NLC Abstracts

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Detection of lung cancer using a biomarker panel: importance of lung cancer stage

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Background and Aims: Lung cancer is now leading in cancer-related deaths. The stage at diagnosis is of great importance and early detection is pivotal. A blood-based biomarker panel with the ability to detect early-stage lung cancer would be of great benefit.

Methods: A high-risk cohort was formed at Lillebælt Hospital, Vejle. All participants were referred from their GP on suspicion of lung cancer. Prior to diagnostic work-up, a blood-based biomarker panel consisting of CEA, CYFRA, and CA125 was taken. Patients where lung cancer was ruled out served as controls and a ROC cross-validated prediction model was computed for the detection of stage I–II vs. stage III–IV lung cancer.

Results: Of the 250 participants, 79 were diagnosed with lung cancer. The ROC curves yielded an AUC value of 0.54 for detection of stage I–II lung cancer vs. AUC of 0.88 for detection of stage III–IV lung cancer. If tobacco history was added to the computed models, the AUC improved when detecting stage I–II lung cancer (0.65), while the AUC remained unchanged when detecting stage III–IV lung cancer (0.88).

Conclusions: The biomarker panel performed best in detection of stage III–IV lung cancer. Hence, this panel could potentially serve as a marker of disseminated disease, while it is less useful for screening purposes with the aim of detecting early stage resectable lung cancer cases.

Sex, anxiety, and the interplay with physiological variables of stress: a clinical study of patients about to undergo bronchoscopy

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Background and Aim: Women often report more anxiety than men, but there are divergent results regarding the putative correlation between physiological variables, such as cortisol, blood pressure, heart rate, and the experienced emotional states. The aim of the present study was to evaluate sex differences in anxiety, and the relation between serum cortisol, blood pressure, and heart rate.

Methods: We used data from two pooled studies with participants from the same population (N = 405) facing a real-life stressor, bronchoscopy, as part of examination for lung cancer. At admission, blood pressure and heart rate were recorded, and a blood sample was taken for analysis of serum cortisol. Participants then completed Spielberger’s State Trait Anxiety Inventory (STAI).

Results: Patients had elevated anxiety measured with STAI state compared to relevant age and sex stratified norm scores. Women had significantly higher STAI state score than men (mean = 44.9, SD = 13.2 vs mean = 36.2, SD = 10.7; \( t \) (403) = 7.25, \( p < 0.001 \)).
Conclusion: Taken together, this study shows that women experience significantly more anxiety than men.

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Multidisciplinary approaches to identifying and managing global airways disease: an expert consensus

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Background: Chronic rhinosinusitis with nasal polyps (CRSwNP) and asthma are diseases of the upper and lower airway, respectively, but frequently co-exist and share many pathologic features. Taking a ‘global’ treatment approach benefits diagnosis and treatment of both conditions, but such approaches are not yet widespread within clinical practice.

Objective: To build a consensus of expert opinion on practical suggestions to (a) help identify patients needing a global airways approach; (b) enhance cross-specialty collaboration and referral; and (c) promote broad knowledge to support the diagnosis and management of patients with possible concomitant CRSwNP and asthma.

Methods: Sixteen practicing physicians from northern Europe were invited for their national and/or international standing in treating asthma and/or CRS. Employing the Appreciative Inquiry approach, including interviews and virtual meetings, experts developed practical consensus recommendations to supplement existing guidelines.

Results: Key themes arising were screening and referral, collaboration on management, awareness and education, and research. Provided are key screening criteria and suggestions for optimizing referrals to specialist care, as well as pointers for physicians to optimize their knowledge of global airways disease. Collaborative working is underscored, and practical suggestions are given for multidisciplinary team working within global airways clinics. Research gaps are identified.

Conclusion: This consensus report gives practical suggestions for optimizing the care of patients with CRSwNP and asthma, although its principles will likely benefit patients with related conditions. Its primary focus was on northern European countries, but it is likely also relevant to other countries with similar healthcare systems.

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Disease control, not severity, drives welfare resource utilization in young adults with asthma: a 15-year nationwide cohort study

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Background: The impact of asthma and disease control on welfare use in young adults over time is sparsely investigated. This study aims to describe the overall welfare resource utilization (WRU) across asthma severities and describe the possible influence of asthma control.

Methods: REASSESS comprises a nationwide cohort of Danish asthma patients aged 18–45 using controller medication between 2014 and 2018 followed for up to 15 years using national databases. Impact of asthma was investigated using negative binomial regression adjusted for age, sex, Charlson score, and level of education and presented as adjusted incidence rate ratios with 95% confidence intervals.

Results: A total of 60,534 patients with asthma (median age 33 (25, 39), 55% female, 19% uncontrolled disease and 5.7% possible severe asthma) were followed for 12.7 (6.5–14.8) years. The prevalence of any WRU was relatively more common in both mild-to-moderate and possible severe asthma compared to the background population (68, 81, and 62%, respectively; p < 0.0001.) Compared to the background population, mild-to-moderate and possible severe asthma had a higher use of temporary sick leave (1.37 (1.33–1.42); 1.78 (1.62–1.96)), unemployment (1.11 (1.07–1.14); 1.26 (1.15–1.38)) and disability benefits (1.67 (1.66–1.67); 2.64 (2.63–2.65)). Uncontrolled asthma had increased temporary sick leave (1.42 (1.34–1.50)), unemployment (1.40 (1.32–1.48)), and disability (1.26 (1.26–1.27)) when compared to controlled disease. Significant increases in WRU could be measured already at 100 annual doses of rescue medication (1.09 (1.04–1.14)), patients’ first moderate and severe exacerbations (1.31 (1.15–1.49) and 1.31 (1.24–1.39), respectively). Further increases in WRU were observed with increasing rescue medication use and severe exacerbations.

Conclusion: Welfare consumption is consistently increased among young asthmatics compared to the background population. Increases in welfare use were seen already at >100 annual doses of rescue medication, representing substantial and potentially avoidable welfare use in a population expected to be active members of the workforce.

Magnesium sulfate for the treatment of acute severe asthma in adults: a systematic review and meta-analysis

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Background and Aim: The use of add-on magnesium sulfate in treatment refractory asthma exacerbations has been much debated. The aim of this review and meta-analysis is, therefore, to provide an update on the present evidence for the effect of MgSO4 in the treatment of acute refractory asthma in adults.

Methods: Systematic review performed in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses-guidelines. The search was carried out in the PubMed database (updated in August 2021). For the meta-analysis a random-effects model was performed using the metafor package for RStudio Version 1.2.5001 2009–2019 RStudio, Inc.

Results: A total of 17 randomized controlled trials (RCTs) were included. Of the seven included studies addressing treatment with intravenous magnesium sulfate, three found significant effect on lung function compared to placebo, three did not, and one study did not measure lung function. Of the six studies investigating hospital admission/discharge rates, five found no effect of MgSO4 and only one study found a statistically significant effect. Eleven studies investigated the effect of nebulized magnesium sulfate compared to placebo, and seven of these studies detected a favorable effect on FEV1/PEFR, four did not. Five studies looked into the effect on hospital admission, two found an effect of MgSO4, three did not. The meta-analysis showed that patients receiving either nebulized or iv-magnesium sulfate treatment on average had higher peak expiratory flow compared to placebo. However, the average peak expiratory flow was lower in patients receiving iv-magnesium compared to those receiving nebulized magnesium sulfate treatment.

Conclusion: The findings concerning treatment of acute asthma with magnesium sulfate are conflicting when assessed by lung function and hospital admissions. No adverse reactions were reported. The meta-analysis
suggests that the effect of nebulized magnesium sulfate on lung function is better than intravenous administration.

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**Adherence in global airways**

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**Background:** There is an increased awareness, for treating both upper and lower airways (global airway) diseases simultaneously, because they have the similar inflammatory mechanisms. About 9% of the adult population suffers from chronic rhinosinusitis (CRS). Four percent of these have CRS with nasal polyps (CRSwNP) and 5% does not have nasal polyps (CRSsNP). In addition, 7–10% of the Danish population suffers from asthma. About 40–70% of these have both CRSwNP and asthma – depending of the severity of the nasal disease, the more severe the disease and the more frequent asthma as a comorbidity. All in all, there is a large population with airway diseases and a large overlap between upper and lower respiratory diseases. CRS has a multifactorial background, where CRSwNP has an impact on asthma control and well-controlled asthma has an impact at CRS-control. This can be recognized in the daily practice, where patient experience high burden of diseases who has a large impact on their daily lives and thereby also resulting in significant reduced quality of life. Several studies show that those with asthma have low adherence, but there are few studies on adherence in CRS. The patients are depended on seeing different specialists (ENT and pulmonary) to improve their adherence in the upper and lower airways.

**Aim:** The aim is to investigate patients’ adherence with diseases of the global airways, and to analyses whether their patients’ adherence with diseases of the global airways should and can be improved.

**Method:** Patients with CRS and asthma will be randomized into a control or intervention group where their adherence will be measure by MARS-5. Patients in the intervention group receive systematic and structured supervision about their disease and treatment. Patients in the control group only receive usual supervision.

**Results and Conclusion:** The study has not yet been completed.

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**Upper airways: association between olfactory training and quality of life in patients with impaired sense of taste and smell following COVID-19**

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**Background:** Loss of the sense of taste and smell occurs in 65–88% of patients infected with corona virus. In contrast to previous post-viral olfactory loss, it is often younger patients with milder symptoms of COVID-19, who experience chemosensory dysfunction. The duration of the impaired sense of taste and smell ranges from a few days to weeks after the end of the infection. Moreover, 20–28% of the patients have persistent impaired sense of taste and smell, which is also a frequently reported sequelae after infection with COVID-19. Previous studies show that loss of the sense of taste and smell is associated with a decline in quality of life. Olfactory training has been shown to be effective in other patient groups, while in olfactory dysfunction in COVID-19 there is not yet evidence on the long-term effect of olfactory training and whether it can improve quality of life.

**Aim:** The primary aim is to investigate whether systematic olfactory training with essential oils to improve impaired sense of taste and smell following COVID-19 can improve patients’ quality of life. The secondary aim is to investigate the effect of olfactory training.

**Method:** Patients with anosmia or hyposmia following COVID-19 will be randomized to the intervention or control group. The intervention group received essential oils with scents of orange, lavender, clove, and peppermint. The control group received the four same containers, but with fragrance-free oils. Both groups will be
instructed to do olfactory training with each of the oils for 30 s in the morning and evening for 3 months. Subjective olfactory status and quality of life will be evaluated with Taste and Smell Tool for Evaluation at baseline and at 3-month follow-up. The effect of olfactory training will be evaluated with Sniffin’ Sticks.  

**Results and Conclusion:** The study has not yet been completed.

**Extended-release morphine for chronic breathlessness in chronic obstructive pulmonary disease: a randomized controlled trial with blinded up-titration over 3 weeks**

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**Background:** Chronic breathlessness is a major cause of suffering and limited activity in patients with chronic obstructive pulmonary disease (COPD). Regular, low-dose morphine might relieve breathlessness, but evidence on patient selection, efficacy, and optimal dose is conflicting or lacking.  

