COPD/Emphysema PubMed search results covering the period 26/10/19 to 17/01/2020
Cohort and case-control studies

Search strategy: ("pulmonary disease, chronic obstructive"[MeSH Major Topic] OR "emphysema"[MeSH Major Topic]) AND ("Cohort Studies"[MeSH Terms] OR "Case-Control Studies"[MeSH Terms]) AND English[lang] AND ("2019/07/20"[CDAT] : "3000"[CDAT])

Amegadzie, J. E., J. Gorgui, et al. (2019). **"Comparative safety and effectiveness of inhaled bronchodilators and corticosteroids for treating asthma-COPD overlap: a systematic review and meta-analysis."** J Asthma: 1-16.

Objective: To determine the safety and effectiveness of current pharmacotherapies consisting of long-acting beta2-agonist (LABA) and/or inhaled corticosteroids (ICS) in patients with asthma-COPD overlap.Data sources: A systematic search was conducted using the PubMed, EMBASE, and Web of Science databases up to June 2018.Study selections: Only studies comparing the safety and effectiveness of LABA and/or ICS in patients with asthma-COPD overlap were included. A meta-analysis was performed to calculate risk ratio (RR) and 95% confidence interval (CI) using Inverse Variance Random-effects model.Results: From a total of 3382 articles retrieved, three randomized controlled trials (RCTs), six cohort studies (CS), one nested case control study fulfilled the inclusion criteria for three independent meta-analyses representing 181,603 participants. Three CS results show LABA was associated with decreased risk of myocardial infarction (combined RR: 0.80, 95% CI 0.74-0.87) versus non-LABA use; ICS/LABA was associated with a lower risk of death or hospitalization (combined RR: 0.82, 95% CI 0.75-0.90) compared to no use. Results from RCTs, no clear difference in lung function decline in FEV1 was found (combined mean difference: 0.08, 95% CI 0.15-0.32) in patients receiving ICS and/or LABA compared to placebo. However, due to lack of data, exacerbations, fractures and nontuberculous mycobacterial pulmonary disease outcomes were not meta-analyzed.Conclusions: Among patients with asthma-COPD overlap, LABA is associated with decreased risk of myocardial infarction; and the combination therapy of ICS/LABA appears to reduce the risk of death or hospitalization. More studies of quality data and larger number of patients are needed.REGISTRATION: PROSPERO (CRD42018090863).

Armstrong, M., A. Winnard, et al. (2019). **"Use of pedometers as a tool to promote daily physical activity levels in patients with COPD: a systematic review and meta-analysis."** Eur Respir Rev **28**(154)The aim of this study was to examine the use of pedometers as a tool to promote daily physical activity levels in patients with COPD.A systematic review meta-analysis of pedometer physical activity promotion in patients with COPD was conducted. Medline/PubMed, Cochrane Library, Web of Science and CINAHL were searched from inception to January 2019. The search strategy included the following keywords: physical activity promotion, pulmonary rehabilitation and daily physical activity. The eligibility criteria for selecting studies were randomised controlled trials reporting pedometer physical activity promotion in patients with COPD.Improvements in steps per day were found with pedometer physical activity promotion either standalone (n=12, mean 0.53 (95% CI 0.29-0.77); p=0.00001) or alongside pulmonary rehabilitation (n=7, 0.51 (0.13-0.88); p=0.006). A subgroup analysis reported significant differences in the promotion of physical activity based on baseline physical activity levels and the type of instrument used to assess levels of physical activity.Future trials should consider the way in which pedometers are used to promote physical activity to inform clinical practice in the setting of pulmonary rehabilitation.

Benz, E., K. Trajanoska, et al. (2019). **"Sarcopenia in COPD: a systematic review and meta-analysis."** Eur Respir Rev **28**(154)COPD is associated with a progressive loss of muscle mass and function. However, there is an unmet need to define and standardise methods to estimate the prevalence of sarcopenia in COPD patients.We performed a systematic review and meta-analysis of the prevalence of this extrapulmonary manifestation in COPD patients. We searched Embase, Medline (Ovid), CINAHL (EBSCO), Web of Science, Scopus and Google Scholar for studies published up to January 17, 2019, assessing sarcopenia in COPD patients based on low muscle mass and decreased muscle function. Interventional studies, in vitro experiments, protocols or reviews and meta-analyses were excluded. We estimated heterogeneity (I(2)) and assessed significance (Q) using a Chi-squared test for estimates obtained from random-effects models.4465 articles were initially identified. After removing the duplicates and applying the selection criteria, we reviewed 62 full-text articles. Finally, 10 articles (n=2565 COPD patients) were included in this systematic review and meta-analyses. Overall, the prevalence of sarcopenia in patients with COPD was 21.6% (95% CI 14.6-30.9%, I(2)=94%), ranging from 8% in population-based to 21% in clinic-based studies, and 63% in COPD patients residing in nursing homes.Sarcopenia is frequently observed in COPD patients, with varying prevalence across population settings. Sarcopenia in COPD should be assessed using standardised tests and cut-off points from sarcopenia consensus criteria for clinical practice and international comparisons.

Bonnevie, T., M. Elkins, et al. (2019). **"Nasal High Flow for Stable Patients with Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-Analysis."** Copd **16**(5-6): 368-377.

There is a growing body of evidence supporting the use of nasal high flow (NHF) to treat acute respiratory failure, particularly in Chronic Obstructive Pulmonary Disease (COPD) patients. Conversely, there are sparse data evaluating its effects in stable COPD patients.We identified randomized controlled trial comparing the effects of delivering air or oxygen via NHF, compared with delivering the same gas without NHF, in stable COPD patients through a systematic search using MEDLINE, CENTRAL, Science Direct, and others sources until January 2019. Study selection, data extraction and assessment of the risk of bias (using the Cochrane Risk of Bias tool) was performed by two independent authors.We included 6 studies (339 participants). Our meta-analysis showed a significant reduction of arterial carbon dioxide pressure ($PaCO_2$) at long (two studies, MD -3 mmHg, [95% Confidence interval (CI) -4 to -2]) and short-term (two studies, MD -3 mmHg [95% CI -4 to -2]). NHF significantly improved quality of life on the St George's Respiratory Questionnaire (two studies, MD -5 out of 100, [95% CI -8 to -2]). NHF significantly reduced the rate of acute exacerbation at 1 year (one study, rate ratio: 0.6, [95% CI 0.6 to 0.7]). NHF did not significantly improve exercise capacity, hospitalization rate or mortality, but improved breathing pattern.NHF reduced $PaCO_2$, acute exacerbation and improved quality of life in stable COPD patients. Further long-term studies are needed to confirm the present results and provide more data on patient-centered outcome such as quality of life, exacerbation, hospitalization and mortality.

Chen, F. Y., M. Xiao, et al. (2019). **"Vitamin D does not improve lung function decline in COPD: a meta-analysis."** Eur Rev Med Pharmacol Sci **23**(19): 8637-8644.

OBJECTIVE: Vitamin D deficiency plays an important role in chronic obstructive pulmonary disease (COPD). However, the effects of vitamin D supplementation on lung function decline in COPD were inconsistently reported and a meta-analysis is thus needed. MATERIALS AND METHODS: Eligible cohort and randomized controlled trials (RCTs) were searched from databases including PubMed, Embase, and Web of Science. Pooled standardized mean difference (SMD) with 95% confidence interval (CI) was calculated in a random or fixed effects model. RESULTS: Eight studies reaching the inclusion criteria and involving 687 COPD patients were included. Pooled effect size showed vitamin D treatment resulted in no significant improvements in FEV1 (SMD: 0.38, 95% CI: -0.13 to 0.88, p= 0.144), FVC (SMD: 0.55, 95% CI: -0.49 to 1.58, p=0.299), and FEV1/FVC (SMD: 0.00, 95% CI: -0.27-0.27, p=0.995) in COPD patients.

Subgroup analysis revealed neither short-term (<6 months) (SMD: 0.10, 95% CI: -0.17 to 0.37, p=0.479) nor long-term (>/=6 months) (SMD: 0.52, 95% CI: -0.23 to 1.27, p=0.172) vitamin D exposure could significantly benefit lung function decline in COPD. CONCLUSIONS: This meta-analysis shows neither short-term nor long-term additional supplementation of vitamin D can benefit the lung function decline in COPD. Moreover, large scale RCTs focusing on COPD smokers with low level of vitamin D should be considered.

Dalon, F., N. Roche, et al. (2019). **"Dual versus triple therapy in patients hospitalized for COPD in France: a claims data study."** Int J Chron Obstruct Pulmon Dis **14**: 1839-1854.

Purposes: Following a hospitalization for COPD, dual and triple therapies were compared in terms of persistence and relations with outcomes (exacerbations, health care resource use and costs). Methods: This was a historical observational database study. All patients aged >/=45 hospitalized for COPD between 2007 and 2015 were identified in a 1/97(th) random sample of French claims data. Patients receiving dual therapy within 60 days after hospitalization were compared to patients receiving triple therapy, after propensity score matching on disease severity. Results: Of the 3,089 patients hospitalized for COPD, 1,538 (49.8%) received either dual or triple therapy in the 2 months following inclusion, and 1,500 (48.6%) had at least 30 days of follow-up available; 846 (27.4%) received dual therapy, and 654 (21.2%) received triple therapy. After matching, the number of exacerbations was 2.4 per year in the dual vs 2.3 in the triple group (p=0.45). Among newly treated patients (n=206), persistence at 12 months was similar in the dual and triple groups (48% vs 41%, respectively, p=0.37). As compared to patients on dual therapy, more patients on triple therapy received oral corticosteroids (49.1 vs 40.4%, p=0.003) or were hospitalized for any reason (67% vs 55.8%, p=0.0001) or for COPD (35.3 vs 25.1%, p=0.0002) during follow-up. Cost of care was higher for patients on triple than for those on dual therapy (euro11,877.1 vs euro9,825.1, p=0.01). Conclusion: Following hospitalizations for COPD, patients on dual and triple therapy experienced recurrent exacerbations, limited adherence to therapies and high cost of care. Patients on triple therapy appeared more severe than those on dual therapy, as reflected by exacerbations and health care resource use.

Dong, J., Z. Li, et al. (2020). **"Efficacy of pulmonary rehabilitation in improving the quality of life for patients with chronic obstructive pulmonary disease: Evidence based on nineteen randomized controlled trials."** Int J Surg **73**: 78-86.

BACKGROUND: Increasing studies have shown that application of pulmonary rehabilitation may improve the quality of life of chronic obstructive pulmonary disease (COPD) patients. However, the results of some studies still remained controversial and sample size of them limited to small number of participants. A systematic review and meta-analysis was designed to evaluate the efficacy of pulmonary rehabilitation for improving the quality of life in patients with COPD. METHODS: We searched the Cochrane Library, PubMed, EMBASE and Web of Science up to March 29, 2019 to identify relevant randomized controlled trials (RCTs) analyzing and evaluating the efficacy of pulmonary rehabilitation (PR) in patients with COPD. Participants were randomly assigned to receive PR (intervention group) or usual care (controller group). We used St. George's Respiratory Questionnaire (SGRQ) scores as evaluating indicators of quality of life. Mean differences (MDs) with 95% confidence intervals (CIs) were estimated to compare the outcomes of the groups. We also performed subgroup analysis for the pooled results of pulmonary rehabilitation effects in COPD patients. Besides, sensitivity analysis was performed to examine the stability of the combined results. Two reviewers assessed trial quality and extracted data independently. All statistical analyses were performed using standard statistical procedures provided in Review Manager 5.2 and Stata 12.0. RESULTS: Nineteen randomized controlled trials (N = 1146 participants) were identified for the present analysis. Comparing pulmonary rehabilitation groups with usual care groups (control groups), statistically significant improvements were noted in total score of SGRQ, with MD of -6.53. In

addition, life quality improvement of SGRQ scores was better than 5 units in symptoms score, impacts score and activity score, with MDs of -5.01, -7.23 and -6.08, respectively. CONCLUSIONS: Rehabilitation may constitute one of important components of the management of COPD and may be beneficial in improving the quality of life. Future research should focus on identifying which components of pulmonary rehabilitation are essential, its ideal length and location, the degree of supervision and intensity of training required and how long treatment effects persist.

Ernst, P., M. Dahl, et al. (2019). **"Comparative Effectiveness Of Fluoroquinolone Antibiotic Use In Uncomplicated Acute Exacerbations Of COPD: A Multi-Cohort Study."** Int J Chron Obstruct Pulmon Dis **14**: 2939-2946.

Purpose: Fluoroquinolone antibiotics are associated with rare, but severe adverse events. They are frequently used for the treatment of acute exacerbations of COPD (AECOPD). While their effectiveness in severe exacerbations requiring hospitalisation has been well documented, the potential benefit in the ambulatory setting is less clear, especially in uncomplicated patients with COPD. Patients and characteristics: We carried out a retrospective cohort study using health care databases from six Canadian provinces in subjects visiting their physician for uncomplicated COPD. Subjects dispensed either a quinolone or other antibiotics were compared using inverse probability of treatment weights with high dimensional propensity scores on 30-day outcomes, including repeat visits, hospitalisation for AECOPD and subsequent antibiotic prescription. Results from each province were combined by random effects meta-analysis. Results: We identified 286,866 AECOPD events among 203,642 unique individuals. The frequency of fluoroquinolone use, mostly levofloxacin and moxifloxacin, varied by province and ranged from 8% to 32% of AECOPD antibiotic prescriptions. The risk of a repeat ambulatory care visit was increased among patients who were dispensed a fluoroquinolone compared with other antibiotics (OR 1.32, 95% CI 1.27-1.36). The risk of a hospitalisation for AECOPD was also higher with fluoroquinolones (OR 1.52, 95% CI 1.33-1.74). There was no difference in subsequent antibiotic prescriptions (OR 1.00, 95% CI 0.94-1.07). Conclusion: There is no apparent benefit in short-term outcomes with fluoroquinolones as compared to other antibiotics for the ambulatory treatment of AECOPD in uncomplicated patients. These findings support current recommendations that fluoroquinolones be reserved for AECOPD in patients with recurrent exacerbations, significant co-morbidity or requiring hospitalisation.

Fernandez-Jane, C., J. Vilaro, et al. (2019). **"Filiform needle acupuncture for copd: A systematic review and meta-analysis."** Complement Ther Med **47**: 102182.

BACKGROUND: This is the first part of a larger spectrum systematic review which aims to identify and evaluates the effectiveness of all different non-pharmacological acupuncture techniques used for COPD. In this first publication, we describe the results of filiform needle acupuncture METHODS: Randomised controlled trials up to May 2019 were searched in 11 databases. Data extraction and risk of bias assessment was conducted in pairs independently. RevMan 5.3 was used for the meta-analysis. RESULTS: 28 trials using filiform needle alone or in combination of other techniques were included. Compared with no acupuncture, no difference was seen for dyspnoea, but statistical benefits were found on quality of life (Std. MD: -0.62, 95%CI: -0.90, -0.34), exercise capacity (stable subgroup) (6MWT MD: 33.05m, 95%CI: 19.11, 46.99) and lung function (FEV1% MD: 1.58, 95%CI: 0.51, 2.66). Compared with sham, statistical benefits were found on dyspnoea (Std. MD: -1.07, 95%CI: -1.58, -0.56), quality of life (Std. MD: -0.81, 95%CI: -1.12, -0.49), exercise capacity (6MWT MD: 76.68m, 95% CI: 39.93, 113.43) and lung function (FEV1% MD: 5.40, 95%CI: 2.90, 7.91; FEV1/FVC MD: 6.64, 95%CI: 3.44, 9.83). CONCLUSIONS: Results show that filiform needle acupuncture might be beneficial for COPD, but due to the low quality of the studies this should be confirmed by future well-designed trials. PROTOCOL REGISTRATION: PROSPERO (identifier: CRD42014015074).

Harries, T. H., V. Rowland, et al. (2020). **"Blood eosinophil count, a marker of inhaled corticosteroid effectiveness in preventing COPD exacerbations in post-hoc RCT and observational studies: systematic review and meta-analysis."** Respir Res **21**(1): 3.

BACKGROUND: Blood eosinophil count has been proposed as a predictor of response to inhaled corticosteroid (ICS) in the prevention of acute exacerbations of COPD. An optimal threshold of blood eosinophil count for prescribing ICS has not been agreed. Doubt has been cast on the role by observational studies. The role of inhaled corticosteroids in this relationship, independent of long-acting bronchodilators, has not been examined. METHODS: We conducted a systematic review of post-hoc analyses of randomised controlled trials (RCTs) and observational studies examining three blood eosinophil thresholds and the independent role of ICS. Included studies were categorised by the form (relative or absolute count) and cut point of eosinophil threshold used. Thresholds assessed were relative eosinophil count of 2%, and absolute counts of 150 cells/muL and 300 cells/muL. Three meta-analyses of the effect of ICS use in post-hoc analyses of RCTs based on these counts were carried out. Initial analysis included all studies of ICS vs. any non-ICS regimen. Further analysis examined the effect of ICS, independent of the effect of long-acting bronchodilators. RESULTS: Sixteen studies examined the association between blood eosinophil count and response of exacerbation risk to ICS, in COPD patients. Eleven studies (25,881 patients) were post-hoc analyses of RCTs. Five studies (109,704 patients) were retrospective observational studies. The independent effect of ICS on the reduction of exacerbation risk was 20% at >/=2% blood eosinophil threshold (RR, 0.80; 95% CI, 0.74-0.85), 35% at >/=150 cells/muL blood eosinophil threshold (RR, 0.65; 0.52-0.79), and 39% at >/=300 cells/muL blood eosinophil threshold (RR, 0.61; 0.44-0.78). No association was found in four out of five observational studies. CONCLUSION: This is the first systematic review to assess, in post-hoc analyses of RCTs, the independent effect of ICS in reducing the risk of COPD exacerbation across a range of blood eosinophil thresholds. Association between ICS prescription and reduced exacerbation risk at these thresholds was confirmed. The lack of association found in the observational studies questions the relevance of these observations to a "real world" COPD population. To clarify the clinical utility of this biomarker, the association should be tested in prospective effectiveness studies.

Hartley, B. F., N. C. Barnes, et al. (2020). **"Risk factors for exacerbations and pneumonia in patients with chronic obstructive pulmonary disease: a pooled analysis."** Respir Res **21**(1): 5.

BACKGROUND: Patients with chronic obstructive pulmonary disease (COPD) are at risk of exacerbations and pneumonia; how the risk factors interact is unclear. METHODS: This post-hoc, pooled analysis included studies of COPD patients treated with inhaled corticosteroid (ICS)/long-acting beta2 agonist (LABA) combinations and comparator arms of ICS, LABA, and/or placebo. Backward elimination via Cox's proportional hazards regression modelling evaluated which combination of risk factors best predicts time to first (a) pneumonia, and (b) moderate/severe COPD exacerbation. RESULTS: Five studies contributed: NCT01009463, NCT01017952, NCT00144911, NCT00115492, and NCT00268216. Low body mass index (BMI), exacerbation history, worsening lung function (Global Initiative for Chronic Obstructive Lung Disease [GOLD] stage), and ICS treatment were identified as factors increasing pneumonia risk. BMI was the only pneumonia risk factor influenced by ICS treatment, with ICS further increasing risk for those with BMI <25 kg/m(2). The modelled probability of pneumonia varied between 3 and 12% during the first year. Higher exacerbation risk was associated with a history of exacerbations, poorer lung function (GOLD stage), female sex and absence of ICS treatment. The influence of the other exacerbation risk factors was not modified by ICS treatment. Modelled probabilities of an exacerbation varied between 31 and 82% during the first year. CONCLUSIONS: The probability of an exacerbation was considerably higher than for pneumonia. ICS reduced exacerbations but did not influence the effect of risks associated with prior exacerbation history, GOLD stage, or female sex. The only identified risk factor for

ICS-induced pneumonia was BMI <25 kg/m(2). Analyses of this type may help the development of COPD risk equations.

Hegelund, A., I. C. Andersen, et al. (2019). **"The impact of a personalised action plan delivered at discharge to patients with COPD on readmissions: a pilot study."** Scand J Caring SciBACKGROUND: Self-management interventions in COPD, including action plans, have the potential to increase quality of life and to reduce respiratory-related hospitalisations. However, knowledge is still sparse of the effectiveness of a personally tailored action plan introduced at or right after discharge from hospital. AIM: This pilot study aimed to test whether a personalised, stepwise action plan supported with a short instruction provided at or postdischarge after an acute exacerbation in chronic obstructive pulmonary disease admission as an addition to usual care reduces readmissions and symptom burden, including anxiety and depression levels at 3-month follow-up. METHODS: The study was carried out in a randomised controlled design with follow-up after 3 months. In all, 75 participants were randomly assigned to either an intervention group that received an action plan, including the COPD Assessment Test (CAT), or to a control group that received usual care. The incidence of COPD-related readmissions was measured as the primary outcome. RESULTS: Compared to the control group, the action plan group significantly reduced the incidence of readmissions. The action plan group showed a trend towards a significant decrease in HADS-depression, but none in HADS-anxiety. Significant improvements in CAT scores were observed for the participants in the intervention group. Only inferior minor differences were found in use of inhalation therapy. CONCLUSIONS: A personally tailored action plan introduced at or postdischarge combined with follow-up support is an effective self-management tool to support recovery and to reduce unnecessary readmissions. In future follow-up care, the healthcare professional must initiate the action plan at discharge and immediately after having the opportunity to follow the patient at home. This might require healthcare professionals working across healthcare sectors, who support patients until they have the needed confidence and competence in using the plan.

Hill, K., L. W. C. Ng, et al. (2019). **"Effect of Using a Wheeled Walker on Physical Activity and Sedentary Time in People with Chronic Obstructive Pulmonary Disease: A Randomised Cross-Over Trial."** LungPURPOSE: To determine the effects of providing a wheeled walker (WW) for use in the home and community, on daily physical activity (PA) and sedentary time (ST) in people with chronic obstructive pulmonary disease (COPD). METHODS: A randomised cross-over study in which participants with COPD characterised by a 6-min walk distance </= 450 m, who had recently finished pulmonary rehabilitation, completed two 5-week phases. During one phase, participants were provided a WW to use, whereas during the other phase, the WW was not available. The order of the phases was randomised. For the final week of each phase, measures of PA and ST were collected using wearable devices and health-related quality of life was measured using the Chronic Respiratory Disease Questionnaire (CRDQ). Wheeled walker use was also measured using an odometer attached to the device. RESULTS: 17 participants [FEV1 = median (interquartile range) 33 (25) % pred; ten males] aged mean (SD) 73 (9) years completed the study. Comparing the data collected when the WW was not available for use, the daily step count was greater (mean difference [MD] 707 steps/day (95% confidence interval [CI] 75 to 1340) and participants tended to report less dyspnoea during daily life (MD 0.5 points per item, 95% CI - 0.1 to 1.0) when WW was available. No differences were observed for ST, upright time or stepping time. The WW was used over 4504 m/week (95% CI 2746 to 6262). CONCLUSION: These data demonstrated that, when provided to selected patients with COPD, WWs increased daily step count. CLINICAL TRIAL REGISTRATION NUMBER: ACTRN12609000332224.

Hosseini, M., A. Almasi-Hashiani, et al. (2019). **"Global prevalence of asthma-COPD overlap (ACO) in the general population: a systematic review and meta-analysis."** Respir Res **20**(1): 229.

BACKGROUND: Asthma-COPD overlap (ACO) is a term that encompasses patients with features of both asthma and COPD. To date, the global prevalence of ACO in the general population remains unknown. The objective of this study was to estimate the prevalence of ACO in the general population using a systematic review and meta-analysis. METHODS: A systematic search of ISI Web of Knowledge, MEDLINE/PubMed, and Scopus was performed up to May 2019 to identify studies reporting the prevalence of ACO. Reference lists from identified studies and relevant review articles were also searched. Eligibility criteria were studies reporting the prevalence of ACO, performed in general population, and published in English language. Pooled prevalence of ACO with 95% confidence interval (CI) was calculated using random effects Meta-analysis. RESULTS: A total of 27 studies were included in this meta-analysis. The Cochran Q test and I(2) statistics revealed substantial heterogeneity among studies. Based on the random-effects model, the pooled prevalence of ACO was 2.0% (95% CI: 1.4-2.6%) in the general population, 26.5% (95% CI: 19.5-33.6%) among patients with asthma, and 29.6% (95% CI: 19.3-39.9%) among patients with COPD. In addition, for included studies, the global prevalence of asthma-only was 6.2% (95% CI: 5.0-7.4%) and COPD-only was 4.9% (95% CI: 4.3-5.5%). CONCLUSION: We estimated the global prevalence of ACO based on population-based studies and found that 2.0% of the general population is affected. However, the prevalence of ACO depends on its diagnostic criteria. Therefore, there is a vital need to better define the ACO diagnostic criteria, management and treatment. It is worth noting that the limitations of the present study include lack of studies in some region of the world and small number of studies included in the subgroup analyses.

Huang, C., Y. Liu, et al. (2020). **"A systematic review with meta-analysis of gastroesophageal reflux disease and exacerbations of chronic obstructive pulmonary disease."** BMC Pulm Med **20**(1): 2.

BACKGROUND: Gastroesophageal reflux disease (GERD) was suggested to be associated with exacerbations of chronic obstructive pulmonary disease (COPD) in recent years. The aim of this study was to examine the association between GERD and COPD exacerbation through a meta-analysis. METHODS: Databases including EMBASE, MEDLINE, and the Cochrane Central Register of Controlled Trials were searched with a systematic searching strategy for original articles, published until Jan 2019, without language restriction. RESULTS: A total of 13,245 patients from 10 observational articles were included in the meta-analysis. The meta-analysis indicated that GERD is associated with increased risk of COPD exacerbation (OR: 5.37; 95% CI 2.71-10.64). Patients with COPD and GERD had increased number of exacerbation (WMD: 0.48; 95% CI: 0.31 to 0.65). CONCLUSIONS: The meta-analysis showed that there was a significant correlation between GERD and COPD exacerbation.

Ingadottir, A. R., A. M. Beck, et al. (2019). **"Oral nutrition supplements and between-meal snacks for nutrition therapy in patients with COPD identified as at nutritional risk: a randomised feasibility trial."** BMJ Open Respir Res **6**(1): e000349.

Introduction: Intervention studies have mainly used oral nutritional supplements (ONS) for the management of patients with chronic obstructive pulmonary disease (COPD) identified as at nutritional risk. In this 12-month randomised feasibility trial, we assessed the (1) feasibility of the recruitment, retention and provision of two interventions: ONS and between-meal snacks (snacks) and (2) the potential impact of the provision of snacks and ONS on body weight and quality of life in patients with COPD. Methods: Hospitalised patients with COPD, at nutritional risk, were randomised to ONS (n=19) or snacks (n=15) providing 600 kcal and 22 g protein a day in addition to regular daily diet. The intervention started in

hospital and was continued for 12 months after discharge from the hospital. Results: Study recruitment rate was n=34 (45%) and retention rate at 12 months was similar for both groups: n=13 (68%) in the ONS group and n=10 (67%) in the Snacks group. Both groups gained weight from baseline to 12 months (2.3+/-4.6 kg (p=0.060) in the ONS group and 4.4+/-6.4 kg (p=0.030) in the Snacks group). The St George's Respiratory Questionnaire total score improved from baseline to 12 months in both groups (score 3.9+/-11.0 (p=0.176) in the ONS group and score 8.9+/-14.1 (p=0.041) in the Snacks group). Discussion: In patients with COPD who are at nutritional risk snacks are at least as feasible and effective as ONS, however, adequately powered trials that take account of the difficulties in recruiting this patient group are required to confirm this effect.

Jayadev, A., R. Stone, et al. (2019). **"Time to NIV and mortality in AECOPD hospital admissions: an observational study into real world insights from National COPD Audits."** BMJ Open Respir Res **6**(1): e000444.

Background: Randomised control trial (RCT)-derived survival figures for acute exacerbation of chronic obstructive pulmonary disease admissions managed with non-invasive ventilation (NIV) have not been replicated in UK clinical audits. Subsequent guidelines have emphasised the need for timely NIV application. Methods: Data from the 2008 and 2014 national chronic obstructive pulmonary disease audits was used to analyse the association between time to NIV and mortality. Results: 1032 patients received NIV in 2008, and 1612 in 2014. Overall mortality rates reduced between the audits from 24.9% in 2008 to 16.8% in 2014 but time to NIV lengthened. In 2014, 20.9% of patients received NIV within 60 min versus 24.9% in 2008 (p=0.001). The proportion of patients receiving NIV between 3 and 24 hours increased from 31.3% in 2008 to 39% in 2014 (p=0.001). Patients admitted with hypercapnic acidotic respiratory failure who received NIV within 3 hours had lower in-patient mortality than those who received NIV between 3 and 24 hours, 15.9% versus 18.4%, but this did not reach statistical significance (p=0.425), but acidotic patients receiving NIV >24 hours after admission had significantly higher mortality (28.9%, p=0.002). A second cohort admitted with hypercapnia but normal range pH, who developed later acidosis, had higher mortality (24.6%), compared with those acidotic on admission (18% p</=0.001) and an extremely high mortality when NIV was given >24 hours after admission (42.6%). Conclusion: Survival rates for those treated with NIV has improved between the two audits but remains lower than reported in RCTs. Patients who developed acidosis after admission and received NIV later in the hospital stay have even higher mortality and deserve further study and clinical attention.

Jiang, C. G., Q. Fu, et al. (2019). **"Prognosis of combined pulmonary fibrosis and emphysema: comparison with idiopathic pulmonary fibrosis alone."** Ther Adv Respir Dis **13**: 1753466619888119.

BACKGROUND: Combined pulmonary fibrosis and emphysema (CPFE) is a syndrome characterized by the coexistence of upper lobe emphysema and lower lobe fibrosis. However, whether CPFE has a higher or lower mortality than idiopathic pulmonary fibrosis (IPF) alone is still not clear. In this study we conducted a meta-analysis to assess the survival rate (SR) of CPFE versus IPF alone in clinical trials. METHODS: We performed a systematic search of PubMed, Embase, and the Cochrane Central Register of Controlled Trials for trials published prior to 31 March 2018. Extracts from the literature were analyzed with Review Manager version 5.3. RESULTS: Thirteen eligible trials were included in this analysis (involving 1710 participants). Overall, the pooled results revealed that no statistically significant difference was detected in the 1-year [relative risk (RR) = 0.98, 95% confidence interval (CI): 0.94-1.03, p = 0.47], 3-year (RR = 0.83, 95% CI: 0.68-1.01, p = 0.06), and 5-year (RR = 0.80, 95% CI: 0.59-1.07, p = 0.14) SRs of CPFE versus IPF alone. CONCLUSIONS: CPFE exhibits a very poor prognosis, similar to IPF alone. Additional studies are needed to provide more convincing data to investigate the natural history and outcome of patients with CPFE in comparison to IPF. The reviews of this paper are available via the supplemental material section.

Jin, J., H. Zhang, et al. (2019). **"Effectiveness of Xin Jia Xuan Bai Cheng Qi Decoction in treating acute exacerbation of chronic obstructive pulmonary disease: study protocol for a multicentre, randomised, controlled trial."** BMJ Open **9**(11): e030249.

INTRODUCTION: Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) brings a serious impact on patients' quality of life, and has extremely high morbidity and mortality worldwide. Although there are many therapies being developed to alleviate symptoms and reduce mortality, a few studies have supported which treatment method is the best. Traditional Chinese medicine (TCM) has shown good potential in the prevention and treatment of AECOPD, especially in terms of supplementation and reduction of dosage and adverse effect of Western medicine. The purpose of this study is to compare the effectiveness of combination of TCM and Western medicine with conventional therapy alone for AECOPD, and to ensure whether the combined therapy may reduce the use of systemic glucocorticoid in AECOPD without influencing efficacy. METHODS AND ANALYSIS: A multicentre, randomised, double-blind, placebo-controlled study was conducted to enrol a total of 360 eligible patients who will be randomised into integrated Chinese and Western medicine group A, B and Western standard Medicine group C. After 5 days of intervention and 1 month of follow-up, the efficacy and safety of Xin Jia Xuan Bai Cheng Qi Decoction in patients with AECOPD will be observed. The results of evaluation indicators include: clinical symptoms, biochemical indicators such as blood gas analysis, inflammatory markers, hospitalisation time, TCM syndrome evaluation, biological indicators such as airway, intestinal flora sequencing. ETHICS AND DISSEMINATION: This trail has been approved by the Ethics Committee of China-Japan Friendship Hospital. The results will be disseminated in international peer-reviewed journals and be presented in academic conferences. The results will also be disseminated to patients by telephone, inquiring on patient's poststudy health status during the follow-up. TRIAL REGISTRATION NUMBER: ChiCTR1800016915.

Kopsaftis, Z., K. V. Carson-Chahhoud, et al. (2020). **"Oxygen therapy in the pre-hospital setting for acute exacerbations of chronic obstructive pulmonary disease."** Cochrane Database Syst Rev **1**: Cd005534.

BACKGROUND: Chronic obstructive pulmonary disease (COPD) is a global leading cause of morbidity and mortality, characterised by acute deterioration in symptoms. During these exacerbations, people are prone to developing alveolar hypoventilation, which may be partly caused by the administration of high inspired oxygen concentrations. OBJECTIVES: To determine the effect of different inspired oxygen concentrations ("high flow" compared to "controlled") in the pre-hospital setting (prior to casualty/emergency department) on outcomes for people with acute exacerbations of COPD (AECOPD). SEARCH METHODS: The Cochrane Airways Group Specialised Register, reference lists of articles and online clinical trial databases were searched. Authors of identified randomised controlled trials (RCTs) were also contacted for details of other relevant published and unpublished studies. The most recent search was conducted on 16 September 2019. SELECTION CRITERIA: We included RCTs comparing oxygen therapy at different concentrations or oxygen therapy versus placebo in the pre-hospital setting for treatment of AECOPD. DATA COLLECTION AND ANALYSIS: Two review authors independently assessed trial quality and extracted data. The primary outcome was all-cause and respiratory-related mortality. MAIN RESULTS: The search identified a total of 824 citations; one study was identified for inclusion and two studies are awaiting classification. The 214 participants involved in the included study were adults with AECOPD, receiving treatment by paramedics en route to hospital. The mean age of participants was 68 years. A reduction in pre/in-hospital mortality was observed in favour of the titrated oxygen group (two deaths in the titrated oxygen group compared to 11 deaths in the high-flow control arm; risk ratio (RR) 0.22, 95% confidence interval (CI) 0.05 to 0.97; 214 participants). This translates to an absolute effect of 94 per 1000 (high-flow oxygen) compared to 21 per 1000 (titrated oxygen), and a number needed to treat for an additional beneficial outcome (NNTB) of 14 (95% CI 12 to 355) with

titrated oxygen therapy. Other than mortality, no other adverse events were reported in the included study. Wide confidence intervals were observed between groups for arterial blood gas (though this may be confounded by protocol infidelity in the included study for this outcome measure), treatment failure requiring invasive or non-invasive ventilation or hospital utilisation. No data were reported for quality of life, lung function or dyspnoea. Risk of bias within the included study was largely unclear, though there was high risk of bias in domains relating to performance and attrition bias. We judged the evidence to be of low certainty, according to GRADE criteria. AUTHORS' CONCLUSIONS: The one included study found a reduction in pre/in-hospital mortality for the titrated oxygen arm compared to the high-flow control arm. However, the paucity of evidence somewhat limits the reliability of these findings and generalisability to other settings. There is a need for robust, well-designed RCTs to further investigate the effect of oxygen therapies in the pre-hospital setting for people with AECOPD.

Labarca, G., L. Drake, et al. (2019). **"Association between inflammatory bowel disease and chronic obstructive pulmonary disease: a systematic review and meta-analysis."** BMC Pulm Med **19**(1): 186.

INTRODUCTION: There is evidence of an association between inflammatory bowel disease (IBD) and lung conditions such as chronic obstructive pulmonary disease (COPD). This systematic review and meta-analysis explored the risk of new onset IBD in patients with COPD and new onset COPD in IBD patients. METHODS: We performed a systematic review of observational studies exploring the risk of both associations. Two independent reviewers explored the EMBASE, MEDLINE, LILACS and DOAJ databases, and the risk of bias was evaluated using the ROBBINS-I tool. Data from included studies was pooled in a random effect meta-analysis following a DerSimonian-Laird method. The quality of the evidence was ranked using GRADE criteria. RESULTS: Four studies including a pooled population of 1355 new cases were included. We found association between new onset IBD in COPD population. The risk of bias was low in most of them. Only one study reported tobacco exposure as a potential confounding factor. The pooled risk ratio (RR) for a new diagnosis of IBD in COPD patients was 2.02 (CI, 1.56 to 2.63), I(2) = 72% (GRADE: low). The subgroup analyses for Crohn's disease and ulcerative colitis yielded RRs of 2.29 (CI, 1.51 to 3.48; I(2) = 62%), and 1.79 (CI, 1.39 to 2.29; I(2) = 19%.), respectively. DISCUSSION: According to our findings, the risk of new onset IBD was higher in populations with COPD compared to the general population without this condition. Based on our analysis, we suggest a potential association between IBD and COPD; however, further research exploring the potential effect of confounding variables, especially cigarette smoking, is still needed. REVIEW REGISTER: (PROSPERO: CRD42018096624).

Lahham, A., C. F. McDonald, et al. (2019). **"The impact of home-based pulmonary rehabilitation on people with mild chronic obstructive pulmonary disease: A randomised controlled trial."** Clin Respir JINTRODUCTION: People with mild chronic obstructive pulmonary disease (COPD) experience exercise intolerance, dyspnoea and poor quality of life. However, the role of pulmonary rehabilitation (PR) in this group is unclear. OBJECTIVES: This randomised controlled trial aimed to explore the effects of home-based PR in people with mild COPD. METHODS: People with mild COPD (FEV1 /FVC < 70%; FEV1 > 80%predicted) with a smoking history of >/=10 packet years were randomised to either 8 weeks of home-based PR (one home visit and seven once-weekly telephone calls) or standard care (weekly social telephone calls). Six minute walk distance (6MWD), and Modified Medical Research Council Dyspnoea Scale (mMRC) and Chronic Respiratory Disease Questionnaire (CRQ) scores were compared. RESULTS: A total of 58 participants (34 males, mean age 68 (SD 9) years, FEV1 %predicted 90 (7), 6MWD 496 (105) m) were included with 31 participants randomised to home-based PR. Participants attended an average of 6.8 of the 8 scheduled sessions, ranging from 3 to 8 sessions. Both groups showed improvements in exercise capacity, symptoms and health-related quality of life (HRQoL) over time, however there was no difference in 6MWD at end-intervention (mean difference -3 m, 95% confidence interval (CI) -64 to 58) or 6 months (7 m, 95% CI -59 to 72). At 6 months home-based PR participants were more likely to have

clinically important improvements in CRQ emotional function (50% of home PR vs 0% control, P < 0.001) and CRQ total score (45% vs 17%, P = 0.05). CONCLUSION: For people with mild COPD, home-based PR did not improve exercise capacity more than standard care. The trial was registered at the Australia New Zealand clinical trial registry (https://www.anzctr.org.au, Trial ID: ACTRN12616000965404).

Lahousse, L., D. Bos, et al. (2019). **"Atherosclerotic calcification in major vessel beds in chronic obstructive pulmonary disease: The Rotterdam Study."** Atherosclerosis **291**: 107-113.

BACKGROUND AND AIMS: COPD is associated with an increased risk of cardiovascular morbidity and mortality, potentially by mechanisms of atherosclerosis. Insight into location-specific vulnerability to atherosclerosis in COPD, including intracranial arteries, is lacking. We aimed to investigate the relation between COPD and atherosclerosis in multiple vessel beds within a large population-based cohort study. METHODS: From 2003 to 2006, a random sample of 2187 elderly participants (mean age, 69.6+/-6.8 years; 50.9% female; 11.7% COPD) from the population-based Rotterdam Study underwent computed tomography to quantify atherosclerotic coronary artery calcification (CAC), aortic arch calcification (AAC), extracranial carotid artery calcification (ECAC), and intracranial carotid artery calcification (ICAC). We investigated the association of COPD [ratio of forced expiratory volume in the first second to forced vital capacity (FEV1/FVC)<70%] with the presence of calcification and with calcification volumes in each vessel bed using logistic and linear regression, with adjustments for cardiovascular risk factors including smoking. RESULTS: The prevalence of CAC, AAC and ECAC was significantly higher in subjects with COPD compared to those without. After adjusting for age and smoking, COPD remained associated with the presence of ECAC (odds ratio 1.46 [95% confidence interval, 1.02-2.07, p=0.037]). COPD was significantly associated with larger calcification volumes in all four vessel beds in people in whom calcification was present. CONCLUSIONS: The results of this study suggest that COPD plays a role in extracranial carotid artery atherosclerosis initiation and systemic atherosclerosis aggravation.

Langham, S., J. Lewis, et al. (2019). **"Single-inhaler triple therapy in patients with chronic obstructive pulmonary disease: a systematic review."** Respir Res **20**(1): 242.

BACKGROUND: Guidelines recommend that treatment with a long-acting beta2 agonist (LABA), a long-acting muscarinic antagonist (LAMA), and inhaled corticosteroids (ICS), i.e. triple therapy, is reserved for a select group of symptomatic patients with chronic obstructive pulmonary disease (COPD) who continue to exacerbate despite treatment with dual therapy (LABA/LAMA). A number of single-inhaler triple therapies are now available and important clinical questions remain over their role in the patient pathway. We compared the efficacy and safety of single-inhaler triple therapy to assess the magnitude of benefit and to identify patients with the best risk-benefit profile for treatment. We also evaluated and compared study designs and population characteristics to assess the strength of the evidence base. METHODS: We conducted a systematic search, from inception to December 2018, of randomised controlled trials (RCTs) of single-inhaler triple therapy in patients with COPD. The primary outcome was the annual rate of moderate and severe exacerbations. RESULTS: We identified 523 records, of which 15 reports/abstracts from six RCTs were included. Triple therapy resulted in the reduction of the annual rate of moderate or severe exacerbations in the range of 15-52% compared with LAMA/LABA, 15-35% compared to LABA/ICS and 20% compared to LAMA. The patient-based number needed to treat for the moderate or severe exacerbation outcome ranged between approximately 25-50 (preventing one patient from having an event) and the event-based number needed to treat of around 3-11 (preventing one event). The absolute benefit appeared to be greater in patients with higher eosinophil counts or historical frequency of exacerbations and ex-smokers. In the largest study, there was a significantly higher incidence of pneumonia in the triple therapy arm. There were important differences in study designs and populations impacting the interpretation of the results and indicating there would be significant heterogeneity in cross-trial comparisons. CONCLUSION: The decision to prescribe triple

therapy should consider patient phenotype, magnitude of benefit and increased risk of adverse events. Future research on specific patient phenotype thresholds that can support treatment and funding decisions is now required from well-designed, robust, clinical trials. TRIAL REGISTRATION: PROSPERO #CRD42018102125 .

Le Mao, R., C. Tromeur, et al. (2019). **"Effect of Early Initiation of Varenicline on Smoking Cessation in COPD Patients Admitted for Exacerbation: The Save Randomized Clinical Trial."** Copd: 1-8.

Our main objective was to demonstrate that, in smoker patients hospitalised for Chronic Obstructive Pulmonary Disease (COPD) exacerbation, early initiation of varenicline during 12 weeks, combined with an intensive counselling, is associated with a higher continuous abstainers rate (CAR) at one year as compared to intensive counselling alone. In this multicenter, prospective, double-blind, randomised study, 81 smoking COPD patients hospitalised for an acute exacerbation for at least 24 h were allocated to receive either varenicline (n = 42) or placebo (n = 39) for 12 weeks, in association with an intensive counselling in the 2 groups, and followed up for 40 weeks. The primary outcome was CAR at week 52. Secondary outcomes included CAR at week 12 and 26, partial abstinence rate (PAR) at week 12, 26 and 52, nicotinic substitute consumption and adverse events. At week 52, CAR was not different in placebo and varenicline groups (25.6%). At week 12, CAR was significantly higher in the varenicline group (50%) as compared to placebo group (27%) (p = 0.041). Nicotine consumption was significantly higher at week 52 in the placebo group (55.3%) as compared to the varenicline group (24.4%) (p = 0.005). There was no significant difference in PAR at week 12, 26 and 52; the frequency of adverse events was similar between the two groups. Among active smoker COPD patients with exacerbation, 12-week varenicline associated with intensive counselling for smoking cessation increased the rate of continuous abstainers as compared to placebo. However, benefit was not maintained after varenicline discontinuation.Clinical Trials Registration: URL: http://www.controlled-trials.com. Unique identifier: NCT01694732.

Lee, H. W., J. Park, et al. (2019). **"Comparisons of exacerbations and mortality among regular inhaled therapies for patients with stable chronic obstructive pulmonary disease: Systematic review and Bayesian network meta-analysis."** PLoS Med **16**(11): e1002958.

