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Original Research

Mortality of asthma, COPD, and asthma-COPD overlap during an 18-year follow up

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ABSTRACT

Background: We studied asthma, COPD, and asthma-COPD overlap (ACO) to predict mortality in a cohort of Finnish adults with an 18-year follow up.
Methods: A national health examination survey representing Finnish adults aged ≥30 years was performed in 2000–2001. The study cohort included 5922 participants (73.8% of the sample) with all relevant data, including a comprehensive clinical examination and spirometry. These participants were followed continuously from baseline until end of 2018 for total, cardiovascular, cancer, and respiratory mortality through a record linkage. Asthma, COPD, and ACO were defined based on the survey data, including spirometry and register data. There were three separate groups of obstructive subjects (one definition excluding the others).
Results: Asthma and COPD were significantly associated with higher total mortality in Cox's model adjusted for sex, age, smoking, education level, BMI, leisure time physical activity, cardiovascular disease, diabetes, and hypertension. Hazard ratios (HR) (95% confidence interval [CI]) for asthma, COPD, and ACO were 1.29 (1.05–1.58), 1.50 (1.20–1.88), and 1.26 (0.97–1.65), respectively. Additionally, asthma (HR 1.47, 95% CI 1.09–1.97) and COPD (HR 1.53, 95% CI 1.08–2.16) were associated with cardiovascular mortality. Although ACO did not predict mortality in the whole cohort, there was a significant association with mortality risk among those with hs-CRP 1–2.99 mg/l.
Conclusions: Asthma or COPD predicts higher total mortality and premature death from cardiovascular diseases.

1. Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are obstructive airway diseases and globally underdiagnosed public health problems. The global prevalence is approximately 3.6% for asthma and 3.9% for COPD (in those aged ≥30 years) [1–3]. The pathophysiology and patient characteristics are different in asthma and COPD [2–6].

There are multiple clinical phenotypes and endotypes in asthma and COPD [3,6,7]. Asthma-COPD overlap (ACO) has features of both diseases. It is estimated that about 27% of those with COPD have ACO. Male sex, smoking exposure, lower lung function in spirometry, and impaired physical performance are associated more with COPD and ACO than asthma [3,4,8–12]. However, compared with those with COPD, subjects with ACO are younger, more often female, and have higher BMI, lower lifetime smoking exposure, and more symptoms and exacerbations [8,13].

Frequency of comorbidities varies in asthma, COPD, and ACO. Those with asthma often have diseases such as allergic rhinitis and conjunctivitis, atopic skin disease, and obesity [6,7,14,15]. In COPD, comorbidities are generally associated with multi-morbidity; the most prevalent conditions include cardiovascular disease, diabetes, sarcopenia, and depression [3,16]. Those with ACO have comorbidities characteristic of both asthma and COPD [8,13,17].

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Abbreviations

ACO	asthma-COPD overlap
BTPS	body temperature and pressure, saturated with water vapour
CI	confidence interval
FEV_1	forced expiratory volume per 1 s
FVC	forced vital capacity
HR	hazard ratio
hs-CRP	high sensitivity C-reactive protein
ICD-10	*International Classification of Diseases*
OR	odds ratio
Th2	T-helper cell type 2

Subjects with asthma, COPD, and ACO have an increased risk of mortality [3,5,10,11,18–20]. In asthma, mortality is associated with current smoking, decreased lung function, exacerbations, and comorbidities, including COPD and cancer [18,20,21]. In COPD, mortality is associated with severity of obstruction, decreased forced expiratory volume per 1 s (FEV_1), amount of comorbidities and exacerbations, and level of systemic inflammation [3,19,22]. The long-term prognosis of ACO is associated with decreased lung function and resembles COPD more than asthma [9,10,12].

In this study, we report the comorbidities and total and cause-specific mortality in subjects with asthma, COPD, and ACO from an 18-year follow up in a Finnish national population health survey.

