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DISEASES WITH ORAL MANIFESTATIONS AMONG ADULT ASTHMATICS

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ABSTRACT

Objectives: Many comorbidities are associated to adult asthma and may increase the asthma burden. Aim of this study was to investigate the hazard rate of oral diseases or oral manifesting diseases in asthmatic adults compared to non-asthmatic adults.

Design: Population-based matched cohort study with 13.8 years of follow-up.

Setting: A baseline questionnaire and follow-up data from the national hospital discharge registry of the National Institute for Health and Welfare in Finland.

Participants: Total of 1,394 adults with asthma were matched with 2,398 adults without asthma by gender, age and area of residence. Asthmatic adults were identified from the Drug Reimbursement Register of the Finnish Social Insurance Institution, as those who had a special drug reimbursement right due to asthma. Participiants without asthma were identified from the Population Register.

Main outcomes and measures: Oral health related main diagnoses were retrieved using codes of International Classification of Diseases (ICD-10), and divided into disease groups. Cox's proportional hazards models stratified by matching unit (sex, age and area of residence), and models matched and adjusted for pack-years, education level, and body mass index (when possible), were used to evaluate the matched and additionally adjusted hazard ratios (HR) of diseases between asthmatic and non-asthmatic groups.

Results: Adult asthma was associated with an any oral manifesting disease (adjusted hazard ratio 1.41, confidence interval 1.11–1.80), herpes zoster (adjusted HR 6.18, 1.21–31.6), benign tumors of

oral cavity and pharynx (matched HR 1.94, 1.05–3.56), and dermatological diseases (pemphigus, pemphigoid, dermatitis herpetiformis, psoriasis, and lichen planus, HR 1.67, 1.01–2.78).

Conclusions: Risk of having an oral disease or oral manifesting disease was increased among adult asthmatics.

Strengths and limitations of this study

- This study is a population-based, matched cohort set up with almost 14 years of follow-up.
- Ashma diagnosis was confirmed with a medical doctor, and based on lung function tests and typical medical history.
- The study lacks data of primary care, where common dental or oral problems, such as periodontitis, are usually treated.
- There is a possibility of detection bias due to the more intensive use of healthcare services by asthmatics (and people with any moderate to severe chronic disease) than non-asthmatic subjects, which could have affected the results.

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INTRODUCTION

Asthma is recognized for its characteristic pattern of symptoms, such as timing, triggers and response to treatments. Common symptoms include wheezing, shortness of breath, chest tightness, and cough, yet careful history taking is crucial for differential diagnosis. Asthma is one of the most common chronic diseases in children and adults. Prevalence of asthma in adults is ranging from 0.2% to 21.0%, being highest in developed countries and is most likely underestimated in poorer ones. [1] In addition to socioeconomic class and genetic predisposition, megatrends such as climate change, ageing and urbanisation are impacting asthma [2–4]. Even though asthma has been considered as a single disease, recent studies have shown that it consists of multiple phenotypes [5]. Asthma varies considerably across the life course, and is different in adults and in children. Where childhood asthma is characterized by a predominance of allergic multi-morbidity and higher prevalence among boys, asthma in adults is associated with more respiratory symptoms and asthma medications [6]. Risk factors for adult asthma are genetic predisposition, female gender, overweight, allergies, upper airway diseases, and exposure to tobacco smoke or other irritants. [7] The main adult asthma phenotypes that have been identified include (1) early-onset allergic asthma, (2) early-onset allergic moderate-to-severe remodelled asthma, (3) late-onset nonallergic eosinophilic asthma, and (4) late-onset nonallergic noneosinophilic asthma but overlap of commonly reported asthma phenotypes has also been observed, with implications for objective asthma outcomes [5,8]. Definition of “early-onset” varies by studies. A study investigating severe asthma subgroups defined late-asthma onset as after the age of 12 years [9] where others refer to early-onset adult asthma when the onset of asthma has been reported to be 12–15 years [10]. More severe form of adult asthma is less stable than childhood-onset disease with more relapses and less remissions, and associated with increased IgE, eosinophilia, poorer adherence to therapy, recurrent infections, obesity, smoking, and low socioeconomic status [1,6]. Various classifications and subgroups of phenotypes of asthma have been proposed but clear consensus has not been reached among the scientific community. Heterogeneity of severe asthma phenotypes have led to the

development of new asthma treatments targeting specific immune pathways, and although they may have limited utility among general asthma population, may they benefit a subset of patients with asthma [11].

Studies have demonstrated that many comorbidities coexist with asthma and may even contribute to lower life expectancy [12]. We have previously detected increased all-cause mortality of asthmatics in the Finnish adult population, largely explained by development of chronic obstructive pulmonary disease in smoking asthmatics, malignant respiratory tract neoplasms, and cardiovascular diseases [13].

In the Finnish population the most common comorbidities of adult asthma are hypertension, diabetes, severe psychiatric disorders and ischemic heart disease [14]. Other known asthma-related comorbidities include rhinitis, chronic sinusitis, gastroesophageal reflux disease, obstructive sleep apnea, hormonal disorders, obesity, hyperventilation, glottic dysfunction, and respiratory infections [15]. In a population-based cross-sectional study covering 1.4 million Scottish people, comorbidities associated with asthma in adults were chronic obstructive pulmonary disease, bronchiectasis, eczema/psoriasis, dyspepsia, depression and anxiety [16].

Oral cavity is closely connected with the lower airways by anatomical location, functions such as in conducting and modifying inhaled air and speech. When it comes to oral health related diseases, asthma has previously been associated with herpes zoster, tooth decay, dental erosion, oral candidiasis, periodontal disease and psoriasis [16–23]. However, findings of the studies are controversial, and many other associations between asthma and oral diseases are less studied. There is a clear need for better understanding of co-morbid conditions and their impact on burden of asthma.

Study aim

Aim of this cohort study was to investigate the hazard rate of oral manifesting diseases in asthmatic adults compared to non-asthmatic adults. We hypothesized that asthmatics have more oral manifesting diseases than non-asthmatics.

METHODS

Study design

This population-based matched cohort study with follow-up started with a questionnaire collected in 1997, in which questions about living environment, allergies, smoking duration and quantity, weight, and education level were asked from asthmatics and matched non-asthmatics. The questionnaire was sent to 4,958 people of which 3,792 responded. Altogether 1,394 asthmatics and 2,398 adults without asthma were included in this study. Follow-up data, all diagnose codes, of all responded participants were collected from the national hospital discharge registry of the National Institute for Health and Welfare from 1997 to 2014.

Patient and Public Involvement: Participants of the study were not involved in the planning of the study design. Extended data from the registers was collected with the approval of the National Institute for Health and Welfare. Results of the study are published only in peer-reviewed journals, no other information of the results of the study are provided to the participants.

Ethics statement: Approval for the study was obtained from the ethical committee at Tampere University Hospital (R15030) and a written consent was obtained from all subjects.

Study population

Participants with asthma and without asthma were matched by sex, age (±2 years) and area of residence by postal code. Total of 1400 asthmatic adults were identified from the Drug Reimbursement Register of the Finnish Social Insurance Institution, as those who had a special drug reimbursement right due to asthma. Population register was used to identify 2800 matched non asthmatics. Altogether 248 asthmatics and 511 non asthmatics were recruited from the Mini Finland Health Survey [24]. All asthmatics fulfilled the criteria for doctor-diagnosed asthma: typical history, clinical features and asthma course, and lung function tests. Participants were over 30 years old (Table 1). Nearly 62 % were male and 38 % women. An estimate of the participants lifetime tobacco exposure at baseline was calculated in pack-years [25]. Body mass index was presented in four categories and level of education was divided into three categories based on the Finnish education system. The study population has previously been described in more detail [13].