BACKGROUND: Although exacerbation and mortality are the most important clinical outcomes of stable chronic obstructive pulmonary disease (COPD), the drug classes that are the most efficacious in reducing exacerbation and mortality among all possible inhaled drugs have not been determined. METHODS AND FINDINGS: We performed a systematic review (SR) and Bayesian network meta-analysis (NMA). We searched Medline, EMBASE, the Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, the European Union Clinical Trials Register, and the official websites of pharmaceutical companies (from inception to July 9, 2019). The eligibility criteria were as follows: (1) parallel-design randomized controlled trials (RCTs); (2) adults with stable COPD; (3) comparisons among long-acting muscarinic antagonists (LAMAs), long-acting beta-agonists (LABAs), inhaled corticosteroids (ICSs), combined treatment (ICS/LAMA/LABA, LAMA/LABA, or ICS/LABA), or a placebo; and (4) study duration >/= 12 weeks. This study was prospectively registered in International Prospective Register of Systematic Reviews (PROSPERO; CRD42017069087). In total, 219 trials involving 228,710 patients were included. Compared with placebo, all drug classes significantly reduced the total exacerbations and moderate to severe exacerbations. ICS/LAMA/LABA was the most efficacious treatment for reducing the exacerbation risk (odds ratio [OR] = 0.57; 95% credible interval [CrI] 0.50-0.64; posterior probability of OR > 1 [P(OR > 1)] < 0.001). In addition, in contrast to the other drug classes, ICS/LAMA/LABA and ICS/LABA were associated with a significantly higher probability of reducing mortality than placebo (OR = 0.74, 95% CrI 0.59-0.93, P[OR > 1] = 0.004; and OR = 0.86, 95% CrI 0.76-0.98, P[OR > 1] = 0.015, respectively). The results minimally changed, even in various sensitivity and covariate-adjusted meta-regression analyses. ICS/LAMA/LABA tended to lower the risk of cardiovascular mortality but did not show significant results.

ICS/LAMA/LABA increased the probability of pneumonia (OR for triple therapy = 1.56; 95% CrI 1.19-2.03; P[OR > 1] = 1.000). The main limitation is that there were few RCTs including only less symptomatic patients or patients at a low risk. CONCLUSIONS: These findings suggest that triple therapy can potentially be the best option for stable COPD patients in terms of reducing exacerbation and all-cause mortality.

Li, L. S. K., S. Butler, et al. (2019). **"Comparing the impact of different exercise interventions on fatigue in individuals with COPD: A systematic review and meta-analysis."** Chron Respir Dis **16**: 1479973119894855.

To systematically review randomized controlled trials that compared the effectiveness of different types of exercise on the symptom of fatigue in individuals with chronic obstructive pulmonary disease (COPD). MEDLINE, EMBASE, EMcare, PsychINFO, and Cochrane library were searched from inception to October 2018. Studies were included if individuals with COPD were randomized into two or more physical exercise interventions that reported fatigue. Of the 395 full-texts reviewed, 17 studies were included. Fifteen studies reported the impact of exercise on health-related quality of life with fatigue as a subdomain. Reduction in fatigue was observed following endurance, resistance, or a combination of both exercises. There was no significant difference between continuous and interval training (n = 3 studies, pooled standardized mean difference (SMD) = -0.17, 95% CI = -0.47, 0.12, p = 0.25) or between endurance and resistance training (n = 3 studies, SMD = -0.35, 95% CI = -0.72, 0.01, p = 0.07) on fatigue in people with COPD. Fatigue reduction is not usually a primary outcome of exercise interventions, but it is frequently a secondary domain. The type of exercise did not influence the impact of exercise on fatigue, which was reduced in endurance, resistance, or a combination of both exercises, enabling clinicians to personalize training to match targeted outcomes.

Li, Z., S. Liu, et al. (2019). **"Mind-Body Exercise for Anxiety and Depression in COPD Patients: A Systematic Review and Meta-Analysis."** Int J Environ Res Public Health **17**(1)OBJECTIVES: Mind-body exercise has been generally recognized as a beneficial strategy to improve mental health in those with Chronic Obstructive Pulmonary Disease (COPD). However, to date, no attempt has been made to collate this literature. The aim of the present study was to systematically analyze the effects of mind-body exercise for COPD patients with anxiety and depression and provide scientific evidence-based exercise prescription. METHODS: both Chinese and English databases (PubMed, the Cochrane Library, EMBASE, Web of Science, Google Scholar, Chinese National Knowledge Infrastructure, Wanfang, Baidu Scholar) were used as sources of data to search randomized controlled trials (RCT) relating to mind-body exercise in COPD patients with anxiety and depression that were published between January 1982 to June 2019. 13 eligible RCT studies were finally used for meta-analysis. RESULTS: Mind-body exercise (tai chi, health qigong, yoga) had significant benefits on COPD patients with anxiety (SMD= -0.76, 95% CI -0.91 to -0.60, p=0.04, I(2)=47.4%) and depression (SMD= -0.86, 95% CI -1.14 to -0.58, p=0.000, I(2)=71.4%). Sub-group analysis indicated that, for anxiety, 30-60 min exercise session for 24 weeks of health qigong or yoga had a significant effect on patients with COPD who are more than 70 years and have more than a 10-year disease course. For depression, 2-3 times a week, 30-60 min each time of health qigong had a significant effect on patients with COPD patients who are more than 70 years old and have less than a 10-year disease course. CONCLUSIONS: Mind-body exercise could reduce levels of anxiety and depression in those with COPD. More robust RCT are required on this topic.

Lu, Y., P. Li, et al. (2019). **"Effects of Home-Based Breathing Exercises in Subjects With COPD."** Respir CareBACKGROUND: We sought to investigate the effects of home-based breathing exercises on pulmonary function, respiratory muscle strength, exercise capacity, dyspnea, and health-related quality of life in patients with COPD. METHODS: All randomized, controlled trials involving the use of home-based breathing exercises as an intervention in patients with COPD were searched on PubMed, Embase, Web of Science, EBSCO, CNKI, and Wangfang Data databases from January 1, 2008, to December 31, 2018. Two researchers independently extracted data and assessed the quality of the literature that met the inclusion criteria. RESULTS: A total of 13 studies were included, with a total of 998 subjects. The intervention methods consisted of diaphragmatic breathing, yoga breathing, breathing gymnastics, and singing. Meta-analysis showed that, compared with the control group, home-based breathing exercises had significant effects on the percent of predicted FEV1 (mean difference = 3.26, 95% CI 0.52-5.99, P = .02), FEV1/FVC (mean difference = 2.84, 95% CI 1.04-4.64, P = .002), maximum inspiratory pressures (mean difference = 20.20, 95% CI 11.78-28.61, P < .001), maximum expiratory pressures (mean difference = 26.35, 95% CI 12.64 to 40.06, P < .001), 6-min walk distance (mean difference = 36.97, 95% CI 25.06-48.89, P < .001), the modified Medical Research Council dyspnea scale (mean difference= -0.80, 95% CI -1.06 to -0.55, P < .001), and the St George Respiratory Questionnaire (mean difference= -8.62, 95% CI -13.09 to -4.16, P < .001). CONCLUSIONS: As an alternative method of home-based pulmonary rehabilitation program, breathing exercises can improve pulmonary function, respiratory muscle strength, exercise capacity, dyspnea, health-related quality of life in patients with COPD.

Luo, L., J. Li, et al. (2019). **"Using machine learning approaches to predict high-cost chronic obstructive pulmonary disease patients in China."** Health Informatics J: 1460458219881335.

The accurate identification and prediction of high-cost Chronic obstructive pulmonary disease (COPD) patients is important for addressing the economic burden of COPD. The objectives of this study were to use machine learning approaches to identify and predict potential high-cost patients and explore the key variables of the forecasting model, by comparing differences in the predictive performance of different variable sets. Machine learning approaches were used to estimate the medical costs of COPD patients using the Medical Insurance Data of a large city in western China. The prediction models used were logistic regression, random forest (RF), and extreme gradient boosting (XGBoost). All three models had good predictive performance. The XGBoost model outperformed the others. The areas under the ROC curve for Logistic Regression, RF and XGBoost were 0.787, 0.792 and 0.801. The precision and accuracy metrics indicated that the methods achieved correct and reliable results. The results of this study can be used by healthcare data analysts, policy makers, insurers, and healthcare planners to improve the delivery of health services.

Ma, R. C., Y. Y. Yin, et al. (2019). **"Effectiveness of cognitive behavioural therapy for chronic obstructive pulmonary disease patients: A systematic review and meta-analysis."** Complement Ther Clin Pract **38**: 101071.

BACKGROUND: and purpose: Cognitive behavioural therapy (CBT) has gained increasing attention for the treatment of psychological disorders. This study aims to establish the effectiveness of CBT on psychological and physical outcomes in patients with chronic obstructive pulmonary disease (COPD). METHODS: Two waves of electronic searches of the PubMed, Cochrane library, EMBASE, Web of Science and China National Knowledge Infrastructure databases were conducted. Statistical analyses were performed using Revman Manager 5.3 and Stata 12.0 software. RESULTS: Sixteen randomized controlled trials were eligible. There were significant improvements in anxiety (SMD=-0.23; 95% CI: -0.42 to -0.04; P=0.02), depression (SMD=-0.29, 95% CI: -0.40 to -0.19, P<0.01), quality of life (MD=-5.21; 95% CI: -10.25 to -0.17; P=0.04), and mean visits to emergency departments in the CBT groups. No statistically

significant differences were observed in fatigue (SMD=0.88, 95% CI: -0.58 to 2.35, P=0.24), exercise capacity (MD=28.75, 95% CI: -28.30 to 85.80, P=0.32), self-efficacy (SMD=0.15, 95% CI: -0.05 to 0.34, P=0.14), or sleep quality (MD=1.21, 95% CI: -0.65 to 3.06, P=0.20). CONCLUSION: This meta-analysis suggests that CBT can serve as a complementary therapy to improve anxiety, depression, and quality of life in COPD patients and deserves more widespread application in clinical practice.

Ma, Y., D. Zong, et al. (2019). **"Feasibility of mean platelet volume as a biomarker for chronic obstructive pulmonary disease: A systematic review and meta-analysis."** J Int Med Res **47**(12): 5937-5949.

Machado, A., A. Oliveira, et al. (2020). **"Effects of a community-based pulmonary rehabilitation programme during acute exacerbations of chronic obstructive pulmonary disease - A quasi-experimental pilot study."** Pulmonology **26**(1): 27-38.

BACKGROUND: Pulmonary rehabilitation (PR) is a cornerstone intervention for the management of patients with stable chronic obstructive pulmonary disease (COPD). However, its role during acute exacerbations (AECOPD) is controversial since most studies have been conducted in hospitalised patients, when more than 80% of AECOPD are managed on an outpatient basis. This quasi-experimental pilot study assessed the effects of a community-based PR programme during mild-to-moderate AECOPD. METHODS: Outpatients were recruited from hospitals and allocated to experimental (EG) or control (CG) groups. EG received standard medication plus 3-weeks of PR. The CG received standard medication. Dyspnoea (mMRC), quadriceps muscle strength (QMS), functionality (5-repetition sit-to-stand test) and impact of the disease (COPD assessment test (CAT)) were assessed within 48h of the AECOPD onset and after PR. Symptoms of dyspnoea and fatigue (mBorg), heart and respiratory (RR) rates and peripheral oxygen saturation (SpO2) were assessed at rest and monitored in all PR sessions. Need for hospitalisation was monitored during the 3-weeks. RESULTS: Twelve patients (69+/-7 years, FEV1 52+/-27 pp) in the EG and eleven in the CG (66+/-9 years, FEV1 55+/-22 pp) were enrolled. The EG presented significant improvements on QMS (Pre 21.0 vs. Post 25.0, p=0.012), CAT (Pre 23.0 vs. Post 14.5, p=0.008), symptoms of dyspnoea at rest (Pre 3.0 vs. Post 1.0, p=0.008), SpO2 (Pre 94.0 vs. Post 96.0, p=0.031) and RR (Pre 24.0 vs. Post 20.5, p=0.004). No significant improvements were found in the CG. CONCLUSION: Adding PR to the management of mild-to-moderate AECOPD seems to result in improvements on parameters usually associated with an increased risk of re-exacerbation and poor prognosis. Randomised studies with larger samples are needed to confirm these results.

Majid, A., G. Labarca, et al. (2020). **"Efficacy of the Spiration Valve System in Patients with Severe Heterogeneous Emphysema: A Systematic Review and Meta-Analysis."** Respiration **99**(1): 62-72.

BACKGROUND: Spiration Valve System (SVS) is an alternative for patients with severe heterogeneous emphysema; however, data about efficacy from randomized controlled trials (RCT) are unclear. OBJECTIVES: To explore both efficacy and safety of SVS in patients with severe emphysema and hyperinflation. METHODS: We included PubMed, EMBASE, Coch-rane database. All searches were performed until August 2019. Only RCTs were included for analysis. Risk of bias was assessed using Cochrane risk of bias tool. A meta-analysis evaluated change in forced expiratory volume in 1 s (FEV1), 6-min walking test (6MWT), residual volume, modified medical research council (mMRC) and Saint George respiratory questionnaire (SGRQ), all-cause mortality, risk of pneumothorax, and risk of acute exacerbation of chronic obstructive pulmonary disease (AECOPD). Quality of the evidence was rated

using GRADE approach. RESULTS: Four RCTs including 629 subjects were included. SVS showed an overall change of 0.03 L (-0.07 to 0.13, I2 = 90%) in the in FEV1 (L) and a 2.03% (-2.50 to 6.57, I2 = 96%) in the predicted FEV1 (%) compared to baseline; however, studies without collateral ventilation (CV) showed an improvement of 0.12 L (95% CI 0.09-0.015, I2 = 0%), This subgroup also reported better results in SGRQ -12.27 points (95% CI -15.84 to -8.70, I2 = 0%) and mMRC -0.54 (95% CI -0.74 to -0.33, I2 = 0%). We found no benefit in 6MWT mean difference = 4.56 m (95% CI -21.88 to 31.00, I2 = 73%). Relative risk of mortality was 2.54 (95% CI 0.81-7.96, I2 = 0%), for pneumothorax 3.3 (95% CI 0.61-18.12, I2 = 0%) and AECOPD 1.68 (95% CI 1.04-2.70, I2 = 0%). CONCLUSION: In patients with severe heterogeneous emphysema and hyperinflation without CV, SVS is an alternative that showed an improvement in pulmonary function, quality of life, and dyspnea score with an acceptable risk profile.

Malliaraki, N., K. Lakiotaki, et al. (2019). **"Translating vitamin D transcriptomics to clinical evidence: Analysis of data in asthma and chronic obstructive pulmonary disease, followed by clinical data meta-analysis."** J Steroid Biochem Mol Biol **197**: 105505.

Vitamin D (VitD) continues to trigger intense scientific controversy, regarding both its bi ological targets and its supplementation doses and regimens. In an effort to resolve this dispute, we mapped VitD transcriptome-wide events in humans, in order to unveil shared patterns or mechanisms with diverse pathologies/tissue profiles and reveal causal effects between VitD actions and specific human diseases, using a recently developed bioinformatics methodology. Using the similarities in analyzed transcriptome data (c-SKL method), we validated our methodology with osteoporosis as an example and further analyzed two other strong hits, specifically chronic obstructive pulmonary disease (COPD) and asthma. The latter revealed no impact of VitD on known molecular pathways. In accordance to this finding, review and meta-analysis of published data, based on an objective measure (Forced Expiratory Volume at one second, FEV1%) did not further reveal any significant effect of VitD on the objective amelioration of either condition. This study may, therefore, be regarded as the first one to explore, in an objective, unbiased and unsupervised manner, the impact of VitD levels and/or interventions in a number of human pathologies.

Maltais, F., L. Bjermer, et al. (2019). **"Efficacy of umeclidinium/vilanterol versus umeclidinium and salmeterol monotherapies in symptomatic patients with COPD not receiving inhaled corticosteroids: the EMAX randomised trial."** Respir Res **20**(1): 238.

BACKGROUND: Prospective evidence is lacking regarding incremental benefits of long-acting dual- versus mono-bronchodilation in improving symptoms and preventing short-term disease worsening/treatment failure in low exacerbation risk patients with chronic obstructive pulmonary disease (COPD) not receiving inhaled corticosteroids. METHODS: The 24-week, double-blind, double-dummy, parallel-group Early MAXimisation of bronchodilation for improving COPD stability (EMAX) trial randomised patients at low exacerbation risk not receiving inhaled corticosteroids, to umeclidinium/vilanterol 62.5/25 mug once-daily, umeclidinium 62.5 mug once-daily or salmeterol 50 mug twice-daily. The primary endpoint was trough forced expiratory volume in 1 s (FEV1) at Week 24. The study was also powered for the secondary endpoint of Transition Dyspnoea Index at Week 24. Other efficacy assessments included spirometry, symptoms, heath status and short-term disease worsening measured by the composite endpoint of clinically important deterioration using three definitions. RESULTS: Change from baseline in trough FEV1 at Week 24 was 66 mL (95% confidence interval [CI]: 43, 89) and 141 mL (95% CI: 118, 164) greater with umeclidinium/vilanterol versus umeclidinium and salmeterol, respectively (both $p < 0.001$). Umeclidinium/vilanterol demonstrated consistent improvements in Transition Dyspnoea Index versus both monotherapies at Week 24 (vs umeclidinium: 0.37 [95% CI: 0.06, 0.68], $p = 0.018$; vs salmeterol: 0.45 [95% CI: 0.15, 0.76], $p = 0.004$) and all other symptom measures at all time points. Regardless of the clinically important deterioration definition considered, umeclidinium/vilanterol significantly reduced the

risk of a first clinically important deterioration compared with umeclidinium (by 16-25% [p < 0.01]) and salmeterol (by 26-41% [p < 0.001]). Safety profiles were similar between treatments. CONCLUSIONS: Umeclidinium/vilanterol consistently provides early and sustained improvements in lung function and symptoms and reduces the risk of deterioration/treatment failure versus umeclidinium or salmeterol in symptomatic patients with low exacerbation risk not receiving inhaled corticosteroids. These findings suggest a potential for early use of dual bronchodilators to help optimise therapy in this patient group.

Michael, F., S. Whitelaw, et al. (2019). **"Transitional care quality indicators to assess quality of care following hospitalisation for chronic obstructive pulmonary disease and heart failure: a systematic review protocol."** BMJ Open **9**(12): e032764.

INTRODUCTION: The period following hospitalisation for chronic obstructive pulmonary disease (COPD) or heart failure (HF)-when patients transition between settings and clinicians-is one of high risk. Transitional care services that bridge the gap from hospital to home can improve outcomes, but there are no widely accepted indicators to assess their quality. METHODS AND ANALYSIS: In this systematic review, we will summarise transitional care quality indicators, and describe their associations with clinical, patient-reported and cost outcomes. We will search MEDLINE, Embase, CINAHL and HealthSTAR, as well as grey literature and reference lists of included articles. We will screen all studies published between January 1990 and October 2019 that test an intervention that aims to improve the hospital-to-home transition for patients with COPD and/or HF; and measure at least one process (eg, medication errors), clinical (eg, hospital readmissions) or patient-reported (eg, health-related quality of life) outcome which will serve as a transitional care quality indicator . We will include randomised controlled trials, cohort studies, cross-sectional studies, interrupted time series studies and before-after studies. We will extract data in duplicate and classify transitional care quality indicators as structural, process-related or outcome-related. When possible, we will assess associations between transitional care quality indicators and clinical outcomes. In anticipation of conceptual and statistical heterogeneity, we will provide a qualitative synthesis and narrative review of the results. ETHICS AND DISSEMINATION: This review will provide a list of transitional care quality indicators and their associations with clinical outcomes. These results can be used by hospitals, administrators and clinicians for assessing the quality of transitional care provided to patients with COPD and HF. The findings can also be used by policy-makers to assess and incentivise transitional care quality. We will disseminate results through publications, social media releases and presentations. PROSPERO REGISTRATION NUMBER: This study is registered on PROSPERO.

Nishimura, K., M. Kusunose, et al. (2019). **"Comparison between electronic and paper versions of patient-reported outcome measures in subjects with chronic obstructive pulmonary disease: an observational study with a cross-over administration."** BMJ Open **9**(12): e032767.

OBJECTIVES: A wide range of electronic devices can be used for data collection of patient-reported outcome (PRO) measures in subjects with chronic obstructive pulmonary disease (COPD). Although comparisons between electronic and paper-based PRO measures have been undertaken in asthmatics, it is currently uncertain whether electronic questionnaires work equally as well as paper versions in elderly subjects with COPD. The aim of this study was to compare the responses to paper and electronic versions of the Evaluating Respiratory Symptoms in COPD (E-RS) and the COPD Assessment Test (CAT). DESIGN: A randomised cross-over design was used to compare the responses to paper and electronic versions of the two tools. The interval between the two administrations was 1 week. SETTING: Electronic versions were self-administered under supervision using a tablet computer at our outpatient clinic (secondary care hospital in Japan) while paper questionnaires completed at home were requested to be returned by mail. It was intended that half of the patients completed the electronic versions of both questionnaires first, followed by the paper versions while the other half completed the paper versions fi rst. PARTICIPANTS: Eighty-one subjects with stable COPD were included. RESULTS: The E-RS total scores

(possible range 0-40) were 6.8+/-7.4 and 5.0+/-6.6 in the paper-based and electronic versions, respectively, and the CAT scores (possible range 0-40) were 10.0+/-7.4 and 8.6+/-7.8. In both questionnaires, higher scores indicate worse status. The relationship between electronic and paper versions showed significant reliability for both the E-RS total score and CAT score (intraclass correlation coefficient=0.82 and 0.89, respectively; both p<0.001). However, both the E-RS total and CAT scores were significantly higher in the paper versions (p<0.05). CONCLUSIONS: In both cases, the two versions of the same questionnaire cannot be used interchangeably even though they have both been validated.

Obeidat, M., A. Faiz, et al. (2019). **"The pharmacogenomics of inhaled corticosteroids and lung function decline in COPD."** Eur Respir J **54**(6)Inhaled corticosteroids (ICS) are widely prescribed for patients with chronic obstructive pulmonary disease (COPD), yet have variable outcomes and adverse reactions, which may be genetically determined. The primary aim of the study was to identify the genetic determinants for forced expiratory volume in 1 s (FEV1) changes related to ICS therapy.In the Lung Health Study (LHS)-2, 1116 COPD patients were randomised to the ICS triamcinolone acetonide (n=559) or placebo (n=557) with spirometry performed every 6 months for 3 years. We performed a pharmacogenomic genome-wide association study for the genotype-by-ICS treatment effect on 3 years of FEV1 changes (estimated as slope) in 802 genotyped LHS-2 participants. Replication was performed in 199 COPD patients randomised to the ICS, fluticasone or placebo.A total of five loci showed genotype-by-ICS interaction at p<5x10(-6); of these, single nucleotide polymorphism (SNP) rs111720447 on chromosome 7 was replicated (discovery p=4.8x10(-6), replication p=5.9x10(-5)) with the same direction of interaction effect. ENCODE (Encyclopedia of DNA Elements) data revealed that in glucocorticoid-treated (dexamethasone) A549 alveolar cell line, glucocorticoid receptor binding sites were located near SNP rs111720447. In stratified analyses of LHS-2, genotype at SNP rs111720447 was significantly associated with rate of FEV1 decline in patients taking ICS (C allele beta 56.36 mL.year(-1), 95% CI 29.96-82.76 mL.year(-1)) and in patients who were assigned to placebo, although the relationship was weaker and in the opposite direction to that in the ICS group (C allele beta -27.57 mL.year(-1), 95% CI -53.27- -1.87 mL.year(-1)).The study uncovered genetic factors associated with FEV1 changes related to ICS in COPD patients, which may provide new insight on the potential biology of steroid responsiveness in COPD.

Selzler, A. M., R. Habash, et al. (2019). **"Self-efficacy and health-related quality of life in chronic obstructive pulmonary disease: A meta-analysis."** Patient Educ CounsOBJECTIVE: To determine the association between self-efficacy and health-related quality of life (HRQoL) in people with Chronic Obstructive Pulmonary Disease (COPD) and the moderating effect of self-efficacy type (exercise task, exercise barrier, COPD symptom, general) and HRQoL type (generic, COPD specific). METHODS: Databases were searched systematically from inception to January 2019. Methodological quality was assessed, and a meta-analysis was conducted following PRISMA guidelines (PROSPERO protocol: CRD42018114846). RESULTS: Across 31 coefficients, there was a positive relationship between self-efficacy and HRQoL (r=0.38, 95 %CI [0.32, 0.45]). Exercise barrier self-efficacy had the strongest relationship to HRQoL (r=0.42, 95 % CI [0.30, 0.52]), followed by COPD symptoms (r=0.41, 95 % CI [0.33, 0.49]), exercise tasks (r=0.40, 95 % CI [0.29, 0.50]), and general self-efficacy (r=0.21, 95 % CI [0.14, 0.28]). Generic HRQoL had a similar relationship to self-efficacy (r=0.38, 95 % CI [0.28, 0.47]) as COPD specific HRQoL (r=0.38, 95 % CI [0.30, 0.46]). CONCLUSION: There is a moderate positive relationship between self-efficacy and HRQoL in COPD, with the relationship stronger for exercise and COPD symptoms than general self-efficacy.

Siddiqui, M. K., P. Shukla, et al. (2019). **"Systematic review and network meta-analysis of the efficacy and safety of glycopyrrolate/formoterol fumarate metered dose inhaler in comparison with other long-acting muscarinic antagonist/long-acting beta2-agonist fixed-dose combinations in COPD."** Ther Adv Respir Dis **13**: 1753466619894502.

BACKGROUND: Dual bronchodilation with a long-acting muscarinic antagonist (LAMA)/long-acting beta2-agonist (LABA) fixed-dose combination (FDC) is an established treatment strategy for chronic obstructive pulmonary disease (COPD). The relative efficacy and safety of glycopyrrolate/formoterol fumarate metered dose inhaler (GFF MDI 18/9.6 mug) in patients with moderate-to-very severe COPD, compared with other licensed LAMA/LABA FDCs, was investigated using an integrated Bayesian network meta-analysis (NMA). METHODS: A systematic literature review and subsequent screening process identified randomized controlled trials of 10 weeks' duration that enrolled patients aged 40 years with moderate-to-very severe COPD and included at least one LAMA/LABA FDC or open LAMA + LABA treatment arm. NMAs were conducted for outcomes including change from baseline in forced expiratory volume in 1 s (FEV1), St George's Respiratory Questionnaire (SGRQ), and transition dyspnea index (TDI) parameters, annualized rate of exacerbations, use of rescue medication, adverse events, and all-cause withdrawals. Meta-regression and sensitivity analyses accounted for heterogeneity across studies. RESULTS: In total, 29 studies including 34,617 patients contributed to the NMA for efficacy or safety outcomes at week 24 or exacerbations. For all LAMA/LABA FDCs with data available, significantly greater improvements in FEV1 [trough, peak, and area under the curve (AUC)0-4], SGRQ total score and TDI focal score at week 24, and annualized rate of moderate-to-severe exacerbations, were observed versus placebo. Where indirect comparisons were possible, differences between GFF MDI and other LAMA/LABA FDCs were small relative to established margins of clinical relevance, and not statistically significant. The safety and tolerability profile of GFF MDI was consistent with other LAMA/LABA FDCs and placebo. The results of the meta-regression were generally similar to the base case. CONCLUSIONS: GFF MDI demonstrated comparable efficacy and safety outcomes to other LAMA/LABA FDCs. Personalization of treatment choice within the class on the basis of other factors such as patient preference may be appropriate.

Smalley, K. R., L. Aufegger, et al. (2019). **"Which behaviour change techniques are most effective in improving healthcare utilisation in COPD self-management programmes? A protocol for a systematic review."** BMJ Open Respir Res **6**(1): e000369.

Introduction: Self-management interventions are often presented as a way to improve the quality of care for patients with chronic illness. However, self-management is quite broadly defined and it remains unclear which types of interventions are most successful. This review will use the Theoretical Domains Framework (TDF) as a lens through which to categorise self-management interventions regarding which programmes are most likely to be effective and under which circumstances.The aim of this study is to (1) describe the types of self-management programmes that have been developed in chronic obstructive pulmonary disease (COPD) and identify the common elements between these to better classify self-management, and (2) evaluate the effect that self-management programmes have on the healthcare behaviour of patients with COPD by classifying those programmes by the behaviour change techniques used. Methods and analysis: A systematic search of the literature will be performed in MEDLINE, EMBASE, HMIC and PsycINFO. This review will be limited to randomised controlled trials and quasi-experimental studies. The review will follow PRISMA-P guidelines, and will provide a PRISMA checklist and flowchart. Risk of bias in individual studies will be assessed using the Cochrane Risk of Bias criteria, and the quality of included studies will be evaluated using the GRADE criteria, and will be reported in a Summary of Findings table.The primary analysis will be a catalogue of the interventions based on the components of the TDF that were used in the intervention. A matrix comparing included behaviour change techniques to improvements in utilisation will summarise the primary outcomes. Ethics and dissemination: Not applicable, as this is a secondary review of the literature. Prospero registration number: CRD42018104753.

Sohanpal, R., H. Pinnock, et al. (2020). **"Tailored, psychological intervention for anxiety or depression in people with chronic obstructive pulmonary disease (COPD), TANDEM (Tailored intervention for ANxiety and DEpression Management in COPD): protocol for a randomised controlled trial."** Trials **21**(1): 18.

BACKGROUND: People with chronic obstructive pulmonary disease (COPD) are at increased risk of depression and anxiety, which greatly reduces their quality of life and is associated with worse outcomes; but these psychological co-morbidities are under-recognised and undertreated in COPD patients. Pulmonary rehabilitation (PR) improves mood for up to 6 months but health practitioners under-refer, and patients commonly fail to attend/complete PR. Research suggests that complex non-pharmacological interventions, including both psychological and exercise components, may reduce anxiety and depression in COPD. We have developed a tailored, cognitive behavioural approach (CBA) intervention for patients with COPD and co-morbid anxiety and/or depression ('TANDEM'), which precedes and optimises the benefits of currently offered PR. We hypothesise that such a psychological intervention, delivered by supervised, trained respiratory healthcare professionals, will improve mood in patients with mild to moderate anxiety and/or depression and encourage uptake and completion of PR. METHODS: We will conduct a multi-centre, pragmatic, randomised controlled trial of the TANDEM intervention compared to usual care across the Midlands, London, the South East and Bristol, UK. We will train healthcare professionals familiar with COPD to deliver the manualised, tailored, face-to-face, one-to-one intervention weekly for 6-8 weeks. We will recruit 430 participants from primary, community and secondary care with confirmed COPD and moderate to very severe airflow limitation, who are eligible for assessment for PR, and who screen positive for symptoms of mild/moderate depression and/or anxiety using the Hospital Anxiety and Depression scale (HADS). Participants will be randomised 1.25:1 (intervention: usual care). The co-primary outcomes are the HADS anxiety and depression subscale scores at 6 months; participants will be followed up to 12 months. Secondary outcomes include uptake and completion of PR and healthcare resource use. There will be a parallel process evaluation and a health economic evaluation. DISCUSSION: The TANDEM intervention has the potential to optimise the unrealised synergy between a psychological intervention and PR. The CBA sessions will precede PR and target individuals' cognitions, behaviours and symptoms associated with anxiety and depression to decrease psychological morbidity and increase effective self-management amongst patients with COPD. TRIAL REGISTRATION: ISRCTN, ID: ISRCTN59537391. Registered on 20 March 2017. Protocol version 6.0, 22 April 2018.

Suissa, S., S. Dell'Aniello, et al. (2019). **"Inhaled corticosteroid use and the incidence of lung cancer in COPD."** Eur Respir JBACKGROUND: Inhaled corticosteroids (ICS) are suggested as potential chemoprevention of lung cancer. Several observational studies in patients with COPD reported inconsistent results, either significant reductions in lung cancer incidence with ICS use or no effect. We assessed this association, using an approach that avoided biases affecting some of the studies. METHODS: A cohort of patients with COPD, new users of long-acting bronchodilators over 2000-2014, was formed using the Quebec healthcare databases, and followed until 2015 for a first diagnosis of lung cancer. A one-year delay after cohort entry was used to avoid protopathic bias and a one-year latency period was included after the initiation of ICS use. A time-dependent Cox regression model was used to estimate the hazard ratio (HR) of lung cancer associated with ICS exposure, adjusted for covariates. RESULTS: The cohort involved 58 177 subjects, including 63% receiving ICS, with 954 lung cancers occurring during a mean follow-up of 5 years. The adjusted HR of lung cancer associated with any ICS exposure was 0.94 (95% CI: 0.81-1.07), relative to no ICS use. The HR with longer (>4 years) time since ICS initiation was 0.86 (95% CI: 0.70-1.07), while with higher mean daily ICS dose (>1000 mcg fluticasone equivalents) was 1.50 (95% CI: 0.88-2.57). CONCLUSIONS: Inhaled corticosteroid use is not associated with a reduction in lung cancer incidence in patients with COPD. Observational studies reporting such reduction may have been affected by time-related biases and the inclusion of patients with asthma. The proposition of a randomised trial warrants some caution.

Sun, Y., S. Milne, et al. (2019). **"BMI is associated with FEV1 decline in chronic obstructive pulmonary disease: a meta-analysis of clinical trials."** Respir Res **20**(1): 236.
BACKGROUND: There is considerable heterogeneity in the rate of lung function decline in chronic obstructive pulmonary disease (COPD), the determinants of which are largely unknown. Observational studies in COPD indicate that low body mass index (BMI) is associated with worse outcomes, and overweight/obesity has a protective effect - the so-called "obesity paradox". We aimed to determine the relationship between BMI and the rate of FEV1 decline in data from published clinical trials in COPD. METHODS: We performed a systematic review of the literature, and identified 5 randomized controlled trials reporting the association between BMI and FEV1 decline. Four of these were included in the meta-analyses. We analyzed BMI in 4 categories: BMI-I (< 18.5 or < 20 kg/m(2)), BMI-II (18.5 or 20 to < 25 kg/m(2)), BMI-III (25 to < 29 or < 30 kg/m(2)) and BMI-IV (>/=29 or >/= 30 kg/m(2)). We then performed a meta-regression of all the estimates against the BMI category. RESULTS: The estimated rate of FEV1 decline decreased with increasing BMI. Meta-regression of the estimates showed that BMI was significantly associated with the rate of FEV1 decline (linear trend p = 1.21 x 10(- 5)). CONCLUSIONS: These novel findings support the obesity paradox in COPD: compared to normal BMI, low BMI is a risk factor for accelerated lung function decline, whilst high BMI has a protective effect. The relationship may be due to common but as-of-yet unknown causative factors; further investigation into which may reveal novel endotypes or targets for therapeutic intervention.

Wang, C., X. Chen, et al. (2019). **"Comparison of machine learning algorithms for the identification of acute exacerbations in chronic obstructive pulmonary disease."** Comput Methods Programs Biomed **188**: 105267.
OBJECTIVES: Identifying acute exacerbations in chronic obstructive pulmonary disease (AECOPDs) is of utmost importance for reducing the associated mortality and financial burden. In this research, the authors aimed to develop identification models for AECOPDs and to compare the relative performance of different modeling paradigms to find the best model for this task. METHODS: Data were extracted from electronic medical records (EMRs) of patients with chronic obstructive pulmonary disease who admitted to the China-Japan Friendship Hospital between February 2011 and March 2017. Five machine learning algorithms (random forest, support vector machine, logistic regression, K-nearest neighbor and naive Bayes) were used to develop the AECOPDs identification models. Feature selection was performed to find an optimal feature subset. 10-folds cross-validation was used to find the best hyperparameters for each model. The following metrics: area under the receiver operating characteristic curve, sensitivity, specificity, positive predictive value, and negative predictive value were used to evaluate the performance of these models. RESULTS: A total of 303 EMRs (AECOPDs patients:135; None AECOPDs patients: 168) were included in the study. The SVM model obtained the best performance (sensitivity: 0.80, specificity: 0.83, positive predictive value:0.81, negative predictive value:0.85 and area under the receiver operating characteristic curve: 0.90) after performing feature selection. CONCLUSIONS: Our research confirms that the proposed model based on the support vector machine is a powerful tool to identify AECOPDs patients, and it is promising to provide decision support for clinicians when they are struggling to give a confirmed clinical diagnosis.

Wang, G., W. Shang, et al. (2019). **"Benefits of statins in chronic obstructive pulmonary disease patients with pulmonary hypertension: A meta-analysis."** Eur J Intern Med **70**: 39-42.

PURPOSE: This meta-analysis was performed to evaluate the efficacy of statins in chronic obstructive pulmonary disease (COPD) patients with pulmonary hypertension (PH). METHODS: A systematic search was made of MEDLINE, Cochrane, ISI Web of Science and SCOPUS databases. Randomized clinical trials on treatment of COPD-PH with the statins, compared with placebo, were reviewed. Studies were pooled to weighted mean differences (WMD), with 95% confidence interval (CI). RESULTS: Five trials (enrolling 270 participants) met the inclusion criteria. Compared with placebo, the statins presented significant effects on systolic pulmonary artery pressure (WMD -4.52mmHg; 95% CI -6.32 to -2.72mmHg) and 6-min walk distance (6MWD) (WMD 32.46 m; 95% CI 13.63-51.29 m). CONCLUSIONS: Statins therapy significantly improves PH and 6MWD in COPD patients with PH.

Wang, H., F. Li, et al. (2019). **"Serum Surfactant Protein D is a Potential Biomarker for Chronic Obstructive Pulmonary Disease: a Systematic Review and Meta-analysis."** Clin Lab **65**(12)BACKGROUND: A number of studies have been conducted to investigate the association between serum surfactant protein D (SP-D) concentration and chronic obstructive pulmonary disease (COPD) risk. However, the results are inconsistent. This systematic review and meta-analysis aim to investigate whether serum SP-D concentration is a potential biomarker for COPD diagnosis. METHODS: We searched Web of Science, PubMed, China National Knowledge Infrastructure (CNKI), and Wanfang Database from inception through July 18, 2018. The standardized mean difference (SMD) with 95% confidence interval (CI) was used to investigate the effect sizes. RESULTS: Seventeen eligible studies from a total of 4,639 subjects were finally included in this systematic review and meta-analysis. The results indicated that serum SP-D levels in COPD patients were significantly higher than those in controls (SMD = 1.01, 95% CI = 0.62 - 1.41, $p < 0.001$). We also found that serum SP-D concentration in acute exacerbation of chronic obstructive pulmonary disease (AECOPD) patients was significantly higher than that in stable COPD patients (SMD = 1.50, 95% CI = 0.92 - 2.08, $p < 0.001$), and serum SP-D concentration was higher in smokers than in nonsmokers in healthy population (SMD = 1.50, 95% CI = 0.35 - 2.64, $p = 0.025$). CONCLUSIONS: The current systematic review and meta-analysis indicates that serum SP-D levels may be a promising biomarker for COPD. In particular, increased serum SP-D levels appear to be associated with acute exacerbation of COPD and smoking in healthy population.

Wang, Y. Q., X. Liu, et al. (2019). **"Active video games as an adjunct to pulmonary rehabilitation of patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis."** Am J Phys Med RehabilOBJECTIVE: This review aimed to investigate the effectiveness of active video games as an adjunct to pulmonary rehabilitation for patients with chronic obstructive pulmonary disease. DESIGN: All entries to the following databases were searched up until 3 April, 2019: PubMed, EMBASE Ovid, the Cochrane Central Register of Randomized Controlled Trials, Web of Science, Wanfang, Weipu, and Chinese National Knowledge Infrastructure databases. RESULTS: A total of seven articles (three randomized controlled trials and four quasi-experimental studies) with 249 patients were included. Active video games can increase the 6-minute walk distance by 30.9 meters on average. Four studies assessed quality of life and showed significant improvement. Four studies have reported that patients with chronic obstructive pulmonary disease found active video games to be enjoyable. Patient adherence was assessed in two studies and showed high adherence with active video games. No adverse events related to active video games were reported. CONCLUSIONS: The review demonstrated that active video games as an adjunct to pulmonary rehabilitation of patients with chronic obstructive pulmonary disease may prove to be useful and enjoyable. Additional studies should explore the differences between different types of active video games in order to create more effective game interventions for pulmonary rehabilitation.

Whittaker, H. R., D. Jarvis, et al. (2019). **"Inhaled corticosteroids and FEV1 decline in chronic obstructive pulmonary disease: a systematic review."** Respir Res **20**(1): 277.

Rate of FEV1 decline in COPD is heterogeneous and the extent to which inhaled corticosteroids (ICS) influence the rate of decline is unclear. The majority of previous reviews have investigated specific ICS and non-ICS inhalers and have consisted of randomised control trials (RCTs), which have specific inclusion and exclusion criteria and short follow up times. We aimed to investigate the association between change in FEV1 and ICS-containing medications in COPD patients over longer follow up times.MEDLINE and EMBASE were searched and literature comparing change in FEV1 in COPD patients taking ICS-containing medications with patients taking non-ICS-containing medications were identified. Titles, abstract, and full texts were screened and information extracted using the PICO checklist. Risk of bias was assessed using the Cochrane Risk of Bias tool and a descriptive synthesis of the literature was carried out due to high heterogeneity of included studies.Seventeen studies met our inclusion criteria. We found that the difference in change in FEV1 in people using ICS and non-ICS containing medications depended on the study follow-up time. Shorter follow-up studies (1 year or less) were more likely to report an increase in FEV1 from baseline in both patients on ICS and in patients on non-ICS-containing medications, with the majority of these studies showing a greater increase in FEV1 in patients on ICS-containing medications. Longer follow-up studies (greater than 1 year) were more likely to report a decline in FEV1 from baseline in patients on ICS and in patients on non-ICS containing medications but rates of FEV1 decline were similar.Further studies are needed to better understand changes in FEV1 when ICS-containing medications are prescribed and to determine whether ICS-containing medications influence rate of decline in FEV1 in the long term. Results from inclusive trials and observational patient cohorts may provide information more generalisable to a population of COPD patients.

Yang, M., Y. Xu, et al. (2019). **"Benefits and risks of low molecular weight heparin in patients with acute exacerbation of chronic obstructive pulmonary disease: a meta-analysis of randomized controlled trials."** InflammopharmacologyBACKGROUND: Low molecular weight heparin (LMWH) is an anticoagulant that has recently been found benefit in the acute exacerbation stage of chronic obstructive pulmonary disease (COPD). But its efficacy is controversial. The objective of this paper is to compare the harm/benefit of LMWH combined with conventional therapy versus single conventional therapy in the acute exacerbation stage of COPD. METHODS: PubMed, Cochrane Library, EMBASE, CNKI, and Clinical Trials.gov were searched from inception until March 2019. Randomized control trials were included if they reported the use of LMWH for the treatment of COPD. Continuous variable data were reported as mean difference (MD), risk difference (RD), and Peto odds ratio (OR) with corresponding 95% CIs. RESULTS: Twelve RCTs (N = 1086 subjects) were included in the meta-analysis. Pooled results exhibited that LMWH treatment significantly improved the levels of arterial partial pressure of oxygen (PaO2) (MD = 4.58, 95% CI: 1.78-7.39, P = 0.001), forced expiratory volume in 1 s (FEV1) (MD = 0.19, 95% CI: 0.09-0.29, P = 0.0002), and FEV1/forced vital capacity (FVC) (MD = 10.44, 95% CI: 5.40-15.48, P < 0.0001), and significantly reduced the risk of thrombosis (RD, - 0.03; 95% CI, - 0.07 to 0.00; P = 0.05). There was a marginally but nonsignificant improvement in PaCO2 levels vs non-LMWH treatment. Moreover, pooled results exhibited that LMWH may increase the risk of hemorrhage. Subgroup analyses exhibited that LMWH treatment only was associated with a significantly increased risk of minor bleeding but not major hemorrhage. CONCLUSIONS: When compared with single conventional therapy, addition of LMWH to conventional therapy may provide more clinical benefits in the acute exacerbation stage of COPD.

Zhou, Z., W. Zheng, et al. (2020). **"Efficacy and safety of Chuankezhi injection in patients with chronic obstructive pulmonary disease: A systematic review and meta-analysis protocol."** Medicine (Baltimore) **99**(2): e18620.

