



# Major cardiovascular events in patients with severe COPD with and without asthma: a nationwide cohort study

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Among patients with COPD and pre-existing cardiovascular disease, asthma as a comorbid condition is associated with substantially increased risk of cardiovascular events.

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## Abstract

**Background** Chronic low-grade inflammation as in asthma may lead to a higher risk of cardiovascular events. We evaluated whether patients with COPD and asthma have a higher risk of acute cardiovascular events than patients with COPD without asthma.

**Methods** Nationwide multicentre retrospective cohort study of Danish outpatients with a specialist diagnosis of COPD with or without asthma. Patients with both COPD and asthma were propensity-score matched 1:2 to patients with COPD without asthma. The primary end-point was severe major adverse cardiac events (MACE), defined as mortal cardiovascular events and events requiring revascularisation or hospitalisation.

**Results** A total of 52 386 Danish patients with COPD were included; 34.7% had pre-existing cardiovascular disease, and 20.1% had asthma in addition to their COPD. Patients with pre-existing cardiovascular disease were then propensity-score matched: 3690 patients with COPD and asthma *versus* 7236 patients with COPD without asthma, and similarly, for patients without pre-existing cardiovascular disease (6775 matched with 13 205). The risk of MACE was higher among patients with asthma and COPD *versus* COPD without asthma: hazard ratio (HR) 1.25 (95% CI 1.13–1.39,  $p < 0.0001$ ) for patients with pre-existing cardiovascular disease and HR 1.22 (95% CI 1.06–1.41,  $p = 0.005$ ) for patients without pre-existing cardiovascular disease.

**Conclusion** Among patients with COPD, asthma as a comorbid condition is associated with substantially increased risk of cardiovascular events. The signal was an increased risk of 20–25%. Based on our study and other smaller studies, asthma can be considered a risk factor for cardiovascular events among COPD patients.

## Introduction

Cardiovascular diseases share many risk factors with COPD, and the two are frequently found together [1–3]. Patients with asthma seem to have an elevated level of chronic low-grade inflammation with elevated pro-inflammatory biomarkers such as high sensitivity C-reactive protein [4, 5]. This inflammation may induce a prothrombotic stage causing an increased risk of cardiovascular disease seen in patients with asthma [6–11]. An asthma-inflammation-driven increased risk of cancer has also been proposed [12]. Randomised clinical trials have even shown that inhibition of interleukin-1 $\beta$  by canakinumab [13] and of tubulin by colchicine [14] reduces the risk of ischaemic heart disease, thus proving that low-grade inflammation plays a causative role in the development of ischaemic heart disease and its events.



It seems plausible that asthma *per se* increases systemic inflammation and could cause an increase in the risk of cardiovascular events. Current knowledge regarding cardiovascular disease in patients with COPD and asthma is sparse. Only a few uncontrolled studies have examined cardiovascular comorbidity in patients with COPD and asthma. These studies pointed to a possibly higher risk of cardiovascular disease in patients with asthma [15–19]. However, many of these studies were based on small populations, with substantial loss to follow-up and insufficient confounder control.

We aimed to examine whether the risk of cardiovascular events is higher in patients with COPD and asthma, as compared to those with COPD without asthma. We used nationwide data and complete follow-up, and with a possibility to match for important confounders such as age, smoking status, percentage predicted forced expiratory volume in 1 s (FEV<sub>1</sub>) and comorbidities. Our hypothesis was that patients who have asthma in addition to COPD have an increased risk of cardiovascular events.

## Methods

### Study design

A nationwide multicentre retrospective cohort study was conducted by combining information from the following registries:

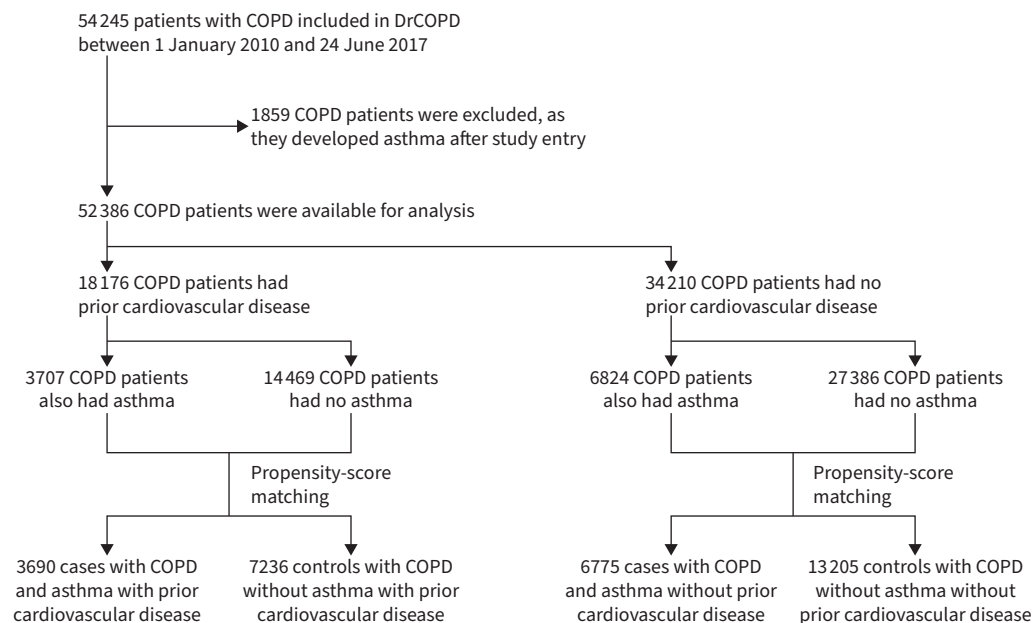
- 1) The Danish Register of Chronic Obstructive Pulmonary Disease (DrCOPD) was established in 2008. It is a nationwide database containing information on the quality of treatment of all patients with COPD who are treated by a respiratory medicine specialist at a Danish hospital [20]. Covariates included in this study were age, lung function assessed as FEV<sub>1</sub> % predicted, body mass index (BMI; kg·m<sup>-2</sup>), dyspnoea assessed using the Medical Research Council (MRC) dyspnoea scale and smoking status.
- 2) All citizens in Denmark acquire a unique personal identification number at birth or upon immigration. This unique personal identification number links individual information for each resident to information on name, sex, date of birth and vital status. The data are registered in the Danish Civil Registration System [21].
- 3) The Danish National Health Service Prescription Database holds information on all prescriptions dispensed by Danish pharmacies since 2004 (coded according to Anatomical Therapeutic Chemical classification), including data on dispensation date, quantity dispensed, strength and formulation. All pharmacies are required by Danish legislation to provide information that ensures complete and accurate registration [22].
- 4) The Danish National Patient Registry holds information on all admissions to Danish hospitals since 1977, and hospital outpatient clinic visits since 1995. Each visit is coded by physicians with one primary diagnosis and one or more secondary diagnoses, according to the International Classification of Diseases, eighth revision (ICD-8) codes until 1994 and ICD-10 thereafter [23].

