COPD/Emphysema PubMed search results covering the period 26/04/2019-19/07/2019
Systematic reviews and clinical trials

Search strategy: (("pulmonary disease, chronic obstructive"[MeSH Terms] OR "emphysema"[MeSH Terms]) AND ((systematic[sb] OR Clinical Trial[ptyp]) AND English[lang]) AND ("2019/01/19"[CDAT] : "3000"[CDAT])) AND ((systematic[sb] OR Clinical Trial[ptyp]) AND English[lang]) AND ((systematic[sb] OR Clinical Trial[ptyp]) AND English[lang])

Akil, A., M. Semik, et al. (2019). **"Use of a Powered Stapling System for Minimally Invasive Lung Volume Reduction Surgery: Results of a Prospective Double-Blind Single-Center Randomized Trial."** Thorac Cardiovasc Surg **67**(3): 216-221.

BACKGROUND: Video-assisted thoracoscopic surgery (VATS)-lung volume reduction surgery (LVRS) represents an important treatment option for patients with advanced lung emphysema. For VATS lung resection, endoscopic staplers are routinely used. Recently, a new generation of electronically powered stapling systems was developed. In this study, the iDrive powered stapling system (Covidien, Germany) was first tested during VATS-LVRS and compared with a non-electronic conventional device. METHODS: Forty patients with advanced emphysema were enrolled in a prospective randomized trial. All patients underwent bilateral VATS-LVRS. Patients were randomized for iDrive use on the right lung (n = 20) or left lung resection (n = 20). A conventional endoscopic stapler (EndoGIA, Covidien) was used for contralateral resection in same patients. Therefore, 40 resections were performed with the iDrive and 40 with the EndoGIA. The duration of surgery, air leakage after extubation, and on postoperative day 1 (POD1), as well as length of chest tube therapy, were documented. RESULTS: The application of the new system was uneventful. Mean duration of surgery was 52 +/- 2.5 minute in the iDrive group compared with 54 +/- 3.8 minute in the EndoGIA-group (p = 0.5). After extubation, the mean air leakage in the iDrive-group did not differ significantly from that in the EndoGIA-group (p = 0.6). This was also observed on POD1 (p = 0.7). Moreover, length of drainage therapy also did not show significant differences between both groups (p = 0.6). CONCLUSION: The iDrive powered stapling system offers one-handed, push-button operation, which eliminates the manual firing force and possibly enables more precise resection. In the current study, the novel system led to comparable results with the conventional mechanical stapler without any disadvantages in patients undergoing bilateral VATS-LVRS.

https://www.thieme-connect.com/products/ejournals/pdf/10.1055/s-0037-1606313.pdf

Ancochea, J., F. Garcia-Rio, et al. (2018). **"Efficacy and costs of telehealth for the management of COPD: the PROMETE II trial."** Eur Respir J **51**(5)

https://erj.ersjournals.com/content/51/5/1800354

Armitage, J., D. B. A. Tan, et al. (2018). **"Mesenchymal stromal cell infusion modulates systemic immunological responses in stable COPD patients: a phase I pilot study."** Eur Respir J **51**(3)

https://erj.ersjournals.com/content/51/3/1702369

Beeh, K. M., A. M. Kirsten, et al. (2018). **"Indacaterol acetate/mometasone furoate provides sustained improvements in lung function compared with salmeterol xinafoate/fluticasone propionate in patients with moderate-to-very-severe COPD: results from a Phase II randomized, double-blind 12-week study."** Int J Chron Obstruct Pulmon Dis **13**: 3923-3936.

Background and purpose: Fixed-dose combinations of a long-acting beta agonist and an inhaled corticosteroid are more effective than the individual components in COPD. The primary study objective was to demonstrate that the combination indacaterol acetate/mometasone furoate (IND/MF [QMF149]) was non-inferior to the twice-daily combination salmeterol xinafoate/fluticasone propionate (Sal/Flu) in terms of trough FEV1 at week 12 (day 85). Secondary objectives were to compare the efficacy of IND/MF (QMF149) vs Sal/Flu with respect to other lung function parameters, COPD exacerbations, symptoms and dyspnea, health status/health-related quality of life, and rescue medication use. Materials and methods: This was a 12-week multicenter, randomized, double-blind, double-dummy, parallel-group, Phase II study in patients with moderate-to-very-severe COPD, who were randomized (1:1) to IND/MF (QMF149) (150/160 microg once daily; n=316) or Sal/Flu (50/500 microg twice daily; n=313). Results: Over 90% of patients completed the study: 94.6% in the IND/MF (QMF149) group and 92.0% in the Sal/Flu group. The primary objective of non-inferiority of IND/MF (QMF149) to Sal/Flu for trough FEV1 at week 12 (day 85) was met: the lower limit of the CI (95% CI: 27.7, 83.3 mL) was greater than -60 mL. The analysis for superiority of IND/MF (QMF149) to Sal/Flu demonstrated superiority of IND/MF (QMF149), with a difference of 56 mL (P<0.001). In addition, IND/MF (QMF149) treatment significantly improved COPD exacerbation-related parameters during the 12-week period. Other significant improvements with IND/MF (QMF 149) vs Sal/Flu were noted for dyspnea at week 12 and other COPD symptoms and COPD rescue medication use over the 12 weeks. The safety and tolerability profiles of both the treatments were similar. Conclusion: IND/MF (QMF149) (150/160 microg once daily) offered superior lung function and symptom efficacy and a favorable safety profile compared with Sal/Flu (50/500 microg twice daily) in patients with moderate-to-very severe COPD.

https://www.dovepress.com/getfile.php?fileID=46791

Bhatt, S. P., J. A. Anderson, et al. (2018). **"Cigarette smoking and response to inhaled corticosteroids in COPD."** Eur Respir J **51**(1)
https://erj.ersjournals.com/content/51/1/1701393

Bonnevie, T., F. E. Gravier, et al. (2018). **"Home-based Neuromuscular Electrical Stimulation as an Add-on to Pulmonary Rehabilitation Does Not Provide Further Benefits in Patients With Chronic Obstructive Pulmonary Disease: A Multicenter Randomized Trial."** Arch Phys Med Rehabil **99**(8): 1462-1470.
OBJECTIVE: To assess the additional effect of a home-based neuromuscular electrical stimulation (NMES) program as an add-on to pulmonary rehabilitation (PR), on functional capacity in subjects with chronic obstructive pulmonary disease (COPD). DESIGN: Single-blind, multicenter randomized trial. SETTING: Three PR centers. PARTICIPANTS: Subjects with severe to very severe COPD (N=73; median forced expiratory volume in 1 second, 1L (25th-75th percentile, 0.8-1.4L) referred for PR. Twenty-two subjects discontinued the study, but only 1 dropout was related to the intervention (leg discomfort). INTERVENTION: Subjects were randomly assigned to either PR plus quadricipital home-based NMES (35Hz, 30min, 5 time per week) or PR without NMES for 8 weeks. MAIN OUTCOME MEASURE: The 6-minute walk test (6MWT) was used to assess functional capacity. RESULTS: Eighty-two percent of the scheduled NMES sessions were performed. In the whole sample, there were significant increases in the distance walked during the 6MWT (P<.01), peak oxygen consumption (P=.02), maximal workload (P<.01), modified Medical Research Council dyspnea scale (P<.01), and Saint George's Respiratory Questionnaire total score (P=.01). There was no significant difference in the magnitude of change for any outcome between groups. CONCLUSIONS: Home-based NMES as an add-on to PR did not result in further improvements in subjects with severe to very severe COPD; moreover, it may have been a burden for some patients.

https://www.archives-pmr.org/article/S0003-9993(18)30100-X/fulltext

Campbell, B., S. R. Davis, et al. (2018). **"Menopause, lung function and obstructive lung disease outcomes: a systematic review."** Climacteric **21**(1): 3-12.

BACKGROUND: The menopausal transition may have significant consequences for respiratory health, risk of chronic respiratory disease and management strategies. OBJECTIVE: To systematically summarize the literature regarding the impact of menopause status on respiratory health outcomes. METHODS: PubMed was searched systematically to identify population-based studies investigating the associations between menopause status and respiratory outcomes including asthma, chronic obstructive pulmonary disease (COPD), respiratory symptoms and lung function. RESULTS: Ten publications were identified for full review. Evidence on menopause and asthma was conflicting, while studies on COPD were scarce. The findings generally support an association between menopause and clinically significant reductions in lung function in a non-obstructive pattern. However, the effects of menopause are clouded by aging, menopausal hormone therapy use, and increased risk of metabolic syndrome during this period. CONCLUSIONS: As the global burden associated with respiratory conditions continues to rise, the need to understand the associations between menopause and respiratory health is essential to identify potentially modifiable risk factors for respiratory disease in adult women. More studies are needed to clarify the impact of menopause on obstructive lung disease.

https://www.tandfonline.com/doi/full/10.1080/13697137.2017.1392504

Di Mussi, R., S. Spadaro, et al. (2018). **"High-flow nasal cannula oxygen therapy decreases postextubation neuroventilatory drive and work of breathing in patients with chronic obstructive pulmonary disease."** Crit Care **22**(1): 180.

BACKGROUND: The physiological effects of high-flow nasal cannula O2 therapy (HFNC) have been evaluated mainly in patients with hypoxemic respiratory failure. In this study, we compared the effects of HFNC and conventional low-flow O2 therapy on the neuroventilatory drive and work of breathing postextubation in patients with a background of chronic obstructive pulmonary disease (COPD) who had received mechanical ventilation for hypercapnic respiratory failure. METHODS: This was a single center, unblinded, cross-over study on 14 postextubation COPD patients who were recovering from an episode of acute hypercapnic respiratory failure of various etiologies. After extubation, each patient received two 1-h periods of HFNC (HFNC1 and HFNC2) alternated with 1 h of conventional low-flow O2 therapy via a face mask. The inspiratory fraction of oxygen was titrated to achieve an arterial O2 saturation target of 88-92%. Gas exchange, breathing pattern, neuroventilatory drive (electrical diaphragmatic activity (EAdi)) and work of breathing (inspiratory trans-diaphragmatic pressure-time product per minute (PTPDI/min)) were recorded. RESULTS: EAdi peak increased from a mean (+/-SD) of 15.4 +/- 6.4 to 23.6 +/- 10.5 muV switching from HFNC1 to conventional O2, and then returned to 15.2 +/- 6.4 muV during HFNC2 (conventional O2: $p < 0.05$ versus HFNC1 and HFNC2). Similarly, the PTPDI/min increased from 135 +/- 60 to 211 +/- 70 cmH2O/s/min, and then decreased again during HFNC2 to 132 +/- 56 (conventional O2: $p < 0.05$ versus HFNC1 and HFNC2). CONCLUSIONS: In patients with COPD, the application of HFNC postextubation significantly decreased the neuroventilatory drive and work of breathing compared with conventional O2 therapy.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6091018/pdf/13054_2018_Article_2107.pdf

Dicker, A. J., M. L. Crichton, et al. (2018). **"Neutrophil extracellular traps are associated with disease severity and microbiota diversity in patients with chronic obstructive pulmonary disease."** J Allergy Clin Immunol **141**(1): 117-127.

BACKGROUND: Neutrophil extracellular traps (NETs) have been observed in the airway in patients with chronic obstructive pulmonary disease (COPD), but their clinical and pathophysiologic implications have not been defined. OBJECTIVE: We sought to determine whether NETs are associated with disease severity in patients with COPD and how they are associated with microbiota composition and airway neutrophil function. METHODS: NET protein complexes (DNA-elastase and histone-elastase complexes), cell-free

DNA, and neutrophil biomarkers were quantified in soluble sputum and serum from patients with COPD during periods of disease stability and during exacerbations and compared with clinical measures of disease severity and the sputum microbiome. Peripheral blood and airway neutrophil function were evaluated by means of flow cytometry ex vivo and experimentally after stimulation of NET formation. RESULTS: Sputum NET complexes were associated with the severity of COPD evaluated by using the composite Global Initiative for Obstructive Lung Disease scale (P < .0001). This relationship was due to modest correlations between NET complexes and FEV1, symptoms evaluated by using the COPD assessment test, and higher levels of NET complexes in patients with frequent exacerbations (P = .002). Microbiota composition was heterogeneous, but there was a correlation between NET complexes and both microbiota diversity (P = .009) and dominance of Haemophilus species operational taxonomic units (P = .01). Ex vivo airway neutrophil phagocytosis of bacteria was reduced in patients with increased sputum NET complexes. Consistent results were observed regardless of the method of quantifying sputum NETs. Failure of phagocytosis could be induced experimentally by incubating healthy control neutrophils with soluble sputum from patients with COPD. CONCLUSION: NET formation is increased in patients with severe COPD and associated with more frequent exacerbations and a loss of microbiota diversity.

https://www.jacionline.org/article/S0091-6749(17)30746-7/pdf

Hasanin, A., K. Taha, et al. (2018). **"Evaluation of the effects of dexmedetomidine infusion on oxygenation and lung mechanics in morbidly obese patients with restrictive lung disease."** BMC Anesthesiol **18**(1): 104.

BACKGROUND: Dexmedetomidine infusion improves oxygenation and lung mechanics in patients with chronic obstructive lung disease; however, its effect in patients with restrictive lung disease has not been thoroughly investigated yet. The aim of this work was to evaluate the effects of dexmedetomidine infusion on oxygenation and lung mechanics in morbidly obese patients with restrictive lung disease. METHODS: Forty-two morbidly obese patients scheduled for bariatric surgery were included in the study. Patients were randomized to receive either dexmedetomidine infusion at a bolus dose of 1mcg/Kg followed by infusion at 1 mcg/Kg/hour for 90 min (Dexmedetomidine group), or normal saline infusion (Control group). Both groups were compared with regard to: oxygenation {P/F ratio: PaO2/fraction of inspired oxygen (FiO2)}, lung compliance, dead space, plateau pressure, blood pressure, and heart rate. RESULTS: Dexmedetomidine group showed significant improvement of the PaO2/FiO2 ratio, and higher lung compliance compared to control group by the end of drug infusion. Dexmedetomidine group demonstrated decreased dead space, plateau pressure, blood pressure, and heart rate compared to control group by the end of drug infusion. CONCLUSION: A 90-min dexmedetomidine infusion resulted in moderate improvement in oxygenation and lung mechanics in morbidly obese patients with restrictive lung disease. TRIAL REGISTRATION: clinicaltrials.gov : NCT02843698 on 20 July 2016.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6090793/pdf/12871_2018_Article_572.pdf

Irwin, R. S., C. L. French, et al. (2018). **"Classification of Cough as a Symptom in Adults and Management Algorithms: CHEST Guideline and Expert Panel Report."** Chest **153**(1): 196-209.

BACKGROUND: We performed systematic reviews using the population, intervention, comparison, outcome (PICO) format to answer the following key clinical question: Are the CHEST 2006 classifications of acute, subacute and chronic cough and associated management algorithms in adults that were based on durations of cough useful? METHODS: We used the CHEST Expert Cough Panel's protocol for the systematic reviews and the American College of Chest Physicians (CHEST) methodological guidelines and Grading of Recommendations Assessment, Development, and Evaluation framework. Data from the systematic reviews in conjunction with patient values and preferences and the clinical context were used to form recommendations or suggestions. Delphi methodology was used to obtain the final grading. RESULTS: With respect to acute cough (< 3 weeks), only three studies met our criteria for quality

assessment, and all had a high risk of bias. As predicted by the 2006 CHEST Cough Guidelines, the most common causes were respiratory infections, most likely of viral cause, followed by exacerbations of underlying diseases such as asthma and COPD and pneumonia. The subjects resided on three continents: North America, Europe, and Asia. With respect to subacute cough (duration, 3-8 weeks), only two studies met our criteria for quality assessment, and both had a high risk of bias. As predicted by the 2006 guidelines, the most common causes were postinfectious cough and exacerbation of underlying diseases such as asthma, COPD, and upper airway cough syndrome (UACS). The subjects resided in countries in Asia. With respect to chronic cough (> 8 weeks), 11 studies met our criteria for quality assessment, and all had a high risk of bias. As predicted by the 2006 guidelines, the most common causes were UACS from rhinosinus conditions, asthma, gastroesophageal reflux disease, nonasthmatic eosinophilic bronchitis, combinations of these four conditions, and, less commonly, a variety of miscellaneous conditions and atopic cough in Asian countries. The subjects resided on four continents: North America, South America, Europe, and Asia. CONCLUSIONS: Although the quality of evidence was low, the published literature since 2006 suggests that CHEST's 2006 Cough Guidelines and management algorithms for acute, subacute, and chronic cough in adults appeared useful in diagnosing and treating patients with cough around the globe. These same algorithms have been updated to reflect the advances in cough management as of 2017.

https://journal.chestnet.org/article/S0012-3692(17)32918-5/pdf

Jing, G., J. Li, et al. (2019). **"Comparison of high flow nasal cannula with noninvasive ventilation in chronic obstructive pulmonary disease patients with hypercapnia in preventing postextubation respiratory failure: A pilot randomized controlled trial."** Res Nurs Health **42**(3): 217-225.

High flow nasal cannula (HFNC) has been shown to improve extubation outcomes in patients with hypoxemia, but the role of HFNC in weaning patients with chronic obstructive pulmonary disease (COPD) with hypercapnia from invasive ventilation is unclear. We compared the effects of HFNC to noninvasive ventilation (NIV) on postextubation vital signs and arterial blood gases (ABGs) among patients with COPD. Other outcomes included comfort scores, need for bronchoscopy, use of pulmonary medications, and chest physiotherapy. Forty-two COPD patients who had persistent hypercapnia at extubation were assigned randomly to receive HFNC (22) or NIV (20). Twenty patients in each group were enrolled for per-protocol analysis with regard to primary outcomes. Vital signs and ABGs before extubation were similar between groups. At 3 hr after extubation, pH in the NIV group was lower than HFNC group (7.42 +/- 0.06 vs. 7.45 +/- 0.05, p = 0.01). At 24 hr after extubation, patients' mean arterial pressure (82.97 +/- 9.04 vs. 92.06 +/- 11.11 mmHg, p = 0.05) and pH (7.42 +/- 0.05 vs. 7.46 +/- 0.03, p = 0.05) in the NIV group were lower than in the HFNC group. No significant differences were found at 48 hr after extubation. In the HFNC group, comfort scores were better (3.55 +/- 2.01 vs. 5.15 +/- 2.28, p = 0.02) and fewer patients needed bronchoscopy for secretion management within 48 hr after extubation (2/22 vs. 9/20, p = 0.03). HFNC is a potential alternative to NIV to wean hypercapnic COPD patients with regard to vital signs and ABGs, HFNC improved patients' comfort and secretion clearance.

https://onlinelibrary.wiley.com/doi/abs/10.1002/nur.21942

Kesten, S., E. Israel, et al. (2018). **"Development of a novel digital breath-activated inhaler: Initial particle size characterization and clinical testing."** Pulm Pharmacol Ther **53**: 27-32.

BACKGROUND: Delivery of inhaled respiratory medications have been associated with variable delivery of drug due to errors in device operations and have not been designed to monitor true delivery of medication. A fully digital breath-activated inhaled (DBAI) delivery platform has been developed with integrated firmware and software to address these limitations. METHODS: the device was designed to produce similar aerosol particle output to a marketed albuterol MDI and to the albuterol/ipratropium combination in a soft mist inhaler (SMI). Cascade impactor studies were conducted to demonstrate comparable aerodynamic particle size distribution (APSD) metrics. Efficacy was evaluated by pharmacodynamic studies involving spirometry in two separate protocols with adult subjects having

COPD (albuterol DBAI vs. albuterol MDI - Study A, albuterol/ipratropium DBAI single arm - Study B). RESULTS: The total emitted doses (TED) were 81.9+/-10.3, 109.3+/-15.0 and 121.9+/-7.0 mug/actuation for the DBAI, SMI and MDI respectively, and the fine (respirable) particle doses (FPD) were 56.2+/-6.0, 61.7+/-5.5 and 79.4+/-2.7 mug/actuation. MMADs for albuterol sulfate were 1.93+/-0.11, 1.75+/-0.19, and 2.65+/-0.05mum for the DBAI, Respimat soft mist inhaler (SMI) and MDI respectively. The corresponding GSDs were 1.96+/-0.16, 2.79+/-0.25, and 1.48+/-0.02mum. The corresponding respirable fractions were 68.7+/-3.2%, 57.3+/-10.5%, and 65.2+/-2.4%. Spirometric study A enrolled 23 subjects (age 64+/-7.3 years, 39% male, FEV1 45+/-14% predicted). Study B enrolled 23 subjects (age 65+/-8.6 years, 43% male, FEV1 47+/-10% predicted). For Study A, FEV1 at 20min post-dose improved by 120 (167) mL (p=0.002) for the DBAI device and 109 (183) mL (p=0.008) for the MDI device (p=0.86 for between group differences). For Study B, FEV1 (20min post-dose) improved by 216 (126) mL (p<0.001). CONCLUSION: The DBAI generated highly respirable aerosols containing albuterol sulfate that were similar to the MDI and SMI in respirable fraction but lower in dose. Subsequent pharmacodynamic studies delivering albuterol sulfate alone and in combination with ipratropium bromide confirmed similar responses for the DBAI compared with the other inhalers, which could possibly be related to a response ceiling. The DBAI breath-activated capability combined with the ability to monitor actual delivery of medication may improve effectiveness by overcoming patient miscoordination.

https://pdf.sciencedirectassets.com/272345/1-s2.0-S1094553918X00066/1-s2.0-S1094553918301251/main.pdf?X-Amz-Security-Token=AgoJb3JpZ2luX2VjEAEaCXVzLWVhc3QtMSJHMEUCIQDVmY0sFJ%2Bm3anHvetDDdQAU0XWM9mXemI2iwWrrvzYQgIgR%2F%2FmirwzPw4CQy2uX8nZ7smyiVodkRYdxQgUkrEtfAQq2gMIahACGgwwNTkwMDM1NDY4NjUiDKecbCL7hEhSabbWUyq3AxxUGbuSNdgCV1MGgh8wslVR2KNO5FHA6fSNUogm0ZTQQLwPfYFlBCjyS0yaXOTk6KpMos88bCzvexNTchS5kwBt%2FCzofXsOJ8ELQs9Zd4CL3MUQfNzGsAQJ9O8zkJ6D%2FRLFiYPdWL3jcD5qsGEWV6dv%2FM5UZ6SOK4KoMwhyUxiVifcLtqkLJ9XA%2BMAF0Hv4dpN0rtMsCYJF%2FJvmfpXePeVEd0vxvtFLZbXRs4a4XHOi9gWqU%2B7lhSkOBvrc1s7hVUw92m%2BTZhiR9eKCSDp3sFDm4s%2BeI8UtA5zNGRMjoZWrAiP3w04%2FRftwvJKGN2frf7LhAwrcqyOVg1B8Y24h8xvxJLlsrdfHFYIpORoMwc2zZHqiolk4NPJuYDFZd%2FeYS45VKjljAk3Myn66Kp%2FSdbxrpPb21ZeccA0CDC5clPC%2B3jbUe%2Fo3D9C4gunqXXjHXjKFavZ3EKFiYGzuYS7KfJly9tepqISUHCYzJqjtd4KHkUoCAY9mLk3NyiRmFyzDWHqs9MFjKFkrx8U8QHnsWRQ2Ai7cJ1i8xAWAhcaQyuuYk60pdcuNX1ZCgGuhBGaogT8eeIKqnH0wya3E6QU6tAHwwCw2Sz6ifJ%2FBBlvWqEtLFLuzBX2in2fyF6CTZa8qH%2BPz%2Fw91v9ebLZWTB%2F%2BPpUQBPPJOE838iCXtrCSMpk1zHz27LN%2FLKlOAOvyxIUKeyFUY%2BxnZ9FP26Pa218wVItNZvBEEJFgn6trVVLYKvravdJBSfCitgZjEt5Vzg3cWF8fvFQQhdZL1AoXpNLtSUgj3kHqU%2FNm1Sr9QyehhQiGD0PglbyvRR10rXmzGU8ta5bEuKGA%3D&X-Amz-Algorithm=AWS4-HMAC-SHA256&X-Amz-Date=20190719T022130Z&X-Amz-SignedHeaders=host&X-Amz-Expires=300&X-Amz-Credential=ASIAQ3PHCVTY46A2QA75%2F20190719%2Fus-east-1%2Fs3%2Faws4_request&X-Amz-Signature=b16ffeec7a7bd821dd6abd990f900c46958cc958f32cd68085fe737cf2a640d1&hash=c14e6beff241d8f6c2892bd57491f2328d593048eadc5e5e7efb6be338c1e92c&host=68042c943591013ac2b2430a89b270f6af2c76d8dfd086a07176afe7c76c2c61&pii=S1094553918301251&tid=spdf-9cc53659-8891-4c62-adc2-24991ac33188&sid=ed3efb987d8a374be97bde61814aa9d67edcgxrqa&type=client

Kim, Y. S., G. Hong, et al. (2018). **"The role of FGF-2 in smoke-induced emphysema and the therapeutic potential of recombinant FGF-2 in patients with COPD."** Exp Mol Med **50**(11): 150.

