

ORIGINAL ARTICLE

Airway Diseases

Higher mortality of adults with asthma: A 15-year follow-up of a population-based cohort

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Abstract

Background: Higher all-cause mortality in asthmatics has been shown previously. Polysensitization is associated with higher morbidity among asthmatic children, and allergic rhinitis and/or allergic conjunctivitis (AR/AC) are associated with higher morbidity in adult asthmatics. Little is known about the effect of AR/AC and other factors on mortality among adult asthmatics. The aim was to study mortality and its risk factors in adults with and without asthma.

Methods: We randomly selected 1648 asthmatics with age over 30 years from national registers and matched the asthma sample with one or two controls. Baseline information was obtained by a questionnaire in 1997, and the study population was linked with the death certificate information of Statistics Finland from 1997 to 2013. Overall and cause-specific survival between the groups was compared in several adjusted models.

Results: During a mean follow-up period of 15.6 years, 221 deaths among 1052 asthma patients and 335 deaths among 1889 nonasthmatics were observed. Cardiovascular diseases were the main cause of death in both groups. Asthma was associated with increased all-cause mortality (adjusted HR 1.25; 95% CI 1.05-1.49, $P = .011$) as well as mortality from chronic obstructive pulmonary disease (HR 12.0, 4.18-34.2, $P < .001$) and malignant neoplasms of respiratory organs (HR 2.33, 1.25-4.42, $P = .008$). Among asthmatics, smoking was associated with increased all-cause mortality, and self-reported AR/AC was associated with decreased mortality. Among nonasthmatics, smoking, and obesity were associated with increased all-cause mortality, whereas female gender showed an association with a decreased risk.

Conclusions: Increased mortality among adult asthmatics was largely explained by the development of COPD, malignant respiratory tract neoplasms, and cardiovascular diseases. Smoking cessation is important for reduction in total mortality in both asthmatic and nonasthmatic adults. AR/AC was associated with decreased mortality only in asthmatics. Thus, studies in other populations of larger size are needed to explore further the nature of this association.

Abbreviations: AC, allergic conjunctivitis; AR/AC, allergic rhinitis and/or allergic conjunctivitis; AR, allergic rhinitis; BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; FEV1, forced expiratory volume during the first second; HR, hazard ratio; ICD-10, International Classification of Diseases; PEF, peak expiratory flow.

Toppila-Salmi and Haukka are shared last author.

KEYWORDS

allergic conjunctivitis, allergic rhinitis, asthma, chronic obstructive pulmonary disease, mortality

1 | INTRODUCTION

The increased prevalence of asthma and allergic diseases is a major public health problem affecting 1%-18% of the population worldwide.¹ Late-onset asthma is frequently associated with female gender, obesity, depression, gastroesophageal reflux disease, chronic obstructive pulmonary disease (COPD), and higher rate of hospitalizations.²⁻⁵ Asthma is also shown to be associated with increased risk of coronary heart disease, cerebrovascular disease, and heart failure.⁶ Increased all-cause mortality has been demonstrated among asthmatic adults.^{7,8} Limited evidence exists on the effect of allergic rhinitis and/or allergic conjunctivitis (AR/AC) or other risk factors on mortality among asthmatic patients.

We have previously demonstrated that polysensitization and allergic rhinitis and/or allergic conjunctivitis (AR/AC) co-associate with adult asthma population.^{9,10} Polysensitization is associated with higher morbidity among asthmatic children.¹¹ Despite the fact that AR causes significant work impairment,¹² studies suggest that AR/AC would putatively not be associated with adult asthma morbidity.^{10,13} Yet, limited evidence exists on the effect of AR/AC or other risk factors for mortality among adult asthmatic patients.¹⁴

The aim of the study was to examine risk factors for mortality in individuals with asthma. We hypothesized that there would be differences between all-cause and disease-specific mortality between asthma patients and nonasthmatic subjects and that smoking or the presence of AR/AC associates with higher risk of death in asthmatics.

2 | METHODS

This study, Adult Asthma in Finland, is a population-based matched cohort study with follow-up conducted in 1997-2015. This study collected information from 1648 asthma patients older than 30 years of age. Of these, 248 asthmatics were from the longitudinal, population-based Mini Finland Health Survey,¹⁵ and 1400 were recently diagnosed asthmatics drawn from the Finnish Drug Reimbursement Register (Figure 1).

All asthmatics fulfilled the following criteria for doctor-diagnosed asthma: typical history, clinical features, and asthma course, at least one of the following physiologic criteria: (i) a variation of 20% or greater in diurnal peak expiratory flow (PEF) recording (reference to maximal value); (ii) an increase of 15% or greater in PEF or forced expiratory volume in 1 second (FEV1) with β -agonist; or (iii) an decrease of 15% or greater in PEF or FEV1 in exercise testing. This method of case ascertainment has been validated earlier.^{16,17} Approval for the study was obtained from the ethical committee at Tampere University Hospital, and a written consent was obtained from all subjects.

For each asthma case, one or two controls without asthma were selected, 511 from The Mini Finland Health Survey, and 2800 through a population register. Asthma patients and nonasthmatic controls were matched for age (± 2 years), gender, and area of residence by postal code. Questionnaire consisted of demographic questions (for both groups) and asthma-specific questions for asthma patients. All responders were asked whether they had doctor-diagnosed asthma to confirm the asthma status.

