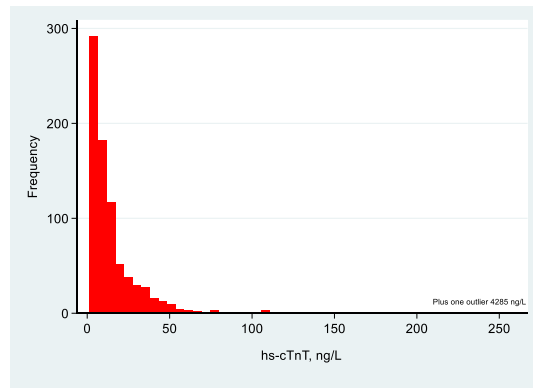


Online figure 1. Distribution of high-sensitivity Troponin T (hs-cTnT).



(The outlier had acute myocardial infarction).

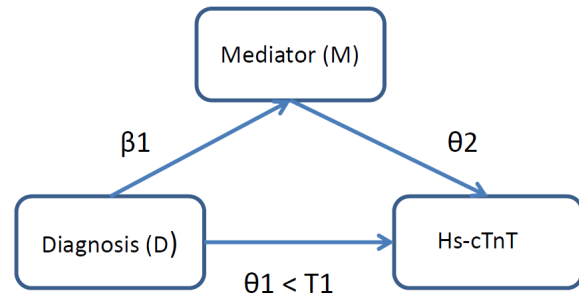
#### Mediation, prerequisites:

In our settings, the variable (M) was considered as a mediator of the relationship between the disease (D) and hs-cTnT provided that:

1. M was significantly associated with D ( $\beta_1$ , Equation 1).
2. In a model with hs-cTnT as the outcome using D and M as explanatory variables, M was significantly associated with hs-cTnT ( $\theta_2$ , Equation 2).
3. In a model without M, D was significantly associated with hs-cTnT ( $T_1$ , Equation 3).
4. In a model with M and D, the association between D and the hs-cTnT attenuated substantially ( $\theta_1$ , Equation 2).

In these analyses, we first investigated the association between M and D between M and relevant covariates (c), (eq 1). In these analyses, CRP as well as leucocytes were log-transformed. Thereby, we estimated the coefficients ( $\beta_1$ ) between M and D. Second, we investigated the relationship between the outcome variable expressed as log-transformed hs-cTnT ( $\ln\_cnt$ ), using D, M and relevant covariates (c) as explanatory covariates (eq 2). Thereby, we estimated the relationship between  $\ln\_cnt$  and D ( $\theta_1$ ). Third, we removed M from eq 2 and estimated the relationship between  $\ln\_cnt$  and D ( $T_1$ ) unconditionally of M but kept the covariates (c). Finally, the indirect association between  $\ln\_cnt$  was calculated as the difference between  $\beta_1$  and  $\beta_0$  (eq 3:  $IE = \beta_1 - \beta_0$ ). The corresponding z-score (and p-values) were obtained using bootstrapping.

Online figure 2.



- Eq 1:  
 $E(M | D, c1) = \beta_0 + \beta_1 * D + \beta_{11} * c1$
- Eq 2:  
 $E(\ln\_cntnt | D, M, c2) = \theta_0 + \theta_1 * D + \theta_2 * M + \beta_{22} * c2$
- Eq 3:  
 $E(\ln\_cntnt | D, c2) = T_0 + T_1 * D + \beta_{32} * c2$
- Direct effect:  $\theta_1$
- Indirect effect:  $IE = T_1 - \theta_1$
- Total effect:  $T_1$
- $c1, c2$ : other covariates in eq 1, eq 2 and 3, respectively.

The relationship between  $\ln\_cntnt$  as the outcome variable and diagnoses with biomarkers as well as baseline hs-cTnT and follow-up time as covariates were estimated using linear mixed model (four models). In these analyses we used multiple imputations for C-reactive protein, oxygen tension, and creatinine (we had complete data for leucocytes, see online table 2). Standard errors for IE, and thereby the corresponding p-values, were obtained using bootstrapping. The continuous covariates were included in quartiles.

Online table 1a. The geometric mean of high sensitivity cardiac Troponin T (hs-cTnT), the ratio of hs-cTnT between index-group (Yes) and reference group (No) with geometric standard error (gse) and p-value by categorical covariables and study group at baseline (n = 380).