Although the positive effects of recombinant fibroblast growth factor-2 (rFGF-2) in chronic obstructive pulmonary disease (COPD) have been implicated in previous studies, knowledge of its role in COPD remains limited. The mechanism of FGF2 in a COPD mouse model and the therapeutic potential of rFGF-2 were investigated in COPD. The mechanism and protective effects of rFGF-2 were evaluated in cigarette smoke-exposed or elastase-induced COPD animal models. Inflammation was assessed in alveolar cells and lung tissues from mice. FGF-2 was decreased in the lungs of cigarette smoke-exposed mice. Intranasal use of rFGF-2 significantly reduced macrophage-dominant inflammation and alveolar destruction in the lungs. In the elastase-induced emphysema model, rFGF-2 improved regeneration of the lungs. In humans, plasma FGF-2 was decreased significantly in COPD compared with normal subjects (10 subjects, P = 0.037). The safety and efficacy of inhaled rFGF-2 use was examined in COPD patients, along with changes in respiratory symptoms and pulmonary function. A 2-week treatment with inhaled rFGF-2 in COPD (n = 6) resulted in significantly improved respiratory symptoms compared with baseline

levels (P < 0.05); however, the results were not significant compared with the placebo. The pulmonary function test results of COPD improved numerically compared with those in the placebo, but the difference was not statistically significant. No serious adverse events occurred during treatment with inhaled rFGF-2. The loss of FGF-2 production is an important mechanism in the development of COPD. Inhaling rFGF-2 may be a new therapeutic option for patients with COPD because rFGF-2 decreases inflammation in lungs exposed to cigarette smoke.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6235987/pdf/12276_2018_Article_178.pdf

Kostikas, K., M. Aalamian-Mattheis, et al. (2018). **"Early Changes in eDiary COPD Symptoms Predict Clinically Relevant Treatment Response at 12 Weeks: Analysis from the CRYSTAL Study."** Copd **15**(2): 185-191.

Early detection of treatment response is important in the long-term treatment and management of patients with chronic obstructive pulmonary disease (COPD). This analysis evaluated whether early improvement in symptoms, recorded in the first 7 or 14 days via an electronic diary (eDiary) compared with baseline, can predict clinically meaningful treatment responders at 12 weeks. CRYSTAL was a 12-week, randomized, open-label study that demonstrated the increased effectiveness of indacaterol/glycopyrronium (IND/GLY) or glycopyrronium (GLY), after a direct switch from on-going baseline therapies, in patients with symptomatic COPD and moderate airflow obstruction. The co-primary endpoints were trough forced expiratory volume in 1 second (FEV1) and transition dyspnea index (TDI) at Week 12. Patients' symptom status was recorded daily in an eDiary. Of 4,389 patients randomized, 3,936 and 3,855 reported symptoms on Days 7 and 14, respectively. Patients who reported an early decrease in symptoms on Day 7 or 14 were more likely to achieve the minimal clinically important difference of >/=100 mL in trough FEV1 or >/= 1 point in TDI at Week 12. Using stepwise multivariate regression models we identified as best predictors of FEV1 responders the decrease in wheeze on Day 7, and nighttime symptoms and wheeze on Day 14; best predictors of TDI responders were decrease in nighttime symptoms and wheeze on Day 7, and nighttime symptoms, sputum and wheeze on Day 14. Early symptom improvement at Day 7 or 14, especially wheeze and nighttime symptoms, may identify patients with clinically important improvement in lung function and dyspnea at Week 12.

https://www.tandfonline.com/doi/full/10.1080/15412555.2018.1445213

Leelarungrayub, J., R. Puntumetakul, et al. (2018). **"Preliminary study: comparative effects of lung volume therapy between slow and fast deep-breathing techniques on pulmonary function, respiratory muscle strength, oxidative stress, cytokines, 6-minute walking distance, and quality of life in persons with COPD."** Int J Chron Obstruct Pulmon Dis **13**: 3909-3921.

Background: Lung volume therapy with the Voldyne((R)) device can improve lung volume and has a nonsignificant benefit on respiratory muscle strength via the slow deep-breathing technique (SDBT); whereas respiratory muscle training with a respiratory muscle trainer via the fast deep-breathing technique (FDBT) has produced a significant improvement in people with COPD. Thus, the aim of this study was to compare the efficiency of lung volume therapy with the Voldyne((R)) device with the SDBT and FDBT on pulmonary function, respiratory muscle strength, oxidative stress, cytokines, walking capacity, and quality of life (QoL) in people with COPD. Methods: A total of 30 COPD patient volunteers with mild (stage I) to moderate (stage II) severity were randomized into two groups: SDBT (n=15) and FDBT (n=15). Pulmonary function (FVC, FEV1, and FEV1/FVC), maximal inspiratory mouth pressure (PImax), oxidative stress status (total antioxidant capacity [TAC], glutathione [GSH], malondialdehyde [MDA], and nitric oxide [NO]), inflammatory cytokines (tumor necrosis factor-alpha [TNF-alpha] and IL-6), 6-minute walking distance (6MWD), and total clinical COPD questionnaire (CCQ) score were evaluated before and after 4 weeks of training. Results: All the parameters had no statistical difference between the groups before training. The PImax, TAC, IL-6, total QoL score, and 6MWD changed significantly in the SDBT group after the 4-week experiment as compared to those in the pre-experimental period, whereas FVC, FEV1, FEV1%, FEV1/FVC%, PImax, TAC, MDA, NO, TNF-alpha, IL-6,

6MWD, and total CCQ score changed significantly in the FDBT group as compared to those in the pre-experimental period. The FEV1%, PImax, TNF-alpha, IL-6, and total CCQ score differed significantly in the FDBT group in the post-experimental period as compared to those in the SDBT group. Conclusion: This preliminary study concluded that the application of incentive spirometry with the Voldyne((R)) device via fast deep breathing possibly improved respiratory muscle strength and QoL and reduced inflammatory cytokines, MDA, and NO better than that via slow deep breathing among people with COPD.

https://www.dovepress.com/getfile.php?fileID=46727

Lin, H. C., N. Kasi, et al. (2019). **"Alpha1-Antitrypsin Deficiency: Transition of Care for the Child With AAT Deficiency into Adulthood."** Curr Pediatr Rev **15**(1): 53-61.

IMPORTANCE: Alpha1-antitrypsin (AAT) deficiency is a common, but an underdiagnosed genetic condition, affecting 1 in 1500 individuals. It can present insidiously with liver disease in children. Although clinical practice guidelines exist for the management of AAT deficiency, especially with regards to pulmonary involvement, there are no published recommendations that specifically relate to the management of the liver disease and monitoring for lung disease associated with this condition, particularly in children. OBJECTIVE: To review the literature on the management of AAT deficiency-associated liver disease in adults and children. EVIDENCE REVIEW: A systematic search for articles indexed in PubMed and published was undertaken. Some earlier selected landmark references were included in the review. Search terms included: "alpha1-antitrypsin deficiency"; "liver disease"; "end-stage liver disease"; "liver transplantation" and "preventative management". Recommendations for the management of children with suspected or confirmed AAT deficiency were made according to the Strength of Recommendation Taxonomy scale. FINDINGS: Liver complications arising from AAT deficiency result from the accumulation of mutated AAT protein within hepatocytes. Liver disease occurs in 10% of children, manifested by cholestasis, pruritus, poor feeding, hepatomegaly, and splenomegaly, but the presentation is highly variable. A diagnostic test for AAT deficiency is recommended for these children. Baseline liver function tests should be obtained to assess for liver involvement; however, the only curative treatment for AAT deficiency-associated liver disease is organ transplantation. Conclusion and Relevance: There should be a greater vigilance for AAT deficiency testing among pediatricians. Diagnosis should prompt assessment of liver involvement. Children with AATdeficiency- associated liver disease should be referred to a liver specialist and monitored throughout their lifetimes for the symptoms of AAT-deficiency-related pulmonary involvement.

http://docserver.ingentaconnect.com/deliver/connect/ben/15733963/v15n1/s10.pdf?expires=1563504617&id=0000&titleid=11441&checksum=E8F94A58AB23047BE61E16A02A432D42

Lv, J., H. Zhang, et al. (2018). **"Comparison of CT radiogenomic and clinical characteristics between EGFR and KRAS mutations in lung adenocarcinomas."** Clin Radiol **73**(6): 590.e1-590.e8.

AIM: To compare computed tomography (CT) radiogenomic and clinical characteristics between patients with epidermal growth factor receptor (EGFR) and Kirsten rat sarcoma viral oncogene (KRAS) mutations in lung adenocarcinomas. MATERIALS AND METHODS: This study was a retrospective analysis of patients with histopathologically confirmed lung adenocarcinoma, who had complete clinical and imaging data, and were tested for EGFR and KRAS mutations. Of the 313 included patients, 116 had effective EGFR mutations (EGFR group), 31 had KRAS mutations (KRAS group), and 166 had no EGFR or KRAS mutations (control group). Multivariate analysis was used to evaluate CT imaging features and clinical data. RESULTS: Multivariate analysis showed that significant variables between the EGFR and control groups were spiculation (odds ratio [OR] 2.70, 95% confidence interval [CI]: 1.54-4.75, p=0.001), and multiple small metastatic nodules (OR=7.52, 95% CI: 1.44-39.17, p=0.017). Significant variables between the KRAS and the control group were multiple small metastatic nodules (OR=7.65, 95% CI: 1.18-49.50, p=0.033). CONCLUSIONS: Patients with EGFR or KRAS mutations are prone to multiple metastases in both lungs. In addition, effective EGFR mutations mostly occurred in patients with multiple spiculations.

https://www.clinicalradiologyonline.net/article/S0009-9260(18)30033-3/fulltext

Mannan, H., S. W. Foo, et al. (2019). **"Does device matter for inhaled therapies in advanced chronic obstructive pulmonary disease (COPD)? A comparative trial of two devices."** BMC Res Notes **12**(1): 94.

OBJECTIVE: COPD patients have challenges for effective use of inhalers due to advanced age, fixed airflow obstruction and comorbid medical conditions. Published clinical trials investigate drug efficacy but rarely consider the inhaler device. This trial investigates device efficacy, comparing clinical outcomes for the same medication via two different devices. Our intention was to communicate the results and to critically appraise the study protocol to inform planning of future device comparison research. Subjects with spirometry confirming at least moderate COPD were randomly assigned to inhaler sequence; starting with Accuhaler or metered dose inhaler and spacer (MDI/s). After baseline testing, subjects were assigned to fluticasone propionate/salmeterol xinafoate (SFC) 500/50 mcg twice daily via the first device for 6 weeks' duration, then changed to the alternate device for the following 6 weeks. Subjects were reassessed in terms of health-related quality of life (HRQL), exercise endurance and lung function after each exposure period. RESULTS: The recruitment target was not achieved due to unanticipated developments within the pharmaceutical industry, potentially compromising the study's power. Study outcomes did not differ significantly according to the allocated inhaler device even after adjusting for baseline lung function or inhaler technique. Recommendations for future device comparison protocols are offered. Trial registration Australia and New Zealand Clinical Trials Registry, Current Controlled Trials ACTRN12618000075280, date of registration: 18.01.2018. Retrospectively registered.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6383223/pdf/13104_2019_Article_4123.pdf

Markun, S., T. Rosemann, et al. (2018). **"Care in Chronic Obstructive Lung Disease (CAROL): a randomised trial in general practice."** Eur Respir J **51**(5)Disease management of chronic obstructive pulmonary disease (COPD) is complex and shortcomings in general practice care for COPD are common. A care bundle is a disease management aid used as a reminder and for steering specific elements of care. Our objectives were to test whether a COPD care bundle delivered to general practitioners (GPs) and practice assistants increases the implementation of key elements of COPD care.The study was a cluster-randomised clinical trial, with 1:1 randomisation of GPs and a 1-year follow-up. The intervention introduced a COPD care bundle and aimed at enhancing collaboration between GPs and practice assistants. The control group continued usual care. The primary outcome measure was the composite score from nine key elements of COPD care measured at the patient level.We enrolled 35 GPs and 216 patients with a median age of 69 years, 59% female, 69% Global Initiative for Chronic Obstructive Lung Disease group A or B. After 1 year, the between-group difference in change of the primary outcome measure was +2.2 (95% CI +1.5- +2.9) in favour of the intervention group. The intervention was associated with significantly higher implementation rates in seven out of nine key elements of care.Disease management using a COPD care bundle increased the implementation of key elements of COPD care in general practice.

https://erj.ersjournals.com/content/51/5/1701873

Medrinal, C., G. Prieur, et al. (2018). **"Functional Electrical Stimulation-A New Therapeutic Approach to Enhance Exercise Intensity in Chronic Obstructive Pulmonary Disease Patients: A Randomized, Controlled Crossover Trial."** Arch Phys Med Rehabil **99**(8): 1454-1461.

OBJECTIVE: To evaluate the effect of quadriceps functional electrical stimulation (FES)-cycling on exertional oxygen uptake (V o2) compared with placebo FES-cycling in patients with chronic obstructive pulmonary disease (COPD). DESIGN: A randomized, single-blind, placebo-controlled crossover trial. SETTING: Pulmonary rehabilitation department. PARTICIPANTS: Consecutive patients (N=23) with COPD Global

Initiative for Chronic Obstructive Lung Disease stage 2, 3, or 4 (mean forced expiratory volume during the first second, 1.4+/-0.4L [50.3% predicted]) who had recently begun a respiratory rehabilitation program. INTERVENTION: Two consecutive 30-minute sessions were carried out at a constant load with active and placebo FES-cycling. MAIN OUTCOME MEASURES: The primary outcome was mean V o2 during the 30-minute exercise session. The secondary outcomes were respiratory gas exchange and hemodynamic parameters averaged over the 30-minute endurance session. Lactate values, dyspnea, and perceived muscle fatigue were evaluated at the end of the sessions. RESULTS: FES-cycling increased the physiological response more than the placebo, with a greater V o2 achieved of 36.6mL/min (95% confidence interval [CI], 8.9-64.3mL/min) (P=.01). There was also a greater increase in lactate after FES-cycling (+1.5mmol/L [95% CI, .05-2.9mmol/L]; P=.01). FES-cycling did not change dyspnea or muscle fatigue compared with the placebo condition. CONCLUSIONS: FES-cycling effectively increased exercise intensity in patients with COPD. Further studies should evaluate longer-term FES-cycling rehabilitation programs.

https://www.archives-pmr.org/article/S0003-9993(18)30153-9/fulltext

Miranda, E. F., W. A. Diniz, et al. (2019). **"Acute effects of photobiomodulation therapy (PBMT) combining laser diodes, light-emitting diodes, and magnetic field in exercise capacity assessed by 6MST in patients with COPD: a crossover, randomized, and triple-blinded clinical trial."** Lasers Med Sci **34**(4): 711-719.

Chronic obstructive pulmonary disease (COPD) is characterized by dyspnea, as well as musculoskeletal and systemic manifestations. Photobiomodulation therapy (PBMT) with use of low-level laser therapy (LLLT) and/or light-emitting diode therapy (LEDT) is an electrophysical intervention that has been found to minimize or delay muscle fatigue. The aim of this study was to evaluate the acute effect of PBMT with combined use of lasers diodes, light-emitting diodes (LEDs), magnetic field on muscle performance, exercise tolerance, and metabolic variables during the 6-minute stepper test (6MST) in patients with COPD. Twenty-one patients with COPD (FEV1 46.3% predicted) completed the 6MST protocol over 2 weeks, with one session per week. PBMT/magnetic field or placebo (PL) was performed before each 6MST (17 sites on each lower limb, with a dose of 30 J per site, using a cluster of 12 diodes 4 x 905 nm super-pulsed laser diodes, 4 x 875 nm infrared LEDs, and 4 x 640 nm red LEDs; Multi Radiance Medical, Solon, OH, USA). Patients were randomized into two groups before the test according to the treatment they would receive. Assessments were performed before the start of each protocol. The primary outcomes were oxygen uptake and number of steps, and the secondary outcome was perceived exertion (dyspnea and fatigue in the lower limbs). PBMT/magnetic field applied before 6MST significantly increased the number of steps during the cardiopulmonary exercise test when compared to the results with placebo (129.8 +/- 10.6 vs 116.1 +/- 11.5, p = 0.000). PBMT/magnetic field treatment also led to a lower score for the perception of breathlessness (3.0 [1.0-7.0] vs 4.0 [2.0-8.0], p = 0.000) and lower limb fatigue (2.0 [0.0-5.0] vs 4.0 [0.0-7.0], p = 0.001) compared to that with placebo treatment. This study showed that the combined application of PBMT and magnetic field increased the number of steps during the 6MST and decreased the sensation of dyspnea and lower limb fatigue in patients with COPD.

https://link.springer.com/article/10.1007%2Fs10103-018-2645-z

Papp, M. E., M. Henriques, et al. (2018). **"Experiences of hatha yogic exercises among patients with obstructive pulmonary diseases: A qualitative study."** J Bodyw Mov Ther **22**(4): 896-903.

BACKGROUND AND AIM: Obstructive pulmonary diseases can involve dyspnea and deconditioning. Hatha yogic exercises are a form of psychophysical attention-based activity. Research of experiences after participating in an adapted hatha yoga (YE) intervention remains limited. The aim of the present study was to explore the experiences of patients with obstructive pulmonary diseases (asthma and chronic obstructive pulmonary disease) in a 12-week hatha yoga intervention (YE). METHOD: Fifteen patients (10 women and 5 men, median age = 61, range: 44-76 years) who had participated in YE were interviewed after the intervention. Interview data were analyzed using qualitative content analysis. RESULTS: Three

main categories emerged: "To focus and be aware of oneself", "To gain new knowledge through practice" and "To master one's own situation". The overall theme "From limitation to opportunity - to experience breathing as a tool in daily life" illustrates a learning process on different levels. The participants described improved physical symptoms and breathing techniques, greater energy/stamina and body awareness along with a new sense of control over their breathing in different situations. CONCLUSIONS: Patients with obstructive pulmonary diseases may strengthen their self-awareness and improve control of symptoms and learning new ways of breathing after practicing YE, which may provide a tool to control disease symptoms in daily life. Trial registration number NCT02233114.

https://www.bodyworkmovementtherapies.com/article/S1360-8592(17)30321-2/fulltext

Polastri, M., V. Comellini, et al. (2018). **"Magnetic Stimulation Therapy in Patients with COPD: A Systematic Review."** Copd **15**(2): 165-170.

Magnetotherapy (MT) is a therapeutic treatment based on the use of magnetic fields (MF) that can have an anti-inflammatory and analgesic effect. MT represents a possible treatment or an ancillary therapeutic intervention for a wide range of diseases and it is often used in the field of physiotherapeutic practices. A crucial point in the treatment of chronic obstructive pulmonary disease (COPD) patients, to counteract muscular depletion and respiratory symptoms, is represented by physiotherapy. Nevertheless, the knowledge about the application of MF as a therapeutic option in COPD patients is very limited. The purpose of the present study was to define what is currently known about the use of MF in patients with COPD. A systematic review of the literature was conducted during the month of October 2017, searching three main databases. Only those citations providing detailed informations about the use of MF to treat COPD symptoms either during an acute or a chronic phase of the disease, were selected. Following the selection process three articles were included in the final analysis. The present review focused on a total of thirty-six patients with COPD, and on the effects of the application of MF. In the majority of cases, the treatment sessions with MF were carried-out in an outpatient setting, and they differed with regard to the duration; frequency of application; dosage; intensity of the applied MF. Basing on the available informations, it seems that MF is a feasible, well tolerated, safe therapeutic option, for the treatment of motor-related COPD symptoms.

https://www.tandfonline.com/doi/full/10.1080/15412555.2018.1439910

Poole, P., K. Sathananthan, et al. (2019). **"Mucolytic agents versus placebo for chronic bronchitis or chronic obstructive pulmonary disease."** Cochrane Database Syst Rev **5**: Cd001287.