BACKGROUND: Chuankezhi injection (CKZ) is gaining increasing popularity for chronic obstructive pulmonary disease (COPD) treatment, yet their comparative effectiveness and safety remain unclear. Therefore, we will provide a protocol to assess the efficacy and safety of CKZ for COPD. METHODS: From now until June 2020, we will conduct a comprehensive and systematic literature search in 4 Chinese and 4 English databases, and the use of CKZ in the treatment of COPD will be included in randomized controlled trials, as well as all the treatment of stable COPD during the treatment of all CKZ. The risk assessment of the bias tool in Cochrane 5.1.0 will be combined with the quality of the trial. The 2 investigators will independently perform quality assessments and data extractions for the included studies in strict accordance with inclusion and exclusion criteria and perform the meta-analysis with Stata 15 software (version 15.0, StataCorp, College Station, TX). RESULTS: Further evidence of CKZ treatment for COPD will be provided by this study. CONCLUSION: The efficacy and safety assessment of CKZ for COPD will be supported by this protocol. PROSPERO REGISTRATION NUMBER: ROSPERO CRD 42019134133.

Cohort and case-control studies – in process

Search strategy: (COPD[Title] OR Emphysema[Title] OR Chronic Obstructive Pulmonary Disease[Title] OR Chronic Bronchitis[Title]) AND (inprocess[sb] OR Publisher[sb]) AND ("cohort"[All Fields] OR "follow-up"[All Fields] OR "longitudinal"[All Fields] OR "prospective"[All Fields] OR "retrospective"[All Fields] OR "Case-control"[All Fields]) AND English[lang]

Acero Colmenares, R. and C. E. Lombo Moreno (2019). **"SaO2 as a predictor of exercise-induced hypoxemia in chronic obstructive pulmonary disease at moderate altitude."** Int J Chron Obstruct Pulmon Dis **14**: 1951-1958.

Background: Given the high prevalence of chronic obstructive pulmonary disease (COPD) in Bogota (2630 m above the sea), screening methods are required for COPD patients who develop exercise-induced hypoxemia (EIH). Objective: The objective was to measure the productive capacity of basal oxygen saturation for the detection of EIH during the 6-min walking test (6MWT) in patients diagnosed with COPD in a hospital in Bogota. Design: This was a cross-sectional, retrospective study. Population: Patients diagnosed with COPD with SaO2>/=88% who attended the Pneumology Section of the FSFB for a 6MWT between 2013 and 2017 were included in the study. Measurements: Age, sex, anthropometric data, SaO2, SaO2 during 6MWT, and spirometry were evaluated. Results: Ninety-two patients with EIH and 32 patients without EIH were studied. Statistically significant differences were found in SaO2, minimum SaO2 during 6MWT, and BMI (90.8% vs 93%, 80.3% vs 88.9%, and 26.7 kg/m(2) vs 23.8 kg/m(2), respectively). FEV1 was without statistically significant differences (74.1% vs 78.6%). The ROC curve showed a better cut-off point for detecting EIH with basal SaO2</=92% (sensitivity 76.1%, specificity 62.5%, NPV 47.6%, and PPV 85.4%) and SaO2</=94% as the best sensitivity point (sensitivity 94.6%, specificity 15.6%, NPV 76.3%, and PPV 50%). Conclusion: SaO2 is not a good screening test for EIH in COPD patients at moderate altitude.

Adas-Okuma, M. G., S. S. Maeda, et al. (2019). **"COPD as an independent risk factor for osteoporosis and fractures."** Osteoporos IntFractures are common in individuals with COPD and occur at higher bone mass values than expected. COPD appears to be an important risk factor for bone fragility. INTRODUCTION: Patients with chronic obstructive pulmonary disease (COPD) have an increased risk of osteoporosis and fractures, but screening and prophylactic measures to prevent both disorders are often neglected in this population. This case-control study assessed the prevalence of osteopenia, osteoporosis, and fractures in patients with COPD, and identified potential risk factors for fractures in this population. METHODS: Overall, 91 patients with COPD (COPD group; COPDG) and 81 age- and sex-matched controls (control group; CG) were assessed with bone mineral density (BMD), thoracic/lumbar spine radiographs, and serum PTH and 25-hydroxyvitamin D (25[OH]D) levels. The occurrence of prior fractures was retrieved from clinical history. RESULTS: The prevalence of total fractures in the COPDG was 57.1% (odds of fracture 4.7 times greater compared with the CG), and the femoral neck T-score emerged as the best predictor of fractures. Compared with the CG, the COPDG had lower spine and femoral BMD (p </= 0.01) and 25(OH)D levels (p = 0.01) and 2.6 times greater odds of osteoporosis. Among men, vertebral fractures were more prevalent in the COPDG versus CG (25.9% vs. 6.5%, respectively, p = 0.01). The odds of fracture increased with femoral neck T-scores </= - 2.7 in the CG and </= - 0.6 in the COPDG. CONCLUSION: These results add robust evidence to an increased odds of osteoporosis and fractures in COPD. Fractures in the COPDG occurred at higher BMD values than expected, suggesting that COPD may be an independent marker of fracture risk, reinforcing a need for regular osteoporosis screening with BMD measurement and prophylaxis of fractures in patients with this disorder.

Ahn, J. H., J. H. Chung, et al. (2019). **"Critical Inhaler Handling Error Is an Independent Risk Factor for Frequent Exacerbations of Chronic Obstructive Pulmonary Disease: Interim Results of a Single Center Prospective Study."** Int J Chron Obstruct Pulmon Dis **14**: 2767-2775.

Objective: Chronic obstructive pulmonary disease (COPD) acute exacerbations are significant causes of morbidity and mortality. "Frequent exacerbator" phenotypes are considered a distinct subgroup and this phenotype has a negative effect on lung function, quality of life, activity, hospital admission, and mortality. We assess inhaler handling technique and adherence, and evaluate risk factors associated with frequent exacerbations in COPD patients. Methods: This study was a cross-sectional, case-control study. We prospectively enrolled 189 COPD patients from Yeungnam University Hospital from January 2018 to November 2018. Subjects were tested regarding their inhaler technique in face-to-face interviews with an advanced practice nurse of inhaler upon study entry. Frequency of moderate to severe COPD exacerbations were reviewed via electronic medical records during 12 months prior to study entry. Frequent exacerbations were defined as >/=2 moderate to severe exacerbations in the prior 12 months. Multivariate logistic regression was performed to identify risk factors for frequent exacerbations. Results: Among 189 COPD patients, 50 (26.5%) were frequent exacerbators. Based on univariate analyses, body mass index (BMI) < 25 kg/m(2), lower forced expiratory volume in 1 s (FEV1), higher mMRC, lower feeling of satisfaction with the inhaler, and any critical errors were potential risk factors for frequent exacerbations. Multivariate logistic regression analyses revealed that BMI < 25 kg/m(2) (OR, 2.855, 95% CI, 1.247-6.534; p=0.013), higher mMRC (OR, 1.625, 95% CI, 1.072-2.463; p=0.022), and any critical error (OR, 2.020, 95% CI, 1.021-3.999; p=0.044) were risk factors. Conclusion: Any critical error, BMI < 25 kg/m(2) and high mMRC are independent risk factors for frequent exacerbations in COPD patients. Careful monitoring and education around inhaler devices, particularly in frequent exacerbators, are important components of COPD treatment.

Akar, E., M. A. Haberal, et al. (2020). **"Efficacy of Surgical Tissue Glues and Supporters for Treatment of Prolonged Air Leaks in Bullous Emphysema."** J Coll Physicians Surg Pak **30**(1): 57-61.

OBJECTIVE: To investigate the effect of collagen matrix tissue supporter made of bovine pericardium and polyethylene glycol (PEG) tissue glue on prolonged air leak and postoperative complications in patients with bullous emphysema. STUDY DESIGN: A retrospective study. PLACE AND DURATION OF STUDY: Department of Thoracic Surgery, Health Sciences University, Bursa Yuksek Ihtisas Training and Research Hospital, Bursa, Turkey, from January 2010 to December 2018. METHODOLOGY: A total of 60 patients (57 males, 3 females) with radiologically confirmed bullous emphysema, who underwent surgery for secondary spontaneous pneumothorax were reviewed, and grouped into three: Group 1 underwent endostapler/ peristrips (20 patients); Group 2 underwent endostapler / coseal (18 patients), and Group 3 underwent endostapler/ peristrips / coseal (22 patients). All groups underwent video-assisted thoracoscopic surgery. The groups were compared for complications, time for removal of chest tube, and duration of hospital stay. RESULTS: The groups were similar with respect to age and gender. The mean time to chest tube removal was 7.57 +/-4.73 days (range; 3-21 days); the mean duration of hospital stay was 9.23 +/-5.00 days (range; 4-23 days). Group 3 had the shortest time to chest tube removal and duration of hospital stay (5.82 +/-2.87 and 7.36 +/-3.04; p=0.010 and p=0.006). Significant inter-group difference originated between Group 2 and Group 3 (p=0.008 and p=0.005). Group 2 had the longest time to chest tube removal and duration of hospital stay (10.22 +/-5.11 and 12.22 +/-5.36). Group 3 had significantly a lower rate of prolonged air leak (9.1% n=1; p=0.021). CONCLUSION: Using coseal with a tissue supporter like Peristrips reduces postoperative complications, time to chest tube removal, and duration of hospital stay compared to its stand alone use.

Ali, A., L. F. Giraldo-Cadavid, et al. (2019). **"Frequency of emergency department visits and hospitalizations due to chronic obstructive pulmonary disease exacerbations in patients included in two models of care."** Biomedica **39**(4): 748-758.

INTRODUCTION: Exacerbations of chronic obstructive pulmonary disease (COPD) have a huge impact on lung function, quality of life and mortality of patients. Emergency Department visits and hospitalizations due to exacerbations cause a significant economic burden on the health system. OBJECTIVE: To describe the differences in the number of emergency visits and hospitalizations due to exacerbations of COPD among patients included in two models of care of the same institution. MATERIALS AND METHODS: A historical cohort study in which COPD patients who are users of two models of care were included: COPD integrated care program (CICP) and general consultation of pulmonology (GCP). The first model, unlike the second one, offers additional educational activities, 24/7 telephone service, and priority consultations. The number of emergency visits and hospitalizations due to COPD exacerbations in patients who had completed at least one year of follow-up was evaluated. The multivariable Poisson regression model was used for calculating the incidence rate (IR) and the incidence rate ratio (IRR) with an adjustment for confounding factors. RESULTS: We included 316 COPD patients (166 from the CICP and 150 from the GCP). During the year of follow-up, the CICP patients had 50% fewer emergency visits and hospitalizations than patients from the GCP (IRR=0.50, 95%CI: 0.29-0.87, p=0.014). CONCLUSIONS: COPD patients in the CICP had fewer emergency visits and hospitalizations due to exacerbations. Prospective clinical studies are required to confirm the results and to evaluate the factors that contribute to the differences.

Altiaylik Ozer, P. and O. Nalan (2019). **"Correlation of Neutrophyle/Lymphocyte ratio and pulmonary parameters with optic coherence tomography findings in stable chronic obstructive pulmonary disease."** Clin Respir JINTRODUCTION: To examine the correlation of pulmonary functions and neutrophyle/lymphocyte ratio (NLR) with optic coherence tomography findings in stable chronic obstructive pulmonary disease (COPD). METHODS: Fifty five COPD (110 eyes) and 48 control cases (96 eyes) were enrolled. COPD patients were grouped as Group 1 (mild-moderate) and Group 2 (severe) according to GOLD classification. Subfoveal choroidal thickness (SFCT), ganglion cell inner plexiform layer (GCIP) and retinal nerve fiber length (RNFL) analysis by SD-OCT were performed in follow up. NLR was calculated by blood cell count. RESULTS: Inferior RNFL and average GCIP of COPD were lower than control during the initial and 6th month examination (p=0.002, p<0.001 respectively). Average RNFL and SFCT were lower in COPD patients in 6th month examination (p=0.020, p=0.015 respectively). Average, temporal, inferior, nasal RNFL and SFCT in sixth month examination were significantly lower in severe COPD (p<0.05 for all), but average GCIP were similar (p=0.015). Disease duration, Modified Medical Research Council (mMRC) and attacks/year showed significant negative-whereas Forced Expiratory Volume in 1 second (FEV1) and FEV1/Forced Vital Capasity (FVC) showed significant positive correlations with OCT values. NLR was significantly higher in COPD cases compared to control (p<0.001) and had a negative correlation with GCIP values. CONCLUSION: COPD severity is shown to have a negative effect on OCT measurements. SD-OCT can reflect severity of inflammation, and suggested to be used in follow up of COPD cases. NLR may have a role to predict the ganglion cell damage in COPD patients.

Anazawa, R., N. Kawata, et al. (2019). **"Longitudinal changes in structural lung abnormalities using MDCT in chronic obstructive pulmonary disease with asthma-like features."** PLoS One **14**(12): e0227141.

BACKGROUND: Some patients with chronic obstructive pulmonary disease (COPD) have asthma-like features. However, there have been few reports on the structural lung abnormalities found in this patient population. Multi-detector computed tomography (MDCT) can detect emphysematous low-attenuation areas (LAA) within the lung, airway thickness (wall area percentage, WA%), and the loss of pulmonary vasculature as the percentage of small pulmonary vessels with cross-sectional area (CSA) less than 5

mm2 (%CSA<5). We analyzed differences in structural lung changes over time between patients with COPD and those with COPD with asthma-like features using these CT parameters. MATERIAL AND METHODS: We performed pulmonary function tests (PFTs), MDCT, and a COPD assessment test (CAT) in 50 patients with COPD and 29 patients with COPD with asthma-like features at the time of enrollment and two years later. We analyzed changes in clinical parameters and CT indices over time and evaluated differences in structural changes between groups. RESULTS: The CAT score and FEV1 did not significantly change during the follow-up period in either group. Emphysematous LAA regions significantly increased in both groups. The %CSA<5 showed a small but significant increase in COPD patients, but a significant decrease in patients with COPD with asthma-like features. The WA% at the distal bronchi was significantly decreased in COPD, but did not significantly change in COPD with asthma -like features. CONCLUSION: Emphysematous LAA increased in patients with COPD with and without asthma-like features. The %CSA<5 and WA% at the distal bronchi did not change in parallel with LAA. Furthermore, changes in %CSA<5 were significantly different between patients with COPD and those with COPD with asthma-like features. Patients with COPD with asthma-like features may have different longitudinal structural changes than those seen in COPD patients.

Ariani, A., M. Silva, et al. (2019). **"Overall mortality in combined pulmonary fibrosis and emphysema related to systemic sclerosis."** RMD Open **5**(1): e000820.

Objectives: This multicentre study aimed to investigate the overall mortality of combined pulmonary fibrosis and emphysema (CPFE) in systemic sclerosis (SSc) and to compare CPFE-SSc characteristics with those of other SSc subtypes (with interstitial lung disease-ILD, emphysema or neither). Methods: Chest CTs, anamnestic data, immunological profile and pulmonary function tests of patients with SSc were retrospectively collected. Each chest CT underwent a semiquantitative assessment blindly performed by three radiologists. Patients were clustered in four groups: SSc-CPFE, SSc-ILD, SSc-emphysema and other-SSc (without ILD nor emphysema). The overall mortality of these groups was calculated by Kaplan-Meier method and compared with the stratified log-rank test; Kruskal-Wallis test, t-Student test and chi(2) test assessed the differences between groups. P<0.05 was considered statistically significant. Results: We enrolled 470 patients (1959 patient-year); 15.5 % (73/470) died during the follow-up. Compared with the SSc-ILD and other-SSc, in SSc-CPFE there was a higher prevalence of males, lower anticentromere antibodies prevalence and a more reduced pulmonary function (p<0.05). The Kaplan-Meier survival analysis demonstrates a significantly worse survival in patients with SSc-CPFE (HR vs SSc-ILD, vs SSc-emphysema and vs other-SSc, respectively 1.6 (CI 0.5 to 5.2), 1.6 (CI 0.7 to 3.8) and 2.8 (CI 1.2 to 6.6). Conclusions: CPFE increases the mortality risk in SSc along with a highly impaired lung function. These findings strengthen the importance to take into account emphysema in patients with SSc with ILD.

Asensio, V. J., A. Tomas, et al. (2019). **"Eosinophilic COPD Patients Display a Distinctive Serum miRNA Profile From Asthma and Non-eosinophilic COPD."** Arch BronconeumolBACKGROUND: Asthma and chronic obstructive pulmonary disease (COPD) are common chronic airway diseases that may overlap in some individuals. Asthma COPD overlap (ACO) is a heterogeneous conditions that includes smoking-asthma (SA) and COPD with eosinophilia (COPDe). MicroRNAs (miRNA) are regulators of gene expression with a great potential as biomarkers. OBJECTIVES: The objective of this study was to identify distinctive miRNA signatures in patients from the whole spectrum of chronic obstructive bronchial disease (SA, COPDe, non-smoking asthmatics (NSA), and COPD) that could serve as diagnostic biomarkers or describe differential molecular mechanisms with potential therapeutic implications. METHODS: From a previously characterized cohort of ACO, COPD and asthma patients, we selected a discovery group of 40 patients for miRNA expression profiling by means of microarray technology. Differential expression of miRNAs were validated by quantitative PCR in the complete cohort (n=274). RESULTS: Thirty differentially expressed miRNAs (eBAYES p<0.05, fold change >/=2) were found among the different groups of

patients regarding COPDe: 19 COPD-vs-COPDe, 13 NSA-vs-COPDe, 11 SA-vs-COPDe. A characteristic down-regulated miRNA expression pattern was identified in COPDe patients. Differential expression of miR-619-5p and miR-4486 in COPDe patients were validated in the complete cohort (n=274). CONCLUSIONS: We postulate that COPDe patients show a characteristic expression profile of miRNAs distinctive from asthma and COPD. Also that SA and COPDe patients, which have been typically clustered in the ACO group, display distinct molecular events.

Barjaktarevic, I. Z., R. G. Buhr, et al. (2019). **"Clinical Significance of Bronchodilator Responsiveness Evaluated by Forced Vital Capacity in COPD: SPIROMICS Cohort Analysis."** Int J Chron Obstruct Pulmon Dis **14**: 2927-2938.

Objective: Bronchodilator responsiveness (BDR) is prevalent in COPD, but its clinical implications remain unclear. We explored the significance of BDR, defined by post-bronchodilator change in FEV1 (BDRFEV1) as a measure reflecting the change in flow and in FVC (BDRFVC) reflecting the change in volume. Methods: We analyzed 2974 participants from a multicenter observational study designed to identify varying COPD phenotypes (SPIROMICS). We evaluated the association of BDR with baseline clinical characteristics, rate of prospective exacerbations and mortality using negative binomial regression and Cox proportional hazards models. Results: A majority of COPD participants exhibited BDR (52.7%). BDRFEV1 occurred more often in earlier stages of COPD, while BDRFVC occurred more frequently in more advanced disease. When defined by increases in either FEV1 or FVC, BDR was associated with a self-reported history of asthma, but not with blood eosinophil counts. BDRFVC was more prevalent in subjects with greater emphysema and small airway disease on CT. In a univariate analysis, BDRFVC was associated with increased exacerbations and mortality, although no significance was found in a model adjusted for post-bronchodilator FEV1. Conclusion: With advanced airflow obstruction in COPD, BDRFVC is more prevalent in comparison to BDRFEV1 and correlates with the extent of emphysema and degree of small airway disease. Since these associations appear to be related to the impairment of FEV1, BDRFVC itself does not define a distinct phenotype nor can it be more predictive of outcomes, but it can offer additional insights into the pathophysiologic mechanism in advanced COPD. Clinical trials registration: ClinicalTrials.gov: NCT01969344T4.

Bertrams, W., K. Griss, et al. (2020). **"Transcriptional analysis identifies potential biomarkers and molecular regulators in pneumonia and COPD exacerbation."** Sci Rep **10**(1): 241.

Lower respiratory infections, such as community-acquired pneumonia (CAP), and chronic obstructive pulmonary disease (COPD) rank among the most frequent causes of death worldwide. Improved diagnostics and profound pathophysiological insights are urgent clinical needs. In our cohort, we analysed transcriptional networks of peripheral blood mononuclear cells (PBMCs) to identify central regulators and potential biomarkers. We investigated the mRNA- and miRNA-transcriptome of PBMCs of healthy subjects and patients suffering from CAP or AECOPD by microarray and Taqman Low Density Array. Genes that correlated with PBMC composition were eliminated, and remaining differentially expressed genes were grouped into modules. One selected module (120 genes) was particularly suitable to discriminate AECOPD and CAP and most notably contained a subset of five biologically relevant mRNAs that differentiated between CAP and AECOPD with an AUC of 86.1%. Likewise, we identified several microRNAs, e.g. miR-545-3p and miR-519c-3p, which separated AECOPD and CAP. We furthermore retrieved an integrated network of differentially regulated mRNAs and microRNAs and identified HNF4A, MCC and MUC1 as central network regulators or most important discriminatory markers. In summary, transcriptional analysis retrieved potential biomarkers and central molecular features of CAP and AECOPD.

Biener, L., D. Skowasch, et al. (2019). **"Endoscopic Lung Volume Reduction in COPD: The Impact of Coil Implantation on Patients' Physical Activity."** Respiration: 1-4.

Endoscopic lung volume reduction (ELVR) is an emerging therapy option for the treatment of severe emphysema in COPD. To which extent patients profit from lung volume reduction via coils (LVRC) regarding morbidity, mortality, and quality of life is not clear yet. In this monocentric prospective cohort study, 13 COPD patients with severe emphysema (residual volume [RV] >225%) were enrolled at the University Hospital of Bonn. Activity measurements were assessed by a validated accelerometer wristband. By LVRC, RV could be reduced by 0.13 L to 5.54 +/- 1.29 L. We could show a clinically relevant improvement in patients' physical activity after LVRC, measured as daily step count (497.7 +/- 72.6 vs. 1,913.7 +/- 182.7 steps/day, p = 0.03) and mean daily active energy expenditure (714.4 +/- 73.6 vs. 2,321.3 +/- 163.9 joules, p = 0.03). This improvement in physical activity is possibly associated with a positive effect on patients' morbidity and mortality.

Blanco, I., B. Valeiro, et al. (2019). **"Effects of Pulmonary Hypertension on Exercise Capacity in Patients With Chronic Obstructive Pulmonary Disease."** Arch BronconeumolINTRODUCTION: The impact of pulmonary hypertension (PH) on exercise tolerance in chronic obstructive pulmonary disease (COPD) has not been fully elucidated. It is necessary to characterize pulmonary hemodynamics in patients with moderate to severe COPD in order to improve their management. The aim of the study was to determine whether in COPD the presence of PH is associated with reduced exercise tolerance in a cohort of stable COPD patients. METHODS: Cross-sectional analysis of 174 COPD patients clinically stable: 109 without PH and 65 with PH (COPD-PH). We assessed socio-demographic data, lung function, quality of life, dyspnea, cardiopulmonary exercise testing (CPET), constant workload endurance time (CWET), and six-minute walk test (6MWT). We elaborated a logistic regression model to explore the impact of PH on exercise capacity in COPD patients. RESULTS: COPD-PH patients showed lower exercise capacity both at maximal (CPET) (43(20) versus 68(27) Watts and 50(19)% versus 71(18)% predicted peak oxygen consumption (VO2peak), COPD-PH and COPD, respectively), and at submaximal tests (6MWT) (382(94) versus 486(95) m). In addition, the COPD-PH group had lower endurance time than the non-PH COPD group (265(113) s and 295(164) s, respectively). CONCLUSIONS: The presence of PH is an independent factor that impairs exercise capacity in COPD.

Bollmeier, S. G. and A. P. Hartmann (2020). **"Management of chronic obstructive pulmonary disease: A review focusing on exacerbations."** Am J Health Syst PharmPURPOSE: Chronic obstructive pulmonary disease (COPD) is a significant cause of morbidity and mortality in the United States. Exacerbations- acute worsening of COPD symptoms-can be mild to severe in nature. Increased healthcare resource use is common among patients with frequent exacerbations, and exacerbations are a major cause of the high 30-day hospital readmission rates associated with COPD. SUMMARY: This review provides a concise overview of the literature regarding the impact of COPD exacerbations on both the patient and the healthcare system, the recommendations for pharmacologic management of COPD, and the strategies employed to improve patient care and reduce hospitalizations and readmissions. COPD exacerbations significantly impact patients' health-related quality of life and disease progression; healthcare costs associated with severe exacerbation-related hospitalization range from $7,000 to $39,200. Timely and appropriate maintenance pharmacotherapy, particularly dual bronchodilators for maximizing bronchodilation, can significantly reduce exacerbations in patients with COPD. Additionally, multidisciplinary disease-management programs include pulmonary rehabilitation, follow-up

appointments, aftercare, inhaler training, and patient education that can reduce hospitalizations and readmissions for patients with COPD. CONCLUSION: Maximizing bronchodilation by the appropriate use of maintenance therapy, together with multidisciplinary disease-management and patient education programs, offers opportunities to reduce exacerbations, hospitalizations, and readmissions for patients with COPD.

Borvik, T., S. K. Braekkan, et al. (2019). **"Chronic Obstructive Pulmonary Disease and Risk of Mortality in Patients with Venous Thromboembolism-The Tromso Study."** Thromb HaemostBACKGROUND: Previous studies have shown increased mortality in venous thromboembolism (VTE) patients with chronic obstructive pulmonary disease (COPD), but it is unknown to what extent the association is influenced by the severity of COPD and physical inactivity. OBJECTIVES: This article investigates whether COPD, and stages of COPD, influenced the risk of mortality after a first episode of VTE when physical inactivity was taken into account. METHODS: Patients with a first lifetime VTE (n = 256) were recruited among individuals who participated and performed spirometry in the fifth (2001-2002) and sixth (2007-2008) surveys of the Tromso Study (n = 9577). All-cause mortality was registered up to December 31, 2015. RESULTS: There were 123 deaths during a median of 2.9 years of follow-up. The overall mortality rate was 11.9 (95% confidence interval [CI] 10.0-14.2) per 100 person-years. The risk of death was twofold higher in COPD patients compared with those with normal airflow (hazard ratio [HR] 2.00, 95% CI 1.30-3.08) after multivariable adjustment. The risk of death increased with the severity of COPD. VTE patients with COPD stage III/IV had a fivefold increased risk of death (HR 5.20, 95% CI 2.65-10.2) compared with those without COPD, and 50% of these patients died within 3.5 months after the incident VTE event. Adjustment for physical inactivity had minor effect on the risk estimates. CONCLUSION: VTE patients with COPD had increased risk of death, particularly patients with severe COPD. The detrimental effect of COPD on mortality in VTE patients was apparently explained by factors other than physical inactivity among patients with COPD.

Bowler, R., M. Allinder, et al. (2019). **"Real-world use of rescue inhaler sensors, electronic symptom questionnaires and physical activity monitors in COPD."** BMJ Open Respir Res **6**(1): e000350.

Background: Chronic obstructive pulmonary disease (COPD) is a heterogeneous disease characterised by airflow obstruction and other morbidities such as respiratory symptoms, reduced physical activity and frequent bronchodilator use. Recent advances in personal digital monitoring devices can permit continuous collection of these data in COPD patients, but the relationships among them are not well understood. Methods: 184 individuals from a single centre of the COPDGene cohort agreed to participate in this 3-week observational study. Each participant used a smartphone to complete a daily symptom diary (EXAcerbations of Chronic pulmonary disease Tool, EXACT), wore a wrist-worn accelerometer to record continuously physical activity and completed the Clinical Visit PROactive Physical Activity in COPD questionnaire. 58 users of metered dose inhalers for rescue (albuterol) were provided with an inhaler sensor, which time stamped each inhaler actuation. Results: Rescue inhaler use was strongly correlated with E-RS:COPD score, while step counts were correlated with neither rescue use nor E-RS:COPD score. Frequent, unpatterned inhaler use pattern was associated with worse respiratory symptoms and less physical activity compared with frequent inhaler use with a regular daily pattern. There was a strong week-by-week correlation among measurements, suggesting that 1 week of monitoring is sufficient to characterise stable patients with COPD. Discussion: The study highlights the interaction and relevance of personal real-time monitoring of respiratory symptoms, physical activity and rescue medication in patients with COPD. Additionally, visual displays of longitudinal data may be helpful for disease management to help drive conversations between patients and caregivers and for risk-based monitoring in clinical trials.

Broxterman, R. M., J. Hoff, et al. (2019). **"Determinants of the Diminished Exercise Capacity in Patients with Chronic Obstructive Pulmonary Disease: Looking Beyond the Lungs."** J PhysiolKEY POINTS: Peak oxygen uptake, a primary determinant of prognosis, mortality, and quality of life, is diminished in patients with COPD, with mounting evidence supporting an important role for peripheral dysfunction, particularly within skeletal muscle. In patients with severe COPD and activity-matched controls, muscle oxygen transport and utilization were assessed at peak effort during single-leg knee-extensor exercise (KE), where ventilation is assumed to be submaximal. This strategy removes ventilation as the major constraint to exercise capacity in COPD, allowing maximal muscle function to be attained and evaluated. During maximal KE, both convective arterial oxygen delivery to the skeletal muscle microvasculature and subsequent diffusive oxygen delivery to the mitochondria were diminished in patients with COPD compared to control subjects. These findings emphasize the importance of factors, beyond the lungs, that influence exercise capacity in this patient population and may, ultimately, influence the prognosis, mortality, and quality of life for patients with COPD. ABSTRACT: Peak oxygen uptake (VO2peak), a primary determinant of prognosis, mortality, and quality of life, is diminished in patients with chronic obstructive pulmonary disease (COPD). Mounting evidence supports an important role of the periphery, particularly skeletal muscle, in the diminished VO2peak with COPD. However, the peripheral determinants of VO2peak have not been comprehensively assessed in this cohort. Thus, the hypothesis was tested that both muscle convective and diffusive oxygen (O2) transport, and therefore skeletal muscle peak O2 uptake (VM O2peak), are diminished in patients with COPD compared to matched healthy controls, even when ventilatory limitations (i.e. attainment of maximal ventilation) are minimized by using small muscle mass exercise. Muscle O2 transport and utilization were assessed at peak exercise from femoral arterial and venous blood samples and leg blood flow (by thermodilution) in 8 patients with severe COPD (FEV1 +/- SE = 0.9 +/- 0.1 L, 30% of predicted) and 8 controls during single leg knee-extensor exercise. Both muscle convective O2 delivery (0.44 +/- 0.06 vs. 0.69 +/- 0.07 l min(-1) , P < 0.05) and muscle diffusive O2 conductance (6.6 +/- 0.8 vs. 10.4 +/- 0.9 ml min(-1) mmHg(-1) , P < 0.05) were approximately 1/3 lower in patients with COPD than controls, resulting in an attenuated VM O2peak in the patients (0.27 +/- 0.04 vs. 0.42 +/- 0.05 l min(-1) , P < 0.05). When cardiopulmonary limitations to exercise are minimized, the convective and diffusive determinants of VM O2peak , at the level of the skeletal muscle, are greatly attenuated in patients with COPD. These findings emphasize the importance of factors, beyond the lungs, that may ultimately influence this population's prognosis, mortality, and quality of life. This article is protected by copyright. All rights reserved.

Castaldi, P. J., A. Boueiz, et al. (2019). **"Machine Learning Characterization of COPD Subtypes: Insights from the COPDGene Study."** ChestCOPD is a heterogeneous syndrome. Many COPD subtypes have been proposed, but there is not yet consensus on how many COPD subtypes there are and how they should be defined. The COPDGene study, which has generated ten-year longitudinal chest imaging, spirometry, and molecular data, is a rich resource for relating COPD phenotypes to underlying genetic and molecular mechanisms. In this article, we place COPDGene clustering studies in context with other highly cited COPD clustering studies, and we summarize the main COPD subtype findings from COPDGene. First, most manifestations of COPD occur along a continuum, which explains why continuous aspects of COPD or disease axes may be more accurate and reproducible than subtypes identified through clustering methods. Second, continuous COPD-related measures can be used to create subgroups through the use of predictive models to define cutpoints, and we review COPDGene research on blood eosinophil counts thresholds as a specific example. Third, COPD phenotypes identified or prioritized through machine learning methods have led to novel biological discoveries, including novel emphysema genetic risk variants and systemic inflammatory subtypes of COPD. Fourth, trajectory-based COPD subtyping captures differences in the longitudinal evolution of COPD, addressing a major limitation of clustering analyses that are confounded by disease severity. Ongoing longitudinal characterization of

subjects in COPDGene will provide useful insights about the relationship between lung imaging parameters, molecular markers, and COPD progression that will enable the identification of subtypes based on underlying disease processes and distinct patterns of disease progression, with the potential to improve the clinical relevance and reproducibility of COPD subtypes.

Chang, T. Y., J. Y. Chien, et al. (2019). **"Comparative Safety and Effectiveness of Inhaled Corticosteroids and Long-Acting beta2 Agonist Combinations in Patients with Chronic Obstructive Pulmonary Disease."** ChestINTRODUCTION: The differential risk of pneumonia among inhaled corticosteroids (ICSs) in patients with chronic obstructive pulmonary disease (COPD) requires more investigation, especially for beclomethasone-containing inhalers. This study aimed to compare the risk and benefit profile of different ICS/long-acting beta2 agonist (LABA) combinations in COPD patients. METHODS: We conducted a retrospective cohort study using national health insurance claims data from the years 2009-2015 in Taiwan and included COPD patients with new ICS/LABA use. Propensity score matching and Cox regression models were used to estimate the hazard ratios of severe pneumonia and acute exacerbation (AE) for different ICS/LABA users. RESULTS: Both budesonide/formoterol (BUD/FOR) dry-powder inhalers (DPIs) and beclomethasone/formoterol (BEC/FOR) metered-dose inhaler (MDIs), compared with fluticasone propionate/salmeterol (FLU/SAL) delivered via the same device type, were associated with a lower risk of severe pneumonia (BUD/FOR HR 0.83 [95% CI 0.70-0.98], BEC/FOR 0.69 [0.58-0.81]) and severe AE (BUD/FOR HR 0.88 [0.78-0.99], BEC/FOR 0.90 [0.84-0.96]). After additionally adjusting for the average daily ICS dose, BUD/FOR DPI users continued to have a significantly decreased risk of severe pneumonia (18%) but not BEC/FOR MDI users. The results were consistent in most of the prespecified subgroups and across all the sensitivity analyses. CONCLUSION: This study augments the existing evidence concerning the different safety and effectiveness outcomes of ICS/LABA combinations in COPD patients, which may be considered when making clinical treatment decisions.

Chen, Y. F., Y. C. Cheng, et al. (2019). **"Major comorbidities lead to the risk of adverse cardiovascular events in chronic obstructive pulmonary disease patients using inhaled long-acting bronchodilators: a case-control study."** BMC Pulm Med **19**(1): 233.

BACKGROUND: While inhaled bronchodilators reduce symptoms and acute exacerbations of chronic obstructive pulmonary disease (COPD), their use is associated with increased cardiovascular events in some studies. This study investigates the risk of adverse events associated with the use of inhaled bronchodilators in COPD patients with multimorbidity. METHODS: A case-control study was conducted between January 2015 and December 2017, and patients with spirometry-confirmed diagnosis of COPD (N = 1565) using inhaled long-acting bronchodilators were enrolled. Medical records were reviewed and clinical data, including age, gender, smoking status, major comorbidities, lung function stage, history of exacerbations, bronchodilator regimens, and treatment duration were analyzed. Major adverse cardiovascular events occurring during long-acting bronchodilator use were recorded. RESULTS: The most common comorbidities were cardiovascular disease (CVD) (53.6%) and chronic kidney disease (CKD) (25.8%). We observed that CVD (odds ratio [OR], 5.77), CKD (OR, 2.02) and history of frequent exacerbations (OR, 2.37) were independent risk factors for cardiovascular events, regardless of the type of bronchodilators use. Moreover, COPD patients with both CKD and CVD had higher risk (6.32-fold) of adverse cardiovascular effects than those with neither comorbidity. Eighty-seven of 1565 (5.56%) COPD patients died during this study period. Of them, 21.8% (19/87) were cardiovascular-related and 73.6% (64/87) patients were respiratory-related mortality. Among COPD patients using long-acting bronchodilators, CKD was the only risk factor to predict cardiovascular events and cardiovascular-related mortality (OR, 4.87; 95% confidence interval [CI], 1.75-13.55]. CONCLUSIONS: COPD patients had higher risk of cardiovascular events were associated with their CVD and/or CKD comorbidities and history of frequent exacerbations, rather than associated with their use of inhaled bronchodilators.

Choi, J. Y., H. K. Yoon, et al. (2019). **"CAT Score and SGRQ Definitions of Chronic Bronchitis as an Alternative to the Classical Definition."** Int J Chron Obstruct Pulmon Dis **14**: 3043-3052.

Purpose: Previous studies have used various definitions to classify chronic obstructive pulmonary disease (COPD) patients into chronic bronchitis (CB) and non-CB patients. This study was performed to identify differences among three definitions of CB based on the classical method, St. George's Respiratory Questionnaire (SGRQ), and the CAT (COPD Assessment Test) score. Patients and methods: We extracted data from the multicenter Korea COPD Subgroup Study (KOCOSS) cohort, for which patients recruited from among 47 medical centers in South Korea beginning in April 2012. Patients were classified according to three different definitions of CB: 1) classical definition; 2) SGRQ (using questions regarding cough and sputum); and 3) CAT score (comprising cough [CAT1] and sputum [CAT2] subscale scores). Results: A total of 2694 patients were enrolled in this study. The proportions of CB were 10.8%, 35.8%, and 24.0% according to the classical, SGRQ, and CAT definitions, respectively. The three definitions yielded consistently significant differences between CB and non-CB patients in modified Medical Research Council dyspnea scale CAT score, SGRQ score, number of moderate-to-severe exacerbations per year and forced expiratory volume in 1 second. By three definitions, CB consistently predicted future risk of exacerbation. The kappa coefficient of agreement between the classical definition and SGRQ definition was 0.29, that of the classical definition and CAT definition was 0.32, and that of the SGRQ definition and CAT definition was 0.44. Conclusion: Patients with CB according to the new definitions based on SGRQ or CAT score showed similar clinical characteristics to those defined according to the classical definition. The new CB definitions may be used as alternatives to the classical definition.

Colak, Y., S. Afzal, et al. (2019). **"Prevalence, Characteristics, and Prognosis of Early COPD: The Copenhagen General Population Study."** Am J Respir Crit Care MedRATIONALE: Identification of younger adults at high risk of developing chronic obstructive pulmonary disease (COPD) could lead to implementation of preventive measures before disease onset and halt progression. OBJECTIVE: To investigate the prevalence, characteristics, and prognosis of individuals with early COPD in the general population. METHODS: We investigated 105 630 randomly chosen adults from a Danish contemporary population-based cohort. Early COPD was defined as forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC)<the lower limit of normal (LLN) in individuals aged <50 years with >/=10 pack-years of tobacco consumption. MEASUREMENTS AND MAIN RESULTS: Among 8064 individuals aged <50 years with >/=10 pack-years of tobacco consumption, 1175 (15%) had early COPD, of whom 58% were current smokers. Individuals with early COPD more often had chronic respiratory symptoms, severe lung function impairment, asthma, and a history with bronchitis/pneumonia. During 14.4 years follow-up, we observed 117 acute hospitalisations with obstructive lung disease, 227 acute hospitalisations with pneumonia, and 185 deaths among the 8064 younger adults. Compared to individuals without COPD, those with early COPD had multivariable adjusted hazard ratios (HRs) of 6.42(95% confidence interval:3.39-12.2) for acute obstructive lung disease hospitalisations, 2.03(1.43-2.88) for acute pneumonia hospitalisations, and 1.79(1.28-2.52) for all-cause mortality. CONCLUSIONS: Among individuals aged <50 years and >/=10 pack-years of tobacco consumption from the general population, 15% fulfil criteria of early COPD. Individuals with early COPD more often have chronic respiratory symptoms and severe lung function impairment, and an increased risk of acute respiratory hospitalisations and early death.

Contoli, M., S. Baraldo, et al. (2020). **"Airway inflammatory profile is correlated with symptoms in stable COPD: A longitudinal proof-of-concept cohort study."** Respirology **25**(1): 80-88.

BACKGROUND AND OBJECTIVE: Symptoms negatively impact the quality of life and long-term prognosis of patients with chronic obstructive pulmonary disease (COPD). Little is known about the relationship linking airway inflammation and symptoms in stable COPD. In this study, we evaluated whether respiratory symptoms in COPD are related to sputum inflammatory cellular profile and whether symptom changes are associated with changes in airway inflammation. METHODS: A total of 40 patients with stable COPD with moderate-to-severe airflow obstruction were enrolled. Patients were visited weekly over 4 weeks. At each visit, patients underwent clinical assessments, lung function tests and sputum induction. Patients recorded daily dyspnoea, sputum and cough scores. RESULTS: The changes between two consecutive visits in the percent of sputum neutrophils and eosinophils were related to the changes in the cough ($P < 0.001$; $r = 0.63$) and dyspnoea scores ($P < 0.001$; $r = 0.58$) of the prior week. Furthermore, using regression analyses, we were able to demonstrate that changes in the cough score were specifically associated to the change in neutrophils, while changes in the dyspnoea score and use of rescue medications were associated with changes in eosinophils numbers. CONCLUSION: Our study showed an association between symptoms and the sputum inflammatory profile. In particular, changes in symptoms (cough and dyspnoea) were correlated with changes in the specific sputum inflammatory cell components of airway inflammation (neutrophils and eosinophils, respectively), providing novel information on the mechanisms of disease manifestation.

Contoli, M., P. Rogliani, et al. (2019). **"Satisfaction with chronic obstructive pulmonary disease treatment: results from a multicenter, observational study."** Ther Adv Respir Dis **13**: 1753466619888128.

BACKGROUND: Understanding the level of patients' satisfaction with treatment and its determinants have the potential to impact therapeutic management and clinical outcome in chronic conditions such as chronic obstructive pulmonary disease (COPD). METHODS: A national, multicenter, longitudinal, observational study of COPD from 20 Italian pulmonary centers to explore patients' satisfaction to treatment [assessed by the Treatment Satisfaction Questionnaire, 9 items (TSQM-9)] and association with clinical parameters [including dyspnea score, COPD Assessment Test (CAT) score, exacerbation rate], adherence to treatment [Morisky Medication-Taking Adherence Scale (MMAS-4)], illness perception [evaluated by Brief Illness Perception Questionnaire (B-IPQ)] in a 1-year follow up. RESULTS: A total of 401 COPD patients were enrolled [69.4% group B Global Initiative for COPD (GOLD), considering 366 patients with available GOLD 2017 classification at enrollment]. At enrollment, satisfaction with treatment was moderate, being TSQM-9 mean scores for effectiveness 64.2 [95% confidence interval (CI) 62.5-65.9], for convenience 75.8 (95% CI 74.2-77.3), and for global satisfaction 65.7 (95% CI 64.0-67.4). Global satisfaction was negatively associated with disease perception (beta = -0.4709, $p < 0.0001$), and grade of dyspnea (beta = -4.2564, $p = 0.009$). Satisfaction with treatment was lower in patients with poor compared with optimal adherence to treatment (beta = -4.5608, $p = 0.002$). Changes in inhalation regimens during follow up did not modify the satisfaction with treatment. CONCLUSIONS: The results of this real-life study showed that the patients' satisfaction with treatments is only moderate in COPD. A high grade of patients' satisfaction is associated mainly with a low perception of the disease, high adherence to treatment and lower level of dyspnea. TRIAL REGISTRATION: Clinicaltrials.gov identifier: NCT02689492 The reviews of this paper are available via the supplemental material section.

Coquart, J. B., N. Heutte, et al. (2019). **"Convergent Validity and Minimal Clinically Important Difference of the Maugeri Foundation Respiratory Failure Questionnaire (MRF-28) and the Chronic Obstructive Pulmonary Disease-Specific Health-Related Quality of Life questionnaire (VQ11)."** Int J Chron Obstruct Pulmon Dis **14**: 2895-2903.

Purpose: Short and easy questionnaires have been developed to assess the health-related quality of life (HRQoL) in patients with chronic obstructive pulmonary disease (COPD), such as the Maugeri Foundation Respiratory Failure Questionnaire (MRF-28) and the COPD-specific HRQoL Questionnaire (VQ11). Both are valid, reliable, and sensitive, but their minimal clinically important differences (MCID) are unknown. Consequently, this study aimed to confirm the convergent validities of the MRF-28 and VQ11 and establish their MCID. A retrospective design was used to evaluate the effect of individual home-based pulmonary rehabilitation (PR) in 400 COPD patients. Patients and methods: Exercise tolerance, anxiety and depression based on the Hospital Anxiety and Depression Scale (HADS), and HRQoL using three questionnaires (MRF-28, VQ11, and the Visual Simplified Respiratory Questionnaire: VSRQ) were assessed before and after an individualized home-based PR program (5 sessions of 30-45 mins/week for 8 weeks, including a weekly session supervised by a team member). Results: PR improved all measured variables ($p < 0.0001$). The correlations were significant ($p < 0.0001$) between VSRQ and MRF-28 ($r = -0.685$ at baseline and $r = -0.686$ after the PR program), and between VSRQ and VQ11 ($r = -0.691$ at baseline and $r = -0.753$ after the PR program). Moreover, changes in score (delta between after and before PR program) of VSRQ were also significantly correlated ($p < 0.0001$) to changes in score of MRF-28 ($r = -0.372$) and VQ11 ($r = -0.423$). Last, we calculated MCID of -5.2 and -2.0 units for MRF-28 and VQ11, respectively. Conclusion: The MRF-28 and VQ11 can be used in routine practice to evaluate the effects of PR on the HRQoL of COPD patients, with MCID of -5.2 and -2.0, respectively.