Table 1 Baseline characteristics

	No asthma n (%)	Asthma n (%)	Missing (%)
Sex			
Men	912 (38.0)	532 (38.2)	
Women	1486 (62.0)	862 (61.8)	
Total	2398	1394	
Age at baseline			
≤59	1506 (62.8)	893 (64.1)	
60–69	699 (29.1)	401 (28.8)	
70–79	166 (6.9)	84 (6.0)	
≥ 80	27 (1.1)	16 (1.1)	
Pack-years			6.7
0	1286 (57.1)	625 (48.6)	
≤19	595 (26.4)	389 (30.2)	
≥ 20	371 (16.5)	273 (21.2)	
BMI (kg x m $^{-2}$)			2.4
Underweight (<18.5)	26 (1.1)	19 (1.4)	
Normal (18.5-24.99)	998 (42.6)	463 (34.0)	
Overweight (25-29.99)	958 (40.9)	577 (42.4)	
Obese (≥ 30)	358 (15.3)	303 (22.2)	
Education level			2.2
Matriculation exam.	435 (18.5)	187 (13.8)	
Secondary school	560 (23.8)	322 (23.7)	
Primary school or less	1356 (57.7)	850 (62.5)	

Lifetime tobacco exposure was calculated in pack-years (number of cigarettes per day/20 x number of years smoked, where 1 pipe = 2.5 cigarettes, 1 cigar = 4 cigarettes) based on which the individuals were divided into three groups: 0, ≤19, and ≥20 pack-years

Body mass index (BMI) assessed as weight in kilograms divided by the square of the height in meters was presented in four categories according to World Health Organization classification

Level of education was obtained by the questionnaire and divided based on Finnish education system into three categories: matriculation examination (13 years, reference value), secondary school or equivalent (9 years), and primary school or less (≤6 years)

Outcomes

In this study we focused on oral diseases and diagnoses that can manifest in the oral cavity. The diagnoses were identified from the data on hospital visits and hospitalizations obtained from the

national hospital discharge registry of the National Institute for Health and Welfare from 1997 to 2014. Only main diagnoses were retrieved using codes of International Classification of Diseases (ICD-10), and were divided into five disease groups: infections, malign neoplasms, benign neoplasms, dental diseases, and dermatological diseases. The first group consisted of viral and fungal infections (herpes simplex (B00.1), herpes zoster (B02), hand, foot and mouth disease (B08.4), herpangina (B08.5), HIV disease resulting in candidiasis (B20.4), Kaposi sarcoma (B21.0), Burkitt lymphoma (B21.1), mumps (B26.9), Epstein-Barr (B27.0), candidiasis (B37), and tonsillar aspergillosis (B44.2). Malign neoplasms group consisted of malignant neoplasms of lip, oral cavity and pharynx (C00-C14, malignant melanoma of lip (C43.0), and basal cell carcinoma of lip (C44.0). Benign neoplasms included benign tumors (D00.0, D03.0, D03.3), in situ neoplasms (D23.0), and other benign neoplasms of lip, oral cavity, pharynx or bone of skull and face (D10, D11, D16.4, D16.5, D37.0). Dental diseases included diseases of oral cavity, salivary glands and jaws (K00–K14). The last group included dermatological diseases (pemphigus L10), pemphigoid (L12), dermatitis herpetiformis (L13.0), psoriasis (L40), and lichen planus (L43).

We used one year wash-out period from the start of follow-up in 1997 to identify and exclude those with pre-existing diseases of interest. For each outcome of interest, those eligible for follow-up (e.g. without diagnoses during wash-out period) were followed up to the first occurrence defined as the first hospital visit/hospitalization with diagnosis of interest, death or end of follow-up (31st December 2014).

Statistical analyses

We assessed and reported the incidence of the diseases of interest. Cox's proportional hazards models stratified by matching unit (sex, age and area of residence by postal code), and models matched and adjusted for smoking, education level, and body mass index (when possible), were

used to evaluate the matched and additionally adjusted hazard ratios (HR) of diseases between asthmatic and non-asthmatic groups. Each comorbidity was modelled separately. The differences in comorbidity-free survival between asthmatics and non-asthmatics were also assessed by plotting the Kaplan-Meier survival curves and performing log-rank tests. P-values <.05 were considered statistically significant. All data analyses were performed with version 3.6.1 of R statistical software [26].

RESULTS

Mean follow-up period was 13.8 years. Total of 58,113 person years accumulated for 3,792 persons. Risk of having an any oral health related disease was increased among asthmatics (matched HR 1.61, 95% confidence interval (CI) 1.24–2.10, P<0.001, Table 2), and Kaplan-Meier plot (Figure 1) showed a clear difference between the asthmatic and non-asthmatic group. Result remained significant after adjusting for pack-years, education level and body mass index (HR 1.41, 1.11–1.80, P=0.001).

Only a few cases of candidiasis and herpes simplex infections were recorded in the first comorbidity group. As it consisted mostly of herpes zoster, we decided to calculate the HR for herpes zoster cases only. Hazard rate of herpes zoster was nearly seven times more common in the asthmatic group (matched HR 6.94, 1.50–32.1, P<0.05) compared to non-asthmatics. After adjusting for pack-years, the association persisted (adjusted HR 6.18, 1.21–31.6, P<0.05). Benign tumors were 1.5-fold more common among asthmatics (matched HR 1.94, 1.05–3.56, P<0.05). Most common benign tumors in the head area were neoplasms of inner mouth and tumors of parotid gland and other major salivary glands.

Asthma was not significantly associated with increased hazard rate of malignant neoplasm of lip, oral cavity or pharynx (matched HR 2.33, 0.91–5.99, P=0.080). Cancers of lip, oral cavity or pharynx as well as melanoma or basal cell carcinoma of lip were recorded. Hazard rate of non-neoplastic conditions of head and neck region, diseases of oral cavity, salivary glands and jaws was not significantly increased among asthmatics (HR 1.21, 0.84–1.73, P=0.059). Dental diseases grouped together such as caries, chronic apical periodontitis and periapical abscess were not significantly associated with adult asthma neither in univariate analysis (matched HR 1.21, 0.84–1.73, P=0.307) nor after adjustment (HR=1.40, 0.93–2.12). Matched HR for dental caries solely was 2.13, 0.90–5.05, P=0.085.

We finally observed dermatological diseases that may have oral manifestations and found that the investigated diseases associated with asthma in the matched cohort (matched HR 1.67, 1.01–2.78, P=0.048) but after after adjusting for pack-years, education level and body mass index the association attenuated (adjusted HR 1.72, 0.85–3.47, P=0.129). Psoriasis and lichen planus were the most common skin diseases with 89% representation of all studied skin diseases among asthmatic adults (Table 3). Among adults without asthma, psoriasis and lichen planus comprised 77% of all skin diseases investigated in this study. Other dermatological diseases found were pemphigus, pemphigoid and dermatitis herpetiformis.

Table 2 Comparing the non-asthmatic and asthma groups in respect with oral comorbidities. Hazard ratios based on Cox's proportional hazards regression. In the first model only matching is taken into account as strata. The second model is mached and adjusted by background variables.