**Methods:** Multisite, phase III, double-blind, placebo-controlled, randomized trial of patients with COPD and chronic breathlessness (modified Medical Research Council score 3–4) randomized (1:1:1) to daily, oral extended-release (ER) morphine 8 mg, 16 mg, or placebo. After 1 and 2 weeks, participants were further randomized (1:1) to adding either ER morphine 8 mg or placebo. Primary endpoint was intensity of worst breathlessness (previous 24 h) after 1 week. Secondary endpoints included daily steps (Actigraphy), functional status, anxiety/depression, health-related quality of life, and adverse events, at 1 and 3 weeks.

**Results:** A total of 156 patients with COPD (48% female) were randomized to daily morphine 8 mg (n = 55), 16 mg (n = 51), or placebo (n = 50) for week 1 and analyzed by intention-to-treat. Treatment groups after 3 weeks were as follows: morphine 8 mg (n = 39), 16 mg (n = 52), 24 mg (n = 40), 32 mg (n = 12), or placebo (n = 13). Baseline characteristics were similar between groups. Primary endpoint of worst breathlessness after 1 week was similar with morphine vs. placebo, mean difference −0.25 (95% confidence interval, −0.83–0.33) on a 0–10 numerical rating scale. Secondary endpoints were similar by treatment group both after 1 and 3 weeks. Morphine increased harms including serious adverse events.  

**Conclusion:** Morphine did not systematically improve breathlessness, physical activity or other secondary outcomes, but increased harms in COPD patients during 3 weeks up-titration.  

Trial registration: NCT02720822.
increased odds ratio for COPD in individuals with parental COPD. Four studies reported on parental smoking history and nine studies reported on smoking history in offspring. Three studies evaluated the association between parental COPD and COPD-related outcomes in patients with COPD. **Interpretation:** This review indicates that parental COPD is associated with a higher risk of COPD in offspring. The literature is sparse, and we identified a knowledge gap on whether parental COPD is a risk factor for severe COPD and other health conditions in offspring.

**Sing-a-Lung: are changes in physical exercise capacity and quality of life associated after a 10 weeks’ Singing for Lung Health programme within pulmonary rehabilitation for patients with COPD?**

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**Background and aims:** Recently, an RCT demonstrated that Singing for Lung Health (SLH) was effective in improving both Six-Minute Walking Test Distance (6MWD) and quality of life (St. George’s Respiratory Questionnaire (SGRQ Total Score)) within a 10 week pulmonary rehabilitation (PR) programme (NCT03280355) [1]. However, associations between reaching the minimal important difference (MID) in both 6MWD (MID = ≥30 m) and SGRQ (MID = =5-4 units) remain unknown.

**Methods:** We performed post-hoc analyses in the per-protocol population receiving SLH. We used logistic regression models, Cohen’s kappa, and Cochran–Mantel–Haenszel test to investigate correlation, association, and agreement concerning the reaching of MID in both 6MWD and SGRQ.

**Results:** Baseline characteristics in the SLH group (n = 108) were as follows: Females: 57%; mean age 71 ± 8 years; pack years 41 ± 22; body mass index (BMI): 28 ± 6 kg/m²; and FEV1% predicted: 51% ±17%. 6MWD MID was achieved by 31 (29%) patients, and SGRQ MID by 53 (49%). Baseline outcomes associated with achieving MID of either outcome were higher BMI, lower FEV1, shorter 6MWD, and higher SGRQ. Achieving MID in 6MWD did not agree significantly with achieving MID in SGRQ and vice versa (agreement: 57.4%; κ = 0.14; p = 0.14).

**Conclusions:** Achieving MID in 6MWD or SGRQ was associated with poor baseline performance. Achieving MID in SGRQ was more common than achieving MID in 6MWD. Moreover, achieving MID in one outcome agreed surprisingly poorly with improvement in the other.

1. Use of Singing for Lung Health as an alternative training modality within pulmonary rehabilitation for COPD: an RCT. M. Kaasgaard, D. Bech Rasmussen, K. Andreasson, A. Løkke, P. Vuust, O. Hilberg, U. Bødtker. *European Respiratory Journal* 2021. DOI: 10.1183/13993003.01142–2021

**Lung cancer registries in Denmark, Finland, Norway, and Sweden**

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**Background:** There are significant differences in lung cancer survival between the Nordic countries. Historically, Denmark has had the both the highest lung cancer incidence and the lowest survival, based on data from the respective national cancer registries. The Nordic countries have similar demographics and tax-funded health-care systems. Denmark, Finland, Norway, and Sweden all have national population-based cancer registries.

**Aim:** This study aimed to describe and compare the lung cancer registries of the four most populous Nordic countries.

**Methods:** We collected documentation describing the composition of each register, how data are collected
and reported. Moreover, we compared the key endpoints from the latest annual reports.

**Results:** Denmark, Finland, Norway, and Sweden all have lung cancer or cancer registries including data on lung cancer with a high level of completeness. Even though the information in the Nordic Cancer Registries is comparable, there are still numerous differences in registration practices, classification systems and level of detail among the registries. Denmark has a separate clinical lung cancer registry, which collects data from both the National Patient Registry and via practicing clinicians and not the Danish Cancer Registry. This registry contains more detailed information on diagnostic procedures and treatment. However, it does not receive data from the Cause of Death Registry. Finland and Norway report lung cancer survival as relative survival, whereas Denmark and Sweden report overall survival.

**Conclusion:** Although the Nordic lung cancer registries are largely comparable, investigators and policymakers should be aware of possible differences in data composition and reported survival statistics.

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**Characteristics of patients developing anxiety after admission for COPD exacerbation**

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**Aim:** Patients with COPD have an increased risk of developing anxiety. This study aimed to assess which patient characteristics alter the risk of developing anxiety in a COPD population.

**Method:** This cohort study used the Danish National Patient Registry. Patients aged 40–90 years admitted for COPD between 01.01.99 and 31.12.18, without mental disorders within the previous 10 years, were included. Sex, age, inhaled medication, educational level, and comorbidities (heart failure, diabetes, and cancer) were evaluated.

**Results:** A total of 97,929 patients were included. Possible outcomes were either hospital admission/outpatient care with anxiety or anxiolytic treatment (ATC N05B).

The risk of hospital treatment decreased with age (age 40–50 hazard ratio [HR] 2.3 [95% confidence interval (95% CI) 1.14–4.62] compared to age 81–90 HR 0.54 [95% CI 0.31–0.95]). The risk of requiring anxiolytics increased with age (age 40–50 HR 0.71 [95% CI 0.57–0.90] compared to age 71–80 HR 1.14 [95% CI 1.06–1.24]). The risk of redemption of anxiolytics increased with male sex (HR 1.32 [95% CI 1.18–1.41]), whereas the risk of hospital treatment decreased (HR 0.56 [95% CI 0.38–0.81]). There was a decreased risk of redeeming anxiolytics in those with higher educational level (HR 0.9 [95% CI 0.84–0.97]). There was an increased risk of hospital treatment in patients requiring triple therapy (HR 1.61 [95% CI 1.04–2.50]), whereas a decreased risk of redeeming anxiolytics was seen in those patients (HR 0.88 [95% CI 0.8–0.97]). An increased risk of redemption of anxiolytics was seen in patients with concomitant cancer (HR 1.27 [95% CI 1.14–1.42]), whereas a decreased risk was seen in patients with concomitant diabetes (HR 0.77 [95% CI 0.69–0.85]).

**Conclusion:** Inconsistencies are found between those receiving hospital treatment for anxiety and those redeeming prescribed anxiolytics. This suggests that there are several clinical manifestations of anxiety in a COPD population, dependent on age and disease severity. Further investigation is needed to understand these clinical pictures.

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**The prevalence of severe asthma, use of oral corticosteroid, and management strategies in the Nordic countries: results from the pan-Nordic NORDSTAR cohort**

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Background: The Nordic countries share similar health-care systems, but the prevalence and management of severe asthma have not previously been evaluated and compared between the countries.

Aim: Using data from the NORDic Dataset for asthma (NORDSTAR) cohort, we compare the prevalence of severe asthma, the use of oral corticosteroids (OCS) in severe asthma, and to which extent these patients are followed in specialist care in the Nordic countries.

Methods: NORDSTAR is a population-based, observational dataset of asthma patients based on Nordic registries. Using a cross-sectional design, we identified adult patients with severe asthma according to the ERS/ATS definition in 2018. High cumulative OCS use was defined as dispensed fillings ≥5 mg/day in 2018. Patients managed in specialist care were those with an asthma-related outpatient contact (only available in Sweden and Finland).

Results: We identified N = 6,477, N = 6,999, and N = 8,476 severe asthma patients corresponding to 3.5, 5.4 and 5.2% of all asthma patients aged ≥18 in Sweden, Norway, and Finland, respectively. Most patients with severe asthma had a high cumulative use of OCS; 53, 66, and 63% in the three countries, respectively. In Sweden and Finland, 33 and 39% of the patients with high cumulative OCS use were currently managed in specialist care.

Conclusion: Population-based nationwide data demonstrate a comparable prevalence of severe asthma and a high cumulative OCS use in the Nordic countries. Most patients with severe asthma and high cumulative OCS use are currently not managed by a respiratory specialist, indicating the need for increased awareness of severe asthma in primary care.

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Characterization of patients with severe fatigue after hospitalization with Covid-19

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**Background:** SARS-CoV-2 virus, causing Covid-19, continues to be a public health concern. Long-term sequelae after infection with Covid-19 has been reported worldwide and holds the risk of becoming a major health concern. Ongoing symptoms more than 3 months after infection is now defined as long Covid. Fatigue and psychological distress are among the most common symptoms in long Covid.

**Aim:** To investigate severe fatigue and psychological distress after hospitalization in patients with Covid-19.

**Methods:** Patients hospitalized with Covid-19 in the Central Denmark Region were invited for follow-up 3–6 months after discharge. Psychological distress was measured by Hospital Anxiety and Depression Scale (HADS) with a HADS score ≥8 identifying cases of anxiety and depression in the two subdomains. Fatigue was assessed using Fatigue Assessment Scale (FAS) with a FAS ≥35 indicating severe fatigue. Basic characteristics from the hospitalization were registered.

**Results:** A total of 218 patients (mean age 59.9 (95% CI 58.2, 61.7), 59% men) reported a mean HADS of 7.9 (95% CI 6.95, 8.93). Cases of anxiety and depression were found in 23 and 16% of all patients, respectively. Overall, a mean FAS of 25.6 (95% CI 24.3, 26.9) was found with 34 patients (18%) reporting severe fatigue. Patients with severe fatigue (mean age of 54.2 (95% CI 50.3, 58.1), 47% males), cases of anxiety and depression was reported by 59 and 62%, respectively. Analyses of FAS in subdomains on mental and physical fatigue showed mean scores of 19.3 (95% CI 18.5, 20.2) and 20.6 (95% CI 19.8, 21.5), respectively.

**Conclusion:** Severe fatigue is common after hospitalization in patients with Covid-19 and includes both mental and physical fatigue. In addition, cases of anxiety and depression are common in patients with severe fatigue.

**High-pressure NIV for acute hypercapnic respiratory failure in COPD: improved survival in a Danish cohort**

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**Background:** Updated treatment guidelines for acute hypercapnic respiratory failure (AHRF) in chronic obstructive pulmonary disease (COPD) with non-invasive ventilation (NIV) in 2016 recommended a rapid increase in inspiratory positive airway pressure (IPAP) to 20 cmH2O with possible further increase for patients not responding. Previous guidelines from 2006 suggested a more conservative algorithm and maximum IPAP of 20 cmH2O.