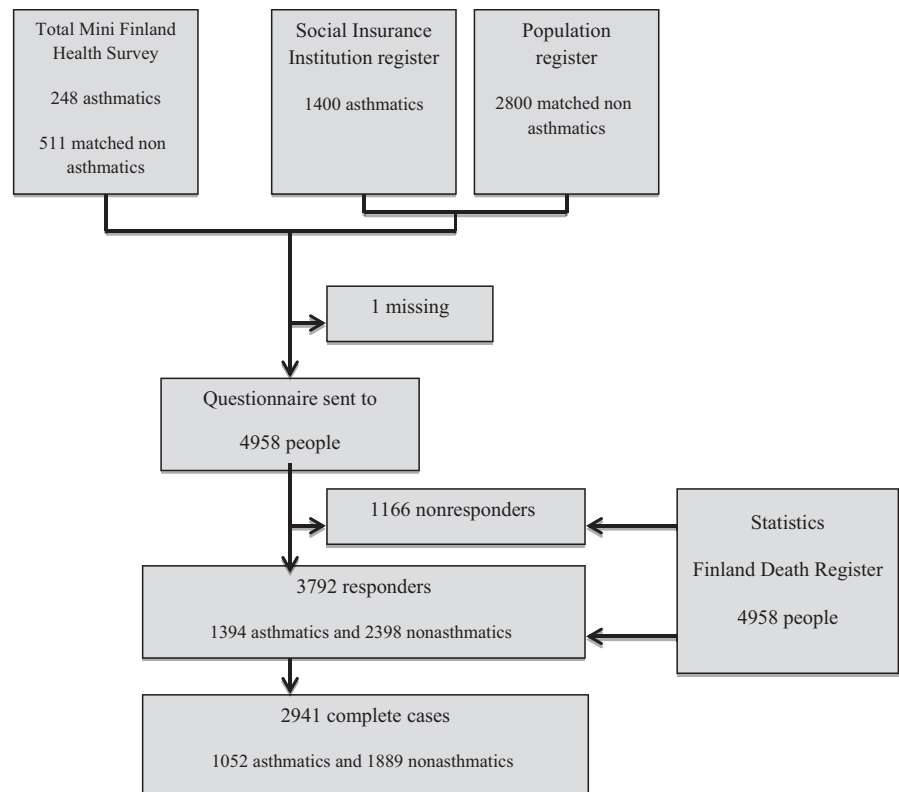
All individuals were followed from January 1, 1997, until death or end of follow-up on December 31, 2013, whichever occurred first. Follow-up data on deaths were obtained from the register of death records of the Statistics Finland through a computerized register linkage using unique personal identification codes, which are assigned to every resident in Finland. Along with date of death, mortality data also included cause of death, coded according to the tenth revision of the International Classification of Diseases (ICD-10). The Finnish death certification validation procedure has been shown to serve the coding of causes of death for mortality statistics appropriately.¹⁸

2.1 | Information retrieved from the questionnaire

All covariate data were self-reported. The following covariates were used in this study: gender, age, smoking, weight, height, education, and AR/AC. All individuals were asked whether they ever have had cough/dyspnoea with wheeze. Only the asthma group was asked the place where asthma was diagnosed, the age of asthma onset, and the severity of current asthma. The asthma onset was asked by a question: "When did your asthma symptoms begin? In childhood; at school age; over 15 years of age; in adulthood". The severity of asthma was determined asking the following five questions. (i) "How severe are your asthma symptoms? Mild or nearly none (hereafter referred as none to mild), Moderate, Severe"; (ii) "How much do your asthma symptoms harm you? Not at all, Quite little, Moderately, Quite much, Very much"; (iii) "Does your asthma disrupt your work or other daily activities? No, Yes rarely; Yes randomly, Yes continuously"; (iv) "Have you woken up at night due to asthma or wheeze during the year 1997? Yes nearly every night; Yes at least once a week, Yes a few times per month; Yes more rarely, No"; (v) "Have you used peroral corticosteroid tablets due to your respiratory symptoms during the past year? No, Yes I have used them continuously, Yes I have used courses of corticosteroid tablets."

Baseline information along with the additional questions of age at asthma onset and asthma symptom severity was available for 1052 asthmatics. Altogether, 851 individuals with missing covariate information (342 asthmatics and 509 nonasthmatics) were excluded from the analysis.

FIGURE 1 Flowchart of the study population. Mini Finland Health Survey was conducted on 1977-1980 by The National Institute for Health and Welfare. Altogether, it consisted of a sample of 8000 Finnish people aged 30 or over. Study included an interview and a health examination. Asthmatics drawn from the Social Insurance Institution register were over 30 y old, recently (in 2 y) diagnosed asthmatics, that had received the right for asthma medication reimbursement. Information about possible death for total of 4958 people was obtained from the Statistics Finland



We used the following two questions to assess the smoking variable: Q1: Do you currently smoke? (Yes, No) Q2: Regular smoking about every day during at least 1 year (Yes, No). Those belonging to the group never smoker or smoked <1 year, responded as Q1: No, or (Q1: Yes and Q2: No). Those smoked regularly at least for a year but quitted were considered as ever smokers, and those smoked regularly or occasionally at baseline as current smokers. An estimate of the subjects' lifetime tobacco exposure was calculated in pack-years (number of cigarettes per day/20 × 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.

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). 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.¹⁹ Allergic rhinitis was asked by the question "Have you ever had hay fever or other rhinitis symptoms that are related to pollens or animals?". Allergic conjunctivitis was asked "Have you ever had allergic eye symptoms?".

2.2 | Outcomes of interest

The primary outcome of interest was all-cause mortality in the asthmatic group compared to the nonasthmatic group. Secondary outcome of interest was cause-specific mortality, as determined according to the underlying cause of death, especially deaths due to

asthma (ICD-10 codes J45-J46), COPD (J44), CVDs (I05-I99), and malignant neoplasms of respiratory organs (C30-39). Third purpose of the study was to investigate the effect of available risk factors on all-cause mortality among both asthmatics and nonasthmatics.

2.3 | Statistical methods

We calculated the crude all-cause and cause-specific mortality rates for asthmatics and nonasthmatics as number of events divided by person-years. For crude rates, the 95% confidence intervals were assessed by assuming that counts of events have a Poisson distribution. The chi-square test and Mann-Whitney Wilcoxon test were used to compare the baseline demographic characteristics of the case and control groups. We assessed the difference in all-cause mortality between asthmatics and nonasthmatics by plotting the Kaplan-Meier survival curves and performing log-rank test. In addition, we modeled the effect of asthma on all-cause and cause-specific mortality by fitting Cox's proportional hazards regression models stratified by matching unit and models adjusted for sex, age, AR/AC, smoking, education, and BMI. Due to small number of cases in BMI classes, some models were not adjusted for BMI (Tables 2, and Table S1 in the online data supplement). From these models, association of each outcome and asthma status was evaluated using hazard ratios (HRs) along with 95% confidence interval.