2. Material and methods

2.1. Study population

Health 2000 was a Finnish national health examination survey representing adults aged ≥18 years and was conducted from 2000 to 2001. A two-stage stratified random sample of 9922 subjects was drawn from the population register and invited to participate in a comprehensive health survey. In addition to collecting other data, those aged ≥30 years (8028 subjects) were invited to participate in a comprehensive clinical examination including spirometry. Of those subjects, 5922 (73.8%) underwent a comprehensive clinical examination including spirometry, physician's evaluation, questionnaires, and serological determinations; these subjects provided the relevant data needed for the current study [23,24].

2.2. Measurements and definition of determinants

Height, weight, and blood pressure were measured with standardized methodology. Body mass index (BMI) (weight [kg]/height^2 [m^2]) was used as a measure of relative weight. Age and sex were obtained from population registers. Age was categorized in the following groups: 30–44, 45–54, 55–64, 65–74, and ≥75 years. A standard interview determined smoking habits; subjects were categorized as never, former (quit smoking minimum 1 month before the survey), and current smokers (all others who had smoked one or more cigarettes, cigars, or pipes during last month) [23].

During the health examination blood samples were taken and stored frozen at ¯20°C and subsequently placed at ¯70°C for long-term storage [23]. Serum high sensitivity C-reactive protein (hs-CRP) was analysed by an automated analyser (Optima, Thermo Electron Oy, Vantaa, Finland) and an ultrasensitive immunoturbidimetric test (Ultrasensitive CRP, Orion Diagnostics, Espoo, Finland) with a limit of quantitation of 0.20 mg/l hs-CRP values were categorized as 0.20–0.99, 1.00–2.99, and ≥3 [25,26].

Physical activity was assessed by questions on the frequency, intensity, and duration of physical activity. Leisure time physical activity was categorized as yes or no and defined as exercise at least four times a week, at least 30 min at a time, and causing at least slight shortness of breath and sweating. Educational level was categorized as the following according to completed years of schooling: basic (<10 years), secondary (10–12 years), and higher (>12 years) [23,24].

At study baseline, a field physician diagnosed cardiovascular disease, diabetes, and hypertension based on all available clinical information. Definition of cardiovascular disease included major cardiovascular disease (as previously presented [27]) or a history of stroke or arteriosclerosis obliterans. Determination of diabetes included a self-reported history of diagnosed diabetes and being treated by a physician for diabetes, a fasting plasma glucose level ≥6.7 mmol/l, or both [23,27]. The definition of hypertension included having a current medication for hypertension or levels of systolic >160 mmHg or diastolic >95 mmHg blood pressure measured in the survey [23].

The basic questionnaire assessed history, symptoms, and possible findings of allergic rhinitis, atopic eczema, and conjunctivitis and categorized as having these or not [23].

Lung functions were measured with Vitalograph bellow spirometers (Vitalograph Ltd., Buckingham, England) and Medikro ® Spiro2000 software by specially trained laboratory technicians who followed standard guidelines. The test procedure was demonstrated individually to all subjects. FEV_1 and forced vital capacity (FVC) were measured. FEV_1/FVC was calculated using the highest readings of FEV_1 and FVC from technically acceptable efforts recorded in BTPS (body temperature and pressure, saturated with water vapour) values. A bronchodilation test was performed for those with FEV_1/FVC <0.7 [19,23,24,28].

In our study, there were three separate groups of obstructive subjects; one definition excluded the others. The definition of asthma included FEV_1/FVC ≥0.7 after bronchodilation test and a significant response (FVC or FEV_1 ≥12% and ≥200 ml) in bronchodilation test measured in survey or two of the following: self-reported asthma diagnosed by a physician, special reimbursed medication for asthma (data from the Social Insurance Institution of Finland), or clinical asthma diagnosis by a physician [2,24,29]. The Finnish criteria for special reimbursement for regular asthma medication were described previously [30]. COPD was defined as FEV_1/FVC <0.7 after bronchodilation test and non-significant response in bronchodilation test. ACO was defined as FEV_1/FVC <0.7 after bronchodilation test and a significant response in bronchodilation test [3].

2.3. Follow up

We used an individual identification number for each participant and followed the cause of death continuously from Statistics Finland from baseline survey until end of the year 2018 [29]. Cause of death was categorized according to the *International Classification of Diseases 10* (ICD-10). Outcomes in cancer, cardiovascular, and respiratory causes included following ICD-10 codes: C00-C97 and D37-D48; I00-I89; and J09-J99, respectively. Mortality from other causes was scarce and is not reported.