### Population

All Danish residents aged >30 years registered with a COPD diagnosis by a pulmonary specialist in an outpatient clinic during the period 1 January 2010 to 24 June 2017 were included. A diagnosis of COPD by a pulmonary specialist is the entry criteria for the DrCOPD database, and was also considered the inclusion criteria for our study. Similarly, asthma diagnosis was verified by a pulmonary specialist at entry into DrCOPD, and hence in our study a diagnosis code of DJ45 and all its subcodes was accepted as a diagnosis of asthma. Patients with FEV<sub>1</sub> >80% and “never smoking” or “passive smoking” status (n=202) were not included. A patient’s study entry date was defined as the date of their first contact. The patients were identified through the DrCOPD database [20]. All patients who developed asthma (DJ45) after the initial contact date were excluded (figure 1).

Due to a significant effect modification between asthma history and pre-existing cardiovascular disease in relation to future major adverse cardiac events (MACE) (p<0.0001), patients were stratified according to pre-existing cardiovascular disease. If patients were registered with a pre-existing cardiovascular illness, defined as pre-existing registry with a diagnosis of cerebral or cardiac ischaemia (DG45, DI20, DI21, DI22, DI23 or DI24), or having been subjected to surgery for cardiac ischaemia (all revascularisation codes; KFNA00, KFNA20, KFNC10-30, KFNE00, KFNG02, KFNG02A, KFNG05 or KFNG05A), or been prescribed ischaemia-related medication (nitroglycerine and antithrombotic treatment with ADP-receptor inhibitors), they were designated to a group with pre-existing cardiovascular disease. All patients who did not fulfil any of these criteria were designated to the group without pre-existing cardiovascular disease.

Hence, the study population consisted of the two cohorts, which were each propensity-score matched. The study cohorts were formed by identifying all patients with asthma in addition to COPD. The control



**FIGURE 1** Flowchart of included patients, cohorts with and without prior cardiovascular disease, and propensity-score match. DrCOPD: Danish Register of Chronic Obstructive Pulmonary Disease.

cohorts were formed by propensity-score matching each case to two patients with COPD without asthma on known and likely confounders: age, gender, tobacco exposure, BMI, MRC dyspnoea score and FEV<sub>1</sub> % pred [24].

### Baseline characteristics

Demographic variables, comorbidities and medical therapy were registered.

### Follow-up

Patients were followed for 2 years after study entry, which served as the study period, during which they were eligible to develop an event. The fixed 2-year follow-up time was chosen in order to capture the developed cardiovascular events, while still anticipating mortality as a not-too-dominant competing risk.

Loss to follow-up was seldom in all investigated groups: in total, 69 (0.2%) patients were lost to follow-up and no meaningful differences were observed between groups.

### Outcomes

Cardiovascular events were registered as lethal cardiovascular events (lethal event diagnosed as DG45, DI20, DI21, DI22, DI23 or DI24), cardiovascular events requiring revascularisation (surgery diagnosed as KFNA00, KFNA20, KFNC10-30, KFNE00, KFNG02, KFNG02A, KFNG05 or KFNG05A), cardiovascular events requiring admission (hospitalisation diagnosed as DG45, DI20, DI21, DI22, DI23 or DI24) and cardiovascular events requiring prescriptions of ADP receptor inhibitors or nitrates. Additionally, a composite end-point of lethal cardiovascular events, cardiovascular events requiring revascularisation and cardiovascular events requiring admission was labelled “severe MACE” [25], and a composite end-point of all aforementioned cardiovascular events including prescriptions of ADP receptor inhibitors and nitrates was labelled “any MACE”. Patients in treatment with ADP receptor inhibitors or nitrates before study entry were not eligible for an event based on prescriptions after study entry.