By fitting Cox's regression models to the data on asthmatics only, for which information on the core and asthma-specific questionnaire was complete (N = 1052), we assessed the effect of all available covariates on all-cause mortality. Goodness of fit of Cox's

HR models to the data was evaluated by performing graphical diagnostic checks to assess the proportional hazards assumption for each covariate and to detect outliers. The effect of other potentially confounding variables was evaluated by two models that differ by the smoking variable. Covariates in Model 1 are age, sex, BMI, education, age at asthma onset, AR/AC, asthma symptom severity, and pack-years. In Model 2, pack-years are replaced by smoking status, as smoking and pack-years might have different risk effects. We also tested the potential interactions between the covariates included into the models. Nonparametric Wilcoxon rank-sum test was used for comparisons. *P*-values <0.05 were considered statistically significant. All data analyses were performed with version 3.3.0 of R statistical software.²⁰

3 | RESULTS

3.1 | Baseline characteristics

The factors putatively related to asthma were evaluated by a questionnaire sent by mail to all cases and controls (*N* = 4958) and altogether 3792 (1394 asthma patients, 2398 nonasthmatics) individuals responded, yielding a response rate of 76%. After exclusion of individuals with the missing covariate information, the study population comprised of 1052 complete asthmatic cases and 1889 nonasthmatic subjects. Table 1 shows baseline characteristics of the study population. Mean age at the time of enrollment was 53.3 years for nonasthmatic subjects and 52.2 years for asthmatic patients, and more than half of study population comprised of women (65% in both groups). Among asthma patients, there were fewer never smokers or those who had smoked <1 year, and more ever smokers and more obese individuals compared to the nonasthmatic group.

The cough/dyspnoea symptom with wheeze ever was asked from all individuals: 8% of asthmatics reported that they had not had this symptom ever and 27% of controls reported that they had had cough/dyspnoea symptom with wheeze ever (Table 1). Among asthmatics, moderate asthma symptoms were reported by 65% while for 10% the symptoms were severe.

Based on self-reported age at asthma onset, more than 90% of the asthma patients had late-onset asthma (onset age 15 years or over). Altogether 99.4% of the asthma group reported that physician had diagnosed their asthma either in primary care or in hospital, and only 0.6% had left unanswered (Table 1).

3.2 | All-cause and cause-specific mortality

During a mean follow-up of 15.6 years (15.4 years for asthma patients, 15.7 years for nonasthmatic subjects), total of 45 974 person-years accumulated for 2941 individuals, and 221 deaths occurred among asthma patients and 335 among nonasthmatic subjects (Table 2). Crude all-cause mortality rate per 1000 person-years was 13.6 (95% CI, 11.9-15.3) for asthma patients and 11.3 (10.1-12.5) for nonasthmatic subjects. Kaplan-Meier plot (Figures 2

TABLE 1 Self-reported baseline characteristics

	Nonasthmatics N = 1889	Asthmatics N = 1052	P value
Age (y), mean (SD)	53.3 (12.0)	52.2 (12.1)	.020
Sex, n (%)			
Male	659 (34.9)	369 (35.1)	.950
Female	1230 (65.1)	683 (64.9)	
Smoking, n (%)			
Never smokers ^a	1181 (62.5)	556 (52.9)	<.001
Ever	324 (17.2)	294 (27.9)	
Current	384 (20.3)	202 (19.2)	
Pack-years, n (%)			
0	1175 (62.2)	555 (52.8)	<.001
1-19	436 (23.1)	287 (27.3)	
≥20	278 (14.7)	210 (20.0)	
BMI (kg × m ⁻²), n (%)			
Normal 18.5-25	819 (43.4)	369 (35.1)	<.001
Underweight <18.5	21 (1.1)	16 (1.5)	
Overweight 25-30	764 (40.4)	434 (41.3)	
Obese ≥30	285 (15.1)	233 (22.1)	
Education level, n (%)			
Matriculation exam.	370 (19.6)	165 (15.7)	.030
Secondary school	472 (25.0)	270 (25.7)	
Primary school or less	1047 (55.4)	617 (58.7)	
Allergic symptoms, n (%)			
Allergic rhinitis (AR)	496 (26.3)	569 (54.1)	<.001
AR doctor-diagnosed	267 (14.1)	387 (36.8)	<.001
Allergic conjunctivitis	358 (19.0)	454 (43.2)	<.001
Atopic dermatitis	432 (22.9)	381 (36.2)	<.001
Age at asthma onset, n (%) ^b			
In childhood	-	43 (4.1)	
At school age	-	25 (2.4)	
Over 15 y of age	-	24 (2.3)	
In adulthood	-	960 (91.3)	
The place of physician-diagnosed asthma, n (%) ^{b,c}			
Primary care	-	269 (25.7)	
Hospital	-	777 (74.3)	
Asthma symptoms, n (%) ^b			
None to mild	-	266 (25.3)	
Moderate	-	681 (64.7)	
Severe	-	105 (10.0)	
Self-reported cough/dyspnoea with wheeze ever ^d			
No	1377 (73.4)	83 (7.9)	<.001
Yes	499 (26.6)	963 (92.1)	

All baseline information was collected by a questionnaire in 1997.

^aNever smoker or smoked <1 y.

^bThe questions were asked only from the asthmatics.

^cThe number of missing responses from asthmatics was 6.

^dThe number of missing responses from asthmatics was 6 and 13 from nonasthmatics.

