Protocol:

The Association Between Severity of Chronic Obstructive Pulmonary Disease and the Risk of Major Adverse Cardiovascular Events.

Background and Rational:

Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory airway disease characterized by persistent airflow limitation resulting from airway narrowing and parenchymal destruction .[1] [2] Common clinical manifestations include cough, wheeze, dyspnoea, increased mucus production, and recurrent infections.[1, 2] Disease severity is classified according to the Global initiative for COPD risk groups (A, B or E) based on symptom burden and exacerbation frequency [1]
COPD and major adverse cardiovascular events (MACE) share several risk factors, including advance age, smoking and socioeconomic deprivation.[3, 5, 6] In addition, acute exacerbations of COPD may precipitate cardiovascular events through pathophysiological mechanisms such as hypoxia, hyperinflation, oxidative stress, and systemic inflammation. [1, 4]
Studies suggest that MACE is 25% more likely to occur in COPD patients compared to patients without COPD.[5] However, the association between COPD severity, particularly exacerbation burden, and subsequent cardiovascular risk remains incompletely characterized. Using nationwide Danish health registers, this study aims to evaluate the association between COPD severity and the risk of MACE.

Hypothesis:

Among patients registered in the Danish COPD Registry, higher COPD severity, defined by GOLD risk group classification and exacerbation frequency, is associated with an increased risk of subsequent major adverse cardiovascular events.

Study design:

This study is a retrospective, nationwide, register-based cohort study.Data sources

- Danish COPD Registry: baseline characteristics, lung function (FEV_1), smoking status, BMI, and comorbidities Danish National Patient Register: hospital

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[1] GOLD report 2025

[2] Medicinsk kompendium

[3] Fabbri LM, Celli BR, Agustí A, Criner GJ, COPD and multimorbidity: recognising and addressing a syndemic occurrence. Lancet Respir Med. 2023

[4] Agustí A, Edwards LD, Rennard SI, MacNee; Persistent systemic inflammation is associated with poor clinical outcomes in COPD: a novel phenotype.

[5] Polman, R., Hurst, Cardiovascular disease and risk in COPD: a state of the art review. Expert Review of Cardiovascular Therapy

[6] Katsuya Onishi, *Total management of chronic obstructive pulmonary disease (COPD) as an independent risk factor for cardiovascular disease*, Journal of Cardiology.

admissions and diagnoses, including MACECivil Registration System: vital status, date of death, and emigration

- Danish National Prescription Registry: prescriptions for systemic corticosteroids, antibiotics, NSAIDs, and other relevant medications

Study population:

Inclusion criteria:

- Patients registered in the Danish COPD registry

Exclusion criteria:

Active malignant disease at baseline**Exposure:**

- Primary Exposure: Number of AECOPD per year, categorized as:
    - No hospitalizations with primary diagnosis of COPD or less than one systemic steroid or antibiotic prescription for acute worsening of respiratory symptoms. (control group)
    - At least one hospitalization with primary diagnosis of COPD or one or more systemic steroid or antibiotic prescription for acute worsening of respiratory symptoms.

- Definition of AECOPD: Hospitalization with primary diagnosis of COPD exacerbation or systemic steroid or antibiotic prescription for acute worsening of respiratory symptoms.
    - Hospital admission with primary diagnosis of COPD: ICD-10: J441+ J440+ J44.9 with duration of at least 24 hours
    - Systemic steroid prescription: H02AB0 with strength 25 mg and pack size smaller than 100, to avoid prescriptions for maintenance treatment. Prescriptions must be at least 30 days apart to count as two separate exacerbations.
    - Antibiotic prescription: J01CA04, J01CR02, J01FA09, J01FA06, J01FA10. Prescriptions must be at least 14 days apart to count as two separate exacerbations.

- Exacerbation frequency will be assessed during the year prior to the index date and updated annually thereafter, treating exacerbation burden as a time-varying exposure.

Outcome:

- The primary outcome was the occurrence of major adverse cardiovascular events (MACE) within 365 days, defined as a composite of:
- Myocardial infarction
- Ischaemic or haemorrhagic stroke
- Cardiovascular death

Covariates

- Age, sex, smoking, BMI,
- Prior MACE
- Hypertension
- Hypercholesterolemia
- Diabetes
- Chronic kidney disease

Statistical Analysis: (?)

Time to first MACE will be analysed using Cox proportional hazards regression, with exacerbation frequency included as a time-varying covariate.

Time scale: days since index date

Competing risk: all-cause death

Models adjusted for all prespecified covariates

The index date is defined as the date of first registration in the Danish COPD Registry.

Strength:

- CPR- register: nationwide register that ensures large sample size and long-term follow-up

Limitations:

- Potential misclassification due to registration errors in the included registries.
- Residual confounding from unmeasured variables

Ethics and Data management:

- The study will be conducted in accordance with Danish data protection legislation. Approval from relevant Danish authorities (Danish Health Data Authority and Data

Protection Agency) will be obtained prior to data access. Data linkage will be performed using the CPR number, and all analyses will be conducted on secure servers.

References:

[1]: Global Initiative for Chronic Obstructive Lung Disease (GOLD). (2025). Global strategy for prevention, diagnosis, and management of COPD: 2025 Report. GOLD. https://gold-copd.org/2025-gold-report/

[2] Medicinsk compendium s. 735

[3] Fabbri LM, Celli BR, Agustí A, Criner GJ, Dransfield MT, Divo M, Krishnan JK, Lahousse L, Montes de Oca M, Salvi SS, Stolz D, Vanfleteren LEGW, Vogelmeier CF. COPD and multimorbidity: recognising and addressing a syndemic occurrence. Lancet Respir Med. 2023 Nov;11(11):1020-1034. doi: 10.1016/S2213-2600(23)00261-8. Epub 2023 Sep 8. PMID: 37696283.

[4] Agustí A, Edwards LD, Rennard SI, MacNee W, Tal-Singer R, Miller BE, Vestbo J, Lomas DA, Calverley PM, Wouters E, Crim C, Yates JC, Silverman EK, Coxson HO, Bakke P, Mayer RJ, Celli B; Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) Investigators. Persistent systemic inflammation is associated with poor clinical outcomes in COPD: a novel phenotype. PLoS One. 2012;7(5):e37483. doi: 10.1371/journal.pone.0037483. Epub 2012 May 18. PMID: 22624038; PMCID: PMC3356313.

[5] Polman, R., Hurst, J. R., Uysal, O. F., Mandal, S., Linz, D., & Simons, S. (2024). Cardiovascular disease and risk in COPD: a state of the art review. *Expert Review of Cardiovascular Therapy*, *22*(4–5), 177–191. https://doi.org/10.1080/14779072.2024.2333786

[6] Katsuya Onishi, *Total management of chronic obstructive pulmonary disease (COPD) as an independent risk factor for cardiovascular disease*, Journal of Cardiology, Volume 70, Issue 2, 2017, Pages 128-134, ISSN 0914-5087, https://doi.org/10.1016/j.jjcc.2017.03.001. (https://www.sciencedirect.com/science/article/pii/S0914508717300552)