		10 000 person-years	Events	Rate (95% CI) per 10 000 person-years	Matched HR (95% CI)	Adjusted HR (95% CI)
Any oral disease	No asthma	33.46	165	4.93 (4.21–5.74)	1	1
	Asthma	18.41	136	7.39 (6.20–8.74)	**1.61 (1.24–2.10)**	**1.41 (1.11–1.80)***
Herpes zoster	No asthma	34.72	4	0.11 (0.03–0.29)	1	1
	Asthma	19.51	14	0.72 (0.39–1.20)	**6.94 (1.50–32.1)**	**6.18 (1.21–31.6)†**
Malign neoplasms	No asthma	34.66	11	0.32 (0.16–0.57)	1	1
	Asthma	19.52	13	0.67 (0.35–1.14)	2.33 (0.91–5.99)	2.13 (0.72–6.34)†
Benign neoplasms	No asthma	34.53	28	0.81 (0.54–1.17)	1	1
	Asthma	19.41	25	1.29 (0.83–1.90)	**1.94 (1.05–3.56)**	1.64 (0.81–3.33)††
Dental diseases	No asthma	34.02	96	2.82 (2.29–3.45)	1	1
	Asthma	19.03	66	3.47 (2.68–4.41)	1.21 (0.84–1.73)	1.40 (0.93–2.12)††
Dermatological diseases	No asthma	34.35	42	1.22 (0.88–1.65)	1	1
	Asthma	19.19	36	1.88 (1.31–2.60)	**1.67 (1.01–2.78)**	1.72 (0.85–3.47)*

Matched HR = participants with asthma and without asthma are only matched for sex, age and area of residence by postal code.
Adjusted HRs:
* Matched for sex, age and area of residence by postal code and adjusted for pack-years, education level and body mass index.
† Matched for sex, age and area of residence by postal code and adjusted for pack-years.
†† Matched for sex, age and area of residence by postal code and adjusted for pack-years and education level.
Bold values denote statistical significance at the $p < 0.05$ level.

Table 3 Frequency of oral diagnoses

	No asthma	Asthma
Virus infections		
Herpes Zoster (B02)	4	14
Other virus infections (B00, B37)	3	1
Oral cancer		
Lip, oral cavity and pharynx (C00-C02, C04, C10, C13, C14)	7	11
Melanoma or basal cell carcinoma of lip (C44)	4	3
Benign tumors		
Mouth and pharynx (D10)	14	16
Major salivary glands (D11)	8	8
Other benign tumors (D03, D23, D37)	7	2
Dental diseases	16	21
Dental caries (K01, K02)		
Diseases of salivary glands (K11)	16	15
Stomatitis and related lesions (K12)	6	5
Diseases of lip and oral mucosa (K13)	17	8
Diseases of tongue (K14)	8	5
Other dental diseases (K03, K04, K10)	33	14
Dermatological diseases		
Psoriasis (L40)	21	22
Lichen planus (L43)	13	12
Pemphigus (L10)	1	0
Pemphigoid (L12)	4	3
Dermatitis herpetiformis (L13.0)	5	1

DISCUSSION

In this population-based cohort study, the hazard rate of being diagnosed with an oral manifesting disease was increased among asthmatics. The differences in the hazard rate of infections, benign neoplasms and dermatological diseases contributed to the overall increase. The hazard of benign oral tumors (including benign salivary gland tumors) was 1.5-fold, and of virus infection, herpes zoster, was nearly seven times higher among asthmatic adults as compared to non-asthmatic adults.

Dermatological diseases, mainly psoriasis and lichen planus, associated with asthma in the matched cohort but hazard was not significant in the adjusted model.

We observed an increased hazard rate of herpes zoster among asthmatic adults. A 8-year follow-up study made in Taiwan with over 40,000 newly diagnosed, adult asthmatics with age- and sex-matched non-asthmatics discovered that the risk of herpes zoster infection was 1.48-fold in the asthma group [27]. Herpes zoster infection in the intraoral region is classically seen as unilateral dermatomal rash with maculopapular appearance, preceded with hard, neuropathic pain [28,29]. It is caused by the reactivation of Varicella Zoster Virus, and may occur spontaneously or due to immune system deficiency. The respiratory viruses associated with asthma exacerbations include respiratory syncytial virus (RSV), influenza viruses, and human rhinoviruses, as well as coronaviruses, parainfluenza viruses, adenoviruses and more recently found metapneumoviruses and bocaviruses [30,31]. It is assumed that age-related decline in immune function and coexistent viral infection promotes persistent chronic inflammation of airways [32].

We have previously shown a higher all-cause mortality of adult asthmatics, which was largely explained by the development of chronic obstructive pulmonary disease, malignant respiratory tract neoplasms, and cardiovascular diseases [13]. Although highly lethal in general, we did not detect increased mortality of oral cancer among asthmatics in our previous study, putatively due to its low incidence compared to other death causes of asthmatics and controls. In line with our previous findings, asthma was not significantly associated with malignant neoplasms of oral cavity or pharynx in the present study.

The results of our study suggested that the hazard rate of bening oral tumors could be increased among astmatic adults compared to non-astmatic adults. To our knowledge, the possible association between benign oral tumors and asthma has not been studied before. Plausible explanation for decreased salivary flow might be the use of β_2 -agonists [33].

We detected that dental diseases (diseases including tooth decay, chronic apical periodontitis, sialadenitis and diseases of periodontal tissue) were not significantly associated with adult asthma. However, our data do not include oral status information routinely collected in the primary care, and therefore no conclusions about the incidence of for example tooth decay or periodontitis cannot be made from these data. According to a meta-analysis and systematic review including 18 studies, asthma roughly doubles the risk of dental caries in both primary and permanent dentition [17]. Plausible mechanisms contributing to tooth decay are decreased saliva secretion rate and decreased salivary pH due to inhaled β_2-agonists and corticosteroids, dry powder inhalers containing lactose monohydrate and increase in *Lactobacilli* and *Streptococcus mutans* in the oral cavity [17,21]. It could be speculated that increased caries risk found in other studies might also be related to decreased biodiversity of oral cavity and aberrant immunity of asthmatics, yet further studies are warranted.

In our study dermatological diseases that may have oral manifestations were more common among asthmatics. Psoriasis is an immune-mediated, genetic skin and joint disease typically characterized with erythematosus plaques with silvery scales [23]. Recent meta-analysis indicated that patients with psoriasis have an increased risk of asthma, especially in older patient groups [22]. Oral manifestations of psoriasis include lesions of small, whitish papules, red and white plaques that follow skin lesions, and bright red patches, all which may also be associated with angular cheilitis, geographic tongue lesions and fissured tongue [34]. Whether psoriasis can manifest solely in the

oral mucosa has been a matter of debate for years. The benefits of relatively large matched cohort set up in our study allowed to detect also connections between rare diseases such as autoimmune diseases.

Based on genome-wide association studies, both asthma and autoimmune diseases are associated with several single-nucleotide polymorphisms (SNPs) in the human 17q12-21 locus [35]. Although rare and difficult to diagnose, some case reports suggest there is a intraoral form of psoriasis. [36] Studies have shown shared genetic variants of asthma and autoimmune diseases [4], which could reflect increased co-existence of asthma and psoriasis compared to controls. Asthma and psoriasis also have shared comorbidities such as cardiovascular diseases, depression, diabetes and obesity [37].

In line with our findings of psoriasis, another autoimmune disease, lichen planus, was among the most common dermatological diseases among asthmatics in our study. Clinical features of oral lichen planus typically include pain and burning in the mouth induced by spicy or acid foods due to lesions in the mucosa. Clinical presentations of oral lichen planus are reticular, erosive, plaque-like, and bullous, which all can occur individually or in combination. Frequently asymptomatic, reticular oral lichen planus is however the most common type [38]. To our knowledge, there are no previous studies concerning the association between lichen planus and asthma.

This study has several strengths and limitations. The strengths of this study include the population-based, matched cohort set up and the fact that asthma diagnosis was confirmed with lung function tests. The study also benefits from the long follow-up time. Limitation of the study is the lack of data of primary care, where common dental problems such as dental caries are usually treated. We used hazard ratios to measure the difference between asthmatic and non-asthmatic groups.

However, using HR, roughly interpreted as the incidence rate ratio, is not totally unproblematic. Use of HR with a causal interpretation is risky because of two things: the HR may change over time, and the HR has a built-in selection bias. [39]. We acknowledge the possibility of detection bias due to the more intensive use of healthcare services by asthmatics (and people with any moderate to severe chronic disease) than non-asthmatic subjects, which could have affected the results. For some of the comorbidities, uncertainty (wide confidence intervals) regarding the magnitudes of the observed relative differences and limited statistical power precluding of observing potentially exsisting associations, should be taken into account, when interpreting the results of our study.