BACKGROUND: Individuals with chronic bronchitis or chronic obstructive pulmonary disease (COPD) may suffer recurrent exacerbations with an increase in volume or purulence of sputum, or both. Personal and healthcare costs associated with exacerbations indicate that therapies that reduce the occurrence of exacerbations are likely to be useful. Mucolytics are oral medicines that are believed to increase expectoration of sputum by reducing its viscosity, thus making it easier to cough it up. Improved expectoration of sputum may lead to a reduction in exacerbations of COPD. OBJECTIVES: Primary objective* To determine whether treatment with mucolytics reduces exacerbations and/or days of disability in patients with chronic bronchitis or COPDSecondary objectives* To assess whether mucolytics lead to improvement in lung function or quality of life* To determine frequency of adverse effects associated with use of mucolytics SEARCH METHODS: We searched the Cochrane Airways Group Specialised Register and reference lists of articles on 12 separate occasions, most recently on 23 April 2019. SELECTION CRITERIA: We included randomised studies that compared oral mucolytic therapy versus placebo for at least two months in adults with chronic bronchitis or COPD. We excluded studies of people with asthma and cystic fibrosis. DATA COLLECTION AND ANALYSIS: This review analysed summary data only, most derived from published studies. For earlier versions, one review author extracted data, which were rechecked in subsequent updates. In later versions, review authors double-checked extracted data and then entered data into RevMan 5.3 for analysis. MAIN RESULTS: We added four studies for the 2019 update. The review now includes 38 trials, recruiting a total of 10,377

participants. Studies lasted between two months and three years and investigated a range of mucolytics, including N-acetylcysteine, carbocysteine, erdosteine, and ambroxol, given at least once daily. Many studies did not clearly describe allocation concealment, and we had concerns about blinding and high levels of attrition in some studies. The primary outcomes were exacerbations and number of days of disability.Results of 28 studies including 6723 participants show that receiving mucolytics may be more likely to be exacerbation-free during the study period compared to those given placebo (Peto odds ratio (OR) 1.73, 95% confidence interval (CI) 1.56 to 1.91; moderate-certainty evidence). However, more recent studies show less benefit of treatment than was reported in earlier studies in this review. The overall number needed to treat with mucolytics for an average of nine months to keep an additional participant free from exacerbations was eight (NNTB 8, 95% CI 7 to 10). High heterogeneity was noted for this outcome (I(2) = 62%), so results need to be interpreted with caution. The type or dose of mucolytic did not seem to alter the effect size, nor did the severity of COPD, including exacerbation history. Longer studies showed smaller effects of mucolytics than were reported in shorter studies.Mucolytic use was associated with a reduction of 0.43 days of disability per participant per month compared with use of placebo (95% CI -0.56 to -0.30; studies = 9; I(2) = 61%; moderate-certainty evidence). With mucolytics, the number of people with one or more hospitalisations was reduced, but study results were not consistent (Peto OR 0.68, 95% CI 0.52 to 0.89; participants = 1788; studies = 4; I(2) = 58%; moderate-certainty evidence). Investigators reported improved quality of life with mucolytics (mean difference (MD) -1.37, 95% CI -2.85 to 0.11; participants = 2721; studies = 7; I(2) = 64%; moderate-certainty evidence). However, the mean difference did not reach the minimal clinically important difference of -4 units, and the confidence interval includes no difference. Mucolytic treatment was associated with a possible reduction in adverse events (OR 0.84, 95% CI 0.74 to 0.94; participants = 7264; studies = 24; I(2) = 46%; moderate-certainty evidence), but the pooled effect includes no difference if a random-effects model is used. Several studies that could not be included in the meta-analysis reported high numbers of adverse events, up to a mean of five events per person during follow-up. There was no clear difference between mucolytics and placebo for mortality, but the confidence interval is too wide to confirm that treatment has no effect on mortality (Peto OR 0.98, 95% CI 0.51 to 1.87; participants = 3527; studies = 11; I(2) = 0%; moderate-certainty evidence). AUTHORS' CONCLUSIONS: In participants with chronic bronchitis or COPD, we are moderately confident that treatment with mucolytics leads to a small reduction in the likelihood of having an acute exacerbation, in days of disability per month and possibly hospitalisations, but is not associated with an increase in adverse events. There appears to be limited impact on lung function or health-related quality of life. Results are too imprecise to be certain whether or not there is an effect on mortality. Our confidence in the results is reduced by high levels of heterogeneity in many of the outcomes and the fact that effects on exacerbations shown in early trials were larger than those reported by more recent studies. This may be a result of greater risk of selection or publication bias in earlier trials, thus benefits of treatment may not be as great as was suggested by previous evidence.

Revitt, O., L. Sewell, et al. (2018). **"Early versus delayed pulmonary rehabilitation: A randomized controlled trial - Can we do it?"** Chron Respir Dis **15**(3): 323-326.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6100167/pdf/10.1177_1479972318757469.pdf

Sanders, K. J. C., K. Klooster, et al. (2019). **"CT-derived muscle remodelling after bronchoscopic lung volume reduction in advanced emphysema."** Thorax **74**(2): 206-207.

Muscle wasting frequently occurs in severe emphysema. Improving respiratory mechanics by bronchoscopic lung volume reduction using endobronchial valves (EBV) might prevent further loss or even increase in muscle mass. CT-derived skeletal muscle mass gain was observed in 39/49 patients 6 months after EBV. Multiple linear regression showed that gain in muscle (beta=2.4; 95% CI 0.2 to 4.6; p=0.036) and intramuscular fat (beta=3.1; 95% CI 0.2 to 5.9; p=0.035) is associated with improved 6 min walk distance

independent of the change in residual volume. Skeletal muscle remodelling associates with improved exercise capacity after EBV, independent of hyperinflation reduction. TRIAL REGISTRATION NUMBER: Clinical trial registered with the Dutch trial register www.trialregister.nl (NTR2876), Results.

https://thorax.bmj.com/content/74/2/206.long

Sundh, J., A. Bornefalk-Hermansson, et al. (2019). **"REgistry-based randomized controlled trial of treatment and Duration and mortality in long-term OXygen therapy (REDOX) study protocol."** BMC Pulm Med **19**(1): 50.

OBJECTIVE: Long-term oxygen therapy (LTOT) during 15 h/day or more prolongs survival in patients with chronic obstructive pulmonary disease (COPD) and severe hypoxemia. No randomized controlled trial has evaluated the net effects (benefits or harms) from LTOT 24 h/day compared with 15 h/day or the effect in conditions other than COPD. We describe a multicenter, national, phase IV, non-superiority, registry-based, randomized controlled trial (R-RCT) of LTOT prescribed 24 h/day compared with 15 h/day. The primary endpoint is all-cause-mortality at 1 year. Secondary endpoints include cause-specific mortality, hospitalizations, health-related quality of life, symptoms, and outcomes in interstitial lung disease. METHODS/DESIGN: Patients qualifying for LTOT are randomized to LTOT 24 h/day versus 15 h/day during 12 months using the Swedish Register for Respiratory Failure (Swedevox). Planned sample size in this pragmatic study is 2126 randomized patients. Clinical follow-up and concurrent treatments are according to routine clinical practice. Mortality, hospitalizations, and incident diseases are assessed using national Swedish registries with expected complete follow-up. Patient-reported outcomes are assessed using postal questionnaire at 3 and 12 months. DISCUSSION: The R-RCT approach combines the advantages of a prospective randomized trial and large clinical national registries for enrollment, allocation, and data collection, with the aim of improving the evidence-based use of LTOT. TRIAL REGISTRATION: Clinical Trial registered with www.clinicaltrials.gov , Title: REgistry-based Treatment Duration and Mortality in Long-term OXygen Therapy (REDOX); ID: NCT03441204.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6390558/pdf/12890_2019_Article_809.pdf

Tal, S., Y. Adir, et al. (2019). **"COPD Exacerbator Phenotype is Inversely Associated with Current Smoking But Not with Haptoglobin Phenotype."** Isr Med Assoc J **21**(1): 19-23.

BACKGROUND: Frequent chronic obstructive pulmonary disease (COPD) exacerbators are at a higher risk of adverse health outcomes when compared to infrequent exacerbators. A COPD frequent exacerbator phenotype and its definition has been reported. Haptoglobin (Hp) polymorphism has been associated with differing clinical outcomes in cardiovascular and renal disease. The Hp 2-2 phenotype has been found to have bacteriostatic properties, while the Hp 1-1 phenotype was found to be associated with infections. OBJECTIVES: To determine the correlation in haptoglobin phenotypes and the frequent exacerbator status compared to COPD non-exacerbators. METHODS: Inclusion criteria included previous diagnosis of COPD and presence of at least two documented exacerbations of COPD in the previous 12 months (frequent exacerbator group) or absence of such exacerbations in the previous 24 months (non-exacerbator group). Descriptive data was analyzed using Fisher's exact test and the nonparametric Kruskal-Wallis test. Multivariate logistic regression analysis was performed. RESULTS: The multivariate logistic regression yielded a model in which haptoglobin phenotype did not have a statistically significant association with frequent exacerbator status. Smoking status was found to be negatively related with the frequent exacerbator status (odds ratio [OR] 0.240, 95% confidence interval (95%CI) 0.068-0.843, P = 0.03). Number of pack-years was negatively related to being a frequent exacerbator (OR 0.979, 95%CI 0.962-0.996, P = 0.02). CONCLUSIONS: We found no relationship between haptoglobin polymorphism and frequent exacerbator status. However, frequent exacerbator status had a statistically significant association with COPD Assessment Test scores and pack-years and a negative correlation with current smoking status.

Thoonsen, B., S. H. M. Gerritzen, et al. (2019). **"Training general practitioners contributes to the identification of palliative patients and to multidimensional care provision: secondary outcomes of an RCT."** BMJ Support Palliat Care **9**(1): e18.
INTRODUCTION: To support general practitioners (GPs) in providing early palliative care to patients with cancer, chronic obstructive pulmonary disease or heart failure, the RADboud university medical centre indicators for PAlliative Care needs tool (RADPAC) and a training programme were developed to identify such patients and to facilitate anticipatory palliative care planning. We studied whether GPs, after 1 year of training, identified more palliative patients, and provided multidimensional and multidisciplinary care more often than untrained GPs. METHODS: We performed a survey 1 year after GPs in the intervention group of an RCT were trained. With the help of a questionnaire, all 134 GPs were asked how many palliative patients they had identified, and whether anticipatory care was provided. We studied number of identified palliative patients, expected lifetime, contact frequency, whether multidimensional care was provided and which other disciplines were involved. RESULTS: Trained GPs identified more palliative patients than did untrained GPs (median 3 vs 2; p 0.046) and more often provided multidimensional palliative care (p 0.024). In both groups, most identified patients had cancer. CONCLUSIONS: RADPAC sensitises GPs in the identification of palliative patients. Trained GPs more often provided multidimensional palliative care. Further adaptation and evaluation of the tools and training are necessary to improve early palliative care for patients with organ failure. TRIAL REGISTRATION NUMBER: NTR2815; post results.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6579494/pdf/bmjspcare-2015-001031.pdf

Townsend, S. A., R. G. Edgar, et al. (2018). **"Systematic review: the natural history of alpha-1 antitrypsin deficiency, and associated liver disease."** Aliment Pharmacol Ther **47**(7): 877-885.
BACKGROUND: Alpha-1 antitrypsin deficiency (AATD) is estimated to affect three million people worldwide. It causes liver disease in a proportion of carriers of the PiS and PiZ allele due to the formation and retention of polymers within the endoplasmic reticulum of hepatocytes. The reason for this selective penetrance is not known. Although clinical trials are underway, liver transplantation is the only effective treatment for liver disease due to AATD. AIMS: To report the prevalence and natural history of liver disease among individuals with AATD, and assess the outcomes of liver transplantation through systematic review. METHODS: A comprehensive search was conducted across multiple databases. Two independent authors selected the articles and assessed bias using the Newcastle-Ottawa Scale. Data were pooled for analysis, where comparable outcomes were reported. RESULTS: Thirty-five studies were identified related to disease progression and 12 for the treatment of AATD. Seven per cent of children were reported to develop liver cirrhosis, with 16.5% of individuals presenting in childhood requiring liver transplantation. Of those surviving to adulthood, 10.5% had liver cirrhosis and 14.7% required transplantation. Liver transplantation was the only effective treatment reported and outcomes compare favourably to other indications, with 5-year survival reported as over 90% in children and over 80% in adults. DISCUSSION: The clinical course of liver disease in individuals with AATD remains poorly understood, but affects about 10% of those with AATD. More research is required to identify those patients at risk of developing liver disease at an early stage, and to provide alternative treatments to liver transplantation.

https://onlinelibrary.wiley.com/doi/pdf/10.1111/apt.14537

Ubolsakka-Jones, C., K. Pongpanit, et al. (2019). **"Positive expiratory pressure breathing speeds recovery of postexercise dyspnea in chronic obstructive pulmonary disease."** Physiother Res Int **24**(1): e1750.

OBJECTIVES: Faster recovery of postexertional dyspnea might enable chronic obstructive pulmonary disease (COPD) patients to undertake more physical activity. The purpose of this study was to determine whether breathing with a positive expiratory load to reduce dynamic hyperinflation (DH) would hasten recovery. METHODS: Thirteen male COPD patients (59 +/- 7 years; Global Initiative for Obstructive Lung Disease Stages II and III) took part in a randomized cross-over trial in which they exercised by self-paced spot marching. Interventions at the end of exercise consisted of six breaths against either a 5-cm H2 O expiratory load (positive expiratory pressure [PEP]) or no load (Sham), with 3-hr rest between interventions. Recovery was followed for the next 10 min. Primary outcome measures were dyspnea during recovery and inspiratory capacity (IC), measured at rest, at the end of exercise and after the intervention; oxygen saturation, end-tidal CO2 , heart rate, and breathing frequency were also monitored. RESULTS: Patients exercised for 5 min reaching a heart rate of 70% age-predicted maximum and developed dyspnea of 3-4 on the Modified Borg CR10 scale. Dyspnea recovered significantly faster after the PEP intervention in all patients, taking 2.8 +/- 0.4 min to return to baseline compared with 5.1 +/- 0.6 min for Sham ($p < 0.01$). IC declined at the end of exercise and was improved by PEP (+270 220-460 ml, median, interquartile range) more than Sham (+100, 40-160 ml). However, PEP was equally effective in reducing dyspnea in all patients irrespective of the degree of DH. Changes in oxygen saturation, end-tidal CO2 , heart rate, and breathing frequency were similar in PEP and Sham. CONCLUSIONS: Positive expiratory pressure breathing is an effective means of reducing postexercise dyspnea and DH in COPD. The benefits were not limited to patients with high DH suggesting PEP may be used to speed recovery and increase the volume of exercise during pulmonary rehabilitation sessions and physical activity at home or work.

https://onlinelibrary.wiley.com/doi/pdf/10.1002/pri.1750

Wise, R. A., K. R. Chapman, et al. (2019). **"Effect of Aclidinium Bromide on Major Cardiovascular Events and Exacerbations in High-Risk Patients With Chronic Obstructive Pulmonary Disease: The ASCENT-COPD Randomized Clinical Trial."** Jama **321**(17): 1693-1701.

Importance: There is concern that long-acting muscarinic antagonists increase cardiovascular morbidity or mortality in patients with chronic obstructive pulmonary disease (COPD). Objective: To determine the cardiovascular safety (noninferiority) and efficacy (superiority) of aclidinium bromide, 400 mug twice daily, in patients with COPD and cardiovascular disease or risk factors. Design, Setting, and Participants: Multicenter, randomized, placebo-controlled, double-blind, parallel-design study conducted at 522 sites in North America. A total of 3630 patients with moderate to very severe COPD and either a history of cardiovascular disease or at least 2 atherothrombotic risk factors were randomized; follow-up occurred for up to 3 years until at least 122 major adverse cardiovascular events (MACE) occurred. The first patient was enrolled on October 16, 2013 and the last on August 22, 2016. The final patient completed follow-up on September 21, 2017. Interventions: Patients were randomized to receive aclidinium (n = 1812) or placebo (n = 1818) by dry-powder inhaler, twice daily for up to 3 years. Main Outcomes and Measures: The primary safety end point was time to first MACE over up to 3 years (hazard ratio [HR] 1-sided 97.5% CI noninferiority margin = 1.8). The primary efficacy end point was the annual COPD exacerbation rate during the first year of treatment. Secondary outcomes included an expanded MACE definition (time to first MACE or serious cardiovascular event of interest) and annual rate of exacerbations requiring hospitalization. Results: Among 3589 patients analyzed (mean age, 67.2 years; 58.7% male), 2537 (70.7%) completed the study. Of these, 69 (3.9%) aclidinium and 76 (4.2%) placebo patients had a MACE (HR, 0.89; 1-sided 97.5% CI, 0-1.23); the expanded MACE definition included 168 (9.4%) aclidinium vs 160 (8.9%) placebo patients with events (HR, 1.03; 1-sided 97.5% CI, 0-1.28). Annual moderate to severe exacerbation rates (aclidinium, 0.44; placebo, 0.57; rate ratio, 0.78; 2-sided 95% CI, 0.68-0.89; $P < .001$) and rate of exacerbations requiring hospitalization (aclidinium, 0.07; placebo, 0.10; rate ratio, 0.65; 2-sided 95% CI, 0.48-0.89; $P = .006$) decreased significantly with aclidinium vs placebo. The most common adverse events were pneumonia (aclidinium, 109 events [6.1%]; placebo, 105 events [5.8%]), urinary tract infection (aclidinium, 93 events [5.2%]; placebo, 89 events [5.0%]), and upper respiratory tract infection (aclidinium, 86 events [4.8%]; placebo, 101 events [5.6%]). Conclusions and Relevance: Among patients with COPD and increased cardiovascular risk, aclidinium was noninferior to placebo for risk of MACE over 3 years. The rate of moderate to severe COPD exacerbations was reduced over the first year. Trial Registration: ClinicalTrials.gov Identifier: NCT01966107.

https://jamanetwork.com/journals/jama/articlepdf/2732574/jama_wise_2019_oi_190041.pdf

Xu, H. and X. Lu (2019). **"Inhaled Glucocorticoid with or without Tiotropium Bromide for Asthma-Chronic Obstructive Pulmonary Disease Overlap Syndrome."** J Coll Physicians Surg Pak **29**(3): 249-252.

OBJECTIVE: To compare the efficacy of inhaled glucocorticoid with or without tiotropium bromide in the treatment of patients with asthma-chronic obstructive pulmonary disease overlap syndrome (ACOS). STUDY DESIGN: An experimental study. PLACE AND DURATION OF STUDY: Department of Respiratory Medicine, Wuwei People's Hospital, Gansu Province, China, from October 2016 to October 2017. METHODOLOGY: A total of 86 ACOS patients were randomly divided into the control group and the observation group, with 43 cases in each group. Control group was given inhaled glucocorticoid. Observation group was treated with tiotropium bromide on the basis of the control group. The asthma control test (ACT) score, chronic obstructive pulmonary disease assessment test (CAT) score, serum high-sensitivity C-reactive protein (hs-CRP) and IL-6 levels were compared. RESULTS: Before treatment, there was no significant difference in ACT score, CAT score, serum hs-CRP and IL-6 levels between the two groups (p=0.808, 0.612, 0.872 and 0.921, respectively). After treatment, ACT score in observation group was higher than that in control group (p <0.001). CAT score, serum hs-CRP, and IL-6 levels in observation group were lower than those in control group (all p <0.001). The incidence of adverse reactions was lower in observation group than that in control group (p=0.033). CONCLUSION: Compared with inhaled glucocorticoid, inhaled glucocorticoid combined with tiotropium bromide treatment can more effectively reduce the serum levels of hs-CRP and IL-6 and is beneficial to control the development of ACOS.

Zheng, W., M. Li, et al. (2019). **"Traditional Chinese exercise (TCE) on pulmonary rehabilitation in patients with stable chronic obstructive pulmonary disease: Protocol for a systematic review and network meta-analysis."** Medicine (Baltimore) **98**(27): e16299.

BACKGROUND: Chronic obstructive pulmonary disease (COPD) has the characteristics of high incidence, mortality, disability rate, and heavy economic burden. Symptomatic measures such as anti-inflammatory, antispasmodic and anti-asthmatic are widely used in the treatment of COPD, and pulmonary rehabilitation has not been fully utilized. It is reported that up to 10 different kinds of Traditional Chinese exercises (TCEs) are often used for treating stable COPD. There are many randomized controlled trials (RCTs) and systematic reviews that have evaluated the efficacy of various TCEs for COPD. However, most of these studies were designed in comparison with conventional western medicine or health education. There are rarely studies to compare different TCEs head to head. Therefore, there remains uncertainty regarding the comparative efficacy among different TCEs. Thus, we plan to conduct a systematic review and Network meta-analysis (NMA) to compare the efficacy among 5 different TCEs and rank their benefits relative to each other. It is hoped that the findings of this study will facilitate the management and application of TCEs in the treatment of COPD. METHODS: A systematic and comprehensive literature search will be performed from inception to April 2019 in both English and Chinese databases, involving Medline, Cochrane Library, Embase, China National Knowledge Infrastructure Database, Wanfang Database, China Biomedical Literature Database, and Chongqing VIP information. RCTs related to TCE in the treatment of COPD will be included. Quality of included trials will be assessed according to the risk of bias tool of Cochrane Handbook 5.1.0. The GRADE approach will be used to rate the certainty of the evidence of estimates derived from NMA. Data analysis will be conducted by using STATA 14.0. RESULTS: This systematic review and NMA aims to summarize the direct and indirect evidence for different kinds of TCEs and to rank these TCEs. The findings of this NMA will be reported according to the PRISMA-NMA statement. The results of the NMA will be submitted to a peer-reviewed journal once completed. CONCLUSION: Using NMA, this study will provide an evidence profile which will be helpful to inform the selection of TCE for treating patients with COPD. The results will inform clinicians, bridge

the evidence gaps, and identify promising TCE for future trials. PROSPERO REGISTRATION NUMBER: PROSPERO CRD 42019132970.

Systematic reviews and clinical trials – 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 ("meta-analysis"[All Fields] OR "meta-analyses"[All Fields] OR "randomised"[All] OR "random"[All Fields]) AND English[lang]

(2019). **"Correction: Comparative safety and effectiveness of long-acting inhaled agents for treating chronic obstructive pulmonary disease: a systematic review and network meta-analysis."** BMJ Open **9**(4): e009183corr1.

https://bmjopen.bmj.com/content/bmjopen/9/4/e009183corr1.full.pdf

Alghamdi, S. M., T. Janaudis-Ferreira, et al. (2019). **"Acceptance, adherence and dropout rates of individuals with COPD approached in telehealth interventions: a protocol for systematic review and meta-analysis."** BMJ Open **9**(4): e026794.