2.4. Statistical analysis

We constructed models to analyse characteristics associated with asthma, COPD, or ACO and to predict mortality according to previous literature. We performed a separate preliminary analysis about interaction with each possible characteristic (age, sex, smoking history, BMI, cardiovascular disease, diabetes, hs-CRP, education [in years], leisure time physical activity, and hypertension) and obstruction variables (no obstruction, asthma, COPD, or ACO). All these characteristics appeared relevant to our study for confounding or effect-modifying factors and were included in our analysis. History of atopic disease, conjunctivitis, and allergic rhinitis were included in the primary analysis but excluded from the full model, because they showed no association with mortality.

We analysed the cross-sectional associations between those with asthma and those without any obstruction and baseline characteristics using logistic regression and expressed results as model-adjusted odds ratios (OR) with 95% confidence intervals (CI). A similar analysis was performed for those with COPD and ACO. We analysed the strength of the associations between asthma, COPD, and ACO and total and cause-specific mortality by using Cox's proportional hazards regression model. The results were expressed as model-adjusted hazard ratios (HR) with 95% CIs. We constructed the following three models: unadjusted (1), adjusted for age and sex (2), and further for smoking, educational level, BMI, leisure time physical activity, cardiovascular disease, diabetes, and hypertension (3, full model). We analysed Kaplan Meier curves for mortality in those without any obstruction, and with asthma, COPD, and ACO. We studied effect modification by entering all the interaction terms of asthma, COPD, ACO, and each characteristic, individually, into the full model. The statistical significance of each interaction was tested with likelihood ratio test. In addition to the potential confounding factors described above, hs-CRP, history of atopic dermatitis, conjunctivitis, and allergic rhinitis were considered as potential effect-modifying factors. All analyses were performed using SAS System for Windows (version 9.3, SAS Institute, Inc., Cary, NC, USA).

2.5. Ethical considerations

The Ethics Committee for Epidemiology and Public Health in the Hospital District of Helsinki and Uusimaa approved the Health 2000 Survey. All participants provided written informed consent and participated on a voluntary basis in compliance with the principles of the World Medical Association's Declaration of Helsinki.

3. Results

Baseline characteristics are shown in Table 1. There were 320 (5.4%) subjects with asthma, 151 (2.5%) with COPD, and 99 (1.7%) with ACO. Mean age (range) of those with asthma, COPD, and ACO were 56.5 (30–90), 63.9 (35–89), and 66.7 (36–90) years, respectively. Mean (range) BMI values were 27.9 (15.8–37.8), 26.0 (16.5–42.6), and 26.9 (16.7–47.9) kg/m^2, respectively. Of those with baseline asthma, COPD, and ACO, 51 (15.9%), 68 (45.0%), and 36 (36.3%) were current smokers, respectively.

Characteristics associated with asthma, COPD, and ACO included age, sex, and smoking history. Asthma and ACO, but not COPD, were associated with cardiovascular disease. Asthma, but not COPD or ACO, was associated with diabetes. Additionally, asthma only was associated with history of atopic eczema, conjunctivitis, and allergic rhinitis.

During the follow up there were 1324 (22.4%) deaths in the total population, while of those with asthma 109 (34.1%), COPD 90 (59.6%), and ACO 64 (64.6%) died. At baseline the mean ages (SD's) of the whole population, those who died, and those who survived were 52.3 (14.5), 68.4 (12.9), and 47.7 (11.3) years, respectively. Asthma (HR 1.29, 95% CI 1.05–1.58) and COPD (HR 1.50, 95% CI 1.20–1.88) were associated with total mortality in the full model (Table 2). Kaplan Meier curves show the unadjusted ratios for mortality in those without any obstruction and those with asthma, COPD, and ACO (Fig. 1). Of all the deaths 1221 (92.2%) were due to natural causes. The HR's (95% CI's) of all-cause natural mortality for asthma, COPD, and ACO were 1.26

Table 1
Baseline characteristics and association with asthma, COPD, and ACO[a].