One of the most common oral health problems, periodontitis, has a two-way relationship with diabetes mellitus, and is presumably associated with severe asthma in adults [40,41]. Periodontitis is diagnosed and mostly treated in the primary care. Incidence of this chronic inflammatory disease of tissues surrounding the teeth cannot thus be investigated from this data. Clinical features of the cases were not available due to register-based study design. In cases of herpes zoster and psoriasis, ICD-10 coding does not separate anatomical sites of disease manifestation. However, to our knowledge the incidence of oral manifestations of these diseases is not clear, and it is therefore important to take each case into account.

CONCLUSIONS

Risk of having an oral manifesting disease was increased among adult asthmatics. Viral and fungal infections were the most common oral disease among asthmatics but also risk of having a benign tumor, or dermatological disease was increased among adult asthmatics. These results emphasize the significance of good oral care in asthmatics. Identifying the most common asthma related oral

diseases may result in early diagnosis and better management of comorbid conditions and overall health of asthmatics.

Contributorship statement: R. Lemmetyinen, S. Toppila-Salmi, J. Karjalainen, and J. Haukka contributed to data acquisition, analysis, interpretation, and design, and revised the manuscript for critical intellectual content. A. But, R. Renkonen, and J. Pekkanen critically revised the manuscript. All authors agree to be accountable for all aspects of the work.

Competing interests: None declared.

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Data sharing statement: The data that support the findings of this study are available from Statistics Finland, and the National Institute for Health and Welfare, but restrictions apply to the availability of these data, which were used under licence for the current study, and so are not publicly available. Data are, however, available from the authors upon reasonable request and with permission of Statistics Finland, and the National Institute for Health and Welfare.

Figure 1 legend: **Figure 1** Kaplan-Meier survival curve showing the difference in oral health related diseases between asthmatics and non-asthmatics. P-value by log-rank test.

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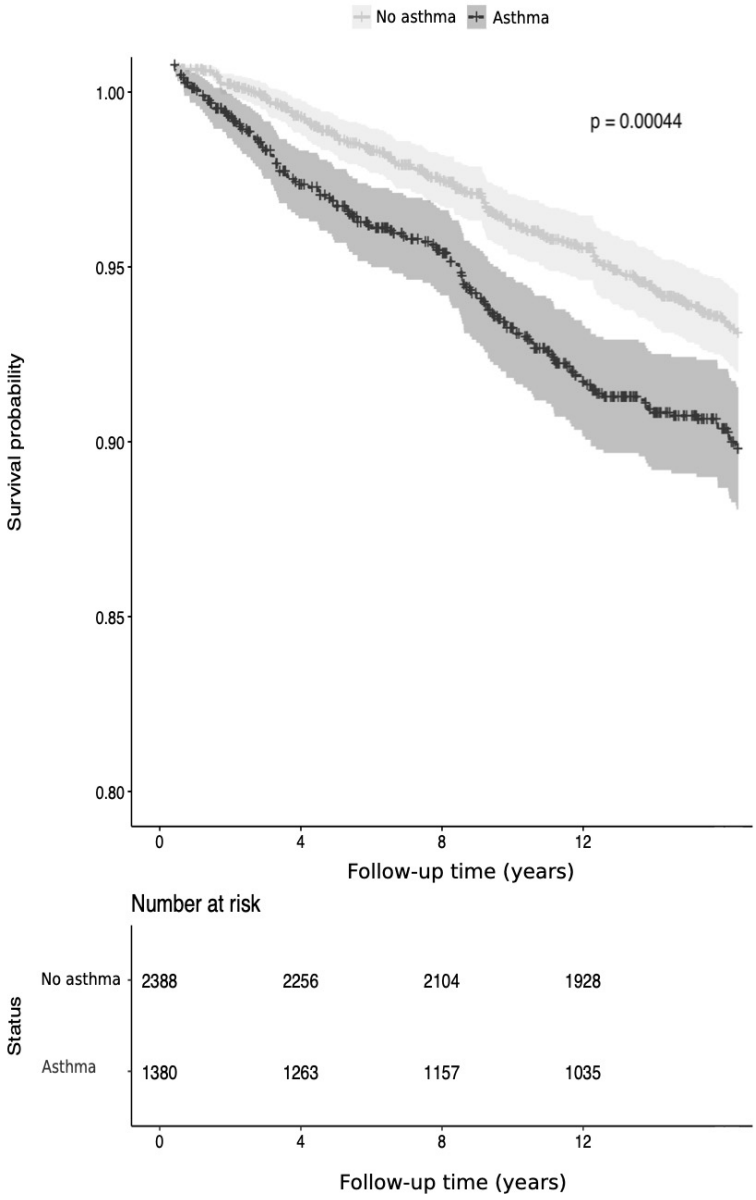

Figure 1 Kaplan–Meier survival curve of the difference in oral health–related diseases amongst asthmatics and nonasthmatics. P-value for the log-rank test.

366x457mm (72 x 72 DPI)

STROBE (Strengthening The Reporting of OBservational Studies in Epidemiology) Checklist

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Section and Item	Item No.	Recommendation	Reported on Page No.
Title and Abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/Rationale	2	Explain the scientific background and rationale for the investigation being reported	3-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5, 6-7
Methods			
Study Design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7

Section and Item	Item No.	Recommendation	Reported on Page No.
Data Sources/ Measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	12
Study Size	10	Explain how the study size was arrived at	6
Quantitative Variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical Methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	9
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	6
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	6
		(c) Consider use of a flow diagram	6
Descriptive Data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7, 19
		(b) Indicate number of participants with missing data for each variable of interest	19
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	7
Outcome Data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	7-9, 20, 21
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	

Section and Item	Item No.	Recommendation	Reported on Page No.
Main Results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	20
		(*b*) Report category boundaries when continuous variables were categorized	19
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other Analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key Results	18	Summarise key results with reference to study objectives	9, 13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
Other Information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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DISEASES WITH ORAL MANIFESTATIONS AMONG ADULT ASTHMATICS IN FINLAND - A POPULATION-BASED MATCHED COHORT STUDY

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DISEASES WITH ORAL MANIFESTATIONS AMONG ADULT ASTHMATICS IN FINLAND: A POPULATION-BASED MATCHED COHORT STUDY

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ABSTRACT

Objectives: Many comorbidities are associated with adult asthma and may exacerbate the asthma burden of disease. This study aims to investigate the risk for major oral diseases or oral-manifesting diseases in asthmatic compared to nonasthmatic adults.

Design: We conducted a population-based matched cohort study with a 13.8-year follow-up.

Setting: A baseline questionnaire was completed by participants in 1997 and follow-up data were extracted from the national hospital discharge registry of the National Institute for Health and Welfare in Finland from 1997 through 2014.

Participants: A total of 1394 adults with asthma were matched with 2398 adults without asthma based on sex, age and area of residence. Asthmatic adults were identified from the Drug Reimbursement Register of the Finnish Social Insurance Institution based on a special drug reimbursement right resulting from asthma. Participants without asthma were identified from the Population Register.

Main outcomes and measures: Oral health–related primary diagnoses were retrieved using codes from the International Classification of Diseases, tenth edition (ICD-10) and divided into groups of diseases. Cox's proportional hazards models stratified by matching unit and models matched and adjusted for pack-years, education level and body mass index (when possible) were used to evaluate the matched and further adjusted hazard ratios (HR) for diseases comparing asthmatic and nonasthmatic cohorts.

Results: Adult asthma was associated with a higher risk for any oral-manifesting disease (adjusted HR 1.41, 95% confidence interval [CI] 1.11–1.80), herpes zoster (adjusted HR 6.18, 95% CI 1.21–31.6), benign tumours of the oral cavity and pharynx (matched HR 1.94, 95% CI 1.05–3.56) and dermatological diseases (pemphigus, pemphigoid, dermatitis herpetiformis, psoriasis and lichen planus, HR 1.67, 95% CI 1.01–2.78).

