# Major cardiovascular events in patients with severe chronic obstructive pulmonary disease with and without asthma: a nationwide cohort study

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# Abstract

**Background:** Chronic low-grade inflammation as in asthma may lead to a higher risk of cardiovascular events. We evaluated if patients with chronic obstructive pulmonary disease (COPD) and asthma have a higher risk of acute cardiovascular events than patients with COPD without asthma.

**Methods:** Nationwide multi-center 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 endpoint was severe major adverse cardiac events (MACE), defined as mortal cardiovascular events and events requiring revascularization or hospitalization.

**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: 3,690 patients with COPD and asthma vs. 7,236 patients with COPD without asthma. Similarly, for patients without pre-existing cardiovascular disease (6,775 matched with 13,205).

The risk of MACE was higher among patients with asthma and COPD vs. COPD without asthma: Hazard ratio (HR): 1.25 (CI 1.13-1.39, p<0.0001) for patients with pre-existing cardiovascular disease and HR 1.22 (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.

**Key words:** COPD, asthma, cardiovascular disease, Ischemic heart disease, Ischemic stroke, MACE

# 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]. Randomized clinical trials have even shown that inhibition of Interleukin-1$\beta$ by Canakinumab [13] and of tubulin by Colchicine [14] reduces the risk of ischemic heart disease, thus proving that low-grade inflammation plays a causative role in the development of ischemic 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 for 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 like age, smoking status, $FEV_1$% (forced expired volume in the first second) and co-morbidities. Our hypothesis was that patients who in addition to COPD also have asthma have an increased risk of cardiovascular events.

# Methods

**Study design**

A nationwide multicenter 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 $FEV_1$% predicted, BMI (body mass index) assessed as kilograms per square meter, dyspnea assessed using the Medical Research Council (MRC) Dyspnea Scale, and smoking status.

2. All citizens in Denmark acquire a unique personal identification number at birth or 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 is 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 ATC classification), including date 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 older than 30 years registered with a COPD diagnosis by a pulmonary specialist in an outpatient clinic during the period January 1$^{st}$ 2010 to June 24$^{th}$ 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 $FEV_1\% > 80\%$ 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 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 ischemia (DG45, DI20, DI21, DI22, DI23, or DI24), or having been subjected to surgery for cardiac ischemia (all revascularization codes; KFNA00, KFNA20, KFNC10-30, KFNE00, KFNG02, KFNG02A, KFNG05, or KFNG05A), or been prescribed ischemia-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 fulfill 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 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, and $FEV_1$% as percent of predicted [24].

**Baseline characteristics**

Demographic variables, comorbidities and medical therapy were registered.

**Follow-up**

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

Loss to follow-up was seldom in all investigated groups: In total $N$=69 (0.2%) 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 revascularization (surgery diagnosed as KFNA00, KFNA20, KFNC10-30, KFNE00, KFNG02, KFNG02A, KFNG05, or KFNG05A), cardiovascular events requiring admission (hospitalization diagnosed as DG45, DI20, DI21, DI22, DI23, or DI24), and cardiovascular events requiring prescriptions of ADP receptor inhibitors or nitrates. Additionally, a composite endpoint of lethal cardiovascular events, cardiovascular events requiring revascularization, and cardiovascular events requiring admission was labeled severe MACE [25], and a composite endpoint of all before-mentioned cardio-vascular events including prescriptions of ADP receptor inhibitors, and nitrates was labeled 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 will most often be specialist verified in a Danish hospital setting.

**ICS analysis**

For the post hoc analysis on ICS we divided patients into two groups: High dose ICS (budesonide equivalent dose ≥ 947 µg daily) was compared to ICS dosage of budesonide equivalent dose < 947 µg 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 [26]) 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 $FEV_1\%$ (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 [27]. We used the propensity score matching method developed by the Mayo clinic (Greedy match). The rigor of the matching allowed for slightly fewer than 2 controls per case.

Baseline characteristics were compared by chi-square test. Cox regression model and Grays 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 minimize 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 endpoint was severe MACE, and our secondary endpoints was any MACE, as well as events analyzed on other cohorts than the propensity scored groups and cumulative incidence curves analyzed by Grays analysis. As some patients had more than one event during the follow-up period, only the first event was counted. The endpoints were analyzed by Cox regression analysis with non-cardiovascular mortality as competing risk and by cumulative incidence curves and Grays analysis.

The primary analysis was unadjusted Cox analysis of Severe MACE among propensity score matched groups of patients with COPD and asthma vs. 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 visualized by 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 $FEV_1\%$).

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 $FEV_1\%$). 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. A two-sided 95% confidence interval was considered statistically significant. Cumulative Incidence plots were customized by the NewSurv macro [28].

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 ischemia, or having been subjected to surgery for cardiac ischemia (all revascularization codes), or been prescribed ischemia-related medication (nitroglycerine and antithrombotic treatment), they were designated to a group with pre-existing cardiovascular illness. All patients who did not fulfill 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.