Sensitivity analyses were performed for diabetes (ICD codes DALAL22, DE10, DE11, DE12, DE13, DE14, DE15, DH334B, DH360, DN083, DZ213A1 or DZ863D) and renal insufficiency (DN02, DN03, DN04, DN05, DN06, DN07, DN08, DI10, DI20, DI31, DI32, DE102, DE112, DE122, DE132, DE142, DN11, DN14, DN17, DN18, DN19, DN25, DN26, DN158, DN159, DN160, DN161, DN162, DN163, DN164, DN165, DN168 or DZ992). These diagnoses are most often specialist-verified in a Danish hospital setting.

### *Analysis of inhaled corticosteroids*

For the *post hoc* analysis on inhaled corticosteroids (ICS), we divided patients into two groups: high-dose ICS (budesonide equivalent dose  $\geq 947$   $\mu\text{g}$  daily) was compared to ICS dosage of budesonide equivalent dose  $< 947$   $\mu\text{g}$  daily. We subsequently performed adjusted Cox regression analysis to test for an inhibitory effect of ICS on the development of MACE. The analysis adjusted for the below-mentioned known and suspected confounders.

### *Statistical analysis*

Patients with COPD and asthma were propensity-score matched (using the Greedy Match algorithm from the Mayo Clinic: <http://bioinformaticstools.mayo.edu/research/gmatch>) to patients with COPD without asthma by the following known and suspected confounders: age (as a continuous variable), gender, tobacco exposure (divided into the categories “never smoking”, “passive smoking”, “previous smoking”, “active smoking” and “unknown tobacco exposure”), MRC (with the options 1, 2, 3, 4 and 5), BMI (as a continuous variable) and FEV<sub>1</sub> % (as a continuous variable) at inclusion. Missing values on scoring variables were imputed before propensity-score match. The propensity-score method aims to control for confounding by balancing confounders between cases and controls [26]. We used the propensity score matching method developed by the Mayo clinic (Greedy match). The rigour of the matching allowed for slightly fewer than two controls per case.

Baseline characteristics were compared by Chi-squared test. Cox regression modelling and Gray’s analysis was used to assess the risk of events in the various compared groups.

Subsequent to competing risk analysis the patients were stratified into two groups depending on pre-existing cardiovascular disease before analysis, in order to minimise the risk of differences in outcome from differences in underlying risk of cardiovascular disease driven by known underlying cardiovascular disease. Death from all causes (other than MACE) was handled as a competing risk in the Cox analyses.

The primary end-point was severe MACE, and our secondary end-points were any MACE, as well as events analysed on other cohorts than the propensity-scored groups and cumulative incidence curves analysed by Gray’s analysis. As some patients had more than one event during the follow-up period, only the first event was counted. The end-points were analysed by Cox regression analysis with non-cardiovascular mortality as competing risk and by cumulative incidence curves and Gray’s analysis.

The primary analysis was unadjusted Cox analysis of severe MACE among propensity score matched groups of patients with COPD and asthma *versus* COPD patients without asthma, divided by pre-existing cardiovascular disease. Secondary analyses included cumulative incidence analyses with significance determined by Gray’s K-sample corresponding to the primary unadjusted Cox analyses, as well as analyses of any MACE, and adjusted Cox analyses analysis of the groups without propensity-score matching, with the results visualised using forest plots.

For sensitivity analysis, we conducted an adjusted Cox proportional hazard regression model in the unmatched population. The Cox proportional hazard regression model on the unmatched population was adjusted for the variables included in the propensity-score match (age, gender, tobacco exposure, MRC, BMI and FEV<sub>1</sub> %).

Furthermore, an adjusted Cox proportional hazards regression analysis was performed on the group of propensity-matched patients, with adjustment (for age, gender, tobacco exposure, MRC, BMI and FEV<sub>1</sub> %). Model control investigating the proportional hazards assumption was performed to validate the Cox proportional hazards regression, in all cases yielding p-values  $> 0.05$ .

All statistical analyses were performed using SAS 9.4 (Cary, NC, USA), and Microsoft Excel (Windows 365; Microsoft, Redmond, WA, USA). A two-sided 95% confidence interval was considered statistically significant. Cumulative incidence plots were customised by the NewSurv macro [27].

A competing risk analysis was performed for pre-existing cardiovascular disease, after which the patients were stratified into two groups depending on cardiovascular disease before study entry: if patients were registered with a pre-existing cardiovascular illness, defined as pre-existing registry with a diagnosis of cerebral or cardiac ischaemia, or having been subjected to surgery for cardiac ischaemia (all revascularisation codes), or been prescribed ischaemia-related medication (nitroglycerine and antithrombotic treatment), they were designated to a group with pre-existing cardiovascular illness. All

patients who did not fulfil any of these requirements were designated to the group without pre-existing cardiovascular disease.

### Ethics

The study was approved by the Capital region of Denmark by the Knowledge Center for Data Reviews (P-2021-280). In Denmark, retrospective use of register data does not require ethical approval or patient consent.