INTRODUCTION: Telehealth interventions have the potential of improving exacerbation and health outcomes for individuals with chronic obstructive pulmonary disease (COPD), by delivering care in between clinical visits. However, the precise impact on avoiding exacerbation and reducing the incidence of hospital readmissions remains inconclusive. This lack of knowledge on the effectiveness of telehealth for COPD care might be due to non-adherence or partial adherence to intervention programmes and/or the withdrawal of participants over the course of previous studies. OBJECTIVES: To conduct a systematic review of trials of telehealth interventions (including randomised control trials (RCT), crossover and pre-post studies) to: (1) estimate the acceptance, adherence and dropout rates; (2) identify the reasons for dropout from telehealth interventions among individuals with COPD; (3) evaluate the impact of trial-related, sociodemographic and intervention-related factors on the acceptance, adherence and dropout rates and (4) estimate the extent to which the acceptance, adherence and dropout rates impact outcomes in comparison with usual monitoring. METHODS AND ANALYSIS: A systematic literature review of four databases from earliest records to November 2018 will be carried out using CINAHL, Medline (Ovid), Cochrane Library and Embase. Randomised and non-randomised control studies will be included, in addition to crossover and pre-studies post-studies comparing telehealth with standard monitoring among individuals with COPD only. Two independent reviewers will screen all relevant abstracts and full-text studies to determine eligibility, assess the risk of bias and extract the data using structured forms. If the included studies are sufficiently homogenous in terms of interventions, populations and objectives, a meta-analysis will be performed. ETHICS AND DISSEMINATION: Ethical considerations are not required for this research. TRIAL REGISTRATION NUMBER: CRD42017078541.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6501945/pdf/bmjopen-2018-026794.pdf

Alma, H. J., C. de Jong, et al. (2019). **"Thresholds for clinically important deterioration versus improvement in COPD health status: results from a randomised controlled trial in pulmonary rehabilitation and an observational study during routine clinical practice."** BMJ Open **9**(6): e025776.

OBJECTIVES: Chronic Obstructive Pulmonary Disease (COPD) is a progressive disease. Preventing deterioration of health status is therefore an important therapy goal. (Minimal) Clinically Important Differences ((M)CIDs) are used to interpret changes observed. It remains unclear whether (M)CIDs are similar for both deterioration and improvement in health status. This study investigates and compares these clinical thresholds for three widely-used questionnaires. DESIGN AND SETTING: Data were retrospectively

analysed from an inhouse 3-week pulmonary rehabilitation (PR) randomised controlled trial in the German Klinik Bad Reichenhall (study 1), and observational research in Dutch primary and secondary routine clinical practice (RCP) (study 2). PARTICIPANTS: Patients with COPD aged >/=18 years (study 1) and aged >/=40 years (study 2) without respiratory comorbidities were included for analysis. PRIMARY OUTCOMES: The COPD Assessment Test (CAT), Clinical COPD Questionnaire (CCQ) and St George's Respiratory Questionnaire (SGRQ) were completed at baseline and at 3, 6 and 12 months. A Global Rating of Change scale was added at follow-up. Anchor-based and distribution-based methods were used to determine clinically relevant thresholds. RESULTS: In total, 451 patients were included from PR and 207 from RCP. MCIDs for deterioration ranged from 1.30 to 4.21 (CAT), from 0.19 to 0.66 (CCQ), and from 2.75 to 7.53 (SGRQ). MCIDs for improvement ranged from -3.78 to -1.53 (CAT), from -0.50 to -0.19 (CCQ), and from -9.20 to -2.76 (SGRQ). Thresholds for moderate improvement versus deterioration ranged from -5.02 to -3.29 vs 3.89 to 8.14 (CAT), from -0.90 to -0.72 vs 0.42 to 1.23 (CCQ), and from -15.85 to -13.63 vs 7.46 to 9.30 (SGRQ). CONCLUSIONS: MCID ranges for improvement and deterioration on the CAT, CCQ and SGRQ were somewhat similar. However, estimates for moderate and large change varied and were inconsistent. Thresholds differed between study settings. TRIAL REGISTRATION NUMBER: Routine Inspiratory Muscle Training within COPD Rehabilitation trial: #DRKS00004609; MCID study: #UMCG201500447.

https://bmjopen.bmj.com/content/bmjopen/9/6/e025776.full.pdf

Andell, P., S. James, et al. (2019). **"Oxygen therapy in suspected acute myocardial infarction and concurrent normoxemic chronic obstructive pulmonary disease: a prespecified subgroup analysis from the DETO2X-AMI trial."** Eur Heart J Acute Cardiovasc Care: 2048872619848978.

BACKGROUND: The DETermination of the role of Oxygen in suspected Acute Myocardial Infarction (DETO2X-AMI) trial did not find any benefit of oxygen therapy compared to ambient air in normoxemic patients with suspected acute myocardial infarction. Patients with chronic obstructive pulmonary disease may both benefit and be harmed by supplemental oxygen. Thus we evaluated the effect of routine oxygen therapy compared to ambient air in normoxemic chronic obstructive pulmonary disease patients with suspected acute myocardial infarction. METHODS AND RESULTS: A total of 6629 patients with suspected acute myocardial infarction were randomly assigned in the DETO2X-AMI trial to oxygen or ambient air. In the oxygen group (n=3311) and the ambient air group (n=3318), 155 and 141 patients, respectively, had chronic obstructive pulmonary disease (prevalence of 4.5%). Patients with chronic obstructive pulmonary disease were older, had more comorbid conditions and experienced a twofold higher risk of death at one year (chronic obstructive pulmonary disease: 32/296 (10.8%) vs. non-chronic obstructive pulmonary disease: 302/6333 (4.8%)). Oxygen therapy compared to ambient air was not associated with improved outcomes at 365 days (chronic obstructive pulmonary disease: all-cause mortality hazard ratio (HR) 0.99, 95% confidence interval (CI) 0.50-1.99, Pinteraction=0.96); cardiovascular death HR 0.80, 95% CI 0.32-2.04, Pinteraction=0.59); rehospitalisation with acute myocardial infarction or death HR 1.27, 95% CI 0.71-2.28, Pinteraction=0.46); hospitalisation for heart failure or death HR 1.08, 95% CI 0.61-1.91, Pinteraction=0.77]); there were no significant treatment-by-chronic obstructive pulmonary disease interactions. CONCLUSIONS: Although chronic obstructive pulmonary disease patients had twice the mortality rate compared to non-chronic obstructive pulmonary disease patients, this prespecified subgroup analysis from the DETO2X-AMI trial on oxygen therapy versus ambient air in normoxemic chronic obstructive pulmonary disease patients with suspected acute myocardial infarction revealed no evidence for benefit of routine oxygen therapy consistent with the main trial's findings. CLINICAL TRIALS REGISTRATION: NCT02290080.

Corsico, A. G., F. Braido, et al. (2019). **"Healthcare costs of the SATisfaction and adherence to COPD treatment (SAT) study follow-up."** Respir Med **153**: 68-75.

BACKGROUND: Chronic obstructive pulmonary disease (COPD) is characterised by recurring exacerbations. We estimated the costs of healthcare resources for COPD management funded by the Italian National Healthcare Service (INHS) for one year. METHODS: We examined the demographic, clinical, and economic variables at enrolment and follow-up visits (at 6 and 12 months) of COPD patients participating in the SAT study and referred to 20 Italian pulmonary centres with different institutional characteristics. Costs were expressed in Euro (euro) 2018. A random effects log-linear panel regression model was performed to predict the average cost per patient. RESULTS: Most of the centres were public institutions (90%; public university hospital: 30%). The total average cost of COPD was euro2647.38/patient and ICS/LABA/LAMA therapy contributed the most (euro1541.45). The average cost was euro6206.19/patient for severe COPD (+139.67% vs the cost/patient with mild or moderate COPD). The regression model showed that, others things being equal, increases in the predicted average logged cost per patient were due to liquid oxygen therapy (+468.31%), three COPD exacerbations during the follow-up (+254.54%), and ICS/LABA or ICS/LABA/LAMA associated therapy (+59.26%). Moreover, a 1.19% increment was observed for each additional score of the CAT questionnaire. Conversely, a 36.52% reduction in the predicted average logged cost was reported for hospitals managed by local healthcare authorities. CONCLUSIONS: The health econometric approach is innovative in the management of COPD patients in Italy. The results of the random effects log-linear panel data regression model may help clinicians estimate INHS costs when managing COPD patients. Clinicaltrials.gov ID# NCT02689492.

https://www.resmedjournal.com/article/S0954-6111(19)30176-3/fulltext

Ding, H., M. Karunanithi, et al. (2019). **"Evaluation of an innovative mobile health programme for the self-management of chronic obstructive pulmonary disease (MH-COPD): protocol of a randomised controlled trial."** BMJ Open **9**(4): e025381.

INTRODUCTION: Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death globally. In outpatient care, the self-management of COPD is essential, but patient adherence to this remains suboptimal. The objective of this study is to examine whether an innovative mobile health (mHealth)-enabled care programme (MH-COPD) will improve the patient self-management and relevant health outcomes. METHODS AND ANALYSIS: A prospective open randomised controlled trial has been designed. In the trial, patients with COPD will be recruited from The Prince Charles Hospital, Brisbane, Australia. They will then be randomised to participate in either the MH-COPD intervention group (n=50 patients), or usual care control group (UC-COPD) (n=50 patients) for 6 months. The MH-COPD programme has been designed to integrate an mHealth system within a clinical COPD care service. In the programme, participants will use a mHealth application at home to review educational videos, monitor COPD symptoms, use an electronic action plan, modify the risk factors of cigarette smoking and regular physical activity, and learn to use inhalers optimally. All participants will be assessed at baseline, 3 months and 6 months. The primary outcomes will be COPD symptoms and quality of life. The secondary outcomes will be patient adherence, physical activity, smoking cessation, use of COPD medicines, frequency of COPD exacerbations and hospital readmissions, and user experience of the mobile app. ETHICS AND DISSEMINATION: The clinical trial has been approved by The Prince Charles Hospital Human Research Ethics Committee (HREC/16/QPCH/252). The recruitment and follow-up of the trial will be from January 2019 to December 2020. The study outcomes will be disseminated according to the Consolidated Standards of Reporting Trials statement through a journal publication, approximately 6 months after finishing data collection. TRIAL REGISTRATION NUMBER: ACTRN12618001091291.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6502041/pdf/bmjopen-2018-025381.pdf

Eklof, J., R. Sorensen, et al. (2019). **"Pseudomonas aeruginosa and risk of death and exacerbations in patients with chronic obstructive pulmonary disease: an observational cohort study of 22.053 patients."** Clin Microbiol InfectOBJECTIVES: The role of Pseudomonas aeruginosa on long-term prognosis in COPD is unknown. The purpose of this study was to determine whether P. aeruginosa is associated with increased risk of exacerbations or death in patients with chronic obstructive pulmonary disease (COPD).

METHODS: This is a multiregional epidemiological study based on complete data on COPD outpatients between 1 January 2010 and 31 October 2017 and corresponding microbiology and national register data. Time-dependent Cox proportional hazards models and propensity matching was used to estimate hospitalisation-demanding exacerbations and death after two years, separately and in combination. RESULTS: A total of 22.053 COPD outpatients were followed for a median of 1.082 days (interquartile-range: 427-1.862). P. aeruginosa was present in 905 (4.1%) patients. During 730 days of follow-up, P. aeruginosa strongly and independently predicted an increased risk of hospitalisation for exacerbation or all-cause death (HR 2.8, 95% CI 2.2-3.6; p<0.0001) and all-cause death (HR 2.7, 95% CI 2.3-3.4; p<0.0001) in analyses adjusted for known and suspected confounders. The signal remained unchanged in unadjusted analyses as well as propensity-matched subgroup analyses. Among patients "ever-colonized" with P. aeruginosa, the incidence of hospital-demanding exacerbations doubled after the time of the first colonization. CONCLUSIONS: COPD patients with P. aeruginosa cultured from the airways had a markedly increased risk of exacerbations and death. It is still not clear whether this risk can be reduced by offering patients targeted antipseudomonal antibiotics. A randomised trial is currently recruiting patients to clarify this (ClinicalTrials.gov: NCT03262142).

Fujita, M., K. Nagashima, et al. (2019). **"Handheld flow meter improves COPD detectability regardless of using a conventional questionnaire: A split-sample validation study."** RespirologyBACKGROUND AND OBJECTIVE: Improved detectability of chronic obstructive pulmonary disease (COPD) using a handheld flow meter (HFM) with symptom-based questionnaires has not been sufficiently evaluated. This study aimed to identify the benefit of using an HFM in COPD screening. METHODS: A total of 2008 participants, who were >/= 40 years of age, from Isumi City, Japan, were recruited. We developed two novel point systems for detecting COPD, one incorporated score of HFM alone (sHFM) and the other incorporated the score of International Primary Care Airway Group questionnaire (IPAG) and HFM (sIPAG + HFM). Validation using random sample allocation (split-sample validation) was carried out to assess the predictive performance of these models. RESULTS: Participants were assigned to a data set for model creation (n = 1007) or a data set for model assessment (n = 1001) to perform split-sample validation. Decision curve analysis showed that the net benefits of sHFM and sIPAG + HFM were higher than that of the IPAG score (sIPAG) and specificity of the former two were also significantly higher than that of sIPAG. However, the curves of sHFM and sIPAG + HFM were crossing and practically the same with no significant difference in sensitivity and specificity. CONCLUSION: This study confirms that HFM is significantly advantageous in detecting COPD despite the use of a conventional questionnaire.

https://onlinelibrary.wiley.com/doi/abs/10.1111/resp.13602

Gao, L., D. Si, et al. (2019). **"Tai Chi for the treatment of chronic obstructive pulmonary disease: A systematic review protocol."** Medicine (Baltimore) **98**(26): e16097.

BACKGROUND: Chronic obstructive pulmonary disease (COPD) is a common chronic respiratory disease with increasing morbidity and mortality that cause huge social and economic loss. Although recommended by guidelines, pulmonary rehabilitation has not been widely applied in clinics because of its inherent limitations. Free from restrictions of specific training venues and equipment, Tai Chi, as a kind of pulmonary rehabilitation, has been used to cure the COPD, yet the efficacy and safety of Tai Chi remains to be assessed. In this study, we aim to draw up a protocol for systematic review to evaluate the efficacy and safety of Tai Chi for COPD. METHODS: We will search the following electronic databases from inception to December 31, 2018: PubMed, Web of Science, Medline, Cochrane Central Register of Controlled Trials, Springer, EMBASE, the China National Knowledge Infrastructure Database, Wan Fang Database, the Chinese Scientific Journal Database, and Chinese Biomedical Literature Database. Clinical trial registrations, potential gray literatures, relevant conference abstracts and reference list of identified studies will also be searched. The literature selection, data extraction, and quality assessment will be completed by 2 independent authors. Either the fixed-effects or random-effects model will be used for

data synthesis based on the heterogeneity test. Changes in lung function will be evaluated as the primary outcome. Symptom assessment, quality of life (SGRQ), medication usage, exacerbations, and adverse events will be assessed as the secondary outcomes. The RevMan V.5.3.5 will be used for Meta-analysis. RESULTS: This study will provide a synthesis of current evidence of Tai Chi for COPD from several aspects, such as lung function, SGRQ, medication usage, exacerbations, and adverse events. CONCLUSION: The conclusion of our study will provide updated evidence to judge whether Tai Chi is an effective solution to COPD patients. PROSPERO REGISTRATION NUMBER: PROSPERO CRD42019122791.

Gordon, C. S., J. W. Waller, et al. (2019). **"Effect of Pulmonary Rehabilitation on Symptoms of Anxiety and Depression in COPD: A Systematic Review and Meta-Analysis."** Chest **156**(1): 80-91.

BACKGROUND: Pulmonary rehabilitation (PR) improves exercise capacity and quality of life in people with COPD; however, its effect on anxiety and depression symptoms is less clear. Existing data are difficult to apply to clinical PR because of diverse interventions and comparators. This review evaluated the effectiveness of PR on anxiety and depression symptoms in people with COPD. METHODS: A systematic review and meta-analysis (PROSPERO CRD42018094172) was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines on randomized controlled trials comparing PR (>/= 4 weeks' duration) with usual care. Four electronic databases were searched to February 2018 using terms related to COPD, PR, anxiety, and depression. Data were extracted by two assessors using standardized templates. Study quality was appraised via the PEDro scale, and evidence was rated according to the Grading of Recommendations Assessment, Development and Evaluation. Data were analyzed in RevMan 5.3, with pooled effect estimates reported as standardized mean differences (SMDs). The effect of the program duration (</= 8 vs > 8 weeks) was explored via subgroup analysis. RESULTS: Eleven studies comprising 734 participants (median PEDro score, 4/10) were included. Compared with usual care, PR conferred significant benefits of a moderate magnitude for anxiety symptoms (SMD, -0.53; 95% CI, -0.82 to -0.23) and large magnitude for depression symptoms (SMD, -0.70; 95% CI, -0.87 to -0.53). The certainty of evidence for each outcome was moderate. Effects were not moderated by program duration. CONCLUSIONS: PR confers significant, clinically relevant benefits on anxiety and depression symptoms. Because further studies involving no treatment control groups are not indicated, these robust estimates of treatment effects are likely to endure.

https://journal.chestnet.org/article/S0012-3692(19)30873-6/fulltext

Hosseinzadeh, H. and M. Shnaigat (2019). **"Effectiveness of chronic obstructive pulmonary disease self-management interventions in primary care settings: a systematic review."** Aust J Prim HealthChronic obstructive pulmonary disease (COPD) is one of the more disabling diseases and the third cause of mortality worldwide. Self-management is considered an effective strategy for controlling and managing COPD. This review aims to summarise the available evidence on the effectiveness of COPD self-management in primary care settings. Social Sciences, Citation Index, MEDLINE, CINAHL, Academic Search Complete and Scopus were searched for randomised controlled trials of COPD self-management in general practice between 2001 and 2018. Ten randomised controlled trials of COPD self-management trials conducted in primary care settings were included in this review. The identified trials have recruited stable patients; a majority having mild to moderate COPD. The trials implemented different types of interventions and measured improvements in knowledge, skills and behaviours of self-management, mental health, self-efficacy and endpoint outcomes such as hospitalisation and quality of life. The findings showed that COPD self-management trials had positive effects on COPD knowledge and improved self-management behaviours such as adherence to medication, physical activities and smoking cessation in some cases; however, the effect of trials on hospitalisation rate, quality of life and healthcare utilisation were not conclusive. There was also not enough evidence to suggest that the trials were efficient in improving self-efficacy, a major driver of self-management behaviours. Primary care COPD self-management trials are efficient in improving surrogate outcomes such as knowledge of and

adherence to self-management behaviours; however, such improvements are less likely to be sustainable in the absence of self-efficacy. Future studies should also focus on improving endpoint self-management outcomes like hospitalisation rate and quality of life to benefit both patient and healthcare system.

https://www.publish.csiro.au/py/pdf/PY18181

Ingadottir, A. R., E. B. Bjorgvinsdottir, et al. (2019). **"Effect of two different nutritional supplements on postprandial glucose response and energy- and protein intake in hospitalised patients with COPD: A randomised cross-over study."** Clin NutrINTRODUCTION: Oral nutrition support is frequently used in treatment of malnutrition in patients with chronic obstructive pulmonary disease (COPD). Considering the use of corticoidsteroids in patients with COPD, little is known about the effect on postprandial glucose response and if they might interfere with glucose control. Our aims were to compare the effect of a liquid oral nutritional supplement (ONS) and semi solid inbetween meal snack (snack) on postprandial glucose and energy- and protein intake, and to compare the effect of timing of each intervention on postprandial glucose and energy- and protein intake. METHODS: Patients with COPD (n = 17) admitted to the Department of Pulmonary Medicine, Iceland and defined as at low or medium nutritional risk (score 0-3) were recruited. In a randomised cross-over design, subjects consumed ONS or snack either in a fasting state (study 1) or following breakfast (study 2) and postprandial glucose responses were assessed at regular intervals for two hours (t = 15, t = 30, t = 45, t = 60, t = 90, t = 120 min). Energy- and protein intake was estimated using a validated plate diagram sheet. Wilcoxon Signed-Rank test was used to compare the two interventions. RESULTS: In study 2, following breakfast, postprandial glucose was significantly higher after consuming ONS than the snack after 60 min (9.7 +/- 2.4 mmol/L vs. 8.2 +/- 3.2 mmol/L, p = 0.013 and 120 min 9.2 +/- 3.2 mmol/L vs. 7.9 +/- 2.4 mmol/L, p = 0.021, respectively). No difference was found in postprandial glucose concentrations between ONS and the snack when consumed after overnight fasting (study 1). No difference in energy or protein intake from hospital food was seen between supplement types neither in study 1 or 2. CONCLUSION: Lower postprandial glucose concentrations were associated with the snack compared to ONS when taken after a meal compared to either type directly after overnight fasting. The clinical relevance of higher postprandial blood glucose after consuming a liquid ONS after breakfast compared with a semi solid snack needs to be studied further.

https://www.clinicalnutritionjournal.com/article/S0261-5614(19)30183-9/fulltext

Labarca, G., J. P. Uribe, et al. (2019). **"Bronchoscopic Lung Volume Reduction with Endobronchial Zephyr Valves for Severe Emphysema: A Systematic Review and Meta-Analysis."** Respiration: 1-11.