# Results:

A total of 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, 3,690 patients with COPD and asthma were propensity matched 1:2 with 7,236 patients with COPD without asthma. Among patients who did not have pre-existing cardiovascular disease, 6,775 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 vs. 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% vs. 3.6%, p<0.0001 among patients with pre-existing cardiovascular disease and 15.4% vs. 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 HR for asthma was 1.25 (CI 1.13-1.39, p<0.0001). Among the patients without pre-existing cardiovascular disease, the MACE HR for asthma was similar (HR 1.22, CI 1.06-1.41, p=0.005), table 2. Sensitivity analysis using Grays 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, CI 1.12-1.37,p<0.0001) in patients with pre-existing cardiovascular disease, and HR 1.17 (CI 1.02-1.35, p=0.03) in patients without pre-existing cardiovascular disease, figure 2.

*Secondary outcome analysis – any MACE*

Analysis of *any MACE* confirmed the risks estimates from the primary analysis (HR 1.22, CI 1.11-1.34, p<0.0001) for patients with pre-existing cardiovascular disease and (HR 1.22, 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 risk of revascularization (HR 1.53, CI 1.19-1.97, p=0.0009) and cardiovascular hospitalization (HR 1.28, CI 1.15-1.43, p<0.0001) was increased, but not cardiovascular mortality (HR 1.14, CI 0.86-1.51, p=0.36). Prescriptions of ADP receptor inhibitors and nitrates were not more frequent among patients with asthma (HR 1.14, 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 hospitalization due to a severe MACE was increased (1.25, CI 1.08-1.45, p=0.003), but not revascularization (HR 1.09, CI 0.75-1.57, p=0.65) or cardiovascular mortality (HR 0.92, CI 0.65-1.29, p=0.61).

*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 depicted 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, CI 1.11-1.34, p<0.0001) and without pre-existing cardiovascular disease (HR 1.21, 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 4,117 patients were treated with high dose ICS (≥ 947 µg daily budesonide equivalent dose) in the year before inclusion, and they were compared to the remaining 6,414 patients treated with lower ICS dose. This analysis yielded a HR of 1.01 for severe MACE in patients treated with high dose ICS (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 CI 0.94-1.10 p=0.68 for diabetes, HR 0.98 CI 0.91-1.06, p=0.65 for renal insufficiency). Exacerbations in the year prior to inclusion was associated to severe MACE (HR 1.14 CI 1.06-1.22, p=0.0006), however even when analyzing exacerbations, asthma remained associated with severe MACE (HR 1.36 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 hos analysis, we decided to explore if the increased risk of MACE could be reversed by use of inhaled corticosteroids. This did not seem to be the case.

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 is highly associated with cardiovascular events. Most diagnoses were not specialist verified, most were cross-sectional, though 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 our country´s COPD outpatient clinics visit a respiratory medicine specialist at least annually, and the diagnoses of COPD and asthma are thus specialist confirmed, spirometry supported, and prescription collection history was compatible with diagnoses of obstructive pulmonary disease. Further, we could control for several important confounders like smoking status, spirometry measures, BMI, and age, since these are meticulously registered. MACE-defining events are all registered in our national databases, and as such, these events can in reality not 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 $FEV_1\%$ [29], and hence in a large epidemiological study 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 $FEV_1\%$, MRC, BMI values or tobacco exposure. We thus 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 was 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 [30-33], 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. Especially diabetes and renal insufficiency are also both associated with alterations to the

immune system and may affect inflammation level [34, 35]. 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 and patients without preexisting 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 biologically explain 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.

## Conflict of interest statement:

## Funding:

## References

1. Decramer, M., W. Janssens, and M. Miravitlles, *Chronic obstructive pulmonary disease.* Lancet, 2012. **379**(9823): p. 1341-51.
2. Curkendall, S.M., et al., *Cardiovascular disease in patients with chronic obstructive pulmonary disease, Saskatchewan Canada cardiovascular disease in COPD patients.* Ann Epidemiol, 2006. **16**(1): p. 63-70.
3. Agarwal, S.K., et al., *Airflow obstruction, lung function, and risk of incident heart failure: the Atherosclerosis Risk in Communities (ARIC) study.* Eur J Heart Fail, 2012. **14**(4): p. 414-22.
4. Takemura, M., et al., *High sensitivity C-reactive protein in asthma.* Eur Respir J, 2006. **27**(5): p. 908-12.
5. Yun, H.D., et al., *Asthma and proinflammatory conditions: a population-based retrospective matched cohort study.* Mayo Clin Proc, 2012. **87**(10): p. 953-60.
6. Cepelis, A., et al., *Asthma, asthma control and risk of acute myocardial infarction: HUNT study.* Eur J Epidemiol, 2019. **34**(10): p. 967-977.
7. Tattersall, M.C., et al., *Asthma predicts cardiovascular disease events: the multi-ethnic study of atherosclerosis.* Arterioscler Thromb Vasc Biol, 2015. **35**(6): p. 1520-5.
8. Chung, W.S., et al., *Increased stroke risk among adult asthmatic patients.* Eur J Clin Invest, 2014. **44**(11): p. 1025-33.