Characteristics		Total (n)	Asthma (n)	OR[b]	95% Cl	COPD (n)	OR[b]	95% Cl	ACO (n)	OR[b]	95% Cl
Sex	Men	2714	101			108			53		
	Women	3208	219	1.84	1.44–2.34	43	0.29	0.20–0.41	46	0.63	0.42–0.95
Age, years	30–44	2038	87			6			5		
	45–54	1564	67	1.01	0.73–1.40	34	7.43	3.11–17.75	10	2.60	0.89–7.62
	55–64	1048	57	1.29	0.91–1.81	37	12.64	5.31–30.09	19	7.54	2.81–20.26
	65–74	748	68	2.21	1.59–3.07	38	19.21	8.07–45.70	42	24.65	9.71–62.56
	>75	524	41	1.78	1.21–2.62	36	29.91	12.49–71.66	23	19.82	7.48–52.48
Smoking	Non-smoker	3042	186			38			23		
	Former smoker	1308	83	1.30	0.98–1.73	45	1.79	1.12–2.88	40	4.68	2.65–8.28
	Current smoker	1572	51	0.69	0.49–0.96	68	5.93	3.76–9.37	36	8.55	4.73–15.47
Educational level	1–9 years	2270	153			95			61		
	10–12 years	1933	82	0.78	0.58–1.05	37	0.78	0.52–1.17	25	1.04	0.64–1.70
	>12 years	1719	85	0.88	0.65–1.19	19	0.58	0.34–0.97	13	0.79	0.42–1.49
BMI[c], kg/m^2	<20	196	18			11			2		
	20–24.9	2009	80	0.43	0.25–0.73	58	0.29	0.14–0.60	42	1.46	0.34–6.23
	25–29.9	2404	130	0.59	0.35–1.00	58	0.18	0.09–0.36	30	0.63	0.15–2.74
	30–34.9	1001	61	0.62	0.35–1.09	19	0.13	0.06–0.29	17	0.79	0.18–3.52
	≥35	312	31	1.01	0.54–1.89	5	0.14	0.05–0.42	8	1.40	0.29–6.86
Leisure time physical activity	No	4771	254			125			85		
	Yes	1044	57	1.20	0.89–1.63	20	0.84	0.51–1.37	11	0.78	0.41–1.48
Cardiovascular Disease	No	5162	254			108			60		
	Yes	760	66	1.41	1.01–1.96	43	1.10	0.73–1.66	39	1.65	1.05–2.60
Diabetes	No	5490	281			135			85		
	Yes	432	39	1.61	1.12–2.31	16	0.83	0.48–1.42	14	1.13	0.63–2.03
Hypertension	No	3122	184			86			66		
	Yes	2800	136	1.34	1.03–1.73	65	0.69	0.49–0.97	33	0.91	0.58–1.42
History of atopic Eczema[a]	No	4734	225			133			81		
	Yes	1188	95	1.82	1.41–2.34	18	0.67	0.40–1.11	18	1.13	0.67–1.91
Conjunctivitis	No	4968	201			135			83		
	Yes	954	119	3.35	2.63–4.28	16	0.85	0.50–1.45	16	1.25	0.72–2.17
Allergic rhinitis	No	4174	95			113			71		
	Yes	1748	225	6.77	5.26–8.71	38	1.01	0.69–1.48	28	1.16	0.74–1.82
hs-CRP[d]	0.20–0.99	3417	166			70			40		
	1–2.99	1494	84	1.08	0.82–1.42	37	0.94	0.62–1.42	35	1.49	0.93–2.37
	≥3	1011	70	1.29	0.96–1.73	44	1.70	1.15–2.53	24	1.44	0.85–2.42

[a] Association with COPD, asthma, and ACO with baseline variables (separately in each group).
[b] Odds ratio (OR) for asthma, COPD, and ACO with 95% confidence intervals (CIs), sex adjusted for age, age for sex, and the other variables for both sex and age.
[c] Body mass index.
[d] High sensitivity C-reactive protein (mg/l).

Table 2
Associations of asthma, COPD, ACO, and baseline characteristics with total mortality.