BACKGROUND: Endoscopic lung volume reduction using Zephyr(R) valves has been recently adopted as a treatment option for patients with severe emphysema without collateral ventilation (CV). OBJECTIVES: To assess the efficacy and safety of Zephyr valves in such a population. METHODS: Studies were identified from MEDLINE and EMBASE databases. All searches were current until June 2018. We performed a systematic review and meta-analysis of randomized controlled trials (RCTs) evaluating the efficacy and safety of Zephyr. We defined as outcome: change in forced expiratory volume in 1 s (FEV1), in the 6-min walking test (6MWT), in the St George's Respiratory Questionnaire (SGRQ), and in residual volume (RV). Safety analysis included relative risk (RR) of pneumothorax. We assessed the quality of the evidence using GRADE. RESULTS: 7 RCTs reported on Zephyr valves and 5 RCTs included only patients without CV. Zephyr improved FEV1 with a mean difference (MD) of 17.36% (CI, 9.28-25.45, I2 = 78%). Subgroup analysis showed significant FEV1 improvement following Zephyr placement in patients with heterogeneous distribution: MD = 21.78% (CI, 8.70-34.86, I2 = 89%) and 16.27% (CI, 8.78-23.76, I2 = 0%) in patients with homogeneous emphysema. Studies with a follow-up of 3 months reported FEV1 MD = 17.19% (CI, 3.16-31.22, I2 = 89%) compared to studies with a follow-up of 6-12 months, which showed a consistent improvement of FEV1 MD = 17.90% (CI, 11.47-24.33, I2 = 0%). Zephyr also showed improvement of SGRQ, 6MWT, and RV. RR of pneumothorax was 6.32 (CI, 3.74-10.67, I2 = 0%). CONCLUSION: In this population, Zephyr valves provided significant and clinically meaningful short-term

improvements in either homogeneous or heterogeneous emphysema without CV but with an increase in adverse events.

https://www.karger.com/Article/Abstract/499508

Lambe, T., P. Adab, et al. (2019). **"Model-based evaluation of the long-term cost-effectiveness of systematic case-finding for COPD in primary care."** Thorax **74**(8): 730-739.

INTRODUCTION: 'One-off' systematic case-finding for COPD using a respiratory screening questionnaire is more effective and cost-effective than routine care at identifying new cases. However, it is not known whether early diagnosis and treatment is beneficial in the longer term. We estimated the long-term cost-effectiveness of a regular case-finding programme in primary care. METHODS: A Markov decision analytic model was developed to compare the cost-effectiveness of a 3-yearly systematic case-finding programme targeted to ever smokers aged >/=50 years with the current routine diagnostic process in UK primary care. Patient-level data on case-finding pathways was obtained from a large randomised controlled trial. Information on the natural history of COPD and treatment effects was obtained from a linked COPD cohort, UK primary care database and published literature. The discounted lifetime cost per quality-adjusted life-year (QALY) gained was calculated from a health service perspective. RESULTS: The incremental cost-effectiveness ratio of systematic case-finding versus current care was pound16 596 per additional QALY gained, with a 78% probability of cost-effectiveness at a pound20 000 per QALY willingness-to-pay threshold. The base case result was robust to multiple one-way sensitivity analyses. The main drivers were response rate to the initial screening questionnaire and attendance rate for the confirmatory spirometry test. DISCUSSION: Regular systematic case-finding for COPD using a screening questionnaire in primary care is likely to be cost-effective in the long-term despite uncertainties in treatment effectiveness. Further knowledge of the natural history of case-found patients and the effectiveness of their management will improve confidence to implement such an approach.

https://thorax.bmj.com/content/thoraxjnl/74/8/730.full.pdf

Li, C., W. Cheng, et al. (2019). **"Relationship of inhaled long-acting bronchodilators with cardiovascular outcomes among patients with stable COPD: a meta-analysis and systematic review of 43 randomized trials."** Int J Chron Obstruct Pulmon Dis **14**: 799-808.

Background: Long-acting muscarinic antagonists (LAMAs) and long-acting beta2-agonists (LABAs) are the mainstay of maintenance therapy for chronic obstructive pulmonary disease (COPD). Although previous studies have supported inhaled long-acting bronchodilators (ILABs) for overall cardiovascular safety, the risk of specific cardiovascular outcomes such as arrhythmia, heart failure and stroke is still unknown. Materials and methods: We systematically searched from PubMed, the Embase database and the Cochrane Library for published studies on ILABs and COPD, from its inception to November 10, 2018, with no language restrictions. The RRs and corresponding 95% CIs were pooled to evaluate ILAB/placebo. Results: Finally, 43 randomized controlled trials were included. Compared with placebo, ILABs do not increase the risk of overall and specific cardiovascular adverse events (AEs); on the contrary, they can reduce the incidence of hypertension (RR 0.73, 95% CI 0.55-0.98;I(2)19.9%; P= 0.221). However, when stratified according to the specific agents of ILABs, olodaterol might reduce the risk of overall cardiovascular adverse events (OCAEs) (RR 0.65, 95% CI 0.49-0.88;I(2)27.5%; P= 0.000), and the protective effect of lowing blood pressure disappeared. Similarly, the use of inhaled LABA might increase the risk of cardiac failure (RR 1.71, 95% CI 1.04-2.84;I(2)0%; P= 0.538), but this risk disappeared when stratified according to the specific agents of LABA. Besides, formoterol might decrease the risk of cardiac ischemia (RR 0.53, 95% CI 0.32-0.91; I(2)0%; P= 0.676). Conclusions: Overall, the use of ILABs was not associated with overall cardiovascular AEs in patients with stable COPD. When stratified according to the specific agents of LABA, olodaterol might reduce the risk of OCAE; and formoterol might decrease the risk of cardiac ischemia. LABA might reduce the incidence of hypertension, but might increase the risk of heart failure. Therefore, COPD patients with a history of heart failure should use it with caution.

https://www.dovepress.com/getfile.php?fileID=49088

Li, J., J. Luo, et al. (2019). **"Effects of flow rate on transnasal pulmonary aerosol delivery of bronchodilators via high-flow nasal cannula for patients with COPD and asthma: protocol for a randomised controlled trial."** BMJ Open **9**(6): e028584.

INTRODUCTION: Both in vitro and in vivo radiolabelled studies on nebulisation via high-flow nasal cannula showed that inhaled dose decreases as the administered gas flow increases. In our previous in vitro study, we investigated the effects of the ratio of gas flow to subject's peak inspiratory flow (GF:IF) on the aerosol deposition, which increased as the GF:IF decreased, with an optimal GF:IF between 0.1 and 0.5 producing a stable 'lung' deposition in both quiet and distressed breathing. Thus, we aim to validate our in vitro findings in subjects with reversible airflow limitations by assessing their response to inhaled bronchodilator. METHODS AND ANALYSIS: This is a single-centre, randomised controlled trial. Subjects with chronic obstructive pulmonary disease or asthma with positive response to 400mug albuterol via metered dose inhaler and valved holding chamber will be enrolled and consented. After a washout period (1-3 days), subjects will be randomly assigned to inhale albuterol with one of three gas flows: 50 L/min, GF:IF=1.0 and GF:IF=0.5. In each arm, subjects will inhale 2 mL saline, followed by escalating doubling doses (0.5, 1, 2 and 4 mg) of albuterol in a fill volume of 2 mL, delivered by a vibrating mesh nebuliser via heated nasal cannula set up at 37 degrees C. An interval of 30 min between each dose of albuterol, with spirometry measured at baseline and after each inhalation. Titration will be terminated if forced expiratory volume in 1 s improvement is <5%, or adverse event is observed. ETHICS AND DISSEMINATION: This trial has been approved by the Ethic Committee of People's Liberation Army General Hospital, Beijing, China (no. S2018-200-01). The results will be disseminated through peer-reviewed journals, national and international conferences. TRIAL REGISTRATION NUMBER: NCT03739359; Pre-results.

https://bmjopen.bmj.com/content/bmjopen/9/6/e028584.full.pdf

Li, W., Y. Pu, et al. (2019). **"Effectiveness of pulmonary rehabilitation in elderly patients with COPD: A systematic review and meta-analysis of randomized controlled trials."** Int J Nurs Pract: e12745.

AIM: The review aimed to evaluate the effects of pulmonary rehabilitation in elderly patients with chronic obstructive pulmonary disease (COPD). BACKGROUND: With an increase in published reports on pulmonary rehabilitation, there is a need for a meta-analysis to measure the effects of pulmonary rehabilitation in elderly COPD patients. DESIGN: A systematic review and meta-analysis. DATA SOURCES: The Cochrane library (Issue 4, 2018), Web of Science (1975 to April 2018), Embase (1974 to April 2018), Pubmed (1966 to April 2018), CINAHL (1982 to April 2018), JBI (The Joanna Briggs Institute) (1996 to April 2018), CNKI (China National Knowledge Infrastructure) (1979 to April 2018), CBM (SinoMed) (1982 to April 2018), and Wanfang Data (1900 to April 2018) were searched. REVIEW METHODS: Six outcome indicators were utilized for the effects of pulmonary rehabilitation. Two reviewers selected trials, evaluated the quality, and extracted data. Meta-analysis was performed by using the RevMan 5.3 software. RESULTS: Eight studies recruited 414 elderly patients. Pulmonary rehabilitation resulted in significantly improved exercise capacity and quality of life in elderly people but with no influence on oxygen saturation compared with the control group. CONCLUSION: There is a need to provide more detailed pulmonary rehabilitation programs for elderly patients with COPD.

https://onlinelibrary.wiley.com/doi/abs/10.1111/ijn.12745

Liao, Y., C. Huang, et al. (2019). **"Association of Surfactant-Associated Protein D Gene Polymorphisms with the Risk of COPD: a Meta-Analysis."** Clinics (Sao Paulo) **74**: e855.

The relationship between surfactant-associated protein D polymorphisms and chronic obstructive pulmonary disease risk remains controversial. This article is the first to systematically evaluate this relationship. A comprehensive worldwide search was conducted for relevant literature on surfactant-associated protein D gene mutations and chronic obstructive pulmonary disease risk prediction. Study quality was evaluated using the Newcastle-Ottawa scale. After four genetic models (the allele, additive, recessive, and dominant models) were identified, odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) were applied in this meta-analysis. The meta-analysis included 659 individuals in the case group and 597 in the control group. In the Asian population, none of the four genetic models revealed any significant association between rs2243639 genotype and the risk of chronic obstructive pulmonary disease. In Caucasians, however, the recessive model exhibited significant risk associated with rs2243639. Furthermore, there was a significant association between rs721917 genotype and the risk of chronic obstructive pulmonary disease in the Asian population. In contrast, none of the four gene models revealed any significant risk associated with this gene in the Caucasian population. This meta-analysis suggests that rs2243639 is not related to the risk of chronic obstructive pulmonary disease in the Asian population but is related to this risk in the Caucasian population. Regarding rs721917, the T allele may increase the risk of chronic obstructive pulmonary disease in the Asian population.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6512347/pdf/cln-74-855.pdf

Lin, F. L., M. L. Yeh, et al. (2019). **"Two-month breathing-based walking improves anxiety, depression, dyspnoea and quality of life in chronic obstructive pulmonary disease: A randomised controlled study."** J Clin NursAIMS AND OBJECTIVES: To examine the effects of the two-month breathing-based walking intervention and its follow-up on anxiety, depression, dyspnoea and quality of life in patients with chronic obstructive pulmonary disease. BACKGROUND: Mind-body-related exercises improve bio-psychological symptoms and quality of life in chronic diseases, but these improvements are not proven for chronic obstructive pulmonary disease. DESIGN: This was a randomised controlled study and applied the Consolidated Standards of Reporting Trials (CONSORT) statement. METHODS: Outpatients diagnosed with chronic obstructive pulmonary disease were recruited from a medical centre in Taiwan and randomly assigned to two groups. The walking group (n = 42) received breathing, meditation and walking for two months, and the control group (n = 42) did not. Data from the outcomes of anxiety, depression, dyspnoea and quality of life were collected at baseline and in Month 1, Month 2 and Month 3. Clinical trial registration was done (ClinicalTrials.gov.: NCT03388489). FINDINGS: The results showed significant changes in anxiety, depression, dyspnoea and quality of life in the walking group across three months, compared to those in the control group and at baseline. CONCLUSION: This breathing-based walking intervention is promising to achieve bio-psychological well-being for patients with chronic obstructive pulmonary disease. RELEVANCE TO CLINICAL PRACTICE: This breathing-based walking, as a mind-body exercise, could serve as an evidence-based nursing care that contributes to improving anxiety, depression, dyspnoea and quality of life in stable chronic obstructive pulmonary disease outpatients. The feasibility and acceptability of the breathing-based walking were met the requirement of the chronic obstructive pulmonary disease outpatients, which could be considered as home-based exercise.

https://onlinelibrary.wiley.com/doi/abs/10.1111/jocn.14960

Long, H., K. Howells, et al. (2019). **"Does health coaching improve health-related quality of life and reduce hospital admissions in people with chronic obstructive pulmonary disease? A systematic review and meta-analysis."** Br J Health PsycholPURPOSE: To systematically review the evidence for health coaching as an intervention to improve health-related quality of life (HRQoL) and reduce hospital admissions in people with chronic obstructive pulmonary disease (COPD). METHODS: We systematically searched MEDLINE, EMBASE, PsycINFO, and CINAHL from database inception to August 2018 to identify all randomized controlled trials (RCTs) of health coaching for people with COPD. Eligible health coaching interventions had to include three components: goal setting, motivational interviewing, and COPD-

related health education. Data were extracted on study characteristics and the effects of the intervention on HRQoL, hospital admissions, physical activity, self-care behaviour, and mood. Study quality was appraised by two authors using the Cochrane tool for assessing the risk of bias in RCTs. Effect sizes (standardized mean differences [SMD] or odds ratios [OR]) with 95% confidence intervals (CIs) were calculated and pooled using random effects meta-analyses. RESULTS: Of 1578 articles, 10 RCTs were included. Meta-analysis showed that health coaching has a significant positive effect on HRQoL (SMD = -0.69, 95% CI: -1.28, -0.09, p = .02, from k = 4) and leads to a significant reduction in COPD-related hospital admissions (OR = 0.46, 95% CI: 0.31, 0.69, p = .0001, from k = 5), but not in all-cause hospital admissions (OR = 0.70, 95% CI: 0.41-1.12, p = .20, from k = 3). Three of four studies reported significant improvements to self-care behaviours such as medication adherence and exercise compliance. CONCLUSIONS: This is the first systematic review to show that health coaching may be a candidate intervention to improve HRQoL and reduce costly hospital admissions in people with COPD. Statement of contribution What is already known on this subject? COPD is a leading cause of death worldwide and considerably reduces HRQoL. In turn, HRQoL is associated with a range of adverse health outcomes in COPD. Health coaching is a self-management intervention for people with long-term conditions such as COPD. Studies have examined whether health coaching improves HRQOL and other health outcomes in people with COPD, but no systematic review has been conducted. What does this study add? The first systematic review and meta-analysis of RCTs of health coaching for people with COPD. Health coaching may be a candidate intervention for improving HRQoL and reducing COPD-related hospital admissions in people with COPD. The need to establish the most effective health coaching components, delivery modality, and economic impact.

https://onlinelibrary.wiley.com/doi/pdf/10.1111/bjhp.12366

Luo, L., S. Zhao, et al. (2019). **"Association between chronic obstructive pulmonary disease and risk of erectile dysfunction: a systematic review and meta-analysis."** Int J Impot ResChronic obstructive pulmonary disease (COPD) is a common chronic disease. Mounting evidence shows that male patients with COPD have an increased risk of developing erectile dysfunction (ED). The aim of this meta-analysis was to assess the relationship between COPD and the risk of ED. To identify relevant studies, the PubMed, Cochrane Library and Embase databases, Chinese Biomedical Literature (CBM), China National Knowledge Infrastructure (CNKI) were systematically searched up to September 2018. Relative risks (RR) and corresponding 95% confidence intervals (CI) were used to estimate the strength of association between COPD and the risk of ED by using random-effects models. Finally, four studies (three cross-sectional, one cohort study) involving 58,307 participants were included. Synthesis results demonstrated that patients with COPD was not significantly associated with an increased overall prevalence of ED (RR = 1.31, 95% CI: 0.95-1.81, P = 0.099) compared to the healthy controls. However, the subgroup analyses showed that the prevalence of moderate ED (RR = 2.44, 95% CI: 1.29-4.59, P = 0.006) and severe ED (RR = 2.77, 95% CI: 1.57-4.94, P = 0.001) were significantly higher in patients with COPD. Evidence from this meta-analysis revealed that patients with COPD had a significantly increased susceptibility to moderate and severe ED, which should remind both clinicians and patients to be aware of the potential hazardous effect of COPD for developing ED.

https://www.nature.com/articles/s41443-019-0165-4

Ma, Y., H. Tong, et al. (2019). **"Chronic obstructive pulmonary disease in rheumatoid arthritis: a systematic review and meta-analysis."** Respir Res **20**(1): 144.

BACKGROUND: The risk and prevalence of chronic obstructive pulmonary disease (COPD) in rheumatoid arthritis (RA) is still obscure. The current study was aimed to systematically review and meta-analyse the risk ratio (RR) and prevalence of COPD in RA. METHODS: A comprehensive systematic review was conducted based on PubMed, Web of Science and Cochrane Library from inception to April 30, 2018. The primary outcome of our study was the RR of COPD in RA patients compared with controls, and secondary was the prevalence of COPD in RA patients. Pooled effect sizes were calculated according to fixed effect

model or random effects model depending on heterogeneity. RESULTS: Six and eight studies reported the RR and prevalence of COPD in RA respectively. Compared with controls, RA patients have significant increased risk of incident COPD with pooled RR 1.82 (95% CI = 1.55 to 2.10, P < 0.001). The pooled prevalence of COPD in RA patients was 6.2% (95% CI = 4.1 to 8.3%). Meta-regression identified that publication year was an independent covariate negatively associated with the RR of COPD, and smoker proportion of RA population was also positively associated with the prevalence of COPD significantly in RA patients. CONCLUSIONS: The present meta-analysis has demonstrated the significant increased risk and high prevalence of COPD in RA patients. Patients with RA had better cease tobacco use and rheumatologists should pay attention to the monitoring of COPD for the prevention and control of COPD.

https://respiratory-research.biomedcentral.com/track/pdf/10.1186/s12931-019-1123-x

Machado, A., A. Oliveira, et al. (2019). **"Effects of a community-based pulmonary rehabilitation programme during acute exacerbations of chronic obstructive pulmonary disease - A quasi-experimental pilot study."** PulmonologyBACKGROUND: 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.

https://pdf.sciencedirectassets.com/318509/AIP/1-s2.0-S2531043719300960/main.pdf?X-Amz-Security-Token=AgoJb3JpZ2luX2VjEAIaCXVzLWVhc3QtMSJGMEQCIBTwLw%2Bfy%2BhOH%2F%2Fs4zu%2FJVYjIOK%2BvuM%2BGdrGOQ2wF%2BKCAiANHOT%2FexvJ1UmitcvKk33Ung6ZtAGHdKfIJ676zG8GqyraAwhrEAIaDDA1OTAwMzU0Njg2NSIMEwUL1cBs%2BgDQtsIbKrcDDmQj9jBswzXl03AagxzPOrGEN3BRIQXzsvtPmEPYRyoQMq28k6jddaNiw5VdD5G6WsxCqaNQHu8oqxJYlPCJzfUEDpKtbvSoouK0TH6m3Wa8MOORwra21WXw7ijbFptdiGPVI7UAk4AkA1ZbS8Q7I5onbwCnM4ZB%2FVVTOpYnEV%2FgTb0JO8z30XyjkoR8GMTQe2sKQyQSZHD0DO%2FVAj12SBKge%2B9zXJT0h9kSiA0qeTgTVqYYE2YGT5ibz1Gt44yyVub08GlE6K8Wnqo7HZoeBF%2BSvsYaJxnbI58MAS6YuNmT8%2FD4BVMh6qF2OHiwnpcwwdGebAPRYxiyQeLD2maPHMigiy6hJehK9YuKEtQMX4ecNDFEIKY4vVtXAHG88KupSZ87uZOrswv2vkQjFTG4onNmVhUmEkpKink2hT0eNMN3tvePIbutP5ctbUmKEpXSKb54%2F8iqyFGz6eDfhAhbhF6xymnEaNffMII2Yf%2BwbKe5NuWq0YH5lHz8bi%2FqQtyfyvyBkyfg71eoeOX1L8%2FydkJZR8I45k1IriQd2YkefxkGrIk8%2BLk6EFmT3n3FewdYcMCVrDrZRzCSvMTpBTq1Ab6fiBo6oS0eXSIJ34KcLdUINeg1lVlvhInEq5M2hraHf%2F7Ges%2Bs5hqZtiHxgDkkEHvlinFkkLTM2Ak2wvloSp3Kj8xDv5%2F6v8ja54D7d5BCgAK7OpGBszGRb8qfWrispqc14Ab5Ps5hb8mcz5e6Ky1XN2uhCCkDaOp3skAdOSAqXUGXyx7p7%2FP874y6uRyoqEFmO9Lk2h9quiZ9jKW5f1%2BqTbmInjNiaFVMDn8R8RAMMr%2BGoqk%3D&X-Amz-Algorithm=AWS4-HMAC-SHA256&X-Amz-Date=20190719T023251Z&X-Amz-SignedHeaders=host&X-Amz-Expires=300&X-Amz-Credential=ASIAQ3PHCVTYRJUOV3ZV%2F20190719%2Fus-east-1%2Fs3%2Faws4_request&X-Amz-Signature=4f264dd69e7c15682a0d464537c3f4a3b7e3dc0603884de400d1fb36d3ea54f7&hash=6f4387615f2e45e8abd803bf7046b2cc5cd716c7d74cddb84dc214e907f1bfea&host=68042c943591013ac2b2430a

89b270f6af2c76d8dfd086a07176afe7c76c2c61&pii=S2531043719300960&tid=spdf-0bc4f227-5941-4c5d-b9da-75d421b57dc3&sid=ed3efb987d8a374be97bde61814aa9d67edcgxrqa&type=client

Morton, K., E. Sanderson, et al. (2019). **Health Services and Delivery Research**. Care bundles to reduce re-admissions for patients with chronic obstructive pulmonary disease: a mixed-methods study. Southampton (UK), NIHR Journals Library

BACKGROUND: Chronic obstructive pulmonary disease (COPD) is the commonest respiratory disease in the UK, accounting for 10% of emergency hospital admissions annually. Nearly one-third of patients are re-admitted within 28 days of discharge. OBJECTIVES: The study aimed to evaluate the effectiveness of introducing standardised packages of care (i.e. care bundles) as a means of improving hospital care and reducing re-admissions for COPD. DESIGN: A mixed-methods evaluation with a controlled before-and-after design. PARTICIPANTS: Adults admitted to hospital with an acute exacerbation of COPD in England and Wales. INTERVENTION: COPD care bundles. MAIN OUTCOME MEASURES: The primary outcome was re-admission to hospital within 28 days of discharge. The study investigated secondary outcomes including length of stay, total number of bed-days, in-hospital mortality, 90-day mortality, context, process and costs of care, and staff, patient and carer experience. DATA SOURCES: Routine NHS data, including numbers of COPD admissions and re-admissions, in-hospital mortality and length of stay data, were provided by 31 sites for 12 months before and after the intervention roll-out. Detailed pseudo-anonymised data on care during admission were collected from a subset of 14 sites, in addition to information about delivery of individual components of care collected from random samples of medical records at each location. Six case study sites provided data from interviews, observation and documentary review to explore implementation, engagement and perceived impact on delivery of care. RESULTS: There is no evidence that care bundles reduced 28-day re-admission rates for COPD. All-cause re-admission rates, in-hospital mortality, length of stay, total number of bed-days, and re-admission and mortality rates in the 90 days following discharge were similar at implementation and comparator sites, as were resource utilisation, NHS secondary care costs and cost-effectiveness of care. However, the rate of emergency department (ED) attendances decreased more in implementation sites than in comparator sites {implementation: incidence rate ratio (IRR) 0.63 [95% confidence interval (CI) 0.56 to 0.70]; comparator: IRR 1.14 (95% CI 1.04 to 1.26) interaction $p < 0.001$}. Admission bundles appear to be more complex to implement than discharge bundles, with 3.7% of comparator patients receiving all five admission bundle elements, compared with 7.6% of patients in implementation sites, and 28.3% of patients in implementation sites receiving all five discharge bundle elements, compared with 0.8% of patients in the comparator sites. Although patients and carers were unaware that care was bundled, staff view bundles positively, as they help to standardise working practices, support a clear care pathway for patients, facilitate communication between clinicians and identify post-discharge support. LIMITATIONS: The observational nature of the study design means that secular trends and residual confounding cannot be discounted as potential sources of any observed between-site differences. The availability of data from some sites was suboptimal. CONCLUSIONS: Care bundles are valued by health-care professionals, but were challenging to implement and there was a blurring of the distinction between the implementation and comparator groups, which may have contributed to the lack of effect on re-admissions and mortality. Care bundles do appear to be associated with a reduced number of subsequent ED attendances, but care bundles are unlikely to be cost-effective for COPD. FUTURE WORK: A longitudinal study using implementation science methodology could provide more in-depth insights into the implementation of care bundles. TRIAL REGISTRATION: Current Controlled Trials ISRCTN13022442. FUNDING: This project was funded by the National Institute for Health Research Health Services and Delivery Research programme and will be published in full in Health Services and Delivery Research; Vol. 7, No. 21. See the NIHR Journals Library website for further project information.