9.  Sneeboer, M.M.S., et al., *Prothrombotic state in patients with severe and prednisolone-dependent asthma.* J Allergy Clin Immunol, 2016. **137**(6): p. 1727-1732.

10. Strand, L.B., et al., *Is having asthma associated with an increased risk of dying from cardiovascular disease? A prospective cohort study of 446 346 Taiwanese adults.* BMJ Open, 2018. **8**(5): p. e019992.

11. Odeberg, J., et al., *Influence of pre-existing inflammation on the outcome of acute coronary syndrome: a cross-sectional study.* BMJ Open, 2016. **6**(1): p. e009968.

12. Bonnesen, B., Sivapalan, P., Jordan, A., Pedersen, JW., Bergsoe, CM., Eklöf, J., Toennesen, LL., Jensen, SG., Naqibullah, M., Saghir, Z., Jensen, JS., *Risk of Malignancy in Patients with Asthma-COPD Overlap Compared to Patients with COPD without Asthma.* Biomedicines, 2022. **10**(7): p. 1463-75.

13. Ridker, P.M., et al., *Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease.* N Engl J Med, 2017. **377**(12): p. 1119-1131.

14. Tardif, J.C., et al., *Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction.* N Engl J Med, 2019. **381**(26): p. 2497-2505.

15. Llanos, J.P., et al., *Health characteristics of patients with asthma, COPD and asthma-COPD overlap in the NHANES database.* Int J Chron Obstruct Pulmon Dis, 2018. **13**: p. 2859-2868.

16. Pleasants, R.A., et al., *Chronic obstructive pulmonary disease and asthma-patient characteristics and health impairment.* COPD, 2014. **11**(3): p. 256-66.

17. Senthilselvan, A. and J. Beach, *Characteristics of asthma and COPD overlap syndrome (ACOS) in the Canadian population.* J Asthma, 2019. **56**(11): p. 1129-1137.

18. Yeh, J.J., et al., *Association of asthma-chronic obstructive pulmonary disease overlap syndrome with coronary artery disease, cardiac dysrhythmia and heart failure: a population-based retrospective cohort study.* BMJ Open, 2017. **7**(10): p. e017657.

19. Kumbhare, S. and C. Strange, *Mortality in Asthma-Chronic Obstructive Pulmonary Disease Overlap in the United States.* South Med J, 2018. **111**(5): p. 293-298.

20. Lange, P., et al., *Danish Register of chronic obstructive pulmonary disease.* Clin Epidemiol, 2016. **8**: p. 673-678.

21. Schmidt, M., L. Pedersen, and H.T. Sorensen, *The Danish Civil Registration System as a tool in epidemiology.* Eur J Epidemiol, 2014. **29**(8): p. 541-9.

22. Ehrenstein, V., S. Antonsen, and L. Pedersen, *Existing data sources for clinical epidemiology: Aarhus University Prescription Database.* Clin Epidemiol, 2010. **2**: p. 273-9.

23. Schmidt, M., et al., *The Danish National Patient Registry: a review of content, data quality, and research potential.* Clin Epidemiol, 2015. **7**: p. 449-90.

24. Miller, M.R., et al., *Standardisation of spirometry.* Eur Respir J, 2005. **26**(2): p. 319-38.

25. Ducrocq, G., et al., *Effect of a Restrictive vs Liberal Blood Transfusion Strategy on Major Cardiovascular Events Among Patients With Acute Myocardial Infarction and Anemia: The REALITY Randomized Clinical Trial.* JAMA, 2021. **325**(6): p. 552-560.

26. Research, D.o.Q.H.S.M.C. *http://bioinformaticstools.mayo.edu/research/gmatch/*. 2022 [cited 2022 21.1].

27. Groenwold, R.H., et al., *Balance measures for propensity score methods: a clinical example on beta-agonist use and the risk of myocardial infarction.* Pharmacoepidemiol Drug Saf, 2011. **20**(11): p. 1130-7.

28. Meyers, J., *NewSurv macro.* https://communities.sas.com/t5/SAS-Communities-Library/Kaplan-Meier-Survival-Plotting-Macro-NEWSURV/ta-p/479747, 2021.

29. Dockery, D.W., et al., *Cumulative and reversible effects of lifetime smoking on simple tests of lung function in adults.* Am Rev Respir Dis, 1988. **137**(2): p. 286-92.

30. Alshabanat, A., et al., *Asthma and COPD Overlap Syndrome (ACOS): A Systematic Review and Meta Analysis.* PLoS One, 2015. **10**(9): p. e0136065.