**Aim:** To determine whether updated guidelines recommending higher IPAP during NIV were related with improved outcome in patients with COPD admitted with AHRF, compared to NIV with lower IPAP.

**Methods:** A retrospective cohort study comparing patients with COPD admitted with AHRF requiring NIV in 2012–2013 and 2017–2018.

**Results:** A total of 101 patients were included in the 2012–2013 cohort with low IPAP regime and 80 patients in the 2017–2018 cohort with high IPAP regime. Baseline characteristics, including age, FEV1, pH, and PaCO2 at initiation of NIV, were comparable. Median IPAP in the 2012–2013 cohort was 12 cmH2O (IQR 10–14) and 20 (18–24) in the 2017–2018 cohort, p < 0.001. In-hospital mortality was 40.5% in the 2012–2013 cohort and 13.8% in the 2017–2018 cohort, p < 0.001. The 30 days and 1-year mortality were significant lower in the 2017–2018 cohort. With a Cox model, 1-year survival analysis, adjusted for age, sex, FEV1, and pH at NIV initiation, the hazard ratio was 0.45 (95% CI: 0.27–0.74, p = 0.002).

**Conclusions:** Short- and long-term of survival rates were substantially higher in the cohort treated with...
higher IPAP. Our data support the current strategy of rapid increase and use of higher pressure.

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Feasibility of quick functional capacity assessment of citizens with COPD in limited settings

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Background: Assessing changes in functional capacity is highly relevant in the treatment of citizens with chronic obstructive pulmonary disease (COPD). In Denmark, most citizens with COPD are followed in general practice, where traditional functional tests, like shuttle and 6-minute walk tests, require too much time and space. Therefore, there is an urgent need for a quick functional capacity test that can be performed in a limited setting such as general practice.

Aims: To identify a quick test to measure functional capacity in citizens with COPD and identify which factors could affect the implementation of such a test in general practice.

Method: A mixed-method feasibility study composed of a literature review and fieldwork using qualitative interviews. Studies describing short functional tests were searched and then evaluated with the COSMIN checklist. For the fieldwork, 50 general practices and 14 general practitioners (GPs) participated in interviews. Responses were categorised and thematically analysed.

Results: The 1-minute sit-to-stand (1 M STS) was suitable for a general practice setting. The COSMIN checklist rated it sufficient in reliability (ICC 0.90–0.99), measurement error (MID 2.5–3), construct validity and responsiveness (AUC 0.72), and found a moderate to strong correlation in criterion validity ($r = 0.4–0.75$). Several GPs wished for a quick functional test and emphasised evidence, information, and limitations as essential when deciding on implementation. Other factors identified included time, other tests, and economy.

Conclusion: 1 M STS is a valid, reliable, and responsive test for assessing functional capacity in citizens with COPD. The test is quick and can easily be performed within a standard consultation time. Reference values and protocols for 1 M STS are available, yet GPs still hesitate to use the 1 M STS.

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A comparison of pharmacological asthma treatment from 2005 to 2015: results from the PRAXIS study

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Background and Aims: Underuse of inhaled corticosteroids (ICS) and overuse of short acting β2-agonists (SABA) is common in asthma patients, and overuse of SABA is related to increased risk of asthma exacerbations and mortality. The aim of this study was to investigate the change in asthma treatment over time and to identify factors related to pharmacological asthma treatment.

Methods: Adult patients with doctor-diagnosed asthma were randomly selected from 14 hospitals and 56 primary health-care centres in Sweden and were sent questionnaires about their symptoms,
maintenance treatment and use of any rescue medication more than two times the previous week. The study was conducted in two different cohorts: from 2005 with 1182 patients and 2015 with 1225 patients included. In 2015, the questionnaire also included Asthma Control Test.

**Results:** From 2005 to 2015, maintenance treatment with ICS in combination with long-acting β2-agonists (LABA) and/or leukotriene antagonists (LTRA) increased from 39.2% to 44.2% ($p = 0.012$). Use of ICS-LABA as rescue medication increased (11.1% to 18.9%, $p < 0.001$). There was no significant difference over time in total use of rescue medication (51.2% vs. 49.4%, $p = 0.39$) or in total use of regular ICS (54.2% vs. 57.2%, $p = 0.14$). Older age, previous smoking, and poor asthma control were related to a higher likelihood of treatment with ICS-LABA/LTRA. In 2015, 22.7% reported daily use of SABA (no data from 2005). Among patients with neither regular nor periodical ICS 5.6% used SABA daily. Higher level of maintenance treatment, older age, obesity, low educational level, current smoking, allergic asthma, and low as well as very high physical activity were associated with daily SABA-use.

**Conclusions:** The results indicate that there is still a need to increase the use of ICS among asthma patients and that SABA-overuse occurs in all treatment steps.

**Prognostic factors for COPD outcome: a nationwide cohort study**

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**Background:** Chronic obstructive pulmonary disease (COPD) is a chronic disease with deterioration in lung function and increasing risk of hospitalization over time. This study aimed to investigate the impact of clinical factors on COPD exacerbations and hospitalizations.

**Methods:** The study was a nationwide, population-based cohort study utilizing Danish health registries. In total, 44,733 patients ≥40 years of age, with an in- and/or outpatient diagnosis of COPD (ICD-10 J44) in 2008–2017, were identified in the nationwide Danish COPD Registry. Multiple descriptive data were registered such as marital status, education, comorbidities, MRC, smoking status, and body mass index. Patients were followed for 12 months, and Poisson regression as well as Cox Regression were used to calculate the impact of these data on exacerbations, hospitalizations, and deaths. Exacerbations were divided into moderate (short-term oral corticosteroid use) or severe (emergency visit or hospitalization). Index was the date of the first outpatient visit.

**Results:** In all, 44,733 patients with COPD (mean age, 69.2 years; 52% females) were included. COPD-related exacerbations and hospitalizations were associated with a number of comorbidities, MRC, and FEV1. Similar results were found for hospitalization due to any diagnosis. According to survival, results were similar. Furthermore, smoking status was important for survival as never smokers had a significantly lower mortality ratio (HR 0.75, ref. former smokers) than present smokers (HR 1.2, ref. former smokers).

**Conclusion:** This study shows a significant impact on smoking cessation for comorbidities, exacerbations, and hospitalizations. Smoking is the most important modifiable risk factor for COPD and smoking cessation is recommended to all COPD patients. Furthermore, smoking is also an important risk factor for other diseases influencing the prognosis for COPD. Results from this study can help health-care professionals motivating patients to smoking cessation.

**Clinical response and remission in patients with severe asthma treated with biologic therapy: findings from the nationwide Danish Severe Asthma Registry**

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Background: There is growing interest in the ability of biologic treatment to induce remission of severe asthma, and clinical remission on treatment has recently been defined as complete control of exacerbations, oral corticosteroid (OCS) use, lung function, and asthma symptoms. We assessed response rates and baseline characteristics associated with these outcomes in a real-life setting.

Methods: The Danish Severe Asthma Registry is a nationwide register including all patients receiving biologic treatment for severe asthma in Denmark. We defined 'clinical response' to treatment after 12 months as ≥50% reduction in exacerbations, and/or a ≥50% reduction in OCS dose. 'Clinical remission on treatment' was defined by cessation of exacerbations and maintenance OCS, as well as a normalization of lung function (FEV1% >80%) and an Asthma Control Questionnaire score ≤ 1.50.

Results: In 274 bionaive patients, 225 (82%) had a clinical response, of whom 43 (19%) fulfilled our criteria of clinical remission, whereas 49 (18%) patients were non-responders. Compared to patients who obtained a clinical response, patients with clinical remission were more likely to be male (71% vs. 48%), have disease duration less than 10 years (47% vs. 29%), have higher baseline blood eosinophils (0.48 vs. 0.32 × 10^9/L), and higher immunoglobulin E levels (231 vs. 136 kU/A/L).

Conclusion: A majority of patients obtained a clinically significant response. Clinical remission was predicted by shorter disease duration, and higher levels of T2 biomarkers; further studies are required to assess whether timing of biological treatment is crucial for better long-term outcomes.

Characteristics and outcomes of patients with severe asthma treated with biologics, stratified according to baseline FEV1: the nationwide Danish Severe Asthma Registry (DSAR)

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Background: To our knowledge, there is limited evidence on whether the effect of biological treatment of severe asthma could depend on baseline FEV1. We hypothesized that real-life severe asthma patients with FEV1 ≤ 60% predicted have different characteristics and a poorer response to treatment.

Methods: The Danish Severe Asthma Registry (DSAR) consists of all patients initiating treatment with biologics in Denmark since 2017. We studied baseline characteristics of patients with FEV1 ≤ 60% or >60%, differences in exacerbation rates and use of maintenance oral corticosteroids (mOCS), as well as secondary outcomes of symptoms and levels of inflammatory biomarkers (blood eosinophils, total immunoglobulin E, FeNO) at 12 months of follow-up.

Results: Of 584 patients included, 197 (34%) had FEV1 ≤ 60% and 387 (66%) had FEV1 > 60%. Patients with FEV1 ≤ 60% were older, had a longer disease duration and more pack-years, were more symptomatic, and had a higher prevalence of bronchiectasis, but less with allergic rhinitis and nasal polyposis at baseline. Surprisingly, patients with FEV1 ≤ 60% had a similar reduction in exacerbation rate (3.30–0.73 vs. 3.05–0.76, p = 0.37) and reduction in use of mOCS (27–12% vs. 30–13%, p = 0.67), and similar effect on symptoms and levels of inflammatory biomarkers after 12 months.

Conclusion: In patients with severe asthma treated with biologics, stratified by FEV1, we found important baseline differences. Surprisingly, in patients with FEV1 ≤ 60% the effect of biologics on exacerbations,
The impact on number of hospitalizations and length of hospital stay for patients with advanced COPD affiliated with a cross-sectorial lung team

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Background: As the severity of chronic obstructive pulmonary disease (COPD) advances, the risk of hospitalization due to acute exacerbations of COPD (AECOPD) becomes more frequent, and often it leads to hospitalization. The aim of this study was to investigate the effect of affiliation with a cross-sectorial lung team (lung team) on number of hospitalizations and length of hospital stay in patients with advanced COPD.

Methods: In the study period 2017–2020, a randomized controlled trial was conducted. The patients were randomized to affiliation with the lung team for receiving usual care. They were included for 1 year. In case of worsening in respiratory symptoms, patients affiliated with the lung team were able to contact the team day and night. The lung team offered acute home visits and was able to initiate home treatment. The lung team consisted of respiratory nurses from the hospital and community nurses. Patients receiving usual care contacted the general practitioners, doctors on call or emergency service in case of any worsening in respiratory symptoms. The patients had to have FEV1 <50% predicted and have ≥ one severe or two moderate AECOPD events within a year. In total, 56 patients were affiliated with the lung team (Mean: age 71.6 years, FEV1 37%) and 57 patients received usual care (Mean: age 71.5 years, FEV1 34%).

