty obtaining statistically significant differences, could be another.

All four papers in this thesis have revealed a difference in caries between individuals with asthma and non-asthmatic individuals. This difference in caries prevalence is in agreement with several studies which have shown a correlation between asthma and dental caries (see Table 2). In the present studies, individuals with asthma aged between 3 and 24 years had a higher caries prevalence than their healthy controls. This difference was more pronounced for initial caries lesions. In individuals with several initial caries lesions, as found in these studies, the risk of initial lesions progressing to manifest caries is high¹³². This group can therefore be classified as a risk group for the development of manifest caries lesions later in life.

The difference in caries prevalence was clearly confirmed in the adolescents with asthma. In this group, the caries prevalence (both initial and manifest caries) was three times higher in the asthmatics than in the control group. This may indicate that asthma triggers caries development and appears to cause a more serious caries situation in asthmatics than in non-asthmatics. In the County of Jönköping, where these studies were conducted, a basic dental preventive programme starts at 1 year of age and invites all children and adolescents living in this area to participate. This preventive programme includes information about preventive measures and recommendations about regular toothbrushing with fluoridated toothpaste. Furthermore, individually intensified preventive programmes are designed for children with special needs, such as a high caries risk or mental or physical disabilities. In spite of this, these preventive programmes do not appear to be enough for individuals with asthma disease.

There may be a numerous of reasons for the higher caries prevalence in asthmatics compared to non-asthmatics. Factors that may influence the caries development in the individuals with asthma in the present studies are, decreased salivary secretion rate, higher intake of sugary drinks and higher frequency of mouth breathing compared to healthy controls. This is in line with the findings of other studies investigating some of these factors in individuals with asthma^{74,83-85}. It therefore, seems important with risk assessment for oral diseases in individuals with asthma. Factors that may directly or indirectly influence the caries risk like general diseases, medication, dietary habits, oral hygiene routines and fluoride exposure must be considered. To assess the caries risk in the study with adolescents a computer evaluated program "Cariogram" seems useful. The asthmatic adolescents had a statistical significant lower "chance of avoiding caries" in the Cariogram test compared to their healthy controls. This higher risk profiles were dependent of fluoride exposure, lower saliva secretion rate and diet factors. The lower stimulated saliva secretion rate in the asthma group could be the main explanation for the higher caries risk for the asthmatics compared to the non-asthmatics in the studies of adolescents and young adults.

In the present study, children with immigrant background and asthma had a higher caries prevalence than children with immigrant background but without asthma. This is in line with several studies which report a correlation between immigrant background, low socio-economic status and dental caries in children and adolescents^{19,32-34,134,124}. However, it is difficult to determine whether these factors affect the outcome in this study. The majority of the participants in the present studies came from geographical areas with a high socio-economic profile and had a lower caries prevalence and lower counts of cariogenic bacteria than a random sample of individuals from the Municipality of Jönköping⁷. No analyses of this association have been performed in the present studies with adolescents and young adults due to the small number of participants with an immigrant background.

The lower saliva flow rate in adolescents and in the young adults (Study III and IV) with asthma is in agreement with earlier studies^{82,104} but differs from studies by Hyppä et al.^{103,107} who found no statistically significant difference in saliva secretion between individuals with asthma and healthy individuals. The saliva secretion rate measurements were only conducted in the studies with adolescents and young adults.

The main reason for excluding saliva secretion rate measurements in the younger children was difficulty finding a suitable methodological approach for these young children. It has been suggested that individuals with asthma have increased levels of mutans streptococci and lactobacilli^{83,90}, but, in the present studies, no such statistical connection was found, even if the counts of lactobacilli were slightly higher in the 6-year-olds and in the adolescents with asthma compared with the healthy controls. In Study III and IV, lower initial and final pH values up to 40 minutes after a sucrose rinse were found in both adolescents and young adults with asthma compared with their healthy controls. This reduced saliva flow rate may influence plaque pH and is in agreement with findings by Kargul et al.⁸⁴, who found decreased pH values after inhalation with asthma medication in both plaque and saliva in 6- to 14-year-old children with asthma.