Characteristics		Deaths/n	HR[a]	95% Cl	HR[b]	95% Cl	Deaths/n	HR[c]	95% Cl
Sex	Men	661/2714					642/2664		
	Women	663/3208	0.82	0.74–0.92	0.61	0.55–0.68	628/3151	0.66	0.58–0.75
Age, years	30–44	62/2038					61/2024		
	45–54	171/1564	3.77	2.82–5.04	3.76	2.81–5.03	168/1543	3.58	2.66–4.82
	55–64	211/1048	7.23	5.45–9.60	7.32	5.52–9.72	207/1029	6.65	4.94–8.96
	65–74	394/748	23.93	18.30–31.28	24.87	19.02–32.52	348/731	21.17	15.74–28.48
	>75	486/524	81.20	62.17–106.06	88.72	67.86–115.99	450/488	71.27	52.32–97.09
Smoking	Non-smoker	681/3042					645/2975		
	Former smoker	363/1308	1.30	1.15–1.48	1.12	0.97–1.29	352/1290	1.07	0.93–1.24
	Current smoker	280/1572	0.79	0.68–0.90	2.22	1.89–2.59	273/1550	2.13	1.80–2.52
Educational level	1–9 years	864/2270					821/2196		
	10–12 years	288/1933	0.34	0.30–0.39	0.79	0.68–0.90	280/1911	0.84	0.73–0.97
	>12 years	172/1719	0.22	0.68–0.90	0.62	0.53–0.74	169/1708	0.07	0.59–0.83
BMI[d], kg/m^2	<20	37/196					36/192		
	20–24.9	373/2009	0.96	0.68–1.35	0.51	0.36–0.72	355/1975	0.54	0.38–0.77
	25–29.9	558/2404	1.23	0.88–1.71	0.47	0.34–0.66	534/2359	0.50	0.35–0.70
	30–34.9	268/1001	1.44	1.02–2.03	0.48	0.34–0.68	259/982	0.47	0.33–0.67
	≥35	88/312	1.53	1.05–2.25	0.64	0.44–0.95	86/307	0.60	0.40–0.89
Leisure time physical activity	No	1129/4771					1129/4771		
	Yes	141/1044	0.53	0.45–0.64	0.70	0.59–0.84	141/1044	0.83	0.70–0.99
Obstruction	No	1061/5352					1017/5263		
	Asthma	109/320	1.89	1.55–2.31	1.41	1.16–1.72	104/311	1.29	1.05–1.58
	COPD	90/151	4.15	3.35–5.15	1.72	1.38–2.14	87/145	1.50	1.20–1.88
	ACO	64/99	4.72	3.66–6.07	1.52	1.18–1.96	62/96	1.26	0.97–1.65
Cardiovascular Disease	No	826/5162					799/5088		
	Yes	498/760	6.27	5.60–7.01	1.60	1.41–1.81	471/727	1.51	1.32–1.71
Diabetes	No	1101/5490					1054/5395		
	Yes	223/432	3.21	2.78–3.71	1.50	1.30–1.74	216/420	1.43	1.23–1.67
Hypertension	No	368/3122					353/3077		
	Yes	959/2800	3.32	2.95–3.75	1.21	1.06–1.37	917/2738	1.20	1.05–1.37

[a] Hazard ratios (HRs) with 95% confidence intervals (CIs), unadjusted ratios.
[b] Hazard ratios (HRs) with 95% confidence intervals (CIs), sex adjusted for age, age for sex, and other variables for sex and age.
[c] Hazard ratios (HRs) with 95% confidence intervals (CIs) adjusted for all characteristics included in this table (sex, age, smoking, education level, BMI, leisure time physical activity, obstruction, cardiovascular disease, diabetes, and hypertension).
[d] Body mass index.