Results: On average, patients affiliated with the lung team had fewer hospitalizations due to AECOPD than patients receiving usual care (lung team: 0.59 (95% CI: 0.35–0.83), usual care: 1.86 (95% CI: 1.12–2.20) (p = 0.002)). On average, patients affiliated with the lung team had shorter length of hospital stay due to AECOPD (lung team: 3.27 (95% CI: 2.39–4.15), usual care: 4.47 (95% CI: 3.70–5.24) (p = 0.045)).

Conclusions: Affiliation with the cross-sectorial lung team reduced both number of hospitalizations and length of hospital stay due to AECOPD compared to usual care.

Productive vs non-productive chronic cough associated with worse lung health and higher morbidity and mortality in the general population

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Background: Whether productive or non-productive chronic cough is worse in the general population is unknown. We tested the hypothesis that productive vs non-productive chronic cough is associated with worse lung health and higher morbidity and mortality in the general population.

Methods: We included 44,436 random adults from the Copenhagen General Population Study and defined productive chronic cough as a cough lasting more than 8 weeks with mucus production during the day as long as 3 consecutive months a year. We investigated differences in lung function, accompanying respiratory symptoms, morbidity, and mortality.

Results: Among 44,436 individuals, 1416 (3%) had productive chronic cough and 1380 (3%) non-productive chronic cough. Individuals with productive vs non-productive chronic cough had lower lung function (FEV1 88% vs 95% predicted, FVC 97% vs 101% predicted, and FEV1/FVC 0.72 vs 0.75), and more often accompanying respiratory symptoms (dyspnoea 5% vs 3% and wheezing 53% vs 29%), gastroesophageal reflux disease (36% vs 28%), and diabetes (11% vs 7%), and higher levels of inflammatory biomarkers in blood at baseline examination. Individuals with productive chronic cough vs controls had adjusted hazard ratios (HRs) of 7.2 (95% confidence interval: 4.3–12) for COPD exacerbation, 2.9 (2.2–3.8) for pneumonia, and 2.1 (1.6–2.6) for all-cause mortality. Corresponding
HRs for non-productive chronic cough were 3.0 (1.4–6.2), 1.8 (1.2–2.5), and 1.5 (1.1–2.1), respectively.

**Conclusion:** Individuals with productive versus non-productive chronic cough have worse lung health and higher risk of morbidity and mortality.

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**Factors associated with medication adherence among adults with asthma**

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**Background:** Asthma medication adherence is of crucial importance for successful disease management. The aim of this study was to identify and rank factors associated with medication adherence among adults with asthma in the general population.

**Methods:** We used data on physician-diagnosed asthma, medication adherence, and factors associated with asthma medication adherence from the Danish General Suburban Population Study. We ranked factors associated with asthma medication adherence based on magnitude of odds ratios, and the population attributable fractions.

**Results:** Among 20,032 individuals from the general population, 1,128 (6%) suffered from asthma and 822 (73%) of these were adherent to asthma medications. Based on odds ratios, the three top-ranked factors associated with asthma medication adherence were asthma attacks within the past year (4.0; 95% CI: 2.9–5.5), allergy medication use (3.8; 2.6–5.6), and age above median (3.4; 2.4–4.7), followed by asthma severity markers like airway obstruction and coughing with mucus. Based on population attributable fractions, the three top-ranked factors associated with adherence to asthma medications were asthma attacks within the past year (70%), age above median (57%), and use of allergy medication (49%).

**Conclusion:** The study showed that in the general population, recent asthma attacks, higher age, and taking allergy medication were the three most important factors associated with asthma medication adherence.

The importance of maintaining adherence to asthma medications even in the absence of severe disease or expressed asthma symptoms should be better communicated to the general population.

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**Inhaled corticosteroids in patients with chronic obstructive pulmonary disease and risk of acquiring *Streptococcus pneumoniae* infection: a multiregional epidemiological study**

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**Background:** Inhaled corticosteroids (ICS) are associated with an increased risk of clinical pneumonia among patients with chronic obstructive pulmonary disease (COPD). It is unknown whether the risk of microbiologically verified pneumonia such as pneumococcal pneumonia is increased in ICS users.

**Methods:** The study population consists of all patients with COPD followed in outpatient clinics in eastern Denmark during 2010–2017. ICS use was categorized into four categories based on accumulated use. A Cox proportional hazard regression model was used adjusting for age, body mass index, sex, airflow limitation, use of oral corticosteroids, smoking, and year of cohort entry. A propensity score-matched analysis was performed for sensitivity analyses.

**Findings:** A total of 21,438 patients were included. Of these patients, 582 (2.6%) acquired a positive lower airway tract sample with *S. pneumoniae* during follow-up. In the multivariable adjusted analysis, ICS-use was associated with a dose-dependent risk of *S. pneumoniae* as follows: low ICS dose: HR 1.11, 95% CI 0.84 to 1.45, \( p = 0.5 \); moderate ICS dose: HR 1.47, 95% CI 1.13 to 1.90, \( p = 0.004 \); high ICS dose: HR 1.77, 95% CI 1.38–2.29, \( p < 0.0001 \). Sensitivity analyses confirmed these results.

**Conclusion:** Interpretation use of ICS in patients with severe COPD was associated with an increased and dose-dependent risk of acquiring *S. pneumoniae*, but only for moderate and high dose. Caution should be taken when administering high dose of ICS to patients with COPD. Low dose of ICS seemed not to carry this risk.

**Francisella tularensis mimicking malignancy**

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**Background:** Tularemia, known as rabbit fever, is a rare zoonotic disease caused by the bacteria *Francisella tularensis*. It can be transferred to humans via vector bites, direct contact with infected animals, consumption of contaminated water or food, or inhalation of aerosols.

**Case description**
Case 1: In October 2020, a 43-year-old woman (gardener and smoker) was admitted to hospital with pneumonia, fever, headache, skin rash, low back pain, and a nasal septum wound. She was treated with piperacillin/tazobactam. The symptoms, however, did not improve.

After 2 weeks, computed tomography and positron emission tomography-computed tomography displayed enlarged mediastinal lymph nodes and suspicious infiltrative changes.

An endoscopic bronchial ultrasound (EBUS) was performed 4 weeks after hospitalization. EBUS was without signs of cancer, molds, or bacteria. The lymph nodes revealed necrotic granulomas. Two weeks later, serological tests for *F. tularensis* antibodies were positive. Doxycycline treatment improved her clinical condition. The patient’s nasal septum was necrotic, and an operation was required.

Case 2: In November 2020, a 42-year-old man with a medical history of rheumatoid and psoriatic arthritis presented with fever, fatigue, and lymphadenopathy in thorax. C-reactive protein and leukocytes were normal, and malignancy was not found. One month later, the patient was diagnosed with necrotizing granulomatous inflammation in the lymph nodes. In January 2021, serology tests for *F. tularensis* were positive. Although almost asymptomatic, the patient was treated with ciprofloxacin.

Both patients recovered completely.

**Conclusion:** Although rare, *F. tularensis* should be kept in mind in the diagnostic workup for unexplained lung infiltrates.

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**Pre-COVID-19 obesity-related asthma phenotypes and risk of COVID-19 infection**

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**Background:** Incidence and clinical outcomes of COVID-19 appear to differ between allergic and non-
allergic asthma, but evidence for other asthma phenotypes, such as obesity-related asthma, is scarce. We sought to determine whether pre-COVID-19 obesity-related asthma phenotypes are associated with risk of COVID-19 incidence in a Swedish population-representative adult cohort.

**Method:** Clinical examination data from 2,006 subjects aged 16–75 years collected during 2009–2012 were linked to register data of COVID-19 diagnosis, based on real-time polymerase chain reaction or ICD-10 codes set by clinicians. Obese asthma was defined as current asthma and body mass index ≥30 kg/m². Allergic obese asthma was further based on sensitization to any aeroallergen measured by specific immunoglobulin E.

**Results:** In total, 344 (17.1%) of the subjects had COVID-19. After adjustment for gender, age, allergy history, farm childhood, urbanization, dust exposure, smoking, education, and occupation, there was no association between having allergic obese asthma (adjusted risk ratio (aRR) 0.92, 95% CI 0.63–1.34), non-allergic obese asthma (aRR 0.94, 95% CI 0.68–1.29), or any obese asthma (aRR 0.93, 95% CI 0.72–1.19), and getting COVID-19. Stratifying by gender and age produced similar results.

**Conclusion:** We found no association between pre-COVID-19 obesity-related asthma phenotypes and being diagnosed with COVID-19. Further analyses are needed regarding long-term outcomes and disease severity of COVID-19 in relation to obesity-related asthma phenotypes.

**Pre-COVID-19 asthma phenotypes and risk of COVID-19 diagnosis**

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**Background:** Previous studies have indicated that asthma phenotypes may play a role in the risk of COVID-19 infection and disease severity, but generalizable data with pre-COVID-19 assessment of asthma are scarce. We examined the relationship between asthma phenotypes and susceptibility of COVID-19 in a population-representative adult cohort from Sweden.

**Method:** Register data on COVID-19 diagnosis based on real-time polymerase chain reaction or ICD-10 codes set by clinicians were linked to clinical data collected in 2012 of subjects aged 16–75 years. The definition of allergic asthma was based on atopy assessed by measurements of specific immunoglobulin E or skin prick test. Multi-symptom asthma was defined as physician-diagnosed asthma with ≥4 signs of active asthma.

**Results:** In total, 878 subjects with current asthma underwent the clinical investigation, of which 166 (18.9%) had COVID-19. Ninety-eight (59%) of these had pre-COVID-19 allergic asthma and 47 (28.3%) had multi-symptom asthma. After adjustment for gender, age, body mass index, allergy history, farm childhood, urbanization, dust exposure, smoking, education, and occupation, there was no association between allergic asthma and COVID-19 infection (adjusted risk ratio (aRR) 1.02, 95% CI 0.76–1.37) or non-allergic asthma and COVID-19 infection (aRR 0.98, 95% CI 0.73–1.32). Multi-symptom asthma was also not associated with COVID-19 infection (aRR 1.29, 95% CI 0.96–1.76).

**Conclusion:** We found no association between having allergic, non-allergic, or multi-symptom asthma, and being diagnosed with COVID-19. Further analyses are needed to assess the relationship between asthma phenotypes and disease severity in patients with COVID-19.

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**Biomarkers of coagulative properties in patients with AECOPD**

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Background: Cardiovascular diseases are common in patients with COPD. Endothelial damage secondary to systemic inflammation may help in explaining this.

Aim: The aim was to determine whether biomarkers of endothelial damage and clot resolution predicted major cardiovascular events (MACE) within 36 months in patients with severe COPD.

Methods: Biological samples from the CORTICO-COP trial, which included patients admitted with acute exacerbation of COPD. We assessed von Willebrand factor (vWF)-activated, vWF-non-active and a fibrin degradation product (X-FIB) vs. time-to-first MACE within 36 months, using multivariable Cox proportional hazards. Interaction with previous MACE was explored.

Results: A total of 299/318 patients in the trial had samples available. Of these 299 patients, 132 had a MACE event. No association were observed between the biomarkers and MACE within 36 months; vWF-a: HR 1.06 [95% CI 0.67–1.67], X-FIB: HR 1.03 [95% CI 0.69–1.53], although vWF-n almost reached significance: HR 1.41 [95% CI 0.98–2.04]. Due to a positive interaction, results for vWF-a and X-FIB were stratified according to known heart failure. For patients with previous heart failure, vWF-a had an HR of 0.41 [95% CI 0.19–0.92] for future MACE.