31. Leung, J.M. and D.D. Sin, *Asthma-COPD overlap syndrome: pathogenesis, clinical features, and therapeutic targets.* BMJ, 2017. **358**: p. j3772.
32. Kim, M., et al., *Association between asthma/chronic obstructive pulmonary disease overlap syndrome and healthcare utilization among the US adult population.* Curr Med Res Opin, 2019. **35**(7): p. 1191-1196.
33. Barrecheguren, M., et al., *Identification and definition of asthma-COPD overlap: The CanCOLD study.* Respirology, 2020. **25**(8): p. 836-849.
34. Pradhan, A.D., et al., *Effects of initiating insulin and metformin on glycemic control and inflammatory biomarkers among patients with type 2 diabetes: the LANCET randomized trial.* JAMA, 2009. **302**(11): p. 1186-94.
35. Steiger, S., et al., *Secondary Immunodeficiency Related to Kidney Disease (SIDKD)-Definition, Unmet Need, and Mechanisms.* J Am Soc Nephrol, 2022. **33**(2): p. 259-278.

**Table 1**

| Characteristic | Patients with pre-existing cardiovascular disease | | Patients without pre-existing cardiovascular disease | |
|---|---|---|---|---|
| | Patients with COPD and asthma ($N$ = 3,690) | Patients with COPD without asthma ($N$ = 7,236) | Patients with COPD and asthma ($N$ = 6,775) | Patients with COPD without asthma ($N$ = 13,205) |
| Age, years | 72.4 (65.2 – 79.1) | 72.6 (65.7 – 78.9) | 66.2 (57.1 – 74.7) | 66.4 (58.4 – 74.3) |
| Gender, female | 2,058 (55.8) | 3,989 (55.1) | 4,024 (59.4) | 7,761 (58.8) |
| Tobacco exposure: 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 | 2,156 (58.4) | 4,529 (62.6) | 3,675 (54.2) | 7,367 (55.8) |
| Active smoking | 981 (26.6) | 1,998 (27.6) | 2,217 (32.7) | 4,581 (34.7) |
| Unknown tobacco exposure | 333 (9.0) | 468 (6.5) | 548 (8.1) | 825 (6.2) |
| MRC | 3 (3 – 4) | 3 (3 – 4) | 3 (2 – 3) | 3 (2 – 4) |
| BMI | 25 (23 – 29) | 25 (22 – 30) | 25 (22 - 29) | 25 (21 - 29) |
| $FEV_1\%$ | 49 (37 - 61) | 49 (37 - 61) | 49 (36 - 61) | 49 (35 - 61) |
| Comorbidities: Hypertension | 1,898 (51.4) | 3,622 (50.1) | 1,525 (22.5) | 2,872 (21.7) |
| Hypercholesterolemia | 1,018 (27.6) | 2,188 (30.2) | 326 (4.8) | 571 (4.3) |
| Atrial fibrillation | 864 (23.4) | 1,695 (23.4) | 618 (9.1) | 1,261 (9.5) |
| Diabetes | 724 (19.6) | 1,305 (18.0) | 660 (9.7) | 1,136 (8.6) |
| Osteoporosis or osteopenia | 1,013 (27.5) | 1,584 (21.9) | 1,438 (21.2) | 2,339 (17.7) |
| Renal insufficiency | 2,017 (54.7) | 3,843 (53.1) | 1,807 (26.7) | 3,338 (25.3) |
| Liver insufficiency | 114 (3.1) | 258 (3.6) | 210 (3.1) | 372 (2.8) |
| Malignancy | 854 (23.1) | 1,561 (21.6) | 1,131 (16.7) | 2,111 (16.0) |
| Atopy or allergy | 562 (15.2) | 264 (3.6) | 1,042 (15.4) | 377 (2.9) |
| Depression | 292 (7.9) | 442 (6.1) | 333 (4.9) | 516 (3.9) |
| Exacerbations requiring admission within the last year prior to inclusion | 1,426 (38.6) | 2,334 (32.3) | 2,146 (31.7) | 3,613 (27.4) |