Conclusions: In this study, adult asthmatics experienced a higher risk for a major oral disease or oral-manifesting disease.

Strengths and limitations of this study

- This study is a population-based, matched cohort design with a nearly 14-year follow-up.
- A detection bias was possible given the more intensive use of healthcare services amongst asthmatics (and people with any moderate to severe chronic disease) compared with nonasthmatics, potentially impacting the results.
- The possible causal relationship between asthma and oral health conditions may be confounded by asthma medications, which decrease salivary flow and lower the pH in the oral cavity.
- An asthma diagnosis was confirmed by a medical doctor and based on lung function tests and typical medical history.
- The study lacks data from primary care, where common dental or oral problems, such as periodontitis or oral candidiasis, are typically treated.

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INTRODUCTION

Asthma is one of the most common chronic diseases in children and adults, recognised for its characteristic pattern of symptoms, such as its timing, triggers and response to treatment. Typical symptoms include wheezing, shortness of breath, chest tightness and a cough, yet a careful patient history remains crucial for the differential diagnosis. The prevalence of asthma in adults ranges from 0.2% to 21.0%, remaining highest in developed countries and most likely underestimated in poorer countries [1]. In addition to socioeconomic class and a genetic predisposition, megatrends such as climate change, ageing and urbanisation impact asthma prevalence [2–4]. Whilst asthma has been considered a single disease, recent studies have shown that it consists of multiple phenotypes [5]. Furthermore, asthma varies considerably across a patient's life, presenting differently in adults versus children. Where childhood asthma is characterised by a predominance of allergic multimorbidity and a higher prevalence amongst boys, adult asthma is associated with more respiratory symptoms and asthma medications [6]. Risk factors for adult asthma consist of a genetic predisposition, female gender, overweight, allergies, upper airway diseases and exposure to tobacco smoke or other irritants [7]. The primary adult asthma phenotypes identified thus far include (1) early-onset allergic asthma, (2) early-onset allergic moderate-to-severe remodelled asthma, (3) late-onset nonallergic eosinophilic asthma and (4) late-onset nonallergic noneosinophilic asthma, whereby an overlap of commonly reported asthma phenotypes has also been observed carrying implications for objective asthma outcomes [5,8]. Furthermore, the definition of 'early onset' varies across studies. For instance, a study investigating severe asthma subgroups defined late-asthma onset as occurring after the age of 12 years [9], whilst other studies refer to early-onset adult asthma when asthma onset was reported at 12–15 years [10]. More severe forms of adult asthma appear less stable than childhood-onset disease with more relapses and less remission, and have been associated with an increased IgE, eosinophilia, poorer adherence to therapy, recurrent infections, obesity,

smoking and a lower socioeconomic status [1,6]. Various classifications and subgroups of asthma phenotypes have been proposed, but a clear consensus has not yet emerged within the scientific community. The heterogeneity of severe asthma phenotypes has resulted in the development of new asthma treatments targeting specific immune pathways, with perhaps a limited utility amongst the general asthma population, but carrying a potential benefit to a subset of asthma patients [11].

Studies have demonstrated that many comorbidities coexist with asthma, possibly even contributing to a lower life expectancy [12]. We previously detected an increased all-cause mortality amongst asthmatics in the Finnish adult population, largely explained by the development of chronic obstructive pulmonary disease in smoking asthmatics, malignant respiratory tract neoplasms and cardiovascular diseases [13]. In the Finnish population, the most common comorbidities of adult asthma consist of hypertension, diabetes, severe psychiatric disorders and ischemic heart disease [14]. Other known asthma-related comorbidities include rhinitis, chronic sinusitis, gastroesophageal reflux disease, obstructive sleep apnoea, hormonal disorders, obesity, hyperventilation, glottic dysfunction and respiratory infections [15]. In a population-based cross-sectional study covering 1.4 million Scottish patients, comorbidities associated with asthma in adults included chronic obstructive pulmonary disease, bronchiectasis, eczema/psoriasis, dyspepsia, depression and anxiety [16].

Asthma was previously associated with herpes zoster, tooth decay, dental erosion, oral candidiasis, periodontal disease, psoriasis and gastroesophageal reflux disease [16–25]. A cross-sectional, self-reported study investigated the association of oral health and asthma/allergic rhinitis/atopic dermatitis in a large population of Korean adolescents over a 12-month period [26]. Poor oral health was significantly correlated with the prevalence of asthma/allergic rhinitis/atopic dermatitis. That study benefited from a large sample of over 130 000 participants, although the assessment of

causality was limited due to its cross-sectional design [26]. The oral cavity is closely connected with the lower airways given the anatomical location and in terms of functions such as conducting and modifying inhaled air and speech. A recent review outlined one theory suggesting that the lung microbiota results from the random immigration of bacteria originally from the oral microbiota, random bacterial reproduction in the lung and the random exclusion of lung bacteria [27]. That same review suggested that associations between asthma and oral health are explained by asthma medications, mainly β_2-agonists and inhaled steroids. Specifically, asthma inhalers decrease saliva production and its components, which protect and rinse the oral cavity and teeth. They also contain sugary components and create a pH <5.5, thus inducing dental caries and erosion [27,28]. The direct effects of asthma on periodontal health may involve dehydrating the alveolar mucosa due to mouth breathing, and altering the immune response via an increased concentration of IgE, which may cause periodontal destruction [25,29]. Furthermore, obesity is a major risk factor for asthma, and closely connected to overeating and the high consumption of sweet foods and drinks, possibly leading to poor oral health [25,30].

Study aim

This cohort study aimed to investigate the hazard rate of major oral-manifesting diseases in asthmatic adults compared with nonasthmatic adults. We hypothesised that asthmatics experience more major oral diseases than nonasthmatics.

METHODS

Study design

This population-based, matched cohort study with follow-up began with a questionnaire completed in 1997, which collected data from asthmatics and matched nonasthmatics on their living environment, allergies, smoking duration and quantity, weight and education level. The

questionnaire was sent to 4958 individuals, 3792 of whom responded. Altogether, this study consisted of 1394 asthmatics and 2398 adults without asthma. Follow-up data including all diagnostics codes for the participants who responded were collected from the national hospital discharge registry of the National Institute for Health and Welfare from 1997 to 2014.

Patient and Public Involvement Study participants were not involved in planning the study design. Extended data from the registers were collected with approval from the National Institute for Health and Welfare. Study results have been published only in peer-reviewed journals, with no other information related to the results provided to participants.

Ethics statement Approval for the study was obtained from the ethical committee at Tampere University Hospital (R15030) and written informed consent was obtained from all subjects.

Study population

Participants with and without asthma were matched based on sex, age (±2 years) and area of residence by postal code. A total of 1400 asthmatic adults were identified from the Drug Reimbursement Register of the Finnish Social Insurance Institution based on a special drug reimbursement right due to an asthma diagnosis. The population register was used to identify 2800 matched nonasthmatics. In total, 248 asthmatics and 511 nonasthmatics were recruited from the Mini Finland Health Survey [31]. All asthmatics fulfilled the criteria for physician-diagnosed asthma, criteria which included a typical history, clinical features and asthma course and lung function tests. Participants were over 30 years old (Table 1), nearly 62% were male and 38% women. An estimate of participants' lifetime tobacco exposure at baseline was calculated in pack-years [32]. The body mass index was grouped according to four categories, while level of education

was divided into three categories based on the Finnish education system. The study population was described in further detail elsewhere [13].