Conclusion: In patients with COPD having an AECOPD, vWF-n seemed associated with future MACE, although this association was not quite significant. Explanations include Type II error hiding a real association and residual confounding.

Mortality in association with occupational exposure and respiratory diagnosis in Helsinki, Finland: a 24-year follow-up

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Background: Both asthma and COPD may have a relation to occupational exposure. In particular, occupational exposure in manual occupations has been linked with earlier mortality.

Aim: To explore differences in mortality between different obstructive respiratory diseases together with an estimated occupational exposure with the use of a large, randomized population-based cohort.

Methods: This study included 6062 individuals from the FinEsS-Helsinki study with 1014 deaths
during a 24-year follow-up. We applied a Job-exposure Matrix to an occupational categorization to estimate an occupational exposure to airborne particles. The individuals were divided into groups according to their self-reported physician diagnosed asthma, COPD, or the combination of both, or without asthma or COPD, and combined with the exposure estimation. The survival model was adjusted for age, education level, sex, and tobacco smoking status, and used healthy without exposure as reference.

**Results:** High occupational exposure together with asthma 2.06 (95% CI, 1.19–3.57), COPD 4.44 (2.62–7.53) and both diagnoses combined 8.79 (4.51–17.1), had the highest hazard ratios (HR) in the crude model. High exposure alone had HR 1.93 (1.62–2.31). In the adjusted model, the HRs were as follows: asthma 1.71 (0.93–3.12), COPD 1.80 (1.00–3.25), combined 1.94 (1.10–3.42), and high exposure alone 1.35 (1.11–1.63). The combined group also showed a sub-hazard ratio for respiratory mortality 7.21 (3.92–13.3).

**Conclusions:** High occupational exposure alone increases overall mortality but not respiratory related, while the combination of asthma and COPD carries the highest hazard of overall and respiratory mortality.

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**Change in exercise capacity in a cystic fibrosis population after treatment with gene modifying therapy**

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**Background:** Studies have shown improved lung function after initiation treatment with cystic fibrosis transmembrane conductance regulator modulators and patient experience improved physical capacity. The aim of this study was to investigate change in exercise capacity after initiation of lumacaftor/ivacaftor and tezacaftor/ivacaftor treatment (LUM/IVA, TEZ/IVA).

**Methods:** We performed a single-group prospective observational cohort study with follow-up at 6 and 12 months. The study examined change in exercise capacity in people with cystic fibrosis initiating treatment with LUM/IVA and TEZ/IVA, measured by cardiopulmonary exercise testing. Primary outcomes were change in VO2peak and maximal workload.

**Results:** We included 91 patients. The mean change in VO2peak and maximum workload from baseline to 12-months follow-up was 145.7 (91.2;200.2) ml/min and 14.2 (95% CI 9.1;19.2) watt.

**Conclusions:** Patients improved their exercise capacity by a statistically significant increase in VO2peak and maximal workload 12 months after initiation of treatment with LUM/IVA and TEZ/IVA.

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**Severe α1-antitrypsin deficiency is associated with increased risk of heart failure: nationwide and cohort studies**

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**Background and aims:** Individuals with severe α1-antitrypsin deficiency (AATD) have increased elastase activity resulting in continuous degradation of elastin and an early onset of chronic obstructive pulmonary disease. It has been suggested that the increased elastase activity over time also affects the elastic properties of other organs, for instance the heart. We tested whether severe AATD is associated with susceptibility to heart failure events in the Danish population.

**Methods:** We genotyped 91,429 individuals from the Copenhagen General Population Study and 187 patients from the Danish AATD registry and recorded admissions and deaths due to heart failure during
9 years of follow-up. We validated our findings in a nationwide cohort of 2,209 patients with AATD and 21,871 controls without AATD matched on birthday, sex, and municipality. There was no overlap between the two study cohorts.

**Results:** Persons with severe AATD had an increased risk of heart failure hospitalization during follow-up compared with individuals without AATD (HR adjusted: 2.38, 95% CI: 2.03–2.79). In the nationwide cohort study, patients with severe AATD also had a higher risk of heart failure hospitalization compared with individuals without this condition (HR adjusted: 1.77, 1.14–2.74). The risk of heart failure hospitalization was attenuated but remained significant among patients with myocardial infarction (HR adjusted: 1.49, 1.08–2.06), atrial fibrillation (HR adjusted: 1.42, 1.07–1.89) and hypertension (HR adjusted: 1.67, 1.29–2.16). Risk of heart failure death or all-cause mortality during follow-up was higher in individuals with severe AATD compared with individuals without AATD (heart failure death: HR adjusted: 2.14, 1.47–3.11; all-cause mortality: HR adjusted: 3.04, 2.79–3.30).

**Conclusions:** Individuals with severe AATD have an increased risk of heart failure admission and death due to heart failure in the Danish general population.

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**Severe α1-antitrypsin deficiency associated with lower blood pressure and reduced risk of ischemic heart disease: a cohort study of 91,540 individuals and a meta-analysis**

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**Background and Aims:** Increased elastase activity in α1-antitrypsin deficiency may affect elasticity of the arterial walls, and thereby blood pressure and susceptibility to cardiovascular disease. We hypothesized that severe α1-antitrypsin deficiency is associated with reduced blood pressure and susceptibility to cardiovascular disease.

**Methods:** We genotyped 91,353 adults randomly selected from the Danish general population and 187 patients from the Danish α1-Antitrypsin Deficiency Registry and recorded baseline blood pressure, baseline plasma lipids, and cardiovascular events during follow-up. In total, 185 participants carried the ZZ genotype, 207 carried the SZ genotype, and 91,148 carried the MM genotype.

**Results:** α1-Antitrypsin deficiency was associated with decreases in blood pressure of up to 5 mmHg for systolic blood pressure and up to 2 mmHg for diastolic blood pressure, in ZZ vs SZ vs MM individuals (trend test, \( P \leq 0.01 \)). Plasma triglycerides and remnant cholesterol were reduced in ZZ individuals compared with MM individuals (\( t \)-test, \( P < 0.001 \)). α1-Antitrypsin deficiency was associated with lower risk of myocardial infarction (trend test \( P = 0.03 \)), but not with ischemic heart disease, ischemic cerebrovascular disease or hypertension (trend test, \( P \geq 0.59 \)). However, when results for ischemic heart disease were summarized in meta-analysis with results from four previous studies, individuals with versus without α1-antitrypsin deficiency had an odds ratio for ischemic heart disease of 0.66 (95%CI: 0.53–0.84).

**Conclusions:** Individuals with severe α1-antitrypsin deficiency have lower systolic and diastolic blood pressure, lower plasma triglycerides and remnant cholesterol, reduced risk of myocardial infarction, and a 34% reduced risk of ischemic heart disease.

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**Risk of hospital admissions and 1-year mortality rate in COPD patients with alcohol abuse**

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**Background:** Nicotine use and alcohol have long been known to go hand in hand. Approximately 70% of alcoholics are heavy smokers (more than 20 cigarettes per day), compared to 10% of the general population. Tobacco smoking is the main cause of COPD. This
study aims to describe the risk of hospital admission and 1-year mortality rate in COPD patients with alcohol abuse (COPDA) defined as more than 7/14 drinks/week for women and men, compared to patients with alcohol consumption (COPDB) less than 7/14 drinks/week.

Methods: A retrospective cohort study including 675 patients admitted with acute exacerbations of COPD (AECOPD) in 2018. Outcomes were comparison in demographics, difference in readmission within 30 days, number of readmissions within 12 months, and risk of death after baseline admission with AECOPD. Binominal logistic regression was conducted for the statistical analysis. Furthermore, adjustments were made for the following co-variants: age, sex and number of comorbidities. An independent t-test was used to compare the co-variant means between the two groups.

Results: In total, 76 patients identified as COPDA and 599 as COPDB were included. In total, 64% (49/76) vs 42% (253/599) were male, with a mean age of 71 years. vs 79 years (p = 0.001) in COPDA and -B, respectively. No differences were found in 30-day readmission (p = 0.195, 95% CI = 0.797–3.05) or the number of readmissions within 12 months (p = 0.079, 95% CI = 0.45–1.82). Patients in the COPDA group had a significantly higher risk of death than patients with no alcohol abuse did, OR = 1.965 (95% CI = 1.15–3.36) (p = 0.014).

Conclusion: Patients with alcohol abuse admitted for AECOPD were significantly younger. Patients with an alcohol consumption above 7/14 drinks/week have a significantly higher mortality risk. No differences were found between the two groups according to 30-days’ and 12 months’ readmission.

Anxiety and depression in women with asthma undergoing fertility treatment

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Background and Aim: Female asthma is associated with higher need for fertility treatment compared to healthy controls. Furthermore, anxiety and depression have been shown to be common comorbidities in asthma patients. This study aims to investigate symptoms of anxiety and depression in asthmatic women undergoing fertility treatment.

Methods: Asthmatic women (positive asthma test) were recruited from fertility clinics in Eastern Denmark underwent clinical examination, measurements of lung function, and fractional exhaled nitric oxide. Anxiety and depressive symptoms were assessed using the Hospital Anxiety and Depression Scale (HADS). A score greater than 7 in both the HADS-A and HADS-D subscale was defined as anxiety or depression. Data were analysed using SPSS statistical software version 28.

Results: Eighty-six women (mean age 31.7 (4.7) years and mean body mass index 25.8 (4.7) kg/m²) were evaluated. And, 60.5% (n = 52) had a positive skin prick test, 12.8% (n = 11) were current smokers, and 20.9% (n = 18) were former smokers. Mean values for lung function parameters were within the reference range and mean FeNO was 16.8 ppb (13.1), and 24.4% had an ACQ-5 score greater than 1.5, i.e. uncontrolled asthma. The mean HADS-A and HADS-D score was 6.02 (3.59) and 2.62 (2.28), respectively. Twenty-five patients (29.1%) had anxiety, whereas 3 (3.5%) had depression (all 3 with concomitant anxiety). Stratified according to asthma control (ACQ-5 score >/≤1.5), 42.9% of the women with uncontrolled asthma had anxiety compared to 24.6% of those with well-controlled asthma (p = 0.109).

Conclusions: Our study suggests that symptoms of anxiety are common among women with asthma undergoing fertility treatment, whereas depression is less prominent in this group.

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Smoking is a predictor of complications in all types of surgery: a machine learning-based database study

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Background and Aims: Machine learning algorithms (MLAs) are promising tools for smoking status classification in large patient data sets. Smoking is an established risk factor for postoperative complications in major surgery. Whether this applies to all types of surgery on a population level remains to be determined. Our study aim was to develop an MLA for smoking status classification, and determine whether smoking and former smoking predict complications in all types of surgery.

Methods: This retrospective cohort study lasted from January 2015 to December 2019. We included all types of surgical procedures performed in the HUS (Helsingin ja Uudenmaan sairaanhoitopiiri) hospital district in southern Finland, retrieving data from the HUS Tietoallas database. Exclusion criteria were age below 16, unknown smoking status and unknown ASA (American Society of Anesthesiologists) class. The main outcome was complications occurring within 90 days after surgery. Secondary outcomes were complications occurring within 90 days after surgery in the orthopedic surgery and gastroenterological surgery subgroups.