Dalon, F., G. Devouassoux, et al. (2019). **"Impact of Therapy Persistence on Exacerbations and Resource Use in Patients Who Initiated COPD Therapy."** Int J Chron Obstruct Pulmon Dis **14**: 2905-2915.

Purpose: This study assessed therapy persistence in patients with chronic obstructive pulmonary disease (COPD) in France, and the impact of non-persistence on exacerbations and described COPD-related healthcare resource use (HRU). Methods: Patients aged >/=45 years who received >/=1 dispensed bronchodilator per quarter over three consecutive quarters between 2007 and 2014 and initiated specific COPD therapy were selected from the Echantillon Generaliste des Beneficiaires (EGB) database. Persistence, defined as the absence of dispensing gaps of >90 days, was measured at 12 months. Exacerbations were compared between persistent and non-persistent patients during follow-up after patient matching and adjustment for confounding factors. COPD-related HRU during follow-up was described. Results: Among 4020 patients with COPD, 2164 initiated a specific therapy. Of these, 54.4% stopped treatment within 12 months. Persistence with all COPD therapy regimens was low, particularly for inhaled corticosteroid (ICS; 25.6%) and ICS/twice-daily long-acting beta-agonist (39.4%) regimens. Among 721 persistent patients who were matched with 721 non-persistent patients, there was no difference in the number of moderate or severe exacerbations at 12 months. However, medical procedures (for instance, pulmonary function testing and chest X-rays) were more frequently observed among persistent patients than among non-persistent patients, suggesting worse disease severity. Conclusion: Patients receiving specific treatment(s) for COPD demonstrated low persistence for all examined therapy regimens, with no clear impact of persistence status on the frequency of exacerbations at 12 months.

d'Andrea, A., C. Banfi, et al. (2019). **"The use of extracorporeal carbon dioxide removal in acute chronic obstructive pulmonary disease exacerbation: a narrative review."** Can J AnaesthChronic obstructive pulmonary disease (COPD) exacerbation induces hypercapnic respiratory acidosis. Extracorporeal carbon dioxide removal (ECCO2R) aims to eliminate blood carbon dioxide (CO_2) in order to reduce adverse effects from hypercapnia and the related acidosis. Hypercapnia has deleterious extra-pulmonary consequences in increasing intracranial pressure and inducing and/or worsening right heart failure. During COPD exacerbation, the use of ECCO2R may improve the efficacy of non-invasive ventilation (NIV) in terms of CO_2 removal, decrease respiratory rate and reduce dynamic hyperinflation and intrinsic positive end expiratory pressure, which all contribute to increasing dead space. Moreover, ECCO2R may

prevent NIV failure while facilitating the weaning of intubated patients from mechanical ventilation. In this review of the literature, the authors will present the current knowledge on the pathophysiology related to COPD, the principles of the ECCO2R technique and its role in acute and severe decompensation of COPD. However, despite technical advances, there are only case series in the literature and few prospective studies to clearly establish the role of ECCO2R in acute and severe COPD decompensation.

de Lima, F. F., C. A. Camillo, et al. (2019). **"Effects of combining functional exercises with exercise training on daily physical activities and functionality in patients with COPD: a protocol for a randomized clinical trial."** Trials **20**(1): 680.

INTRODUCTION: Functional training has been shown to be a viable alternative for the elderly and patients with chronic obstructive pulmonary disease (COPD). However, whether the combination of this type of training with aerobic and resistance training, commonly performed in pulmonary rehabilitation (PR) programs, induces more pronounced effects on daily physical activities and functionality remains unclear. The aims of the study will be to evaluate the short-term and sustained effects of the combination of a functional circuit program with a training program consisting of aerobic and resistance exercise. METHODS: In this randomized controlled trial, patients with COPD will be randomly assigned (1:1:1) to an 8-week training program to follow one of the three a priori defined groups: (I) resistance and aerobic and functional exercises, (II) a conventional program including only resistance and aerobic exercises, or (III) a usual care program. Patients will be evaluated before and upon completion of 8 weeks of training regarding physical activity in daily life (PADL) using an activity monitor (accelerometer), activities of daily living (London Chest Activity of Daily Living), functional exercise capacity (6-minute walk test), and muscle strength (dynamometry). Additionally, the sustained effects of the interventions will be evaluated 22 weeks after commencing the study. DISCUSSION: The inclusion of a protocol of functional physical training in the training conventionally performed by patients with COPD as an alternative to increase PADL and functionality may provide subsidies for the treatment of these patients, representing an advance and impacting on the physical training of patients with COPD. TRIAL REGISTRATION: Brazilian Clinical Trials Registry (ReBEC) ID: RBR-3zmh3r. Registered: March 7, 2018.

Di Domenicantonio, R., G. Cappai, et al. (2019). **"A Systematic Review of Case-Identification Algorithms Based on Italian Healthcare Administrative Databases for Two Relevant Diseases of the Respiratory System: Asthma and Chronic Obstructive Pulmonary Disease."** Epidemiol Prev **43**(4 Suppl 2): 75-87.

OBJECTIVES: to identify and describe all asthma and Chronic Obstructive Pulmonary Disease (COPD) case-identification algorithms by means of Italian Healthcare Administrative Databases (HADs), through the review of papers published in the past 10 years. METHODS: this study is part of a project that systematically reviewed case-identification algorithms for 18 acute and chronic conditions by means of HADs in Italy. PubMed was searched for original articles, published between 2007 and 2017, in Italian or English. The search string consisted of a combination of free text and MeSH terms with a common part that focused on HADs and a disease-specific part. All identified papers were screened by two independent reviewers; exclusion criteria were the following: no description of reported algorithms, algorithm developed outside of the Italian context, exclusive use of death certificates, pathology register, general practitioner or pediatrician data. Pertinent papers were classified according to the objective for which the algorithm had been used, and only articles that used algorithms for primary objectives (I disease occurrence; II population/cohort selection; III outcome identification) were considered for algorithm extraction. The HADs used (hospital discharge records, drug prescriptions, etc.), ICD-9 and ICD-10 codes, ATC classification of drugs, follow-back periods, and age ranges applied by the algorithms have been reported. Further information on specific objective(s), accuracy measures, sensitivity analyses and the contribution of each HAD, have also been recorded. RESULTS: the search string led to the

identification of 98 and 147 papers, respectively for asthma and COPD. By screening the references, 2 papers for asthma and 7 for COPD were added. At the end of the screening process, 14 pertinent papers were identified for asthma and 31 for COPD. Half of these used healthcare data covering a time period between 2008 and 2014. More than 75% considered the age range 6-17 for asthma and >=45 for COPD. About one-third of the articles used algorithms to estimate the occurrence of these diseases. Fourteen algorithms for asthma and 16 for COPD were extracted from the papers and characterized. The Drug Prescription Database (DPD) was used by almost all asthma case-identification algorithms, while only 7 COPD algorithms used this data source. The spectrum of active ingredients was strongly overlapping between the two diseases, with different combinations of drugs and administration routes, as well as specific number of prescriptions, follow-back years, and age ranges. Age class and chronic treatment were the main disease-specific traits that emerged from the algorithms. Three external validation processes have been performed for asthma and three for COPD. High accuracy levels have been found for asthma. COPD sensitivity analyses were unsatisfactory, while a high specificity was found for algorithms based on hospital discharge records. CONCLUSION: elements from the review on the use of healthcare administrative databases represent a useful tool to decide which algorithm to adopt, based on the algorithm's individual requirements, limits, and accuracy, taking into account the specific research objective.

Dickens, A. P., D. A. Fitzmaurice, et al. (2020). **"Accuracy of Vitalograph lung monitor as a screening test for COPD in primary care."** NPJ Prim Care Respir Med **30**(1): 2.

Microspirometry may be useful as the second stage of a screening pathway among patients reporting respiratory symptoms. We assessed sensitivity and specificity of the Vitalograph(R) lung monitor compared with post-bronchodilator confirmatory spirometry (ndd Easy on-PC) among primary care chronic obstructive pulmonary disease (COPD) patients within the Birmingham COPD cohort. We report a case-control analysis within 71 general practices in the UK. Eligible patients were aged >/=40 years who were either on a clinical COPD register or reported chronic respiratory symptoms on a questionnaire. Participants performed pre- and post-bronchodilator microspirometry, prior to confirmatory spirometry. Out of the 544 participants, COPD was confirmed in 337 according to post-bronchodilator confirmatory spirometry. Pre-bronchodilator, using the LLN as a cut-point, the lung monitor had a sensitivity of 50.5% (95% CI 45.0%, 55.9%) and a specificity of 99.0% (95% CI 96.6%, 99.9%) in our sample. Using a fixed ratio of FEV1/FEV6 < 0.7 to define obstruction in the lung monitor, sensitivity increased (58.8%; 95% CI 53.0, 63.8) while specificity was virtually identical (98.6%; 95% CI 95.8, 99.7). Within our sample, the optimal cut-point for the lung monitor was FEV1/FEV6 < 0.78, with sensitivity of 82.8% (95% CI 78.3%, 86.7%) and specificity of 85.0% (95% CI 79.4%, 89.6%). Test performance of the lung monitor was unaffected by bronchodilation. The lung monitor could be used in primary care without a bronchodilator using a simple ratio of FEV1/FEV6 as part of a screening pathway for COPD among patients reporting respiratory symptoms.

do Nascimento, I. B. and R. Fleig (2020). **"Mobility impact and methods of diaphragm monitoring in patients with chronic obstructive pulmonary disease: a systematic review."** Clinics (Sao Paulo) **75**: e1428.

The objectives of the study were to identify the factors that limit diaphragmatic mobility and evaluate the therapeutic results of the monitoring methods previously used in patients with chronic obstructive pulmonary disease. The PubMed, Web of Science, Scopus, and LILACS databases were used. A gray literature search was conducted with Google scholar. PRISMA was used, and the bias risk analysis adapted from the Cochrane Handbook for clinical trials and, for other studies, the Downs and Black checklist were used. Twenty-five articles were included in the qualitative synthesis analysis on physiotherapeutic techniques and diaphragmatic mobility. Eight clinical trials indicated satisfactory domains, and on the Downs and Black scale, 17 cohort studies were evaluated to have an acceptable

score. Different conditions must be observed; for example, for postoperative assessments the supine position is suggested to be the most appropriate position to verify diaphragm excursion, although it has been shown to be associated with difficulty of restriction and matching in samples. Therefore, we identified the need for contemporary adjustments and strategies that used imaging instruments, preferably in the dorsal position. Therapeutic evidence on the association between the instrumental method and diaphragmatic mobility can be controversial. The ultrasound measurements indicated some relevance for different analyses, for pulmonary hyperinflation as well as diaphragm thickness and mobilization, in COPD patients. In particular, the study suggests that the ultrasound technique with B-mode for analysis and M-mode for diaphragmatic excursion be used with a 2 - 5 MHz with the patient in the supine position. However, the methods used to monitor diaphragm excursion should be adapted to the conditions of the patients, and additional investigations of their characteristics should be performed. More selective inclusion criteria and better matching in the samples are very important. In addition, more narrow age, sex and weight categories are important, especially in patients with chronic obstructive pulmonary disease.

Dong, W., Y. Zhu, et al. (2019). **"Impact of severe-to-very severe chronic obstructive pulmonary disease on the prognosis of patients with non-small cell lung cancer who received chemotherapy."** Clin Respir JINTRODUCTION: Chronic obstructive pulmonary disease (COPD) is associated with poor prognosis in non-small cell lung cancer (NSCLC) patients. There are limited data about the impact of severe-to-very severe COPD on prognosis in patients with NSCLC receiving first-line chemotherapy. OBJECTIVES: To investigate whether severe-to-very severe COPD impacted survival of patients with NSCLC receiving first-line chemotherapy. METHODS: A retrospective review was performed on 513 consecutive NSCLC patients receiving first-line chemotherapy between February 2014 and May 2018. Prognostic impact of severe-to-very severe COPD was analysed using regression analyses. RESULTS: Totally 258 NSCLC patients (118 non-COPD, 96 mild-to-moderate COPD and 44 severe-to-very severe COPD) were evaluated retrospectively. Kaplan-Meier analysis showed that the median overall survival times in the severe-to-very severe COPD, mild-to-moderate COPD and non-COPD groups were 14.0 months [95% confidence interval (CI): 11.0-17.0], 18 months (95% CI: 14.8-21.2) and 19 months (95% CI: 15.3-22.7), respectively. The difference was significant between patients with severe-to-very severe COPD and those without COPD (chi(2) = 6.8, P = 0.009) and between patients with severe-to-very severe COPD and those with mild-to-moderate COPD (chi(2) = 4.0, P = 0.045). Multivariate analysis showed that survival time was significantly shorter in the severe-to-very severe COPD group than in the non-COPD group (adjusted hazard ratio: 1.876, 95% CI: 1.161-3.030, P = 0.01) and mild-to-moderate COPD group (adjusted hazard ratio: 1.782, 95% CI: 1.046-3.034, P = 0.033). CONCLUSION: Severe-to-very severe COPD may worsen the prognosis of NSCLC patients who received first-line chemotherapy.

Dreher, M., P. C. Neuzeret, et al. (2019). **"Prevalence Of Chronic Hypercapnia In Severe Chronic Obstructive Pulmonary Disease: Data From The HOmeVent Registry."** Int J Chron Obstruct Pulmon Dis **14**: 2377-2384.

Background: Non-invasive ventilation (NIV) has been shown to improve survival and quality of life in COPD patients with chronic hypercapnic respiratory failure. However, the proportion of COPD patients with chronic hypercapnia is not yet known and clinical data enabling better identification of patients are scarce. The HOmeVent registry was initiated to determine the prevalence of chronic hypercapnia in COPD in an outpatient setting and to evaluate the predictors of hypercapnia. Methods: HOmeVent is a multicenter, prospective, observational, non-interventional patient registry that includes COPD patients in GOLD stage 3 or 4. Eligible patients were identified and enrolled in an outpatient setting during routine clinic visits. Assessments included blood gas analyses, pulmonary function testing and quality of life assessment. Results: Ten outpatient clinics in Germany enrolled 231 COPD patients in the registry

(135 in GOLD stage 3 (58%) and 96 in GOLD stage 4 (42%)). Arterial carbon dioxide pressure (PaCO2) was >/=45 mmHg in 58 patients (25%); of these, 20 (9%) had PaCO2 >/=50 mmHg. The prevalence of hypercapnia at both cut-off values was numerically higher for patients in GOLD stage 4 versus 3. An increased body mass index, a decreased forced vital capacity and an increased bicarbonate level were significant independent predictors of hypercapnia. The proportion of patients who received NIV was 6% overall and 22% of those with hypercapnia. Conclusion: A relevant proportion of COPD patients in GOLD stage 3 and 4 exhibits chronic hypercapnia and might, therefore, be candidates for long-term domiciliary NIV treatment.

Elbehairy, A. F., H. McIsaac, et al. (2019). **"Impact of a Specialized Ambulatory Clinic on Refractory Breathlessness in Subjects With Advanced COPD: A Retrospective Analysis."** Respir CareBACKGROUND: Severe exertional dyspnea is a commonly reported symptom in patients with COPD, especially in the advanced stages. Our objective was to assess the preliminary impact of comprehensive, individualized management provided by a specialized tertiary center clinic on exertional dyspnea and patient-centered outcomes in patients with advanced COPD. METHODS: This retrospective analysis included 45 subjects with COPD who were evaluated in a newly established dyspnea clinic over 3 years. Those with severe exertional dyspnea (Medical Research Council dyspnea score of >/=4/5), despite optimal disease-targeted therapy were eligible for referral. We used the revised Edmonton Symptom Assessment System (ESAS-r) to assess symptoms. Responders were defined as those whose change from baseline to 2-months met the minimum clinically important difference of </=-1 in ESAS-r score for shortness of breath. RESULTS: Subjects (mean +/- SD age 70 +/- 7 years) had an average FEV1 of 36 +/- 18% predicted and a Medical Research Council dyspnea score of 4.7 +/- 0.4. Responses to the intervention were variable and mean change in the ESAS-r score for shortness of breath in the total group was -0.32 +/- 3.39, P = .53. Forty-seven percent of the subjects were identified as responders, and 42, 40, 40, and 33% met the minimum clinically important difference for improvement in ESAS-r scores for tiredness, anxiety, well-being, and depression, respectively. Responders had fewer emergency department annual visits in the 2 years after their first clinic visit compared with nonresponders (mean +/- SD, 1.38 +/- 1.63 vs 4.45 +/- 5.52, P = .034). CONCLUSIONS: Although the impact of our specialized advanced dyspnea clinic was variable, as evaluated by the ESAS-r, it provided measurable additional clinically important benefit to almost half of the subjects with advanced COPD and severe refractory dyspnea.

El-Gazzar, A. G., M. H. Kamel, et al. (2020). **"Prognostic value of platelet and neutrophil to lymphocyte ratio in COPD patients."** Expert Rev Respir Med **14**(1): 111-116.

Background: Chronic obstructive pulmonary disease (COPD) is the third driving reason for death around the world and a real number of patients suffers from disease exacerbation. Platelet lymphocyte ratio (PLR) and neutrophil lymphocyte ratio (NLR) are novel biomarkers in acute exacerbation of COPD (AECOPD) and related to expanded 90-day mortality in patients with COPD.Objectives: This work aimed to assess NLR and PLR in COPD patients.Methods: This case-control study was carried out on 100 COPD patients and 60 healthy subjects. Complete blood count (CBC) with differential was made during and after exacerbation to define NLR and PLR.Results: The cases and controls groups were matched as regards age, sex, and body mass index (BMI) (P-values: 0.3, 0.2, and 0.06 respectively). NLR and PLR were increased significantly in COPD patients (2.24 +/- 0.56 and 157.1 +/- 28.36) compared to control group (1.31 +/- 0.23 and 102.82 +/- 3.99) (P-value < 0.0001). During exacerbation NLR and PLR were elevated significantly compared to stable condition (P-value < 0.0001). NLR and PLR show a significant positive correlation with smoking index, COPD stage, and dyspnea severity.Conclusion: NLR and PLR increased in stable COPD patients and further increased during exacerbation that can predict in hospital mortality.

Elnemr, R., R. A. Sweed, et al. (2019). **"Diaphragmatic motor cortex hyperexcitability in patients with chronic obstructive pulmonary disease."** PLoS One **14**(12): e0217886.

BACKGROUND AND OBJECTIVES: Respiratory muscles dysfunction has been reported in COPD. Transcranial magnetic stimulation (TMS) has been used for assessing the respiratory corticospinal pathways particularly of diaphragm. We aimed to study the cortico-diaphragmatic motor system changes in COPD using TMS and to correlate the findings with the pulmonary function. METHODS: A case control study recruited 30 stable COPD from the out-patient respiratory clinic of Main Alexandria University hospital-Egypt and 17 healthy control subjects who were subjected to spirometry. Cortical conduction of the diaphragm was performed by TMS to all participants followed by cervical magnetic stimulation of the phrenic nerve roots. Diaphragmatic resting motor threshold (DRMT), cortical motor evoked potential latency (CMEPL), CMEP amplitude (CMEPA), peripheral motor evoked potential latency (PMEPL), PMEP amplitude (PMEPA) and central motor conduction time (CMCT) were measured. RESULTS: 66.7% of COPD patients had severe and very severe COPD with median age of 59 (55-63) years. There was statistically significant bilateral decrease in DRMT, CMEPA and PMEPA in COPD group versus healthy subjects and significant increase in CMEPL and PMEPL ($p < 0.01$). Left CMCT was significantly prolonged in COPD group versus healthy subjects ($p < 0.0001$) but not right CMCT. Further, there was significant increase in CMEPL and CMCT of left versus right diaphragm in COPD group ($p = 0.003$ and 0.001 respectively) that inversely correlated with FEV1% and FVC% predicted. Right and left DRMT were insignificantly different in COPD group ($p > 0.05$) but positively correlated with FEV1/FVC, FEV1% and FVC% predicted. CONCLUSION: Central cortico-diaphragmatic motor system is affected in COPD patients with heterogeneity of both sides that is correlated with pulmonary function. SIGNIFICANCE: Coticospinal pathway affection could be a factor for development of diaphragmatic dysfunction in COPD patients accordingly its evaluation could help in personalization of COPD management especially pulmonary rehabilitation programs.

Farias, R., M. Sedeno, et al. (2019). **"Innovating the treatment of COPD exacerbations: a phone interactive telesystem to increase COPD Action Plan adherence."** BMJ Open Respir Res **6**(1): e000379.

Introduction: Self-management interventions with Written Action Plans and case management support have been shown to improve outcomes in patients with chronic obstructive pulmonary disease (COPD). Novel telehealth technologies may improve self-management interventions. The objectives of this study were to determine whether the use of an interactive phone telesystem increases Action Plan adherence, improves exacerbation recovery and reduces healthcare use in a real-life practice of a COPD clinic. Methods: Initially, 40 patients were followed by a COPD telesystem for 1 year. Detailed data from patients' behaviours during exacerbations was recorded. The telesystem use was then extended to 256 patients from a real-life COPD clinic. Healthcare utilisation for the year before and after telesystem enrolment was then assessed through hospital administrative databases. Results: Thirty-three of the 40 patients completed the initial 1-year study. Eighty-one exacerbations were reported in the 1-year follow-up. Action Plan adherence was observed for 72% of the exacerbations and those who were adherent had a significantly faster exacerbation recovery time. The large-scale implementation of the telesystem resulted in a significant decrease in the proportion of patients with >/=1 respiratory-related emergency room (ER) visits (120 before vs 110 after enrolment, $p<0.001$) and with >/=1 COPD-related hospitalisations (75 before vs 65 after enrolment, $p<0.001$). Discussion: COPD Written Action Plan adherence was further enhanced with the use of telehealth technologies in a specialised clinic with experience in COPD self-management. Patients followed by the telesystem recovered faster from exacerbations and had a further decrease in COPD-related ER visits and hospitalisations. Trial registration number: NCT02275078.

Feiring, E. and T. Friis (2019). **"Facilitators and barriers to clinicians' use of COPD action plans in self-management support: A qualitative study."** Patient Educ CounsOBJECTIVE: Written action plans for patients with chronic obstructive pulmonary disease (COPD) aim at early recognition of exacerbations and self-initiation of interventions. Previous research suggest underuse of COPD action plans. We wanted to 1) examine which factors clinicians in specialist healthcare perceived as influencing clinicians' use of written action plans in COPD-self management support and 2) propose a framework for understanding the factors affecting clinicians' use of action plans in routine practice. METHODS: We performed a theory-driven retrospective qualitative study. Documentary data were collected to describe the COPD action plan in context. In-depth interviews with clinicians (n=8) were carried out. Interview data were thematically analyzed, using a predetermined model for understanding behavior. RESULTS: Our study revealed that a number of factors influenced clinicians' use of action plans, including their capabilities (knowledge and skills to identify "the right patient" and to individualize the plan template) and motivations (beliefs, reinforcements, and emotions s.a. frustration, fear, and distrust), together with organizational and social opportunities (resources, patient, and GP preferences). CONCLUSION: A multilevel understanding of factors that affect clinicians' use of action plans in self-management support is needed. PRACTICE IMPLICATION: The proposed framework can be used to guide future initiatives to promote targeted self-management support.

Fernandez-Garcia, S., C. Represas-Represas, et al. (2019). **"Dependence IN Performing Activities as a Predictor of Mortality Following Hospitalization for Chronic Obstructive Pulmonary Disease Exacerbation."** Arch BronconeumolINTRODUCTION: Scant evidence is available on whether dependency for basic (BADL) or instrumental (IADL) activities of daily living can be predictors of mortality after severe COPD exacerbation (COPDE). In addition, it is as yet unclear whether the inclusion of this parameter in a multidimensional score can improve the prediction of mortality. METHODOLOGY: Prospective cohort study, with follow-up of patients discharged after COPDE and multivariate analysis of clinical-demographic and dependency variables (Barthel and Lawton and Brody indices) as predictors of mortality. Three scores were generated (including or not including dependency for BADL and IADL) that were compared with each other and with other commonly used multidimensional indices (BODEx, ADO, DOSE, CODEx). RESULTS: In total, 247 patients were included, 112 (45%, 3); and 195 (72.4%) had some dependency for BADL and IADL. Survival was 631.7 (258.8) days, 95% confidence interval (95% CI), 60-912 days. Fifty-four (21.9%, 95% CI 17-27) patients died. Age> 60 years, FEV1 <50% and Charlson score >/= 3 were independent predictors in the 3 models generated. Dependency for BADL and IADL were predictors in each of the models in which they were included. The score that included the dependency for BADL presented the best predictive capacity (area under the curve 0.818, 95% CI 0.757-0.879). Stratification into tertiles differentiated groups with a higher risk of death from the beginning of the follow-up (P<.01). CONCLUSIONS: Dependence for activities of daily living, especially the most elementary ones, is an independent predictor of mortality after a severe COPDE that is comparable to clinical variables. Its inclusion in multidimensional scores clearly improves predictive capacity.

Figueira Goncalves, J. M., M. A. Garcia Bello, et al. (2019). **"Dyslipidaemia and other cardiovascular risk factors in relation to manifest cardiovascular disease in patients with chronic obstructive pulmonary disease in the Canary Islands."** Rev Clin EspINTRODUCTION: Cardiovascular disease has a negative impact on the vital prognosis of patients with chronic obstructive pulmonary disease (COPD), where dyslipidaemia (DLP) and arterial hypertension (AHT) are considered the most prevalent risk factors. The

objective of this study was 1) to assess the relationship between diagnosed DLP and cardiovascular disease in COPD patients and compare it with other known cardiovascular risk factors and 2) to determine the relationship between the different cardiovascular comorbidities and the severity groups according to the GOLD 2017 classification. METHODS: A cross-sectional, observational study was performed in 454 outpatients with COPD during their follow up. We calculated the prevalence of each of the cardiovascular comorbidities and the probability of each of the cardiovascular risk factors to occur jointly with a vascular disease (RRij). RESULTS: A total of 66.7% of the patients had DLP, whereby DLP was related to cerebrovascular accidents (CVA) (RRij 1.36, P=.0054), chronic kidney disease (CKD) (RRij 1.34, P=.00023), and peripheral arterial disease (PAD) (RRij 1.38, P=.00015). AHT was mostly related to CVA (RRij 1.41, P=.0014) and CKD (RRij 1.42, P<.0001). Type 2 diabetes mellitus (T2DM) correlated with PAD (RRij 1.90, P=.0001), heart failure (HF) (RRij 1,74, P=.0002), and CKD (RRij 1.76, P<.0001), and obesity was associated with HF (RRij 1.60, P=.0009) and CKD (RRij 1.54, P=.0001). CONCLUSION: DLP was related to CVA, CKD, and PAD. AHT and T2DM are the conditions that mostly relate to HF and CVA.

Finch, S., I. F. Laska, et al. (2019). **"Validation of the COPD Assessment Test (CAT) as an Outcome Measure in Bronchiectasis."** ChestBACKGROUND: Objective assessment of symptoms in bronchiectasis is important for research and in clinical practice. The COPD Assessment Test (CAT) is a short, simple assessment tool widely used in COPD. The items included in the CAT are not specific to COPD and also reflect the dominant symptoms of bronchiectasis. We therefore performed a study to validate the CAT as an outcome measure in bronchiectasis. METHODS: The CAT was administered to two cohorts of bronchiectasis patients along with other quality of life questionnaires. Patients underwent comprehensive clinical assessment. One cohort had repeated questionnaires collected before-and-after treatment of acute exacerbations. We analyzed convergent validity, repeatability, and responsiveness of the score and calculated the minimum clinically important difference (MCID) using a combination of distribution and anchor-based methods. RESULTS: In both cohorts there were positive correlations between the CAT and the St. George's Respiratory Questionnaire (r = 0.90, P < .0001 and r = 0.87, P < .0001). There was an inverse relationship between CAT and Quality of Life - Bronchiectasis Respiratory Symptoms Scale (r = -0.75, P < .0001) and Leicester Cough Questionnaire score (r = -0.77, P < .0001). Patients with more severe disease, based on the bronchiectasis severity index, had significantly higher CAT scores. CAT also correlated with FEV1 % predicted and 6-min walk distance (6MWD). CAT increased significantly at exacerbation and fell at recovery. The intraclass correlation coefficient for two measurements four-weeks apart while clinically stable was 0.88 (95% CI, 0.73-0.95, P < .0001). An MCID of 4 was most consistent. CONCLUSIONS: CAT is a valid, responsive symptom assessment tool in bronchiectasis. The MCID is estimated as 4 points.

Gagne, M., S. Lauzier, et al. (2020). **"COPD-Specific Self-Management Support Provided by Trained Educators in Everyday Practice is Associated with Improved Quality of Life, Health-Directed Behaviors, and Skill and Technique Acquisition: A Convergent Embedded Mixed-Methods Study."** Patient **13**(1): 103-119.

BACKGROUND: There is a necessity to better document the effect of continuing education activities targeted at respiratory educators providing self-management support for patients with chronic obstructive pulmonary disease (COPD). We therefore sought to describe real-life COPD-specific self-management support delivered by respiratory educators who participated in a lecture-based continuing education activity and assess the outcomes of patients with COPD. METHODS: We conducted a convergent embedded mixed-methods study. Respiratory educators attended a 7-h, lecture-based continuing education activity on self-management support held in Quebec, Canada. Four months after the continuing education activity, in their professional practice, trained educators provided self-management support to patients with COPD. One month later, to describe the components of self-

management support provided, individual telephone interviews were conducted with educators. Interviews were transcribed verbatim and were qualitatively analyzed. Before self-management support and 6 months afterwards, we assessed the following clinical outcomes of patients with COPD: (1) quality of life (St. George's Respiratory Questionnaire for COPD patients, Impact domain; score 0-100; minimal clinically important difference = - 4; telephone administered); (2a) whether patients had one or more unscheduled doctor visit, (2b) one or more emergency room visit, and (2c) one or more hospitalization in the 6 preceding months (Survey on Living with Chronic Diseases in Canada; telephone administered); and (3a) health-directed behaviors and (3b) skill and technique acquisition (Health Education Impact Questionnaire; score 1-4; self-administered at home). We used mixed models to estimate mean differences and prevalence ratios, with associated 95% confidence intervals. RESULTS: Trained respiratory educators (nurse: n = 1; respiratory therapist: n = 3; >/= 15 years of experience of care with patients with chronic disease) invited 75 patients with COPD to participate in the study. Fifty-four individuals with COPD (age, mean +/- standard deviation: 68 +/- 8 years; men: n = 31) were enrolled and received self-management support. Qualitative analyses revealed that self-management support consisted of one to two visits that included: (1) provision of information on COPD; (2) training in inhalation technique; and (3) smoking cessation advice. No educator reported implementing two or more follow-up visits because of a lack of time and human resources in their work setting. Among patients with COPD, improvements in quality of life were clinically important (adjusted mean difference = - 12.75; 95% confidence interval - 18.79 to - 6.71; p = 0.0001). Health-resource utilization was not different over time (all p values > 0.05). Improvements in health-directed behaviors and skill and technique acquisition were statistically significant (health-directed behaviors: adjusted mean difference = 0.50; 95% confidence interval 0.23-0.77; p = 0.0005; skill and technique acquisition: adjusted mean difference = 0.12; 95% confidence interval 0.01-0.23; p = 0.0293). CONCLUSIONS: Following a 7-h, lecture-based continuing education activity on COPD-specific self-management support, respiratory educators with significant experience of care provided self-management support that included provision of information, inhalation technique training, and smoking cessation advice. This resulted in enhanced patient quality of life, health-directed behaviors, and skill and technique acquisition. To decrease health resource utilization, the training could employ active learning methods. More time and resources could also be devoted to implementing regular follow-up visits. CLINICAL TRIALS REGISTRATION NO: NCT02870998.

Gentene, A. J., M. R. Guido, et al. (2019). **"Multidisciplinary Team Utilizing Pharmacists in Multimodal, Bundled Care Reduce Chronic Obstructive Pulmonary Disease Hospital Readmission Rates."** J Pharm Pract: 897190019889440.

BACKGROUND: Chronic obstructive pulmonary disease (COPD) is a major contributor of morbidity and mortality in the United States resulting in high hospitalization and readmission rates. For health systems, identifying an effective strategy to reduce COPD readmissions has remained difficult. Multiple COPD care bundles have been developed with varying degrees of success. Bundles that were multidisciplinary and included pharmacists were successful in reducing readmissions. OBJECTIVE: To describe and assess a multidisciplinary, 5-element, COPD care bundle that was implemented in an academic, urban safety-net hospital to reduce COPD readmissions and the role of pharmacists in bundle implementation. METHODS: A multidisciplinary team collaborated to develop a 5-element COPD care bundle that met unmet patient needs. The bundle elements included the following, with pharmacy responsible for the first two: optimization of COPD inhalers, 30-day supply of insurance-compatible inhalers, individualized patient inhaler teaching, provision of standardized discharge instructions, and scheduling of a 15-day discharge follow-up appointment. Bundle was implemented with multiple Plan-Do-Study-Act (PDSA) cycles to develop intra- and interdepartment processes. RESULTS: Prior to bundle implementation, the health system COPD readmission rates were 22.7%. Reliable implementation of the bundle reduced readmissions to 14.7% over a 6-month period. Pharmacy adherence to completion of the bundle was over 95% over 2 years of bundle use. CONCLUSION: Pharmacists have a crucial role in hospital-based transitions of care to reduce COPD readmissions.

Gong, Y., X. Han, et al. (2019). **"Not All COPD Patients Benefit from Prophylactic Noninvasive Ventilation After Scheduled Extubation: An Exploratory Study."** Int J Chron Obstruct Pulmon Dis **14**: 2809-2814.

Background: Prophylactic noninvasive ventilation (NIV) after scheduled extubation can benefit patients with chronic respiratory disorders, among which chronic obstructive pulmonary disease (COPD) is a significant example. However, it is not known whether all COPD patients benefit from prophylactic NIV. Methods: We performed a post hoc analysis of prospectively collected data. COPD patients who successfully completed a spontaneous breathing trial were enrolled. In the prophylactic NIV group, NIV was applied immediately after extubation. In the usual care group, conventional oxygen therapy was used. Patients were followed up to 90 days post-extubation. Results: Among patients with PaCO2 > 45 mmHg, 128 and 40 received prophylactic NIV and usual care, respectively. Prophylactic NIV led to lower rates of re-intubation (4% vs 30% at 72 h and 11% vs 35% at 7 days, both p < 0.01) and hospital mortality (18% vs 40%, p < 0.01) than usual care. The proportion of 90-day mortality was also lower in the prophylactic NIV group (log rank test, p = 0.04). Among patients with PaCO2 </= 45 mmHg, 32 and 21 received prophylactic NIV and usual care, respectively. In this cohort however, prophylactic NIV neither reduced re-intubation (6% vs 5% at 72 h, p > 0.99, and 9% vs 14% at 7 days, p = 0.67) nor hospital mortality (19% vs 24%, p = 0.74). The proportion of 90-day mortality did not differ between the two groups (log rank test, p = 0.79). Conclusion: This exploratory study shows that prophylactic NIV benefits COPD patients with PaCO2 > 45 mmHg, but it may not benefit those with PaCO2 </= 45 mmHg. Further study with a larger sample size is required to confirm this.

Granados-Santiago, M., M. C. Valenza, et al. (2019). **"Shared decision-making and patient engagement program during acute exacerbation of COPD hospitalization: A randomized control trial."** Patient Educ CounsOBJECTIVE: To evaluate the effectiveness of a shared decision-making and patient engagement (SDM-PE) program concerning in-hospital stay during acute exacerbation of COPD and determine its impact on patients' perceived health status. METHODS: Patients were randomly allocated to a control group that received standard treatment or an intervention group that received an individualized SDM-PE program in addition to standard treatment. The SDM-PE program included personalized health care focused on information about the disease, healthcare management, and reinforcement of behaviors regarding nutrition and exercise taking into account patients' preferences. RESULTS: A comparative analysis between groups showed a significant improvement in perceived health status at discharge in patients included in the experimental group compared to those in the control group (60.28 +/- 21.65 vs. 54.13 +/- 22.69, p = 0.036). In addition, perceived health status, COPD knowledge, adherence to pharmacological treatment, general functionality, and healthy lifestyle measures were significantly better at 3-month follow-up in the intervention group. CONCLUSION: An SDM-PE program significantly enhanced all the clinical measures assessed during hospitalization at 3-month follow-up. PRACTICE IMPLICATIONS: COPD patients and professionals need to work together to select the best care and treatment model for patients, taking into account individual values and preferences.

Grosbois, J. M., J. Heluain-Robiquet, et al. (2019). **"Influence Of Socioeconomic Deprivation On Short- And Long-Term Outcomes Of Home-Based Pulmonary Rehabilitation In Patients With Chronic Obstructive Pulmonary Disease."** Int J Chron Obstruct Pulmon Dis **14**: 2441-2449.

Background: Pulmonary rehabilitation (PR) improves exercise tolerance and quality of life in patients with chronic obstructive pulmonary disease (COPD), regardless of disease severity. Socioeconomic deprivation has been linked to the incidence of COPD; however, little is known about its impact on PR outcomes.

Methods: In this retrospective observational study, 459 COPD patients were enrolled and dichotomized into socially deprived (n=276) and non-socially deprived (n=183) groups based on a cut-off of 30.17 in the EPICES questionnaire (Evaluation of Deprivation and Inequalities in Health Centers), which evaluates socioeconomic disadvantage. The PR program consisted of once-weekly home sessions for 8 weeks, and consisted of an individualized plan of retraining exercises, physical activities, therapeutic education, and psychosocial and motivational support. Exercise tolerance, anxiety and depression, and quality of life were assessed using the 6 min stepper test (6MST), Hospital Anxiety and Depression Scale (HADS), and Visual Simplified Respiratory Questionnaire (VSRQ). Assessments were made before the PR program (baseline) and then at 2 (T2), 8 (T8), and 14 (T14) months after baseline. Results: Compared with the non-socially deprived group, socially deprived patients were younger, more frequently women, active smokers, and living alone, and belonged to lower socioprofessional categories. At baseline, 6MST, VSRQ, and HADS measures were lower for the socially deprived than the non-socially deprived group. At T2, T8, and T14, there were no significant between-group differences in any outcome, and the percentage of patients showing clinically important improvements was the same in both groups. Conclusion: Home-based PR is effective for COPD patients in the short and long term, regardless of socioeconomic status.

Gurbani, N., J. M. Figueira Goncalves, et al. (2019). **"Prognostic ability of the distance-saturation product in the 6-minute walk test in patients with chronic obstructive pulmonary disease."** Clin Respir JINTRODUCTION: The product (DSP) of the distance walked (meters) and minimum oxygen saturation obtained during the 6-minute walk test (6MWT) has been proposed as a predictor of mortality in idiopathic pulmonary fibrosis and in bronchiectasis not related to cystic fibrosis. OBJECTIVE: The aim of this study was to determine the DSP's ability to predict mortality in patients with chronic obstructive pulmonary disease (COPD) at the outpatient level and compare it to the BODE index and meters walked in the 6MWT. MATERIAL AND METHODS: Descriptive observational study in a cohort of patients with COPD being treated at outpatient pulmonology clinics. Each of the patients completed the 6MWT following ATS/ERS protocols and their BODE index and DSP were calculated. RESULTS: About 103 patients were included. The average length of follow-up was 36 months. Patients who died showed a lower number of meters walked in the 6MWT ($P < 0.001$), as well as a lower DSP ($P < 0.001$). A 6MWT < 334 m, a DSP < 290 and a BODE >/= 4 showed good prognostic ability at 3 years (AUC 71%, 69% and 70.4%, respectively). The 6MWT was superior to the BODE index in predicting mortality during the first year of follow-up ($P = 0.023$). We did not find any differences between DSP and meters walked in the 6MWT. CONCLUSIONS: The DSP is a good predictor of mortality, although it does not offer a better prognostic ability than that of meters walked in the 6MWT.

Harvey-Dunstan, T. C., S. J. Singh, et al. (2019). **"Are the measurement properties of incremental exercise tests similar between patients with COPD and CHF?"** Chron Respir Dis **16**: 1479973119887965.

We investigated whether the differences in exercise limitation between patients with chronic obstructive pulmonary disease (COPD) or chronic heart failure (CHF) affect the repeatability or responsiveness of incremental exercise tests. Patients with COPD (Medical Research Council dyspnoea grade 2-5) and patients with CHF (New York Heart Association class II-IV) performed two incremental shuttle walk tests (ISWT) following familiarisation and two incremental cycle ergometer tests (ICE) within 2 weeks. Both tests were repeated on completion of a pulmonary rehabilitation (PR) programme. One hundred and twelve patients were recruited. In response to exercise, patients with COPD were more likely than patients with CHF to have a ventilatory limitation ($p < 0.001$) and less likely to have a cardiovascular limitation ($p < 0.001$). The ISWT distance and ICE peak volume of oxygen uptake (VO2Peak) were similarly repeatable ($p = 0.11$ and $p = 0.47$ for time and disease effect) and responsive to PR ($p = 0.44$ and $p = 0.67$) between diseases. There was no difference in repeatability or responsiveness with either a ventilatory or cardiovascular limitation to exercise ($p > 0.20$ for all comparisons). The coefficient of

repeatability across the cohort was 60 m for the ISWT and 0.270 L/minute for ICE VO2Peak. The minimum important difference (MID) for the ISWT in both diseases for PR was 30 m. The repeatability and responsiveness of the ISWT distance and ICE VO2Peak are similar between patients with COPD and CHF and are unaffected by differences in exercise limitation. A change of 60 m in the ISWT or 0.270 L/minute in ICE VO2Peak is required to be 95% certain that a true change has occurred within an individual patient. For a group of patients with either COPD or CHF, the MID for the ISWT distance is estimated to be 30 m.

Henkel, M., J. Partyka, et al. (2019). **"Follistatin-like 1 Attenuation Causes Spontaneous Smoke-Resistant Pulmonary Emphysema."** Am J Respir Crit Care MedRATIONALE: The role of follistatin-like 1 (FSTL-1) in lung homeostasis is unknown. OBJECTIVES: We aimed to define the impact of FSTL-1 attenuation on lung structure and function and identify FSTL-1-regulated transcriptional pathways in the lung. Further, we aimed to analyze the association of FSTL1 SNPs with lung disease. METHODS: FSTL-1 hypomorphic mice (FSTL-1 Hypo) underwent lung morphometry, pulmonary function testing and micro-CT. Fstl1 expression was determined in wild-type lung cell populations from three independent research groups. RNA sequencing of wild-type and FSTL-1 Hypo mice identified FSTL-1-regulated gene expression, followed by validation and mechanistic in vitro examination. FSTL1 SNP analysis was performed in the COPDGene cohort. MEASUREMENTS AND MAIN RESULTS: FSTL-1 hypomorphic mice developed spontaneous emphysema, independent of smoke exposure. Fstl1 is highly expressed in the lung by mesenchymal and endothelial cells, but not immune cells. RNA sequencing of whole lung identified 33 FSTL-1-regulated genes, including Nr4a1, an orphan nuclear hormone receptor that negatively regulates NF-kappaB signaling. In vitro, recombinant FSTL-1 treatment of macrophages attenuated NF-kappaB p65 phosphorylation in an Nr4a1-dependent manner. Within the COPDGene cohort, several SNPs in the FSTL1 region corresponded to COPD and lung function. CONCLUSIONS: This work identifies a novel role for FSTL-1 protecting against emphysema development independent of smoke exposure. This FSTL-1-deficient emphysema implicates regulation of immune tolerance in lung macrophages through Nr4a1. Further study of the mechanisms involving FSTL-1 in lung homeostasis, immune regulation and NF-kappaB signaling may provide additional insight into the pathophysiology of emphysema and inflammatory lung diseases.