Table 1 Baseline characteristics collected from Finnish patients via questionnaire in 1997

	No asthma, n (%)	Asthma, n (%)	Missing (%)
Sex			
Men	912 (38.0)	532 (38.2)	
Women	1486 (62.0)	862 (61.8)	
Total	2398	1394	
Age at baseline (in years)			
≤59	1506 (62.8)	893 (64.1)	
60–69	699 (29.1)	401 (28.8)	
70–79	166 (6.9)	84 (6.0)	
≥80	27 (1.1)	16 (1.1)	
Pack-years			6.7
0	1286 (57.1)	625 (48.6)	
≤19	595 (26.4)	389 (30.2)	
≥20	371 (16.5)	273 (21.2)	
BMI (kg x m $^{-2}$)			2.4
Underweight (<18.5)	26 (1.1)	19 (1.4)	
Normal (18.5–24.99)	998 (42.6)	463 (34.0)	
Overweight (25–29.99)	958 (40.9)	577 (42.4)	
Obese (≥30)	358 (15.3)	303 (22.2)	
Education level			2.2
Matriculation exam	435 (18.5)	187 (13.8)	
Secondary school	560 (23.8)	322 (23.7)	
Primary school or less	1356 (57.7)	850 (62.5)	

Lifetime tobacco exposure was calculated in pack-years (number of cigarettes per day/20 x number of years smoked, where 1 pipe = 2.5 cigarettes and 1 cigar = 4 cigarettes) upon which individuals were divided into three groups: 0, ≤19 and ≥20 pack-years.

Body mass index (BMI) assessed as weight in kilograms divided by the square of the height in metres, then divided into four categories according to World Health Organisation classification.

Level of education was obtained through a questionnaire and categorised based on the Finnish education system: matriculation examination (13 years, reference value), secondary school or equivalent (9 years) and primary school or less (≤6 years).

Outcomes

In this study, we focused on oral diseases and diagnoses that can manifest in the oral cavity. The diagnoses were identified from hospital visit and hospitalisation data obtained from the national hospital discharge registry of the National Institute for Health and Welfare from 1997 to 2014. Only the primary diagnoses were retrieved using codes from the International Classification of Diseases, tenth edition (ICD-10), and were divided into five disease groups: infections, malign neoplasms,

benign neoplasms, dental diseases and dermatological diseases. The first group consisted of viral and fungal infections (herpes simplex (B00.1); herpes zoster (B02); hand, foot and mouth disease (B08.4); herpangina (B08.5); HIV disease resulting in candidiasis (B20.4); Kaposi sarcoma (B21.0); Burkitt lymphoma (B21.1); mumps (B26.9); Epstein-Barr (B27.0); candidiasis (B37); and tonsillar aspergillosis (B44.2). Malign neoplasms consisted of malignant neoplasms of the lip, oral cavity and pharynx (C00-C14); malignant melanoma of the lip (C43.0); and basal cell carcinoma of the lip (C44.0). Benign neoplasms included benign tumours (D00.0, D03.0 and D03.3), in situ neoplasms (D23.0) and other benign neoplasms of the lip, oral cavity, pharynx or bone of the skull and face (D10, D11, D16.4, D16.5 and D37.0). Dental diseases included diseases of the oral cavity, salivary glands and jaws (K00–K14). The last group included dermatological diseases (pemphigus L10), pemphigoid (L12), dermatitis herpetiformis (L13.0), psoriasis (L40) and lichen planus (L43). We used a one-year wash-out period from the beginning of follow-up in 1997 to identify and exclude those with a pre-existing disease of interest. For each outcome of interest, those eligible for follow-up (e.g., individuals without diagnoses during the wash-out period) were followed up until the first occurrence defined as the first hospital visit/hospitalisation with a diagnosis of interest, death or the end of follow-up (31 December 2014). Therefore, each diagnosis was recorded only once.

Statistical analyses

We assessed and reported the incidence of the diseases of interest. Cox proportional hazards models stratified by the matching criteria (sex, age and area of residence by postal code) and models matched and adjusted for smoking, education level and body mass index (when possible) were used to evaluate the matched and additionally adjusted hazard ratios (HRs) for diseases comparing asthmatic and nonasthmatic individuals. We modelled each comorbidity separately. The differences in comorbidity-free survival between asthmatics and nonasthmatics were also assessed by plotting

the Kaplan–Meier survival curves and performing log-rank tests. In all analyses, we considered P<0.05 statistically significant. All data analyses were performed using the R statistical software package, version 3.6.1 [33].

RESULTS

The mean follow-up period was 13.8 years. A total of 58 113 person-years accumulated for 3792 individuals. Overall, 71% of asthmatic patients used inhaled corticosteroids and 76% used any inhaled asthma medication at baseline (in 1997). The risk of experiencing any oral health–related disease (including all diseases investigated) was higher amongst asthmatics (matched HR 1.61, 95% confidence interval [CI] 1.24–2.10, P<0.001, Table 2), with the Kaplan-Meier plot (Figure 1) showing a clear difference between asthmatics and nonasthmatics individuals. These results remained significant after adjusting for pack-years, education level and body mass index (HR 1.41, 95% CI 1.11–1.80, P=0.001).

Only a few cases of candidiasis and herpes simplex infections were recorded in the Infections-group. Since these cases primarily consisted of herpes zoster, we calculated the HR for herpes zoster cases only. We found that the rate of herpes zoster was nearly seven times higher in the asthmatic group (matched HR 6.94, 95% CI 1.50–32.1, P<0.05) compared with nonasthmatics. After adjusting for pack-years, this association persisted (adjusted HR 6.18, 95% CI 1.21–31.6, P<0.05). Benign tumours were 1.5-fold more frequent amongst asthmatics (matched HR 1.94, 95% CI 1.05–3.56, P<0.05). The most common benign tumours in the head area included neoplasms of the inner mouth and tumours of the parotid gland and other major salivary glands.

Asthma was not significantly associated with an increased risk for malignant neoplasms of the lip, oral cavity or pharynx (matched HR 2.33, 95% CI 0.91–5.99, P=0.080). Cancers of the lip, oral

cavity or pharynx as well as melanoma or basal cell carcinoma of the lip were recorded. The risk for of non-neoplastic conditions of the head and neck region, in addition to diseases of the oral cavity, salivary glands and jaws was not significantly higher amongst asthmatics (HR 1.21, 95% CI 0.84–1.73, P=0.059). Similarly, dental diseases such as caries, chronic apical periodontitis and periapical abscess taken together were not significantly associated with adult asthma neither in a univariate analysis (matched HR 1.21, 95% CI 0.84–1.73, P=0.307) nor after adjustment (HR 1.40, 95% CI 0.93–2.12). A higher risk for dental caries on its own emerged amongst adult asthmatics (matched HR 2.13, 95% CI 0.90–5.05, P=0.085) but the association was not statistically significant.

Finally, we examined dermatological diseases that may have oral manifestations, finding that the investigated diseases associated with asthma in the matched cohort (matched HR 1.67, 95% CI 1.01–2.78, P=0.048). However, after adjusting for pack-years, education level and body mass index, the association diminished (adjusted HR 1.72, 95% CI 0.85–3.47, P=0.129). Psoriasis and lichen planus were the most common skin diseases representing 89% of all skin diseases examined amongst asthmatic adults (Table 3). Furthermore, amongst adults without asthma, psoriasis and lichen planus comprised 77% of all skin diseases investigated in this study. Other dermatological diseases indentified included pemphigus, pemphigoid and dermatitis herpetiformis.