TABLE 2 Mortality rates and hazard ratios (HR) for all-cause and cause-specific mortality among nonasthmatics subjects (N = 1889) and asthmatics (N = 1052)

Cause of death	Number of events	Mortality rate	Crude HR (95% CI)	P-value	Adjusted HR (95% CI)	P-value
All-cause						
No asthma	335	11.3 (10.1-12.5)	1		1	
Asthma	221	13.6 (11.9-15.5)	1.21 (1.02-1.44)	.03	1.25 (1.05-1.49)	.011
Neoplasms (C00-C26, C40-D48)						
No asthma	87	2.93 (2.34-3.61)	1		1	
Asthma	35	2.15 (1.50-3.00)	0.97 (0.59-1.58)	.901	0.73 (0.49-1.08)	.118
Neoplasms of respiratory organs (C30-C39)						
No asthma	16	0.54 (0.31-0.87)	1		1	
Asthma	25	1.54 (1.00-2.27)	3.74 (1.56-8.98)	.003	2.35 (1.25-4.42)	.008
Mental and behavioral disorders (F00-F99)						
No asthma	10	0.34 (0.16-0.62)	-		-	
Asthma	2	0.12 (0.01-0.44)	-	-	-	-
Diseases of the nervous system (G00-G26, G30-G99)						
No asthma	26	0.87 (0.57-1.28)	1		1	
Asthma	10	0.62 (0.30-1.13)	0.56 (0.22-1.46)	.236	0.78 ¹ (0.37-1.63)	.508
Cardiovascular diseases (I05-I25, I60-I99)						
No asthma	136	4.57 (3.84-5.41)	1		1	
Asthma	82	5.05 (4.01-6.27)	1.47 (1.00-2.17)	.051	1.23 (0.93-1.63)	.145
COPD (J44)						
No asthma	4	0.13 (0.04-0.34)	1		1	
Asthma	30	1.85 (1.25-2.64)	14.0 (3.26-60.1)	<.001	12.0 (4.18-34.2)	<.001
Asthma (J45-J46)						
No asthma	1	0.03 (0.00-0.19)	-		-	
Asthma	2	0.12 (0.01-0.44)	-	-	-	-
Other respiratory diseases (J00-J43, J47-J99)						
No asthma	13	0.44 (0.23-0.75)	1		1	-
Asthma	4	0.25 (0.07-0.63)	0.65 (0.15-2.74)	.556	0.56 ¹ (0.18-1.74)	.313
Digestive diseases (K00-K93)						
No asthma	13	0.44 (0.23-0.75)	1		1	
Asthma	13	0.80 (0.43-1.37)	1.47 (0.60-3.57)	.400	1.77 ¹ (0.81-3.83)	.150
Others ^a						
No asthma	28	0.94 (0.63-1.36)	1		1	
Asthma	17	1.05 (0.61-1.68)	1.28 (0.58-2.85)	.538	1.22 ¹ (0.66-2.24)	.526

Causes of deaths according to the International Classification of Diseases, Tenth Revision (ICD-10).

Mortality rate per 1000 person-years = amount of deaths per year per 1000 individuals; HR = hazards ratio; 95% confidence interval; Crude HR = matched for age, sex, and area of residence at baseline; Adjusted HR = adjusted for age, sex, pack-years, education, and body mass index (BMI) at baseline; Adjusted HR¹ = adjusted for age, sex, pack-years, and education level at baseline. BMI could not be included to all adjusted models due to lack of statistical power; Adjusted models could not be estimated for all causes of death due to lack of statistical power; COPD = chronic obstructive pulmonary disease.

^aIncluding infectious and parasitic diseases (A00-B99), endocrine and metabolic diseases (E00-E90), skin diseases (L00-L99), musculoskeletal and connective tissue diseases (M00-M99), genitourinary diseases (N00-N99), congenital deformations (Q00-Q99), not elsewhere classified (R00-R99), and accidents and suicides (V01-Y34). Bold text indicates statistically significant P-value (P<0.05).

and S1–Online data supplement) demonstrated a persistent difference in overall survival between asthmatics and nonasthmatics. Based on log-rank test, this difference was significant (P = .03). Compared to matched nonasthmatic subjects, asthma was associated with a higher all-cause mortality (crude HR 1.21; 95% CI, 1.02-1.44; P = .03), and this association was significant after

adjustment for age, sex, smoking (both status and exposure covariates), education level, and BMI (HR 1.25, 1.05-1.49, P = .01) (Tables 2 and S1–Online data supplement). The difference between the groups was nonsignificant when the log-rank test was applied to nonsmoking groups only (1181 nonasthmatics and 556 asthmatics, HR 0.87, 0.68-1.13, P = .299).

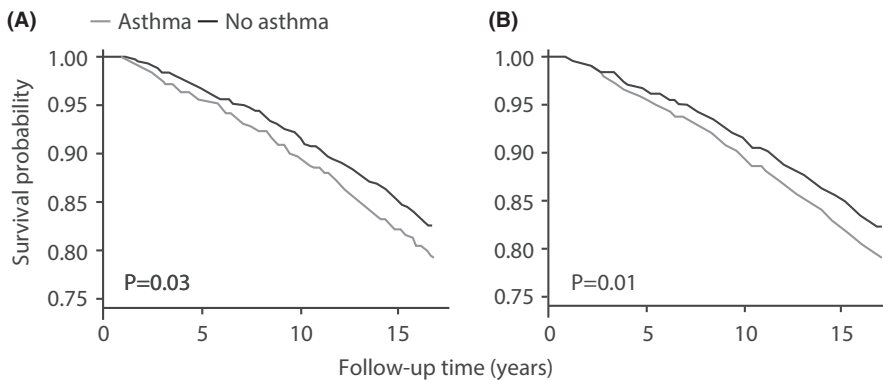


FIGURE 2 Kaplan-Meier survival curves. A, Overall curves, in which the cases and the controls were matched for age, sex, and area of residence at baseline. B, Adjusted curves, in which the cases and the controls were adjusted for age, sex, pack-years, education, and body mass index at baseline. *P*-value by log-rank test

Cardiovascular diseases (CVDs) were the main cause of death in both groups, but the difference between the groups was not significant. Only complete cases with all covariate information were used in this study. However, in the additional model where subjects with missing allergy information were taken into account, CVDs associated significantly with higher mortality among asthmatics (HR 1.53, 1.08-2.18, $P = .017$). Only partial adjustment was feasible in some models due to small number of subjects in subgroups corresponding to different levels of covariates.