Heraganahally, S. S., S. L. Wasgewatta, et al. (2019). **"Chronic obstructive pulmonary disease with and without bronchiectasis in Aboriginal Australians - a comparative study."** Intern Med JAIMS: In this retrospective study we evaluated the demographic and clinical characteristic of adult Aboriginal Australian patients with a clinical diagnosis of COPD with and without bronchiectasis from the remote communities of the Northern Territory of Australia. METHOD: Clinical records were reviewed to extract information on demographics, respiratory and medical co-morbid conditions, COPD directed treatment, hospital admission frequency and exacerbations. Chest radiology were reviewed to evaluate the presence or absence of bronchiectasis. Spirometry results, sputum culture and cardiac investigations were also recorded. RESULTS: Of the 767 patients assessed in the remote community respiratory outreach clinics 380 (49%) patients had a clinical diagnosis of COPD. Chest X-Ray and CT scan were available to evaluate the presence of bronchiectasis in 258 patients. Of the 258/380 patients 176/258 (68.2%) were diagnosed to have COPD alone and 82/258 (31.8%) had bronchiectasis along with COPD. The mean age was 56 and 59 years among patients with and without bronchiectasis respectively and 57 % were males with bronchiectasis. Patients with bronchiectasis had lower BMI (22v24), frequent hospital admissions (2.0vs1.5/year) and productive cough (32.1v28.9%). Spirometry showed 77% had FEV1 /FVC ratio < 0.7. In 81% and 75% of patients with and without bronchiectasis the FEV1/FVC ratio was < 0.7 and the mean FEV1 was 39% and 43 % respectively. CONCLUSION: About 32% of Aboriginal Australians had co-existent bronchiectasis with COPD Lower BMI, productive cough, frequent hospital admission

and marginally more severe reduction in lung function was noted among patients with COPD and bronchiectasis compared to those with COPD in isolation.

Herth, F. J. F., D. J. Slebos, et al. (2019). **"Protocol of a Randomized Controlled Study of the PneumRx Endobronchial Coil System versus Standard-of-Care Medical Management in the Treatment of Subjects with Severe Emphysema (ELEVATE)."** Respiration **98**(6): 512-520.

BACKGROUND: The PneumRx endobronchial coil system for patients with severe emphysema has been shown to improve quality of life, exercise capacity, and pulmonary function in patients with emphysema. A post hoc analysis of the RENEW trial has identified patient characteristics and lobar selection methods associated with improved outcomes, which have to be confirmed prospectively. METHODS: The ELEVATE trial is a prospective, multicenter, open label, randomized (2:1), controlled trial comparing outcomes in patients treated with endobronchial coils (treatment) to a medically managed control group (control). The trial aims to enroll 210 patients (140 in the treatment group and 70 in the control group) with severe emphysema. Control patients will be eligible to crossover to coil treatment after 6 months of follow-up. The co-primary effectiveness endpoints are percent change in forced expiratory volume in 1 s and quality of life measured by change in St. George's Respiratory Questionnaire from baseline to 6 months. Secondary objectives are determination of responder rates of clinical endpoints and mean change in other functional and physiologic endpoints. All patients will be followed for 24 months after initial treatment. Adverse events will be collected on an ongoing basis throughout the trial. DISCUSSION: The primary objective of the ELEVATE trial is to prospectively confirm the safety and effectiveness profile of the coil system for the treatment of severe emphysema in consideration of the findings of previous randomized controlled trials. Secondary objectives are the determination of responder rates in all clinical endpoints and mean change in physiologic endpoints.

Hsu, W. L., H. Y. Chen, et al. (2019). **"Does chronic obstructive pulmonary disease increase the risk of prostate cancer? A nationwide population-based study."** Int J Chron Obstruct Pulmon Dis **14**: 1913-1921.

Purpose: Chronic obstructive pulmonary disease (COPD) is a major pulmonary disease. However, few studies have investigated the relationship between COPD and prostate cancer (PCa). This study aimed to investigate the association between COPD severity and PCa risk. Patients and methods: We conducted a nationwide population-based cohort study utilizing data from 2001 to 2013 from the National Health Insurance Research Database of Taiwan. Cox proportional hazards models with 1:1 propensity score-matched analysis were used to investigate the association between COPD and PCa risk. We further divided the COPD group according to severe complications (including acute respiratory failure, cardiopulmonary arrest, pneumonia, and acute exacerbation) to test for the relationship between COPD severity and PCa risk. Results: This study included 47,634 patients (23,817 COPD patients and 23,817 matched non-COPD controls). Among them, 756 (1.59%) were diagnosed with PCa during a mean follow-up period of 7.05+/-4.13 years; 387 (1.62%) were from the COPD group and 369 (1.55%) were from the control group. Compared with the patients without COPD, the adjusted hazard ratio (HR) for PCa in the COPD patients was 1.10 (95% confidence interval [CI] 0.95-1.27), while that in the COPD patients with complications was 2.46 (95% CI 1.96-3.61). Conclusions: An increased risk for PCa was found among the COPD patients with complications. COPD complications included acute respiratory failure, cardiopulmonary arrest, pneumonia, and acute exacerbation. These findings may help physicians in treating COPD with complications and in remaining alert to the potential development of PCa.

Huang, T. H., C. Z. Chen, et al. (2019). **"Enhanced risk of traumatic brain injury in patients with chronic obstructive pulmonary disease."** J Investig MedThis study tests our hypothesis that patients with chronic obstructive pulmonary disease (COPD) have an increased risk of traumatic brain injury (TBI).In this nationwide retrospective cohort study, we used a subset of Taiwan's National Health Insurance Research Database, involving 1 million randomly selected beneficiaries. Patients with newly diagnosed COPD between 2000 and 2008 were identified. They were subgrouped as 'COPDAE+' (if they had severe acute exacerbation of COPD during the follow-ups) or 'COPDAE-' (if they had no acute exacerbation), and were frequency matched with randomly selected subjects without COPD (the 'non-COPD' group). Baseline differences were balanced by the inverse probability of treatment weighting based on the propensity score. For each patient, the risk of TBI during the subsequent 5 years was determined. The competing risk of death was controlled.We identified 3734 patients in 'COPDAE+', and frequency matched them with 11,202 patients in 'COPDAE-' and 11,202 subjects in 'non-COPD'. Compared with those in 'non-COPD', patients in 'COPDAE+' and 'COPDAE-' had an increased risk of TBI: the adjusted HR for 'COPDAE+' was 1.50, 95% CI 1.31 to 1.73, and that for 'COPDAE-' was 1.21, 95% CI 1.09 to 1.34. The highest risk was observed in the 'COPDAE+' group that aged <65 (the adjusted HR was 1.92; 95% CI 1.39 to 2.64).COPD has been linked to complications beyond the respiratory system. In this study we showed that COPD is associated with an increased risk of TBI.

Humphries, S. M., A. M. Notary, et al. (2019). **"Deep Learning Enables Automatic Classification of Emphysema Pattern at CT."** Radiology: 191022.

BackgroundPattern of emphysema at chest CT, scored visually by using the Fleischner Society system, is associated with physiologic impairment and mortality risk.PurposeTo determine whether participant-level emphysema pattern could predict impairment and mortality when classified by using a deep learning method.Materials and MethodsThis retrospective analysis of Genetic Epidemiology of COPD (COPDGene) study participants enrolled between 2007 and 2011 included those with baseline CT, visual emphysema scores, and survival data through 2018. Participants were partitioned into nonoverlapping sets of 2407 for algorithm training, 100 for validation and parameter tuning, and 7143 for testing. A deep learning algorithm using convolutional neural network and long short-term memory architectures was trained to classify pattern of emphysema according to Fleischner criteria. Deep learning scores were compared with visual scores and clinical parameters including pulmonary function tests. Cox proportional hazard models were used to evaluate relationships between emphysema scores and survival. The algorithm was also tested by using CT and clinical data in 1962 participants enrolled in the Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE) study.ResultsA total of 7143 COPDGene participants (mean age +/- standard deviation, 59.8 years +/- 8.9; 3734 men and 3409 women) were evaluated. Deep learning emphysema classifications were associated with impaired pulmonary function tests, 6-minute walk distance, and St George's Respiratory Questionnaire at univariate analysis ($P < .001$ for each). Testing in the ECLIPSE cohort showed similar associations ($P < .001$). In the COPDGene test cohort, deep learning emphysema classification improved the fit of linear mixed models in the prediction of these clinical parameters compared with visual scoring ($P < .001$). Compared with participants without emphysema, mortality was greater in participants classified by the deep learning algorithm as having any grade of emphysema (adjusted hazard ratios were 1.5, 1.7, 2.9, 5.3, and 9.7, respectively, for trace, mild, moderate, confluent, and advanced destructive emphysema; $P < .05$).ConclusionDeep learning automation of the Fleischner grade of emphysema at chest CT is associated with clinical measures of pulmonary insufficiency and the risk of mortality.(c) RSNA, 2019Online supplemental material is available for this article.

Jang, J. G., J. S. Kim, et al. (2019). **"Comprehensive Effects of Organized Education for Patients with Chronic Obstructive Pulmonary Disease."** Int J Chron Obstruct Pulmon Dis **14**: 2603-2609.

Background: Despite the increasing prevalence of chronic obstructive pulmonary disease (COPD) worldwide, knowledge and awareness of COPD remain extremely low. This prospective study aimed to demonstrate the effectiveness of organized educational intervention. Patients and methods: The study participants included patients diagnosed with COPD and receiving inhaler treatment. In this prospective study, the patients made three sequential visits to the hospital (baseline, 1 month, 3 months). On their first and second visits, patients received systematic education about COPD. On their first and third visits, each patient was evaluated using a COPD Assessment Test, COPD Knowledge Questionnaire, Hospital Anxiety and Depression Scale, and Rosenberg Self-Esteem Scale. Results: Fifty-five participants were enrolled in the study. The mean COPD knowledge score before and after education was 12.51+/-3.19 and 17.89+/-1.37, respectively, indicating a significant increase in the score post-education (P<0.001). The measure of patients' inhaler technique also significantly improved after education (5.40+/-1.50 vs 6.83+/-0.37 P=0.01). The rate of depression and anxiety after education decreased by 10.9% and 12.7%, respectively (P<0.001). In subgroup analysis, we compared the groups whose knowledge score increased by more than 5 points (Group B) and those whose score did not improve (Group A). In Group B, the mean CAT score significantly improved (2.61+/-5.88 vs -2.41+/-7.48, P=0.01), and the duration of their COPD diagnosis before enrollment was significantly shorter (2.72+/-2.43 vs 5.22+/-5.11 years, P=0.038) compared to those in Group A. Conclusion: An organized educational program resulted in improved disease-specific knowledge. Disease-specific education is an important part of the treatment of COPD that affects the quality of life and emotional status of patients. Early education after COPD diagnosis can be beneficial.

Johnson, K. M., A. Khakban, et al. (2019). **"Healthcare system encounters before COPD diagnosis: a registry-based longitudinal cohort study."** ThoraxBACKGROUND: There is high interest in strategies for improving early detection of chronic obstructive pulmonary disease (COPD). These strategies often rely on opportunistic encounters between patients with undiagnosed COPD and the healthcare system; however, the frequency of these encounters is currently unknown. METHODS: We used administrative health data for the province of British Columbia, Canada, from 1996 to 2015. We identified patients with COPD using a validated case definition, and assessed their visits to pharmacists, primary care and specialist physicians in the 5 years prior to the initial diagnosis of COPD. We used generalised linear models to compare the rate of outpatient visits between COPD and non-COPD comparator subjects matched on age, sex and socioeconomic status. RESULTS: We assessed 112 635 COPD and non-COPD pairs (mean 68.6 years, 51.0% male). Patients with COPD interacted with pharmacists most frequently in the 5 years before diagnosis (mean 14.09, IQR 4-17 visits/year), followed by primary care (10.29, IQR 4-13 visits/year) and specialist (8.11, IQR 2-11 visits/year) physicians. In the 2 years prior to diagnosis, 72.1% of patients with COPD had a respiratory-related primary care visit that did not result in a COPD diagnosis. Compared with non-COPD subjects, patients with COPD had higher rates of primary care (rate ratio (RR) 1.40, 95% CI 1.39 to 1.41), specialist (RR 1.35, 95% CI 1.34 to 1.37) and pharmacist (RR 1.62, 95% CI 1.60 to 1.63) encounters. CONCLUSIONS: Patients with COPD used higher rates of outpatient services before diagnosis than non-COPD subjects. Case detection technologies implemented in pharmacy or primary care settings have opportunities to diagnose COPD earlier.

Johnson, M., L. Rigge, et al. (2019). **"Primary care risk stratification in COPD using routinely collected data: a secondary data analysis."** NPJ Prim Care Respir Med **29**(1): 42.

Most clinical contacts with chronic obstructive pulmonary disease (COPD) patients take place in primary care, presenting opportunity for proactive clinical management. Electronic health records could be used to risk stratify diagnosed patients in this setting, but may be limited by poor data quality or completeness.

We developed a risk stratification database algorithm using the DOSE index (Dyspnoea, Obstruction, Smoking and Exacerbation) with routinely collected primary care data, aiming to calculate up to three repeated risk scores per patient over five years, each separated by at least one year. Among 10,393 patients with diagnosed COPD, sufficient primary care data were present to calculate at least one risk score for 77.4%, and the maximum of three risk scores for 50.6%. Linked secondary care data revealed primary care under-recording of hospital exacerbations, which translated to a slight, non-significant cohort average risk score reduction, and an understated risk group allocation for less than 1% of patients. Algorithmic calculation of the DOSE index is possible using primary care data, and appears robust to the absence of linked secondary care data, if unavailable. The DOSE index appears a simple and practical means of incorporating risk stratification into the routine primary care of COPD patients, but further research is needed to evaluate its clinical utility in this setting. Although secondary analysis of routinely collected primary care data could benefit clinicians, patients and the health system, standardised data collection and improved data quality and completeness are also needed.

Karampitsakos, T., G. Hillas, et al. (2019). **"Prospective evAluatIon foR inhalation devices in Greek patients with COPD and asthma: The PAIR study."** Pulm Pharmacol Ther **60**: 101882.

INTRODUCTION: Chronic obstructive pulmonary disease (COPD) and asthma remain a major health burden. Adherence to inhaled therapy is critical in order to optimize treatment effectiveness. Properly designed questionnaires can assess patients' satisfaction with their inhaler devices. PATIENTS AND METHODS: A total of 766 patients with COPD, asthma or Asthma-COPD Overlap (ACO) were initially enrolled. During their first visit, patients were classified into three groups (Diskus, Elpenhaler(R), Turbuhaler(R)). Patients completed the FSI-10 questionnaire on Day 0 and Day 60. Test-retest reliability was evaluated. RESULTS: A total of 705 patients completed the study. FSI-10 questionnaire had good test-retest reliability (Total Intraclass Correlation Coefficient: 0.86). All dry powder inhaler (DPIs) yielded satisfactory results. Median score of FSI-10 questionnaire in first visit (FSI-10-I) was significantly higher for patients receiving Elpenhaler(R) (45, 95% CI: 44 to 46) than patients receiving Diskus (42, 95% CI: 41 to 43) and Turbuhaler(R) (42, 95% CI: 41 to 43) ($p<0.001$). Accordingly, median score of FSI-10 questionnaire in the final visit (FSI-10-II) was significantly higher for patients receiving Elpenhaler(R) (46, 95% CI: 45 to 47) than patients receiving Diskus (42, 95% CI: 41 to 43) and Turbuhaler(R) (43, 95% CI: 42 to 44) ($p<0.001$). CONCLUSION: FSI-10 questionnaire had good test-retest reliability and thus can be used in the follow-up of patients with COPD, asthma and ACO. All DPIs were highly acceptable among all study groups. Elpenhaler(R) achieved significantly higher ratings than Diskus and Turbuhaler(R) in FSI-10 score and presented higher preference among patients with obstructive lung diseases.

Keene, S. J., R. E. Jordan, et al. (2019). **"External Validation Of The Updated ADO Score In COPD Patients From The Birmingham COPD Cohort."** Int J Chron Obstruct Pulmon Dis **14**: 2395-2407.

Background: Reviews suggest that the ADO score is the most discriminatory prognostic score for predicting mortality among chronic obstructive pulmonary disease (COPD) patients, but a full evaluation and external validation within primary care settings is critical before implementation. Objectives: To validate the ADO score in prevalent and screen-detected primary care COPD cases at 3 years and at shorter time periods. Patients and methods: One thousand eight hundred and ninety-two COPD cases were recruited between 2012 and 2014 from 71 United Kingdom general practices as part of the Birmingham COPD Cohort study. Cases were either on the practice COPD register or screen-detected. We validated the ADO score for predicting 3-year mortality with 1-year and 2-year mortality as secondary endpoints using discrimination (area-under-the-curve (AUC)) and calibration plots. Results: One hundred and fifty-four deaths occurred within 3 years. The ADO score was discriminatory for predicting 3-year mortality (AUC= 0.74; 95% CI: 0.69-0.79). Similar performance was found for 1- (AUC= 0.73; 0.66-0.80) and 2-year mortality (0.72; 0.67-0.76). The ADO score showed reasonable calibration for predicting 3-year mortality

(calibration slope 0.95; 0.70-1.19) but over-predicted in cases with higher predicted risks of mortality at 1 (0.79; 0.45-1.13) and 2-year (0.79; 0.57-1.01) mortality. Discussion: The ADO score showed promising discrimination in predicting 3-year mortality in a primary care population including screen-detected cases. It may need to be recalibrated if it is used to provide risk predictions for 1- or 2-year mortality since, in these time-periods, over-prediction was evident, especially in cases with higher predicted mortality risks.

Khanji, M. Y., I. S. Stone, et al. (2019). **"Chronic Obstructive Pulmonary Disease as a Predictor of Cardiovascular Risk: A Case-Control Study."** Copd: 1-9.

Chronic obstructive pulmonary disease (COPD) is a complex multi-morbid disorder with significant cardiac mortality. Current cardiovascular risk prediction models do not include COPD. We investigated whether COPD modifies future cardiovascular risk to determine if it should be considered in risk prediction models.Case-control study using baseline data from two randomized controlled trials performed between 2012 and 2015. Of the 90 eligible subjects, 26 COPD patients with lung hyperinflation were propensity matched for 10-year global cardiovascular risk score (QRISK2) with 26 controls having normal lung function. Patients underwent cardiac magnetic resonance imaging, arterial stiffness and lung function measurements. Differences in pulse wave velocity (PWV), total arterial compliance (TAC) and aortic distensibility were main outcome measures.PWV (mean difference 1.0 m/s, 95% CI 0.02-1.92; p = 0.033) and TAC (mean difference -0.27 mL/m(2)/mmHg, 95% CI 0.39-0.15; p < 0.001) were adversely affected in COPD compared to the control group. The PWV difference equates to an age, sex and risk-factor adjusted increase in relative risk of cardiovascular events and mortality of 14% and 15%, respectively.There were no differences in aortic distensibility. In the whole cohort (n = 90) QRISK2 (beta = 0.045, p = 0.005) was associated with PWV in multivariate analysis. The relationship between QRISK2 and PWV were modified by COPD, where the interaction term reached significance (p = 0.014). FEV1 (beta = 0.055 (0.027), p = 0.041) and pulse (B = -0.006 (0.002), p = 0.003) were associated with TAC in multivariate analysis.Markers of cardiovascular outcomes are adversely affected in COPD patients with lung hyperinflation compared to controls matched for global cardiovascular risk. Cardiovascular risk algorithms may benefit from the addition of a COPD variable to improve risk prediction and guide management.HAPPY London ClinicalTrials.gov: NCT01911910 and HZC116601; ClinicalTrials.gov: NCT01691885.

Kim, J., C. H. Lee, et al. (2019). **"The Ability of Different Scoring Systems to Predict Mortality in Chronic Obstructive Pulmonary Disease Patients: A Prospective Cohort Study."** Respiration **98**(6): 495-502.

BACKGROUND: Chronic obstructive pulmonary disease (COPD) is a leading cause of mortality, therefore the prediction of mortality in COPD patients is crucial. In the current study, the abilities of different categorization systems to predict mortality in stable COPD patients from a prospective cohort were compared. METHODS: The ability to predict mortality was compared in terms of discrimination by Harrell's C (HC) index and calibration using graphical comparison among the GOLD (Global Initiative for Chronic Obstructive Lung Disease) 2011, GOLD 2017, GOLD grade, BODE (BMI, Airflow Obstruction, Dyspnea, Exercise), updated BODE, BODEx (BMI, Airflow Obstruction, Dyspnea, Exacerbation), e-BODE (Exacerbation and BODE), ADO (Age, Dyspnea, Airflow Obstruction), COPD prognostic index (CPI), and simplified/optimized B-AE-D (BMI, Acute Exacerbation, Dyspnea) indexes. RESULTS: The study included 520 patients, of whom 63 died during a median 40-month follow-up period. Combined prediction systems exhibited higher discrimination properties than single predictors. The CPI exhibited the highest with a HC of 0.768, followed by the simplified B-AE-D (HC 0.761), ADO (HC 0.760), and optimized B-AE-D (HC 0.756). The BODE and its variants other than the ADO exhibited relatively lower HCs (0.656-0.705), and GOLD exhibited the lowest discrimination ability among the combined indices (HCs 0.628-0.637). Subjective symptom questionnaires such as the modified Medical Research Council (mMRC) scale (HC

0.693) and SGRQ (HC 0.679) exhibited the highest ability to predict mortality among the single indices. CONCLUSION: The ADO, simplified B-AE-D, optimized B-AE-D, and GOLD 2017 exhibited good calibration properties, but the CPI did not. The simplified and optimized B-AE-Ds and the ADO index had good discrimination and calibration properties for the prediction of mortality in stable COPD patients.

Kim, T., H. Choi, et al. (2019). **"Association Between Dietary Nutrient Intake and Chronic Obstructive Pulmonary Disease Severity: A Nationwide Population-Based Representative Sample."** Copd: 1-10.

Several nutrients have been suggested to protect against airway destruction via antioxidant activity. The present study aimed to evaluate the association between disease severity and dietary nutrient intake in chronic obstructive pulmonary disease (COPD) patients using the Korea National Health and Nutrition Examination Survey. Of the 22,948 participants, 702 patients (418 men and 284 women) with COPD, who were defined as the fifth percentile from a reference population were selected. The severity of airflow limitation was measured by the predicted percentage of forced expiratory volume in 1 second (FEV1%). The Jonckheere-Terpstra test was used to evaluate the dose-dependent association between nutrient intake and disease severity. Multivariate linear regression analysis was used to evaluate the relationship between dietary nutrient intake and predicted FEV1%. Vitamin A intake showed a positive association with FEV1% in men in a model adjusted for covariates. Carbohydrate, protein, fiber, thiamin, riboflavin, niacin, and vitamin C intake were significantly associated with decreased disease severity in elderly men (aged >/=60 years). On the contrary, statistical significance was not observed for all the nutrients in women. In conclusion, intake of carbohydrate, protein, fiber, thiamin, riboflavin, niacin, and vitamin C was associated with decreased severity of airway impairment in elderly men with COPD. Our results are in line with those of previous studies into the importance of nutritional status in airway disease. A longitudinal study is required to clarify the mechanisms underlying the association between dietary nutrient intake and COPD severity.

Lai, R. S., C. F. Chen, et al. (2019). **"The effect of emphysema on survival in patients with idiopathic pulmonary fibrosis: A retrospective study in Taiwan."** J Chin Med Assoc **82**(12): 922-928.

BACKGROUND: Idiopathic pulmonary fibrosis (IPF) is a rare and chronic fibrosing interstitial lung disease. However, the clinical features and outcomes of IPF in Taiwan have not been well studied. In addition, the survival difference between patients with IPF alone and combined pulmonary fibrosis and emphysema (CPFE) remains controversial. METHODS: Patients diagnosed with IPF between 2006 and 2016 were retrospectively enrolled in this study. IPF was defined according to the 2011 American Thoracic Society/European Respiratory Society guideline. The clinical features, comorbidities, and outcomes of CPFE group and IPF-alone group were compared. The extents of emphysema and fibrosis were evaluated. RESULTS: In total, 114 patients with IPF were enrolled, and 86.8% of them were men with a mean age of 77.8 years. The median survival was 3.33 years in all patients with IPF. Moreover, 30 patients (26.3%) met the CPFE criteria. The CPFE group had a higher percentage of smokers (90% vs 50%, $p < 0.001$), higher forced vital capacity (82% vs 59%, $p < 0.001$), and lower fibrosis scores (8.5 +/- 2.9 vs 10 +/- 3.2, $p = 0.022$) than did the IPF-alone group. The baseline room air saturation and percentage of pulmonary hypertension were similar between the two groups. The survival time was not significantly different between the CPFE and IPF-alone groups (median survival, 3.58 vs 2.39 years, $p = 0.163$). In the multivariate analysis, higher fibrosis score, room air saturation < 90%, and lung cancer were significant factors associated with mortality. CONCLUSION: Our study showed that emphysema had no significant effect on the survival of patients with IPF. The outcome of IPF was mainly determined by the baseline disease severity and other comorbidities.

Lampela, P., A. M. Tolppanen, et al. (2020). **"Asthma and Chronic Obstructive Pulmonary Disease as a Comorbidity and Association with the Choice of Antidementia Medication Among Persons with Alzheimer's Disease."** J Alzheimers DisBACKGROUND: Asthma and chronic obstructive pulmonary disease (COPD) are common comorbidities in persons with Alzheimer's disease (AD). However, pharmacotherapy of these diseases may have opposite mechanisms of action; anticholinergics in asthma/COPD and acetylcholinesterase inhibitors (AChEI) in AD. OBJECTIVE: To investigate whether existing asthma/COPD affects the choice of AD medication, and the survival of the patients with AD. METHODS: In this retrospective cohort study, data from the MEDALZ-study, which includes all community-dwelling persons with AD during 2005-2011 in Finland (n = 70718) was utilized. Persons with asthma/COPD (N = 7211) were defined as having a special reimbursement for asthma/COPD, or long-term use (>/=250 days) of inhaled anticholinergics, inhaled corticosteroids, or leukotriene antagonists during the year before AD diagnosis. We compared persons with and without asthma/COPD regarding the choice of the initial antidementia medication (AChEI versus memantine) with logistic regression and mortality with Cox regression model during the follow-up (up to end of 2015). RESULTS: Memantine was favored over AChEIs as first-line treatment to AD in persons with asthma/COPD compared to those without asthma/COPD (odds ratio 1.23, 95% confidence interval (CI) 1.15-1.31). Memantine was also more commonly used among those who used multiple asthma/COPD medications (26.3% of memantine initiators used >/=3 asthma/COPD medications compared with 20.6% of those who initiated with AChEI). Mortality was higher in persons with asthma/COPD compared to those without asthma/COPD (adjusted hazard ratio 1.10, 95% CI 1.07-1.13). CONCLUSION: More frequent use of memantine instead of AChEI may result from an attempt to prevent possible worsening of asthma/COPD by AChEIs. Vulnerable persons with both AD and asthma/COPD need individually assessed pharmacotherapy for their medical conditions.

Lee, J. H., K. L. Hailey, et al. (2019). **"Cigarette Smoke Triggers IL-33-associated Inflammation in a Model of Late-Stage Chronic Obstructive Pulmonary Disease."** Am J Respir Cell Mol Biol **61**(5): 567-574.

Chronic obstructive pulmonary disease (COPD) is a worldwide threat. Cigarette smoke (CS) exposure causes cardiopulmonary disease and COPD and increases the risk for pulmonary tumors. In addition to poor lung function, patients with COPD are susceptible to bouts of dangerous inflammation triggered by pollutants or infection. These severe inflammatory episodes can lead to additional exacerbations, hospitalization, further deterioration of lung function, and reduced survival. Suitable models of the inflammatory conditions associated with CS, which potentiate the downward spiral in patients with COPD, are lacking, and the underlying mechanisms that trigger exacerbations are not well understood. Although initial CS exposure activates a protective role for vascular endothelial growth factor (VEGF) functions in barrier integrity, chronic exposure depletes the pulmonary VEGF guard function in severe COPD. Thus, we hypothesized that mice with compromised VEGF production and challenged with CS would trigger human-like severe inflammatory progression of COPD. In this model, we discovered that CS exposure promotes an amplified IL-33 cytokine response and severe disease progression. Our VEGF-knockout model combined with CS recapitulates severe COPD with an influx of IL-33-expressing macrophages and neutrophils. Normally, IL-33 is quickly inactivated by a post-translational disulfide bond formation. Our results reveal that BAL fluid from the CS-exposed, VEGF-deficient cohort promotes a significantly prolonged lifetime of active proinflammatory IL-33. Taken together, our data demonstrate that with the loss of a VEGF-mediated protective barrier, the CS response switches from a localized danger to an uncontrolled long-term and long-range, amplified, IL-33-mediated inflammatory response that ultimately destroys lung function.

Lee, S. H., H. Lee, et al. (2019). **"Social support is a strong determinant of life satisfaction among older adults with chronic obstructive pulmonary disease."** Clin Respir JINTRODUCTION: Older adults with chronic obstructive pulmonary disease (COPD) are frequently compromised in terms of social life and functional capacity, triggering reduced in life satisfaction (LS). We investigated the level of LS among elderly patients with COPD and factors associated with LS. MATERIALS AND METHODS: This was a prospective cross-sectional survey enroling a sample of 160 COPD subjects aged 65 y or older. At enrolment, all patients completed measures of LS (the Satisfaction with Life Scale; SWLS) and social support (Personal Resource Questionnaire; PRQ). The health-related quality of life (HRQL) was measured using St. George's Respiratory Questionnaire (SGRQ) and 36-item Short-Form Health Survey (SF-36). Anxiety and depression were assessed using the Hospital Anxiety and Depression Scale (HADS). RESULTS: About 30.6% of the patients reported that they were satisfied or highly satisfied with their lives. In univariate analysis, post-bronchodilator FEV1, percentage predicted was significantly associated with SWLS score (r = 0.205, P = .009). Age (r = 0.207), diabetes (r = 0.209), osteoporosis (r = -0.190), PRQ (r = 0.388), SGRQ total (r = -0.291), SF-36 PCS (r = 0.233), SF-36 MCS (r = 0.274), HADS-A (r = -0.291) and HADS-D (r = -0.352) were also associated with SWLS score (all P < .05). Multivariate analysis revealed that FEV1 (r = 0.223, P = .04) and PRQ (r = .244, P = .002) were independently associated with SWLS score. CONCLUSIONS: Less than one-third of older adults with COPD reported that they were satisfied with their lives. Better lung function and greater social support were independently associated with high LS.

Leem, A. Y., Y. S. Kim, et al. (2019). **"Serum bilirubin level is associated with exercise capacity and quality of life in chronic obstructive pulmonary disease."** Respir Res **20**(1): 279.

BACKGROUND: Bilirubin has antioxidant properties against chronic respiratory diseases. However, previous studies are limited by acquisition of serum bilirubin level at one time point and its analysis with clinical parameters. We evaluated the association of serum bilirubin levels with various clinical outcomes of chronic obstructive pulmonary disease (COPD) in Korean Obstructive Lung Disease (KOLD) cohort. METHODS: We included 535 patients with COPD from the KOLD cohort. Serum bilirubin levels and various clinical parameters, such as lung function, 6-min walking (6 MW) distance, quality of life (QoL), and exacerbation, were evaluated annually; their association was analyzed using generalized estimating equations and the linear mixed model. RESULTS: Among 535 patients, 345 (64.5%) and 190 (35.5%) were categorized into Global Initiative for Chronic Obstructive Lung Disease (GOLD) I-II and GOLD III-IV groups, respectively. 6 MW distance was positively associated with serum bilirubin levels, especially in the GOLD I-II group (estimated mean = 41.5). Among QoL indexes, the COPD assessment test score was negatively associated with serum bilirubin levels only in the GOLD I-II group (estimated mean = - 2.8). Higher serum bilirubin levels were independently associated with a higher number of acute exacerbation in the GOLD III-IV group (estimated mean = 0.45, P = 0.001). Multivariate analysis revealed that lung function and mortality were not associated with serum bilirubin levels. CONCLUSIONS: Higher serum bilirubin levels were associated with a longer 6 MW distance and better QoL, especially in the GOLD I-II group, whereas they were related to a higher risk of acute exacerbation, especially in the GOLD III-IV group. Bilirubin levels may represent various conditions in COPD.

Li, K., Y. Gao, et al. (2019). **"Influence of Emphysema and Air Trapping Heterogeneity on Pulmonary Function in Patients with COPD."** Int J Chron Obstruct Pulmon Dis **14**: 2863-2872.

Purpose: To explore the influence of emphysema and air trapping heterogeneity on pulmonary function changes in patients with stable chronic obstructive pulmonary disease (COPD). Patients and methods: One hundred and seventy-nine patients with stable COPD were enrolled in this prospective study. All patients underwent low-dose inspiratory and expiratory CT scanning and pulmonary-function tests. CT quantitative data for the emphysema index (EI) on full-inspiration and air trapping (AT) on full-expiration

were measured for the whole lung, the right and left lungs, and the cranial-caudal lung zones. The heterogeneity index (HI) values for emphysema and air trapping were determined as the ratio of the difference to the sum of the respective indexes. The cranial-caudal HI and left-right lung HI were compared between mild-to-moderate (GOLD stage I and II) and severe (GOLD stage III and IV) disease groups. The associations between HI and pulmonary-function measurements adjusted for age, sex, height, smoking history, EI and AT of the total lung were assessed using multiple linear regression analysis. Results: The absolute values for cranial-caudal HI (AT_CC_HI) and left-right lung HI (AT_LR_HI) on full-expiration were significantly larger in the mild-to-moderate group, while no significant intergroup differences were observed on full-inspiration. COPD patients with lower-zone and/or left-lung predominance showed significantly lower pulmonary function than those with upper-zone and/or right-lung predominance on full-expiration, whereas no significant differences were observed on full-inspiration. The absolute values of AT_CC_HI and AT_LR_HI significantly correlated with pulmonary-function measurements. Higher AT_CC_HI and lower AT_LR_HI absolute values indicated better pulmonary function, after adjusting for age, sex, height, smoking history, EI and AT of the total lung. Conclusion: Subjects with more heterogeneous distribution and/or upper-zone predominant and/or right-lung predominant patterns on full-expiration tend to have better pulmonary function. Thus, in comparison with emphysema heterogeneity, AT heterogeneity better reflects the pulmonary function changes in COPD patients.

Lichtblau, M., M. Furian, et al. (2020). **"Right-to-left shunts in lowlanders with COPD traveling to altitude: a randomized controlled trial with dexamethasone."** J Appl Physiol (1985) **128**(1): 117-126.

Right-to-left shunts (RLS) are prevalent in patients with chronic obstructive pulmonary disease (COPD) and might exaggerate oxygen desaturation, especially at altitude. The aim of this study was to describe the prevalence of RLS in patients with COPD traveling to altitude and the effect of preventive dexamethasone. Lowlanders with COPD [Global Initiative for Chronic Obstructive Lung Disease (GOLD) grades 1-2, oxygen saturation assessed by pulse oximetry (SpO2) >92%] were randomized to dexamethasone (4 mg bid) or placebo starting 24 h before ascent from 760 m and while staying at 3,100 m for 48 h. Saline-contrast echocardiography was performed at 760 m and after the first night at altitude. Of 87 patients (81 men, 6 women; mean +/- SD age 57 +/- 9 yr, forced expiratory volume in 1 s 89 +/- 22% pred, SpO2 95 +/- 2%), 39 were assigned to placebo and 48 to dexamethasone. In the placebo group, 19 patients (49%) had RLS, of which 13 were intracardiac. In the dexamethasone group 23 patients (48%) had RLS, of which 11 were intracardiac (P = 1.0 vs. dexamethasone). Eleven patients receiving placebo and 13 receiving dexamethasone developed new RLS at altitude (P = 0.011 for both changes, P = 0.411 between groups). RLS prevalence at 3,100 m was 30 (77%) in the placebo and 36 (75%) in the dexamethasone group (P = not significant). Development of RLS at altitude could be predicted at lowland by a higher resting pulmonary artery pressure, a lower arterial partial pressure of oxygen, and a greater oxygen desaturation during exercise but not by treatment allocation. Almost half of lowlanders with COPD revealed RLS near sea level, and this proportion significantly increased to about three-fourths when traveling to 3,100 m irrespective of dexamethasone prophylaxis.NEW & NOTEWORTHY The prevalence of intracardiac and intrapulmonary right-to-left shunts (RLS) at altitude in patients with chronic obstructive pulmonary disease (COPD) has not been studied so far. In a large cohort of patients with moderate COPD, our randomized trial showed that the prevalence of RLS increased from 48% at 760 m to 75% at 3,100 m in patients taking placebo. Preventive treatment with dexamethasone did not significantly reduce the altitude-induced recruitment of RLS. Development of RLS at 3,100 m could be predicted at 760 m by a higher resting pulmonary artery pressure and arterial partial pressure of oxygen and a more pronounced oxygen desaturation during exercise. Dexamethasone did not modify the RLS prevalence at 3,100 m.

Lim, C. G., K. M. Shin, et al. (2020). **"Emphysema is associated with the aggressiveness of COPD-related adenocarcinomas."** Clin Respir JOBJECTIVES: To compare the differences in radiologic and pathologic features of surgically resected COPD-related adenocarcinomas according to the presence of emphysema. METHODS: A total of 216 smokers with surgically resected lung adenocarcinoma were included in this retrospective study, and 102 patients were diagnosed with COPD. We classified COPD patients as emphysematous or non-emphysematous group based on the emphysema severity on CT and evaluated the differences in the CT and pathologic features between the 2 groups. The relationship between emphysema and disease-free survival was assessed using a Kaplan-Meier curve. RESULTS: Lung adenocarcinomas in emphysema group presented a more aggressive pathologic grade and higher prevalence of solid lesions (versus subsolid lesions) on CT than those in non-emphysematous group (p = 0.006 and <0.001, respectively). After adjustment for age, sex, smoking pack-years, and tumor size, emphysema group had a greater risk for higher histologic grade and higher prevalence of solid lesions than non-emphysema group (odds ratio, 3.445; 95% confidence interval, 1.124 - 10.564; p = 0.030, odds ratio, 6.192; 95% confidence interval, 1.804-21.254; p = 0.004, respectively). Kaplan-Meier survival curves showed that patients with emphysema had significantly impaired disease-free survival compared with those without emphysema (median disease-free survival = 37.0 vs. 57.5 months, p =0.038). CONCLUSION: Adenocarcinomas in emphysema-present COPD had more aggressive features of pathology and CT findings, and worse disease-free survival than those without emphysema. These findings might provide an insight into the different pathobiology and prognostic implications of lung adenocarcinomas according to the presence of emphysema in patients with COPD.

Lim, S. Y., G. Lim, et al. (2019). **"Ultrasound Assessment Of Diaphragmatic Function During Acute Exacerbation Of Chronic Obstructive Pulmonary Disease: A Pilot Study."** Int J Chron Obstruct Pulmon Dis **14**: 2479-2484.

Purpose: Impairment of diaphragmatic function is one of the main pathophysiological mechanisms of chronic obstructive pulmonary disease (COPD) and is known to be related to acute exacerbation. Ultrasonography (US) allows for a simple, non-invasive assessment of diaphragm kinetics. The purpose of this study was to investigate the changes in diaphragmatic function during acute exacerbation of COPD, by US. Methods: This single-center, prospective study included patients with acute exacerbation of COPD symptoms. US measurements were performed within 72 hrs after exacerbation and after improvement of symptoms. Diaphragmatic excursion and its thickening fraction (TF) were measured as markers of diaphragmatic function. TF was calculated as (thickness at end inspiration - thickness at end expiration)/thickness at end expiration. Results: Ten patients were enrolled. All patients were male, and the mean age was 79.8 years. The TF of the right diaphragm showed a significant increase from the initial to the follow-up values (80.1 +/- 104.9 mm vs. 159.5 +/- 224.6 mm, p = 0.011); however, the diaphragmatic excursion did not vary significantly between the initial and follow-up values (22 +/- 6 mm vs 23 +/-12 mm). The change in excursion between the stable and exacerbation periods was positively correlated with time to the next exacerbation and negatively correlated with the time taken to recover from the exacerbation. Conclusion: These data support the possibility that a defect in diaphragm thickening is related to acute exacerbation of COPD.

Lisspers, K., K. Larsson, et al. (2019). **"Gender differences among Swedish COPD patients: results from the ARCTIC, a real-world retrospective cohort study."** NPJ Prim Care Respir Med **29**(1): 45.

The present study aimed to generate real-world evidence regarding gender differences among chronic obstructive pulmonary disease (COPD) patients, especially as regards the diagnosis and outcomes in order to identify areas for improvement and management and optimize the associated healthcare resource allocation. ARCTIC is a large, real-world, retrospective cohort study conducted in Swedish COPD patients and a matched reference population from 52 primary care centers in 2000-2014. The

incidence of COPD, prevalence of asthma and other comorbidities, risk of exacerbations, mortality rate, COPD drug prescriptions, and healthcare resource utilization were analyzed. In total, 17,479 patients with COPD were included in the study. During the study period, COPD was more frequent among women (53.8%) and women with COPD experienced more exacerbations vs. men (6.66 vs. 4.66). However, the overall mortality rate was higher in men compared with women (45% vs. 38%), but no difference for mortality due to COPD was seen between genders over the study period. Women seemed to have a greater susceptibility to asthma, fractures, osteoporosis, rheumatoid arthritis, rhinitis, depression, and anxiety, but appeared less likely to have diabetes, kidney diseases, and cardiovascular diseases. Furthermore, women had a greater risk of COPD-related hospitalization and were likely to receive a significantly higher number of COPD drug prescriptions compared with men. These results support the need to reduce disease burden among women with COPD and highlight the role of healthcare professionals in primary care who should consider all these parameters in order to properly diagnose and treat women with COPD.

Liu, M., Y. Yue, et al. (2019). **"Association between chronic obstructive pulmonary disease and activity of daily living among oldest-old in China: based on Chinese Longitudinal Health Longevity Survey."** Int J Chron Obstruct Pulmon Dis **14**: 1959-1966.

Aims: This study was designed to investigate the association between COPD and activity of daily living among oldest-old in People's Republic of China. Patients and methods: The data of Chinese Longitudinal and Health Longevity Study in 2014 was used, and those who were aged more than 80 years old were included. Both basic activity of daily living (BADL) and instrumental activity of daily living (IADL) were measured. Results: A total of 4621 oldest-old (>/=80 years old) were included. 32.1% (1482) of the oldest-old had BADL disability and 79.0% (3129) had IADL disability. The BADL disability and IADL disability rates were higher for participants with COPD than those without, and this difference was more robust among male (31.8% vs 25.6%, p=0.018). The IADL disability rate showed similar trends. Multivariate logistic regression analysis showed that the odds ratios of COPD on BADL disability and IADL disability were 1.261 (95% CI: 1.044-1.525) and 2.014 (95% CI: 1.561-2.598), respectively. The odds ratios of COPD on moderate to severe BADL disability and IADL disability were 1.007 (95% CI: 0.790-1.284) and 1.713 (95% CI: 1.397-2.100), respectively. Conclusion: There were independent associations between COPD and disability among oldest-old in People's Republic of China, and the associations were greater among male population. Besides, COPD had a profound influence on the mild disability of BADL, while had a greater impact on the moderate and severe disability of IADL.

Long, G. H., T. Southworth, et al. (2020). **"The stability of blood Eosinophils in chronic obstructive pulmonary disease."** Respir Res **21**(1): 15.

Blood eosinophils are a predictive biomarker of inhaled corticosteroid response in chronic obstructive pulmonary disease (COPD). We investigated blood eosinophil stability over 1 year using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2019 thresholds of < 100, 100- < 300 and >/= 300 eosinophils/muL in 225 patients from the COPDMAP cohort. Blood eosinophils showed good stability (rho: 0.71, p < 0.001, ICC 0.84), and 69.3% of patients remained in the same eosinophil category at 1 year. 85.3% of patients with eosinophils < 100 cells/muL had stable counts. The majority of blood eosinophil counts remain stable over 1 year using the GOLD 2019 thresholds.

Manon-Jensen, T., L. L. Langholm, et al. (2019). **"End-product of fibrinogen is elevated in emphysematous chronic obstructive pulmonary disease and is predictive of mortality in the ECLIPSE cohort."** Respir Med **160**: 105814.

BACKGROUND: Chronic obstructive pulmonary disease (COPD) is characterized by abnormal epithelial repair process that may result in intra-airway accumulation of fibrin. Given that plasma fibrinogen is the only FDA approved biomarker that predicts mortality and COPD exacerbations, we hypothesized that changes in the processing of fibrinogen may provide additional characterization of disease phenotype and COPD progression. METHODS: A subpopulation of subjects with COPD, (n=983) smoker (n=205) and non-smoker controls (n=98) were included from The Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE) cohort. Two biomarkers that specifically target the thrombin-mediated conversion of fibrinogen into fibrin (PRO-FIB), and plasmin-mediated degradation of cross-linked fibrin (X-FIB) were measured and compared with fibrinogen measurements. RESULTS: X-FIB had a predictive value for two-year mortality, with an adjusted hazard ratio of 1.48 per SD (n=980; 95% CI 1.18-1.84; p<0.0001), and comparable to the fibrinogen hazard ratio of 1.59 per SD (n=983; 95% CI 1.29-1.96; p=0.0003). X-FIB (p<0.001), fibrinogen (p<0.0001) and PRO-FIB (p<0.05) were significantly elevated in symptomatic COPD (mMRC>/=2) as compared to asymptomatic COPD. X-FIB was the only biomarker that was associated with emphysema (p<0.001), and only plasma fibrinogen (p<0.05) was associated with exacerbations. CONCLUSION: There is a need for biomarkers to characterize the heterogeneity of COPD, to continuously improve clinical trial design and to identify disease progressors for efficient health care utilization. Each of three fibrinogen biomarkers studied provide information representing distinct aspects of COPD which may be used to characterize disease endotypes and to assess mortality risk in COPD.