**TABLE 1** Baseline characteristics of the propensity-matched cohorts stratified by pre-existing cardiovascular disease

	Patients with pre-existing cardiovascular disease		Patients without pre-existing cardiovascular disease	
	Patients with COPD and asthma	Patients with COPD without asthma	Patients with COPD and asthma	Patients with COPD without asthma
<b>Patients</b>	3690	7236	6775	13 205
<b>Age years</b>	72.4 (65.2–79.1)	72.6 (65.7–78.9)	66.2 (57.1–74.7)	66.4 (58.4–74.3)
<b>Female</b>	2058 (55.8)	3989 (55.1)	4024 (59.4)	7761 (58.8)
<b>Tobacco exposure</b>				
Never smoking	219 (5.9)	241 (3.3)	334 (4.9)	432 (3.3)
Passive smoking	1 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Previous smoking	2156 (58.4)	4529 (62.6)	3675 (54.2)	7367 (55.8)
Active smoking	981 (26.6)	1998 (27.6)	2217 (32.7)	4581 (34.7)
Unknown tobacco exposure	333 (9.0)	468 (6.5)	548 (8.1)	825 (6.2)
<b>MRC dyspnoea score</b>	3 (3–4)	3 (3–4)	3 (2–3)	3 (2–4)
<b>BMI kg·m<sup>-2</sup></b>	25 (23–29)	25 (22–30)	25 (22–29)	25 (21–29)
<b>FEV<sub>1</sub> % pred</b>	49 (37–61)	49 (37–61)	49 (36–61)	49 (35–61)
<b>Comorbidities</b>				
Hypertension	1898 (51.4)	3622 (50.1)	1525 (22.5)	2872 (21.7)
Hypercholesterolaemia	1018 (27.6)	2188 (30.2)	326 (4.8)	571 (4.3)
Atrial fibrillation	864 (23.4)	1695 (23.4)	618 (9.1)	1261 (9.5)
Diabetes	724 (19.6)	1305 (18.0)	660 (9.7)	1136 (8.6)
Osteoporosis or osteopenia	1013 (27.5)	1584 (21.9)	1438 (21.2)	2339 (17.7)
Renal insufficiency	2017 (54.7)	3843 (53.1)	1807 (26.7)	3338 (25.3)
Liver insufficiency	114 (3.1)	258 (3.6)	210 (3.1)	372 (2.8)
Malignancy	854 (23.1)	1561 (21.6)	1131 (16.7)	2111 (16.0)
Atopy or allergy	562 (15.2)	264 (3.6)	1042 (15.4)	377 (2.9)
Depression	292 (7.9)	442 (6.1)	333 (4.9)	516 (3.9)
<b>Exacerbations requiring admission within the year prior to inclusion</b>	1426 (38.6)	2334 (32.3)	2146 (31.7)	3613 (27.4)
<b>Medical treatment for respiratory disease within the year prior to inclusion</b>				
Oral corticosteroid	2207 (59.8)	3113 (43.0)	3703 (54.7)	5276 (40.0)
Inhaled corticosteroid	3252 (88.1)	4892 (67.6)	5983 (88.3)	8887 (67.3)
Long-acting $\beta_2$ -agonist	3253 (88.2)	5435 (75.1)	5920 (87.4)	9736 (73.7)
Long acting muscarinic receptor antagonist	2715 (73.6)	5167 (71.4)	4730 (69.8)	9074 (68.7)
Short-acting $\beta_2$ -agonist	2905 (78.7)	4590 (63.4)	5172 (76.3)	8194 (62.1)
Short-acting muscarinic receptor antagonist	208 (5.6)	249 (3.4)	250 (3.7)	357 (2.7)
<b>Medical treatment for cardiovascular disease within the year prior to inclusion</b>				
Blood pressure medication	3070 (83.2)	6212 (85.8)	3739 (55.2)	7631 (57.8)
Cholesterol-lowering medication	2080 (56.4)	4458 (61.6)	1403 (20.7)	3157 (23.9)
ADP-receptor inhibitors	666 (18.0)	1532 (21.2)	NA	NA
Acetyl sialic acid	1841 (49.9)	3838 (53.0)	1002 (14.8)	2213 (16.8)
Nitrates	964 (26.1)	1799 (24.9)	NA	NA
<b>Medical treatment for diabetes within the year prior to inclusion</b>				
Insulin	229 (6.2)	448 (6.2)	225 (3.3)	392 (3.0)
Non-insulin antidiabetics	637 (17.3)	1185 (16.4)	657 (9.7)	1311 (9.9)

Data are presented as n, median (interquartile range) or n (%). Patients with COPD and asthma and with COPD without asthma were propensity matched 1:2 by age, gender, tobacco exposure, Medical Research Council (MRC) dyspnoea score, body mass index (BMI) and forced expiratory volume in 1 s (FEV<sub>1</sub>) % stratified into populations based on pre-existing cardiovascular disease. NA: not applicable.

## Results

52 386 patients were included in this study; 34.7% (18 176 patients) had a pre-existing cardiovascular disease, and 20.1% (10 531 patients) had asthma in addition to their COPD.

For the primary analysis, among patients with pre-existing cardiovascular disease, 3690 patients with COPD and asthma were propensity matched 1:2 with 7236 patients with COPD without asthma. Among patients who did not have pre-existing cardiovascular disease, 6775 patients with COPD and asthma were propensity matched 1:2 with 13 205 COPD patients without asthma.

Baseline data of the propensity score matched cohorts with COPD and asthma *versus* with COPD without asthma stratified by pre-existing cardiovascular disease are shown in table 1. There were few differences in the baseline characteristics; atopy was markedly higher among patients with COPD and asthma compared to patients with COPD without asthma (15.2% *versus* 3.6%,  $p < 0.0001$  among patients with pre-existing cardiovascular disease and 15.4% *versus* 2.9%,  $p < 0.0001$  without pre-existing cardiovascular disease) (table 1).

An effect modification between asthma history and pre-existing cardiovascular disease in relation to future MACE ( $p < 0.0001$ ) in the full included population was detected. Hence, the included patients were stratified into two separate cohorts based on diagnosis of cardiovascular disease before study entry.