Explanatory variables	Hs-cTnT, ng/L		Ratio (gse, p-value)
	Yes	No	
Female gender: Yes vs. No	5.4	8.7	0.62 (1.1, <0.001)
Coronary heart disease: Yes vs. No	8.8	6.8	1.3 (1.2, 0.207)
q-wave in electrocardiogram: Yes vs. No	10.5	6.8	1.5 (1.2, 0.034)
Arterial hypertension: Yes vs. No	8.5	5.9	1.4 (1.1, <0.001)
Current smoking: Yes vs. No	5.9	7.4	0.79 (1.2, 0.024)

Online table 1b. The geometric mean of high sensitivity cardiac Troponin T (hs-cTnT) and the ratio of hs-cTnT (Ratio =  $\text{hs-cTnT}_{Q_{n+1}} / \text{hs-cTnT}_{Q_n}$ ) between quartiles (Q1-4) of hs-cTnT with geometric standard error (gse), by continuous covariates in quartiles measured at baseline (n = 380).

Variables (quartile limits)	Q1	Q2	Q3	Q4	Ratio <sup>§</sup>	gse	p-value
Age, years (60.0; 65.0; 70.0)	4.7	6.3	7.2	10.6	1.3	1.04	<0.001
Leucocytes, x10 <sup>9</sup> /litres (5.7; 6.8; 8.1)	5.8	6.2	7.3	8.6	1.1	1.05	0.002
CRP, mg/litres (1.0; 3.0; 4.0)	6.3	6.2	6.7	8.5	1.1	1.04	0.031
Creatinine, mmol/litres (63.0; 72.0; 84.0)	6.1	5.5	7.0	9.5	1.2	1.04	<0.001
FEV1, litres (0.9; 1.3; 2.0)	10.2	6.8	5.4	5.8	0.82	1.04	<0.001
FVC, litres (2.1; 2.7; 3.5)	8.4	6.9	6.4	5.9	0.89	1.05	0.011
Arterial O2-tension, kPa (8.4; 9.2; 10.2)	10.0	7.1	6.4	6.3	0.86	1.05	0.003
Heart Rate, 1/minutes (63; 72; 80)	6.0	6.0	6.9	10.0	1.2	1.05	0.001
Tobacco, pack-years (0.4; 26.4; 45.0)	6.1	6.8	7.1	7.7	2.1	1.04	0.086

§ Ratio =  $Q_n / Q_{n-1}$

Online Table 1c. Baseline ratio of high-sensitivity troponin T and different levels of relevant covariates in three models using ordinary least square regression with missing values and a model using multiple imputations for missing values.

Observations (N)	Ordinary Least Square Regression without imputation									Multiple Imputation		
	N = 380			N = 310			N = 270			N = 380		
Group	Ratio	GSE	p-value	Ratio	GSE	p-value	Ratio	GSE	p-value	Ratio	GSE	p-value
References	1.00	-	-	1.00	-	-	1.00	-	-	1.00	-	-
LTOT candidates	2.82	1.25	<0.001	2.25	1.28	0.001	Omitted			1.43	1.41	0.295
Rehabilitation group												
Outpatients	1.33	1.17	0.065	1.24	1.18	0.193	0.67	1.29	0.118	1.08	1.36	0.794
Institutional	1.36	1.14	0.017	1.46	1.15	0.007	0.67	1.26	0.086	1.03	1.34	0.930
COPD outpatients	1.09	1.17	0.578	Omitted			0.39	1.27	<0.001	0.60	1.36	0.102
Sex: female vs. male	0.60	1.09	<0.001	0.63	1.11	<0.001	0.60	1.13	<0.001	0.59	1.11	<0.001
Age in quartiles	1.25	1.04	<0.001	1.22	1.05	<0.001	1.12	1.05	0.035	1.16	1.04	<0.001
Pack-years in quartiles				0.95	1.05	0.302	1.01	1.05	0.901	0.97	1.04	0.488
Arterial hypertension: Y vs. N				1.30	1.11	0.013	1.25	1.11	0.040	1.24	1.10	0.018
Coronary arterial disease: Y vs. N				1.25	1.25	0.302	1.06	1.25	0.793	1.03	1.21	0.880
Q-wave ECG: Y vs. N				1.22	1.20	0.286	1.18	1.20	0.352	1.17	1.17	0.317
Heart rate in quartiles				1.19	1.05	<0.001	1.07	1.05	0.201	1.09	1.04	0.040
Continuous covariates in quartiles												
Creatinine							1.12	1.06	0.032	1.14	1.05	0.006
C-reactive protein							1.00	1.05	0.920	1.02	1.04	0.657
Peripheral leucocytes							1.04	1.05	0.387	1.05	1.04	0.224
FEV1							0.76	1.06	<0.001	0.76	1.05	<0.001
Arterial O2-tension							0.93	1.06	0.197	0.93	1.05	0.116