Marietta von Siemens, S., P. Alter, et al. (2019). **"CAT score single item analysis in patients with COPD: Results from COSYCONET."** Respir Med **159**: 105810.

The COPD Assessment Test (CAT) is in widespread use for the evaluation of patients with chronic obstructive pulmonary disease (COPD). We assessed whether the CAT items carry additional information beyond the sum score regarding COPD characteristics including emphysema. Patients of GOLD grades 1 to 4 from the COPD cohort COSYCONET (German COPD and Systemic Consequences - Comorbidities Network) with complete CAT data were included (n=2270), of whom 493 had chest CT evaluated for the presence of emphysema. Comorbidities and lung function were assessed following standardised procedures. Cross-sectional data analysis was based on multiple regression analysis of the single CAT items against a panel of comorbidities, lung function, or CT characteristics (qualitative score, 15th percentile of mean lung density), with age, BMI and gender as covariates. This was supported by exploratory factor analysis. Regarding the relationship to comorbidities and emphysema, there were marked differences between CAT items, especially items 1 and 2 versus 3 to 8. This grouping was basically confirmed by factor analysis. Items 4 and 5, and to a lower degree 1, 2 and 6, appeared to be informative regarding the presence of emphysema, whereas the total score was not or less informative. Regarding comorbidities, similar findings as for the total CAT score were obtained for the modified Medical Research Council scale (mMRC) which was also informative regarding emphysema. Our findings suggest that the usefulness of the CAT can be increased if evaluated on the basis of single items which may be indicating the presence of comorbidities and emphysema.

Martinez-Garcia, M. A., R. Faner, et al. (2020). **"Inhaled Steroids, Circulating Eosinophils, Chronic Airway Infection and Pneumonia Risk in Chronic Obstructive Pulmonary Disease: A Network Analysis."** Am J Respir Crit Care MedRATIONALE: Treatment of chronic obstructive pulmonary disease (COPD) with inhaled corticosteroids (ICS) is controversial because it can reduce the risk of future exacerbations of the disease at the expense of increasing the risk of pneumonia. OBJECTIVE: To assess the relationship

between the presence of chronic bacterial infection (CBI), reduced number of circulating eosinophils, ICS treatment and the risk of pneumonia in COPD patients. METHODS AND MEASUREMENTS: Post-hoc long-term observational study of an historical cohort of 201 COPD patients (GOLD II-IV) who were carefully characterized (including airway microbiology) and followed for a median of 84 months. Results were analysed by multivariate Cox regression and network analysis. MAIN RESULTS: Mean age was 70.3 years, 90.5% of patients were male, mean FEV1 was 49%, 71.6% of patients were treated with ICS, 57.2% of them had bronchiectasis and 20.9% <100 blood eosinophils/microL. Pathogenic microorganisms were isolated in 42.3% of patients (22.4% of patients fulfilled the definition of chronic bronchial infection (CBI). During follow-up, 38.8% of patients suffered >/=1 pneumonia, CBI (HR, 1.635) and <100 eosinophils/microL (HR, 1.975) being independently associated with the risk of pneumonia, particularly when both coexist (HR, 3.126). ICS treatment increased the risk of pneumonia in those patients with <100 eosinophils/microL and CBI (HR, 2.925). CONCLUSIONS: Less than 100 circulating eosinophils/L combined with the presence of CBI increase the risk of pneumonia in COPD patients treated with ICS.

Matsuda, Y., T. Morita, et al. (2019). **"Morphine for dyspnoea in chronic obstructive pulmonary disease: a before-after efficacy study."** BMJ Support Palliat CareOBJECTIVES: Dyspnoea in patients with chronic obstructive pulmonary disease (COPD) is frequent and often persists despite conventional treatment. This study aimed to evaluate the efficacy and safety of oral morphine for dyspnoea in Japanese COPD patients. METHODS: We conducted a multi-institutional, prospective, before-after study of morphine in COPD patients with dyspnoea at rest in seven hospitals. Patients received 12 mg of oral morphine per day (or 8 mg per day if low body weight or renal impairment). Primary outcome was change in the numerical rating scale (NRS) of current dyspnoea in the evening from Day 0 to Day 2. Secondary outcomes included changes in dyspnoea intensity in the evening from Day 0 to Day 1, dyspnoea intensity between the morning from Day 0 to Day 1 and Day 2, vital signs, nausea, somnolence, anorexia and other adverse events (AEs). RESULTS: A total of 35 patients were enrolled in this study between October 2014 and January 2018. One patient did not receive study treatment. Data from 34 patients was analysed. The NRS of dyspnoea intensity in the evening significantly decreased from 3.9 on Day 0 (95% CI: 3.1 to 4.8) to 2.4 on Day 2 (95% CI: 1.7 to 3.1; p=0.0002). Secondary outcomes significantly improved in a similar manner. There were no apparent changes in the mean scores of the opioid-related AEs and vital signs. One patient experienced grade 3 lung infection not associated with morphine. Other AEs were mild. CONCLUSION: Oral morphine is effective in alleviating dyspnoea in Japanese COPD patients.Trial registrationUMIN000015288 (http://www.umin.ac.jp/ctr/index.htm).

McDonald, C. F. (2020). **"Eosinophils in chronic obstructive pulmonary disease: are they just another biomarker?"** Curr Opin Pulm MedPURPOSE OF REVIEW: Interest in blood eosinophils as a biomarker of responsiveness to therapy in chronic obstructive pulmonary disease (COPD) continues to grow, with recommendations regarding their adjunctive use incorporated into the GOLD 2019 treatment algorithm. The present review summarizes some key recent papers referencing differential treatment effects based on blood eosinophil counts. RECENT FINDINGS: Post-hoc analyses of trials of inhaled corticosteroids in COPD have shown greater treatment responses in patients with higher blood eosinophil levels, with some exceptions. Eosinophil-directed treatment with oral corticosteroids showed equivalent benefits to noneosinophil-directed therapy, with reduced corticosteroid exposure. Prespecified analyses of recent prospective trials of therapies incorporating inhaled corticosteroids were generally supportive of previous findings, so evidence for the use of blood eosinophils as biomarkers is gathering. Nonetheless, the anti-interleukin (IL)-5 receptor antagonist benralizumab, which depletes blood eosinophils, showed no treatment benefit in patients with COPD selected for eosinophilic phenotype and treatment of COPD with the IL-5 antagonist, mepolizumab showed inconsistent results. SUMMARY: The 2019 GOLD COPD Strategy document embraced the use of the blood eosinophil to guide ICS therapy in management of

patients with stable COPD and frequent exacerbations. Although post-hoc and several prospective studies with prespecified subgroup analyses have supported this approach, questions still remain about how to incorporate this new assessment tool into real-life management of COPD and more research is required to validate its adoption into clinical practice. There is an absence of data to support the use of biologic therapy in patients with an eosinophilic COPD phenotype at this stage.

McKay, G. J., R. V. McCarter, et al. (2020). **"Simple non-mydriatic retinal photography is feasible and demonstrates retinal microvascular dilation in Chronic Obstructive Pulmonary Disease (COPD)."** PLoS One **15**(1): e0227175.

BACKGROUND: Chronic Obstructive Pulmonary Disease (COPD) is associated with an increased risk of myocardial infarction and stroke but it remains unclear how to identify microvascular changes in this population. OBJECTIVES: We hypothesized that simple non-mydriatic retinal photography is feasible and can be used to assess microvascular damage in COPD. METHODS: Novel Vascular Manifestations of COPD was a prospective study comparing smokers with and without COPD, matched for age. Non-mydriatic, retinal fundus photographs were assessed using semi-automated software. RESULTS: Retinal images from 24 COPD and 22 control participants were compared. Cases were of similar age to controls (65.2 vs. 63.1 years, p = 0.38), had significantly lower Forced Expiratory Volume in one second (FEV1) (53.4 vs 100.1% predicted; p < 0.001) and smoked more than controls (41.7 vs. 29.6 pack years; p = 0.04). COPD participants had wider mean arteriolar (155.6 +/-15 uM vs. controls [142.2 +/- 12 uM]; p = 0.002) and venular diameters (216.8 +/-20.7 uM vs. [201.3+/- 19.1 uM]; p = 0.012). Differences in retinal vessel caliber were independent of confounders, odds ratios (OR) = 1.08 (95% confidence intervals [CI] = 1.02, 1.13; p = 0.007) and OR = 1.05 (CI = 1.01, 1.09; p = 0.011) per uM increase in arteriolar and venular diameter respectively. FEV1 remained significantly associated with retinal vessel dilatation r = -0.39 (p = 0.02). CONCLUSIONS: Non-mydriatic retinal imaging is easily facilitated. We found significant arteriole and venous dilation in COPD compared to age-matched smokers without COPD associated with lung function independent of standard cardiovascular risk factors. Retinal microvascular changes are known to be strongly associated with future vascular events and retinal photography offers potential to identify this risk. TRIAL REGISTRATION: clinicaltrials.gov NCT02060292.

Menga, G., M. Fernandez Acquier, et al. (2019). **"Prevalence of Alpha-1 Antitrypsin Deficiency in COPD Patients in Argentina. The DAAT.AR Study."** Arch BronconeumolINTRODUCTION: Alpha-1 antitrypsin deficiency (AATD) is still underdiagnosed, despite the recommendation to determine AAT in patients with chronic obstructive pulmonary disease (COPD). OBJECTIVE: To estimate the prevalence of AATD in COPD patients adjusted according to the population of the COPD prevalence study in Argentina (EPOC.AR). MATERIAL AND METHODS: This was a multicenter prospective cross-sectional study of a population aged>/=30 years of age diagnosed with COPD, involving AAT quantification in dry blood spot and subsequent genotyping in subjects with<1.5mg/dL AAT in dry blood spot (<80mg/dL in serum). AAT was defined as the detection of variants ZZ or SZ on genotyping. The EPOC.AR study population was used to calculate local adjusted prevalence. RESULTS: We included 3,254 patients (544 with AAT<80mg/dL) with a spirometric diagnosis of COPD. The prevalence of AATD in the total study population was 1.29% (95% CI 0.93-1.74), of which 0.92% (95% CI 0.62-1.31) were Pi*ZZ and 0.37% (95% CI 0.19-0.64) Pi*SZ. The adjusted prevalence of AATD in COPD patients>/=40 years of age was 0.83% (95% CI 0.23-2.08). We found that AATD was negatively associated with age (OR 0.94; 95% CI 0.90-0.98; P=.006), smoking habit (OR 0.98; 95% CI 0.96-0.99; P=.009), and FEV1% (OR 0.95; 95% CI 0.91-0.99; P=.015). CONCLUSIONS: The prevalence of AATD in the adult population with COPD in Argentina is estimated to be 0.83%, which could represent 17,000 cases in our country.

Milan, S., P. Bondalapati, et al. (2019). **"Positive Expiratory Pressure Therapy With And Without Oscillation And Hospital Length Of Stay For Acute Exacerbation Of Chronic Obstructive Pulmonary Disease."** Int J Chron Obstruct Pulmon Dis **14**: 2553-2561.

Introduction: Pharmacologic management of acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is well-established. Our aim in the current study is to determine if therapy with a positive expiratory pressure (PEP) device with or without an oscillatory mechanism (OM) in addition to standard care results in a reduction in hospital length of stay (LOS) among patients hospitalized for AECOPD. Methods: Two studies were performed and are reported here. Study 1: Patients admitted with AECOPD and sputum production were enrolled in a prospective trial comparing PEP therapy versus Oscillatory PEP (OPEP) therapy. Study 2: A retrospective historical cohort, matched in a 2 to 1 manner by age, gender, and season of admission, was compared with the prospectively collected data to determine the effect of PEP +/- OM versus standard care on hospital LOS. Results: In the prospective trial (Study 1; 91 subjects), median hospital LOS was 3.2 (95% CI 3.0-4.3) days in the OPEP group and 4.8 (95% CI 3.9-6.1) days in the PEP group (p=0.16). In fully adjusted models comparing the prospective trial data with the retrospective cohort (Study 2; 182 subjects), cases had a median hospital LOS of 4.2 days (95% CI 3.8-5.1) versus 5.2 days (95% CI 4.4-6.0) in controls, consistent with a shorter hospital LOS with adjunctive PEP+/-OM therapy versus standard care (p=0.04). Conclusion: Adjunctive therapy with a PEP device versus standard care may reduce hospital LOS in patients admitted for AECOPD. Although the addition of an OM component to PEP therapy suggests a further reduction in hospital LOS, comprehensive multicenter randomized controlled trials are needed to confirm these findings. Clinical trial registration number: NCT03094806.

Molinos-Castro, S., P. M. Pesqueira-Fontan, et al. (2020). **"Clinical factors associated with pulmonary aspergillosis in patients with chronic obstructive pulmonary disease."** Enferm Infecc Microbiol Clin **38**(1): 4-10.

OBJECTIVE: To explore the clinical and epidemiological characteristics of chronic obstructive pulmonary disease (COPD) patients with Aspergillus spp. isolation from respiratory samples, and to identify which factors may help us to distinguish between colonisation and infection. METHODS: A retrospective cohort study was performed. All patients with COPD and respiratory isolation of Aspergillus spp. over a 12-year period were included. Patients were assigned to 2 categories: colonisation and pulmonary aspergillosis (PA), which includes the different clinical forms of aspergillosis. A binary logistic regression model was performed to identify the predictive factors of PA. RESULTS: A total of 123 patients were included in the study: 48 (39.0%) with colonisation and 75 (61.0%) with PA: 68 with probable invasive pulmonary aspergillosis and 7 with chronic pulmonary aspergillosis. Spirometric stages of the GOLD classification were not correlated with a higher risk of PA. Four independent predictive factors of PA in COPD patients were identified: home oxygen therapy (OR: 4.39; 95% CI: 1.60-12.01; P=.004), bronchiectasis (OR: 3.61; 95% CI: 1.40-9.30; P=.008), hospital admission in the previous three months (OR: 3.12; 95% CI: 1.24-7.87; P=.016) and antifungal therapy against Candida spp. in the previous month (OR: 3.18; 95% CI: 1.16-8.73; P=.024). CONCLUSIONS: Continuous home oxygen therapy, bronchiectasis, hospital admission in the previous three months and administration of antifungal medication against Candida spp. in the previous month were associated with a higher risk of pulmonary aspergillosis in patients with COPD.

Monton, C., E. Prina, et al. (2019). **"Nebulized Colistin And Continuous Cyclic Azithromycin In Severe COPD Patients With Chronic Bronchial Infection Due To Pseudomonas aeruginosa: A Retrospective Cohort Study."** Int J Chron Obstruct Pulmon Dis **14**: 2365-2373.

Introduction: Long-term use of nebulized or oral antibiotics is common in the treatment of cystic fibrosis and non-cystic fibrosis bronchiectasis. To date, however, few studies have focused on the use of nebulized antibiotics in COPD patients. The aims of this study are: to establish whether a combination of nebulized colistin plus continuous cyclic azithromycin in severe COPD patients with chronic bronchial infection due to Pseudomonas aeruginosa reduces the frequency of exacerbations, and to assess the effect of this treatment on microbiological sputum isolates. Material and methods: A retrospective cohort was created for the analysis of patients with severe COPD and chronic bronchial infection due to P. aeruginosa treated with nebulized colistin at the Respiratory Day Care Unit between 2005 and 2015. The number and characteristics of COPD exacerbations (ECOPD) before and up to two years after the introduction of nebulized colistin treatment were recorded. Results: We analyzed 32 severe COPD patients who received nebulized colistin for at least three months (median 17 months [IQR 7-24]). All patients but one received combination therapy with continuous cyclic azithromycin (median 24 months [IQR 11-30]). A significant reduction in the number of ECOPD from baseline of 38.3% at two years of follow-up was observed, with a clear decrease in P. aeruginosa ECOPD (from 59.5% to 24.6%) and a P. aeruginosa eradication rate of 28% over the two-year follow-up. Conclusion: In patients with severe COPD and chronic bronchial infection due to P. aeruginosa, combination therapy with nebulized colistin and continuous cyclic azithromycin significantly reduced the number of ECOPD, with a marked decrease in P. aeruginosa sputum isolates.

Morais, L. A., S. Cavalcante, et al. (2020). **"Evaluating the disease and treatment information provided to patients with chronic obstructive pulmonary disease at the time of discharge according to GOLD discharge guidelines."** Einstein (Sao Paulo) **18**: eAO4706.

OBJECTIVE: To evaluate the disease and treatment information provided to patients with chronic obstructive pulmonary disease at hospital discharge. METHODS: This was a cross-sectional study including hospitalized patients with chronic obstructive pulmonary disease at three tertiary hospitals. The study was based on seven items of the Global Initiative for Obstructive Lung Disease (GOLD) discharge guidelines. Two hospitals in this study had a Medical Residency Program in Pulmonology, and one did not have the program. RESULTS: Fifty-four patients were evaluated. Large amounts of information were provided concerning effective pharmacological maintenance (item 1), blood gas evaluation/measurement of oxygen saturation (item 2), assessment of inhalation technique (item 4), and maintenance therapy (item 5). Less information was provided regarding comorbidity management planning (item 3), the completion of antibiotic/corticosteroid therapy (item 6) and follow-up with the attending physician or specialist (item 7) had less information. We observed significant differences between hospitals for items 1, 4 and 7, and better performance in hospitals with medical residency in pulmonology. CONCLUSION: Hospitalized patients with chronic obstructive pulmonary disease received little to no information about the seven items addressed by GOLD discharge guidelines. This finding suggests that these guidelines should be used more often by clinicians in hospital with or without medical residency in pulmonology. The lack of specialized care resulted in insufficient amount of information for patients with chronic obstructive pulmonary disease at discharge.

Muellers, K. A., L. Chen, et al. (2019). **"Health Literacy and Medication Adherence in COPD Patients: When Caregiver Presence Is Not Sufficient."** Copd **16**(5-6): 362-367.

Limited health literacy (HL) is associated with a lower medication adherence in patients with chronic obstructive pulmonary disease (COPD). In this study, we examined the potential mitigating role of caregiver support on the relationship between HL and adherence to COPD medications. We conducted a prospective

observational study of adults with COPD and their caregivers. HL was assessed using the Short Test of Functional Health Literacy in Adults (S-TOFHLA) and COPD medication adherence was evaluated with the Medication Adherence Rating Scale (MARS). We also collected caregiver HL data for a subset of participants. We tested whether having a caregiver impacted the relationship between HL and medication adherence using cross-sectional data collected between 2011 and 2015. Our sample included 388 COPD patients and 97 caregivers. COPD patients with low HL had a lower medication adherence (odds ratio [OR]: 0.44, 95% confidence interval [CI]: 0.24-0.81) after adjusting for sociodemographic factors. Caregiver presence was not associated with increased patient medication adherence (OR: 1.28, 95% CI: 0.79-2.08). Among the subset of patients with caregivers, low patient HL remained associated with a lower medication adherence (OR: 0.28, 95% CI: 0.09-0.82) when adjusted for caregiver HL and sociodemographic factors. Low HL is associated with lower COPD medication adherence, and this effect is not mitigated by the presence of a caregiver. These findings suggest a need for effective strategies to manage high-risk COPD patients with low HL, even among those with adequate support from caregivers, and to design interventions for both patients and caregivers with low HL.

Omlor, A. J., F. C. Trudzinski, et al. (2019). **"Time-updated resting heart rate predicts mortality in patients with COPD."** Clin Res CardiolHigh resting heart rate (RHR) is associated with higher mortality in the general population and in cardiovascular disease. Less is known about the association of RHR with outcome in chronic obstructive pulmonary disease (COPD). In particular, the time-updated RHR (most recent value before the event) appears informative. This is the first study to investigate the association of time-updated RHR with mortality in COPD. We compared the baseline and time-updated RHR related to survival in 2218 COPD patients of the German COSYCONET cohort (COPD and Systemic Consequences-Comorbidities Network). Patients with a baseline RHR > 72 beats per minute (bmp) had a significantly (p = 0.049) higher all-cause mortality risk (adjusted hazard ratio (HR) of 1.37 (1.00-1.87) compared to baseline RHR </= 72 bpm. The time-updated RHR > 72 bpm was markedly superior (HR 1.79, 1.30-2.46, p = 0.001). Both, increased baseline and time-updated RHR, were independently associated with low FEV1, low TLCO, a history of diabetes, and medication with short-acting beta agonists (SABAs). In conclusion, increased time-updated RHR is associated with higher mortality in COPD independent of other predictors and superior to baseline RHR. Increased RHR is linked to lung function, comorbidities and medication. Whether RHR is an effective treatment target in COPD, needs to be proven in controlled trials.

Ortega, V. E., X. Li, et al. (2019). **"The Effects of Rare SERPINA1 Variants on Lung Function and Emphysema in SPIROMICS."** Am J Respir Crit Care MedRATIONALE: The role of PI type Z heterozygotes and additional, rare variant genotypes in the gene encoding alpha1-antitrypsin (SERPINA1) in determining the COPD risk and severity is controversial. OBJECTIVE: To comprehensively evaluate the effects of rare SERPINA1 variants on lung function and emphysema phenotypes in subjects with significant tobacco smoke exposure using deep gene resequencing and alpha1-antitrypsin concentrations. METHODS: DNA samples from 1,693 non-Hispanic Whites, 385 African Americans, and 90 Hispanics with >/=20 pack-years smoking were resequenced for the identification of rare variants (allele frequency<0.05) in 16.9kB of SERPINA1. MEASUREMENTS AND MAIN RESULTS: White PI Z heterozygotes confirmed by sequencing (MZ, N=74) had lower post-bronchodilator FEV1 (p=0.007), FEV1/FVC (p=0.003), and greater CT-based emphysema (p=0.02) compared to 1,411 Whites without PI Z, S, or additional, rare variants denoted as VR. PI Z-containing compound heterozygotes (ZS/ZVR, N=7) had lower FEV1/FVC (p=0.02) and FEF25-75% (p=0.009). 19 Whites heterozygote for five non-S/Z coding variants associated with lower alpha1-antitrypsin had greater CT-based emphysema compared to those without rare variants. In African Americans, a 5' untranslated region insertion (rs568223361) associated with lower alpha1-antitrypsin and

functional small airways disease (p=0.007). CONCLUSIONS: In this integrative deep sequencing study of SERPINA1 with alpha1-antitrypsin concentrations in a heavy smoker and COPD cohort, we confirmed the effects of PI Z heterozygote and compound heterozygote genotypes. We demonstrate the cumulative effects of multiple SERPINA1 variants on alpha1-antitrypsin deficiency, lung function, and emphysema, thus, significantly increasing the frequency of SERPINA1 variation associated with respiratory disease in at-risk smokers.

Park, J., B. D. Hobbs, et al. (2020). **"Subtyping COPD by Using Visual and Quantitative CT Imaging Features."** Chest **157**(1): 47-60.

BACKGROUND: Multiple studies have identified COPD subtypes by using visual or quantitative evaluation of CT images. However, there has been no systematic assessment of a combined visual and quantitative CT imaging classification. We integrated visually defined patterns of emphysema with quantitative imaging features and spirometry data to produce a set of 10 nonoverlapping CT imaging subtypes, and we assessed differences between subtypes in demographic features, physiological characteristics, longitudinal disease progression, and mortality. METHODS: We evaluated 9,080 current and former smokers in the COPDGene study who had available volumetric inspiratory and expiratory CT images obtained using a standardized imaging protocol. We defined 10 discrete, nonoverlapping CT imaging subtypes: no CT imaging abnormality, paraseptal emphysema (PSE), bronchial disease, small airway disease, mild emphysema, upper lobe predominant centrilobular emphysema (CLE), lower lobe predominant CLE, diffuse CLE, visual without quantitative emphysema, and quantitative without visual emphysema. Baseline and 5-year longitudinal characteristics and mortality were compared across these CT imaging subtypes. RESULTS: The overall mortality differed significantly between groups ($P < .01$) and was highest in the 3 moderate to severe CLE groups. Subjects having quantitative but not visual emphysema and subjects with visual but not quantitative emphysema were unique groups with mild COPD, at risk for progression, and with likely different underlying mechanisms. Subjects with PSE and/or moderate to severe CLE had substantial progression of emphysema over 5 years compared with findings in subjects with no CT imaging abnormality ($P < .01$). CONCLUSIONS: The combination of visual and quantitative CT imaging features reflects different underlying pathological processes in the heterogeneous COPD syndrome and provides a useful approach to reclassify types of COPD. TRIAL REGISTRY: ClinicalTrials.gov; No.: NCT00608764; URL: www.clinicaltrials.gov.

Patel, H. C., C. Hayward, et al. (2020). **"Impact on survival of combination inhalers in patients with COPD at high risk of cardiovascular events."** Int J Cardiol **300**: 237-244.

BACKGROUND: Chronic obstructive pulmonary disease (COPD) and cardiovascular disease often co-exist and are both leading causes of death worldwide. Published data have previously suggested trends toward improved survival for patients taking long-acting beta agonists combined with inhaled corticosteroids (LABA-ICS) through beneficial actions on the respiratory and cardiovascular systems. We sought to explore this in a real-world setting. METHODS: A population-based longitudinal propensity score-matched cohort study was conducted in the United Kingdom, 1998-2015. Patients were identified from the Clinical Practice Research Datalink (CPRD) which is linked to Hospital Episode Statistics (HES) and Office for National Statistics (ONS) mortality records. All patients had a validated diagnosis of COPD and were at high risk for cardiovascular events (history of myocardial infarction, diabetes mellitus, ischaemic heart disease, stroke and peripheral arterial disease). The primary outcome was all-cause mortality. RESULTS: The treatment group was composed of 2687 new users of LABA-ICS with COPD and comparisons were made in a control population of 2687 COPD patients prescribed LABAs alone. At three years follow-up death occurred in 358 (13.3%) patients in the treatment group and 427 (15.9%) patients in the control group. The use of LABA-ICS was modestly associated with improved survival compared to use of LABAs (hazard ratio 0.82, 95% CI 0.71-0.95, $P = 0.007$). CONCLUSIONS: Among patients with

COPD with either established cardiovascular disease or at high risk of an index cardiovascular event, LABA-ICS inhaled therapy, compared with LABAs alone, was associated with a significantly improved survival.

Perea, L., A. Rodrigo-Troyano, et al. (2020). **"Reduced airway levels of fatty-acid binding protein 4 in COPD: relationship with airway infection and disease severity."** Respir Res **21**(1): 21.

BACKGROUND: For still unclear reasons, chronic airway infection often occurs in patients with Chronic Obstructive Pulmonary Disease (COPD), particularly in those with more severe airflow limitation. Fatty-acid binding protein 4 (FABP4) is an adipokine involved in the innate immune response against infection produced by alveolar macrophages (M). We hypothesized that airway levels of FABP4 may be altered in COPD patients with chronic airway infection. METHODS: In this prospective and controlled study we: (1) compared airway FABP4 levels (ELISA) in induced sputum, bronchoalveolar lavage fluid (BALF) and plasma samples in 52 clinically stable COPD patients (65.2 +/- 7.9 years, FEV1 59 +/- 16% predicted) and 29 healthy volunteers (55.0 +/- 12.3 years, FEV1 97 +/- 16% predicted); (2) explored their relationship with the presence of bacterial airway infection, defined by the presence of potentially pathogenic bacteria (PPB) at >/=10(3) colony-forming units/ml in BALF; (3) investigated their relationship with the quantity and proportion of M in BALF (flow cytometry); and, (4) studied their relationship with the severity of airflow limitation (FEV1), GOLD grade and level of symptoms (CAT questionnaire). RESULTS: We found that: (1) airway levels of FABP4 (but not plasma ones) were reduced in COPD patients vs. controls [219.2 (96.0-319.6) vs. 273.4 (203.1-426.7) (pg/ml)/protein, p = 0.03 in BALF]; (2) COPD patients with airway infection had lower sputum FABP4 levels [0.73 (0.35-15.3) vs. 15.6 (2.0-29.4) ng/ml, p = 0.02]; (3) in COPD patients, the number and proportion of M were positively related with FABP4 levels in BALF; (4) BALF and sputum FABP4 levels were positively related with FEV1, negatively with the CAT score, and lowest in GOLD grade D patients. CONCLUSIONS: Airway FABP4 levels are reduced in COPD patients, especially in those with airway infection and more severe disease. The relationship observed between M and airway FABP4 levels supports a role for FABP4 in the pathogenesis of airway infection and disease severity in COPD.

Pereira, A., R. F. Xavier, et al. (2019). **"The Mini-Balance Evaluation System Test Can Predict Falls in Clinically Stable Outpatients With COPD: A 12-MO PROSPECTIVE COHORT STUDY."** J Cardiopulm Rehabil Prev **39**(6): 391-396.

PURPOSE: This study evaluated the accuracy of the Mini-Balance Evaluation System Test (Mini-BESTest) for predicting falls in patients with chronic obstructive pulmonary disease (COPD) and investigated whether postural balance is a risk factor for falls. METHODS: Postural balance was evaluated by the Mini-BESTest at baseline, and the incidence of falls over a 12-mo period was prospectively measured by a self-reported falls diary and confirmed by telephone calls. A discriminative power analysis was performed using receiver operating characteristic (ROC) curve and logistic regression analysis. RESULTS: Sixty-seven outpatients with COPD (mean age +/- SD = 67 +/- 9.3 yr) were included. Twenty-five patients (37.3%) experienced >/=1 fall, and 28.2% of the falls resulted in injuries. The Mini-BESTest predicted falls in patients with COPD at the 6- and 12-mo follow-ups with a cut-off score of 22.5 (area under the curve = 0.85 and 0.87) with good sensitivity and specificity (85.7% and 66.7%; 84% and 73.8%, respectively). Higher scores on the Mini-BESTest were associated with a lower risk of falls at 12 mo (OR = 0.50; 95% CI, 0.36-0.70; P < .001). CONCLUSIONS: Postural balance assessed by the Mini-BESTest is a good predictor of falls in patients with COPD. Our results imply that impaired balance contributes to the risk of falling and that balance training and fall prevention programs may be required for this population.

Pereira de Araujo, C. L., G. Pereira Reinaldo, et al. (2019). **"The effects of pulmonary rehabilitation on endothelial function and arterial stiffness in patients with chronic obstructive pulmonary disease."** Physiother Res Int: e1820.

OBJECTIVES: Cardiovascular disease is a major cause of mortality in chronic obstructive pulmonary disease (COPD) and endothelial dysfunction may enhance the mortality risk. Exercise training has shown to be beneficial for improvement of endothelial function in patients with cardiovascular disease, but this remains unclear in COPD. Thus, this study aimed to assess the effect of exercise-based pulmonary rehabilitation (PR) on endothelium function, arterial stiffness and plasma nitrite levels in patients with COPD. METHODS: Patients with COPD engaged a 48-session PR program. Reactive hyperaemia index (RHI), augmentation index (AIx), and heart rate (HR) assed by peripheral arterial tonometry (PAT), plasma nitrite levels, systemic blood pressure, functional capacity (six-minute walk test) and the BODE index were assessed at baseline and after 24 and 48 sessions of PR. Plasma nitrite levels were also assessed before and after the first session of PR. RESULTS: Twenty-one subjects were included and completed 24 PR sessions, and 16 subjects completed 48 sessions. It was observed that a poorer AIx adjusted for HR in frequent COPD exacerbators (4.67 +/- 16.5 vs. 20.9 +/- 12.9; p = .02). PR improved functional capacity (380 +/- 107 m vs. 442 +/- 115 m; p < .001) and the BODE index (6 [2.8] vs. 4 [3]; p = .001), but did not change HR, systemic arterial pressure, RHI, AIx, and plasma nitrite levels during the follow-up. Plasma nitrite levels reduced after the first session of PR (0.074 [0.079] muM vs. 0.061 [0.04] muM; p = .027). The acute change in plasma nitrite levels correlated with RHI in patients with preserved endothelial function (r = 0.71; p = .01). CONCLUSIONS: Although exercise-based PR improved functional capacity and the BODE index, it did not change endothelial function and arterial stiffness in patients with COPD.

Pezzuto, A. and E. Carico (2020). **"Effectiveness of smoking cessation in smokers with COPD and nocturnal oxygen desaturation: Functional analysis."** Clin Respir J **14**(1): 29-34.

INTRODUCTION: Chronic obstructive pulmonary disease (COPD) is the fourth cause of mortality and it's frequently associated with breathing sleep disorders. OBJECTIVE: The aim of the study is to point out the benefit of smoking cessation over three months in terms of improvement of respiratory functional variables. METHODS: A retrospective analysis was performed evaluating the impact of smoking cessation on 145 patients with COPD and nocturnal oxygen desaturation. For this purpose, for all patients, overnight pulse oxymetry detection on room air, arterial blood sampling, plethysmography and exhaled test for carbon monoxide were performed at baseline and 3 months after the beginning. Smoking cessation was achieved by varenicline plus individual counselling. RESULTS: About 51% of patients quit smoking which was established by exhaledcarbon monoxide (eCO) measure (cut-off 5 ppm). Patients who quit smoking displayed notably better results compared with patients who did not. The eCO significantly decreased by 16 ppm versus 4 (P = 0.01), oxygen desaturation index (ODI) was reduced by 3 points versus 0.8 (P = 0.01) and forced expiratory in 1 second volume increased by 7% of predicted value versus 1% (P = 0.01). The walking test was improved by 102 m versus 25 in sustainers (P = 0.01). The CAT score was also improved by 10 versus 8 in sustainers (P = 0.01) and PaO2 increased by 5 mm Hg versus 0.5 (P = 0.04). The percentage of SaO2 < 90% was improved by 6.7 versus 2.1 (P = 0.04).The logistic regression analysis displayed the possible influence of CAT (P = 0.02) and modified medical research council dyspnea test (P = 0.05) on ODI value. CONCLUSIONS: Smoking cessation notably improves pulmonary functional parameters in quitters reporting nocturnal oxygen desaturation.

Pinner, N., W. Oliver, et al. (2019). **"Frequency of beta-Blocker Use Following Exacerbations of COPD in Patients with Compelling Indication for Use."** South Med J **112**(11): 586-590.

OBJECTIVE: To assess the current use of beta-blockers in patients with compelling indications for use, following the acute exacerbation of chronic obstructive pulmonary disease (COPD). METHODS: We performed a multicenter retrospective observational study using data from all of the patients admitted to five institutions for an acute exacerbation of COPD. Patients were included if they were admitted for an acute exacerbation of COPD and had a compelling indication for the use of a beta-blocker, defined as previous myocardial infarction or heart failure with left ventricular ejection fraction </=40%. RESULTS: There were 396 patients meeting the criteria for inclusion in the study. The population was predominantly white men with myocardial infarction as the most prevalent compelling indication. On admission, 267 (67.4%) patients were receiving beta-blockers, which increased to 278 (70.2%) at discharge. There were 118 (29.8%) patients discharged without beta-blockers. Of the predictors tested, none were significantly predictive of a patient not receiving beta-blockers upon discharge; however, home and in-hospital beta-blockers reduced the likelihood of being discharged without a beta-blocker. Of the 129 patients not receiving beta-blockers prehospitalization, 23 (17.8%) were discharged with a new prescription for a beta-blocker. CONCLUSIONS: Nearly one-third of patients with compelling indications for beta-blockers were not prescribed the therapy at discharge.

Pisani, L., S. Betti, et al. (2020). **"Effects of high-flow nasal cannula in patients with persistent hypercapnia after an acute COPD exacerbation: a prospective pilot study."** BMC Pulm Med **20**(1): 12.

BACKGROUND: Persistent hypercapnia after COPD exacerbation is associated with excess mortality and early rehospitalization. High Flow Nasal cannula (HFNC), may be theoretically an alternative to long-term noninvasive ventilation (NIV), since physiological studies have shown a reduction in PaCO2 level after few hours of treatment. In this clinical study we assessed the acceptability of HFNC and its effectiveness in reducing the level of PaCO2 in patients recovering from an Acute Hypercapnic Respiratory Failure (AHRF) episode. We also hypothesized that the response in CO2 clearance is dependent on baseline level of hypercapnia. METHODS: Fifty COPD patients recovering from an acute exacerbation and with persistent hypercapnia, despite having attained a stable pH (i.e. pH > 7,35 and PaCO2 > 45 mmHg on 3 consecutive measurements), were enrolled and treated with HFNC for at least 8 h/day and during the nighttime RESULTS: HFNC was well tolerated with a global tolerance score of 4.0 +/- 0.9. When patients were separated into groups with or without COPD/OSA overlap syndrome, the "pure" COPD patients showed a statistically significant response in terms of PaCO2 decrease (p = 0.044). In addition, the subset of patients with a lower pH at enrolment were those who responded best in terms of CO2 clearance (score test for trend of odds, p = 0.0038). CONCLUSIONS: HFNC is able to significantly decrease the level of PaCO2 after 72 h only in "pure" COPD patients, recovering from AHRF. No effects in terms of CO2 reduction were found in those with overlap syndrome. The present findings will help guide selection of the best target population and allow a sample size calculation for future long-term randomized control trials of HFNC vs NIV. TRIAL REGISTRATION: This study is registered with www. clinicaltrials.gov with identifier number NCT03759457.

Portoles-Callejon, A., R. Lopez-Alfaro, et al. (2019). **"Adequacy and prognostic impact of treatment for severe exacerbation of chronic obstructive pulmonary disease."** Rev Clin EspOBJECTIVE: To define the clinical characteristics of patients hospitalised in pneumology and internal medicine departments for chronic obstructive pulmonary disease (COPD) exacerbation, to assess the compliance with the recommendations of the clinical practice guidelines and to determine the impact on the patients' prognosis. METHODOLOGY: We conducted a retrospective longitudinal study that randomly included patients hospitalised for COPD exacerbation in a tertiary hospital. We collected demographic and clinical variables (degree of dyspnoea and obstruction, previous exacerbations, comorbidities), readmission and mortality data and criteria for compliance with the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines and the Spanish COPD guidelines (GesEPOC). We performed a univariate, multivariate

and survival analysis. RESULTS: The study included 108 patients, and the mean age was 71.48+/-11.65 years. The readmission rate was 26.4% at 3 months and 43.4% at 1 year. The hospital mortality rate was 3.9%, the mortality rate at 3 months was 21.9%, and the mortality rate at 1 year was 27.4%. The patients hospitalised in the internal medicine department had higher mortality during hospitalisation (p=.043), at 3 months (p=.028) and at 1 year (p=.007) compared with the rates for the pneumology department. Overall compliance with the clinical guidelines was 63% for the clinical evaluation (less for the patients in internal medicine: 56.1% vs. 73.8%, p=.063). For the treatment, the compliance was 26.9% for GOLD and 28.7% for GesEPOC. Compliance with the GOLD guidelines in the use of corticosteroids was associated with a lower rate of long-term readmissions (p=.041) and hospital mortality (p=.007) and 3-month mortality (p=.05). CONCLUSIONS: The clinical profile of the patients is currently similar to that previously reported, but their clinical progression was poorer. Overall compliance with the clinical guidelines for drug treatment was low, and only appropriate use of systemic steroids was associated with a reduction in early mortality and in medium-term readmissions.

Price, D. B., J. Voorham, et al. (2019). **"Inhaled corticosteroids in COPD and onset of type 2 diabetes and osteoporosis: matched cohort study."** NPJ Prim Care Respir Med **29**(1): 38.

Some studies suggest an association between onset and/or poor control of type 2 diabetes mellitus and inhaled corticosteroid (ICS) therapy for chronic obstructive pulmonary disease (COPD), and also between increased fracture risk and ICS therapy; however, study results are contradictory and these associations remain tentative and incompletely characterized. This matched cohort study used two large UK databases (1983-2016) to study patients (>/= 40 years old) initiating ICS or long-acting bronchodilator (LABD) for COPD from 1990-2015 in three study cohorts designed to assess the relation between ICS treatment and (1) diabetes onset (N = 17,970), (2) diabetes progression (N = 804), and (3) osteoporosis onset (N = 19,898). Patients had >/= 1-year baseline and >/= 2-year outcome data. Matching was via combined direct matching and propensity scores. Conditional proportional hazards regression, adjusting for residual confounding after matching, was used to compare ICS vs. LABD and to model ICS exposures. Median follow-up was 3.7-5.6 years/treatment group. For patients prescribed ICS, compared with LABD, the risk of diabetes onset was significantly increased (adjusted hazard ratio 1.27; 95% CI, 1.07-1.50), with overall no increase in risk of diabetes progression (adjusted hazard ratio 1.04; 0.87-1.25) or osteoporosis onset (adjusted hazard ratio 1.13; 0.93-1.39). However, the risks of diabetes onset, diabetes progression, and osteoporosis onset were all significantly increased, with evident dose-response relationships for all three outcomes, at mean ICS exposures of 500 microg/day or greater (vs. < 250 microg/day, fluticasone propionate-equivalent). Long-term ICS therapy for COPD at mean daily exposure of >/= 500 microg is associated with an increased risk of diabetes, diabetes progression, and osteoporosis.

Roberts, M. H., D. W. Mapel, et al. (2019). **"Comparative Causal Analysis of the Effects of Long-Acting Muscarinic Antagonist Versus No Long-Acting Bronchodilator Use on Readmission or Mortality After Hospitalization for Chronic Obstructive Pulmonary Disease."** Drugs Real World OutcomesBACKGROUND: Retrospective observational studies may provide real-world evidence about long-acting muscarinic receptor antagonist (LAMA) effectiveness in reducing mortality or COPD-related readmission risk after a COPD hospitalization. Causal inference and competing risk statistical procedures aid in managing confounding and competing outcome events that complicate retrospective analyses. OBJECTIVE: To compare COPD-related readmission and mortality risk among patients receiving a LAMA versus patients receiving no long-acting bronchodilator ("no LABD") within 30 days post-discharge. METHODS: This retrospective observational analysis of patients (aged >/= 40 years) hospitalized for COPD used claims data (years 2004-2012). Events occurring during the period from 31 days through 12 months post-discharge were compared. The hazard ratio (HR) for the combined outcome of COPD-related readmission or mortality was estimated using Cox regression. Confounding was addressed using

inverse probability of treatment weighting (IPTW). The competing risk of non-COPD-related readmission was considered. RESULTS: 10,405 COPD patients were included (LAMA = 751, no LABD = 9654). IPTW achieved a balanced sample (10,518 LAMA, 10,405 no LABD). Unweighted HR (LAMA vs no LABD) for COPD-related readmission or death, adjusted for age, sex, comorbidities, and baseline utilization, was 1.00 [95% confidence interval (CI) 0.84, 1.20]. Weighted (IPTW) adjusted HR was 0.94 (95% CI 0.88, 1.00). Unweighted and weighted HRs further adjusted for competing risk were 0.97 (95% CI 0.82, 1.16) and 0.91 (0.86, 0.98), respectively. CONCLUSIONS: Bias by indication and comorbidities make the measurement of retrospective COPD treatment effectiveness difficult. Using IPTW and additionally considering the competing event risk, LAMA use was associated with a small reduction in risk for COPD-related readmission or death over the period from 31 days to 12 months post-discharge.

Rockenschaub, P., A. Jhass, et al. (2020). **"Opportunities to reduce antibiotic prescribing for patients with COPD in primary care: a cohort study using electronic health records from the Clinical Practice Research Datalink (CPRD)."** J Antimicrob Chemother **75**(1): 243-251.

BACKGROUND: In primary care there is uncertainty about which patients with acute exacerbations of COPD (AECOPD) benefit from antibiotics. OBJECTIVES: To identify which types of COPD patients get the most antibiotics in primary care to support targeted antibiotic stewardship. METHODS: Observational study of COPD patients using a large English primary care database with 12 month follow-up. We estimated the incidence of and risk factors for antibiotic prescribing relative to the number of AECOPD during follow-up, considering COPD severity, smoking, obesity and comorbidity. RESULTS: From 157 practices, 19594 patients were diagnosed with COPD, representing 2.6% of patients and 11.5% of all prescribed antibiotics. Eight hundred and thirty-three (4.5%) patients with severe COPD and frequent AECOPD were prescribed six to nine prescriptions per year and accounted for 13.0% of antibiotics. Individuals with mild to moderate COPD and zero or one AECOPD received one to three prescriptions per year but accounted for 42.5% of all prescriptions. In addition to COPD severity, asthma, chronic heart disease, diabetes, heart failure and influenza vaccination were independently associated with increased antibiotic use. CONCLUSIONS: Patients with severe COPD have the highest rates of antibiotic prescribing but most antibiotics are prescribed for patients with mild to moderate COPD. Antibiotic stewardship should focus on the dual goals of safely reducing the volume of prescribing in patients with mild to moderate COPD, and optimizing prescribing in patients with severe disease who are at significant risk of drug resistance.