Among asthmatics, the major contributors to increased all-cause mortality were COPD and malignant neoplasms compared to nonasthmatics (Table 2). There were only two asthma deaths in the asthma group and one asthma death in the nonasthmatic group. Compared to matched nonasthmatic subjects, asthma was associated with a higher mortality from COPD (HR 14.0, 3.26-60.1, $P < .001$), and malignant neoplasms of respiratory organs (HR 3.74, 1.56-8.98, $P = .003$) (Table 2). After adjustments, these associations remained significant. Thirty-nine of the 41 subjects who were dead due to malignant respiratory neoplasms were current or former smokers.

There was an interaction between smoking (≥ 20 pack-years), asthma and all-cause mortality in the adjusted model ($P = .002$). No essential interaction was observed between smoking (pack-years), asthma, and disease-specific mortality in the adjusted models.

3.3 | Risk factors for all-cause mortality among asthmatics

Adjusted Cox's proportional hazards models showed that a steep increase in mortality among asthmatics was associated with increasing age at baseline. Among other risk factors were ever smoking (Table 3), current smoking, and ≥ 20 pack-years.

In the asthma population, self-reported asthma severity correlated with degree of harm due to asthma ($P < .001$ by Pearson's chi-square test), with disruption in work or other daily activities due to asthma ($P < .001$), and with wake up at night due to asthma or wheeze during the year 1997 ($P < .001$). Similarly, self-reported asthma severity was associated with at least one peroral corticosteroid tablet course due to respiratory symptoms during the past year ($P < .001$). Thus, only one variable (self-reported asthma severity) was used in adjusted survival models. When compared to none to mild asthma symptoms group, risk of death had about 1.5-fold

increase in the group with moderate asthma symptoms and about threefold increase in the group with severe asthma symptoms (Table 3, Model 2).

Adjusted Cox's proportional hazards models showed that decreased risk for mortality was associated with obesity (HR 0.66, 0.46-0.96, $P = .031$, Model 1) and AR/AC (HR 0.64, 0.48-0.84, $P = .001$, Table 3, Model 1) in both models. The presence of AR/AC associated with younger age ($P < .001$). Among asthmatics, the proportion of never smokers was 36.3%, in AR/AC group and 16.5% in non-AR/AC group ($P = .002$). Among nonasthmatics, smoking status did not associate with self-reported AR/AC ever ($P = 1.00$). Gender, age at asthma onset, or education level was not associated with increased mortality.

3.4 | Risk factors for all-cause mortality among nonasthmatic subjects

Among nonasthmatics, increased risk for mortality was associated with increasing age, current smoking at baseline (HR 2.21, 1.64-2.97, $P \leq .001$, Model 2, Table S2), ≥ 20 pack-years (HR 2.00, 1.48-2.69, $P \leq .001$, Model 1, Table S2), and obesity (HR 1.50, 1.11-2.03, $P = .009$, Model 2, Table S2). Decreased risk for mortality was associated with female gender (HR 0.76, 0.59-0.97, $P = .026$, Model 1 and HR 0.66, 0.52-0.83, $P = .026$, Model 2).

3.5 | Nonresponder analysis

Altogether 1166 people did not respond to the questionnaire. The age distribution between responders and nonresponders was similar, although there were more females (62% vs 57%) and asthmatics (37% vs 22%) among responders. The all-cause mortality was significantly decreased among responders (HR 0.55, 0.46-0.66, $P < .001$). However, asthma was associated with higher all-cause mortality after including nonresponders to the analysis (HR 1.27; 95% CI, 1.11-1.45; $P = .004$).

4 | DISCUSSION

In this population-based follow-up study of a matched cohort, a higher all-cause mortality was observed among asthma patients when compared to nonasthmatic subjects, although there were only

TABLE 3 Factors associated with all-cause mortality in asthmatic patients (N = 1052, deaths = 221)

	Model 1 HR (95% CI)	P-value	Model 2 HR (95% CI)	P-value
Age				
≤59	1		1	
60-69	3.59 (2.60-4.96)	<.001	4.55 (3.28-6.33)	<.001
70-79	7.33 (4.78-11.2)	<.001	10.5 (6.76-16.3)	<.001
≥80	56.6 (25.6-125.1)	<.001	68.2 (30.2-154.4)	<.001
Sex				
Male	1		1	
Female	0.96 (0.70-1.32)	.805	0.76 (0.56-1.02)	.064
Smoking status				
Never	-	-	1	
Ever	-	-	1.70 (1.19-2.42)	.003
Current	-	-	3.88 (2.68-5.61)	<.001
Pack-years				
0	1			
≤19	1.43 (0.94-2.15)	.091	-	-
≥20	3.44 (2.40-4.93)	<.001	-	-
BMI				
Normal (18.5-24.99)	1		1	
Underweight (<18.5)	1.29 (0.52-3.19)	.584	1.30 (0.52-3.27)	.577
Overweight (25-29.99)	0.79 (0.58-1.09)	.147	0.80 (0.58-1.09)	.156
Obese ≥30	0.66 (0.46-0.96)	.031	0.68 (0.47-0.99)	.043
Education				
Matric. exam.	1		1	
Secondary school	0.79 (0.42-1.47)	.459	0.82 (0.44-1.53)	.532
Primary school	1.38 (0.80-2.37)	.244	1.38 (0.81-2.37)	.235
Allergic rhinitis and/or conjunctivitis				
No	1		1	
Yes	0.64 (0.48-0.84)	.001	0.65 (0.49-0.86)	.002
Age at asthma onset				
<15 y	1		1	
≥15 y	0.69 (0.36-1.33)	.274	0.70 (0.37-1.35)	.287
Asthma symptoms				
None to mild	1		1	
Moderate	1.48 (0.99-2.20)	.056	1.61 (1.08-2.40)	.019
Severe	2.85 (1.75-4.66)	<.001	3.19 (1.97-5.15)	<.001

Adjusted Cox's multivariate proportional hazards models.

Model 2 includes the same covariates as Model 1, except pack-years are replaced by smoking status.

The effect of smoking was evaluated by pack-years in Model 1 and by smoking status in Model 2.