GSE: geometric standard error, LTOT: long-term oxygen treatment, COPD: chronic obstructive pulmonary disease, ECG: electrocardiogram, FEV1: forced expiratory volume in 1 second.

Online table 2. The number of complete data, the percent of imputed numbers and the total number by baseline model and longitudinal models.

Variable, quartiles	Complete	Imputed, %	Total
Baseline model			
Arterial O <sub>2</sub> -tension	305	20	380
Heart rate	310	18	380
Q-wave ECG	310	18	380
C-Reactive Protein	353	7	380
Longitudinal models			
Arterial O <sub>2</sub> -tension	770	4	801
C-Reactive Protein	800	0	801
Creatinine	667	17	801
Leucocytes	801	0	801
Heart rate	786	2	801

Online table 3. International Classification of Disease code (ICD10), text explanation, the number of hs-cTnT measurements at baseline (N) and during the follow-up (n), and the corresponding geometric mean (gm) and geometric standard deviation (gsd) of high-specific Cardiac Troponin by Diagnoses at the follow-up.

ICD10	Diagnosis, text	N	n	n/N, %	Baseline		Hospitalised	
					gm	gsd	gm	gsd
Acute Exacerbation of COPD								
J44.0	COPD with acute infection in the lower respiratory airways	19	17	89	15.2	1.9	34.9	2.1
J44.1	Unspecified acute exacerbation of COPD	130	122	94	12.2	2.5	18.2	2.1
J96.0	Acute Respiratory Failure	1	1	100	14.4		21.0	
	Sum	150	140	93	12.6	2.4	19.7	2.1
Pneumonia								
J13	Pneumonia due to P.pneumonia	5	4	80	12.2	4.2	17.8	1.8
J14	Pneumonia due to H.Influenzae	1	1	100	13.0		14.0	
J15	Bacterial Pneumonia, not elsewhere classified	22	17	77	14.2	2.1	31.3	2.4
J18	Pneumonia, unspecified organism	52	45	87	13.3	2.7	17.8	2.6
	Sum	80	67	84	13.5	2.6	20.5	2.5
Other Lung diseases								

J09	Influenza due to certain identified viruses	1	1	100	12.9		29.0	
J10	Influenza due to other identified viruses	3	3	100	11.4	2.2	43.7	2.9
J12	Viral pneumonia	3	3	100	5.7	1.3	4.7	2.7
J20	Acute bronchitis	3	2	67	9.7	1.4	28.4	1.1
J22	Unspecified lower respiratory infection	1	0	0	7.1			
J33	Nasal polyp	1	0	0	14.0			
J43	Emphysema	2	1	50	15.8	2.8	15.0	
J44	Other chronic obstructive disease	8	4	50	19.8	3.0	23.8	1.7
J47	Bronchiectasis	1	0	0	10.0			
J84	Other interstitial pulmonary diseases	1	0	0	3.9			
J85	Abscess of lung or mediastinum	2	0	0	38.9	1.3		
J90	Pleural effusion, not elsewhere classified	1	0	0	31.2			
J93	Pneumothorax	5	2	40	6.5	2.4	13.6	4.1
J96	Respiratory failure, not elsewhere classified	11	5	45	6.8	2.2	8.8	1.7
	Sum	43	21	49	10.4	2.5	15.5	2.7
Non-respiratory infections								
A04	Other intestinal infections	1	1	100	6.0		13.5	
A09	Other gastroenteritis and colitis, unspecified agent	3	3	100	5.3	4.3	13.5	2.6
A46	Erysipelas	1	1	100	13.0		15.0	
A49	Bacterial infection, unspecified	1	1	100	45.9		162.0	
	Sum	6	6	100	9.0	3.5	25.4	3.3
Diseases of the circulatory system								
I11	Hypertensive heart disease	1	1	100	11.0		22.0	
I20	Angina pectoris	12	12	100	11.3	1.3	14.6	2.5
I21	Acute myocardial infarction	7	7	100	7.4	2.1	161.5	6.2
I24	Other acute ischaemic heart disease	1	1	100	11.0		11.0	
I25	Chronic ischaemic heart disease	8	7	88	10.6	1.7	15.9	2.8
I26	Pulmonary embolism	2	2	100	12.6	1.4	14.5	1.0
I42	Acute myocarditis	2	2	100	8.7	1.5	78.2	1.5
I46	Cardiac arrest	1	1	100	2.1		6.2	
I48	Atrial fibrillation and flutter	6	6	100	4.6	3.0	28.2	2.1
I50	Heart failure	3	2	67	18.4	2.2	15.5	1.0
I60	Subarachnoid haemorrhage	1	1	100	14.0		262.0	