### Propensity score matched cohort of severe MACE: primary outcome analysis

Both patients with pre-existing cardiovascular disease and patients without pre-existing cardiovascular disease were observed to have higher risks of severe MACE in patients with COPD and asthma compared to patients with COPD without asthma. In patients with pre-existing cardiovascular disease, the hazard ratio (HR) for asthma was 1.25 (95% CI 1.13–1.39,  $p < 0.0001$ ). Among the patients without pre-existing cardiovascular disease, the MACE hazard ratio for asthma was similar (1.22, 95% CI 1.06–1.41;  $p = 0.005$ ) (table 2). Sensitivity analysis using Gray's method confirmed the main result: a higher risk of severe MACE in patients with COPD and asthma compared to patients with COPD without asthma (HR 1.24, 95% CI 1.12–1.37;  $p < 0.0001$ ) in patients with pre-existing cardiovascular disease. Hazard ratio 1.17 (95% CI 1.02–1.35,  $p = 0.03$ ) in patients without pre-existing cardiovascular disease (figure 2).

TABLE 2 Primary end-point outcomes

	Patients with pre-existing cardiovascular disease		Patients without pre-existing cardiovascular disease	
	Patients with COPD and asthma	Patients with COPD without asthma	Patients with COPD and asthma	Patients with COPD without asthma
<b>Patients n</b>	3690	7236	6775	13 205
<b>Primary outcome</b>				
Severe MACE	591 (15.9)	978 (6.8)	301 (4.4)	550 (2.0)
HR (95% CI)	1.25 (1.13–1.39) <sup>#</sup>	Reference	1.22 (1.06–1.41)	Reference
<b>Secondary outcome</b>				
Any MACE	654 (17.6)	1093 (7.6)	388 (5.7)	696 (2.5)
HR (95% CI)	1.22 (1.11–1.34) <sup>#</sup>	Reference	1.22 (1.07–1.38)	Reference
<b>Severe MACE analysis</b>				
Lethal cardiovascular events	72 (1.9)	148 (1.0)	42 (0.6)	88 (0.3)
HR (95% CI)	1.14 (0.86–1.51)	Reference	1.09 (0.75–1.57)	Reference
Nonlethal cardiovascular events requiring revascularisation	102 (2.8)	152 (1.1)	45 (0.7)	113 (0.4)
HR (95% CI)	1.53 (1.19–1.97) <sup>#</sup>	Reference	0.92 (0.65–1.29)	Reference
Non-lethal cardiovascular events requiring admission	417 (11.2)	678 (4.7)	214 (3.1)	349 (1.3)
HR (95% CI)	1.28 (1.15–1.43) <sup>#</sup>	Reference	1.25 (1.08–1.45) <sup>#</sup>	Reference
<b>All-cause mortality (not MACE)</b>	843 (22.7)	1807 (12.5)	991 (14.5)	2169 (7.9)
HR (95% CI)	1.11 (1.03–1.21) <sup>#</sup>	Reference	1.06 (0.98–1.14)	Reference

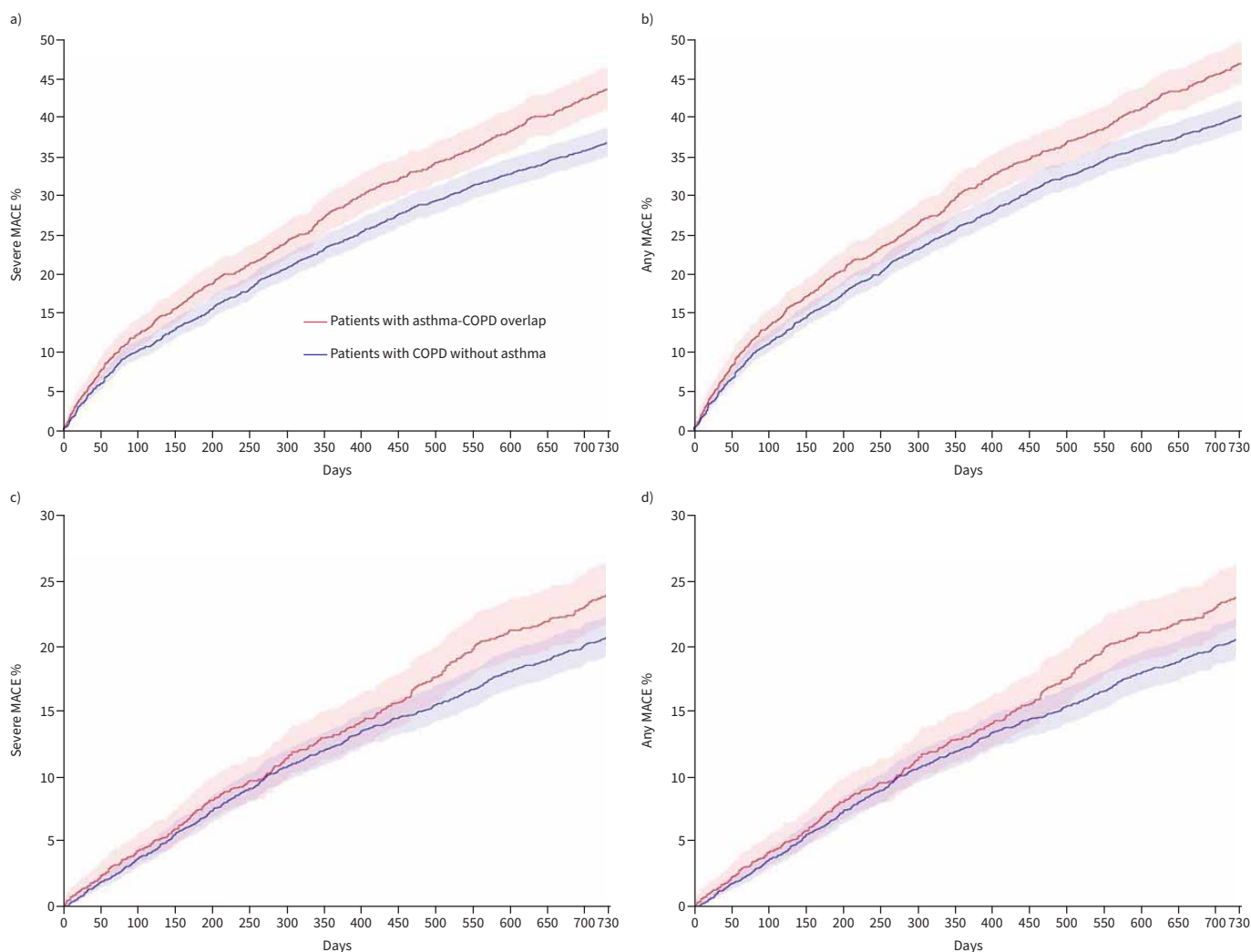
Data are presented as n (%), unless otherwise stated. Hazard ratios (HR) analysed by unadjusted Cox method with other cause mortality as a competing risk on the propensity-matched cohorts stratified by pre-existing cardiovascular disease. Patients with COPD and asthma and with COPD without asthma were propensity matched 1:2 by age, gender, tobacco exposure, Medical Research Council dyspnoea score, body mass index and forced expiratory volume in 1 s stratified into populations based on pre-existing cardiovascular disease. "Severe major adverse cardiac events (MACE)" defined as lethal cardiovascular events, and cardiovascular events requiring revascularisation or hospitalisation; "any MACE" defined as a severe MACE or an event requiring a prescription of ADP receptor inhibitors or nitrates. <sup>#</sup>: statistical significance  $> 0.95$  by regression analysis.