HR = hazards ratio; 95% confidence interval; BMI, Body mass index. Bold text indicates statistically significant *P*-value (*P* < 0.05).

a few deaths caused by asthma itself. One asthma death was found in the nonasthmatic group, as asthma may still be undiagnosed in some cases. CVDs were the main cause of death in both groups and deaths from COPD and malignant neoplasms of respiratory organs were significantly higher in the asthma group. Among asthma patients, higher age, moderate and severe asthma symptoms, and smoking at baseline were associated with a higher all-cause

mortality, whereas AR/AC and obesity showed an association with a decreased risk. Among nonasthmatics, higher age, smoking, and obesity were associated with a higher all-cause mortality, whereas female gender showed an association with a decreased risk.

Although all-cause mortality in patients with asthma is decreasing,²¹⁻²³ mortality among asthmatic patients compared to general population remains higher.^{8,24} Chronic obstructive pulmonary disease

is frequently associated with asthma-related deaths.^{7,25} According to our findings, COPD was over 10 times more common cause of death among asthmatics compared to nonasthmatics. Also, over 20% of the asthmatics had a smoking burden of over 20 pack-years vs 15% of the nonasthmatics. Heavy smoking is a known risk factor for asthma and smoking significantly associates with higher all-cause mortality risk among asthmatics.^{26,27} Smoking is a prime risk factor for the development of COPD in the Western World,²⁸ and asthma alone seems to increase the risk of COPD.²⁹ Therefore, our discovery of higher mortality in asthma patients compared to nonasthmatic controls could in part be explained by smoking-induced excess loss of lung function leading to COPD. We detected an interaction between smoking (≥ 20 pack-years), asthma, and all-cause mortality in adjusted model. However, we did not detect any essential interaction for any end-points (all-cause mortality, neoplasms of respiratory organs, COPD, or CVD).³⁰ The prevalence of doctor-diagnosed COPD in the groups was not computable from the data available in this study. Yet, our observations suggest that higher mortality in the asthmatic group could be explained by COPD and co-existing asthma.

In the studied population, CVDs were main cause of death in both groups, and asthma was associated with a higher CVD mortality when the data were restricted to those with complete information on all covariates except AR/AC. After including AR/AC into the model, the association was no longer significant but this may be explained by a smaller sample size. The link between asthma and CVDs has been previously demonstrated by a study showing that cardiovascular diseases are common comorbidities in more than half of the asthma admissions.³¹ Moreover, Nationwide Survey conducted in Taiwan suggests that increased comorbidities along with cardiovascular diseases might contribute to asthma severity.³² However, a study with a short follow-up of 5-years detected no difference in CVD mortality between the groups, although a higher all-cause mortality rate among older asthmatic patients was seen.²⁶ Chronic obstructive pulmonary disease increases the risk of cardiovascular disease 2- to 3- fold,³³ and asthma itself has been associated with increased risk of CVD.⁶ Our findings suggest that even after adjusting for smoking, there could be factors between asthma, COPD, and CVDs that contribute to higher mortality risk in asthma patients compared to controls. Better understanding of these mechanisms could help to prevent higher mortality among adult asthma patients.

Despite recent improvements in cancer care, lung cancer is highly lethal. We showed that death due to malignant neoplasms of respiratory organs was significantly more common in the asthma group. However, 95.1% of subjects died due to malignant respiratory neoplasms were smokers. A study showed an increased risk of lung cancer mortality among nonsmoking asthmatics in a follow-up study of 17-years.³⁴ Hence, smoking has proved to be risk factor of malignant respiratory neoplasms, whereas the role of asthma still requires further investigation.³⁴

Despite the fact that allergic diseases affect morbidity lifelong,^{11,12} evidence is still lacking on the role of allergies in mortality. This was a preliminary study to investigate factors behind mortality among adult asthmatics. Interestingly, in our study, self-reported AR/

AC was associated with decreased mortality among adult asthmatics. This could in part be explained by the fact that AR/AC, younger age, and never smoking co-exist in asthmatics. On the other hand, adjusted Cox's proportional hazards models showed that AR/AC protected from mortality among asthmatics independently of age or smoking status. One of the potential explanations behind the discrepant effects on asthma morbidity of AR/AC and smoking could be that these represent different asthma phenotypes. Comorbid AR/AC would suggest an allergic, eosinophilic phenotype which is generally responsive to inhaled corticosteroid treatment, whereas the smoking phenotype is associated neutrophilic inflammation, corticosteroid insensitivity, and airflow limitation.³⁵ Interestingly, among nonasthmatics, AR/AC showed no association with mortality. Moreover, among nonasthmatics, the proportion of never smokers did not differ between AR/AC and non-AR/AC groups. Thus, smoking habits and/or other, still unknown, factors could putatively affect the association between AR/AC and decreased mortality in asthmatics. Studies with increased population are mandatory to further evaluate the effect of allergy on mortality.

To the knowledge of the authors, there are only few studies indicating association between an allergic condition and mortality in adult asthmatics.^{13,36} A full-cohort study of US population showed that hay fever did not associate with all-cause or cause-specific mortality, yet the study was not fully able to prove whether hay fever had an effect on excess mortality that was detected among asthmatics in the study population.¹³ A retrospective follow-up study of nearly 20 years, using the state wide population database of Utah, recently found decreased mortality risk (HR 0.80, 0.74-0.85, $P < .0001$) among asthmatics with chronic rhinosinusitis.³⁶ In pediatric populations, polysensitization is associated with excess morbidity of asthma and related conditions such as allergic diseases.^{11,37,38} We demonstrated previously that in adult asthmatic population, AR/AC associates with a polysensitization pattern. Based on the results of the present study, it seems that the association between polysensitization and excess mortality suggested for pediatric patients could be of opposite direction in adults. The mechanisms are not known but our results suggest that allergic phenotype of asthma may be less lethal than nonallergic or smoking-related asthma.