I61	Intracerebral haemorrhage	2	2	100	4.7	1.5	7.1	1.6
I63	Cerebral infarction	3	3	100	13.6	2.5	7.1	4.9
I67	Other cerebrovascular disease	1	1	100	14.0			
I71	Aortic aneurysm and dissection	1	0	0	9.3			
I81	Phlebitis and thrombophlebitis	1	0	0	12.6			
	Sum	52	48	92	9.5	1.9	26.8	3.9
Cancer								
C21	Malignant neoplasm of anus and anal canal	1	0	0	3.0		32.0	
C25	Malignant neoplasm of pancreas	2	1	50	10.8	3.4	32.0	
C34	Malignant neoplasm of bronchus and lung	8	3	38	7.7	1.6	38.7	2.0
C50	Malignant neoplasm of the breast	1	0	0	4.6			
C61	Malignant neoplasm of prostate	1	1	100	12.9		17.0	
C64	Malignant neoplasm of the kidney, except renal pelvis	2	1	50	13.6	3.2	38.0	
C67	Malignant neoplasm of the bladder	3	1	33	8.2		15.0	
C72	Malignant neoplasm of the spinal cord, cranial nerves and others	1	0	0	5.9			
C78	Secondary malignant neoplasm of respiratory and digestive sites	1	1	100	14.4		16.0	
C90	Multiple myeloma	1	1	100	8.9		5.0	
	Sum	21	9	43	8.3	1.9	22.4	2.2
Diseases of the digestive system								
K21	Gastro-oesophageal reflux disease	2	1	50	3.4	1.2	5.0	
K29	Gastritis and duodenitis	4	4	100	14.3	8.4	17.7	2.9
K35	Acute appendicitis	1	0	0	45.5			
K42	Umbilical hernia	1	0	0	14.0			
K44	Diaphragmatic hernia	1	1	100	4.5			
K52	Other noninfective gastroenteritis and colitis	1	0	0	11.0			
K56	Paralytic ileus and intestinal obstruction without hernia	3	0	0	2.6	2.6		
K57	Diverticular disease	4	1	25	9.3	2.6	27.0	
K61	Abscess of anal and rectal regions	1	0	0	1.5			
K62	Other diseases of anus and rectum	1	0	0	12.0			
K63	Other diseases of intestine	1	0	0	19.0			
K72	Hepatic failure, not elsewhere classified	4	2	50	11.0	2.5	9.5	2.5
K82	Other diseases of the gall bladder	1	0	0	10.5		1.0	
K92	Other diseases of the digestive system	1	1	100	7.3		14.0	