| | | | | |
|---|---|---|---|---|
| Medical treatment for respiratory disease within the last year prior to inclusion: | | | | |
| Oral corticosteroid | 2,207 (59.8) | 3,113 (43.0) | 3,703 (54.7) | 5,276 (40.0) |
| Inhaled corticosteroid (ICS) | 3,252 (88.1) | 4,892 (67.6) | 5,983 (88.3) | 8,887 (67.3) |
| Long acting β2-agonist (LABA) | 3,253 (88.2) | 5,435 (75.1) | 5,920 (87.4) | 9,736 (73.7) |
| Long acting muscarinic receptor antagonist (LAMA) | 2,715 (73.6) | 5,167 (71.4) | 4,730 (69.8) | 9,074 (68.7) |
| Short acting β2-agonist (SABA) | 2,905 (78.7) | 4,590 (63.4) | 5,172 (76.3) | 8,194 (62.1) |
| Short acting muscarinic receptor antagonist (SAMA) | 208 (5.6) | 249 (3.4) | 250 (3.7) | 357 (2.7) |
| Medical treatment for cardiovascular disease within the last year prior to inclusion: | | | | |
| Blood pressure medication | 3,070 (83.2) | 6,212 (85.8) | 3,739 (55.2) | 7,631 (57.8) |
| Cholesterol lowering medication | 2,080 (56.4) | 4,458 (61.6) | 1,403 (20.7) | 3,157 (23.9) |
| ADP-receptor inhibitors | 666 (18.0) | 1,532 (21.2) | N/A | N/A |
| Acetyl sialic acid | 1,841 (49.9) | 3,838 (53.0) | 1,002 (14.8) | 2,213 (16.8) |
| Nitrates | 964 (26.1) | 1,799 (24.9) | N/A | N/A |
| Medical treatment for diabetes within the last year prior to inclusion: | | | | |
| Insulin | 229 (6.2) | 448 (6.2) | 225 (3.3) | 392 (3.0) |
| Non-insulin antidiabetics | 637 (17.3) | 1,185 (16.4) | 657 (9.7) | 1,311 (9.9) |

Baseline characteristics of 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, MRC, BMI, and $FEV_1\%$ stratified into populations based on pre-existing cardiovascular disease.

Characteristics are presented as medians and absolute numbers as relevant with interquartile ranges and percentages in parenthesis.

**Table 2**

| Endpoint | Patients with pre-existing cardiovascular disease | | Patients without pre-existing cardiovascular disease | |
|---|---|---|---|---|
| | Patients with COPD and asthma (N = 3,690) | Patients with COPD without asthma (N = 7,236) | Patients with COPD and asthma (N = 6,775) | Patients with COPD without asthma (N = 13,205) |
| **Primary outcome** Severe MACE | | | | |
| N (%) | 591 (15.9) | 978 (6.8) | 301 (4.4) | 550 (2.0) |
| [#]HR | 1.25 (1.13 – 1.39)* | Reference | 1.22 (1.06 – 1.41) | Reference |
| **Secondary outcome** Any MACE | | | | |
| N (%) | 654 (17.6) | 1,093 (7.6) | 388 (5.7) | 696 (2.5) |
| [#]HR | 1.22 (1.11 – 1.34)* | Reference | 1.22 (1.07 – 1.38) | Reference |
| **Severe MACE analysis** | | | | |
| Lethal cardiovascular events | | | | |
| N (%) | 72 (1.9) | 148 (1.0) | 42 (0.6) | 88 (0.3) |
| [#]HR | 1.14 (0.86 – 1.51) | Reference | 1.09 (0.75 – 1.57) | Reference |
| Non-lethal cardiovascular events | | | | |

| Endpoint | | | | |
|---|---|---|---|---|
| requiring revascularization<br>N (%)<br>#HR | 102 (2.8)<br>1.53 (1.19 – 1.97)* | 152 (1.1)<br>Reference | 45 (0.7)<br>0.92 (0.65 – 1.29) | 113 (0.4)<br>Reference |
| Non-lethal cardiovascular events requiring admission<br>N (%)<br>#HR | 417 (11.2)<br>1.28 (1.15 – 1.43)* | 678 (4.7)<br>Reference | 214 (3.1)<br>1.25 (1.08 – 1.45)* | 349 (1.3)<br>Reference |
| **All-cause mortality** (not MACE)<br>N (%)<br>#HR | 843 (22.7)<br>1.11 (1.03 – 1.21)* | 1,807 (12.5)<br>Reference | 991 (14.5)<br>1.06 (0.98 – 1.14) | 2,169 (7.9)<br>Reference |

Primary endpoint outcomes.

Hazard ratios analyzed by unadjusted Cox 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, MRC, BMI and $FEV_1$% stratified into populations based on pre-existing cardiovascular disease.

Severe MACE defined as lethal cardiovascular events, and cardiovascular events requiring revascularization or hospitalization. Any MACE defined as a severe MACE or an event requiring a prescription of ADP receptor inhibitors or nitrates.

Results are presented as absolute numbers and ratios as relevant with percentages and 95 % confidence intervals in parenthesis. * indicates statistical significance > 0.95 by regression analysis.