Ohar, J. A., S. Sharma, et al. (2019). **"Efficacy of Indacaterol/Glycopyrrolate in Patients with COPD by Airway Reversibility at Baseline: A Pooled Analysis of the FLIGHT1 and FLIGHT2 12-Week Studies."** Copd: 1-7.

Bronchodilator reversibility occurs in patients with COPD. Pooled analysis of two 12-week, placebo-controlled randomised studies (FLIGHT1 [NCT01727141]; FLIGHT2 [NCT01712516]) assessed the effect of bronchodilator reversibility on lung function, patient-reported outcomes, and safety in 2,043 patients with moderate-to-severe COPD treated with indacaterol/glycopyrrolate (IND/GLY) 27.5/15.6 microg twice daily. Reversibility was defined as post-bronchodilator increase in forced expiratory volume in one second (FEV1) of >/=12% and >/=0.200 L. Overall, mean reversibility (mean post-bronchodilator FEV1 increase) was 22.8%, and 54.5% of patients met reversibility criteria. IND/GLY resulted in significant ($p < 0.05$) placebo-adjusted improvements from baseline at Week 12 in reversible and non-reversible patients in FEV1 area under the curve from 0 to 12 hours (0.308 L and 0.170 L, respectively), trough FEV1 (0.260 L and 0.174 L), St. George's Respiratory Questionnaire total score (-6.3 and -3.5), COPD Assessment Test total score (-2.3 and -1.2), daily rescue medication use (-1.52 and -0.79), and daily total symptom score (-0.86 and -0.63); Transition Dyspnoea Index focal score also showed improvements (1.93 and 1.29) at Week 12, irrespective of reversibility status. Improvements in lung function and rescue medication use were significantly ($p < 0.05$) greater in IND/GLY patients in the reversible subgroup compared with the non-reversible subgroup. The safety profile was similar across treatment groups and reversibility subgroups. Overall, treatment with IND/GLY led to significant improvements in lung function and PROs in patients with moderate-to-severe COPD, regardless of reversibility status, with greater improvements in the reversible subgroup. Safety profile was not affected by reversibility status.

https://www.tandfonline.com/doi/full/10.1080/15412555.2019.1612341

Parekh, T. M., C. R. Copeland, et al. (2019). **"Application of the community health worker model in adult asthma and COPD in the U.S.: a systematic review."** BMC Pulm Med **19**(1): 116.

BACKGROUND: With rising medical costs, stakeholders and healthcare professionals are exploring community-based solutions to relieve the burden of chronic diseases and reduce health care spending. The community health worker (CHW) model is one example that has proven effective in improving patient outcomes globally. We sought to systematically describe the effectiveness of community health worker interventions in improving patient reported outcomes and reducing healthcare utilization in the adult asthma and chronic obstructive pulmonary disease (COPD) populations in the U.S. METHODS: Studies were included if they were a randomized control trial or involved a pre-post intervention comparison with clearly stated disease specific outcomes, targeted adult patients with asthma or COPD, and were performed in the United States. Risk of bias was assessed using the Cochrane Risk of Bias tool. The review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) criteria and was registered with PROSPERO. RESULT: The search yielded 4013 potential articles, of which 47 were chosen for full-text review and 4 were chosen for inclusion; all focused on asthma and three had a comparison group. CHW interventions demonstrated improvement in asthma-related quality of life, asthma control, home trigger scores, and asthma symptom free days. There were no studies that reported COPD specific outcomes as a result of CHW interventions. CONCLUSION: Emerging evidence suggests CHW interventions may improve some aspects of asthma related disease burden in adults, however additional studies with consistent outcome measures are needed to confirm their effectiveness. Further research is also warranted to evaluate the use of community health workers in the COPD population.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6593583/pdf/12890_2019_Article_878.pdf

Pascoe, S., N. Barnes, et al. (2019). **"Blood eosinophils and treatment response with triple and dual combination therapy in chronic obstructive pulmonary disease: analysis of the IMPACT trial."**

Lancet Respir MedBACKGROUND: Previous studies have highlighted a relationship between reduction in rate of exacerbations with therapies containing inhaled corticosteroids (ICS) and baseline blood eosinophil count in patients with chronic obstructive pulmonary disease (COPD). The IMPACT trial showed that once-daily single-inhaler triple therapy significantly reduced exacerbations versus dual therapies. Blood eosinophil counts and smoking status could be important modifiers of treatment response to ICS. We aimed to model these relationships and their interactions, including outcomes other than exacerbations. METHODS: IMPACT was a phase 3, randomised, double-blind, parallel-group, 52-week global study comparing once-daily single-inhaler triple therapy (fluticasone furoate-umeclidinium-vilanterol) with dual inhaled therapy (fluticasone furoate-vilanterol or umeclidinium-vilanterol). Eligible patients had moderate-to-very-severe COPD and at least one moderate or severe exacerbation in the previous year. We used fractional polynomials to model continuous blood eosinophil counts. We used negative binomial regression for numbers of moderate and severe exacerbations, severe exacerbations, and pneumonia. We modelled differences at week 52 in trough FEV1, St George's Respiratory Questionnaire (SGRQ) total score, and Transition Dyspnoea Index using repeated measurements mixed effect models. IMPACT was registered with ClinicalTrials.gov, number NCT02164513. FINDINGS: The magnitude of benefit of regimens containing ICS (fluticasone furoate-umeclidinium-vilanterol n=4151 and fluticasone furoate-vilanterol n=4134) in reducing rates of moderate and severe exacerbations increased in proportion with blood eosinophil count, compared with a non-ICS dual long-acting bronchodilator (umeclidinium-vilanterol n=2070). The moderate and severe exacerbation rate ratio for triple therapy versus umeclidinium-vilanterol was 0.88 (95% CI 0.74 to 1.04) at blood eosinophil count less than 90 cells per muL and 0.56 (0.47 to 0.66) at counts of 310 cells per muL or more; the corresponding rate ratio for fluticasone furoate-vilanterol versus umeclidinium-vilanterol was 1.09 (0.91 to 1.29) and 0.56 (0.47 to 0.66), respectively. Similar results were observed for FEV1, Transition Dyspnoea Index, and SGRQ total score; however, the relationship with FEV1 was less marked. At blood eosinophil counts less than 90 cells per muL and at counts of 310 cells per muL or more, the triple therapy versus umeclidinium-vilanterol treatment difference was 40 mL (95% CI 10 to 70) and 60 mL (20 to 100) for trough FEV1, -0.01 (-0.68 to 0.66) and 0.30 (-0.37 to 0.97) for Transition Dyspnoea Index score, and -0.01 (-1.81 to 1.78) and -2.78 (-4.64 to -0.92) for SGRQ total score, respectively. Smoking status modified the relationship between observed efficacy and blood eosinophil count for moderate or severe exacerbations, Transition Dyspnoea Index, and FEV1, with former smokers being more corticosteroid responsive at any eosinophil count than current smokers. INTERPRETATION: This analysis of the IMPACT trial shows that assessment of blood eosinophil count and smoking status has the potential to optimise ICS use in clinical practice in patients with COPD and a history of exacerbations. FUNDING: GlaxoSmithKline.

https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(19)30190-0/fulltext

Plishka, C. T., T. Rotter, et al. (2019). **"Effects of Clinical Pathways for COPD on Patient, Professional, and Systems Outcomes: A Systematic Review."** ChestBACKGROUND: COPD has a substantial burden seen in both patient quality of life and health-care costs. One method of minimizing this burden is the implementation of clinical pathways (CPWs). CPWs bring the best available evidence to a range of health-care professionals by adapting guidelines to a local context and detailing essential steps in care. METHODS: A systematic review was conducted to address the following question: What are the effects of CPWs for COPD on patient-, professional-, and systems-level outcomes? The review used methods outlined by the Cochrane Collaboration. We included all studies that met our operational definition for CPWs and focused on COPD. All studies were evaluated for risk of bias, and all data regarding patient, professional, and systems outcomes were extracted. RESULTS: The search strategy identified 497 potentially relevant titles. Of these, 13 studies were included in the review. These studies reported a total of 398 outcomes, with sufficient data for meta-analysis of five outcomes: complications, length of stay, mortality, readmissions, and quality of life. Results showed statistically significant reductions in complications, readmissions, and length of stay but did not show changes in mortality or quality of life. CONCLUSIONS: This systematic review reveals evidence to suggest that CPWs for COPD have the potential to reduce complications, readmissions, and length of stay without negatively influencing mortality or quality of life. However, quality of evidence was generally low. The authors therefore

acknowledge that results should be interpreted with caution and note the need for additional research in this area.

https://journal.chestnet.org/article/S0012-3692(19)31120-1/fulltext

Prins, H. J., R. Duijkers, et al. (2019). **"CRP-guided antibiotic treatment in acute exacerbations of COPD in hospital admissions."** Eur Respir J **53**(5)The role of antibiotics in acute exacerbations of chronic obstructive pulmonary disease (COPD) is controversial and a biomarker identifying patients who benefit from antibiotics is mandatory. We performed a randomised, controlled trial in patients with acute exacerbations of COPD, comparing C-reactive protein (CRP)-guided antibiotic treatment to patient reported symptoms in accordance with the Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy, in order to show a reduction in antibiotic prescription.Patients hospitalised with acute exacerbations of COPD were randomised to receive antibiotics based either on the GOLD strategy or according to the CRP strategy (CRP >/=50 mg.L(-1)).In total, 101 patients were randomised to the CRP group and 119 to the GOLD group. Fewer patients in the CRP group were treated with antibiotics compared to the GOLD group (31.7% versus 46.2%, p=0.028; adjusted odds ratio (OR) 0.178, 95% CI 0.077-0.411, p=0.029). The 30-day treatment failure rate was nearly equal (44.5% in the CRP group versus 45.5% in the GOLD-group, p=0.881; adjusted OR 1.146, 95% CI 0.649-1.187, p=0.630), as was the time to next exacerbation (32 days in the CRP group versus 28 days in the GOLD group, p=0.713; adjusted hazard ratio 0.878, 95% CI 0.649-1.187, p=0.398). Length of stay was similar in both groups (7 days in the CRP group versus 6 days in the GOLD group, p=0.206). On day-30, no difference in symptom score, quality of life or serious adverse events was detected.Use of CRP as a biomarker to guide antibiotic treatment in severe acute exacerbations of COPD leads to a significant reduction in antibiotic treatment. In the present study, no differences in adverse events between both groups were found. Further research is needed for the generalisability of these findings.

https://erj.ersjournals.com/content/53/5/1802014

Rogliani, P., M. G. Matera, et al. (2019). **"Efficacy and safety profile of mucolytic/antioxidant agents in chronic obstructive pulmonary disease: a comparative analysis across erdosteine, carbocysteine, and N-acetylcysteine."** Respir Res **20**(1): 104.

BACKGROUND: To date there are no head-to-head studies comparing different mucolytic/antioxidant agents. Considering the inconsistent evidence resulting from the pivotal studies on mucolytic/antioxidant agents tested in chronic obstructive pulmonary disease (COPD), and the recent publication of Reducing Exacerbations and Symptoms by Treatment with ORal Erdosteine in COPD (RESTORE) study, we have performed a meta-analysis to compare the efficacy and safety of erdosteine 600 mg/day, carbocysteine 1500 mg/day, and N-acetylcysteine (NAC) 1200 mg/day in COPD. METHODS: A pairwise and network meta-analyses were performed to assess the efficacy of erdosteine, carbocysteine, and NAC on acute exacerbation of COPD (AECOPD), duration of AECOPD, and hospitalization. The frequency of adverse events (AEs) was also investigated. RESULTS: Data obtained from 2753 COPD patients were extracted from 7 RCTs published between 2004 and 2017. In the pairwise meta-analysis mucolytic/antioxidant agents significantly reduced the risk of AECOPD (RR 0.74 95%CI 0.68-0.80). The network meta-analysis provided the following rank of effectiveness: erdosteine>carbocysteine>NAC. Only erdosteine reduced the risk of experiencing at least one AECOPD ($P < 0.01$) and the risk of hospitalization due to AECOPD ($P < 0.05$). Erdosteine and NAC both significantly reduced the duration of AECOPD ($P < 0.01$). The AEs induced by erdosteine, carbocysteine, and NAC were mild in severity and generally well tolerated. The quality of evidence of this quantitative synthesis is moderate. CONCLUSIONS: The overall efficacy/safety profile of erdosteine is superior to that of both carbocysteine and NAC. Future head-to-head studies performed on the same COPD populations are needed to definitely confirm the results of this meta-analysis. TRIAL REGISTRATION: CRD42016053762 .

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6537173/pdf/12931_2019_Article_1078.pdf

Salari-Moghaddam, A., A. Milajerdi, et al. (2019). **"Processed red meat intake and risk of COPD: A systematic review and dose-response meta-analysis of prospective cohort studies."** Clin Nutr **38**(3): 1109-1116.

BACKGROUND & AIMS: No earlier study has summarized findings from previous publications on processed red meat intake and risk of Chronic Obstructive Pulmonary Disease (COPD). This systematic review and meta-analysis was conducted to examine the association between processed red meat intake and COPD risk. METHODS: We searched in PubMed/Medline, ISI Web of Knowledge, Scopus, EMBASE and Google Scholar up to April 2018 to identify relevant studies. Prospective cohort studies that considered processed red meat as the exposure variable and COPD as the main outcome variable or as one of the outcomes were included in the systematic review. Publications in which hazard ratios (HRs) were reported as effect size were included in the meta-analysis. Finally, five cohort studies were considered in this systematic review and meta-analysis. RESULTS: In total, 289,952 participants, including 8338 subjects with COPD, aged >/=27 years were included in the meta-analysis. These studies were from Sweden and the US. Linear dose response meta-analysis revealed that each 50 gr/week increase in processed red meat intake was associated with 8% higher risk of COPD (HR: 1.08; 95% CI: 1.03, 1.13). There was an evidence of non-linear association between processed red meat intake and risk of COPD (P < 0.001). CONCLUSIONS: In this systematic review and meta-analysis, we found a significant positive association between processed red meat intake and risk of COPD. PROSPERO REGISTRATION NUMBER: CRD42017077971.

https://www.clinicalnutritionjournal.com/article/S0261-5614(18)30205-X/fulltext

Salimi Asl, M., A. Ahmadi, et al. (2019). **"TNF-alpha -308 G/A variant and susceptibility to chronic obstructive pulmonary disease: A systematic review and meta-analysis."** Cytokine **123**: 154763.

BACKGROUND AND OBJECTIVE: TNF-alpha -308 G/A variant is recognized to play an important role in the pathogenesis of chronic obstructive pulmonary disease (COPD). Although many studies have investigated the association of TNF-alpha-308 and COPD risk, a deep understanding of this association is lacking due to small subjects sizes and insufficiently study designs among different investigations. In this study, a systematic review and meta-analysis was performed based on published reports on the association of TNF-alpha and COPD. METHOD: The published studies concerned the association between TNF-alpha and COPD were identified using a systematic research in Scopus, Google Scholar, and PubMed up to April 2018. A total of 46 different papers studying the rs1800629 variant in TNF-alpha gene were included. Then, human studies were selected to further analysis regardless of papers language. RESULTS: Based on the results, the major outcome of this meta-analysis can be represented as follows: individuals with GG and GA genotypes possess less risk of developing COPD (OR=0.58, 95%CI: (0.44-0.79), P<0.00) compared to AA genotype carriers. In contrast, the AA genotype carriers of the TNF-alpha rs1800629 has a significantly higher risk of developing COPD (OR=1.83, 95%CI: (1.34-2.51), P<0.00) compared to GG carrier. Despite the previous meta-analysis results which reported significantly decreasing of heterogeneity with ethnicity, we found that the source of controls has a significant contribution to observed heterogeneity. CONCLUSIONS: Thanks to the global burden of COPD studies, proving TNF-alpha 308 gene variant as an independent factor in its pathogenesis opens new insights to diagnosis and management of COPD.

https://www.sciencedirect.com/science/article/abs/pii/S1043466619301929?via%3Dihub

Sampaio, M. S., W. A. Vieira, et al. (2019). **"Chronic obstructive pulmonary disease as a risk factor for suicide: A systematic review and meta-analysis."** Respir Med **151**: 11-18.

BACKGROUND: Patients living with chronic obstructive pulmonary disease (COPD) commonly present several limitations in their daily activities, high depression rates, and low quality of life, which makes this

population a risk group for suicide. This study aims to systematically assess the literature on the association between CPOD and the likelihood of suicide. METHODS: The protocol was registered in PROSPERO (CRD42018096618). The Latin-American and Caribbean Health Sciences Literature (LILACS), PubMed, SciELO, Scopus, LIVIVO, Web of Science, and PsychNET databases were used as primary study sources. OpenThesis and OpenGrey were used to partially capture the "grey literature". A manual search was also performed through a systematized analysis of the references of eligible articles. The risk of bias among the studies included was assessed with the Joanna Briggs Institute Critical Appraisal Tools for Systematic Reviews. A random effects meta-analysis was performed to estimate the variation in odds ratio (OR) and 95% confidence intervals (95% CI). RESULTS: The search provided 4762 results, from which only seven met the eligibility criteria and were ultimately included in the qualitative assessment of the review. The studies were published from 2002 to 2015. All studies presented low risk of bias. The total sample included 1390 suicide cases of COPD patients. The meta-analysis, which was based on five eligible case control studies, found that people with history of COPD are more likely to commit suicide (OR=1.90; 95% CI=1.27-2.48; p=0.002). CONCLUSION: COPD patients are 1.9 times more likely to commit suicide than people without COPD.

https://www.resmedjournal.com/article/S0954-6111(19)30093-9/fulltext

Sivapalan, P., T. S. Lapperre, et al. (2019). **"Eosinophil-guided corticosteroid therapy in patients admitted to hospital with COPD exacerbation (CORTICO-COP): a multicentre, randomised, controlled, open-label, non-inferiority trial."** Lancet Respir MedBACKGROUND: Treatment with systemic corticosteroids in patients with acute exacerbations of chronic obstructive pulmonary disease (COPD) is associated with debilitating adverse effects. Therefore, strategies to reduce systemic corticosteroid exposure are urgently required and might be offered by a personalised biomarker-guided approach to treatment. The aim of this study was to determine whether an algorithm based on blood eosinophil counts could safely reduce systemic corticosteroid exposure in patients admitted to hospital with acute exacerbations of COPD. METHODS: We did a multicentre, randomised, controlled, open-label, non-inferiority trial at the respiratory departments of three different university-affiliated hospitals in Denmark. Eligible participants were patients included within 24h of admission to the participating sites, aged at least 40 years, with known airflow limitation (defined as a post-bronchodilator FEV1/forced vital capacity [FVC] ratio </=0.70) and a specialist-verified diagnosis of COPD, who were designated to start on systemic corticosteroids by the respiratory medicine physician on duty. We randomly assigned patients (1:1) to either eosinophil-guided therapy or standard therapy with systemic corticosteroids. Both investigators and patients were aware of the group assignment. All patients received 80 mg of intravenous methylprednisolone on the first day. The eosinophil-guided group were from the second day given 37.5 mg of prednisolone oral tablet daily (for a maximum of up to 4 days) on days when their blood eosinophil count was at least 0.3 x 10(9) cells per L. On days when the eosinophil count was lower, prednisolone was not administered. If a patient was discharged during the treatment period, a treatment based on the last measured eosinophil count was prescribed for the remaining days within the 5-day period (last observation carried forward). The control group received 37.5 mg of prednisolone tablets daily from the second day for 4 days. The primary outcome was the number of days alive and out of hospital within 14 days after recruitment, assessed by intention to treat (ITT). Secondary outcomes included treatment failure at day 30 (ie, recurrence of acute exacerbation of COPD resulting in emergency room visits, admission to hospital, or need to intensify pharmacological treatment), number of deaths on day 30, and duration of treatment with systemic corticosteroids. The non-inferiority margin was 1.2 days (SD 3.8). This trial is registered at ClinicalTrials.gov, number NCT02857842, and was completed in January, 2019. FINDINGS: Between Aug 3, 2016, and Sept 30, 2018, 159 patients in the eosinophil-guided group and 159 patients in the control group were included in the ITT analyses. There was no between-group difference for days alive and out of hospital within 14 days after recruitment: mean 8.9 days (95% CI 8.3-9.6) in the eosinophil-guided group versus 9.3 days (8.7-9.9) in the control group (absolute difference -0.4, 95% CI -1.3 to 0.5; p=0.34). Treatment failure at 30 days occurred in 42 (26%) of 159 patients in the eosinophil-guided group and 41 (26%) of 159 in the control group (difference 0.6%, 95% CI -9.0 to 10.3; p=0.90). At 30 days nine patients (6%) of 159 in the eosinophil-guided group and six (4%) of 159 in the control group had died (difference 1.9%, 95% CI -2.8 to 6.5; p=0.43). Median duration of systemic corticosteroid therapy was lower in the eosinophil-guided group:

2 days (IQR 1.0 to 3.0) compared with 5 days (5.0 to 5.0) in the control group, p<0.0001. INTERPRETATION: Eosinophil-guided therapy was non-inferior compared with standard care for the number of days alive and out of hospital, and reduced the duration of systemic corticosteroid exposure, although we could not entirely exclude harm on some secondary outcome measures. Larger studies will help to determine the full safety profile of this strategy and its role in the management of COPD exacerbations. FUNDING: The Danish Regions Medical Fund and the Danish Council for Independent Research.

https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(19)30176-6/fulltext

Threapleton, C. J., S. Janjua, et al. (2019). **"Head-to-head oral prophylactic antibiotic therapy for chronic obstructive pulmonary disease."** Cochrane Database Syst Rev **5**: Cd013024.

