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Comorbidities associated with adult asthma: a population-based matched cohort study in Finland

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ABSTRACT

Background Asthma is a common chronic disease characterised by variable respiratory symptoms and airflow limitation, affecting roughly 4%–10% of the adult population. Adult asthma is associated with higher all-cause mortality compared to individuals without asthma. In this study, we investigate the comorbidities that may affect the management of asthma.

Methods Total of 1648 adults with asthma and 3310 individuals without asthma aged 30–93 were matched with age, gender and area of residency, and followed from 1 January 1997 to 31 December 2013. Baseline information was collected with questionnaires 1997 and follow-up register data from the national discharge registry Finnish Institute for Health and Welfare. Data included diagnoses from outpatient care and day surgery of specialised health care, and data from inpatient care of specialised and primary health care. We included all main diagnoses that had at minimum 200 events and number of diagnoses based on their common appearance with adult asthma.

Results The mean follow-up time varied between 14.2 and 15.1 years, and age at the time of enrolment was 53.9 years for subjects without asthma and 54.4 years for patients with asthma. Chronic obstructive pulmonary disease was 10 times more common among asthmatics. Risk of acute rhinosinusitis, chronic rhinosinusitis with nasal polyps, atopic dermatitis and vocal cord dysfunction was fourfold and risk of pneumonia, and chronic rhinosinusitis was 2.5 times more common among asthmatics. Sleep apnoea, gastro-oesophageal reflux disease, diabetes, allergic rhinitis and dysfunctional breathing were twofold and cataract nearly twofold higher in the asthmatic group. Adult asthma was also significantly associated with musculoskeletal diseases, incontinence and bronchiectasis.

Conclusions The most common and most severe comorbidity of adult asthma in this study was chronic obstructive pulmonary disease. Other common comorbidities of adult asthma include acute rhinosinusitis, chronic rhinosinusitis with nasal polyps, atopic dermatitis, allergic rhinitis, dysfunctional breathing, diabetes, pneumonia, sleep apnoea and gastro-oesophageal reflux disease.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Adult asthma is often severe and associated with lower life expectancy. Many comorbidities affect the management of asthma but are less studied.

WHAT THIS STUDY ADDS

⇒ During 15 years of follow-up, adult asthma was associated with many comorbidities, of which chronic obstructive pulmonary disease was 10 times more common among asthmatics, and risk of acute rhinosinusitis, chronic rhinosinusitis with nasal polyps and atopic dermatitis was four times more common among asthmatics compared with matched (sex, age and area of residency) non-asthmatics.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

⇒ Identifying and treating the comorbidities that increase the disease burden of adult asthma may reduce costs, contribute to better management of asthma and lead to higher quality of life of patients with asthma.

INTRODUCTION

Asthma is a common chronic disease characterised by variable respiratory symptoms and airflow limitation. Globally, the self-reported doctor-diagnosed asthma in adults is 4.3% being highest in developed countries and lowest in developing ones.[1] Prevalence of asthma in adults over age 65 years is 4%–13% in the world, and it is likely an underestimate as asthma is often underdiagnosed in the elderly.[2] In Finland, the prevalence of asthma in 2014 was 4.6%, and percentage of patients with asthma increased with age reaching nearly 10% in the age group of over 75 years.[3]

Compared with asthma starting at childhood, asthma in adults is commonly non-atopic and associated with faster decline in lung function.[4] Ageing of lungs begins at 25–30 years of age and results in decreased elastic recoil, greater wall rigidity and reduced respiratory muscle strength. Incidence and prevalence are higher in childhood-onset asthma but asthma-related healthcare use and mortality are higher in adults.[5] Adult-onset asthma has a low remission probability of only 3%–18%, whereas 60% of childhood-onset asthma enters into remission.[6] Adult

asthma is the dominant phenotype among women aged 30–40 years in the USA and in Finland, while childhood-onset asthma remains more prevalent in men aged 50–54 years.[6] With increasing longevity of the general population, it is likely that prevalence of adult asthma will only increase in the future.[4]