**Table 3**

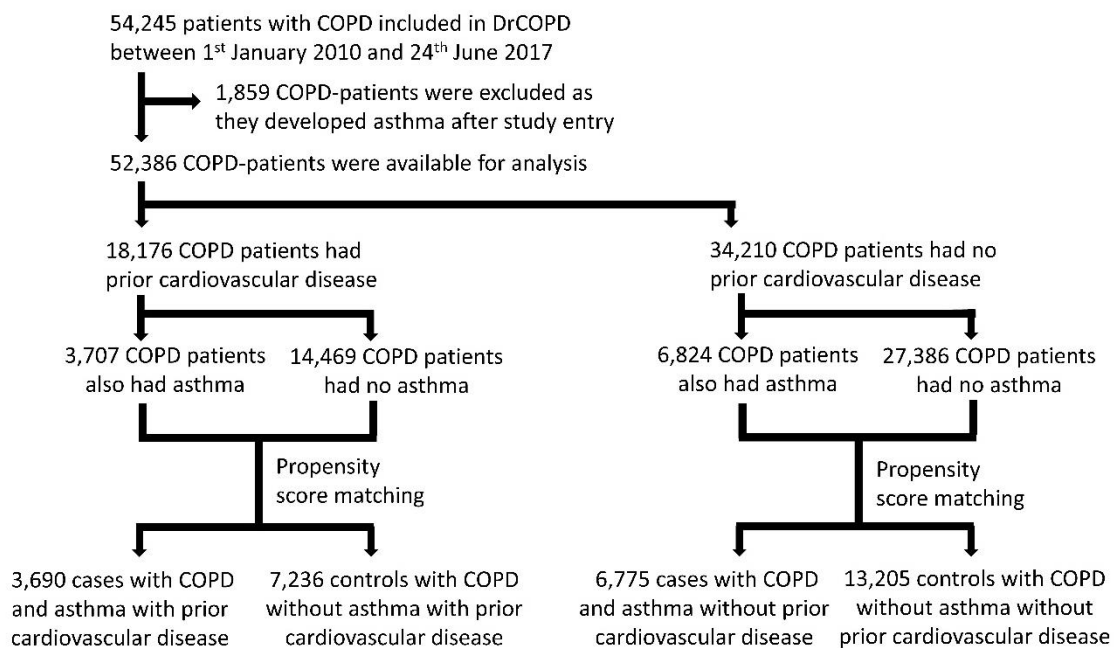| Endpoint | Patients with pre-existing cardiovascular disease | | Patients without pre-existing cardiovascular disease | |
|---|---|---|---|---|
| | Patients with COPD and asthma (N = 3,707) | Patients with COPD without asthma (N = 14,469) | Patients with COPD and asthma (N = 6,824) | Patients with COPD without asthma (N = 27,386) |
| **Severe MACE**<br>N (%)<br>#HR | 593 (16.0)<br>1.22 (1.11 – 1.34)* | 1,984 (13.7)<br>Reference | 302 (4.4)<br>1.21 (1.06 – 1.37)* | 1,240 (4.5)<br>Reference |
| **Any MACE**<br>N (%)<br>#HR | 661 (17.8)<br>1.10 (0.86-1.40) | 2,270 (15.7)<br>Reference | 519 (7.6)<br>1.26 (1.10 – 1.45)* | 2,109 (7.7)<br>Reference |
| **Severe MACE subunit analysis** | | | | |
| Lethal cardiovascular events<br>N (%)<br>#HR | 72 (1.9)<br>1.16 (0.89 – 1.50) | 317 (2.2)<br>Reference | 42 (0.6)<br>1.06 (0.76-1.48) | 218 (0.8)<br>Reference |
| Non-lethal cardiovascular events requiring revascularization<br>N (%)<br>#HR | 102 (2.8)<br>1.51 (1.21 – 1.90)* | 314 (2.2)<br>Reference | 45 (0.7)<br>0.98 (0.71 – 1.35) | 249 (0.9)<br>Reference |
| Non-lethal cardiovascular events requiring admission<br>N (%)<br>#HR | 419 (11.3)<br>1.23 (1.12 – 1.36)* | 1,353 (9.4)<br>Reference | 215 (3.2)<br>1.25 (1.09 – 1.43) | 737 (2.7)<br>Reference |
| **All-cause mortality** (not MACE)<br>N (%)<br>#HR | 843 (22.7)<br>1.08 (1.00 – 1.17)* | 3,914 (27.1)<br>Reference | 993 (14.6)<br>1.02 (0.95 – 1.09) | 5422 (19.8)<br>Reference |

Secondary outcomes

Hazard ratios by Cox analysis with other cause mortality as a competing risk adjusting for age, gender, tobacco exposure, MRC, BMI, and $FEV_1\%$ on cohorts of all included patients stratified by pre-existing cardiovascular disease. Severe MACE defined as lethal cardiovascular events and cardiovascular events requiring revascularization or hospitalization.

Any MACE was defined as a severe MACE or an event requiring a prescription of ADP receptor inhibitors or nitrates.