Table 2 Comparison of Finnish nonasthmatic and asthmatic adults for oral comorbidities, 1997–2014

		10 000 person-years	Events	Rate (95% CI) per 10 000 person-years	Matched HR (95% CI)	Adjusted HR (95% CI)
Any oral disease	No asthma	33.46	165	4.93 (4.21–5.74)	1	1
	Asthma	18.41	136	7.39 (6.20–8.74)	1.61 (1.24–2.10)	1.41 (1.11–1.80)*
Herpes zoster	No asthma	34.72	4	0.11 (0.03–0.29)	1	1
	Asthma	19.51	14	0.72 (0.39–1.20)	6.94 (1.50–32.1)	6.18 (1.21–31.6)†
Malign neoplasms	No asthma	34.66	11	0.32 (0.16–0.57)	1	1
	Asthma	19.52	13	0.67 (0.35–1.14)	2.33 (0.91–5.99)	2.13 (0.72–6.34)†
Benign neoplasms	No asthma	34.53	28	0.81 (0.54–1.17)	1	1
	Asthma	19.41	25	1.29 (0.83–1.90)	1.94 (1.05–3.56)	1.64 (0.81–3.33)††
Dental diseases	No asthma	34.02	96	2.82 (2.29–3.45)	1	1
	Asthma	19.03	66	3.47 (2.68–4.41)	1.21 (0.84–1.73)	1.40 (0.93–2.12)††
Dermatological diseases	No asthma	34.35	42	1.22 (0.88–1.65)	1	1
	Asthma	19.19	36	1.88 (1.31–2.60)	1.67 (1.01–2.78)	1.72 (0.85–3.47)*

Hazard ratios based on Cox proportional hazards regression models. In the first model, matching is considered as strata. The second model is matched and adjusted based on background variables.
Matched HR, participants with asthma and without asthma are only matched for sex, age and area of residence by postal code.
Adjusted HRs:
*Matched for sex, age and area of residence by postal code and adjusted for pack-years, education level and body mass index.
†Matched for sex, age and area of residence by postal code and adjusted for pack-years.
††Matched for sex, age and area of residence by postal code and adjusted for pack-years and education level.
Bold values denote statistical significance at the P<0.05 level.

Table 3 Frequency of oral diagnoses during follow-up, 1997–2014

	No asthma	Asthma
Virus infections		
Herpes zoster (B02)	4	14
Other infections (B00, B37)	3	1
Oral cancer		
Lip, oral cavity and pharynx (C00-C02, C04, C10, C13, C14)	7	11
Melanoma or basal cell carcinoma of lip (C44)	4	3
Benign tumours		
Mouth and pharynx (D10)	14	16
Major salivary glands (D11)	8	8
Other benign tumours (D03, D23, D37)	7	2
Dental diseases	16	21
Dental caries (K01, K02)		
Diseases of the salivary glands (K11)	16	15
Stomatitis and related lesions (K12)	6	5
Diseases of the lip and oral mucosa (K13)	17	8
Diseases of the tongue (K14)	8	5
Other dental diseases (K03, K04, K10)	33	14
Dermatological diseases		
Psoriasis (L40)	21	22
Lichen planus (L43)	13	12
Pemphigus (L10)	1	0
Pemphigoid (L12)	4	3
Dermatitis herpetiformis (L13.0)	5	1

DISCUSSION

In this population-based, cohort study, asthmatics carried a higher risk of experiencing an oral-manifesting disease. The differences in the risks for infections, benign neoplasms and dermatological diseases contributed to the overall increase. The risk for benign oral tumours (including benign salivary gland tumours) was 1.5-fold higher, whilst the risk for a viral infection, specifically, herpes zoster, was nearly seven times higher amongst asthmatic adults compared with nonasthmatic adults. Dermatological diseases, mainly psoriasis and lichen planus, associated with asthma in the matched cohort, although the risk was not significant in the adjusted model.

We observed an increased risk for herpes zoster amongst asthmatic adults. An 8-year follow-up study conducted in Taiwan among over 40 000 newly diagnosed, adult asthmatics compared with age- and sex-matched nonasthmatics found that the risk of herpes zoster was 1.48-fold higher in asthmatics [34]. A meta-analysis of 12 studies investigating the relationship between asthma and herpes zoster found that asthma was associated with a greater risk (risk ratio [RR] 1.24, 95% CI 1.16–1.31, P<0.0001) of infection [35]. Herpes zoster infection in the intraoral region classically presents as a unilateral dermatomal rash with a maculopapular appearance, preceded with hard, neuropathic pain [36,37]. Caused by the reactivation of varicella zoster virus, herpes zoster may occur spontaneously or due to an immune system deficiency. Respiratory viruses associated with asthma exacerbations include respiratory syncytial virus (RSV), influenza viruses and human rhinoviruses, as well as coronaviruses, parainfluenza viruses, adenoviruses and, more recently, metapneumoviruses and bocaviruses [38,39]. Presumably, an age-related decline in immune function and a coexisting viral infection promotes persistent chronic inflammation of the airways [40].

We previously found that a higher all-cause mortality amongst adult asthmatics was largely explained by the development of chronic obstructive pulmonary disease, malignant respiratory tract neoplasms and cardiovascular diseases [13]. Although highly lethal in general, we detected no increased mortality resulting from oral cancer amongst asthmatics in our previous study, presumably due to its low incidence compared to other causes of death amongst both asthmatics and controls. In agreement with our previous findings, asthma did not significantly associate with malignant neoplasms of the oral cavity or pharynx in the study reported here.

Our results suggest that the risk of benign oral tumours could be higher amongst asthmatic adults compared with nonasthmatic adults. To our knowledge, this represents the first study to examine the association between benign oral tumours and asthma. Over 30% of the benign tumours amongst asthmatics consisted of salivary gland tumours. Whilst the cause of salivary gland tumours remains unknown, autoimmune conditions such as diabetes and Sjögren's syndrome are associated with salivary gland swelling [41]. We suspect that the increased risk associated with benign oral tumours is explained by a combination of autoimmune dysfunction, decreased salivary flow (due to the use of β_2-agonists) and a detection bias resulting from the overdiagnosis of benign tumours amongst asthmatics, individuals who consult healthcare services more frequently.

Furthermore, we found that dental diseases (diseases including tooth decay, chronic apical periodontitis, sialadenitis and diseases of periodontal tissue) were not significantly associated with adult asthma. It is widely acknowledged that asthma medication, especially the immunosuppressive effects of inhaled corticosteroids, promote oral candidiasis and tooth decay [25]. According to a meta-analysis and systematic review of 18 studies, asthma roughly doubles the risk of dental caries in both primary and permanent dentition [17]. Plausible mechanisms contributing to tooth decay include decreased saliva secretion and a lower salivary pH due to inhaled β_2-agonists and corticosteroids as well as dry powder inhalers containing lactose monohydrate, and an increase in *Lactobacilli* and *Streptococcus mutans* in the oral cavity [17,21]. An increased risk for caries might also stem from the decreased biodiversity in the oral cavity and an aberrant immunity amongst asthmatics.

The data used in this study were collected from the national hospital discharge registry of the National Institute for Health and Welfare in Finland, which collects data from hospital and health centres. The dental or and/oral diagnoses in this study result from dental specialists working in

specialised healthcare settings. The National Institute for Health and Welfare of Finland began collecting outpatient data from public health services (such as data from dental examination) in 2011, and the initial years of data collection featured poor quality data. Therefore, our data do not include oral status information routinely collected by dentists in primary care settings, and we cannot draw any conclusions about the incidence of, for example, tooth decay from these data. Additionally, oral candidiasis is presumably common amongst patients using inhaled corticosteroids. However, due to its mild symptoms, the condition often remains undiagnosed. In our study, only a few cases of oral candidiasis were recorded. Thus a causal relationship between inhaled asthma medications and oral candidiasis could not be examined from these data.

In our study, dermatological diseases with potential oral manifestations were more common amongst asthmatics. Psoriasis is an immune-mediated, genetic skin and joint disease typically characterised by erythematosus plaques with silvery scales [23]. A recent meta-analysis indicated that patients with psoriasis carry an increased risk for asthma, particularly older patients [22]. Furthermore, oral manifestations of psoriasis include lesions of small, whitish papules, red and white plaques that follow skin lesions and bright red patches, all of which may also be associated with angular cheilitis, geographic tongue lesions and a fissured tongue [42]. Whether psoriasis can manifest solely in the oral mucosa has been a matter of debate for years. The benefits of our relatively large, matched-cohort design used in this study allowed us to also detect associations between rare diseases such as autoimmune diseases.