BACKGROUND: Chronic obstructive pulmonary disease (COPD; including chronic bronchitis and emphysema) is a chronic respiratory condition characterised by shortness of breath, cough and recurrent exacerbations. Long-term antibiotic use may reduce both bacterial load and inflammation in the airways. Studies have shown a reduction of exacerbations with antibiotics in comparison to placebo in people with COPD, but there are concerns about antibiotic resistance and safety. OBJECTIVES: To compare the safety and efficacy of different classes of antibiotics (continuous, intermittent or pulsed) for prophylaxis of exacerbations in patients with COPD. SEARCH METHODS: We searched the Cochrane Airways Group Trials Register and bibliographies of relevant studies. The latest literature search was conducted on 6 February 2019. SELECTION CRITERIA: Randomised controlled trials (RCTs) were selected that compared one prophylactic antibiotic with another in patients with COPD. DATA COLLECTION AND ANALYSIS: We used the standard Cochrane methods. Two independent review authors selected trials for inclusion, extracted data and assessed risk of bias. Discrepancies were resolved by involving a third review author. MAIN RESULTS: We included two RCTs, both published in 2015 involving a total of 391 participants with treatment duration of 12 to 13 weeks. One RCT compared a quinolone (moxifloxacin pulsed, for 5 days every 4 weeks), with a tetracycline (doxycycline continuous) or a macrolide (azithromycin intermittent).The second RCT compared a tetracycline (doxycycline continuous) plus a macrolide (roxithromycin continuous), with roxithromycin (continuous) alone.The trials recruited participants with a mean age of 68 years, with moderate-severity COPD. Both trials included participants who had between two and five exacerbations in the previous one to two years. In one trial, 17% of patients had previously been using inhaled corticosteroids. In the other study, all patients were positive for Chlamydophila pneumoniae (C pneumoniae).Overall, we judged the evidence presented to be of very low-certainty, mainly due to imprecision, but we also had concerns about indirectness and methodological quality of the included studies. The primary outcome measures for this review included exacerbations, quality of life, drug resistance and serious adverse events.Macrolide + tetracycline versus macrolide There was no clear difference between treatments in improvement in quality of life as assessed by the Chronic Respiratory Questionnaire (CRQ). The CRQ scale ranges from 0 to 10 and higher scores on the scale indicate better quality of life. CRQ sub-scales for dyspnoea (mean difference (MD) 0.58, 95% confidence interval (CI) -0.84 to 2.00; 187 participants; very low-certainty evidence), fatigue (MD 0.02, 95% CI -1.08 to 1.12; 187 participants; very low-certainty evidence), emotional function (MD -0.37, 95% CI -1.74 to 1.00; 187 participants; very low-certainty evidence), or mastery (MD -0.79, 95% CI -1.86 to 0.28; 187 participants; very low-certainty evidence) at 12 weeks. For serious adverse events, it was uncertain if there was a difference between combined roxithromycin and doxycycline versus roxithromycin alone at 48 weeks follow-up after active treatment of 12 weeks (odds ratio (OR) 1.00, 95% CI 0.52 to 1.93; 198 participants; very low-certainty evidence). There were five deaths reported in the combined treatment arm, versus three in the single treatment arm at 48 weeks follow-up after active treatment of 12 weeks (OR 1.63, 95% CI 0.38 to 7.02; 198 participants; very low-certainty evidence).Quinolone versus tetracycline There was no clear difference between moxifloxacin and doxycycline for the number of participants experiencing one or more exacerbations (OR 0.44, 95% CI 0.14 to 1.38; 50 participants, very low-certainty evidence) at 13 weeks. There were no serious adverse events or deaths reported in either treatment groups. We did not identify any evidence for our other primary outcomes.Quinolone versus macrolide There was no clear difference between moxifloxacin and azithromycin for the number of participants experiencing one or more exacerbations (OR 1.00, 95% CI 0.32 to 3.10; 50 participants; very low-certainty evidence) at 13 weeks. There were no serious adverse events or deaths reported in either

treatment groups. We did not identify any evidence for our other primary outcomes.Marcolide versus tetracycline There was no clear difference between azithromycin and doxycycline for the number of participants experiencing one or more exacerbations (OR 0.44, 95% CI 0.14 to 1.38; 50 participants; very low-certainty evidence) at 13 weeks. There were no serious adverse events or deaths reported in either treatment groups. We did not identify any evidence for our other primary outcomes.We did not find head-to-head evidence for impact of antibiotics on drug resistance. AUTHORS' CONCLUSIONS: It is not clear from the evidence included in this review whether there is a difference in efficacy or safety between different classes or regimens of prophylactic antibiotic, given for 12 to 13 weeks to people with COPD. Whilst no head-to-head comparisons of antibiotic resistance were identified, concerns about this continue. The sample size in this review is small and both included studies are of short duration. Thus, there is considerable uncertainty in effects observed and the effects of different prophylactic antibiotics requires further research.

Tian, L., Y. Zhang, et al. (2019). **"The efficacy of mindfulness-based interventions for patients with COPD: a systematic review and meta-analysis protocol."** BMJ Open **9**(5): e026061.

INTRODUCTION: Chronic obstructive pulmonary disease (COPD) is a common chronic respiratory disease. It has adverse effects on patients' physical health, mental well-being and quality of life. The purpose of mindfulness-based interventions (MBIs) is to raise non-judgemental awareness and attention to current internal and external experiences. This means the attention is shifted from perceived and involuntary inner activities to current experience, keeping more curious, open and accepting attitudes towards current experience. Although some studies on the intervention effect of MBIs in patients with COPD have been conducted, the results are controversial, especially on dyspnoea, level of mindfulness and quality of life. Therefore, a systematic review of MBIs in patients with COPD is required to provide available evidence for further study. METHODS AND ANALYSIS: In this study, different studies from various databases will be involved. Randomised controlled trials(RCTs)/quantitative studies, qualitative studies and case studies on the effect of MBIs in patients with COPD aged over 18 years will be included. We will search the literature in the databases of PubMed, Excepta Medica Base (EMBASE), Web of Science, Cumulative Index to Nursing and Allied Health Literature (CINAHL), the Cochrane Library, PsycINFO and China National Knowledge Infrastructure(CNKI). The primary outcomes will include efficacy of MBIs for patients with COPD in terms of dyspnoea, depression and anxiety. The secondary outcomes will include efficacy of MBIs in terms of quality of life, mindful awareness, 6-minute walk test(6MWT) and nutritional risk index. Data extraction will be conducted by two researchers independently, and risk of bias of the meta-analysis will be evaluated based on the Cochrane Handbook for Systematic Reviews of Interventions. All data analysis will be conducted by data statistics software Review Manager V.5.3. and Stata V.12.0. ETHICS AND DISSEMINATION: Since this study is a systematic review, the findings are based on the published evidence. Therefore, examination and agreement by the ethics committee are not required in this study. We intend to publish the study results in a journal or conference presentations. PROSPERO REGISTRATION NUMBER: CRD42018102323.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6549636/pdf/bmjopen-2018-026061.pdf

Vitacca, M., I. Pietta, et al. (2019). **"Effect of high-flow nasal therapy during exercise training in COPD patients with chronic respiratory failure: study protocol for a randomised controlled trial."** Trials **20**(1): 336.

BACKGROUND: The benefit of pulmonary rehabilitation (PR) in symptomatic chronic obstructive pulmonary disease (COPD) is well known. However, advanced patients with chronic respiratory failure (CRF), a category excluded from most studies, are frequently unable to sustain a work-load sufficiently high to obtain the full benefit of PR on exercise tolerance. Recent studies involving heated and humidified high flow oxygen therapy (HFOT) showed positive effects on breathing pattern and ventilatory efficiency during effort. We thus plan to compare, in COPD patients with CRF undergoing a high-intensity exercise

programme, the effect of using HFOT versus standard oxygen delivery via Venturi Mask (V-mask), at the same inspiratory oxygen fraction, on improving exercise endurance. METHODS/DESIGN: This is a multicentre randomised controlled trial that will involve 156 COPD inpatients with CRF recruited from seven PR hospitals. Patients will be randomised to one of two groups - V-mask versus HFOT. All patients will undergo the same high-intensity exercise programme using either of the oxygen delivery devices as per their group allocation. Training will consist of 20 sessions, over 1 month (5 sessions per week) within the hospitalisation period. Anthropometric and clinical data, including body mass index, diagnosis, spirometry and comorbidities (Cumulative Rating Scale) will be collected at baseline. At baseline and at the end of the exercise programme (primary assessment time) evaluation will include exercise tolerance (Constant Work Rate Exercise Test) (primary outcome), functional capacity (6-min walk test), maximal inspiratory pressure/maximal expiratory pressure, peripheral muscle strength (biceps and quadriceps) by manual dynamometer, respiratory exchanges (blood gases analysis), disability (Barthel Index and Barthel Dyspnoea Index), impact of disease (COPD Assessment test), and quality of life (Maugeri Respiratory Failure Scale-26). At the end of the training period, patient satisfaction will be evaluated. DISCUSSION: This study will add knowledge about the exercise response in advanced COPD with CRF and verify if an alternative tool, namely HFOT, can increase the benefit obtained from PR. TRIAL REGISTRATION: ClinicalTrials.gov ID NET03322787 Registered: 6 November 2017.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6556225/pdf/13063_2019_Article_3440.pdf

Wang, L., K. Wu, et al. (2019). **"The Effects of Tai Chi on Lung Function, Exercise Capacity and Health Related Quality of Life for Patients With Chronic Obstructive Pulmonary Disease: A Pilot Study."** Heart Lung Circ **28**(8): 1206-1212.

BACKGROUND: Although several studies have assessed the effect of Tai Chi in management of chronic obstructive pulmonary disease (COPD), these studies have a wide sample variation and convey inconclusive results. This study aims to determine if a 3-month Tai Chi program improves lung function, exercise capacity, and health related quality of life (HRQoL) in people with COPD. METHODS: A randomised controlled, single blind trial was undertaken. Patients were randomly allocated to either Tai Chi group (n=26) or control group (n=24). Participants in the Tai Chi group received a Tai Chi exercise program three times weekly for 3-months while participants in the control group were advised to maintain their routine activities. Outcome measures included lung function, 6-minute walk distance (6WMD) and COPD Assessment Test (CAT). The measurements took place at baseline and immediately after the 3-month intervention period. RESULTS: Of 50 participants, 46 completed the intervention. Compared to control, Tai Chi significantly increased 6WMD (mean difference 60.5m, 95% CI 30.27-78.69), and reduced score of CAT (mean difference 14 points, 95% CI 11-24). An 86% compliance to the Tai Chi training was noted and no adverse events were observed in Tai Chi group. CONCLUSIONS: The Tai Chi program is a safe, effective and feasible method to improve exercise capacity and health-related quality of life in people with COPD.

https://www.heartlungcirc.org/article/S1443-9506(18)31833-X/fulltext

Whalley, D., H. Svedsater, et al. (2019). **"Follow-up interviews from The Salford Lung Study (COPD) and analyses per treatment and exacerbations."** NPJ Prim Care Respir Med **29**(1): 20.

The Salford Lung Study in chronic obstructive pulmonary disease (SLS COPD) was a 12-month, Phase III, open-label, randomised study comparing the effectiveness and safety of initiating once-daily fluticasone furoate 100 microg/vilanterol 25 microg (FF/VI) with continuing usual care (UC). Follow-up interviews were conducted among a subset of 400 patients who completed SLS COPD to further understand patients' experiences with treatment outcomes and the impact of COPD, and potential risk factors associated with higher rates of exacerbations during SLS COPD. Another objective was to explore how such patient-centred outcomes differed by randomised treatment. Patients' perceived control over COPD and effects on quality of life (QoL) were similar between treatment groups at the time of the follow-up interview, but more patients in the FF/VI group compared with UC reported perceived

improvements in COPD control and QoL during the study. Of patients who experienced >/=2 exacerbations during SLS COPD, a greater percentage were women, were unemployed or homemakers, or were on long-term sick leave. Having >/=2 exacerbations also appeared to be associated with smoking, seeing a hospital specialist, a feeling of having no/little control over COPD, perceived worsening of feelings of control and reduced overall QoL since the start of the study, being aware of impending exacerbation occurrence and a more severe last exacerbation. Initiation of FF/VI was associated with a greater perceived improvement in patients' control of their COPD and QoL throughout SLS COPD than continuation of UC. Suggestions that smoking status and feelings of control are potentially related to exacerbation require further investigation.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6509249/pdf/41533_2019_Article_123.pdf

Windmon, A., M. Minakshi, et al. (2019). **"TussisWatch: A Smart-Phone System to Identify Cough Episodes as Early Symptoms of Chronic Obstructive Pulmonary Disease and Congestive Heart Failure."** IEEE J Biomed Health Inform **23**(4): 1566-1573.

Chronic obstructive pulmonary disease (COPD) and congestive heart failure (CHF) are leading chronic health concerns among the aging population today. They are both typically characterized by episodes of cough that share similarities. In this paper, we design TussisWatch, a smart-phone-based system to record and process cough episodes for early identification of COPD or CHF. In our technique, for each cough episode, we do the following: 1) filter noise; 2) use domain expertise to partition each cough episode into multiple segments, indicative of disease or otherwise; 3) identify a limited number of audio features for each cough segment; 4) remove inherent biases as a result of sample size differences; and 5) design a two-level classification scheme, based on the idea of Random Forests, to process a recorded cough segment. Our classifier, at the first-level, identifies whether or not a given cough segment indicates a disease. If yes, the second-level classifier identifies the cough segment as symptomatic of COPD or CHF. Testing with a cohort of 9 COPD, 9 CHF, and 18 CONTROLS subjects spread across both the genders, races, and ages, our system achieves good performance in terms of Sensitivity, Specificity, Accuracy, and Area under ROC curve. The proposed system has the potential to aid early access to healthcare, and may be also used to educate patients on self-care at home.

https://ieeexplore.ieee.org/document/8471168/

Wu, J., Y. Ye, et al. (2019). **"Correlation of Inhaled Long-acting Bronchodilators with Adverse Cardiovascular Outcomes in Patients with Stable COPD: A Bayesian Network Meta-Analysis of Randomized Controlled Trials."** J Cardiovasc PharmacolA majority of existing studies have focused on the efficacy of inhaled long-acting bronchodilators (ILABs), such as long-acting muscarinic antagonists (LAMAs) and long-acting beta2-agonists (LABAs), and LABAs combined with LAMAs in treating chronic obstructive pulmonary disease (COPD). The current meta-analysis aimed to investigate the correlation of ILABs with specific cardiovascular adverse events (CAEs). Five electronic databases, including PubMed, Embase, Cochrane Library, Scopus and Web of Science, were systematically retrieved. Finally, 16 randomized controlled trials (RCTs) were enrolled into the current meta-analysis. Typically, the efficacy of 3 major classes of drugs (LABAs, LAMAs, as well as LABAs combined with LAMAs), as well as 7 specific drugs (including Formoterol, Glycopyrrolate, Indacaterol, Olodaterol, Salmeterol, Tiotropium, and Vilanterol) for 4 CAEs, including myocardial infarction (MI), cardiac failure (CF), ischemic heart disease (IHD) and stroke in stable COPD patients, was examined. All the pooled results were analyzed through the odds ratios (ORs) with the corresponding 95% confidence intervals (CIs). The direct meta-analysis results suggested that LABAs could increase the risk of CF in patients with stable COPD compared with placebo controls (OR 1.70, 95%CI 1.00-2.90). In addition, network meta-analysis results indicated that LAMAs combined with LABAs would result in an increased risk of CF in patients with stable COPD (OR 2.31, 95%CI 1.10-5.09). According to the ILABs specific drug analysis, Formoterol might potentially have protective effects on IHD compared with placebo controls (OR 0.45, 95%CI 0.18-1.00). In conclusion, among these three kinds of ILABs, including LAMAs, LABAs, and LABAs /LAMAs, for stable COPD patients, LAMAs and LABAs

are associated with the least possibility to induce MI and stroke, respectively. However, the application of LABAs will probably increase the risk of CF, they should be used with caution for stable COPD patients with CF. In addition, in specific-drug analysis, the use of formoterol can reduce the risk of treatment-related IHD. Nevertheless, more studies on different drug doses are needed in the future to further validate this conclusion.

Ye, Z., X. Ai, et al. (2019). **"The prognostic values of neutrophil to lymphocyte ratio for outcomes in chronic obstructive pulmonary disease."** Medicine (Baltimore) **98**(28): e16371.

OBJECTIVE: Neutrophil to lymphocyte ratio (NLR) is considered as an inflammatory biomarker for clinical outcomes in patients with chronic obstructive pulmonary disease (COPD). We aimed to conduct a meta-analysis to evaluate the prognostic values of NLR for the exacerbation and mortality in patients with COPD. METHODS: We searched the database of Cochrane Central Register of Controlled Trials, EMBASE, and PubMed, before September 2017. The eligible studies were retrieved by 2 authors independently following the criteria. The pooled odds ratios (ORs) of included studies were used to evaluate the prognostic values of NLR. Subgroup analyses were conducted to make the results more accurate. RESULTS: Nine studies with 5140 patients were enrolled in this analysis. The high NLR was associated with higher risk of exacerbation (OR: 3.81, 95% confidence interval [CI]: 1.20-12.13, P = .02) and mortality (OR: 2.60, 95% CI: 1.48-4.57, P < .01). By subgroup analysis, high NLR could predict the mortality in patients >70 years (OR: 2.16, 95% CI: 1.17-3.98, P = .01) but not in patients <70 years (OR: 4.08, 95% CI: 0.91-18.24, P = .07), and had a higher predictive ability in Asian group (OR: 3.64, 95% CI: 1.87-7.08, P < .01) than Eurasia group (OR: 1.82, 95% CI: 1.43-2.32, P < .01). In addition, high NLR could predict the short-term mortality (OR: 2.70, 95% CI: 1.10-6.63, P = .03) and the long-term mortality (OR: 2.61, 95% CI: 1.20-5.65, P = .02). CONCLUSIONS: The NLR may be an independent predictor for incidence of exacerbation in patients with COPD. In addition, high NLR may be associated with higher mortality in patients with COPD, especially for Asian and the patients with higher mean NLR.

Zeng, Y., Y. Li, et al. (2019). **"Chinese oral herbal paste for the treatment of stable chronic obstructive pulmonary disease: Protocol for a systematic review and meta-analysis."** Medicine (Baltimore) **98**(28): e16444.

BACKGROUND: Chronic obstructive pulmonary disease (COPD) is a common chronic respiratory disease with high morbidity and mortality placing heavy social and economic burden. As a kind of complementary therapy for the treatment of stable COPD, Chinese oral herbal paste has been widely used and studied. The study aims to evaluate the clinical efficacy and safety of herbal paste in the treatment of stable COPD, and to provide evidence for its clinical application. METHODS: We will electronically search databases, including Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, EMBASE, PubMed, Chinese National Knowledge Infrastructure (CNKI), WANFANG Database, Chinese Scientific and Technological Periodical Database (VIP), and Chinese Biomedical Database (CBM), from respective inception to June 2019 to collect randomized controlled trials (RCTs) of Chinese oral herbal paste for the treatment of stable COPD. The websites of Chinese clinical trial registry and international clinical trial registry, the reference lists of the retrieved articles, conference proceedings, and gray literature will also be collected. The quality of life, symptom scores, and exacerbation frequency will be measured as primary outcomes. Secondary outcomes include scores of traditional Chinese medicine (TCM) syndrome, clinical effective rates according to criteria in TCM, changes in lung function, 6-minute walking distance, and safety analysis. The Cochrane bias risk assessment and the GRADE method will be used to assess the quality of the original studies included. Merging analysis of data will be performed using Rev Man 5.3 software. RESULTS: The systematic review will provide an evidence on the clinical efficacy and safety of Chinese oral herbal paste for the treatment of stable COPD, and will be submitted for publication in a peer-

reviewed journal. CONCLUSION: The study will confirm whether Chinese oral herbal paste is an effective and safe intervention for the prevention and treatment of stable COPD.

Zheng, W., T. Gao, et al. (2019). **"Thirteen kinds of Chinese medicine injections for acute exacerbation of chronic obstructive pulmonary disease: Protocol for a systematic review and network meta-analysis."** Medicine (Baltimore) **98**(26): e16200.

BACKGROUND: Chinese medicine injections (CMIs) are extensively applied to the therapy of acute exacerbation of chronic obstructive pulmonary disease (AECOPD) in mainland China. Up to 13 different kinds of CMIs are reportedly often used for treating chronic obstructive pulmonary disease, yet, rarely head to head comparison of tests are used to decide the relative consequent among the distinct CMIs. Network meta-analysis (NMA) will be performed to further compare the effects of 13 different CMI, including direct and indirect comparisons of different CMI. METHODS: From now until April 2019, a systematic and comprehensive literature search will be conducted in both English and Chinese databases, including Medline, Embase, Cochrane library, Chongqing VIP information, Wanfang Database, China national knowledge infrastructure database, and Sino Med. Randomized controlled trials will be included related to CMI therapy for AECOPD. We will assess the quality of the included trials in accordance with the risk of bias tools in Cochrane manual 5.1.0. We will use the grading of recommendations assessment development, and evaluation method to assess the certainty of the estimated evidence from the NMA. STATA 14.0 will be used for data analysis. RESULTS: The purpose of this systematic evaluation and NMA was to summarize and rank the direct and indirect evidence for 8 different types of CMI. The NMA's findings will be reported in accordance with preferred reporting items for systematic reviews and meta analyses-NMA statement. Upon completion, NMA results will be submitted to a peer-reviewed journal. CONCLUSION: With NMA, this study will provide evidence for the selection of CMI for patients with AECOPD. The results will provide information to clinicians, bridge the evidence gap and identify promising CMI targets for future trials. PROSPERO REGISTRATION NUMBER: PROSPERO CRD 42019132955.