Results are presented as absolute numbers and ratios as relevant with percentages and 95 % confidence intervals in parenthesis.
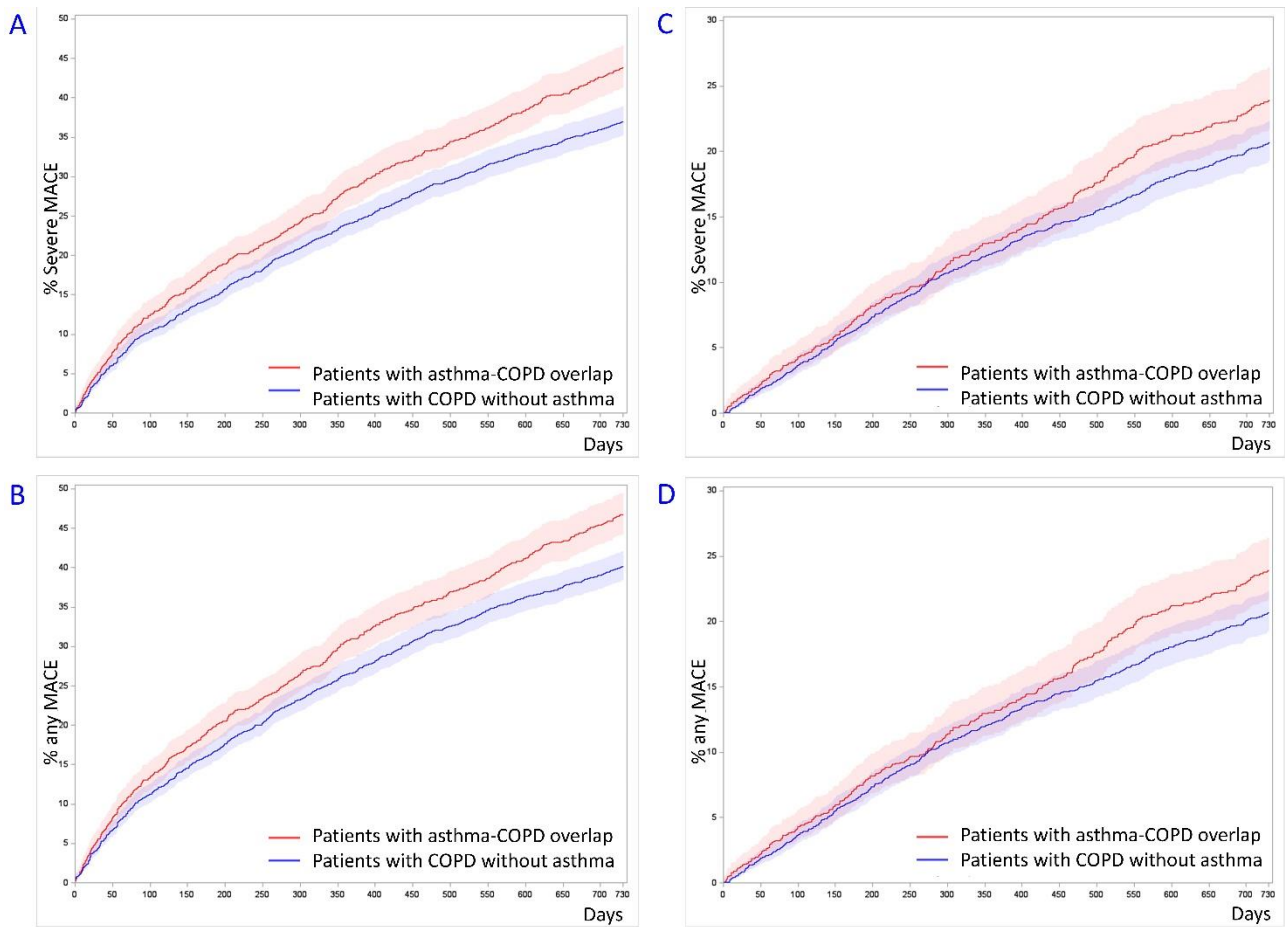
* indicates statistical significance > 0.95 by regression analysis.

Figure 1



54,245 patients with COPD included in DrCOPD
between 1st January 2010 and 24th June 2017

1,859 COPD-patients were excluded as
they developed asthma after study entry

52,386 COPD-patients were available for analysis

18,176 COPD patients had
prior cardiovascular disease

34,210 COPD patients had no
prior cardiovascular disease

3,707 COPD patients
also had asthma

14,469 COPD patients
had no asthma

6,824 COPD patients
also had asthma

27,386 COPD patients
had no asthma

Propensity
score matching

Propensity
score matching

3,690 cases with COPD
and asthma with prior
cardiovascular disease

7,236 controls with COPD
without asthma with prior
cardiovascular disease

6,775 cases with COPD
and asthma without prior
cardiovascular disease

13,205 controls with COPD
without asthma without
prior cardiovascular disease

Flowchart of included patients, cohorts with and without prior cardiovascular disease, and propensity score match.