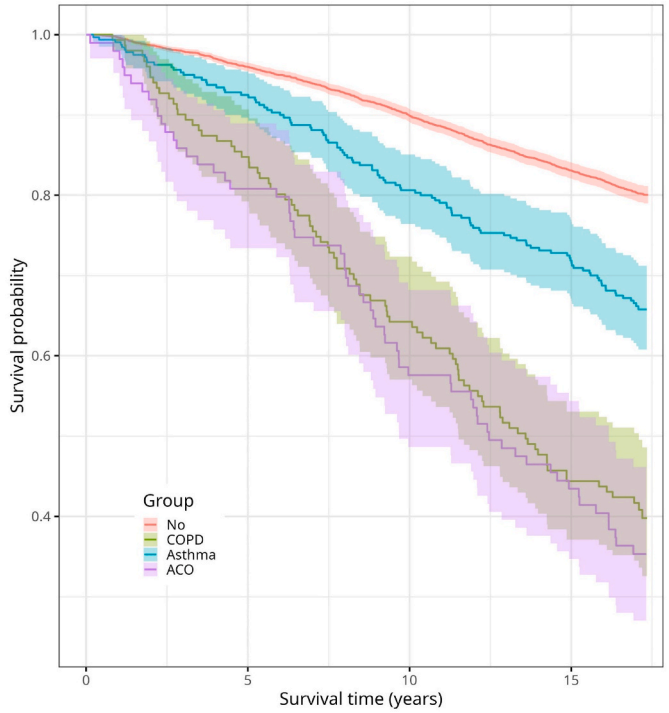

Fig. 1. Kaplan-Meier curves illustrating survival in those without any obstruction (No) and in those with asthma, COPD, and asthma-COPD overlap (ACO)[1]
[1] Unadjusted ratios.

(1.02–1.56), 1.54 (1.23–1.93), and 1.30 (1.00–1.69), respectively. After excluding the 10 first years after the survey, HRs (95% CIs) for total mortality were 1.61 (0.87–2.98) for asthma, 2.09 (1.12–3.89) for COPD, and 0.57 (0.23–1.42) for ACO.

Asthma (HR 1.47, 95% CI 1.09–1.97) and COPD (HR 1.53, 95% CI 1.08–2.16) were associated with cardiovascular deaths. Asthma (HR 2.62, 95% CI 1.13–6.07), COPD (HR 2.32, 95% CI 1.00–5.36), and ACO (HR 3.55, 95% CI 1.73–7.27) were associated with respiratory deaths (Fig. 2). Correspondent unadjusted HRs with 95% CIs for cancer deaths for asthma, COPD, and ACO were 1.25 (0.79–2.00), 4.85 (3.29–7.16), and 4.42 (2.67–7.32); for cardiovascular deaths 2.45 (1.86–3.24), 4.38 (3.14–6.10), and 4.59 (3.07–6.88); and for respiratory deaths 3.58 (1.59–8.04), 10.28 (5.02–23.31), and 25.90 (13.45–49.88), respectively.

Significant interactions for asthma, COPD, ACO, death, and characteristics (p-value <0.05) are shown in supplement Table 3. Although ACO did not predict mortality in the entire material, the risk for death was increased in those with ACO and hs-CRP 1–2.99 mg/l (HR 2.32, 95% CI 1.53–3.52).

4. Discussion

Having asthma or COPD at baseline predicted mortality during an 18-year follow up period in this Finnish national health survey. Mortality risk was comparable with those who had cardiovascular disease or diabetes at baseline. Additionally, asthma and COPD predicted cardiovascular mortality; asthma, COPD, and ACO respiratory mortality; and COPD cancer mortality. ACO did not have a significant association with total mortality in the whole cohort. However, ACO with hs-CRP 1–2.99 mg/l significantly predicted the risk of premature death.