A lower saliva secretion rate was also found in both adolescents and young adults with asthma compared with healthy controls (Study III and IV). This lower saliva secretion rate may affect the initial pH¹³⁵. In addition, a low pH may be a risk factor for dental erosions¹³⁶. Dental erosions were found to be more frequent in the asthma group than in the control group, especially on the labial surfaces of the anterior teeth and on the occlusal surfaces of the posterior teeth, although the difference between asthma and controls was not statistically significant (Study IV). This higher frequency of dental erosions in asthmatics compared with healthy controls is in line with other studies^{74 91 92}. One explanation for erosions may be that dry-powder inhalers have a low pH and sometimes contain lactose monohydrate as a carrier vehicle in proportions of 12-25 mg per dose. This lactose monohydrate makes the inhaler itself acidic⁸⁴. The combination of low pH and the titratable acidity of asthma inhalers may increase the risk of erosions in asthmatics^{93 95 137}. In the present studies, especially in young asthmatics, a higher intake of sugar-containing drinks was found, compared with the control groups. This may be due to a higher frequency of mouth breathing in the asthma groups than in the control group. Individuals who reported frequent mouth breathing (in both the asthma and the control groups) had a higher mean dfs/DFS compared with those who reported nose breathing, but the difference was only statistically significant in the younger age groups. This is in agreement with previous studies, which concluded that mouth breathers are more prone to develop carious lesions than nose breathers^{99,55}.

The majority of participants with asthma in the present studies were suffering from allergy and Linneberg et al.¹³⁸ found an increased prevalence of rhinitis in asthmatics compared with non-asthmatics. The frequent prevalence of rhinitis in asthmatics could be an explanation for more frequent mouth breathing in asthmatics than in non-asthmatics¹³⁹.

In the present studies, the asthma group had more gingival inflammation than their healthy controls. The surfaces with gingival bleeding were mainly located in the front region of the upper jaw. The higher frequency of gingival inflammation in asthmatics in these four studies is in agreement with other studies both in children and in adults^{102,84,105}. Increased gingival inflammation may be due to the higher frequency of mouth breathing⁵², but it could also be due to the higher probability of having gingival bleeding due to a co-existing allergy⁷⁵. Laurikainen et al.⁸⁴ reported that the inflammatory process in asthmatics may affect the periodontal condition. In the present study of young adults, where the volume of gingival crevicular fluid was measured, no differences in the volume of gingival fluid were found between the asthma group and the control group. In the young adults with asthma and allergy (n=15), however, the volume of gingival fluid was larger than in young adults with asthma but without allergy (n=5), even if the difference was not statistically significant. One limitation in Study IV was that no measurement was made of the fluid in the front teeth of the upper jaw. In the present studies, no association has been found between the asthma disease and the prevalence of plaque. This disagrees with some other studies, which have found a connection between plaque and asthma^{74,104,105}, and is in line with other studies, which found no such connection^{102,82}.

Approximately 50% of inhaled corticosteroids is deposited in the oropharynx, and this might affect the oral health¹⁴⁰. In the present studies, the administration of asthma medication was different depending on the age group to which the individuals with asthma belonged. In our studies, only children under 5 years of age medicated with liquid and/or a metered-dose inhaler. All the other participants used dry-powder inhalers. No connection was found between asthmatic children medicating with liquid and a higher caries prevalence. However, the 3-year-olds in the present studies that medicated with liquid only used this medication intermittently. This disagrees with the findings of Reddy et al.¹¹⁵, who found that children who used medication in liquid form had a higher caries prevalence than children who administered their medication in other ways. The fact that the disease fluctuates and may change over time was accentuated in the follow-up study of pre-school children, where 63%

of the children, diagnosed as having asthma and exposed to asthma medication at 3 years of age, had no asthma symptoms and no medication at 6 years of age. This is in line with Martinez et al.¹⁴¹, who found that asthma symptoms during the first 3 years of life had a benign prognosis and that many of these children had no symptoms at 6 years of age. Although the majority of the children with asthma had recovered from their disease, there was a difference in caries prevalence at 6 years compared with the healthy control group. This is in line with Wendt et al.¹⁴², who found a correlation between respiratory infections at 1 year of age and caries at 3 years of age.

In the present studies, there was a tendency for children who medicated regularly with steroids to have a higher caries prevalence compared with children who medicated intermittently, although the difference was not statistically significant. This is in agreement with Milano et al.⁸⁰, who found that an increased frequency of asthma medication (corticosteroids and β_2 -agonists) was associated with an increased likelihood of caries experience later on. In Study I, there was a tendency for participants with severe asthma to have a higher caries prevalence than participants with mild and moderate asthma. However, in Studies II, III and IV, no association was found between caries and the exposure and length of the medication or the severity of the disease. This can be compared with a study by Eloit et al.⁸¹, who found that neither the period of the disease nor the medication resulted in a significant risk of caries in asthmatics.

This thesis points to the importance of developing preventive oral health programmes for young individuals with asthma for both dental and medical personnel. A number of preventive measures can be implemented for these individuals and for individuals with caries. More research in this area should be conducted to investigate how asthma medications influence oral health. In addition, investigations into factors related to the disease, such as mouth breathing, are needed.