Rosas-Alonso, R., R. Galera, et al. (2019). **"Hypermethylation of Anti-oncogenic MicroRNA 7 is Increased in Emphysema Patients."** Arch BronconeumolINTRODUCTION: MicroRNA-7 (miR-7) has a suppressive role in lung cancer and alterations in its DNA methylation may contribute to tumorigenesis. As COPD patients with emphysema have a higher risk of lung cancer than other COPD phenotypes, we compared the miR-7 methylation status among smoker subjects and patients with various COPD phenotypes to identify its main determinants. METHODS: 30 smoker subjects without airflow limitation and 136 COPD patients without evidence of cancer were recruited in a prospective study. Clinical and functional characteristics were assessed and patients were classified into: frequent exacerbator, emphysema, chronic bronchitis and asthma COPD overlap (ACO). DNA collected from buccal epithelial samples was isolated and bisulfite modified. miR-7 methylation status was evaluated by quantitative methylation-specific polymerase chain reaction (qMSP). RESULTS: miR-7 Methylated levels were higher in COPD patients than in smokers without airflow limitation (23.7+/-12.4 vs. 18.5+/-8.8%, p=0.018). Among COPD patients, those with emphysema had higher values of methylated miR-7 (27.1+/-10.2%) than those with exacerbator (19.4+/-9.9%, p=0.004), chronic bronchitis (17.3+/-9.0%, p=0.002) or ACO phenotypes (16.0+/-7.2%, p=0.010). After adjusting for clinical parameters, differences between emphysematous patients and those with other phenotypes were retained. In COPD patients, advanced age, mild-moderate airflow limitation, reduced diffusing capacity and increased functional residual capacity were

identified as independent predictors of methylated miR-7 levels. CONCLUSION: The increase of miR-7 methylation levels experienced by COPD patients occurs mainly at the expense of the emphysema phenotype, which might contribute to explain the higher incidence of lung cancer in these patients.

Sarkar, C., B. Zhang, et al. (2019). **"Environmental correlates of chronic obstructive pulmonary disease in 96 779 participants from the UK Biobank: a cross-sectional, observational study."** Lancet Planet Health **3**(11): e478-e490.

BACKGROUND: The role of environmental exposures in chronic obstructive pulmonary disease (COPD) remains inconclusive. We examined the association between environmental exposures (PM2.5, greenness, and urbanicity) and COPD prevalence using the UK Biobank cohort data to identify key built environment correlates of COPD. METHODS: In this cross-sectional, observational study we used baseline data for UK Biobank participants. Included participants were aged 39 years and older, white, had available spirometry data, and had complete data for phenotypes and exposures. COPD was defined by spirometry with the 2017 Global Initiative for Chronic Obstructive Lung Disease criteria. Environmental exposures were PM2.5 derived from monitoring data and interpolated using land-use regression at the participants' geocoded residential addresses. Built environment metrics of residential greenness were modelled in terms of normalised difference vegetation index from remotely sensed colour infrared data within a 500 m residential catchment, and an urbanicity index derived from spatial analyses and measured with a 1 km buffer around each participant's residential address. Logistic regression models examined the associations between environmental exposures and COPD prevalence adjusting for a range of confounders. Subgroup analyses by urbanicity and effect modification by white blood cell count as an inflammatory marker were also done. FINDINGS: We assessed 96 779 participants recruited between April 4, 2006, and Oct 1, 2010, of which 5391 participants had COPD with a prevalence of 5.6%. Each 10 mug/m(3) increment in ambient PM2.5 exposure at a participant's residential location was associated with higher odds of COPD (odds ratio 1.55, 95% CI 1.14-2.10). Among the built environment metrics, urbanicity was associated with higher odds of COPD (1.05, 1.01-1.08 per interquartile increment), whereas residential greenness was protective, being associated with lower odds of COPD (0.89, 0.84-0.93 for each interquartile increment in greenness). The results remained consistent in models of COPD defined as per lower limit of normal criteria. The highest quartile of white blood cell count was associated with lower lung function and higher COPD risk with a significant interaction between PM2.5 and white blood cell count only in the model of lung function (p=0.0003). INTERPRETATION: In this study of the built environment and COPD, to our knowledge the largest done in the UK, we found that exposure to ambient PM2.5 and urbanicity were associated with a higher risk of COPD. Residing in greener areas, as measured by normalised difference vegetation index, was associated with lower odds of COPD, suggesting the potential value of urban planning and design in minimising or offsetting environmental risks for the prevention and management of COPD. FUNDING: University of Hong Kong, UK Biobank, and UK Economic & Social Research Council.

Schofield, S. J., A. Woods, et al. (2019). **"Chronic Obstructive Pulmonary Disease and Breathlessness in Older Workers Predict Economic Inactivity. A Prospective Cohort Study."** Am J Respir Crit Care Med **200**(10): 1228-1233.

Rationale: There is an aspiration to retain increasing numbers of older workers in employment, and strategies to achieve this need to make provision for the increasing prevalence of chronic diseases with age. There is a consistent body of cross-sectional evidence that suggests that patients with chronic obstructive pulmonary disease are more likely to have adverse employment outcomes.Objectives: We report the findings of the first longitudinal study of this issue.Methods: We recruited full-time employed men and women in their 50s and followed them for a period of 18 months; we examined, after adjustment for potential confounders, the associations between breathlessness and airway obstruction at baseline and

loss of employment in the intervening period.Measurements and Main Results: Among participants responding to the follow-up questionnaire (1,656 of 1,773 [93%]), the majority (78.5%) continued in full-time employment, but 10.6% were in part-time employment and 10.9% were no longer in paid employment. The adjusted risk of loss of employment was significantly increased for those with moderate or severe chronic obstructive pulmonary disease (risk ratio, 2.89; 95% confidence interval, 1.80-4.65) or breathlessness (risk ratio, 3.07; 95% confidence interval, 2.16-4.37) at baseline. There was no evident modification by sex or by manual/nonmanual work.Conclusions: Airway obstruction and breathlessness are independently associated with premature loss from the workforce in older workers; these observations provide strong support to the available cross-sectional evidence and suggest that interventions to help those with chronic obstructive pulmonary disease who wish to remain in work need to be tested.

Scichilone, N., R. Antonelli Incalzi, et al. (2019). **"Circadian rhythm of COPD symptoms in clinically based phenotypes. Results from the STORICO Italian observational study."** BMC Pulm Med **19**(1): 171.

BACKGROUND: Chronic Obstructive Pulmonary Disease (COPD) encompasses various phenotypes that severely limit the applicability of precision respiratory medicine. The present investigation is aimed to assess the circadian rhythm of symptoms in pre-defined clinical COPD phenotypes and its association with health-related quality of life (HR-QoL), the quality of sleep and the level of depression/anxiety in each clinical phenotype. METHODS: The STORICO (NCT03105999) Italian observational prospective cohort study enrolled COPD subjects. A clinical diagnosis of either chronic bronchitis (CB), emphysema (EM) or mixed COPD-asthma (MCA) phenotype was made by clinicians at enrollment. Baseline early-morning, day-time and nocturnal symptoms (gathered via the Night-time, Morning and Day-time Symptoms of COPD questionnaire), HR-QoL (via the St. George's Respiratory Questionnaire), anxiety and depression levels (via the Hospital Anxiety and Depression Scale), quality of sleep (via COPD and Asthma Sleep Impact Scale), physical activity (via the International Physical Activity Questionnaire) as well as lung function were recorded. RESULTS: 606 COPD subjects (age 71.4 +/- 8.2 years, male 75.1%) were studied. 57.9, 35.5 5.3 and 1.3% of the sample belonged to the CB, EM, MCA and EM + CB phenotypes respectively. The vast majority of subjects reported early-morning and day-time symptoms (79.5 and 79.2% in the CB and 75.8 and 77.7% in the EM groups); the proportion suffering from night-time symptoms was higher in the CB than in the EM group (53.6% vs. 39.5%, p = 0.0016). In both CB and EM, indiscriminately, the presence of symptoms during the 24-h day was associated with poorer HR-QoL, worse quality of sleep and higher levels of anxiety/depression. CONCLUSIONS: The findings highlight the primary classificatory role of nocturnal symptoms in COPD. TRIAL REGISTRATION: Trial registration number: NCT03105999 , date of registration: 10th April 2017.

Shah, A., N. Ayas, et al. (2020). **"Sleep Quality and Nocturnal Symptoms in a Community-Based COPD Cohort."** Copd: 1-9.

Small studies have suggested that patients with chronic obstructive pulmonary disease (COPD) have poor sleep quality. Our aim was to examine the prevalence of subjective sleep-related complaints and predictors of poor sleep quality in a large community-based COPD cohort. We analyzed cross-sectional data on sleep questionnaire responses from the Canadian Cohort of Obstructive Lung Disease (CanCOLD) study, a population-based, prospective longitudinal cohort study across Canada. The cohort comprises a COPD group and two matched non-COPD (never-smokers and ever-smokers) groups. Sleep-related symptoms were assessed using questionnaires including Pittsburgh Sleep Quality Index (PSQI). A total score of PSQI > 5 is indicative of poor sleep quality. Health-related quality of life measures and the presence of mood disturbance were assessed using Short Form-36 Health Survey (SF-36) multi-item questionnaires and Hospital Anxiety and Depression Scale (HADS), respectively. Predictors of poor sleep quality were analyzed using multivariable logistic regression analysis. Of the 1123 subjects, 263 were healthy controls,

323 at-risk controls, and 537 had COPD (297 had mild, 240 with moderate to severe disease). The mean PSQI score was not significantly different between groups. COPD patients with poor sleep quality had lower diffusion capacity, higher HADS anxiety and depression scores and lower SF-36 mental and physical component summary scores than COPD patients classified as good sleepers. The presence of restless legs and obstructive sleep apnea symptoms, waist circumference, predicted diffusion capacity and HADS anxiety and depression scores were identified as independent predictors of poor sleep quality.

Shimizu, K., N. Tanabe, et al. (2020). **"Per cent low attenuation volume and fractal dimension of low attenuation clusters on CT predict different long-term outcomes in COPD."** Thorax BACKGROUND: Fractal dimension (D) characterises the size distribution of low attenuation clusters on CT and assesses the spatial heterogeneity of emphysema that per cent low attenuation volume (%LAV) cannot detect. This study tested the hypothesis that %LAV and D have different roles in predicting decline in FEV1, exacerbation and mortality in patients with COPD. METHODS: Chest inspiratory CT scans in the baseline and longitudinal follow-up records for FEV1, exacerbation and mortality prospectively collected over 10 years in the Hokkaido COPD Cohort Study were examined (n=96). The associations between CT measures and long-term outcomes were replicated in the Kyoto University cohort (n=130). RESULTS: In the Hokkaido COPD cohort, higher %LAV, but not D, was associated with a greater decline in FEV1 and 10-year mortality, whereas lower D, but not %LAV, was associated with shorter time to first exacerbation. Multivariable analysis for the Kyoto University cohort confirmed that lower D at baseline was independently associated with shorter time to first exacerbation and that higher LAV% was independently associated with increased mortality after adjusting for age, height, weight, FEV1 and smoking status. CONCLUSION: These well-established cohorts clarify the different prognostic roles of %LAV and D, whereby lower D is associated with a higher risk of exacerbation and higher %LAV is associated with a rapid decline in lung function and long-term mortality. Combination of %LAV and fractal D may identify COPD subgroups at high risk of a poor clinical outcome more sensitively.

Sivapalan, P., T. S. Ingebrigtsen, et al. (2019). **"COPD exacerbations: the impact of long versus short courses of oral corticosteroids on mortality and pneumonia: nationwide data on 67 000 patients with COPD followed for 12 months."** BMJ Open Respir Res **6**(1): e000407.

Introduction: A large group of patients with chronic obstructive pulmonary disease (COPD) are exposed to an overload of oral corticosteroids (OCS) due to repeated exacerbations. This is associated with potential serious adverse effects. Therefore, we evaluated the impact of a recommended reduction of OCS duration in 2014 on the risk of pneumonia hospitalisation and all-cause mortality in patients with acute exacerbation of COPD (AECOPD). Methods: This was a nationwide observational cohort study that was based on linked administrative registry data between 1 January 2010 and 31 October 2017. 10 152 outpatients with COPD (median age 70 years) treated with either a short (</=250 mg) or long course (>250 mg) of OCS for AECOPD were included in the study. Cox proportional hazards regression models were used to derive an estimation of multivariable adjusted HRs (aHRs) for pneumonia hospitalisation or all-cause mortality combined and pneumonia hospitalisation and all-cause mortality, separately. Results: The long course of OCS treatment for AECOPD was associated with an increased 1-year risk of pneumonia hospitalisation or all-cause mortality (aHR 1.3, 95% CI 1.1 to 1.4; p<0.0001), pneumonia hospitalisation (aHR 1.2, 95% CI 1.0 to 1.3; p=0.0110) and all-cause mortality (aHR 1.8, 95% CI 1.5 to 2.2; p<0.0001) as compared with the short course of OCS treatment. These results were confirmed in several sensitivity analyses. Conclusion: The change of recommendations from long courses to short courses of OCS for AECOPD in 2014 was strongly associated with a decrease in pneumonia admissions and all-cause mortality, in favour of short courses of OCS.

Skolnik, N. S., T. S. Nguyen, et al. (2020). **"Current evidence for COPD management with dual long-acting muscarinic antagonist/long-acting beta2-agonist bronchodilators."** Postgrad Med: 1-8.

Long-acting inhaled bronchodilator medications are recommended as initial maintenance therapy for many patients with COPD. These medications include long-acting muscarinic antagonists (LAMA) and long-acting beta2-agonists (LABA). Combinations of long-acting bronchodilator agents (LAMA/LABA) and inhaled corticosteroids combined with LABA (ICS/LABA) are also used as initial or follow-up therapy in patients with more severe symptoms or at risk of COPD exacerbations. This review summarizes the position of LAMA/LABA combinations in treatment recommendations, and the evidence supporting their placement relative to LAMA monotherapy and ICS/LABA combination therapy, as well as differences within the LAMA/LABA class. Most studies show that LAMA/LABA treatment leads to greater improvements in lung function and symptoms than LAMA monotherapy or ICS/LABA treatment. There are fewer studies comparing the impact of different medication classes on patients' risk of exacerbations; however, the available evidence suggests that LAMA/LABA treatment and LAMA monotherapy lead to a similar reduction in exacerbation risk, while the effect of LAMA/LABA compared with ICS/LABA remains unclear. The incidence of adverse events is similar with LAMA/LABA and LAMA alone. There is a lower risk of pneumonia with LAMA/LABA compared with ICS/LABA. This evidence supports the use of LAMA/LABA combinations as an initial maintenance therapy option for symptomatic patients with low exacerbation risk and severe breathlessness or patients with severe symptoms who are at risk of exacerbations, and as follow-up treatment in patients with uncontrolled symptoms or exacerbations on bronchodilator monotherapy.

Slebos, D. J., P. L. Shah, et al. (2019). **"Safety and Adverse Events after Targeted Lung Denervation for Symptomatic Moderate to Severe Chronic Obstructive Pulmonary Disease (AIRFLOW). A Multicenter Randomized Controlled Clinical Trial."** Am J Respir Crit Care Med **200**(12): 1477-1486.

Rationale: Targeted lung denervation (TLD) is a bronchoscopic radiofrequency ablation therapy for chronic obstructive pulmonary disease (COPD), which durably disrupts parasympathetic pulmonary nerves to decrease airway resistance and mucus hypersecretion.Objectives: To determine the safety and impact of TLD on respiratory adverse events.Methods: We conducted a multicenter, randomized, sham bronchoscopy-controlled, double-blind trial in patients with symptomatic (modified Medical Research Council dyspnea scale score, >/=2; or COPD Assessment Test score, >/=10) COPD (FEV1, 30-60% predicted). The primary endpoint was the rate of respiratory adverse events between 3 and 6.5 months after randomization (defined as COPD exacerbation, tachypnea, wheezing, worsening bronchitis, worsening dyspnea, influenza, pneumonia, other respiratory infections, respiratory failure, or airway effects requiring therapeutic intervention). Blinding was maintained through 12.5 months.Measurements and Main Results: Eighty-two patients (50% female; mean +/- SD: age, 63.7 +/- 6.8 yr; FEV1, 41.6 +/- 7.3% predicted; modified Medical Research Council dyspnea scale score, 2.2 +/- 0.7; COPD Assessment Test score, 18.4 +/- 6.1) were randomized 1:1. During the predefined 3- to 6.5-month window, patients in the TLD group experienced significantly fewer respiratory adverse events than those in the sham group (32% vs. 71%, P = 0.008; odds ratio, 0.19; 95% confidence interval, 0.0750-0.4923, P = 0.0006). Between 0 and 12.5 months, these findings were not different (83% vs. 90%; P = 0.52). The risk of COPD exacerbation requiring hospitalization in the 0- to 12.5-month window was significantly lower in the TLD group than in the sham group (hazard ratio, 0.35; 95% confidence interval, 0.13-0.99; P = 0.039). There was no statistical difference in the time to first moderate or severe COPD exacerbation, patient-reported symptoms, or other physiologic measures over the 12.5 months of follow-up.Conclusions: Patients with symptomatic COPD treated with TLD combined with optimal pharmacotherapy had fewer study-defined respiratory adverse events, including hospitalizations for COPD exacerbation.Clinical trial registered with www.clinicaltrials.gov (NCT02058459).

Soler-Cataluna, J. J., B. Alcazar, et al. (2019). **"Evaluation of Changes in Control Status in COPD: An Opportunity for Early Intervention."** ChestBACKGROUND: Control has been proposed as a dynamic tool that can capture changes in the clinical status of patients with COPD. METHODS: This prospective, multicenter, observational study aimed to compare changes in control over a 3-month period with changes in risk level, Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage, and clinical phenotype (nonexacerbator, asthma-COPD overlap, or exacerbator with emphysema or with chronic bronchitis). Control was defined as the presence of low clinical impact, assessed according to the degree of dyspnea, use of rescue medication, physical activity and sputum color, and clinical stability assessed by clinical changes and exacerbations in the last 3 months. Impact and stability were alternatively assessed with COPD Assessment Test (CAT) scores. RESULTS: We included 354 patients, with a mean FEV1 of 49.8% +/- 16.9%. At 3 months, the proportion of controlled patients was 50.3% according to clinical evaluation and 47.8% according to CAT score. Eighty-seven patients (29.2%) changed their control status as assessed by clinical variables, and 85 patients (28.5%) changed their status according to CAT score. In contrast, the risk level only changed in 26 patients (8.7%) (P < .001), 27 patients (9.1%) experienced changes in their clinical phenotype (P < .001), and 59 patients (19.8%) experienced changes in their GOLD stage (P = .008). Patients who showed an improvement in control status had better CAT scores at the end of follow-up (P < .001). CONCLUSIONS: In only 3 months, almost one-third of patients experienced changes in their control status. Changes in control status were significantly more frequent than changes in phenotype, risk level, and GOLD stage, and resulted in significant changes in health status.

Soler-Cataluna, J. J., L. Novella, et al. (2019). **"Clinical Characteristics and Risk of Exacerbations Associated With Different Diagnostic Criteria of Asthma-COPD Overlap."** Arch BronconeumolINTRODUCTION: There is currently no universally accepted definition of asthma-COPD overlap (ACO). OBJECTIVE: To compare the prevalence of ACO in patients with asthma or COPD, and to assess their clinical characteristics and the capacity of the different definitions to predict the risk of exacerbation. METHOD: Prospective observational study with a 12-month follow-up in an asthma cohort and a COPD cohort. Four diagnostic criteria were compared: A) the Spanish 2012 consensus; B) the 2016 international consensus; C) the 2017 consensus between the Spanish COPD guidelines (GesEPOC) and GEMA asthma guidelines; and D) the single criterion of >/=300eosinophils/muL, proposed by GOLD 2019. The risk of exacerbations was evaluated in each group. RESULTS: A total of 345 patients were included, 233 (67.5%) with COPD and 112 (32.5%) with asthma, aged 63+/-14 years, 70.4% men. Fifteen (4.3%) patients met the criteria for ACO according to the criteria described under A above; 30 (8.7%) with the criteria of B; 118 (34.2%) with the criteria of C; and 97 (28.1%), with the D criterion. The ACO-COPD subtype were older, had worse lung function, and an increased risk of exacerbation compared with the ACO-asthma group. Of all the definitions evaluated, those which distinguished a higher risk of exacerbations were the GesEPOC-GEMA consensus and the GOLD proposal. CONCLUSIONS: The prevalence of ACO varies enormously depending on the diagnostic criteria used. The ACO population is heterogeneous, and the ACO-COPD subtype is very different from the ACO-asthma subtype. The definitions that include eosinophilia identify ACO patients with a greater risk of exacerbation.

Spece, L. J., L. M. Donovan, et al. (2020). **"Initiating Low-Value Inhaled Corticosteroids in an Inception Cohort with COPD."** Ann Am Thorac SocRATIONALE: Decreasing medication overuse represents an opportunity

to avoid harm and costs in the era of value-based purchasing. Studies of inhaled corticosteroids (ICS) overuse in COPD has examined prevalent use. Understanding initiation of low-value ICS among complex patients with COPD may help shape de-adoption efforts. OBJECTIVES: Examine ICS initiation among a cohort with low exacerbation risk COPD and test for associations with markers of patient and health system complexity. METHODS: Between 2012 and 2016, we identified Veterans with COPD from 21 centers. Our primary outcome was first prescription of ICS. We used the Care Assessment Needs (CAN) score to assess patient-level complexity as the primary exposure. We used a time-to-event model with time-varying exposures over 1-year follow-up. We tested for effect modification using selected measures of health system complexity. RESULTS: We identified 8,497 patients with COPD without an indication for ICS and did not have baseline use (inception cohort). Follow-up time was 4 quarters. Patient complexity by a continuous CAN score was associated with new dispensing of ICS (HR 1.17 per 10-unit change; 95% CI 1.13 - 1.21). This association demonstrated a dose-response when examining quartiles of CAN score. Markers of health system complexity did not modify the association between patient complexity and first use of low-value ICS. CONCLUSIONS: Patient complexity may represent a symptom burden that clinicians are attempting to mitigate by initiating ICS. Lack of effect-modification by health-system complexity may reflect the paucity of structural support and low prioritization for COPD care.

Stolbrink, M., L. J. Bonnett, et al. (2019). **"Antibiotics for COPD exacerbations: does drug or duration matter? A primary care database analysis."** BMJ Open Respir Res **6**(1): e000458.

Introduction: Antibiotics are routinely given to people with chronic obstructive pulmonary disease (COPD) presenting with lower respiratory tract infection (LRTI) symptoms in primary care. Population prescribing habits and their consequences have not been well-described. Methods: We conducted a retrospective analysis of antibiotic prescriptions for non-pneumonic exacerbations of COPD from 2010 to 2015 using the UK primary care Optimum Patient Care Research Database. As a proxy of initial treatment failure, second antibiotic prescriptions for LRTI or all indications within 14 days were the primary and secondary outcomes, respectively. We derived a model for repeat courses using univariable and multivariable logistic regression analysis. Results: A total of 8.4% of the 9042 incident events received further antibiotics for LRTI, 15.5% further courses for any indication. Amoxicillin and doxycycline were the most common index and second-line drugs, respectively (58.7% and 28.7%), mostly given for 7 days. Index drugs other than amoxicillin, cardiovascular disease, pneumococcal vaccination and more primary care consultations were statistically significantly associated with repeat prescriptions for LRTI ($p<0.05$). The ORs and 95% CIs were: OR 1.28, 95% CI 1.10 to 1.49; OR 1.37, 95% CI 1.13 to 1.66; OR 1.33, 95% CI 1.14 to 1.55 and OR 1.05, 95% CI 1.02 to 1.07, respectively. Index duration, inhaled steroid use and exacerbation frequency were not statistically significant. The derived model had an area under the curve of 0.61, 95% CI 0.59 to 0.63. Discussion: The prescription of multiple antibiotic courses for COPD exacerbations was relatively common-one in twelve patients receiving antibiotics for LRTI had a further course within 2 weeks. The findings support the current preference for amoxicillin as index drug within the limitations of this observational study. Further clinical trials to determine best practice in this common clinical situation appear required.

Suissa, S., S. Dell'Aniello, et al. (2019). **"Comparative Effects of LAMA-LABA-ICS vs LAMA-LABA for COPD: Cohort Study in Real-World Clinical Practice."** ChestBACKGROUND: Triple therapy combinations of a long-acting muscarinic antagonist (LAMA), a long-acting beta2-agonist (LABA), and an inhaled corticosteroid (ICS) for COPD were studied in randomized trials and observational studies, with variable results. We compared the effectiveness and safety of triple therapy with a LAMA-LABA combination in a real-world clinical practice setting. METHODS: We identified a cohort of patients with COPD during 2002 through 2015, >/= 55 years of age, from the UK's Clinical Practice Research Datalink. Patients initiating

LAMA-LABA-ICS were matched 4:1 on time-conditional propensity scores with patients initiating LAMA-LABA, and followed for 1 year for the occurrence of a moderate or severe COPD exacerbation and severe pneumonia. RESULTS: The cohort included 6,921 initiators of LAMA-LABA-ICS matched to 1,932 initiators of LAMA-LABA. The adjusted hazard ratio (HR) of a COPD exacerbation associated with LAMA-LABA-ICS initiation compared with LAMA-LABA initiation was 0.97 (95% CI, 0.87-1.08). For patients with blood eosinophil counts > 6%, the HR was 0.66 (95% CI, 0.46-0.94). For patients with two or more prior exacerbations, it was 0.83 (95% CI, 0.70-0.98). The incidence of severe pneumonia requiring hospitalization was increased with LAMA-LABA-ICS initiation (HR, 1.46; 95% CI, 1.03-2.06). CONCLUSIONS: In a real-world setting of COPD treatment, the triple combination of LAMA, LABA, and ICS inhalers is generally as effective as combining LAMA and LABA inhalers in preventing COPD exacerbations. However, with the possible exception of patients with significant eosinophilia or frequent exacerbators, a LAMA-LABA combination without ICS may be preferable because it is associated with fewer severe cases of pneumonia.

Sulku, J., C. Janson, et al. (2019). **"A Cross-Sectional Study Assessing Appropriateness Of Inhaled Corticosteroid Treatment In Primary And Secondary Care Patients With COPD In Sweden."** Int J Chron Obstruct Pulmon Dis **14**: 2451-2460.

Purpose: Inhaled corticosteroids (ICS) are often more widely prescribed in the treatment of chronic obstructive pulmonary disease (COPD) than what is recommended in the guidelines. The aim of this study was to evaluate the appropriateness of ICS treatment in COPD patients using the algorithm proposed by the International Primary Care Respiratory Group (IPCRG) and to identify factors associated with ICS treatment. Patients and methods: Appropriateness of ICS therapy was studied with respect to concomitant asthma, history of exacerbations and blood eosinophils (B-Eos) in a Swedish cohort of primary and secondary care patients with COPD. Factors associated with ICS were investigated using multivariable logistic regression. Results: Triple treatment was found to be the most common treatment combination, used by 46% of the 561 included patients, and in total 63% were using ICS. When applying the IPCRG algorithm, there was a possible indication for discontinuation of ICS in 55% of the patients with ICS treatment. Of the patients not using ICS, 18% had an indication for starting such treatment. The strongest factors associated with ICS therapy were frequent exacerbations (aOR 8.61, 95% CI 4.06, 20.67), secondary care contacts (aOR 6.99, 95% CI 2.48, 25.28) and very severe airflow limitation (aOR 5.91, 95% CI 1.53, 26.58). Conclusion: More than half of the COPD patients on ICS met the criteria where withdrawal of the treatment could be tried. There was, however, also a subgroup of patients not using ICS for whom there was an indication for starting ICS treatment. Patients using ICS were characterized by more frequent exacerbations and lower lung function.

Sun, Z., Q. L. Zhu, et al. (2019). **"Dynamic changes of gut and lung microorganisms during chronic obstructive pulmonary disease exacerbations."** Kaohsiung J Med SciIncreasing evidence has indicated the intimate relationship between the gastrointestinal tract and respiratory tract. The microbial ecosystem has been confirmed to share key conceptual features with gut-lung microbiome disorder and dysregulation during chronic obstructive pulmonary disease (COPD) exacerbations. However, the dynamic changes of the gut-lung microbiome during COPD exacerbations and its potential role in disease etiology remain poorly understood. The present study investigated the dynamic changes of gut and lung microorganisms during acute exacerbation of chronic obstructive pulmonary disease (AECOPD). A longitudinal 16S ribosomal DNA survey of the gut and lung microbiome was completed on 90 feces and sputum samples collected from 15 subjects with AECOPD at three visits, which were defined as exacerbation, seven-day stable state. The present analysis revealed a dynamic gut-lung microbiota, where changes appeared to be associated with exacerbation events indicative of specific exacerbation phenotypes. Antibiotic and steroid treatments appeared to have differential effects on the

gut-lung microbiome, and the microbiome was associated with disease progression, but not with severity. The abundance and diversity of the microbiome was strongly influenced by the disease progression and therapy. Using culture-independent methods to impact the gut and lung microbiota on AECOPD may be the key to understanding the interactions between the gut and lung, highlighting its potential as a biomarker, and possibly a target for future respiratory therapeutics.

Suzuki, Y., N. Inui, et al. (2019). **"Effect of PD-1 inhibitor on exhaled nitric oxide and pulmonary function in non-small cell lung cancer patients with and without COPD."** Int J Chron Obstruct Pulmon Dis **14**: 1867-1877.

Background: Nivolumab, a programmed death 1 (PD-1) immune checkpoint inhibitor, has been shown to improve survival in non-small cell lung cancer (NSCLC). The possible involvement of PD-1 axis in the pathogenesis of inflammatory lung disease, such as chronic obstructive pulmonary disease (COPD) has also been reported. However, effects of PD-1 blockade on the respiratory system remain unknown. Objectives: This prospective study aimed to investigate whether inhibition of the PD-1 axis altered lung inflammation and pulmonary function in NSCLC patients with and without COPD. Method: This was a prospective multi-center study. Measurements of fractioned exhaled nitric oxide (FeNO) and pulmonary function were performed before and after 4 cycles of nivolumab therapy. Results: A total of 137 patients with NSCLC were initially enrolled, and subsequently 95 patients (41 COPD and 54 non-COPD) receiving 4 cycles of nivolumab administration were included. After anti-PD-1 therapy, FeNO levels were significantly elevated together with increase in peripheral eosinophils. Interestingly, significant FeNO elevation was only found in COPD patients without increased peripheral eosinophils, but this was not the case in non-COPD patients. Additionally, COPD patients exhibited significant increases in FVC and FEV1 but no changes in dyspnea scales, and acute exacerbation did not occur during the therapy. Conclusion: Our observations suggest that anti-PD-1 therapy changed FeNO levels and pulmonary function in NSCLC patients. This therapy does not worsen COPD in terms of symptoms, pulmonary function, or acute exacerbation.

Takei, N., M. Suzuki, et al. (2019). **"Serum Alpha-1 Antitrypsin Levels and the Clinical Course of Chronic Obstructive Pulmonary Disease."** Int J Chron Obstruct Pulmon Dis **14**: 2885-2893.

Purpose: Alpha-1 antitrypsin deficiency is associated with the development of chronic obstructive pulmonary disease (COPD), whereas increased levels of serum alpha-1antitrypsin occur in response to inflammation. The effects of alpha-1 antitrypsin levels on the clinical course of COPD had been unclear. We investigated the association of serum alpha-1 antitrypsin levels with the clinical course of COPD patients based on data from a 10-year prospective cohort study. Patients and methods: We analyzed 278 COPD patients who participated in the Hokkaido COPD cohort study and who did not meet the criteria for alpha-1 antitrypsin deficiency. We divided the subjects into 3 groups according to quartiles of serum alpha-1 antitrypsin levels at baseline: lower group (<116 mg/dL, n = 66); middle group (116 to </=141 mg/dL, n = 145); and higher group (>141 mg/dL, n = 67). The annual change in forced expiratory volume in 1 s (FEV1) and events of COPD exacerbation were monitored during the first 5 years, and mortality was followed-up during the entire 10 years. Results: At baseline, the higher group showed lower body mass index; higher computed tomography emphysema score; lower diffusing capacity; higher levels of acute-phase proteins; and higher blood neutrophil counts. Longitudinal analyses revealed that in the higher group, the annual decline in FEV1 was rapid and the 10-year mortality was higher, but there was no association between serum alpha-1 antitrypsin levels and time to first exacerbation. Conclusion: COPD subjects with higher serum alpha-1 antitrypsin levels were associated with a worse systemic inflammation status and higher 10-year mortality.

Tang, R., A. Fraser, et al. (2019). **"Female reproductive history in relation to chronic obstructive pulmonary disease and lung function in UK biobank: a prospective population-based cohort study."** BMJ Open **9**(10): e030318.

OBJECTIVES: Sex differences in respiratory physiology and predilection for developing chronic obstructive pulmonary disease (COPD) have been documented, suggesting that female sex hormones may influence pathogenesis. We investigated whether aspects of female reproductive health might play a role in risk of COPD among women. DESIGN: Population-based prospective cohort study. SETTING: UK Biobank recruited across 22 centres in the UK between 2006 to 2010. PRIMARY AND SECONDARY OUTCOMES MEASURES: We examined a range of female reproductive health indicators in relation to risk of COPD-related hospitalisation/death (n=271 271) using Cox proportional hazards regression; and lung function (n=273 441) using linear regression. RESULTS: Parity >3 was associated with greater risk of COPD-related hospitalisation/death (adjusted HR 1.45; 95% CI: 1.16 to 1.82) and lower forced expiratory volume at 1 second/forced vital capacity ratio (FEV1/FVC) (adjusted mean difference -0.06; 95% CI: -0.07 to 0.04). Any oral contraception use was associated with lower risk of COPD-related hospitalisation/death (adjusted HR 0.85; 95% CI: 0.74 to 0.97) and greater FEV1/FVC (adjusted mean difference 0.01; 95% CI: 0.003 to 0.03). Late menarche (age >15) and early menopause (age <47) were also associated with greater risk of COPD-related hospitalisation/death (but not lung function), while endometriosis was associated with greater FEV1/FVC (not COPD-related hospitalisation/death). Early menarche (age <12 years) was associated with lower FEV1/FVC (but not COPD hospitalisation/death). Associations with polycystic ovary syndrome (PCOS) or ovarian cysts, any hormone replacement therapy (HRT) use, hysterectomy-alone and both hysterectomy and bilateral oophorectomy were in opposing directions for COPD-related hospitalisation/death (greater risk) and FEV1/FVC (positive association). CONCLUSIONS: Multiple female reproductive health indicators across the life course are associated with COPD-related hospitalisation/death and lung function. Further studies are necessary to understand the opposing associations of PCOS/ovarian cysts, HRT and hysterectomy with COPD and objective measures of airway obstruction.

Teferra, A. A., J. M. Vonk, et al. (2019). **"Longitudinal changes in airway hyperresponsiveness and COPD mortality."** Eur Respir J

Tomaniak, M., P. Chichareon, et al. (2019). **"Impact of chronic obstructive pulmonary disease and dyspnoea on clinical outcomes in ticagrelor treated patients undergoing percutaneous coronary intervention in the randomized GLOBAL LEADERS trial."** Eur Heart J Cardiovasc PharmacotherAIMS: To evaluate long-term safety and efficacy of ticagrelor monotherapy in patients undergoing percutaneous coronary interventions (PCIs) in relation to chronic obstructive pulmonary disease (COPD) at baseline and the occurrence of dyspnoea reported as adverse event (AE) that may lead to treatment non-adherence. METHODS AND RESULTS: This is a non-prespecified, post hoc analysis of the randomized GLOBAL LEADERS trial (n = 15 991), comparing the experimental strategy of 23-month ticagrelor monotherapy following 1-month dual antiplatelet therapy (DAPT) after PCI with the reference strategy of 12-month DAPT followed by 12-month aspirin monotherapy. Impact of COPD and dyspnoea AE (as a time-dependent covariate) on clinical outcomes was evaluated up to 2 years. The primary endpoint was a 2-year all-cause mortality or non-fatal, centrally adjudicated, new Q-wave myocardial infarction. The presence of COPD (n = 832) was the strongest clinical predictor of 2-year all-cause mortality after PCI [hazard ratio (HR) 2.84; 95% confidence interval (CI) 2.21-3.66; P adjusted = 0.001] in this cohort (n = 15 991). No differential treatment effects on 2-year clinical outcomes were found in

patients with and without COPD (primary endpoint: HR 0.88; 95% CI 0.58-1.35; P = 0.562; P int = 0.952). Overall, at 2 years dyspnoea was reported as an AE in 2101 patients, more frequently among COPD patients, irrespective of treatment allocation (27.2% in experimental arm vs. 14.5% in reference arm, P = 0.001). Its occurrence was not associated with a higher rate of the primary endpoint (P adjusted = 0.640) in the experimental vs. the reference arm. CONCLUSION: In this exploratory analysis, COPD negatively impacted long-term prognosis after PCI. Despite higher incidence of dyspnoea in the experimental arm, in particular among COPD patients, the safety of the experimental treatment strategy appeared not to be affected. CLINICAL TRIAL REGISTRATION UNIQUE IDENTIFIER: NCT01813435.

Urwyler, P., M. Boesing, et al. (2019). **"Reduction of corticosteroid use in outpatient treatment of exacerbated COPD - Study protocol for a randomized, double-blind, non-inferiority study, (The RECUT-trial)."** Trials **20**(1): 727.

BACKGROUND: Chronic obstructive pulmonary disease (COPD) is a major public health issue affecting approximately 4% to 7% of the Swiss population. According to current inpatient guidelines, systemic corticosteroids are important in the treatment of acute COPD exacerbations and should be given for 5 to 7 days. Several studies suggest that corticosteroids accelerate the recovery of FEV1 (forced expiratory volume in 1 second), enhance oxygenation, decrease the duration of hospitalization, and improve clinical outcomes. However, the additional therapeutic benefit regarding FEV1 recovery appears to be most apparent in the first 3 to 5 days. No data are available on the optimum duration of corticosteroid treatment in primary-care patients with acute COPD exacerbations. Given that many COPD patients are treated as outpatients, there is an urgent need to improve the evidence base on COPD management in this setting. The aim of this study is to investigate whether a 3-day treatment with orally administered corticosteroids is non-inferior to a 5-day treatment in acute exacerbations of COPD in a primary-care setting. METHODS/DESIGN: This study is a prospective double-blind randomized controlled trial conducted in a primary-care setting. It is anticipated that 470 patients with acutely exacerbated COPD will be recruited. Participants are randomized to receive systemic corticosteroid treatment of 40 mg prednisone daily for 5 days (conventional arm, n = 235) or for 3 days followed by 2 days of placebo (experimental arm, n = 235). Antibiotic treatment for 7 days is given to all patients with CRP >/= 50 mg/l, those with a known diagnosis of bronchiectasis, or those presenting with Anthonisen type I exacerbation. Additional treatment after inclusion is left at the discretion of the treating general practitioner. Follow-up visits are performed on days 3 and 7, followed by telephone interviews on days 30, 90, and 180 after inclusion in the study. The primary endpoint is the time to next exacerbation during the 6-month follow-up period. DISCUSSION: The study is designed to assess whether a 3-day course of corticosteroid treatment is not inferior to the conventional 5-day treatment course in outpatients with exacerbated COPD regarding time to next exacerbation. Depending on the results, this trial may lead to a reduction in the cumulative corticosteroid dose in COPD patients. TRIAL REGISTRATION: ClinicalTrials.gov, NCT02386735. Registered on 12 March 2015.

van Mourik, Y., F. H. Rutten, et al. (2019). **"Clinical research study implementation of case-finding strategies for heart failure and chronic obstructive pulmonary disease in the elderly with reduced exercise tolerance or dyspnea: A cluster randomized trial."** Am Heart J **220**: 73-81.

BACKGROUND: Heart failure (HF) and chronic obstructive pulmonary disease (COPD) often remain undiagnosed in older individuals, although both disorders inhibit functionality and impair health. The aim of the study was to assess the effectiveness of a case-finding strategy of these disorders. METHODS: This is a clustered randomized trial; 18 general practices from the vicinity of Utrecht, the Netherlands, were randomly allocated to a case-finding strategy or usual care. Multimorbid community subjects (>/=65years) with dyspnea or reduced exercise tolerance were eligible for inclusion. The case-finding strategy consisted of history taking, physical examination, blood tests, electrocardiography, spirometry,

and echocardiography. Subsequent treatment decisions were at the discretion of the general practitioner. Questionnaires regarding health status and functionality were filled out at baseline and after 6 months of follow-up. Information regarding changes in medication and health care use during the 6 months follow-up was extracted. RESULTS: A total of 829 participants were randomized: 389 in the case-finding strategy group and 440 in the usual care group. More patients in the case-finding group received a new diagnosis of HF or COPD than the usual care group (cumulative incidence 34% vs 2% and 17% vs. 2%, respectively). Scores for health status, functionality, and health care use were similar between the 2 strategies after 6 months of follow-up. CONCLUSIONS: A case-finding strategy applied in primary care to multimorbid older people with dyspnea or reduced exercise tolerance resulted in a number of new diagnoses of HF and COPD but did not result in short-term improvement of health status compared to usual care.

Venkata, A. N., K. Nalleballe, et al. (2020). **"Prevalence of Chronic Obstructive Pulmonary Disease in Patients Diagnosed with Cerebrovascular Accidents and Its Effect on Health Care Utilization: A Cross-sectional Study."** J Stroke Cerebrovasc Dis **29**(2): 104553.

BACKGROUND: To assess prevalence and to determine the impact of chronic obstructive pulmonary disease (COPD) on health care utilization in patients with cerebrovascular accident (CVA). METHODS: We performed retrospective analysis of data from 12,102 patients who had diagnosis of CVA from 2014 to 2019 at tertiary medical center. We calculated the prevalence of COPD among patients with diagnosis of CVA. We performed unadjusted, covariate adjusted, and propensity-matched analysis to evaluate differences in health care utilization in patients with CVA and COPD compared to patients with CVA without COPD. RESULTS: 12,102 patients were diagnosed with CVA episodes. The prevalence of COPD among CVA patients was 7.65 % (95%CI: 7.18-8.13). The unadjusted and covariate adjusted analysis demonstrated that the average number of hospitalizations among CVA patients with a diagnosis of COPD was significantly higher than CVA patients without COPD. After adjusting for modifiable and nonmodifiable confounders, CVA patients diagnosed with COPD have on average 1 more hospitalization (1.21; 95%CI: 1.12-1.30) than those who are not diagnosed with COPD. Subsequent analysis based on propensity-matched data suggests that CVA patients diagnosed with COPD have on average approximately 1 more hospitalization (1.44; 95% CI: 1.31-1.58) than CVA patients without COPD. CONCLUSIONS: Our study suggests significant prevalence of COPD among CVA patients. The presence of COPD as a comorbidity resulted in patients with COPD and CVA having increased number of hospitalizations compared to CVA patients without COPD.

Viinanen, A., M. I. Lassenius, et al. (2019). **"The Burden Of Chronic Obstructive Pulmonary Disease (COPD) In Finland: Impact Of Disease Severity And Eosinophil Count On Healthcare Resource Utilization."** Int J Chron Obstruct Pulmon Dis **14**: 2409-2421.

Purpose: The burden associated with chronic obstructive pulmonary disease (COPD) is substantial. The objectives of this study were to describe healthcare resource utilization (HCRU) and HCRU-associated costs in patients with COPD in Finland, according to disease severity and blood eosinophil count (BEC). Patients and methods: This non-interventional, retrospective registry study (GSK ID: HO-17-17558) utilized data from the specialist care hospital register. Data extraction was from first hospital visit with a COPD diagnosis (index date) from January 1, 2004 until December 31, 2015 or death. Patients (aged >18 years with >/=1 report of post-bronchodilation forced expiratory volume in 1 s (FEV1)/forced vital capacity (FVC) ratio <0.7) were categorized as having non-severe or severe COPD (FEV1 >50% or </=50% of reference, respectively). Patients who were initially non-severe but progressed to severe were classified as having progressing COPD. Patients without spirometry registry data were classified as having clinically verified COPD. Patients were grouped according to BEC (>/=300 cells/muL, <300 cells/muL or BEC unknown). HCRU, estimated associated costs and mortality were evaluated according to COPD severity

and BEC. Results: There were 9042 patients with COPD; 340 non-severe, 326 progressing, 394 severe, and 7982 clinically verified. BEC was available for 31.8% of patients. The mean follow-up time was 3.7-6.5 years in the classified patient-groups. All-cause mortality was 46% during follow-up. Severe COPD was associated with more COPD-related HCRU and higher mortality than non-severe COPD. Patients with BEC >/=300 cells/muL had higher overall HCRU but improved survival compared with those with BEC <300 cells/muL. Overall direct costs were similar across COPD severity categories, 3300-3900euro/patient-year, although COPD-related costs were higher in patients with severe versus non-severe COPD. Conclusion: This study demonstrated a substantial burden associated with severe and/or eosinophilic COPD for patients in Finland.