Asthma in obese patients may lead to severe exacerbations with unknown mechanisms.^{39,40} Obesity was associated with higher mortality among nonasthmatics but with lower mortality in the asthma group. This "obesity paradox" has also been reported by studies on chronic smoking-related diseases, in which BMI over 25 kg m⁻² has shown to paradoxically associate with decreased mortality.⁴¹ However, the finding in our study may well be affected by competing causes of death among asthmatics and the inter-relationship of smoking, low BMI, and chronic disease (such as COPD, or asthma with co-existing COPD). Similar bias has been suggested among obese individuals with CVD, where better survival was explained by reverse causation (in which weight is a consequence rather than cause of the disease) and confounding by smoking.⁴² Thus, lean smokers with COPD and/or other chronic disease would most probably be those who have strongly increased mortality rate in the asthma group.

Severe asthma symptoms at baseline were reported by 10% of the asthma patients, while 90% reported mild-to-moderate symptoms. Similar representation was seen in a nationwide register study investigating the prevalence of severe asthma among Danish adults; based on antiasthma treatment, severe asthma was identified in 8.1% of the patients.⁴³ A study reported increased mortality among patients with severe asthma.⁴⁴ In our study, self-reported asthma symptoms were significantly associated with higher mortality. Although individual lung function data were unavailable, all asthmatic patients had documented reversible obstruction of the lung, as it is required for the drug reimbursement right. These findings suggest that better control of asthma symptoms could help to prevent excess mortality related to the disease.

We acknowledge that COPD cannot fully be distinguished from asthma and misclassification bias might have occurred. On the other hand, this is a historical cohort of adults born between 1904 and 1966. It may thus not be fully comparable to the current asthma population. Limitations of the study also include the small number of subjects, lack of individual lung function data, and putative recall bias in the questionnaire responses, concerning confounding factors (such as smoking habits). We acknowledge that self-reported severe asthma symptoms do not fully correspond to the true asthma severity and that the data concerning smoking less than 100 cigarettes were not fully available in our questionnaire. Based on the self-reported asthma onset, it seems that some of the patients might have had early childhood asthma or wheeze. A shortcoming is that between 1997 and 2013 longitudinal data were not available to update exposure, covariate, and asthma status. We acknowledge that there was some discrepancy in the responses concerning cough/dyspnoea with wheeze ever. Some asthmatics may have had mild asthma with no or atypical symptoms and/or these patients did not recall to have had symptoms. Some nonasthmatics might have had previous recovered asthma or current asthma-like symptoms without fulfillment of the asthma criteria used in Finnish Drug Reimbursement Register. This study had limited possibilities to use validated questionnaire and register-based data of medication, in order to assess control of asthma and its association with mortality rate. Further studies using this information would thus be important.

The strengths of the study include the large population-based design that mitigates potential for selection bias, long follow-up (of 15 years), and a high responder rate. After including nonresponders to the analysis, asthma was still associated with the risk of increased all-cause mortality. Yet, despite the population-based design, all-cause mortality was significantly decreased among responders compared to matched nonresponders, which might indicate a greater effect of our results in the general public.

5 | CONCLUSION

We identified a significantly increased all-cause mortality and cause-specific mortality to COPD and neoplasms of the respiratory

organs in Finnish adult asthma patients. Cardiovascular diseases also contribute to higher mortality among asthmatics. Smoking cessation is likely to reduce mortality in both asthmatic and nonasthmatic adults. Although previous studies have shown that allergic diseases increase morbidity, AR/AC did not explain excess mortality among asthmatic adults. Further studies of the mechanisms behind this in other populations and with increased number of individuals are needed.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

All authors made contributions to the study design, data acquisition, data analysis, data interpretation, and/or revising of the manuscript for critical intellectual content. The authors had full access to the study data and take full responsibility for the content of the manuscript, including the data and analysis.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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Online Repository.

Figure S1. Kaplan-Meier survival curves, number at risk and cumulative number of events.

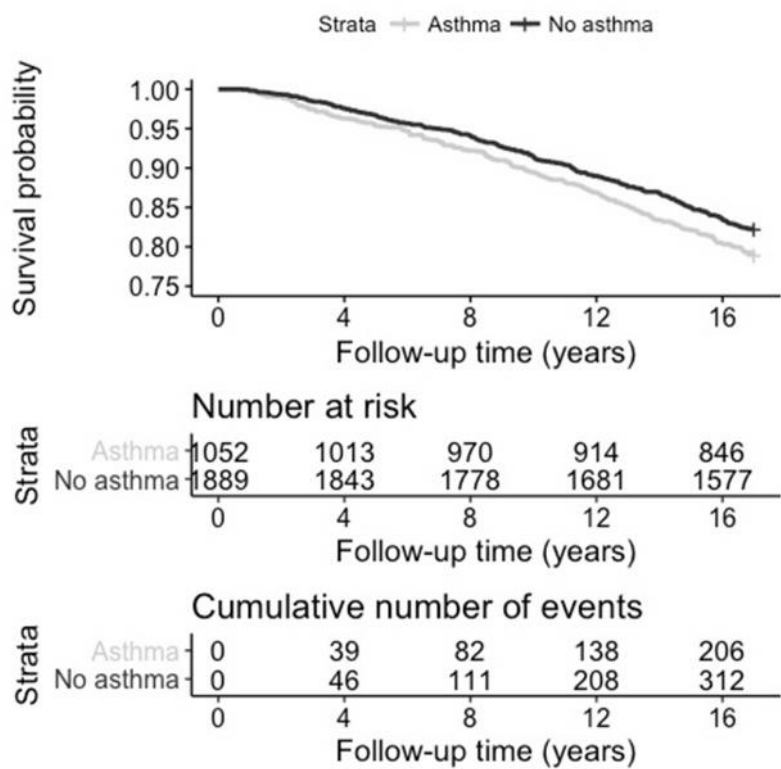


Table S1 Mortality rates and hazard ratios (HR) for all-cause and cause-specific mortality among non-asthmatics subjects (N=1,889) and asthmatics (N=1,052). Table S1 is similar to Table 2, except in the adjusted models smoking status was used instead of pack-years.