### Secondary outcome analysis: any MACE

Analysis of any MACE confirmed the risks estimates from the primary analysis (HR 1.22, 95% CI 1.11–1.34;  $p < 0.0001$ ) for patients with pre-existing cardiovascular disease and (HR 1.22, 95% CI 1.07–1.38;  $p = 0.002$ ) for patients without pre-existing cardiovascular disease (table 2).

### MACE outcome analysis

Among the patients with pre-existing cardiovascular disease, the risks of revascularisation (HR 1.53, 95% CI 1.19–1.97;  $p = 0.0009$ ) and cardiovascular hospitalisation (HR 1.28, 95% CI 1.15–1.43;  $p < 0.0001$ ) were increased, but cardiovascular mortality (HR 1.14, 95% CI 0.86–1.51;  $p = 0.36$ ) was not. Prescriptions of ADP receptor inhibitors and nitrates were not more frequent among patients with asthma (HR 1.14, 95% CI 0.86–1.52;  $p = 0.37$  and HR 1.23, 0.91–1.68;  $p = 0.18$ ). In the cohort without pre-existing cardiovascular disease, hospitalisation due to a severe MACE was increased (1.25, 95% CI 1.08–1.45;  $p = 0.003$ ), but



**FIGURE 2** Cumulated incidence plots of severe and any major adverse cardiac events (MACE) occurring in the propensity-matched cohorts stratified by pre-existing cardiovascular disease with other-cause mortality as a competing risk. Patients with COPD and asthma and with COPD without asthma were propensity matched 1:2 by age, gender, tobacco exposure, Medical Research Council dyspnoea score, body mass index and forced expiratory volume in 1 s stratified into populations based on pre-existing cardiovascular disease. “Severe MACE” was defined as lethal cardiovascular events, and cardiovascular events requiring revascularisation or hospitalisation; “any MACE” was defined as severe MACE or an event requiring a prescription of ADP receptor inhibitors or nitrates. **a)** Severe MACE in the propensity score matched cohort of patients with pre-existing cardiovascular disease ( $n = 10\,926$ ); **b)** any MACE in the propensity score matched cohort of patients with pre-existing cardiovascular disease ( $n = 10\,926$ ); **c)** severe MACE in the propensity score matched cohort of patients without pre-existing cardiovascular disease ( $n = 19\,980$ ); **d)** any MACE in the propensity score matched cohort of patients without pre-existing cardiovascular disease ( $n = 19\,980$ ).

revascularisation (HR 1.09, 95% CI 0.75–1.57;  $p=0.65$ ) and cardiovascular mortality (HR 0.92, 95% CI 0.65–1.29;  $p=0.61$ ) were not.

### Entire population

A multivariable model adjusted for the variables used for matching in the propensity-score match, and stratifying for pre-existing cardiovascular disease was carried out and is presented in table 3 and figure 3.

This analysis confirmed the results from the main analysis. Severe MACE was associated with asthma, both among patients with pre-existing cardiovascular disease (HR 1.22, 95% CI 1.11–1.34;  $p<0.0001$ ) and without pre-existing cardiovascular disease (HR 1.21, 95% CI 1.06–1.37;  $p=0.004$ ).

### ICS analysis

In the *post hoc* analysis on ICS association to MACE, 10 531 patients were available for analysis (all included patients with both COPD and asthma). Among these, 4117 patients were treated with high-dose ICS ( $\geq 947$   $\mu\text{g}$  daily budesonide equivalent dose) in the year before inclusion, and they were compared to the remaining 6414 patients treated with lower ICS dose. This analysis yielded a hazard ratio of 1.01 for severe MACE in patients treated with high-dose ICS (95% CI 0.81–1.27,  $p=0.90$ ).