We have previously shown that mortality of adults with asthma is significantly increased compared with adults without asthma, and that the increased mortality was affected with comorbidities such as cardiovascular diseases and chronic obstructive pulmonary diseases (COPD).[7] We have also shown a dose–response relationship between the number of allergic multimorbidities (allergic rhinitis, allergic conjunctivitis, atopic dermatitis) and asthma.[8] In addition, commonly acknowledged respiratory comorbidities of asthma are vocal cord dysfunction (VCD), obstructive sleep apnoea (OSA), non-allergic rhinitis, chronic rhinosinusitis (CRS) with or without nasal polyps, COPD, allergic bronchopulmonary aspergillosis and fungal sensitisation, bronchiectasis and dysfunctional breathing.[9] Non-respiratory comorbidities of asthma include gastro-oesophageal reflux disease (GERD), obesity, diabetes mellitus, hypertension, cardiovascular diseases, metabolic syndrome, adrenal disorders, thyroid diseases, osteoporosis, rheumatoid arthritis, eosinophilic granulomatosis with polyangiitis and mental health disorders.[9–12] A recent clinical commentary review concluded that strong associations and suspected shared causal pathways exist between obesity, OSA, GERD and asthma.[13]

Study aims

The aim of our study was to explore the comorbidities associated with asthma among the study population and investigate the differences between distribution of the diseases in people with asthma compared with matched controls in this population-based sample. We included all main diagnoses that had minimum of 200 events, which represent approximately 5% of the study population. Based on the literature search, diabetes mellitus, sleep apnoea, GERD, acute and CRS, CRS with nasal polyps (CRSwNP), allergic rhinitis, VCD, bronchiectasis and dysfunctional breathing were considered relevant comorbidities of asthma and were also included in the study.

METHODS AND STUDY POPULATION

This population-based, matched cohort study with follow-up consisted of 1648 adults with asthma and 3310 controls without asthma matched with age, gender and area of residency. Participants were aged 30–93 at the enrolment of the study. All asthmatics fulfilled the criteria for doctor-diagnosed asthma: typical history, clinical features and asthma course, and lung function tests. The study began with a questionnaire completed in 1997, which was sent to adults with asthma with special drug reimbursement right identified from the Drug Reimbursement Register of the Finnish Social Insurance Institution and from the Total Mini Health Finland Survey. Study population was followed from 1 January 1998 to 31 December 2013. The incidence of the diseases in interest was defined by the first hospitalisation (starting after 1 year of follow-up). The end of the follow-up was death or end of follow-up period. Extended data of these subjects were collected from the national discharge registry (HILMO) of the Institute for Health and Welfare from 1997 to 2013. HILMO register data at the time included diagnoses from outpatient care and day surgery of specialised healthcare as well as inpatient care from specialised and primary healthcare. Written consent was obtained from all subjects. Study population and research design have previously been described in more detail.[7]

Investigated comorbidities

The investigated comorbidities were identified using International Classification of Diseases, Tenth Revision (ICD-10) codes. The identified diagnoses with at least 200 events in the whole study population were transient cerebral ischaemic attacks and related syndromes (G45), senile cataract (H25), conductive and sensorineural hearing loss (H90), essential hypertension (I10), ischaemic heart diseases (I20, I21, I25), atrial fibrillation and flutter (I48), heart failure (I50), cerebral infarction (I63), varicose veins of lower extremities (I83), pneumonia (J15, J18), COPD (J44), inguinal hernia (K40), cholelithiasis (K80), diverticular disease of intestine (K57), arthrosis of hip or knee (M16, M17), intervertebral disc disorders or dorsalgia (M51, M54), shoulder lesions and other soft-tissue disorders (M75, M79), other disorders of urinary system (N39) and hyperplasia of prostate (N40).

Based on their common appearance with asthma, we also included the following diagnoses to the study: acute rhinosinusitis (J01), allergic rhinitis (J30), CRS (J32), CRSwNP (J33), VCD (J38.3, J38.5–J38.7, J39.3, J39.8, J39.9), bronchiectasis (J47), atopic dermatitis (L20), diabetes mellitus (E11–E14), sleep apnoea (G47.3), GERD (K21) and breathing dysfunction (R06.1–R06.5).[9]

Statistical methods

We analysed the incidence of the diseases of interest. Cox's proportional hazards models stratified by matching criteria (sex, age and area of residence by postal code) and models matched and adjusted for pack years and/or body mass index, were used to evaluate the matched and additionally adjusted HRs for diseases comparing asthmatic and non-asthmatic groups. We tested proportional hazards assumption.[14] We did not detect any non-proportionality. The differences in survival between individuals with and without asthma were assessed by plotting the Kaplan-Meier survival curves and performing log-rank tests. All data analyses were performed using the R statistical software package, V.4.1.2.[15]