Results: The MLA had the precision 0.958 for smokers, 0.974 for ex-smokers, and 0.95 for never-smokers. The sample included a total of 156,185 surgeries. Of the patients, 45,044 (28.8%) were current smokers, 22,867 (14.6%) ex-smokers, and 88,274 (56.5%) never-smokers. After adjustment for covariates, current smokers had increased odds of complications in all surgeries (OR 1.17, 95% CI 1.14–1.20), orthopedic surgery (OR 1.33, 95% CI 1.23–1.44) and gastroenterological surgery (OR 1.21, 95% CI 1.13–1.29). Ex-smokers only had increased odds of complications in all surgeries (OR 1.11, 95% CI 1.07–1.14). On assessment of relative variable importance, ASA class was the most important predictor.

Conclusions: Utilization of an MLA for smoking status classification appears feasible in large surgical data sets. Current smoking and, to a lesser extent, former smoking predict complications in all types of surgery. Cooperation between smoking cessation clinics and surgical units could be a future goal.

Development in diagnosed comorbidities over a 12-month period in patients with COPD

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Background: Patients with chronic obstructive pulmonary disease (COPD) is one of the largest, most impaired, and comorbid patient populations in the health care system.

Aim: To observe newly diagnosed comorbidities over a 12-month period.

Method: A prospective follow-up of 59 patients with stable COPD. Patients were interviewed, underwent body plethysmography, and high-resolution thoracic computed tomography. Patients’ medical records and redemptions of prescribed medicine were investigated to identify known comorbidities at baseline and after 12 months.

Results: In total 59 patients (32 female/27 male) with a median age of 65 years (IQR 60–71); a median FEV1% of 64% (IQR 46–74%); a median body mass index of 26 kg/m² (IQR 23–30); a median of 35 pack-years (IQR 20–45), and median of 4 (IQR 2–6) comorbidities at baseline. Over 12 months the patients were diagnosed with a median of 1 (IQR 0–1) additional comorbidity. The highest increase in comorbidities occurred in hypercholesterolemia (n = 11), hypertension (n = 8), and depression (n = 7).

Conclusion: The development in number of comorbidities calls for increased focus on comorbidities in COPD.

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Survival amongst patients with malignant pleural effusion caused by lung cancer: a retrospective cohort study

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Background and Aims: Presence of malignant pleural effusion (MPE) in non-small cell lung cancer (NSCLC) denotes stage IVa (TNM – M1a) disease and is associated with poor survival, breathlessness, and increased healthcare burden. Several studies have estimated median survival at 5–8 months, but contemporary data from Nordic countries are absent.

Methods: A cohort of 108 lung cancer patients diagnosed with MPE at our unit between 2016 and 2020 were retrospectively analyzed. A Kaplan–Meier survival plot was calculated and adjusted for sex and age.

Results: At MPE diagnosis, median age was 75 (range, 52–95) years, 53% were female, 63% had a significant smoking history, 83% had a lung adenocarcinoma, and 26% had a history of former cancer. EGFR and PD-L1 mutations were analyzed and positive in 5/17 and 19/39, respectively. Median survival from diagnosis was 139 (IQR range, 44–574) days. There was no significant difference between male and female survival. No significant difference in survival was seen between patients stratified over and under 75 years.

Conclusions: Median survival was 4.5 months from MPE diagnosis in NSCLC and thus comparable with other studies. The mortality risk is high with 25% diseased before day 44. MPE is a serious risk factor for poor survival, especially in patients with NSCLC. The Lent and Promise scores have been developed to help estimate survival in patients with MPE. These can be used to support healthcare professionals, patients, and relatives alike in informed shared decision-making.

Association between thoracic muscle mass assessed by high-resolution computed tomography and static lung volume in patients with COPD: a pilot study

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Background: Patients with chronic obstructive pulmonary disease (COPD) are at risk of progressive muscle mass reduction, but it is unclear whether there is a relationship between thoracic muscle mass and static lung volume.

Aim: To investigate whether there is an association between thoracic muscle mass and static lung volume in patients with COPD.

Methods: An observational study based on outpatients with stable COPD, who received a body plethysmography and high-resolution thoracic computed tomography (HRCT). Skeletal muscle tissue with Hounsfield units between −29 and +150 was segmented on an axial HRCT image at the first slice above the aortic arch using in-house software. Measures of skeletal muscle area were reported as cumulated height-adjusted skeletal muscle index (SMI, cm²/m²), thus excluding the intercostal muscle. Baseline values were reported as median (interquartile range). Linear regression analysis was applied for SMI with the total lung capacity (TLC), residual volume (RV), inspiratory capacity/TLC ratio (IC/TLC) corrected for gender.

Results: In total, 42 patients were included (21 male/21 female), age of 65 (61–69) years, SMI 56.8 cm²/m² (49.4–66.3 cm²/m²), TLC 115.5% (105–122%), RV 160.5% (133–195%), IC/TLC .815 (.695–.991). SMI had a negative linear relationship with TLC (adj R² = .441) and RV (adj R² = .416) and a positive linear relationship with IC/TLC ratio (adj R² = .436) (all p-values = <.0001).

Conclusion: This pilot study indicates that there is a significant linear association between the skeletal muscle measure SMI and the static lung volumes in patients with COPD. Static lung volumes may help to
identify patients with reduced muscle mass. However, further studies are needed.

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Impact of co-existing chronic rhinosinusitis on the effect of biological therapy in severe asthma: Danish nationwide cohort study

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Background and Aims: Chronic rhinosinusitis (CRS) is a common comorbidity in severe asthma (SA) associated with more exacerbations and poor symptom control. Biologics have a greater effect in asthma with high levels of type 2 biomarkers; a typical feature in patients with co-existing CRS with or without nasal polyposis (NP). Our aim was to investigate the impact of co-existing CRS on the effect of biologics on asthma and CRS-related outcomes in patients with SA.

Methods: Prospective data from the nationwide Danish Severe Asthma Register were analysed (N = 493). Patients with and without comorbid CRS (including subgroups with and without NP) were compared at baseline, while the effect of treatment expressed as change in asthma-related (ACQ, exacerbation rate, FEV\textsubscript{1}, oral corticosteroid (OCS) dose, and blood eosinophils) and CRS-related (SNOT-22 score) outcomes was assessed at 12 months after initiation of anti-IgE, anti-IL5/IL5R or anti-IL4/13 R treatment.

Results: Of the 493 bionaive patients, 266 (54\%) had co-existing CRS. Compared to patients without CRS, patients with CRS experienced a larger median OCS reduction (from 11.25 (10.00–17.50) to 9.25 (5.00–10.00) mg vs. from 10.00 (7.50–10.00) to 10.00 (5.00–10.00) mg, p = 0.01) and median blood eosinophil reduction (from 0.40 (0.18–0.65) to 0.08 (0.04–0.14) × 10\textsuperscript{9}/L vs. from 0.26 (0.10–0.59) to 0.08 (0.04–0.20) × 10\textsuperscript{9}/L, p = 0.03). No significant differences between the groups were found for change in exacerbation rate (−2.8 vs. −2.5 annual exacerbations), FEV\textsubscript{1} (0.12 L vs. 0.14 L), ACQ (−0.8 vs. −1.0) or SNOT-22 score (−16.6 vs. −10.3).

Conclusions: Co-existing CRS and SA were associated with better effects of biologics on important asthma-related outcomes. Thus, in the management of SA, co-existing CRS may be a relevant exposure to consider.

Translation of the respiratory symptoms, sleep quality, and NIV-related side-effects (S3-NIV) questionnaire into Danish

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Background: The respiratory symptoms, sleep quality, and non-invasive ventilation (NIV)-related side-effects (S\textsuperscript{3}-NIV) questionnaire is a recently developed questionnaire for evaluating patient-centered outcomes in stable COPD patients in long-term home NIV treatment\textsuperscript{1}. It has 11 items and was originally developed in English (UK).

Objectives: The objective of this study was to translate the S\textsuperscript{3}-NIV into Danish, using established methodology.

Methods: The following translation method (linguistic validation) was used: (1) In-depth analysis of the original (i.e. concept definition) by two independent translators and suggestion of translation alternatives; (2) Pilot study in home-NIV-treated COPD patients
and re-evaluation of the initial S3-NIV Danish version; (3) Forward/backward translation; and (4) Review by a clinician.

**Results:** Six patients with NIV-treated COPD provided feedback on the translation. There were no issues concerning the statements, but the distinction between the possible answers in the Danish translation led to reconsideration. The initial English translation of ‘mostly untrue’ and ‘completely untrue’ to the Danish ‘sjældent rigtigt’ and ‘aldrig rigtigt’ was changed to ‘sjældent’ and ‘aldrig’. The backward translation process did not reveal any significant linguistic issues, nor did the clinical review lead to any concerns.

**Conclusion:** The translation of S3-NIV into Danish followed a rigorous methodology, including patient feedback. This translation is conceptually equivalent to the original questionnaire and can be used for further validation and studies in Danish-speaking COPD-patients, treated with home-NIV.

1. Dupuis-Lozeron E et al. Development and validation of a simple tool for the assessment of home non-invasive ventilation: The S3-NIV questionnaire. *Eur Respir J.* 2018;52(3).

**Associations of low-level air pollution and greenness with mortality in men and women. The Life-GAP project**

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Sex differences in associations of environmental exposure with respiratory health have been observed, but results are not conclusive. This study investigated the associations of exposure to air pollution and greenness with natural-cause mortality in men and women in Northern Europe.

We studied 10,011 participants in the third Respiratory Health in Northern Europe (RHINE III) study in 2010 (age 40–65 years), with exposure to air pollution and greenness in the 20 years before (1990–2010), and with mortality (n = 368) follow-up until 2021. Cox proportional hazard models were used to estimate the associations of long-term particulate matter (PM2.5 and PM10), black carbon (BC), nitrogen dioxide (NO2), ozone (O3), and greenness (normalized difference vegetation index (NDVI)) with mortality, adjusting for body mass index, smoking, education, marital status, and serious respiratory infection before 5 years old. The analyses were done separately for men and women.

The overall mean levels of air pollutants were far below the European Union (EU) standards. In single pollutant models, for women, the adjusted hazard ratios (HRs) of natural-cause mortality were 1.10 (95% confidence interval (CI): 1.06, 1.15), 1.04 (95% CI: 1.01, 1.07), 2.99 (95% CI: 1.87, 4.77), 1.03 (95% CI: 1.01, 1.05) and 0.95 (95% CI: 0.93, 0.98) per 1 μg/m3 increase in PM2.5, PM10, BC, NO2 and O3, respectively. No significant associations were observed
between the air pollutants and mortality in men. Greenness was not associated with mortality in men or women.

Long-term exposure to low-level air pollution is associated with female mortality. Women might be more susceptible to air pollution than men.

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**Impulse oscillometry as a rule-out method for emphysema**

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**Background:** Body plethysmography (BP) is the standard pulmonary function test (PFT) for diagnosing pulmonary emphysema, but not all patients can cooperate to this procedure. An alternative PFT, impulse oscillometry (IOS), has never been investigated in emphysema. We investigate the ability of IOS to discriminate between the presence and absence of emphysema.