	Sum	26	10	38	8.3	3.1	13.3	2.3
Symptoms								
R06	Abnormalities of breathing	1	0	0	1.5			
R07	Pain in chest and throat	17	17	100	8.3	1.9	8.3	1.6
R10	Abdominal and pelvic pain	4	2	50	11.8	2.9	8.9	2.3
R11	Nausea and vomiting	1	1	100	1.5		5.0	
R19	Other symptoms and signs involving the digestive system and bad.	1	1	100	8.5		8.0	
R33	Retention of urine	1	0	0	7.7			
R33	Retention of urine	2	0	0	11.9	1.1		
R42	Dizziness and giddiness	1	1	100	8.5		5.0	
R55	Syncope and collapse	2	2	100	2.1	1.6	11.2	2.4
	Sum	30	24	80	7.2	2.3	8.2	1.6
Other diagnoses								
D1	Benign neoplasms of mouth and pharynx	2	0	0	10.4	1.1		
D3	Benign neoplasm of specified organs	1	0	0	3.0			
D4	Benign neoplasm of uncertain origin	1	0	0	10.0			
D6	Aplastic anaemia	2	1	50	22.8	2.7	34.0	
D7	Other diseases of blood and blood-forming organs	1	0	0	14.0			
E0	Disease of the thyroid gland	1	0	0	5.3			
E1	Diabetes mellitus	2	2	100	15.5	2.7	19.6	2.7
E8	Metabolic disease, unspecified	3	3	100	26.3	1.5	17.0	2.9
F0	Organic mental disorder	2	2	100	32.5	1.0	28.1	1.3
F4	Neurotic disorder	1	1	100	11.0		11.0	
G4	Episodic paroxysmal disorder	4	2	50	6.8	2.6	19.9	3.1
M1	Inflammatory polyarthropathies or arthrosis	4	0	0	6.4	2.1		
M4	Dorsopathies, specified	2	0	0	3.0	1.0		
M5	Dorsopathies, unspecified	3	1	33	1.9	1.5	4.0	
M7	Other tissue disorders	1	1	100	12.9			
N1	Renal tubulo-interstitial diseases	2	2	100	22.5	2.7	73.9	2.5
N3	Other diseases of urinary system	3	2	67	10.9	1.3	12.0	1.1
N8	Noninflammatory disorders of female genital tract	1	0	0	1.5			
Q4	Other congenital malformations of upper alimentary tract	1	0	0	10.4			
S0	Injuries to the head	3	2	67	13.8	12.8	24.6	9.5



S2	Injuries to the thorax	2	0	0	11.2	1.0		
S3	Injuries to the abdomen, lower back, lumbar spine or pelvis	1	0	0	8.0			
S4	Injuries to the shoulder or upper arm	2	0	0	3.4	1.0		
S5	Injuries to the elbow and forearm	1	0	0	3.5			
S6	Injuries to the wrist and hand	1	0	0	1.5			
S7	Injuries to the hip and thigh	6	2	33	14.0	1.7	54.1	2.4
S8	Injuries to the knee or lower leg	1	0	0	1.5			
T4	Poisoning to narcotics and psychodysleptics	4	3	75	6.4	1.7	17.3	1.3
T8	Complication to medical treatment	3	1	33	6.2	3.4	36.0	
Z0	Health investigation	1	1	100	11.0		11.0	
Z4	Persons encountering health services for specific procedures	1	0	0	11.5			
Z5	Persons with health hazards related to socioeconomic circumstances	1	0	0	4.5			
Z9	Persons encountering health services in other circumstances	1	0	0	7.8			
	Sum	65	26	40	8.3	2.7	21.5	2.5

Online table 4. The ratio, geometric standard error (gse) and p-value between leucocytes counts, C-reactive protein, and heart rate, respectively, at hospitalization and stable state by relevant covariates.

Diagnosis Group	Leucocytes			C-reactive protein			Heart rate		
	Ratio	gse	p-value	Ratio	gse	p-value	Ratio	gse	p-value
COPD exacerbation	1.35	1.07	<0.001	4.37	1.25	<0.001	0.99	1.03	0.795
Pneumonia	1.25	1.09	0.012	18.28	1.31	<0.001	0.99	1.03	0.732
Other lung diseases	1.27	1.15	0.086	2.77	1.55	0.020	1.08	1.06	0.165
Non-respiratory infections	1.73	1.22	0.005	9.35	1.87	<0.001	0.93	1.04	0.043
Circulatory diseases	1.28	1.11	0.017	1.55	1.41	0.200	1.03	1.03	0.381
Cancer	1.64	1.25	0.026	2.29	2.04	0.244	0.97	1.08	0.692
Digestive diseases	1.16	1.16	0.320	1.18	1.62	0.738	1.06	1.06	0.258
Symptoms	1.39	1.13	0.009	1.83	1.51	0.142	1.04	1.03	0.297
Other diagnoses	1.37	1.25	0.154	2.03	2.01	0.309	1.01	1.04	0.872
Follow-up time: years	1.01	1.02	0.770	1.00	1.08	0.962	0.97	1.01	<0.001
Continuous covariates: quartiles									
Hs-cTnT at stable state	1.00	1.02	0.790	1.02	1.06	0.740	1.04	1.01	<0.001
Peripheral leucocytes	n.i.			1.38	1.08	<0.001	1.04	1.01	<0.001
C-Reactive protein	1.04	1.02	0.063	n.i.			1.01	1.01	0.324
Creatinine	1.01	1.02	0.450	0.98	1.07	0.798	0.97	1.01	<0.001
Arterial O <sub>2</sub> -tension	1.00	1.02	0.851	0.85	1.07	0.014	0.98	1.01	0.017
Heart rate	1.08	1.02	<0.001	0.99	1.07	0.928	n.i.		