Table 1 Baseline characteristics of the study population

	No asthma, n=2398 (%)	Asthma, n=1394 (%)	Missing (%)
Sex			0.0
Male	912 (38.0)	532 (38.2)	
Female	1486 (62.0)	862 (61.8)	
Age at baseline (in years)			0.0
≤59	1506 (62.8)	893 (64.1)	
60–69	699 (29.1)	862 (61.8)	
70–79	166 (6.9)	84 (6.0)	
≥80	27 (1.1)	16 (1.1)	
Age of asthma onset			4.1
<15	–	86	
≥15	–	1253	
Pack years			2.7
0	1308 (56.0)	627 (46.3)	
≤19	657 (28.1)	453 (33.5)	
≥20	371 (15.9)	273 (20.2)	
BMI (kg × 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)	

Lifetime tobacco exposure was calculated in pack years (number of cigarettes per day/20× number of years smoked, where 1 pipe=2.5 cigarettes and 1 cigar=4 cigarettes) on 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 WHO classification.

RESULTS

Baseline characteristics

For the outcomes of interest, the mean follow-up time varied between 14.2 and 15.1 years, depending on the time of enrolment which varied between individuals. Total of 62% of study population comprised women, and 38% were men (table 1). Mean age at the time of enrolment was 53.9 years for subjects without asthma and 54.4 years for patients with asthma. Among patients with asthma, there were less never smokers, more ever smokers and more individuals with obesity compared with the non-asthmatic group. Based on self-reported age at asthma onset, 90% of the patients with asthma had adult-onset asthma (onset age 15 years or over).

Association of metabolic diseases and adult asthma

The incidence of diabetes mellitus and cardiovascular diseases such as ischaemic heart diseases, atrial fibrillation and flutter, heart failure and cerebral infarction was significantly increased in the asthmatic group and the adjusted hazard rate varied from 1.28 to 2.40 in these disease groups (table 2). Risk of transient cerebral ischaemic attacks and related syndromes, hypertensive diseases or varicose veins of lower extremities was not significantly associated with adult asthma.

Association of respiratory and allergic diseases and adult asthma

Kaplan-Meier survival curves of the main results are presented in figure 1. The curves present the survival within 15 years of follow-up between patients with and without asthma in regards to our four main results which are COPD (A), CRSwNP (B), acute rhinosinusitis (C) and atopic dermatitis (D). Risk of VCD was 4.6-fold and the risk of acute rhinosinusitis, CRSwNP and atopic dermatitis was 4-fold in the asthmatic group whereas pneumonia and chronic sinusitis were 2.5 times more common among asthmatics (tables 2 and 3, figure 1). Risk of allergic rhinitis was nearly 2.3-fold among asthmatics. Bronchiectasis was almost 1.5 times more common among asthmatics and COPD nearly eight times more prevalent among people with asthma and 10 times more common after adjusting for pack years. Breathing dysfunction was over two times more prevalent among asthmatics (table 3).

Association of neurological and gastrointestinal diseases and adult asthma

The incidence of sleep apnoea was over twofold in the asthma group. Risk of GERD was twofold in the asthmatic group. Incidence of senile cataract was nearly 1.7-fold among asthmatics. No association was found between adult asthma and inguinal hernia, cholelithiasis, conductive and sensorineural hearing loss, or diverticular diseases of intestine (table 2, table 3).

Association of musculoskeletal and urinary diseases and adult asthma

Arthrosis of hip or knee was 34% more common in the asthmatic group. Intervertebral disc disorders or dorsalgia was nearly two times more common among asthmatics, and shoulder lesions and other soft-tissue disorders were almost 1.8-fold among individuals with asthma compared with individuals without asthma. Urinary diseases were 1.6 times more prevalent among asthmatics, and consisted of urinary tract infections and incontinence, which was 1.8 times more common among asthmatics. Urinary tract infections were 1.5-fold among asthmatics, but the result was not statistically significant. Hyperplasia of prostate (N40) was not significantly associated with adult asthma (table 3).

Table 2 Matched and adjusted HRs of the investigated diagnoses (E11-J32)