We defined three mutually exclusive groups of obstructive lung

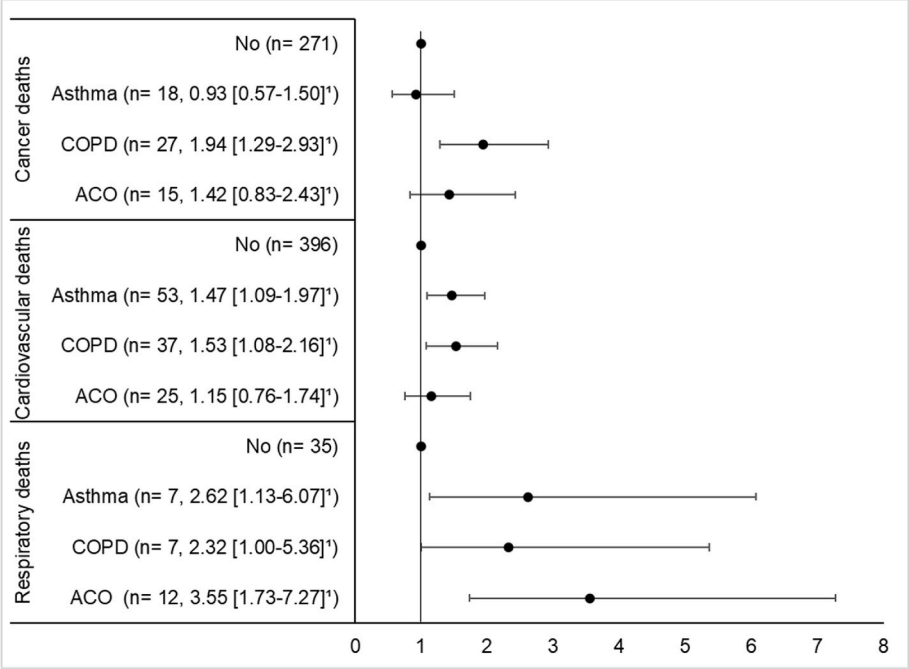

Fig. 2. Associations of asthma, COPD, and ACO with cause-specific mortality
[1] Hazard ratios (HRs) with 95% confidence intervals (CIs) adjusted for sex, age, smoking, education level, BMI, leisure time physical activity, cardiovascular disease, diabetes, and hypertension.

diseases. In our cohort, those with asthma were more often women, never smokers, and had a history of atopic eczema, conjunctivitis, or allergic rhinitis (or combinations thereof). Those with COPD were more often men and current smokers. Those with ACO were categorized between those with asthma or COPD. These clinical characteristics are consistent with previous data [3,7,8,14,15]. There is an international debate on classification of asthma and COPD into various phenotypes and endotypes [3,4,7,14,15]. Although the definition of ACO is not established, ACO is a phenotype with features of both asthma and COPD [8,9,12,17].

In our and previous studies, those with COPD had a higher mortality risk than those with asthma or ACO [9–11]. However, in COPD and ACO, there is no difference in mortality risk among subjects >65 years [9]. In the current study, the adjusted relative risk of premature death among subjects with asthma or COPD was comparable to those with a major cardiovascular disease or diabetes. Our definition for cardiovascular disease included diagnoses of ischemic heart disease, stroke, or arteriosclerosis obliterans, which are associated with an increased risk for total and cardiovascular mortality [31–33]. In a previous survey, HR for total mortality risk in those with type 2 diabetes was 1.80 (95% CI 1.71–1.90) [34], which is similar to our results.

In our current study, asthma was associated with cardiovascular and respiratory mortality but not with cancer deaths. However, the low number of cancer deaths, 18, in those with asthma may have affected our result. In previous studies, those with asthma had an increased risk of death from respiratory diseases (including COPD), cancers [18,20,35], cardiovascular diseases [5,10,20,35], and myocardial infarction [36]. An increased risk for hypertension, ischemic heart disease, acute coronary syndrome, and diabetes was seen in asthmatic populations, where >20% also had COPD [6,37]. Smoking appears to have an important role in the association between asthma and cardiovascular diseases and mortality [5,10,18]. In a Danish study, an increased risk for cardiovascular diseases and death was observed only in those with asthma who smoked [38]. Additionally, current but not former asthma is associated with cardiovascular mortality [20].

COPD patients have an increased cause-specific mortality risk with cardiovascular and respiratory diseases and cancer [3,4,10,11,19]. Our data support this finding. COPD patients with mild obstruction (defined as $FEV_1/FVC < 0.70$ and $FEV_1 \geq 80\%$) died mostly from cardiovascular diseases and cancer; those with more severe obstruction died from non-malignant respiratory diseases [4].