Based on genome-wide association studies, both asthma and autoimmune diseases are associated with several single-nucleotide polymorphisms (SNPs) in the human 17q12-21 locus [43]. Although rare and difficult to diagnose, some case reports suggest that an intraoral form of psoriasis exists [44]. Moreover, studies have shown shared genetic variants of asthma and autoimmune diseases [4],

possibly reflecting an increased co-existence of asthma and psoriasis compared with controls. Asthma and psoriasis also share certain comorbidities such as cardiovascular diseases, depression, diabetes and obesity [45].

In line with our findings for psoriasis, another autoimmune disease, lichen planus, emerged as one of the most common dermatological diseases amongst asthmatics in our study. The clinical features of oral lichen planus typically include pain and burning in the mouth induced by spicy or acidic foods due to lesions in the mucosa. Clinical presentations of oral lichen planus consist of reticular, erosive, plaque-like and bullous lesions, which can occur individually or in combination. Frequently asymptomatic, reticular oral lichen planus is, however, the most common type of lichen planus [46]. To our knowledge, no previous studies examined the association between lichen planus and asthma.

This study has several strengths and limitations. The strengths of this study include the population-based, matched-cohort design and the inclusion of asthma diagnoses confirmed through lung function tests. This study also benefits from its long follow-up period. Conversely, one limitation to this study stems from the lack of primary care data, from which typical dental problems such as dental caries are normally treated. We also note that the possible causal relationship between asthma and oral health conditions may be confounded by asthma medications. Medications commonly used to treat asthma, such as β_2-agonists and inhaled steroids, may promote caries, dental erosion, periodontal disease, erosion and oral candidiasis [25].

We calculated HRs to measure the difference between asthmatic and nonasthmatic patients. However, using HRs, roughly interpreted as the incidence rate ratio, is not completely unproblematic. The use of HRs to indicate a causal relationship is risky for two reasons: first, HR may change over time and, second, HR has a built-in selection bias. [47]. We acknowledge the

possibility of a detection bias due to the more intensive use of healthcare services by asthmatics (and people with any moderate to severe chronic disease) than nonasthmatics, potentially affecting our results. For some comorbidities, uncertainty (wide confidence intervals) regarding the magnitudes of the observed relative differences and a limited statistical power precluding any potentially existing associations should be considered when interpreting our results.

Finally, one of the most common oral health problems, periodontitis, carries a two-way relationship with diabetes mellitus, and is presumably associated with severe asthma in adults [48,49]. Periodontitis is diagnosed and primarily treated in primary care settings. The incidence of this chronic inflammatory disease of the tissue surrounding the teeth thus cannot be investigated with this dataset. The clinical features of cases were not available given the register-based study design. In cases of herpes zoster and psoriasis, ICD-10 codes do not distinguish between anatomical sites of disease manifestation. However, to our knowledge, the incidence of oral manifestations of these diseases remains unclear, and is therefore important to take into account for each case.

CONCLUSIONS

Adult asthmatics experience a higher risk for an oral-manifesting disease. Viral and fungal infections represented the most common oral disease amongst asthmatics, whilst the risk for a benign tumour or dermatological disease was also higher amongst adult asthmatics. Identifying the most common asthma-related oral diseases may result in an early diagnosis and better management of comorbid conditions as well as the overall health of asthmatics. As such, dental professionals are an important part of healthcare teams given their expertise in detecting abnormalities in the oral cavity of asthmatic patients.

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Data sharing statement: The data that support the findings of this study are available from Statistics Finland and the National Institute for Health and Welfare. However, restrictions apply to the availability of these data, which were used under licence for the current study, and thus are not publicly available. Data are, however, available from the authors upon reasonable request and with the permission of Statistics Finland and the National Institute for Health and Welfare.

Figure 1 legend:

Figure 1 Kaplan–Meier survival curve of the difference in oral health–related diseases amongst asthmatics and nonasthmatics. P-value for the log-rank test.

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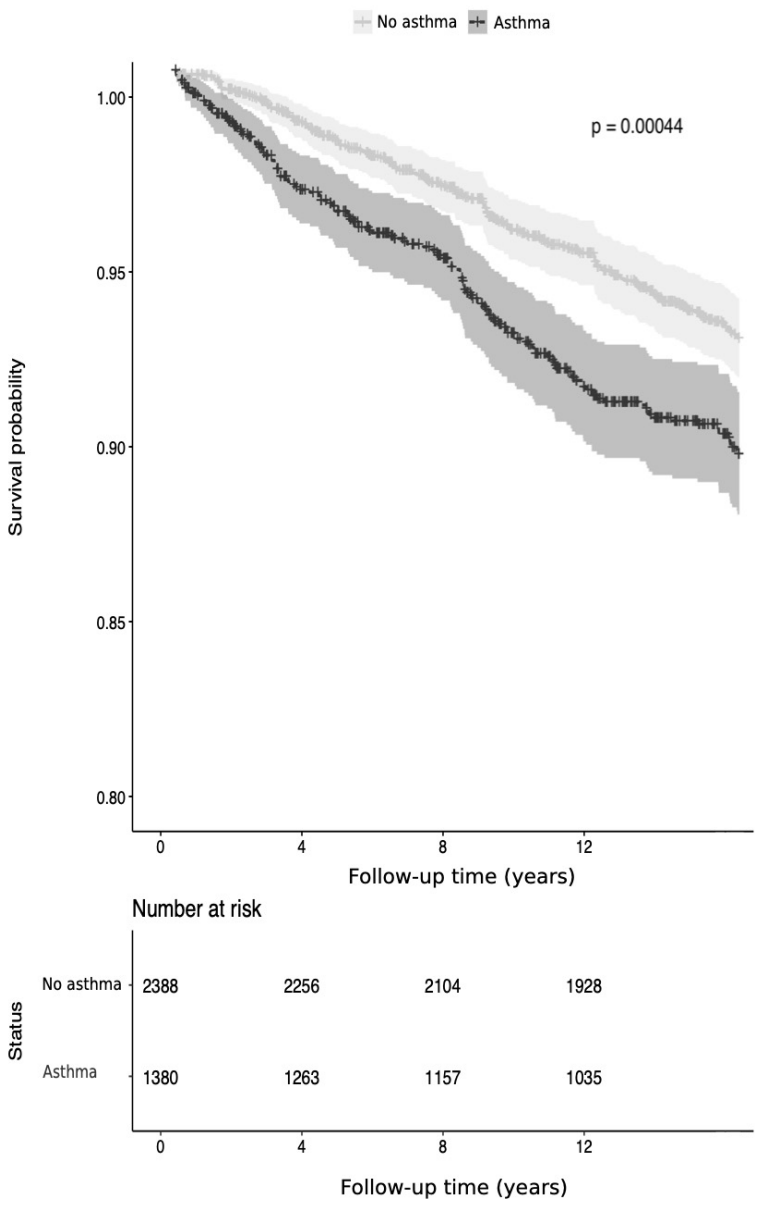

Figure 1 Kaplan–Meier survival curve of the difference in oral health–related diseases amongst asthmatics and nonasthmatics. P-value for the log-rank test.

366x457mm (72 x 72 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3	
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-6	
Objectives	3	State specific objectives, including any prespecified hypotheses	6	
Methods				
Study design	4	Present key elements of study design early in the paper	6-7	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7 N/A N/A	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	7 N/A	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9-10	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*9-10*	
Bias	9	Describe any efforts to address potential sources of bias	18-19	
Study size	10	Explain how the study size was arrived at	7	

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10-11
		(*b*) Describe any methods used to examine subgroups and interactions	10-11
		(*c*) Explain how missing data were addressed	9
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	N/A
		Case-control study—If applicable, explain how matching of cases and controls was addressed	N/A
		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	N/A
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-8
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	11
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*11-13*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	*N/A*
		Cross-sectional study—Report numbers of outcome events or summary measures	*N/A*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	13
		(*b*) Report category boundaries when continuous variables were categorized	9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	19
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19
Generalisability	21	Discuss the generalisability (external validity) of the study results	19
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.