	Per 10 000 person years	Events	Incidence rate (95% CI) per 10 000 person years	Matched HR (95% CI)	Adjusted HR (95% CI)
Diabetes mellitus (E11–14)					
No asthma	36.68	77	2.10 (1.66 to 2.62)	1	1
Asthma	20.47	77	3.76 (2.97 to 4.70)	**1.62 (1.13 to 2.34**)	**2.40 (1.45 to 3.95**) *
Transient cerebral events (G45)					
No asthma	36.37	118	3.24 (2.69 to 3.89)	1	1
Asthma	20.42	77	3.77 (2.98 to 4.71)	1.30 (0.92 to 1.84)	1.35 (0.93 to 1.96) †
Sleep apnoea (G47.3)					
No asthma	34.20	67	1.96 (1.52 to 2.49)	1	1
Asthma	18.85	79	4.19 (3.32 to 5.22)	**2.21 (1.53 to 3.22**)	**2.07 (1.32 to 3.23**) *
Senile cataract (H25)					
No asthma	34.89	406	11.64 (10.53 to 12.83)	1	1
Asthma	19.17	319	16.64 (14.87 to 18.57)	**1.69 (1.39 to 2.04**)	**1.65 (1.35 to 2.03)** †
Hearing loss (H90)					
No asthma	35.90	189	5.27 (4.54 to 6.07)	1	1
Asthma	20.08	129	6.43 (5.35 to 7.64)	1.26 (0.96 to 1.64)	1.38 (1.01 to 1.88) *
Hypertensive diseases (I10)					
No asthma	36.03	168	4.66 (3.98 to 5.42)	1	1
Asthma	20.38	90	4.42 (3.55 to 5.43)	1.10 (0.82 to 1.48)	1.18 (0.86 to 1.62) †
Ischaemic heart diseases (I20, I21, I25)					
No asthma	34.43	359	10.43 (9.38 to 11.56)	1	1
Asthma	19.19	240	12.50 (10.97 to 14.19)	**1.35 (1.11 to 1.64**)	**1.28 (1.02 to 1.61)** *
Atrial fibrillation and flutter (I48), heart failure (I50)					
No asthma	35.59	268	7.53 (6.66 to 8.49)	1	1
Asthma	19.94	198	9.93 (8.60 to 11.41)	**1.43 (1.14 to 1.79**)	**1.35 (1.05 to 1.75)** *
Cerebral infarction (I63)					
No asthma	36.31	134	3.69 (3.09 to 4.37)	1	1
Asthma	20.40	110	5.39 (4.43 to 6.50)	**1.64 (1.20 to 2.23**)	**1.65 (1.15 to 2.35)** *
Varicose veins of lower extremities (I83)					
No asthma	36.00	107	2.97 (2.44 to 3.59)	1	1
Asthma	20.16	79	3.92 (3.10 to 4.88)	1.44 (1.04 to 2.01)	**1.43 (1.01 to 2.03)**†
Acute rhinosinusitis (J01)					
No asthma	36.97	17	0.46 (0.27 to 0.74)	1	1
Asthma	20.36	54	2.65 (1.99 to 3.46)	**4.02 (2.26 to 7.17**)	**4.33 (2.30 to 8.16)** †
Pneumonia (J15, J18)					
No asthma	36.12	230	6.37 (5.57 to 7.25)	1	1
Asthma	19.60	255	13.00 (11.46 to 14.71)	**2.52 (2.00 to 3.17**)	**2.29 (1.79 to 2.93)** †
Allergic rhinitis (J30)					
No asthma	36.96	18	0.49 (0.29 to 0.77)	1	1
Asthma	20.76	22	1.06 (0.66 to 1.60)	1.61 (0.82 to 3.15)	**2.27 (1.18 to 4.35)** *
Chronic rhinosinusitis (J32)					
No asthma	36.58	55	1.50 (1.13 to 1.96)	1	1
Asthma	20.49	53	2.59 (1.94 to 3.38)	**1.83 (1.20 to 2.81**)	**1.82 (1.15 to 2.87)** †

Adjusted Cox's multivariate proportional hazards models.
*Matched for gender, age and area of residence and adjusted for pack years and body mass index.
†Matched for gender, age and area of residence and adjusted for pack years.