Mortality data for ACO are limited. In one study, there were no major differences in the underlying causes of death between those with ACO and COPD [10]. In those with ACO, mortality from cardiovascular diseases, chronic lower respiratory diseases, and cancers was common [35]. Deaths due to lower respiratory diseases were more common in those with COPD and ACO than in those with asthma [35]. In a recent study, those with asthma and COPD had a higher mortality overall and in coronary artery diseases compared to those with only asthma or COPD [39]. In our data, ACO was associated with respiratory deaths but not with total or cardiovascular mortality. A small number of ACO patients and a small number of total or cardiovascular deaths may explain the lack of association with total or cardiovascular mortality.

Systemic inflammation has an important role in the pathophysiology of obstructive diseases [3,14,15]. In our data, ACO predicted total mortality only among the subjects with hs-CRP levels between 1.0 and 2.99 mg/l defined as "silent inflammation" which is shown to predict for instance moderate vascular risk [40]. We did not find such an interaction for asthma or COPD. Previously, hs-CRP had an association with inflammation in asthma and COPD, although the association was stronger in COPD and in those who smoked [41,42].

In asthma, inflammation driven by pathways of T-helper cell type 2 (Th2) is classified as atopic or eosinophilic and causes comorbidities such as allergic rhinitis and atopic eczema [14]. Non-eosinophilic inflammation is associated with obesity and smoking [15]. In asthma, the association between systemic inflammation and hypertension, cardiovascular diseases, and diabetes is a novel finding. In COPD, systemic inflammation is present [3,22,43] and it is possible that this inflammation has a negative impact on comorbidities, such as cardiovascular disease [3,43]. As ACO consists of features of both asthma and COPD, the type of systemic inflammation is heterogenous [8,10,13,17]. We could not find any previous studies that compared markers of systemic inflammation in asthma, COPD, and ACO.

As a strength, our cohort represented the Finnish adult population

and the survey participation rates were representative. We followed participants continuously from baseline until end of the year 2018. As a limitation, Health 2000 was a general health examination survey. As such, only a limited number of participants had asthma, COPD, or ACO, which limited some of our analyses and possibly affected our results. For instance, unlike in previous studies [10,35,39], in our study the association between ACO and total mortality remained below statistical significance. Additionally, data on inhaled medications and smoked pack-years were not collected at baseline. Other factors that are associated with retrospective health examination surveys also apply to our data. Only participants with $FEV_1/FVC < 0.7$ performed the bronchodilation test with spirometry, and therefore, Lower Limit of Normal (LLN) categorization of obstruction could not be used [28]. There is overlapping in our categorization of the obstructive diseases which has possibly affected our results. For instance in long-term asthma a non-reversible chronic obstruction may develop [44]. Documentation of causes of deaths may have undergone minor changes during the follow up which may also have affected our results. Comparing our results with previous data was difficult due to the evolving definitions of obstructive diseases, especially for ACO. During follow up, some changes may have occurred in medical treatment for various diseases and in categorizing and documenting causes of death.

5. Conclusions

In this study, asthma and COPD increased total mortality during an 18-year follow up, and mortality was comparable with that for cardiovascular disease or diabetes. Cardiovascular mortality was increased in those with asthma and COPD. Total mortality was not significantly increased in those with ACO, probably due to the small number of subjects.

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Data sharing statement

None of the data collected for the study are directly available. However, the data used may be applied in a routine protocol with study permission. Other related documents, including memos and plans for this study (mainly in Finnish), will be available 2 years after publication for other researchers upon request (tiina.m.mattila@hus.fi).

CRediT authorship contribution statement

Tiina Mattila: Conceptualization, Methodology, Writing – original draft, Visualization, Project administration, Funding acquisition. **Tuula Vasankari:** Conceptualization, Methodology, Writing – review & editing. **Paula Kauppi:** Conceptualization, Writing – review & editing. **Witold Mazur:** Conceptualization, Writing – review & editing. **Tommi Härkänen:** Writing – review & editing, Methodology. **Markku Heliövaara:** Methodology, Validation, Software, Formal analysis, Investigation, Writing – review & editing.

Declaration of competing interest

The corresponding author TM completed this study through financial support from the Hospital District of Helsinki and Uusimaa. All other co-authors completed the work related to this study as a function of their regular duties. All authors do not have any relevant conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2022.107112.

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