Figure 2



Cumulated incidense plots of severe and any MACE occuring to 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, MRC, BMI, and $FEV_1\%$ stratified into populations based on pre-existing cardiovascular disease.
Severe MACE defined as lethal cardiovascular events, and cardiovascular events requiring revascularization or hospitalization.
Any MACE defined as severe MACE or an event requiring a prescription of ADP receptor inhibitors or nitrates.
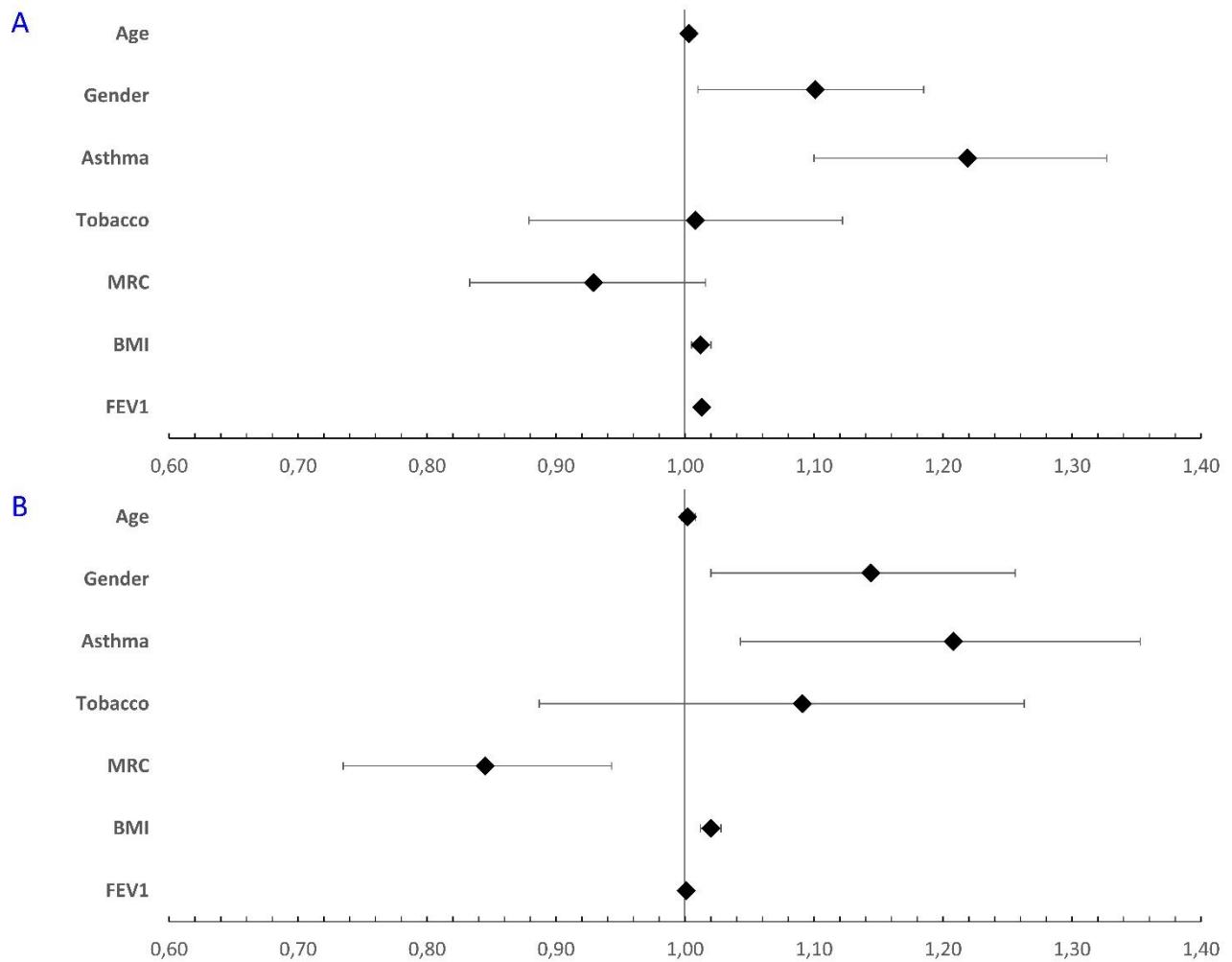A: Severe MACE in the propensity score matched cohort of patients with pre-existing cardiovascular disease ($N$=10,926).
B: Any MACE in the propensity score matched cohort of patients with pre-existing cardiovascular disease ($N$=10,926).
C: Severe MACE in the propensity score matched cohort of patients without pre-existing cardiovascular disease ($N$=19,980).
D: Any MACE in the patients propensity score matched cohort of without pre-existing cardiovascular disease ($N$=19,980).

Figure 3



Forest plots showing hazard ratios for severe 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: Cohort of patients with pre-existing cardiovascular disease ($N$=18,176).

B: Group of patients without pre-existing cardiovascular disease ($N$=34,210).

Age, BMI and $FEV_1$% were analyzed as continous variables, gender, asthma, tobacco exposure and MRC 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. For MRC; patients with MRC ≥3 were compared to patients with MRC ≤ 2.