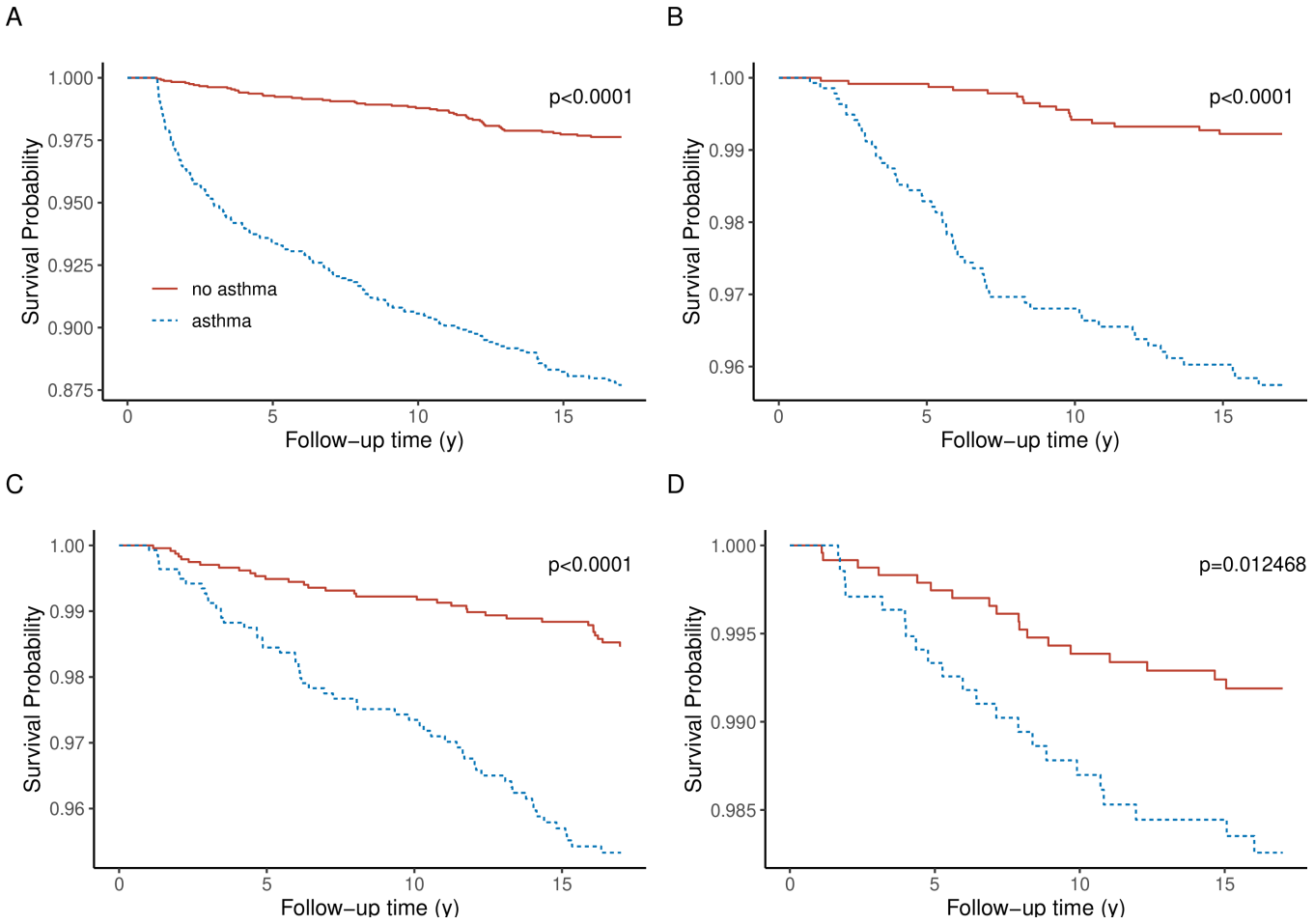

Figure 1 Kaplan-Meier survival curves of the main results. The curves present the survival within 15 years of follow-up between patients with and without asthma. (A) COPD, (B) CRSwNP, (C) acute rhinosinusitis, and (D) atopic dermatitis.

DISCUSSION

In this cohort study with nearly 15 years of follow-up, we investigated all main diagnoses that had minimum of registered 200 events. Our results showed that among diagnoses with over 200 events the most common comorbidities of adult asthmatics are COPD, pneumonia, arthrosis of hip and knee, intervertebral disc disorders or dorsalgia, cardiovascular diseases, incontinence and senile cataract. All diagnoses that were added to the list based on their common appearance with asthma (diabetes, sleep apnoea, acute and CRS, CRSwNP, GERD, atopic dermatitis, VCD, allergic rhinitis, bronchiectasis and breathing dysfunction) were significantly associated with adult asthma. Similar associations between a questionnaire-based allergic rhinitis or allergic dermatitis with asthma have also been shown.[16]

The Kaplan-Meier survival curves of COPD, CRSwNP, acute rhinosinusitis and atopic dermatitis are presented in figure 1. The difference between the slopes is especially vast in COPD, which means that the risk of COPD is substantially higher among adult asthmatics compared with non-asthmatic matched controls. This is in line with our previous finding that smoking asthmatics have increased risk of death due to COPD when compared with non-asthmatic controls.[17] A clear, significant difference between the asthmatic and non-asthmatic groups is also seen with CRSwNP, acute rhinosinusitis and atopic dermatitis, indicating that the risk of having one of these diseases is higher among adult asthmatics than among non-asthmatic matched controls.