Vikjord, S. A. A., B. M. Brumpton, et al. (2019). **"The Association of Bone Mineral Density with Mortality in a COPD Cohort. The HUNT Study, Norway."** Copd **16**(5-6): 321-329.

In individuals with chronic obstructive pulmonary disease (COPD), the presence of comorbidities is associated with increased mortality risk. We wanted to study the association between bone mineral density (BMD) and mortality among individuals with COPD in a population-based cohort study. Participants were recruited from the second (1995-1997) and third (2006-2008) surveys of the HUNT Study and followed until February 2019. Hip and forearm BMD were included as continuous T-scores or categorized according to WHO criteria (normal, osteopenia, and osteoporosis). Hazard ratios with 95% confidence intervals were estimated by multivariable Cox regression models. In total, 2076 and 3239 participants were identified as having COPD by FEV1/FVC below lower limit of normal (LLN) or <0.70, respectively, according to Global Lung Initiative (GLI) and Global Initiative for Chronic Obstructive Lung Disease (GOLD). The prevalence of osteoporosis was 15.7% vs. 16.6% in the GLI-COPD vs. GOLD-COPD cohorts. Mean follow-up was 12.7 and 11.9 years. Lower T-scores were associated with a 5% (95% confidence interval (CI) 1.01-1.09) increased mortality in the GLI-COPD and GOLD-COPD cohorts, respectively. However, the presence of osteoporosis (T < -2.5), compared to normal BMD, was not associated with mortality in neither GLI-COPD (HR 1.13, 95% CI 0.91-1.41) nor GOLD-COPD cohorts (HR 1.22, 95% CI 0.99-1.51). Thus, a small positive association was found between decreasing BMD T-score and mortality in both GLI-COPD and GOLD-COPD. However, osteoporosis as defined by WHO was not associated with mortality, probably due to loss of power upon categorization.

von Siemens, S. M., R. Perneczky, et al. (2019). **"The association of cognitive functioning as measured by the DemTect with functional and clinical characteristics of COPD: results from the COSYCONET cohort."** Respir Res **20**(1): 257.

Alterations of cognitive functions have been described in COPD. Our study aimed to disentangle the relationship between the degree of cognitive function and COPD characteristics including quality of life (QoL).Data from 1969 COPD patients of the COSYCONET cohort (GOLD grades 1-4; 1216 male/ 753 female; mean (SD) age 64.9 +/- 8.4 years) were analysed using regression and path analysis. The DemTect screening tool was used to measure cognitive function, and the St. George's respiratory questionnaire (SGRQ) to assess disease-specific QoL.DemTect scores were < 9 points in 1.6% of patients and < 13 points in 12% when using the original evaluation algorithm distinguishing between < 60 or > =60 years of age. For statistical reasons, we used the average of both algorithms independent of age in all subsequent analyses. The DemTect scores were associated with oxygen content, 6-min-walking distance (6-MWD), C-reactive protein (CRP), modified Medical Research Council dyspnoea scale (mMRC) and the SGRQ impact score. Conversely, the SGRQ impact score was independently associated with 6-MWD, FVC, mMRC and DemTect. These results were combined into a path analysis model to account for direct and indirect effects. The DemTect score had a small, but independent impact on QoL, irrespective of the inclusion of COPD-specific influencing factors or a diagnosis of cognitive impairment.We conclude that in patients with stable COPD lower oxygen content of blood as a measure of peripheral oxygen supply,

lower exercise capacity in terms of 6-MWD, and higher CRP levels were associated with reduced cognitive capacity. Furthermore, a reduction in cognitive capacity was associated with reduced disease-specific quality of life. As a potential clinical implication of this work, we suggest to screen especially patients with low oxygen content and low 6-MWD for cognitive impairment.

Wang, J. X., H. Q. Li, et al. (2019). **"Systemic inflammation and the effects of short-term antibiotic treatment for PPM positive patients with stable COPD."** Int J Chron Obstruct Pulmon Dis **14**: 1923-1932.

Objective: To evaluate patients with stable COPD for the presence of potentially pathogenic microorganisms (PPM), systemic inflammation and the effects of short-term antibiotic therapy in PPM positive patients. Methods: From January 2016 to June 2017, we enrolled 96 stable COPD patients. Bacterial cultures from sputum collections were quantitated, along with markers for systemic inflammation including serum C-reactive protein (CRP), interleukin-8 (IL-8) and plasma fibrinogen (FIB) in all patients. All enrolled patients were followed for 12 months. Forty patients were identified as PPM positive and were randomly divided into an antibiotic group and a control group. The antibiotic group was treated with moxifloxacin orally for 6 days. Lung function and markers for systemic inflammation were repeatedly measured at 30 days and 6 months in PPM positive subjects. Results: Binary logistic regression analysis showed that risk factors for PPM positive are bronchiectasis (OR 4.18, 95% CI 1.20-14.59; P=0.025), COPD assessment test (CAT) >/=20 (OR 17.55, 95% CI 2.82-109.18; P=0.002), spontaneous sputum (OR 15.09, 95% CI 1.36-168.02; P=0.027) and sputum purulence (OR 38.43, 95% CI 5.39-274.21; P=0.000). CRP and IL-8 were higher in PPM positive group than those in PPM negative group (P=0.001, P=0.007, respectively), but there were no differences of FIB between the two groups (P=0.086). Compared to the PPM negative group, the rate of acute exacerbation of COPD was higher (P=0.029) and time to next acute exacerbation was shorter (P=0.030) in PPM positive group. There were no differences in lung function and systemic inflammatory markers either in the control group or the antibiotic group at different time points of follow-up. Conclusion: PPM exists in stable COPD patients and can cause systemic inflammation and is associated with acute exacerbation of COPD. Short-term antibiotic therapy had no effect on systemic inflammation nor on acute exacerbation of COPD.China Clinical Trials Registry: ChiCTR-IOR-15006769.

Wang, Y., J. Liao, et al. (2019). **"Predictive Value of Combining Inflammatory Biomarkers and Rapid Decline of FEV1 for COPD in Chinese Population: A Prospective Cohort Study."** Int J Chron Obstruct Pulmon Dis **14**: 2825-2833.

Background: In China, the high prevalence and mortality rate of Chronic Obstructive Pulmonary Disease (COPD) and the poor intervention effect makes it into a heavy social burden. The main reason is that the current diagnosis of COPD mainly based on the static lung function, which is difficult for early intervention. Through matching a predictive model for high-risk groups of COPD that rewards FEV1 rapid decline as the core, we will establish the early warning model and prove its validity and socio-economic value. Methods: This is a multi-center, prospective, cohort study. A total of 10,000 people aged 40 approximately 75 without lung disease will be recruited and followed for 3 years. Some questionnaires such as St George's Respiratory Questionnaire (SGRQ), income class, educational level, comorbidity, smoking habit, and biomass smoke exposure history will be collected. The baseline level of Interleukin 6 (IL-6), high-sensitivity C-reactive Protein (hs-CRP), microRNAs-23a (miR-23a) in peripheral blood and pH value in exhaled breath condensate (EBC) will be measured, lung spirometry will be tested in the first, second, and fourth years. Primary outcome is the incidence of COPD, multivariate regression analysis will be used to establish the predictive model for COPD in China. Discussion: With the rapid decline of lung function as the core and the baseline inflammatory biomarkers in peripheral blood and pH of the exhaled breath condensate as affecting factors, a predictive model to achieve early detection of high-risk COPD groups will be established and promoted. Trial registration: This study has been registered at

www.ClinicalTrials.gov (registration identifier: NCT03532893) on 21 May 2018, https://register.clinicaltrials.gov.

Waschki, B., P. Alter, et al. (2019). **"High-sensitivity troponin I and all-cause mortality in patients with stable COPD: An analysis of the COSYCONET study."** Eur Respir JChronic obstructive pulmonary disease (COPD) is a leading cause of death with a considerable part of the population dying from cardiovascular diseases. High-sensitivity troponin I (hs-TnI) might help to better identify COPD patients at high risk of mortality. We aimed to study the predictive value of hs-TnI for all-cause mortality beyond established COPD assessments, and after consideration of relevant cardiovascular risk factors and prevalent cardiovascular diseases, in a broad population with stable COPD.Circulating hs-TnI concentrations together with a wide range of respiratory and cardiovascular markers were evaluated in 2085 patients with stable COPD across all severity stages enrolled in the multi-center COSYCONET cohort study. The primary outcome was all-cause mortality over 3 years of follow-up.Hs-TnI was detectable in 2020 (96.9%) patients. The median hs-TnI concentration was 3.8 ng.L(-1) (IQR, 2.56.6 ng.L(-1)) with levels above the 99(th) percentile reference limit of 27 ng.L(-1) observed in 1.8% patients. In Cox regression analyses including adjustments for airflow limitation, dyspnea grade, exercise capacity, and history of severe exacerbations, as well as traditional cardiovascular risk factors, estimated glomerular filtration rate, ankle-brachial index, N-terminal pro-brain natriuretic peptides, and prevalent cardiovascular diseases, hs-TnI was a significant predictor for all-cause mortality, both as a continuous variable (HR for log hs-TnI, 1.28 [95%CI, 1.011.62]) and categorised according to the cut-off of 6 ng.L(-1) (HR, 1.63 [95%CI, 1.102.42]).In patients with stable COPD, hs-TnI is a strong predictor of all-cause mortality beyond established COPD mortality predictors, and independent of a broad range of cardiovascular risk factors and prevalent cardiovascular diseases. Hs-TnI concentrations well-below the upper reference limit provide further prognostic value for all patients with COPD when added to established risk assessments.

Wells, J. M., D. Xing, et al. (2019). **"The matrikine acetyl-proline-glycine-proline and clinical features of COPD: findings from SPIROMICS."** Respir Res **20**(1): 254.

BACKGROUND: Pulmonary and systemic inflammation are central features of chronic obstructive pulmonary disease (COPD). Previous studies have demonstrated relationships between biologically active extracellular matrix components, or matrikines, and COPD pathogenesis. We studied the relationships between the matrikine acetyl-proline-glycine-proline (AcPGP) in sputum and plasma and clinical features of COPD. METHODS: Sputum and plasma samples were obtained from COPD participants in the SPIROMICS cohort at enrollment. AcPGP was isolated using solid phase extraction and measured by mass spectrometry. Demographics, spirometry, quality of life questionnaires, and quantitative computed tomography (CT) imaging with parametric response mapping (PRM) were obtained at baseline. Severe COPD exacerbations were recorded at 1-year of prospective follow-up. We used linear and logistic regression models to measure associations between AcPGP and features of COPD, and Kaplan-Meier analyses to measure time-to-first severe exacerbation. RESULTS: The 182 COPD participants in the analysis were 66 +/- 8 years old, 62% male, 84% White race, and 39% were current smokers. AcPGP concentrations were 0.61 +/- 1.89 ng/mL (mean +/- SD) in sputum and 0.60 +/- 1.13 ng/mL in plasma. In adjusted linear regression models, sputum AcPGP was associated with FEV1/FVC, spirometric GOLD stage, PRM-small airways disease, and PRM-emphysema. Sputum AcPGP also correlated with severe AECOPD, and elevated sputum AcPGP was associated with shorter time-to-first severe COPD exacerbation. In contrast, plasma AcPGP was not associated with symptoms, pulmonary function, or severe exacerbation risk. CONCLUSIONS: In COPD, sputum but not plasma AcPGP concentrations are associated with the severity of airflow limitation, small airways disease, emphysema, and risk for severe AECOPD at 1-year of follow-up. TRIAL REGISTRATION: ClinicalTrials.gov: NCT01969344 (SPIROMICS).

Whelan, M. E., C. Velardo, et al. (2019). **"Mood Monitoring Over One Year for People With Chronic Obstructive Pulmonary Disease Using a Mobile Health System: Retrospective Analysis of a Randomized Controlled Trial."** JMIR Mhealth Uhealth **7**(11): e14946.

BACKGROUND: Comorbid anxiety and depression can add to the complexity of managing treatment for people living with chronic obstructive pulmonary disease (COPD). Monitoring mood has the potential to identify individuals who might benefit from additional support and treatment. OBJECTIVE: We used data from the sElf-management anD support proGrammE (EDGE) trial to examine: (1) the extent to which the mood-monitoring components of a mobile health system for patients with COPD were used by participants; (2) the levels of anxiety and depression symptoms among study participants; (3) the extent to which videos providing advice about coping with low mood were viewed; and (4) the characteristics of participants with differing levels of mood and utilization of mood monitoring. METHODS: A total of 107 men and women with a clinical diagnosis of COPD, aged >/=40 years old, were recruited to the intervention arm of the EDGE trial. Participants were invited to complete the Patient Health Questionnaire-8 and the Generalized Anxiety Disorder-7 test every four weeks using a tablet computer. Mood disturbance based on these measures was defined as a score >/=5 on either scale. Participants reporting a mood disturbance were automatically directed (signposted) to a stress or mood management video. Study outcomes included measures of health status, respiratory quality of life, and symptoms of anxiety and depression. RESULTS: Overall, 94 (87.9%) participants completed the 12-month study. A total of 80 participants entered at least one response each month for at least ten months. On average, 16 participants (range 8-38 participants) entered >/=2 responses each month. Of all the participants, 47 (50%) gave responses indicating a mood disturbance. Participants with a mood disturbance score for both scales (n=47) compared with those without (n=20) had lower health status (P=.008), lower quality of life (P=.009), and greater anxiety (P<.001) and increased depression symptoms (P<.001). Videos were viewed by 64 (68%) people over 12 months. Of the 220 viewing visualizations, 70 (34.7%) began after being signposted. Participants signposted to the stress management video (100%; IQR 23.3-100%) watched a greater proportion of it compared to those not signposted (38.4%; IQR 16.0-68.1%; P=.03), whereas duration of viewing was not significantly different for the mood management video. CONCLUSIONS: Monitoring of anxiety and depression symptoms for people with COPD is feasible. More than half of trial participants reported scores indicating a mood disturbance during the study. Signposting participants to an advisory video when reporting increased symptoms of a mood disturbance resulted in a longer view-time for the stress management video. The opportunity to elicit measures of mood regularly as part of a health monitoring system could contribute to better care for people with COPD.

Winther, H. B., M. Gutberlet, et al. (2020). **"Deep semantic lung segmentation for tracking potential pulmonary perfusion biomarkers in chronic obstructive pulmonary disease (COPD): The multi-ethnic study of atherosclerosis COPD study."** J Magn Reson Imaging **51**(2): 571-579.

BACKGROUND: Chronic obstructive pulmonary disease (COPD) is associated with high morbidity and mortality. Identification of imaging biomarkers for phenotyping is necessary for future treatment and therapy monitoring. However, translation of visual analytic pipelines into clinics or their use in large-scale studies is significantly slowed by time-consuming postprocessing steps. PURPOSE: To implement an automated tool chain for regional quantification of pulmonary microvascular blood flow in order to reduce analysis time and user variability. STUDY TYPE: Prospective. POPULATION: In all, 90 MRI scans of 63 patients, of which 31 had a COPD with a mean Global Initiative for Chronic Obstructive Lung Disease status of 1.9 +/- 0.64 (mu +/- sigma). FIELD STRENGTH/SEQUENCE: 1.5T dynamic gadolinium-enhanced MRI measurement using 4D dynamic contrast material-enhanced (DCE) time-resolved angiography acquired in a single breath-hold in inspiration. [Correction added on August 20, 2019, after first online

publication: The field strength in the preceding sentence was corrected.] ASSESSMENT: We built a 3D convolutional neural network for semantic segmentation using 29 manually segmented perfusion maps. All five lobes of the lung are denoted, including the middle lobe. Evaluation was performed on 61 independent cases from two sites of the Multi-Ethnic Study of Arteriosclerosis (MESA)-COPD study. We publish our implementation of a model-free deconvolution filter according to Sourbron et al for 4D DCE MRI scans as open source. STATISTICAL TEST: Cross-validation 29/61 (# training / # testing), intraclass correlation coefficient (ICC), Spearman rho, Pearson r, Sorensen-Dice coefficient, and overlap. RESULTS: Segmentations and derived clinical parameters were processed in ~90 seconds per case on a Xeon E5-2637v4 workstation with Tesla P40 GPUs. Clinical parameters and predicted segmentations exhibit high concordance with the ground truth regarding median perfusion for all lobes with an ICC of 0.99 and a Sorensen-Dice coefficient of 93.4 +/- 2.8 (mu +/- sigma). DATA CONCLUSION: We present a robust end-to-end pipeline that allows for the extraction of perfusion-based biomarkers for all lung lobes in 4D DCE MRI scans by combining model-free deconvolution with deep learning. LEVEL OF EVIDENCE: 3 Technical Efficacy: Stage 2 J. Magn. Reson. Imaging 2020;51:571-579.

Wu, H. X., K. Q. Zhuo, et al. (2019). **"Peripheral Blood Eosinophil as a Biomarker in Outcomes of Acute Exacerbation of Chronic Obstructive Pulmonary Disease."** Int J Chron Obstruct Pulmon Dis **14**: 3003-3015.

Purpose: Mounting evidence suggests that eosinophil levels correlate with the effects of therapy and phenotype for chronic obstructive pulmonary disease (COPD). This study aimed to clarify the relationship between eosinophil levels and clinical outcomes in patients with acute exacerbation of COPD (AECOPD). Methods: A prospective, multicenter, observational cohort study was performed in three teaching hospitals. Patients were grouped by quartile percentage (0, 0.7, 2.55) and absolute blood eosinophils count (0, 0.05x10(9)/L, 0.17x10(9)/L) and divided into four numbered groups ranked from low to high. Results: The study included 493 AECOPD patients. In the percentile-ranked groups, patients in Group 1 experienced significantly longer hospital stays, higher rates of both noninvasive mechanical ventilation (NIMV), and heart failure than those in Group 4 (12 days vs 10 days, p = 0.005; 29.5% vs 23.6%, p = 0.007; 48.4% vs 28.5%, p = 0.001). Group 1 also had higher frequencies of respiratory failure and pulmonary heart disease compared to Groups 3 and 4 (54.8% vs 34.8%, p = 0.002; 54.8% vs 35%, p = 0.003). In the absolute count-ranked groups, patients in Group 1 had significantly higher rates of NIMV than those in Group 3 (41.1% vs 21.7%, p = 0.001), had higher rates of heart failure, respiratory failure, and pulmonary heart disease than those in Group 3 and 4 (48.1% vs 30.2%, p = 0.003; 48.1% vs 30.4%, p = 0.005; 50.8% vs 32.2%, p = 0.004; 50.8% vs 34.1%, p = 0.008; 51.9% vs 34.1%, p = 0.004; 51.9% vs 33%, p = 0.003). There were outcome differences among the admitting hospital of stays in the absolute count groups (p = 0.002), but the differences were not significant in a pairwise comparison. The proportion of ICU admissions and mortality was different in two cohorts with no difference in a pairwise comparison. Conclusion: Patients with lower eosinophil counts experienced poorer clinical outcomes. Eosinophil levels may be a helpful marker to predict outcomes in AECOPD.

Wurtz, E. T., C. Brasch-Andersen, et al. (2020). **"Heme oxygenase 1 polymorphism, occupational vapor, gas, dust, and fume exposure and chronic obstructive pulmonary disease in a Danish population-based study."** Scand J Work Environ Health **46**(1): 96-104.

Objectives The number of dinucleotide repeats (GT) nmodulate expression of heme oxygenase 1 (HMOX1), a stress response gene. Multiple repeats might affect chronic obstructive pulmonary disease (COPD) susceptibility. We aimed to investigate the association of this polymorphism with COPD and its interaction with occupational exposures (vapor, gas, dust, or fumes). Methods This population-based cross-sectional study included 4703 Danes, aged 45-84 years. HMOX1 (GT) nwas genotyped and grouped as short: </=26, medium: 27-32 and long: >/=33 alleles. COPD was defined by the lower limit

of normal (2.5 (th)FEV 1/FVC and FEV 1centiles). Occupational exposure was defined as ever exposed to vapor, gas, dust, or fume in expert-selected jobs. Associations were analyzed by adjusted mixed logistic regression. Results The population included 6% with COPD, 48% who had smoked >/=10 pack-years, and 46% with occupational exposure. HMOX1 was genotyped in 4423 participants. The adjusted odds ratio (OR) for the association between HMOX1 long allele and COPD was 1.75 [95% confidence interval (CI) 1.18-2.60]. An interaction was evident between HMOX1 long allele and occupational exposure, OR 2.38 (95% CI 1.04-5.46), versus HMOX1 short/medium without exposure. Analyses were replicated in another cohort, aged 20-44 years, N=1168, including 3% with COPD, 25% who had smoked >/=10 pack-years and 20% with occupational exposure. No associations were seen between COPD and HMOX1 long allele here. Conclusions Long alleles in HMOX1 alone and in interaction with occupational exposure seem to be associated with COPD. Failure to replicate data may be due to premature age for COPD development and low occupational exposure prevalence. We propose this long allele may be a genetic contributor to the COPD pathogenesis.

Xiao, W., L. Y. Du, et al. (2019). **"Endotype-driven prediction of acute exacerbations in chronic obstructive pulmonary disease (EndAECOPD): protocol for a prospective cohort study."** BMJ Open **9**(11): e034592.

INTRODUCTION: Current strategies for the prevention of acute exacerbations in chronic obstructive pulmonary disease (COPD) are primarily based on clinical measurements but fail to target the pathophysiological mechanisms, namely endotypes, of the disease. Studies identifying endotypes underlying exacerbation susceptibility and discovering specific biomarkers may lead to the development of targeted therapeutics but are lacking. This study aims to assess a broad spectrum of biomarkers at multiple biological levels (genetics, airway inflammation and respiratory microbiome) for their ability in predicting acute exacerbations of COPD, thus enables high-resolution disease endotyping and may lead to precision treatment of the disease. METHODS AND ANALYSIS: In this prospective cohort study, participants with stable COPD (n=600) will be recruited and assessed for demographics, symptom scores, spirometry, medication use and comorbidities at baseline. Blood will be obtained for genotyping variants in a panel of nine genes. Induced sputum will be collected for the profile of microbiota using 16S rRNA gene sequencing, quantification of bacterial load, inflammatory mediators assay and sputum cytometry. Participants will be followed up for their exacerbations till 12 months and reassessed for the clinical measurements as baseline. The primary outcomes are total number of exacerbations, severe exacerbations, moderate exacerbations and time to first exacerbation. The secondary outcomes are changes in lung function and symptom scores. The effect of biomarkers representing genetic variants, airway inflammation and respiratory microbiome on predicting the frequent exacerbator phenotype and exacerbation frequency will be analysed with multivariable modelling, and time to first exacerbation with a Cox regression model. ETHICS AND DISSEMINATION: The study has been approved by the Clinical Trial and Biomedical Ethics Committee of West China Hospital of Sichuan University (No. 2018-298). The results of the study will be published on peer-reviewed journals. TRIAL REGISTRATION NUMBER: ChiCTR1800019063.

Yamada, H., N. Hida, et al. (2020). **"Effects of Lung Function-Related Genes and TSLP on COPD Phenotypes."** Copd: 1-6.

A weighted genetic risk score (GRS) based on 16 SNPs implicated in reduced lung function in both Japanese and non-Japanese populations was previously associated with the onset of COPD and asthma. We here examine the genetic impact of this lung function GRS on specific COPD phenotypes. A cohort of Japanese COPD patients (N = 270) underwent lung function testing followed by genotyping with allele-specific arrays for 16 SNPs as well as expression quantitative trait loci at TSLP (rs2289276, rs3806933). Lung function GRS scoring and two-step cluster analyses grouped patients into different COPD

phenotypes based on gender, age, smoking index, %FEV1 and lung function GRS. The genetic effect of TSLP on COPD phenotypes was also examined for interactions with the lung function GRS. A total of 270 participants were grouped into 5 clusters. The cluster with the highest levels of lung function GRS was characterized by moderate to severe airflow obstruction and the highest blood eosinophil counts. Regarding TSLP, an increased number of T alleles at both SNPs was found in the cluster characterized by moderate to severe airflow obstruction and heavy smoking (rs2289276, p value = 0.035; rs3806933, p value = 0.047) independent of the lung function GRS. A genetic susceptibility to impaired lung function carries an increased risk of developing COPD characterized by increased eosinophil counts and severe airflow obstruction while individuals with increased TSLP responses to external stimuli have an independent risk of developing severe airflow obstruction in the presence of heavy smoking.

Yang, T., B. Cai, et al. (2020). **"REALizing and improving management of stable COPD in China: a multi-center, prospective, observational study to realize the current situation of COPD patients in China (REAL) - rationale, study design, and protocol."** BMC Pulm Med **20**(1): 11.

BACKGROUND: Chronic obstructive pulmonary disease (COPD) is the fifth leading cause of death in China with a reported prevalence of 8.2% people aged >/=40 years. It is recommended that Chinese physicians follow Global Initiative for Chronic Obstructive Lung Disease (GOLD) and national guidelines, yet many patients with COPD in China remain undiagnosed. Furthermore, missed diagnoses and a lack of standardized diagnosis and treatment remain significant problems. The situation is further complicated by a lack of large-scale, long-term, prospective studies of real-world outcomes, including exacerbation rates, disease severity, efficacy of treatment, and compliance of COPD patients in China. METHODS/DESIGN: The REALizing and improving management of stable COPD in China (REAL) study is a 52-week multi-center, prospective, observational trial. REAL aims to recruit approximately 5000 outpatients aged >/=40 years with a clinical diagnosis of COPD per GOLD 2016. Outpatients will be consecutively recruited from approximately 50 tertiary and secondary hospitals randomly selected across six geographic regions to provide a representative population. Patients will receive conventional medical care as determined by their treating physicians. The primary objective is to evaluate COPD patient outcomes including lung function, health status, exacerbations, hospitalization rate, and dyspnea following 1 year of current clinical practice. Secondary objectives are to assess disease severity, treatment patterns, adherence to medication, and associated risk factors. Data will be collected at two study visits, at patients' usual care visits, and by telephone interview every 3 months. DISCUSSION: Knowledge of COPD among physicians in China is poor. The REAL study will provide reliable information on COPD management, outcomes, and risk factors that may help improve the standard of care in China. Patient recruitment began on 30 June 2017 and the estimated primary completion date is 30 July 2019. TRIAL REGISTRATION: ClinicalTrials.gov identifier: NCT03131362. Registered on 20 March 2017.

Yormaz, B., H. Cebeci, et al. (2020). **"Bone mineral density in emphysema and chronic bronchitis phenotypes in hospitalized male chronic obstructive pulmonary disease patients."** Clin Respir J **14**(1): 47-53.

INTRODUCTION: Risk of osteoporosis known to increase in chronic obstructive pulmonary disease (COPD), but is usually overlooked, especially in male patients. OBJECTIVES: The present study compares the bone mineral density (BMD) measurements of male COPD patients with emphysema and the chronic bronchitis phenotype, and evaluates the association between density of emphysema and osteoporosis. METHODS: Ninety-four patients with COPD, and with emphysema and the chronic bronchitis phenotype, were included in the prospective study. A high-resolution computed tomography (HRCT) was used for the diagnosis of emphysema, and a dual X-ray absorptiometry was used to measure the BMD of the lumbar vertebrae and neck of the femur. RESULTS: Emphysema phenotype 45.75% and chronic bronchitis phenotype 54.25%, based on their clinical findings and a quantitative volumetric analysis by HRCT. Osteoporosis was found 60.47% and 17.65% of patients with emphysema and bronchitis, while

osteopenia was detected 27.91% and 41.18% of patients with emphysema and bronchitis, respectively. A negative correlation was found between HRCT emphysema density and the bone densitometer t-score in patients with osteoporosis. Among the patients with osteoporosis, a positive correlation was found between Body Mass Index (BMI) and the bone densitometer t-score. Only BMI and emphysema score were found to be independent risk factors for a low BMD. One unit drop in BMI increased the risk of osteoporosis by 28% (OR = 1.28, 95% CI 1.14-1.45) (P < 0.001). One unit increase in emphysema score increased the risk of osteoporosis by 6% (OR = 1.06, 95% CI 1.03-1.09) (P < 0.001). CONCLUSION: Especially male patients with emphysema, high dyspnea score, low BMI and frequent exacerbations should be evaluated for osteoporosis.

Yoshimatsu, Y., K. Tobino, et al. (2019). **"Repetitive Saliva Swallowing Test Predicts COPD Exacerbation."** Int J Chron Obstruct Pulmon Dis **14**: 2777-2785.

Introduction: Predicting phenotypes at risk of chronic obstructive pulmonary disease (COPD) exacerbation is extremely important. Dysphagia is becoming recognized as one of these phenotypes. A convenient method of screening for dysphagia and COPD exacerbation risk is desired. The repetitive saliva swallowing test (RSST) is one of the least invasive dysphagia screening methods. We previously reported the possible relation between the RSST result and COPD exacerbation in a retrospective study. Based on this, we performed a prospective study to evaluate the efficacy of RSST as a predictor of COPD exacerbation and to determine its optimal cut-off value for COPD. Methods: Seventy patients with COPD were recruited. Patients underwent the following dysphagia screening tests: the 10-item Eating Assessment Tool, Frequency Scale for the Symptoms of Gastroesophageal Reflux Disease, RSST, water swallowing test, and simple swallow provocation test. After one year, they were classified into two groups according to the presence of COPD exacerbation during the follow-up period. Results: Twenty-seven patients had one or more exacerbations in the past year. During the follow-up period, 28 patients had one or more exacerbations (E group), and 42 had none (non-E group). There were no significant differences between the groups except for the presence of past exacerbations and the results of the RSST, when the cut-off value was set at 2, 3, 4, or 5 swallows. The number of swallows in the RSST was significantly lower in the E group than in the Non-E group. A cut-off value of 5 was the most effective. The time to first exacerbation was significantly longer in those with an RSST value of >5. The RSST was more reliable for differentiating the E group and non-E group than the presence of exacerbation in the past year (hazard ratios: 13.78 and 2.70, respectively). Conclusion: An RSST cut-off value of 5 may be a strong predictor of COPD exacerbation.

Young, A. L., F. J. S. Bragman, et al. (2019). **"Disease Progression Modelling in Chronic Obstructive Pulmonary Disease (COPD)."** Am J Respir Crit Care MedRATIONALE: The decades-long progression of Chronic Obstructive Pulmonary Disease (COPD) renders identifying different trajectories of disease progression challenging. OBJECTIVES: To identify subtypes of COPD patients with distinct longitudinal progression patterns using a novel machine-learning tool called "Subtype and Stage Inference (SuStaIn)", and to evaluate the utility of SuStaIn for patient stratification in COPD. METHODS: We applied SuStaIn to cross-sectional CT imaging markers in 3698 GOLD1-4 patients and 3479 controls from the COPDGene study to identify COPD patient subtypes. We confirmed the identified subtypes and progression patterns using ECLIPSE data. We assessed the utility of SuStaIn for patient stratification by comparing SuStaIn subtypes and stages at baseline with longitudinal follow-up data. MEASUREMENTS AND MAIN RESULTS: We identified two trajectories of disease progression in COPD: a "Tissue-->Airway" subtype (n=2354, 70.4%) in which small airway dysfunction and emphysema precede large-airway wall abnormalities, and an "Airway-->Tissue" subtype (n=988, 29.6%) in which large-airway wall abnormalities precede emphysema and small airway dysfunction. Subtypes were reproducible in ECLIPSE. Baseline stage in both subtypes correlated with future FEV1/FVC decline (r=-0.16 (p<0.001) in the Tissue-->Airway group; r=-0.14

(p=0.011) in the Airway-->Tissue group). SuStaIn placed 30% of smokers with normal lung function at non-baseline stages suggesting imaging changes consistent with early COPD. Individuals with early changes were 2.5 times more likely to meet COPD diagnostic criteria at follow-up. CONCLUSIONS: We demonstrate two distinct patterns of disease progression in COPD using SuStaIn, likely representing different endotypes. One-third of healthy smokers have detectable imaging changes, suggesting a new biomarker of 'early COPD'.

Yu, X. Q., M. H. Wang, et al. (2019). **"Effect of Comprehensive Therapy based on Chinese Medicine Patterns on Self-Efficacy and Effectiveness Satisfaction in Chronic Obstructive Pulmonary Disease Patients."** Chin J Integr Med **25**(10): 736-742.

OBJECTIVE: To evaluate the effect of comprehensive therapy based on Chinese medicine (CM) patterns on self-efficacy and satisfaction with its effectiveness in patients with chronic obstructive pulmonary disease (COPD). METHODS: A total of 216 patients were randomly divided into the trial group (n =108) and the control group (n=108) based on the stratified and block randomization design. Patients in the trial group were treated with conventional Western medicine combined with Bufei Jianpi Granules (), Bufei Yishen Granules (), and Yiqi Zishen Granules () according to the CM patterns respectively, and patients in the control group were treated with conventional Western medicine. The COPD Self-Efficacy Scale (CSES) and the Effectiveness Satisfaction Questionnaire for COPD (ESQ-COPD) were employed in a 6-month treatment and in further 6 month follow-up visit. RESULTS: Among the 216 patients, 191 patients (97 in the trial group and 94 in the control group) fully completed the study. After 12-month treatment and follow-up, the mean scores of the trial group all continued to increase over time, which were significantly higher than those of the control group (P <0.05), and the improvement in the following trial group domain: negative affect domain (12.13%), intense emotional arousal domain (12.21%), physical exertion domain (11.72%), weather/environmental domain (13.77%), behavioral risk domain (7.67%) and total score (10.65%). The trial group also exhibited significantly higher mean scores in the ESQ-COPD (P <0.05) and the improvement in the following domain: capacity for life and work domain (30.59%), clinical symptoms domain (53.52%), effect of therapy domain (35.95%), convenience of therapy domain (35.54%), and whole effect domain (52.47%). CONCLUSIONS: Bufei Jianpi Granules, Bufei Yishen Granules and Yiqi Zishen Granules can improve the self-efficacy and satisfaction of COPD patients.

Zhang, H., J. Li, et al. (2019). **"Effects of Chinese medicine on patients with acute exacerbations of COPD: study protocol for a randomized controlled trial."** Trials **20**(1): 735.

BACKGROUND: The incidence, mortality, and prevalence of chronic obstructive pulmonary disease (COPD) are high in China. Acute exacerbations of COPD (AECOPD) are important events in the management of COPD because they negatively impact health status, rates of hospitalization and readmission, and disease progression. AECOPD have been effectively treated with Chinese medicine for a long time. The aim of this proposed trial is to assess the therapeutic effect of Chinese medicine (CM) on AECOPD. METHODS/DESIGN: This proposed study is a multicenter, double-blind, parallel-group randomized controlled trial (RCT). We will randomly assign 378 participants with AECOPD into two groups in a 1:1 ratio. On the basis of health education and conventional treatment, the intervention group will be treated with CM, and the control group is given CM placebo according to CM syndrome. Patients are randomized to either receive CM or placebo, 10 g/packet, twice daily. The double-blind treatment lasts for 2 weeks and is followed up for 4 weeks. The main outcome is the COPD Assessment Test; secondary outcomes are treatment failure rate, treatment success rate, length of hospital stay, AECOPD readmission rate, intubation rate, mortality, dyspnea, the 36-item Short Form Health Survey, and the COPD patient-reported outcome scale. We will document these outcomes faithfully at the beginning of the study, 2 weeks after treatment, and at the 4 weeks follow-up. DISCUSSION: This high-quality RCT with strict methodology and few design deficits will help to prove the effectiveness of CM for AECOPD.

We hope this trial will provide useful evidence for developing a therapeutic schedule with CM for patients with AECOPD. TRIAL REGISTRATION: ClinicalTrials.gov, NCT03428412. Registered on 4 February 2018.

Zhang, W. Z., M. C. Rice, et al. (2020). **"Association of urine mitochondrial DNA with clinical measures of COPD in the SPIROMICS cohort."** JCI InsightBACKGROUND: Mitochondrial dysfunction, a proposed mechanism of COPD pathogenesis, is associated with the leakage of mitochondrial DNA (mtDNA), which may be detected extracellularly in various bodily fluids. Despite evidence for the increased prevalence of chronic kidney disease in COPD subjects and for mitochondrial dysfunction in the kidneys of murine COPD models, whether urine mtDNA (u-mtDNA) associates with measures of disease severity in COPD is unknown. METHODS: Cell-free u-mtDNA, defined as copy number of mitochondrially-encoded NADH dehydrogenase-1 (MTND1) gene, was measured by real-time quantitative PCR and normalized to urine creatinine in cell-free urine samples from participants in the Subpopulations and Intermediate Outcome Measures in COPD Study (SPIROMICS) cohort. Urine albumin/creatinine ratios (UACR) were measured in the same samples. Associations between u-mtDNA and UACR and clinical disease parameters, including FEV1 % predicted, clinical measures of exercise tolerance, respiratory symptom burden, and chest CT measures of lung structure were examined. RESULTS: U-mtDNA and UACR levels were measured in never smokers (n = 64), smokers without airflow obstruction (n = 109), participants with mild/moderate COPD (n = 142), and participants with severe COPD (n = 168). U-mtDNA was associated with increased respiratory symptom burden, especially among smokers without COPD. Significant sex differences in u-mtDNA levels were observed with females having higher u-mtDNA levels across all study subgroups. U-mtDNA associated with worse spirometry and CT emphysema in males only, and worse respiratory symptoms in females only. Similar associations were not found with UACR. CONCLUSION: U-mtDNA levels may help to identify distinct clinical phenotypes and underlying pathobiological differences in males versus females with COPD.

Zheng, J. P., J. Zhang, et al. (2019). **"Clinical Outcomes Of Using Nebulized Budesonide As The Initial Treatment For Acute Exacerbations Of Chronic Obstructive Pulmonary Disease: A Post-Hoc Analysis."** Int J Chron Obstruct Pulmon Dis **14**: 2725-2731.

Purpose: The current guidelines recommend the use of systemic corticosteroids (SCS) as the optimal treatment for acute exacerbations of chronic obstructive pulmonary disease (AECOPD). The aim of this real-world study was to evaluate whether nebulized budesonide (NBS) could also be used as an initial treatment for AECOPD. Patients and methods: AECOPD patients initially treated with NBS or SCS (oral/intravenous) were enrolled. A large-scale, long-term multicenter cohort study of AECOPD patients was performed to analyze outcomes for each treatment (NCT02051166). Results: Initial NBS and SCS treatment resulted in similar outcomes in terms of improvements in FEV1, PaO2, SaO2, and PaCO2. Disease severity affected outcome similarly in both groups. When the groups were stratified according to whether the initial treatment was subsequently intensified or reduced, more intubation was seen in the groups in which initial treatment was intensified. NBS escalation and SCS reduction groups spent more days in the hospital. The NBS escalation group was associated with the highest medical expenditure and a relatively higher rate of new-onset pneumonia. The NBS maintenance/reduction group showed the lowest mortality rate between groups. Stratification according to initial PaCO2 level showed more intubation in the groups with high initial PaCO2 concentrations. Conclusion: These results indicate that NBS may be used as an initial treatment in certain AECOPD patients, and further studies are needed to better define those most likely to benefit.

Zhi, J., Q. Shan, et al. (2019). **"Low skeletal muscle area as a prognostic marker for chronic obstructive pulmonary disease in elderly patients admitted to ICU."** Sci Rep **9**(1): 19117.

Low L3 skeletal muscle area (SMA), which is assessed on computed tomography (CT) images, has been reported to indicate poor clinical outcomes of patients with acute exacerbation of chronic obstructive pulmonary disease (COPD). The dorsal muscle group area at the T12 vertebral level (T12DMA) was used as an alternative to L3 SMA. This study aimed to investigate whether T12DMA could be used as a predictor of in-hospital mortality and long-term survival in elderly patients with COPD admitted to the intensive care unit (ICU). This single-center retrospective case-control study was performed by analyzing the clinical information and measuring T12DMA on chest CT images of elderly patients with COPD admitted to the ICU between May 2013 and May 2018. This study included 136 patients. The multivariate logistic regression analysis showed that T12DMA, neutrophil-lymphocyte ratio, invasive mechanical ventilation, and systemic steroid therapy were independent risk factors for predicting the hospital mortality. The median survival was significantly higher in the high-T12DMA group (214 days) than in the low-T12DMA group (32 days).

Zhou, A., L. Luo, et al. (2019). **"Prospective development of practical screening strategies for diagnosis of asthma-COPD overlap."** RespirologyBACKGROUND AND OBJECTIVE: ACO is a syndrome with high prevalence. However, a pragmatic diagnostic criterion to differentiate ACO is non-existent. We aimed to establish an effective model for screening ACO. METHODS: A multicentre survey was developed to assess the clinical criteria considered important and applicable by pulmonologists for screening ACO. These experts were asked to take the surveys twice. The expert grading method, analytic hierarchy process and ROC curve were used to establish the model, which was then validated by a cross-sectional study of 1066 patients. The GINA/GOLD document was the gold standard in assessing this model. RESULTS: Increased variability of symptoms, paroxysmal wheezing, dyspnoea, historical diagnosis of COPD or asthma, allergic constitution, exposure to risk factors, the FEV1 /FVC < 70% and a positive BDT were important for screening ACO. According to the weight of each criterion, we confirmed that patients meeting six or more of these eight criteria should be considered to have ACO. We called this Chinese screening model for ACO 'CSMA'. It differentiated patients with ACO with a sensitivity of 83.33%, while the sensitivity of clinician-driven diagnosis had a sensitivity of only 42.73%. CONCLUSION: CSMA is a workable model for screening ACO and provides a simple tool for clinicians to efficiently diagnose ACO.

Zimmermann, M., D. Traxler, et al. (2019). **"Heat shock protein 27 as a predictor of prognosis in patients admitted to hospital with acute COPD exacerbation."** Cell Stress ChaperonesEpisodes of acute exacerbations are major drivers of hospitalisation and death from COPD. To date, there are no objective biomarkers of disease activity or biomarkers to predict patient outcome. In this study, 211 patients hospitalised for an acute exacerbation of COPD have been included. At the time of admission, routine blood tests have been performed including complete blood count, C-reactive protein, cardiac troponin T and NT-proBNP. Heat shock protein 27 (HSP27) serum concentrations were determined at time of admission, discharge and 180 days after discharge by ELISA. We were able to demonstrate significantly increased HSP27 serum concentrations in COPD patients at time of admission to hospital as compared to HSP27 concentrations obtained 180 days after discharge. In univariable Cox regression analyses, a HSP27 serum concentration >/= 3098 pg/mL determined at admission was a predictor of all-cause mortality at 90 days, 180 days, 1 year and 3 years. In multivariable analyses, an increased HSP27 serum concentration at admission retained its prognostic ability with respect to all-cause mortality for up to 1-year follow-up. However, an increased HSP27 serum concentration at admission was not an independent

predictor of long-term all-cause mortality at 3 years. Elevated serum HSP27 concentrations significantly predicted short-term mortality in patients admitted to hospital with acute exacerbation of COPD and could help to improve outcomes by identifying high-risk patients.

Zuo, H., X. Xie, et al. (2019). **"Predictive Value of Novel Inflammation-Based Biomarkers for Pulmonary Hypertension in the Acute Exacerbation of Chronic Obstructive Pulmonary Disease."** Anal Cell Pathol (Amst) **2019**: 5189165.

Recently, there has been an increasing interest in the potential clinical use of several inflammatory indexes, namely, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic-immune-inflammation index (SII). This study aimed at assessing whether these markers could be early indicators of pulmonary hypertension (PH) in patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD). A total of 185 patients were enrolled in our retrospective study from January 2017 to January 2019. Receiver operating characteristic curve (ROC) and area under the curve (AUC) were used to evaluate the clinical significance of these biomarkers to predict PH in patients with AECOPD. According to the diagnostic criterion for PH by Doppler echocardiography, the patients were stratified into two groups. The study group consisted of 101 patients complicated with PH, and the control group had 84 patients. The NLR, PLR, and SII values of the PH group were significantly higher than those of the AECOPD one ($p < 0.05$). The blood biomarker levels were positively correlated with NT-proBNP levels, while they had no significant correlation with the estimated pulmonary arterial systolic pressure (PASP) other than PLR. NLR, PLR, and SII values were all associated with PH ($p < 0.05$) in the univariate analysis, but not in the multivariate analysis. The AUC of NLR used for predicting PH was 0.701 and was higher than PLR and SII. Using 4.659 as the cut-off value of NLR, the sensitivity was 81.2%, and the specificity was 59.5%. In conclusion, these simple markers may be useful in the prediction of PH in patients with AECOPD.