### Analyses for possible confounders

In sensitivity analyses, diabetes and renal insufficiency were not associated with an increased risk of severe MACE (HR 1.02, 95% CI 0.94–1.10;  $p=0.68$  for diabetes; HR 0.98, 95% CI 0.91–1.06;  $p=0.65$  for renal insufficiency). Exacerbations in the year prior to inclusion were associated to severe MACE (HR 1.14, 95% CI 1.06–1.22;  $p=0.0006$ ); however, even when analysing exacerbations, asthma remained associated with severe MACE (HR 1.36, 95% CI 1.25–1.47;  $p<0.0001$ ).

### Discussion

Patients with COPD have a substantially increased risk of cardiovascular events if they also have asthma. The risk associated to asthma pointed in the same direction among patients with COPD with and without pre-existing cardiovascular disease, with a signal of an increased risk of 20–25%.

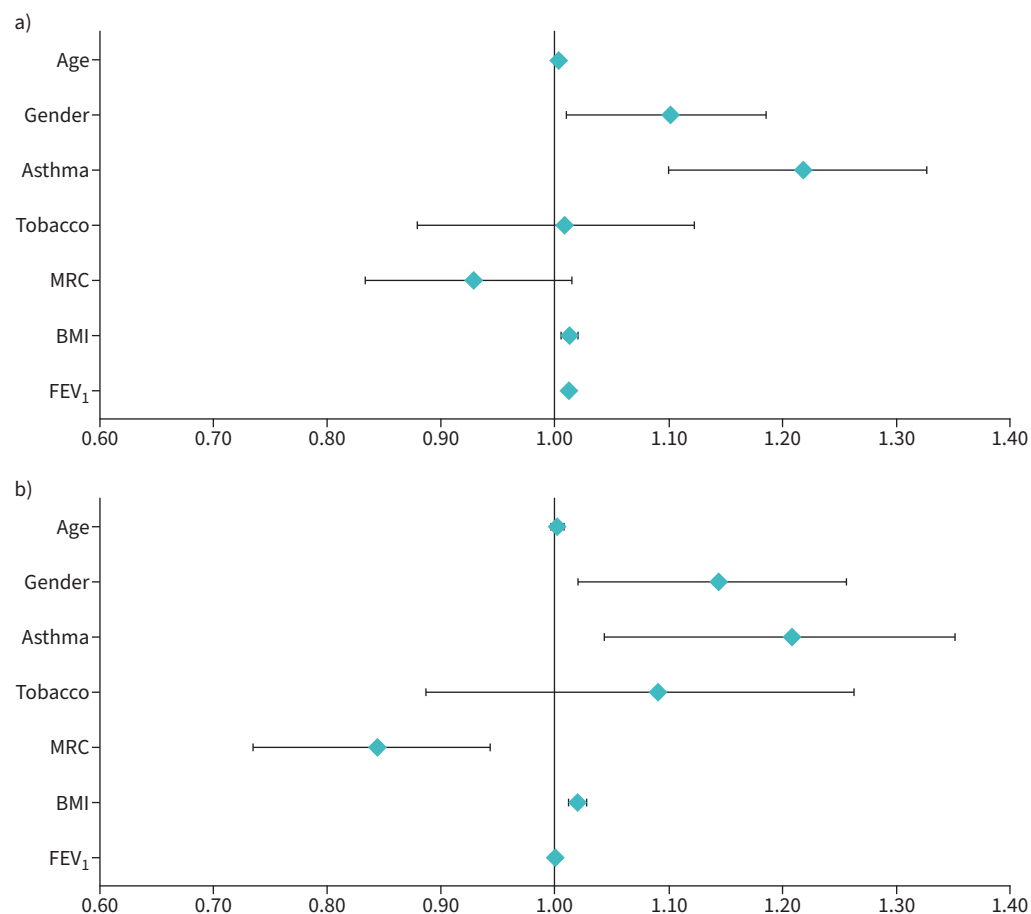
In a *post hoc* analysis, we decided to explore whether the increased risk of MACE could be reversed by use of ICS. This did not seem to be the case.

TABLE 3 Secondary outcomes

	Patients with pre-existing cardiovascular disease		Patients without pre-existing cardiovascular disease	
	Patients with COPD and asthma	Patients with COPD without asthma	Patients with COPD and asthma	Patients with COPD without asthma
<b>Patients</b>	3707	14 469	6824	27 386
<b>Severe MACE</b>	593 (16.0)	1984 (13.7)	302 (4.4)	1240 (4.5)
HR (95% CI)	1.22 (1.11–1.34) <sup>#</sup>	Reference	1.21 (1.06–1.37) <sup>#</sup>	Reference
<b>Any MACE</b>	661 (17.8)	2270 (15.7)	519 (7.6)	2109 (7.7)
HR (95% CI)	1.10 (0.86–1.40)	Reference	1.26 (1.10–1.45) <sup>#</sup>	Reference
<b>Severe MACE subunit analysis</b>				
Lethal cardiovascular events	72 (1.9)	317 (2.2)	42 (0.6)	218 (0.8)
HR (95% CI)	1.16 (0.89–1.50)	Reference	1.06 (0.76–1.48)	Reference
Nonlethal cardiovascular events requiring revascularisation	102 (2.8)	314 (2.2)	45 (0.7)	249 (0.9)
HR (95% CI)	1.51 (1.21–1.90) <sup>#</sup>	Reference	0.98 (0.71–1.35)	Reference
Nonlethal cardiovascular events requiring admission	419 (11.3)	1353 (9.4)	215 (3.2)	737 (2.7)
HR (95% CI)	1.23 (1.12–1.36) <sup>#</sup>	Reference	1.25 (1.09–1.43)	Reference
<b>All-cause mortality (not MACE)</b>	843 (22.7)	3914 (27.1)	993 (14.6)	5422 (19.8)
HR (95% CI)	1.08 (1.00–1.17) <sup>#</sup>	Reference	1.02 (0.95–1.09)	Reference