Most common over 10 times more prevalent disease among adult asthmatics is COPD (J44). It is also one of the deadliest; as in 2019, COPD was the third leading cause of death all over the world.[18] Approximately half of the people who suffer from a chronic respiratory disease have COPD, and it is commonly associated with smoking.[18] When asthma and COPD coexist in a patient, the condition is called asthma–COPD overlap (ACO). Identification of ACO is meaningful because the asthmatic component of ACO should be treated with inhaled corticosteroids (ICS) and possibly with biological agents.[19] A systematic review and meta-analysis of the global ACO prevalence reported that prevalence of ACO among patients with asthma ranged from 3.2% to 51.4%.[20] Results of our study suggest a much higher risk (adjusted HR 10.62, 95% CI 5.14 to 21.96, p<0.001) but a considerable uncertainty was involved in the result because CIs were quite wide.

Table 3 Matched and adjusted HRs of the investigated diagnoses (J33-R06)

	Per 10 000 person years	Events	Incidence rate (95% CI) per 10 000 person years	Matched HR (95% CI)	Adjusted HR (95% CI)
Chronic rhinosinusitis with nasal polyps (J33)					
No asthma	36.87	30	0.81 (0.55 to 1.16)	1	1
Asthma	20.26	70	3.45 (2.69 to 4.36)	**4.08 (2.51 to 6.63)**	**4.28 (2.47 to 7.41)** *
Vocal cord dysfunction (J38.3, J385–J38.7, J39.3, J39.8, J39.9)					
No asthma	37.07	8	0.22 (0.09 to 0.43)	1	1
Asthma	20.86	20	0.96 (0.59 to 1.48)	**4.69 (1.85 to 11.85)**	**4.60 (2.00 to 10.57)** *
Other chronic obstructive pulmonary disease (J44)					
No asthma	36.88	52	1.41 (1.05 to 1.85)	1	1
Asthma	19.81	160	8.08 (6.88 to 9.43)	**7.93 (5.24 to 12.0)**	**10.62 (5.14 to 21.96)** †
Bronchiectasis (J47)					
No asthma	35.66	192	5.38 (4.65 to 6.20)	1	1
Asthma	19.86	153	7.71 (6.53 to 9.03)	**1.58 (1.23 to 2.03)**	**1.45 (1.16 to 1.82)** *
Gastro-oesophageal disease (K21)					
No asthma	36.6	77	2.10 (1.66 to 2.63)	1	**1**
Asthma	20.27	86	4.24 (3.39 to 5.24)	**1.79 (1.26 to 2.54)**	**2.05 (1.40 to 2.99)**†
Inguinal hernia (K40)					
No asthma	36.12	116	3.21 (2.65 to 3.85)	1	1
Asthma	**20.34**	**72**	**3.54 (2.77 to 4.46**)	**1.18 (0.85 to 1.66)**	1.01 (0.70 to 1.47) †
Cholelithiasis (K80)					
No asthma	36.12	131	3.63 (3.03 to 4.30)	1	1
Asthma	20.13	93	4.62 (3.73 to 5.66)	1.33 (0.98 to 1.81)	1.39 (0.99 to 1.96) *
Diverticular disease of intestine (K57)					
No asthma	36.36	131	3.60 (3.01 to 4.28)	1	1
Asthma	20.27	102	5.03 (4.10 to 6.11)	1.29 (0.96 to 1.74)	**1.34 (1.02 to 1.76)** *
Atopic dermatitis (L20)					
No asthma	36.88	33	0.89 (0.62 to 1.26)	**1**	**1**
Asthma	20.55	58	2.82 (2.14 to 3.65)	**3.24 (1.98 to 5.31)**	**4.01 (2.32 to 6.94)** †
Arthrosis of hip or knee (M16,M17)					
No asthma	34.44	315	9.15 (8.16 to 10.22)	1	**1**
Asthma	19.24	215	11.17 (9.73 to 12.77)	**1.34 (1.09 to 1.64)**	**1.31 (1.03 to 1.65)** *
Intervertebral disc disorders or dorsalgia (M51, M54)					
No asthma	35.19	241	6.85 (6.01 to 7.77)	1	1
Asthma	19.13	222	11.60 (10.13 to 13.24)	**1.74 (1.41 to 2.14)**	**1.79 (1.41 to 2.27)** *
Shoulder lesions and other soft-tissue disorders (M75, M79)					
No asthma	35.44	222	6.26 (5.47 to 7.14)	1	1
Asthma	19.34	198	10.24 (8.86 to 11.77)	**1.78 (1.42 to 2.23)**	**1.72 (1.34 to 2.21)** *
Other disorders of urinary system (N39)					
No asthma	36.21	132	3.65 (3.05 to 4.32)	**1**	**1**
Asthma	20.27	103	5.08 (4.15 to 6.16)	**1.60 (1.18 to 2.18)**	**1.61 (1.17 to 2.23)**‡
Hyperplasia of prostate (N40)					
No asthma	36.05	139	3.86 (3.24 to 3.39)	1	1
Asthma	20.32	86	4.23 (3.39 to 5.23)	1.30 (0.94 to 1.82)	1.26 (0.87 to 1.84) †
Breathing dysfunction (R06.1–R06.5)					
No asthma	36.88	25	0.68 (0.44 to 1.00)	1	1