Conclusions

The main conclusions for this thesis are:

- pre-school children with asthma had a higher caries prevalence, a higher prevalence of gingival inflammation, a higher intake of sugary drinks, and were more frequently mouth breathers than healthy individuals in the same ages,
- pre-school children with asthma at 3-years of age had higher increment of initial caries between 3 to 6 years of age. Asthma disease, higher intake of sugary drinks, mouth breathing and caries at 3 years of age were associated with increased caries development between 3 and 6 years of age,
- adolescents with long-term severe asthma had higher caries prevalence than adolescent without asthma. The adolescents with asthma had more gingival inflammation, were more frequently mouth breathing, had lower salivary secretion rate, and lower plaque-pH than a healthy control group, and
- young adults with long-term, controlled asthma had a higher caries prevalence, more gingival inflammation and a lower salivary secretion rate compared to young adults without asthma.

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Damp indoor	yes ()	no ()	don't know ()		
Animals?	cat ()	dog ()	other ()		
Animals for how long?	< 1yr ()	>1>2yr ()	>2yr ()		
Do parents/caretakers smoke?	Mother ()	father ()	both parents ()	other ()	
Immigrant background (child, or at least one parent born outside Nordic countries)	yes ()	no ()	don't know ()		
Frequently mouth breathing (every day)		yes ()	no ()	don't know ()	
Problem to breathe first year of life?		yes ()	no ()	don't know ()	
Use of bronchodilators first year of life?		yes ()	no ()	don't know ()	
Antibiotics first year!	No ()	1-2times ()	>2times ()	don't know ()	
Ear infections first year of life		yes ()	no ()	don't know ()	
Ear infections how often first year		1-4times ()	4-10 times ()	> 10times ()	don't know ()
Allergy	yes ()	no ()	don't know ()		
Kind of allergy?.....					
Physician diagnosed asthma	yes ()	no ()	don't know ()		
Debut of asthma diagnose?.....					
Debut for asthma medication					
Exposure for asthma medication in years?.....					
Asthma medication how often?	Every day ()	intermittent ()	no medication ()		
Medication with bronchodilators?	Every day ()	intermittent ()	no medication ()		
For how long have you medicated with bronchodilators?.....					
Kind of bronchodilators?.....					

Administration of bronchodilators MDI DPI liquid
 () () ()

Medication with steroids? Every day intermittent no medication
 () () ()

For how long have you medicated with steroids?.....

Kind of steroids?.....

Administration of steroids MDI DPI

Medication with other medications? Every day intermittent no medication
 () () ()

If, yes what kind of medication and how often?.....

Medication with combination medication ? Every day intermittent no medication
 () () ()

For how long have you medicated with combination med?.....

Kind of combination medication Seretide Symbicort
 () ()

Administration of combination medication MDI DPI
 () ()

How often :	Never/ rarely	Once a week	2-3 times/week	Once a day	Twice a day	>twice a day
Soft drinks						
lemonade						
juice						
Sweets						
Ice-cream						
Biscuits						
Chips/snacks						
O'boy						

Appendix II

Interview form used in Study III and IV

Number.....

Group.....

Date of Birth.....

Public Dental Service clinic.....

Tooth brushing Frequency/day sometimes () once () twice () more than twice ()

When? Morning and evening () evening () morning () annotation ()

Fluoride toothpaste Frequency/day sometimes () once () twice () more than twice ()

Fluoride supplement Daily yes () no ()

Which kind of fluoride supplement chewing gum () fluid () tablets ()

Number of meals/day.....

Do the child you eat or drink during the night? never () sometimes () once () twice ()

If, What kind of drink, meal?.....

Damp indoor yes () no () don't know ()

Animals? cat () dog () other ()

Animals for how long? <1yr () >1>2yr () >2yr ()

Do you, parents/caretakers smoke (daily)? yes () no () sometimes ()

Immigrant background (you, or at least one parent born outside Nordic countries) yes () no () don't know ()

Frequently mouth breathing (every day) yes () no () don't know ()

Thirsty (every day)? yes no don't know

Problem to breathe first year of life? yes no don't know

Use of bronchodilators first year of life? yes no don't know

Antibiotics first year No 1-2time >2times don't know

Ear infections first year of life yes no don't know

Ear infections how often first year 1-4times 4-10 times > 10times don't know

Allergy yes no don't know

Kind of allergy?.....

Physician diagnosed asthma yes no don't know

Debut of asthma diagnose?.....

Debut for asthma medication

Exposure for asthma medication in years?.....

Asthma medication how often? Every day intermittent no medication

Medication with bronchodilators? Every day intermittent no medication

For how long have you medicated with bronchodilators?.....

Kind of bronchodilators?.....

Administration of bronchodilators MDI DPI liquid

Medication with steroids? Every day intermittent no medication

For how long have you medicated with steroids?.....

Kind of steroids?.....

Administration of steroids MDI DPI

Medication with other medications? Every day intermittent no medication

If, yes what kind of medication and how often?.....