Cause of death		Number of events	Mortality Rate	Crude HR (95% CI)	P-value	Adjusted HR (95% CI)	P-value
All-cause	No asthma	335	11.3 (10.1–12.5)	1		1	
	Asthma	221	13.6 (11.9–15.5)	1.21 (1.02–1.44)	0.03	1.33 (1.12–1.59)	0.001
Neoplasms (C00–C26, C40–D48)	No asthma	87	2.93 (2.34–3.61)	1		1	
	Asthma	35	2.15 (1.50–3.00)	0.97 (0.59–1.58)	0.901	0.76 (0.51–1.14)	0.184
Neoplasms of respiratory organs (C30–C39)	No asthma	16	0.54 (0.31–0.87)	1		1	
	Asthma	25	1.54 (1.00–2.27)	3.74 (1.56–8.98)	0.003	3.03 (1.60–5.73)	<0.001
Mental and behavioral disorders (F00–F99)	No asthma	10	0.34 (0.16–0.62)	–		–	
	Asthma	2	0.12 (0.01–0.44)	–	–	–	–
Diseases of the nervous system (G00–G26, G30–G99)	No asthma	26	0.87 (0.57–1.28)	1		1	
	Asthma	10	0.62 (0.30–1.13)	0.56 (0.22–1.46)	0.236	0.77 ¹ (0.37–1.60)	0.478
Cardiovascular diseases (I05–I25, I60–I99)	No asthma	136	4.57 (3.84–5.41)	1		1	
	Asthma	82	5.05 (4.01–6.27)	1.47 (1.00–2.17)	0.051	1.28 (0.97–1.69)	0.085
COPD (J44)	No asthma	4	0.13 (0.04–0.34)	1		1	
	Asthma	30	1.85 (1.25–2.64)	14.0 (3.26–60.1)	<0.001	17.8 (6.16–51.2)	<0.001
Asthma (J45–J46)	No asthma	1	0.03 (0.00–0.19)	–		–	
	Asthma	2	0.12 (0.01–0.44)	–	–	–	–
Other respiratory diseases (J00–J43, J47–J99)	No asthma	13	0.44 (0.23–0.75)	1		1	
	Asthma	4	0.25 (0.07–0.63)	0.65 (0.15–2.74)	0.556	0.57 ¹ (0.18–1.79)	0.339
Digestive diseases (K00–K93)	No asthma	13	0.44 (0.23–0.75)	1		1	
	Asthma	13	0.80 (0.43–1.37)	1.47 (0.60–3.57)	0.400	2.00 ¹ (0.92–4.32)	0.080
Others §	No asthma	28	0.94 (0.63–1.36)	1		1	
	Asthma	17	1.05 (0.61–1.68)	1.28 (0.58–2.85)	0.538	1.26 ¹ (0.69–2.32)	0.452

Causes of deaths according the International Classification of Diseases, Tenth Revision (ICD-10).
Mortality Rate per 1,000 person-years = amount of deaths per year per 1,000 individuals
HR = hazards ratio; 95% confidence interval
Crude HR = matched for age, sex and area of residence at baseline.
Adjusted HR = adjusted for age, sex, smoking, education, and Body mass index (BMI) at baseline.
Adjusted HR¹ = adjusted for age, sex, smoking, and education level at baseline. BMI could not be included to all adjusted models due to lack of statistical power.
Adjusted models could not be estimated for all causes of death due to lack of statistical power (small number of cause-specific deaths).
COPD = chronic obstructive pulmonary disease
§ Including infectious and parasitic diseases (A00–B99), endocrine and metabolic diseases (E00–E90), skin diseases (L00–L99), musculoskeletal and connective tissue diseases (M00–M99), genitourinary diseases (N00–N99), congenital deformations (Q00–Q99), not elsewhere classified (R00–R99), and accidents and suicides (V01–Y34).
Bold text indicates statistically significant P-value (P<0.05).

Commento [SSK1]: This has been corrected similar to the Table 2 (in the Main Article).
The Authors apologize the mistake.

Commento [SSK2]: This was added as requested

Table S2 Factors associated with all-cause mortality in non-asthmatic patients (N=1889, deaths=335).

	Model 1		Model 2	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age				
≤ 59	1		1	
60–69	4.16 (3.14–5.51)	< 0.001	4.72 (3.54–6.29)	< 0.001
70–79	10.4 (7.41–14.7)	< 0.001	12.0 (8.42–17.0)	< 0.001
≥ 80	61.4 (36.6–103.0)	< 0.001	65.0 (38.6–109.6)	< 0.001
Sex				
Male	1		1	
Female	0.76 (0.59–0.97)	0.026	0.66 (0.52–0.83)	< 0.001
Smoking status				
Never	–	–	1	
Ever	–	–	1.03 (0.75–1.40)	0.858
Current	–	–	2.21 (1.64–2.97)	<0.001
Pack-years				
0	1			
≤ 19	1.19 (0.87–1.62)	0.285	–	–
≥ 20	2.00 (1.48–2.69)	<0.001	–	–
BMI				
Normal (18.5–24.99)	1		1	
Underweight (<18.5)	1.41 (0.44–4.49)	0.564	1.34 (0.42–4.27)	0.617
Overweight (25–29.99)	0.89 (0.69–1.13)	0.332	0.92 (0.72–1.17)	0.497
Obese ≥30	1.35 (1.00–1.82)	0.053	1.50 (1.11–2.03)	0.009
Education				
Matric. exam.	1		1	
Secondary school	1.07 (0.68–1.68)	0.775	1.04 (0.66–1.62)	0.876
Primary school	1.32 (0.90–1.95)	0.157	1.35 (0.92–1.98)	0.128
Allergic rhinitis and/or conjunctivitis				
No	1		1	
Yes	0.91 (0.71–1.17)	0.469	0.93 (0.72–1.20)	0.565

Adjusted Cox’s multivariate proportional hazards models
The effect of smoking was evaluated by pack-years in Model 1, and by smoking status in Model 2.
HR=hazards ratio; 95% confidence interval
BMI = Body mass index
Bold text indicates statistically significant P-value (P<0.05).

Commento [SSK3]: The values have been corrected similarly as in the Table 3 (in the Main article).
The Authors apologize the mistake.

Commento [SSK4]: This was added as requested