Data are presented as n (%), unless otherwise stated. Hazard ratios by Cox analysis with other cause mortality as a competing risk adjusting for age, gender, tobacco exposure, Medical Research Council dyspnoea score, body mass index and forced expiratory volume in 1 s on cohorts of all included patients stratified by pre-existing cardiovascular disease. “Severe major adverse cardiac events (MACE)” defined as lethal cardiovascular events, and cardiovascular events requiring revascularisation or hospitalisation; “any MACE” defined as a severe MACE or an event requiring a prescription of ADP receptor inhibitors or nitrates. <sup>#</sup>: statistical significance  $>0.95$  by regression analysis.





**FIGURE 3** Forest plots showing hazard ratios for severe major adverse cardiac events (MACE) in cohorts of all included patients with COPD and asthma compared to patients with COPD without asthma stratified by pre-existing cardiovascular disease. Hazard ratios were calculated by adjusted Cox analysis. **a)** Patients with pre-existing cardiovascular disease (n=18 176). **b)** Patients without pre-existing cardiovascular disease (n=34 210). Age, body mass index (BMI) and forced expiratory volume in 1 s (FEV<sub>1</sub>) were analysed as continuous variables; gender, asthma, tobacco exposure and Medical Research Council (MRC) dyspnoea score as binary variables. For tobacco exposure, current and previous smokers were compared to never-smokers, passive smokers and patients with unknown smoking status (the latter comprising 9.1% of patients with prior cardiovascular disease and 8.5% in patients without prior cardiovascular disease). Patients with MRC  $\geq 3$  were compared to patients with MRC  $\leq 2$ .

Only one study has previously assessed the prevalence of cardiovascular disease in patients with asthma and COPD compared to COPD alone. It was a cross-sectional study examining 299 patients with COPD and asthma, in comparison to age-matched patients with COPD alone. It did not take pre-existing cardiovascular disease into account, and in that study it was found that patients with COPD and asthma were more likely to have a higher prevalence of diabetes and coronary heart disease [15].

Among all the studies executed in this field, none adjusted for smoking, despite smoking being highly associated with cardiovascular events. Most diagnoses were not specialist-verified; most were cross-sectional, although two had follow-up, one up to 15 years [15–19]. In contrast, our study had a large sample size of unselected patients (all patients in Danish COPD outpatient clinics), and complete follow-up throughout the observation period. The patients in COPD outpatient clinics in Denmark visit a respiratory medicine specialist at least annually, and the diagnoses of COPD and asthma are thus confirmed by specialists and supported by spirometry, and prescription collection history was compatible with diagnoses of obstructive pulmonary disease. Furthermore, we could control for several important confounders such as smoking status, spirometry measures, BMI and age, since these are meticulously registered. MACE-defining events are all registered in Danish national databases, and as such, in reality, these events cannot happen without being detected.

Despite the strengths, some limitations to our study need careful consideration. First, even though we had full follow-up and information on confounders, there is a risk of residual confounding, specifically from unknown and unregistered confounders. Second, due to the observational nature of this study, a causal relationship can only be speculated and indicated, not confirmed, although there is a relevant biological plausibility of a causal relationship. Third, some of our data were available only as categorical data, although it would have been preferred to have continuous data, e.g. tobacco exposure quantified in pack-years. However, existing literature has long reported a linear correlation between lifelong cumulated tobacco exposure and decline in FEV<sub>1</sub> % [28], and hence in a large epidemiological study such as ours, spirometric values can be used as a suitable proxy for tobacco exposure. Fourth, in almost 10% of the patients, data were not complete on FEV<sub>1</sub> %, MRC dyspnoea score, BMI values or tobacco exposure. Thus, we had to impute these values; this may have influenced the results, although the low number of missing values would not indicate a signal change, if data were available.

In our study, exacerbations in the year prior to inclusion was slightly more frequent in patients with asthma and COPD compared to patients with COPD without asthma; this was the case both in patients with pre-existing cardiovascular disease and in patients without. This is a known phenomenon in patients with asthma and COPD compared to patients with COPD without asthma [29–32]; however, it is not a known risk factor for MACE, and hence was not anticipated as a confounder or included in the propensity score match in our study. In addition, diabetes and renal insufficiency are both associated with alterations to the immune system and may affect inflammation level [33, 34]. Similarly, previous exacerbations may be associated to inflammation; however, none of these weakened the signal for asthma in our study.

We stratified the analyses for whether the patient was registered with a diagnosis of cardiovascular disease, and thus, even if there were some differences in baseline characteristics between patients with pre-existing cardiovascular disease and patients without pre-existing cardiovascular disease, this could not have influenced the analyses. In conclusion, among patients with COPD, asthma as a comorbid condition is associated with substantially increased risk of cardiovascular events. The inflammation associated with asthma can help explain biologically that this could be a real causative relationship. If our findings are confirmed in other studies, it can be expected that this risk can be modified by administering immunomodulatory drugs.

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