Continued

Table 3 Continued

	Per 10 000 person years	Events	Incidence rate (95% CI) per 10 000 person years	Matched HR (95% CI)	Adjusted HR (95% CI)
Asthma	20.65	33	1.60 (1.10 to 2.24)	**2.36 (1.34 to 4.15)**	**2.31 (1.35 to 3.96)** †

Adjusted Cox's multivariate proportional hazards models.
*Matched for gender, age and area of residence and adjusted for pack years and body mass index.
†Matched for gender, age and area of residence and adjusted for pack years.
‡Matched for gender, age and area of residence and adjusted for body mass index. Bold values denote statistical significance at the p<0.05 level.

VCD was 4.6-fold among asthmatics compared with non-asthmatics. However, the number of events is very small and diagnosis of VCD is not totally unproblematic. Diagnosis of VCD has become more precise over the past years but at the time of collecting the data used in this research (1997–2014) the clinical diagnosis was often uncertain and the coding for VCD varied. We have therefore included all possible diagnose codes used at that time for VCD.

As compared with non-asthmatics, the hazard of diabetes mellitus among asthmatics was 2.4 in the adjusted model. A meta-analysis with 11 studies also reported an increased risk for diabetes mellitus among asthmatics compared with non-asthmatics (OR 1.25, 95% CI 1.08 to 1.44).[21] In this study, we found an association between asthma and cataract with HR of nearly 1.7. A cataract is a cloudy area in the lens of an eye that leads to a decrease in vision, and it is strongly associated with type 2 diabetes mellitus.[22] Clear evidence of cataract linking directly to asthma remains unfound, yet a Korean cross-sectional study including 715 554 adults aged 40 years or older found asthma to be a significant independent risk factor for cataract (adjusted OR 1.35, 95% CI 1.26 to 1.44).[23] Besides type 2 diabetes, cataract may also be explained by use of systemic corticosteroid use.[24]

According to our findings, OSA was 2.2 times more common among asthmatics. Studies based on self-reported snoring, questionnaires and sleep studies as well as a recent meta-analysis showed a two to three times higher prevalence of OSA among asthmatics, which correlates well with our results.[25] Obesity affects the airflow to the lungs, and difficulties in breathing and lung function can affect the quality of sleep.

In this study, adult asthma was associated with increased incidence of cardiovascular diseases including ischaemic heart diseases (adjusted HR 1.28), atrial fibrillation and flutter and heart failure (adjusted HR 1.35), and cerebral infarction (adjusted HR 1.65). A meta-analysis using The Meta-Analysis of Observational Studies in Epidemiology guidelines investigated total of 10 eligible studies, of which 8 were linking asthma with the increased risk of cardiovascular diseases.[26] Diseases investigated in these studies were coronary heart disease, stroke, acute coronary syndrome and cardiovascular diseases in general.[26] Overall, subjects with asthma had increased risk of CVD events (RR 1.33, 1.15 to 1.53), and the risk was similar compared with our findings.[26] A recent Finnish study with a large setting of almost 200 000 patients with severe asthma investigated the dose-dependency association of oral corticosteroids and high-dose ICS and comorbidities of asthma.[27] We did not have access to the updated medication data but it is noteworthy that the association between asthma and diagnoses such as diabetes mellitus, senile cataract, hypertensive diseases, ischaemic heart diseases, atrial fibrillation, heart failure and pneumonia may be explained by the use of oral corticosteroids, which increase the risk of these diagnoses.