n.i.: not included

Online table 5. Ratio (R) with geometric standard error (gse) and p-value (p) between the level of high-sensitive Troponin T (hs-cTnT) at hospitalisation and stable state by diagnosis, study group, hs-cTnT at baseline and covariates at hospitalisation in five different models.

	Full Model			Leucocytes removed			CRP removed			Heart Rate removed			Leuc. + CRP removed		
	R	gse	p	R	gse	p	R	gse	p	R	gse	p	R	gse	p
AECOPD	1.08	1.12	0.513	1.16	1.12	0.182	1.14	1.12	0.243	1.06	1.12	0.602	1.25	1.11	0.036
Pneumonia	1.01	1.15	0.929	1.08	1.15	0.609	1.14	1.14	0.318	1.00	1.15	0.989	1.25	1.14	0.084
Other Lung Dis.	0.96	1.24	0.839	1.01	1.24	0.953	1.01	1.24	0.975	0.96	1.25	0.865	1.09	1.24	0.708
Non-Resp. Infections	1.79	1.36	0.061	2.03	1.36	0.022	1.94	1.36	0.032	1.73	1.36	0.079	2.28	1.36	0.007
Circulatory Diseases	1.98	1.18	<0.001	2.12	1.18	<0.001	1.97	1.18	<0.001	1.94	1.18	<0.001	2.13	1.18	<0.001
Cancer	0.73	1.42	0.370	0.82	1.42	0.564	0.75	1.42	0.405	0.72	1.42	0.345	0.85	1.42	0.650
Digestive Diseases	1.32	1.27	0.242	1.35	1.27	0.215	1.31	1.27	0.255	1.34	1.27	0.226	1.34	1.27	0.224
Symptom Diagnoses	1.12	1.22	0.578	1.14	1.22	0.506	1.11	1.22	0.595	1.10	1.22	0.636	1.14	1.22	0.515
Remaining Diagn.	1.22	1.41	0.556	1.29	1.41	0.459	1.23	1.41	0.548	1.22	1.41	0.557	1.31	1.41	0.437
Follow-up time. Yrs.	1.12	1.04	0.004	1.13	1.04	0.002	1.12	1.04	0.004	1.11	1.04	0.006	1.13	1.04	0.002
Continuous Covariates in quartiles															
hs-cTnT baseline	1.87	1.03	<0.001	1.87	1.03	<0.001	1.88	1.03	<0.001	1.89	1.03	<0.001	1.87	1.03	<0.001
Continuous Covariates at admission in quartiles															
Leucocytes	1.09	1.04	0.015	removed			1.10	1.04	0.005	1.11	1.04	0.003	removed		
CRP	1.08	1.04	0.038	1.09	1.04	0.015	removed			1.08	1.04	0.034	removed		
Creatinine	1.06	1.03	0.052	1.07	1.03	0.034	1.06	1.03	0.058	1.05	1.03	0.111	1.07	1.03	0.036
Arterial O2	1.01	1.03	0.823	1.01	1.03	0.845	1.00	1.03	0.995	1.00	1.03	0.954	1.00	1.03	0.948
Heart rate	1.08	1.03	0.028	1.09	1.03	0.005	1.08	1.03	0.024	removed			1.10	1.03	0.003

AECOPD: Acute Exacerbation of COPD ·