**Methods:** One hundred patients from the pulmonary outpatient clinic in Vejle, Denmark, were consecutively included in this cross-sectional study. A clinical assessment including disease history, a BP, and an IOS was performed in all patients. A computed tomography scan was performed in 88 of these 100 patients, and emphysema was present on the scan in 20 patients. The ability of BP and IOS in discriminating between emphysema or not was evaluated with two multivariate logistic regression models: BP (FEV1-% predicted, FVC % predicted, TLC % predicted, RV % predicted, DLCOc % predicted) and IOS (R5Hz % predicted, R5-20 Hz, X5Hz, Freq, Ax).

**Results:** BP: AUC 0.933 (95% CI: 0.837–1.00), positive predictive value (PPV) = 61.5%, negative predictive value (NPV) = 95.1%. IOS: AUC = 0.878 (95% CI: 0.794–0.962), PPV = 57.1%, NPV = 92.5%. We found no significant difference between the AUC of the two models (\(p = 0.24\)).

**Conclusions:** BP showed a higher AUC than IOS for discriminating between emphysema or not, but the difference was not significant. IOS showed excellent diagnostic precision. IOS is both quick and easy to perform, and it may be used when BP is impossible and as a reliable rule-out method for emphysema.

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**The association between complement C3 and small airway impairment in asthma**

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**Background:** Complement C3, the central component of the complement system, has been suggested to play a role in asthma pathogenesis and severity. We aimed to explore the association between C3-levels in small airways, the level of small airway impairment and asthma control.

**Methods:** 20 subjects with asthma and 10 healthy controls were examined with spirometry, multiple breath washout (MBW) and the PExA\(^a\) method, which samples small airway lining fluid in the form of exhaled particles. Samples were analysed with the SOMAscan proteomics platform. Subjects with asthma filled out the Asthma Control Questionnaire (ACQ).

**Results:** Subjects with ACQ score \(>1\) had a significantly higher abundance of C3 as compared to subjects with ACQ score \(\leq 1\) (FC = 1.38, \(p = 1.14E-4\)) and healthy controls (FC = 1.18, \(p = 0.042\)). Subjects with asthma were divided into tertiles based on the C3 abundance and comparison revealed that those with the lowest (T1) and the highest (T3) C3 abundance had lower FEF25-75 z-score (T1-T2: \(p = 0.022\); T3-T2: \(p = 0.022\)) and higher LCI (T1-T2: \(p = 0.035\); T3-T2: \(p = 0.035\)) as compared to those in the median tertile (T2). Subjects in T3 also had a higher Sacin z-score (\(p = 0.022\)), hsCRP (\(p = 0.022\)), and ACQ score (\(p = 0.008\)) as compared to T2.

**Conclusions:** We observed that both high and low levels of C3 in the lining fluid were associated with small airway impairment in asthma. Furthermore, high levels of C3 were associated with more systemic inflammation and less asthma control. These findings
highlight the importance of the complement system in the pathogenesis of asthma.

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**Exhaled biomarkers in adults with non-productive cough**

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**Background:** Chronic cough is a common condition, but the disease mechanisms are not fully understood.
**Aim:** To study respiratory biomarkers from the small airways in individuals with chronic cough.
**Methods:** A general population cohort of 107 participants answered detailed questionnaires, performed spirometry, exhaled NO measurement, impulse oscillometry, gave blood samples and particles in exhaled air (PExA) samples. Current smokers (\(N = 38\)) were excluded. A total of 12 participants reported chronic non-productive cough and were non-smokers (cases). A total of 55 participants reported no cough and were non-smokers (control group). PExA samples, previously shown to be derived from small airways, were analysed with the SOMAscan proteomics platform.
**Results:** Participants with chronic cough had similar age, sex distribution, body mass index, and inflammation markers in blood tests, compared with participants without cough. The proteomics analysis found 59 proteins significantly altered among participants with chronic cough compared to controls, after adjusting for age, sex, and investigator performing the PExA measurement (all with \(p\)-value <0.05 and \(q\)-value ≤0.17). This included proteins such as complement factor H (2.5-fold increase), coagulation factor IX (1.8-fold increase), fibrinogen (1.9-fold increase), prothrombin (2.0-fold increase), and immunoglobulin A (1.9-fold increase).
**Conclusions:** This exploratory study on proteomics of exhaled particles among individuals with chronic cough found alterations in 59 proteins. Many of them are involved in immune response and inflammatory pathways, as well as complement activation. Further studies are needed to explore the importance of these findings.

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**Pectoralis muscle index assessed by high-resolution computed tomography and the association to static lung volume in patients with COPD: a pilot study**

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**Background:** Progressive muscle mass reduction is common in patients with COPD, as COPD worsens. The pectoralis muscle mass (PMM) is associated with increased risk of mortality in large COPD cohorts. However, whether there is an association between the PMM and the static lung volumes is uncertain.
**Aim:** To investigate whether there is an association between the PMM and the static lung volume.
**Method:** A cross-sectional study including 42 stable outpatients with COPD investigated with body plethysmography and high-resolution computed tomography (HRCT). The first axial slice above the aortic arch of the HRCT was used to assess the pectoralis muscle. Segmentation was conducted by an in-house semiautomated software ‘Viking slice’, and Hounsfield units (HU) between −29 and +150 HU was regarded as muscle tissue. Muscle measures were reported as height-adjusted pectoralis muscle index (PMI, cm\(^2\)/m\(^3\)). Baseline data were reported as median (interquartile range). Linear regression was applied on PMI with the static lung volume, total lung capacity (TLC), residual volume (RV), and inspiratory capacity/TLC ratio (IC/TLC) corrected for gender.
**Results:** A total of 42 patients were included (21 men, 21 women), age 65 years (61–69 years), PMI 10.1 cm\(^2\)/m\(^3\).
m² (8.1–12.1 cm²/m²), TLC 115.5% (105–122%), RV 160.5% (133–195%), and IC/TLC ratio .815 (.695–.991). PMI had a negative linear relationship with TLC (adj $R^2 = .258, p = .0011$) and RV (adj $R^2 = .214, p = .0034$) and a positive linear relationship with IC/TLC (adj $R^2 = .171, p = .0098$).

**Conclusion:** A linear association was seen between PMI and static lung volumes in patients with COPD, indicating that static lung volumes may be used to predict patients with low PMI. However, further studies are needed.

1. McDonald, M. L. N. et al. (2017) Chest computed tomography-derived low fat-free mass index and mortality in COPD. The European Respiratory Journal. European Respiratory Society, 50(6), p. 1701134. doi:10.1183/13993003.01134–2017.

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**Venous thromboembolism associated with severe dyspnoea and asthma in 21,205 individuals from the general population**

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**Background:** The most recent guideline on acute pulmonary embolism from the European Society of Cardiology indicates possible long-term sequelae such as dyspnoea and chronic thromboembolic pulmonary hypertension after a pulmonary embolism event. However, the effects on lung function or asthma risk have not been evaluated previously in the general population.

**Methods:** We tested whether individuals with a venous thromboembolism have reduced lung function, or greater risk of dyspnoea and asthma using data from 21,205 random adults from the Danish General Suburban Population Study.

**Results:** Prevalence of pulmonary embolism, deep vein thrombosis, and venous thromboembolism were 0.60, 1.7, and 1.9%, respectively. Individuals with pulmonary embolism or deep vein thrombosis versus individuals without venous thromboembolism had reduced FEV1% predicted (86 and 89% versus 95%, t-test: $P < 0.001$) and FVC% predicted (92 and 94% versus 99%, $P < 0.001$). Individuals with venous thromboembolism versus those without had adjusted odds ratios for light, moderate, and severe dyspnoea of 1.6 (95% CI: 1.1–2.2), 1.8 (1.2–2.6), and 2.6 (1.8–3.8), respectively. Individuals with venous thromboembolism versus those without had adjusted odds ratios for asthma and use of asthma medication of 1.6 (1.2–2.2) and 1.9 (1.4–2.6), respectively. Adjusted odds ratios of asthma in individuals with versus without venous thromboembolism, stratified in those who received treatment and no treatment with anticoagulants, were 1.0 (0.6–1.6) and 2.0 (1.4–3.0), respectively.

**Conclusion:** The results show that individuals with venous thromboembolism have worse lung function and higher risks of severe dyspnoea and asthma in the general population.

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**Functional vitamin K status and lung function in the Danish general population: The DanFunD study**

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**Background and Aims:** Vitamin K activates vitamin K-dependent proteins or Gla proteins by a process called γ-carboxylation. The most well-described Gla proteins are coagulation factors. However, other Gla proteins, such as the Matrix Gla Protein (MGP) may also exert important functions. MGP is present in various tissues, including lung tissue. The inactive form of MGP dephosphorylated-uncarboxylated MGP (dp-ucMGP) has been associated with elastin degradation in lungs of patients with chronic obstructive pulmonary disease (COPD), and it has been associated with COVID-19 mortality. Dp-ucMGP has been proposed as a biomarker of functional vitamin K status. We aim to assess the association between functional vitamin K levels and lung function to elaborate on vitamin K’s role in lung diseases.

**Methods:** In a cohort, representative of the Danish general population, the DanFunD study, we will assess the association between functional vitamin K status (reflected by dp-ucMGP plasma levels) and lung function. The 4,096 participants were examined between 2017 and 2020 with a general health examination,
questionnaires, spirometry, step test, and blood and urine samples. Using linear regression models, we estimate the association between dp-ucMGP and continuous measurements of lung function. Furthermore, in multiple logistic regression models, we estimate the association between dp-ucMGP and dichotomous outcomes of respiratory symptoms.

**Results:** Preliminary crude analyses suggest that higher levels of dp-ucMGP are associated with having an FEV1 below 80% of the expected value.

**Conclusions:** Results will be presented at the Nordic Lung Congress.

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**Association between high-potency inflammatory oral bacteria and lung inflammation**

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**Background:** Lipid A is the primary immunostimulatory center of the lipopolysaccharide (LPS). The inflammatory response of LPS varies, e.g. depending on the number of acyl chains in lipid A, which, in turn, depends on the bacterial species or strain. Traditional LPS quantification assays cannot distinguish between different lipid A producers, and therefore little is known about how bacteria of different immunostimulatory potency affect lung inflammation. We aim to explore the association between oral bacteria exhibiting proinflammatory (hexa-acylated LPS) and less inflammatory (penta-acylated LPS) activity with fractional exhaled nitric oxide (FeNO).

**Methods:** Findings are reported from the RHINESSA generally healthy adult cohort from western Norway (mean age: 28, range: 18–47 years; gender: 48% females). We applied the microbiome regression-based kernel association test (MiRKAT) by using the Bray-Curtis distance as a single kernel, to test for associations between FeNO and composition of hexa- or penta-acylated LPS-producing oral bacteria. We adjusted for gender, gum bleeding, smoking, any asthma attack, or use of asthma medication in the last 12 months, and asthma severity.

**Results:** In total, 2.4 and 40.8% of the oral bacteria were hexa- and penta-acylated LPS-producers, respectively. The composition of hexa-acylated LPS-producers was significantly associated with increasing FeNO level regardless of covariate adjustment ($p < 0.05$). No association was observed between smoking, use of any asthma medication, asthma attack, or asthma severity, and the composition of hexa-acylated LPS-producers when modelled separately. No significant association was shown between the composition of penta-acylated LPS-producing oral bacteria and FeNO regardless of covariate adjustment.