It is estimated that 22%–45% of the patients with asthma also suffer from CRS, whereas among general population the prevalence of CRS symptoms is around 10%.[28] Our study found chronic sinusitis and acute sinusitis among asthmatics to occur at 4-fold and 2.5-fold hazard rate, respectively. The high prevalence of CRS in patients with asthma has been attributed to the anatomical and functional similarities between the upper and lower airways, and the shared pathophysiology of both diseases.[25 26] In both diseases, inflammation of the lower airways or paranasal sinuses can lead to obstruction and airflow limitation. Hence, the results of our study are in line with previous findings, and may even be underestimated in our study as these diseases are usually treated in the primary healthcare, and our data only cover the specialised and inpatient care. Association between asthma and community-aquired pneumonia (CAP) was assessed in a systematic review including 29 studies focused on elderly patients. Asthma was considered to be one of the clear risk factors for CAP with adjusted OR of 1.71.[29] In our study, pneumonia was 2.5 times more common among adult asthmatics compared with non-asthmatic adults.

In this study, adult asthma was associated with atopic dermatitis. An Italian study conducted in 2016–2018 including 684 adults with atopic dermatitis showed that atopic comorbidities such as asthma were significantly associated with atopic dermatitis and that the frequency of the disease increased with severity of atopic dermatitis.[30] A cross-sectional US population-based study of 602 adults with atopic dermatitis also reported that atopic dermatitis was associated with higher odds of asthma (adjusted OR 2.09, 95% CI 1.71 to 2.55).[31] In our study, the risk of allergic rhinitis was nearly 2.3-fold among asthmatics. However, because allergic rhinitis is commonly diagnosed and treated at primary care or at the private sector, the results

of this study reflect the very serious or profession-related allergic rhinitis cases that are treated in specialised care.

In a Swedish twin study, the risk of GERD in study participants with asthma was OR 1.52 but additional analyses found no differences in comorbidity estimates for asthma diagnosed in childhood or adulthood.[32] In our study, risk of having GERD was OR 2.05 among people with asthma compared with non-asthmatics.

Arthrosis of hip or knee was 1.3 times more common among adult asthmatics. Osteoarthritis has found to be significantly associated with asthma (OR 1.65) in a nationwide survey with total of 9344 adult subjects.[33] Prevalence of urinal incontinence is significantly higher in people with chronic obstructive respiratory disease, plausibly due to chronic coughing and other mechanisms increasing intra-abdominal pressure, as well as stress, systemic inflammation and side effects of medications.[34] According to our results, urinary incontinence was 1.8 times more common among adult asthmatics. In our study, asthma was also associated with intervertebral disc disorders/dorsalgia and shoulder and other soft-tissue lesions, but to our knowledge studies with the same exact design do not exist.

Use of regular systemic corticosteroid therapy has been associated with increased risk of osteoporosis, pneumonia, cardio-/cerebrovascular diseases, cataract, sleep apnoea, renal impairment, depression/anxiety, type 2 diabetes, weight gain, infection, hypertension and obesity.[24 35] Unfortunately, we were unable to have follow-up data of regular medication use. Adherence to ICS in Finnish patients with adult-onset asthma has shown to be moderate (69%) but adherence to systemic corticosteroid use is unknown.[36]

Strengths of this study include a long follow-up time and a population-based, matched cohort set-up. Asthma diagnosis of the participants was doctor diagnosed and confirmed with lung function tests. Linkage with national registers was made using unique personal identification numbers and performed with high precision by third-party professionals. Only main diagnoses were used, which implicates that people most likely sought treatment for that disease.

There are also some limitations. Register data are based on clinical practice and diagnostic coding practices may vary between hospitals or physicians. The data cover specialised healthcare and some diseases that are diagnosed and treated in the primary care are not registered here. Systemic corticosteroid use as well as other pharmaceutical therapies for asthma may act as an confounding factor. Unfortunately, follow-up data on medications were unavailable. Smoking status, smoking history and weight were asked in a questionnaire conducted in 1997 but follow-up data concerning these variables were unfortunately not available. Furthermore, as our study population comprises older adults, we acknowledge that death is a competing risk event.

CONCLUSIONS

The study found that the most common and most severe comorbidity of adult asthma is COPD. Other significant comorbidities of adult asthma include acute rhinosinusitis, CRSwNP, atopic dermatitis, allergic rhinitis, diabetes, pneumonia, sleep apnoea and GERD. Cardiovascular diseases, CRS, musculoskeletal diseases, incontinence and cataract were also significantly associated with adult asthma. VCD was common among asthmatics, but the number of events was very small. Our study shows that patients with adult asthma suffer from several coexisting diseases that may share similar aetiological and immunological pathways with asthma and decrease the management asthma.

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and authors, but restrictions apply to the availability of these data, which were used under license 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, the Social Insurance Institution, and the National Institute for Health and Welfare (THL).

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