**Conclusions:** A strong association between FeNO and the composition of hexa-acylated LPS-producing oral bacteria was observed in a generally healthy adult cohort. It is likely that oral bacteria of high immunostimulatory potency may reach the lungs through microaspiration or systemic dispersal and thereby induce lung inflammation.

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**Survival of Finnish bronchiectasis patients**

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**Background:** Patients suffering frequent exacerbations of bronchiectasis (BE) are likely to experience more negative effects on quality of life (QoL) and more healthcare utilization. We aimed to study the mortality and predictive factors for poor survival in a cohort of Finnish BE patients.

**Methods:** Non-cystic fibrosis BE patients of Helsinki University Hospital cohort were examined with chest high-resolution computed tomography. Finnish translation of the disease-specific quality of life-bronchiectasis (QoL-B) questionnaire was applied, and scores in the lowest quarter (25%) of the scale were considered to indicate poor QoL. The bronchiectasis severity index (BSI), FACED score, and modified Medical Research Council dyspnea scale were used.

**Results:** Overall, 79% of 95 BE patients were women with mean age of 69 years (SD ± 13). High score of FACED (OR 1.9, 95% CI 1.2–3.1) and BSI (OR 1.2, 95% CI 1.0–1.4) were predictive for poor survival. In
addition, high score of QoL-questionnaire results were protective for poor survival.

**Conclusion:** In our cohort, none of the single variables were predictive for poor survival. Instead, bronchiectasis severity index or equivalent estimation for disease severity give more specific predictive values for survival. In our study, FACED was the strongest predictive tool.

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**Changes in surfactant lipid composition 6 months after severe Covid-19**

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**Background:** SARS-CoV-2 displays high affinity for ACE2 receptors as a vector of pathogenesis. ACE2 receptors are highly expressed on surfactant producing type 2 alveolar cells. These cells produce pulmonary surfactant – a crucial thin layer of surface-active fluid mainly composed of lipids, lining the alveolar epithelial surface. The main function, to reduce the surface tension, is fundamental for proper gas exchange.

**Aims and Objectives:** To investigate changes in surfactant lipid composition and the relationship to long-standing symptoms of post Covid-19 among patients treated in intensive care for Covid-19 infection.

**Methods:** We recruited 43 patients (17 women, aged 44–80 years) who had previously been treated in ICU in a major Swedish hospital, in average 6 months before inclusion. The participants answered a questionnaire regarding symptoms, we collected particles in exhaled air with PExA-instrument (PExA AB) and conducted pulmonary function tests, body plethysmography, and diffusion capacity of the lungs for carbon monoxide. Twenty-two healthy, non-infected, age- and gender-matched controls were enrolled. Lipids were analysed using liquid chromatography with a triple quadrupole mass spectrometer. Statistical analyses were performed with Qlucore.

**Results:** Early results suggest a significant change in the composition of surfactant lipids among post-Covid-19 patients treated in intensive care compared to controls. Early analysis show significant reductions of all measured phosphatidyl-glycerols (PG, n = 14) an increase of all measured phosphatidyl-inositol (PI, n = 4), for example were PG 18:1_18:1 22% lower (p < 0.001, q = 0.04) and PI:16:0:18:1 67% higher (p < 0.001, q = 0.0003) in subjects post-Covid compared to controls.

**Conclusions:** Our findings suggest that surfactant composition is altered also in the recovery after Covid-19 infection, which could be a key component in the post-Covid syndrome and the lingering effects on the respiratory system.

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**Lower percent predicted vital capacity is associated with snoring and nocturnal reflux**

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**Objective:** The aim of the study is to examine the association of percent predicted lung function with
snoring and nocturnal gastroesophageal reflux (nGER) in a general population.

**Methods:** We used data from the RHINESSA study (N = 955, 50% females) from Australia, Denmark, Estonia, Iceland, Norway, Spain, and Sweden. The mean age was 29 years (range, 18–53 years). Information on participant characteristics including habitual snoring and nGER were assessed using structured questionnaires. Force expiratory volume in 1 s (FEV1) and forced vital capacity (FVC) were predicted according to GLI reference value and categorized into three groups, <90, 90–100, and >100%. Multinomial logistic regression was used to study the association between predicted lung function values (considering those who had FEV1 and FVC >100% predicted, respectively, as a reference group) with habitual snoring and nGER.

**Results:** In total 542 participants (56%) reported neither snoring nor nGER, 124 (13%) reported nGER, 220 (23%) reported snoring, and 75 (8%) reported both snoring and nGER. Those who reported both snoring and nGER had higher age and body mass index (BMI) and were more likely to smoke as compared to those with neither condition. The odds ratio of reporting both snoring and nGER vs not having any was [8.5 (95% CI 2.6, 27.9)] times higher for the low predicted lung function (<90% predicted) compared to those with FVC >100% predicted, adjusting for age, gender, BMI, smoking, and study center. However, no association was observed between percentage predicted FEV1 category with snoring and nGER.

**Conclusion:** Lower percent predicted FVC is associated with a higher prevalence of snoring and nocturnal gastroesophageal reflux in a general population.

**Trajectories of GOLD A patients in Denmark: a cohort study**

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**Background:** Risk of future exacerbations in newly diagnosed patients with COPD can be difficult to predict. Our aim was to investigate the impact of a single moderate exacerbation on the odds of subsequent exacerbations and death in GOLD A patients.

**Methods:** A cohort study based on data from the Danish national registers. We included all patients ≥40 years with an in- and/or outpatient ICD-10 J44 diagnosis (COPD Register, 2008–2014). Index was date of first registered modified Medical Research Council score 0–1; baseline period was 12 months pre-index. At index, patients were grouped as follows: A0, no exacerbation; and A1, one moderate exacerbation during the previous year, and followed for one year for moderate exacerbations (defined as short-term course of prednisolone/prednisone ± antibiotic) and severe exacerbations (emergency visit or hospitalization) and death. Using A0 as reference, a Cox model estimated the hazard ratio for exacerbation accounting for recurrent events. Multinomial logistic regression was used to estimate the odds ratio (OR) for exacerbation and death in GOLD A1.

**Results:** In total, 7,191 patients (mean (SD) age 65.6 (10.2) years, 53.1% male) were included, of whom 3,958 had GOLD A0 and 3,233 had GOLD A1. During the 1-year follow-up, 59.6 and 44.9% of GOLD A0 and A1, respectively, had no exacerbations, whereas 40.4 and 55.1% of A0 and A1, respectively, had a severe path with moderate and/or a severe exacerbations or death. In A1 patients, the OR for 1 moderate, ≥2 moderate exacerbations, ≥1 severe exacerbation was 1.50 [95% CI 1.33–1.68], 2.67 [2.30–3.11], 1.88 [1.51–2.34], respectively, compared with A0, whereas the OR for death was 1.55 [1.16–2.10].

**Conclusions:** Even in COPD patients with low symptom burden, one moderate exacerbation increases the odds of subsequent exacerbations and death. The results emphasize the importance of early prevention, treatment, and yearly control of GOLD A patients.

**Long-term effect of dupilumab on lung function in patients with type 2 asthma: LIBERTY ASTHMA TRAVERSE Study**

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Background and Aims: Dupilumab, a human anti-IL-4Ra mAb, blocks interleukin-4/13 signaling, key and central drivers of type 2 inflammation. This post-hoc analysis evaluated lung function in QUEST (NCT02414854) patients enrolled in TRAVERSE (NCT02134028).

Methods: We analyzed mean change [SD] from QUEST parent study baseline (PSBL) in pre-BD FEV1, FEF25-75%, and FVC in patients with type 2 asthma (baseline blood eosinophils ≥150 cells/μL or FeNO ≥25 ppb) who received dupilumab (dupilumab/dupilumab) or placebo (placebo/dupilumab) during QUEST and dupilumab 300 mg q2w for 96 weeks in TRAVERSE.

Results: Mean change from PSBL in FEV1 among 364 dupilumab/dupilumab-treated patients was sustained throughout TRAVERSE (0.35[0.48] L at Wk96). Similar sustained improvements were observed for FEF25-75% (0.41[0.64] L/s at Wk96) and FVC (0.29 [0.51] L at Wk96). Upon dupilumab initiation, 185 placebo/dupilumab-treated patients achieved mean change improvements from PSBL in FEV1 (0.37[0.44] L at Wk96), FEF25-75%(0.42[0.54] L/s at Wk96), and FVC (0.30[0.49] L at Wk96).

Conclusions: Dupilumab demonstrated clinically meaningful lung function improvements that were sustained for up to 3 years in a population with type 2 inflammatory asthma.

Dupilumab improves lung function in children with uncontrolled, moderate-to-severe asthma: LIBERTY ASTHMA VOYAGE

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Background/Aims: In the phase 3 VOYAGE study (NCT02948959), add-on dupilumab every 2 weeks (q2w) demonstrated significant improvements in percent predicted (pp) pre-bronchodilator (BD) FEV1 vs placebo at Week (Wk) 12 in children aged 6–11 years with uncontrolled, moderate-to-severe asthma and a type 2 inflammatory asthma phenotype (defined as blood eosinophils ≥150 cells/μL or FeNO ≥20 ppb at BL). We now report effects on additional lung function parameters.

Methods: Children were randomized (2:1) to receive add-on dupilumab 200 mg or 100 mg q2w based on body weight (>30 or ≤30 kg), or matched placebo q2w for 52 weeks.

Results: At baseline, mean (SD) pre-BD FEV1 (L) and pre-BD FEV1pp was 1.53 (0.46)L and 78.36 (14.51)/1.48 (0.39) L and 77.66 (14.38) in placebo/dupilumab groups, respectively. Pre-BD FEV1 (L) improved from BL in dupilumab vs placebo (least squares [LS] mean [95% CI] difference: Wk2, 0.06 L [0.01–0.12; P = 0.025]; Wk52, 0.17 L [0.09–0.24; P < 0.0001]). Similar benefits were seen in post-BD FEV1, (BL mean [SD]: 1.74 [0.49]/1.75 [0.43]L in placebo/dupilumab groups, respectively; Wk52 LS mean difference [95% CI] vs placebo: 0.09 L [0.02–0.16, P = 0.015]). Additionally, dupilumab vs PBO improved post-BD FEV1pp (BL mean [SD]: 89.66 [15.54]/93.36 [14.7] for placebo/dupilumab; Wk52 LS mean difference [95% CI]: 4.37 percentage points [0.95–7.78]; P = 0.012), FEF25-75% (BL mean [SD]: 1.28 [0.53]/1.27 [0.54] for placebo/dupilumab; Wk52 LS mean difference [95% CI]: 0.30 L/s [0.17–0.44], P < 0.0001), ppFEF25-75% (BL mean [SD]: 54.67 [19.79]/54.82 [20.94] for placebo/dupilumab; Wk52 LS mean difference [95% CI]: 12.02 percentage points [6.70–17.33], P < 0.0001), and FVC (BL mean [SD]: 2.08 [0.57]/2.00 [0.48] for placebo/dupilumab; Wk52 LS mean difference [95% CI]: 0.10 L [0.03–0.17], P = 0.007).

Conclusions: Dupilumab led to significant, rapid, and sustained improvements in lung function, including in measures of the large and small airways in children aged 6–11 years.
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