Aggarwal, T., R. Wadhwa, et al. (2018). **"Biomarkers of oxidative stress and protein-protein interaction in chronic obstructive pulmonary disease."** Arch Physiol Biochem **124**(3): 226-231.

CONTENT: The increased oxidative stress in chronic obstructive pulmonary disease (COPD) patients is the result of increased inhaled oxidants, generated by various cells of the airways. OBJECTIVE: The investigation included measurements of malondiadehyde (MDA), uric acid, ascorbic acid, and matrix metalloproteinase-12 (MMP-12) in COPD patient. We also performed genetic analysis for protein-protein interaction (PPI) network. MATERIALS AND METHODS: The study was conducted on healthy subjects with normal lung function (NS, 14 subjects) and 28 patients (Global Initiative for Chronic Obstructive Lung Disease (Gold) 1 and Gold 2) with COPD. RESULTS: There was significant ($p < .001$) increase in MMP-12, MDA and uric acid levels as compared to healthy controls. A significant ($p < .001$) decline in ascorbic acid level was observed in COPD patients. The PPI was found to be 0.833 which indicated that proteins present in COPD are linked. DISCUSSION AND CONCLUSION: This study suggests oxidative stress plays an important role in COPD and the PPI provide indication that proteins present in COPD are linked.

https://www.tandfonline.com/doi/full/10.1080/13813455.2017.1387796

Andrijevic, I., S. Milutinov, et al. (2018). **"N-Terminal Prohormone of Brain Natriuretic Peptide (NT-proBNP) as a Diagnostic Biomarker of Left Ventricular Systolic Dysfunction in Patients with Acute Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD)."** Lung **196**(5): 583-590.

INTRODUCTION: Left ventricular systolic dysfunction (LVSD) and cardiac decompensation often accompany AECOPD. Differentiation between the two is difficult and mainly relies on clinical and echocardiographic diagnostic procedures. The value of biomarkers, such as NT-proBNP, as diagnostic tools is still insufficiently investigated. The main goals of this trial were to investigate the value of NT-proBNP as a diagnostic tool for LVSD in AECOPD patients and determine its cut-off value which could reliably diagnose LVSD during AECOPD. PATIENTS AND METHODS: This trial prospectively enrolled 209 patients with AECOPD. The patients were divided into four groups-AECOPD plus chronic pulmonary heart disease (CPHD) with or without left ventricular compromise (LVSD), and AECOPD patients without CPHD with or without LVSD. NT-proBNP was measured within first 48 h of hospitalization. RESULTS: Majority of patients were male (61%) active smokers (41.6%), average age of 68 years. High quality of echocardiography was obtained in 63.3 and 22.5% of the patients had LVSD. Average value of NT-proBNP in patients with LVSD was 3303.2 vs. 1092.5 pg/mL in patients without LVSD. Significant differences in NT-proBNP value ($p = 0.0001$) were determined between observed patient groups. At the cut-off value of 1505 pg/mL, sensitivity, specificity, and positive and negative predictive values are 76.6, 83.3, 57.1, and 92.47%, respectively. CONCLUSION: At the cut-off value of 1505 pg/mL NT-proBNP could be used as a diagnostic marker for LVSD in acute exacerbation of COPD.

https://link.springer.com/article/10.1007%2Fs00408-018-0137-3

Bahtouee, M., N. Maleki, et al. (2018). **"The prevalence of chronic obstructive pulmonary disease in hookah smokers."** Chron Respir Dis **15**(2): 165-172.

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality worldwide. Hookah smoking is growing worldwide and particularly in Iran. The aim of this study was to determine the prevalence of obstructive pulmonary dysfunction in hookah smokers. We conducted a population-based study in Bushehr Province, Iran. A total of 245 subjects aged 35 years or older who were taking hookah for at least 15 years and 245 healthy controls were enrolled in the study and spirometry was done. Statistical analyses were performed using SPSS for windows software version 19. The prevalence of COPD among the exposed group of hookah smoke was 10.2%, with the rate being significantly higher in the patients with older age ($p < 0.001$), duration of hookah smoking ($p < 0.001$), men ($p = 0.026$), >/=3 hookahs/day ($p = 0.006$), history of cough for >/=2 years ($p = 0.002$), in patients with a history of

sputum for >/=2 years (p = 0.031), and in patients with a history of dyspnea for >/=2 years (p = 0.001). The results of the logistic regression analysis demonstrated that older age, male gender, smoking, and occupational exposure were independent predictive factors for COPD. The results of our study suggest that hookah smoking significantly increases the risk of COPD. Given the importance of COPD in the global burden of diseases, it is necessary to carry out further studies on the relationship between hookah use and COPD.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5958464/pdf/10.1177_1479972317709652.pdf

Bashir, A., Y. M. Hazari, et al. (2018). **"SERPINA1 Hepatocyte-Specific Promoter Polymorphism Associate with Chronic Obstructive Pulmonary Disease in a Study of Kashmiri Ancestry Individuals."** Lung **196**(4): 447-454.

PURPOSE: Different mutations in coding and non-coding sequences of the SERPINA1 gene have been implicated in the pathogenesis of COPD. However, - 10T/C mutation in the hepatocyte-directed promoter region has not been associated with COPD pathogenesis so far. Here, we report an increased frequency of - 10C genotype that is associated with decreased levels of serum alpha1-antitrypsin (alpha1AT) in COPD patients. METHODS: The quantification of serum alpha1AT was done by ELISA, the phenol-chloroform method was used for DNA extraction, PCR products were directly sequenced. The IBM SPSS Statistics v21 software was used for statistical analyses of the data. RESULTS: The mean serum alpha1AT level was found to be 1.203+0.239 and 3.162+0.160 g/L in COPD cases and in control, respectively. The - 10C allele is associated with an increased risk of COPD [OR, 3.50 (95%CI, 1.86-6.58); p < 0.001]. The combined variant genotype (TT+CC) was significantly found associated with an increased risk of COPD [OR, 3.20 (95% CI, 1.47-6.96); p = 0.003]. A significant association of the family history with COPD (overall p value= 0.0331) suggests that genetics may play an important role in the pathogenesis of COPD. CONCLUSION: The polymorphism associated with hepatocyte-specific promoter region (- 10T/C) is likely to be associated with the pathogenesis of COPD. It is quite possible that the change of the base in the hepatocyte-specific promoter of the SERPINA1 gene can modulate its strength, thereby driving the reduced expression of alpha1AT.

https://link.springer.com/article/10.1007%2Fs00408-018-0124-8

Bchir, S., H. Ben Nasr, et al. (2018). **"MMP-3 (-1171 5A/6A; Lys45Glu) variants affect serum levels of matrix metalloproteinase (MMP)-3 and correlate with severity of COPD: A study of MMP-3, MMP-7 and MMP-12 in a Tunisian population."** J Gene Med **20**(1)BACKGROUND: The present study aimed to examine the role of matrix metalloproteinase (MMP)-3 [(-1171) 5A/6A; Lys45Glu (A/G)], MMP-7 [(-181) A/G] and MMP-12 [(-82) A/G; Asn357Ser (A/G)] variants in the development and severity of chronic obstructive pulmonary disease (COPD) in Tunisians. METHODS: Plethysmography was performed in all participants to measure forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC) and FEV1/FVC parameters. Genotyping of MMP-3, MMP-7 and MMP-12 polymorphisms was carried out in 138 patients with COPD and 216 healthy controls using a polymerase chain reaction-restriction fragment length polymorphism. Serum levels of MMPs and cytokines (interleukin-6, tumor necrosis factor-alpha) were determined by an enzyme-linked immunosorbent assay. RESULTS: No significant correlations were observed between genetic variations in MMP-3, MMP-7 and MMP-12 and the risk of development of COPD. Additionally, no impact of MMP-7 (-181) A/G and MMP-12 [(-82) A/G; Asn357Ser (A/G)] polymorphisms was observed on the respective protein levels and clinical parameters of the disease. Interestingly, both MMP-3 (-1171) 5A/6A and Lys45Glu (A/G) variants were associated with respiratory function, as well as with serum levels of MMP-3 in COPD patients. A relationship was found between the (-1171) 6A and 45Glu (G) alleles of the MMP-3 gene and enhanced airflow limitation among COPD patients. Additionally, carriers of the 6A6A and 45 GG genotypes present higher MMP-3 levels than noncarriers. CONCLUSIONS: MMP-3 (-1171) 5A/6A and Lys45Glu (A/G) polymorphisms were associated with the decline of lung function among COPD patients. These results could be linked to the

upregulation of MMP-3 in serum from COPD patients carrying the (-1171) 6A and 45 G homozygous genotypes.

https://onlinelibrary.wiley.com/doi/abs/10.1002/jgm.2999

Behr, G., E. Mema, et al. (2018). **"Proportion and Clinical Relevance of Intraspinal Air in Patients With Pneumomediastinum."** AJR Am J Roentgenol **211**(2): 321-326.

OBJECTIVE: The purposes of this study were to determine the incidence of pneumorrhachis among patients with pneumomediastinum, determine whether its proportion correlates with the extent of pneumomediastinum, and ascertain its clinical relevance. MATERIALS AND METHODS: The radiologic database was searched for CT reports between January 2009 and September 2013 containing the term "pneumomediastinum" or "mediastinal air." Scans were examined for pneumomediastinum, pneumorrhachis, pneumothorax, sternotomy, and distribution of pneumomediastinum. The age and sex of the patient and probable cause of the abnormality were recorded. Cases that might have had another cause were excluded. RESULTS: The search yielded 422 CT scans. Among these, 242 instances of pneumomediastinum in 241 patients were found. Fifteen of these patients had pneumorrhachis. One was excluded because of recent traumatic spinal penetration. There was no significant difference in age or sex between patients with and those without pneumorrhachis. After application of the exclusion criteria, there were 14 cases of pneumorrhachis, yielding a proportion of 5.8%. Pneumorrhachis was observed more frequently in cases of the most severe grade (grade C) of pneumomediastinum; however, that relationship was not statistically significant (11 cases [8.2%]; $p = 0.304$). Pneumorrhachis was found significantly more frequently in patients with distribution of air in all three mediastinal compartments (13 cases, 16.2%, $p < 0.001$). Pneumorrhachis was overrepresented among subjects with spontaneous compared with those with secondary pneumomediastinum, although the trend did not reach statistical significance. CONCLUSION: Pneumorrhachis was present in 5.8% of patients. It is significantly more common in patients with the broadest distributions of mediastinal air and nonsignificantly more common in association with spontaneous as opposed to secondary pneumomediastinum. Pneumorrhachis in patients with pneumomediastinum is a generally benign, self-resolving condition.

Bernardi, E., C. Merlo, et al. (2018). **"Endothelial Function in COPD Is in an Intermediate Position Between Healthy Subjects and Coronary Artery Disease Patients and Is Related to Physical Activity."** Lung **196**(6): 669-672.

Patients with chronic obstructive pulmonary disease (COPD) have an increased risk of ischemic heart disease. Endothelial dysfunction may play a role in the onset of cardiovascular event. Previous studies showed an impaired endothelial function (measured by flow-mediated dilation, FMD) in COPD patients compared to healthy subjects. To the best of our knowledge no study has compared FMD in COPD and in cardiac (coronary artery disease, CAD) patients. We aimed to assess FMD in healthy subjects, COPD, CAD, and COPD + CAD. The main result is that FMD in COPD is reduced and is in an intermediate position between healthy subjects and CAD or COPD + CAD; this impairment can contribute to explain the higher prevalence of cardiovascular disease in COPD. The only determinant independently associated with FMD in all subjects is the physical activity level, irrespective of the traditional risk factors (i.e., smoke, dyslipidemia, hypertension).

https://link.springer.com/article/10.1007%2Fs00408-018-0168-9

Bhatt, S. P., P. P. Balte, et al. (2019). **"Discriminative Accuracy of FEV1:FVC Thresholds for COPD-Related Hospitalization and Mortality."** Jama **321**(24): 2438-2447.

Importance: According to numerous current guidelines, the diagnosis of chronic obstructive pulmonary disease (COPD) requires a ratio of the forced expiratory volume in the first second to the forced vital capacity (FEV1:FVC) of less than 0.70, yet this fixed threshold is based on expert opinion and remains controversial. Objective: To determine the discriminative accuracy of various FEV1:FVC fixed thresholds for predicting COPD-related hospitalization and mortality. Design, Setting, and Participants: The National Heart, Lung, and Blood Institute (NHLBI) Pooled Cohorts Study harmonized and pooled data from 4 US general population-based cohorts (Atherosclerosis Risk in Communities Study; Cardiovascular Health Study; Health, Aging, and Body Composition Study; and Multi-Ethnic Study of Atherosclerosis). Participants aged 45 to 102 years were enrolled from 1987 to 2000 and received follow-up longitudinally through 2016. Exposures: Presence of airflow obstruction, which was defined by a baseline FEV1:FVC less than a range of fixed thresholds (0.75 to 0.65) or less than the lower limit of normal as defined by Global Lung Initiative reference equations (LLN). Main Outcomes and Measures: The primary outcome was a composite of COPD hospitalization and COPD-related mortality, defined by adjudication or administrative criteria. The optimal fixed FEV1:FVC threshold was defined by the best discrimination for these COPD-related events as indexed using the Harrell C statistic from unadjusted Cox proportional hazards models. Differences in C statistics were compared with respect to less than 0.70 and less than LLN thresholds using a nonparametric approach. Results: Among 24207 adults in the pooled cohort (mean [SD] age at enrollment, 63 [10.5] years; 12990 [54%] women; 16794 [69%] non-Hispanic white; 15181 [63%] ever smokers), complete follow-up was available for 11077 (77%) at 15 years. During a median follow-up of 15 years, 3925 participants experienced COPD-related events over 340757 person-years of follow-up (incidence density rate, 11.5 per 1000 person-years), including 3563 COPD-related hospitalizations and 447 COPD-related deaths. With respect to discrimination of COPD-related events, the optimal fixed threshold (0.71; C statistic for optimal fixed threshold, 0.696) was not significantly different from the 0.70 threshold (difference, 0.001 [95% CI, -0.002 to 0.004]) but was more accurate than the LLN threshold (difference, 0.034 [95% CI, 0.028 to 0.041]). The 0.70 threshold provided optimal discrimination in the subgroup analysis of ever smokers and in adjusted models. Conclusions and Relevance: Defining airflow obstruction as FEV1:FVC less than 0.70 provided discrimination of COPD-related hospitalization and mortality that was not significantly different or was more accurate than other fixed thresholds and the LLN. These results support the use of FEV1:FVC less than 0.70 to identify individuals at risk of clinically significant COPD.

https://jamanetwork.com/journals/jama/article-abstract/2736562

Braunlich, J. and H. Wirtz (2018). **"Oral Versus Nasal High-Flow Bronchodilator Inhalation in Chronic Obstructive Pulmonary Disease."** J Aerosol Med Pulm Drug Deliv **31**(4): 248-254.

BACKGROUND: Nasal high flow (NHF) alters breathing patterns, stabilizes fraction of inspired oxygen (FiO2) during respiratory distress, helps to keep up hemostasis in the airways, and washes out the upper airways. Particularly the support of inspiratory flow and decrease in functional dead space are interesting mechanisms of action with regard to aerosol delivery. Several laboratory investigations have studied aerosol delivery via the nasal route by using NHF, whereas clinical benefits are poorly evaluated. METHODS: Thirty patients with stable chronic obstructive pulmonary disease Gold D were recruited. In a randomized order, they inhaled a salbutamol 2.5 mg/ipratropium bromide 500 mug solution oral or NHF adapted on the second study day. A jet nebulizer was used as aerosol delivery device. The chosen flow rate was 35 L/min. RESULTS: Four patients refused to repeat the procedure, for example, for inconvenience or fear of delayed discharge, and were not included in the intention-to-treat analysis. All remaining patients tolerated both inhalation systems well. Forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), airway resistance (Rtot), and residual volume (RV) were significantly altered after bronchodilator inhalation with each of the both devices. The two different ways of combined bronchodilator inhalation resulted in very comparable changes in FVC, FEV1, relative 1 second-capacity (FEV1%FVC), Rtot, total lung capacity (TLC), RV, and residual volume expressed as percent of TLC (RV%TLC). However, in between devices, no difference was observed on comparing the postinhalational measurements of FVC, FEV1, Rtot, and RV. CONCLUSIONS: We conclude from this proof-of-principle kind of study that inhalation of combined bronchodilators adapted to an NHF device is similarly effective to inhalation with a standard oral aerosol nebulizer. (Clinical Trails NCT02885103).

Button, B. M., A. E. Holland, et al. (2019). **"Prevalence, impact and specialised treatment of urinary incontinence in women with chronic lung disease."** Physiotherapy **105**(1): 114-119.

OBJECTIVES: To determine in women with clinically stable chronic lung disease (CLD) and healthy women; (1) prevalence of urinary incontinence; (2) risk factors for urinary incontinence; (3) effects of a standard course of specialised physiotherapy treatment (PT) in women with CLD. DESIGN: Prospective prevalence study; PT study in CLD subgroup. SETTING: Tertiary metropolitan public hospital. PARTICIPANTS: Women with cystic fibrosis (CF, n=38), chronic obstructive pulmonary disease (COPD, n=27) and 69 healthy women without CLD. PT study - 10 women with CLD. INTERVENTIONS: Five continence PT sessions over 3 months. MAIN OUTCOME MEASURES: Prevalence and impact of incontinence (questionnaire), number of leakage episodes (7-day accident diary), pelvic floor muscle function (ultrasound imaging) and quality of life (King's Health Questionnaire). RESULTS: The majority of women in all three groups reported episodes of incontinence (CF 71%; COPD 70%; healthy women 55%). Compared to age-matched healthy controls, women with CF reported more episodes of incontinence (P=0.006) and more commonly reported stress incontinence (P=0.001). A logistic regression model revealed that women with CLD were twice as likely to develop incontinence than healthy women (P=0.05). Women with COPD reported significantly more 'bother' with incontinence than age-matched women with incontinence. There was a significant reduction in incontinence episodes following treatment, which was maintained after three months. CONCLUSIONS: The presence of CLD is an independent predictor of incontinence in women. In older women this is associated with more distress than in age-matched peers without CLD. Larger treatment studies are indicated for women with CLD and incontinence.

https://www.physiotherapyjournal.com/article/S0031-9406(18)30155-X/pdf

Byers, D. E., K. Wu, et al. (2018). **"Triggering Receptor Expressed on Myeloid Cells-2 Expression Tracks With M2-Like Macrophage Activity and Disease Severity in COPD."** Chest **153**(1): 77-86.

BACKGROUND: Cell and animal models show a key role for Triggering Receptor Expressed on Myeloid Cells (TREM)-2 in chronic airway disease after viral infection, but comparable evidence in humans still needs to be established. METHODS: Lung tissue samples were obtained from lung transplant recipients with Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage IV COPD (n = 16), nontransplantable donor lung tissues (n = 7), and resected lung tissues from patients at risk or with GOLD stage I through IV (n = 55) and were assessed for TREM-2 and TREM-1 messenger RNA (mRNA), protein expression, and other markers of a type 2 immune response. RESULTS: TREM2 (but not TREM1) mRNA levels were increased in GOLD stage IV COPD lung tissues compared with non-COPD lung tissues. TREM2 mRNA was coexpressed with its signaling molecule DAP12 and the macrophage marker CD68 and M2-macrophage markers CD206 and CHIT1. TREM-2 protein was also increased in COPD lung tissues and was localized to CD14(+) macrophages by flow cytometry and CD68(+) and CCR2(+) macrophages by tissue immunostaining. In lung samples from patients at risk and with GOLD stage I through IV COPD, TREM2 but not TREM1 mRNA levels were also increased, and the ratio of TREM2/TREM1 mRNA levels was associated with increases in CHIT1 mRNA and decreases in FEV1 and FEV1/FVC. CONCLUSIONS: TREM-2 expression is increased in lung macrophages in COPD, particularly in comparison with TREM-1. Therefore, TREM-2 levels and the ratio of TREM-2/TREM-1 signifies M2 activation in COPD lung tissues and may help to guide therapeutics directed against the type 2 immune response in patients with this disease.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5812763/pdf/main.pdf

Cabrera Lopez, C., C. Casanova Macario, et al. (2018). **"Comparison of the 2017 and 2015 Global Initiative for Chronic Obstructive Lung Disease Reports. Impact on Grouping and Outcomes."** Am J Respir Crit Care Med **197**(4): 463-469.

RATIONALE: The Global Initiative for Chronic Obstructive Lung Disease (GOLD) document has modified the grading system directing pharmacotherapy, but how this relates to the previous one from 2015 and to comorbidities, hospitalizations, and mortality risk is unknown. OBJECTIVES: The aim of this study was to evaluate the changes in the GOLD groups from 2015 to 2017 and to assess the impact on severity, comorbidities, and mortality within each group. METHODS: We prospectively enrolled and followed, for a mean of 5 years, 819 patients with chronic obstructive pulmonary disease (84% male) in clinics in Spain and the United States. We determined anthropometrics, lung function (FEV1%), dyspnea score (modified Medical Research Council scale), ambulatory and hospital exacerbations, and the body mass index, obstruction, dyspnea, and exercise capacity (BODE) and Charlson indexes. We classified patients by the 2015 and 2017 GOLD ABCD system, and compared the differential realignment of the same patients. We related the effect of the reclassification in BODE and Charlson distribution as well as chronic obstructive pulmonary disease and all-cause mortality between the two classifications. MEASUREMENTS AND MAIN RESULTS: Compared with 2015, the 2017 grading decreased by half the proportion of patients in groups C and D (20.5% vs. 11.2% and 24.6% vs. 12.9%; P < 0.001). The distribution of Charlson also changed, whereas group D was higher than B in 2015, they become similar in the 2017 system. In 2017, the BODE index and risk of death were higher in B and D than in A and C. The mortality risk was better predicted by the 2015 than the 2017 system. CONCLUSIONS: Compared with 2015, the GOLD ABCD 2017 classification significantly shifts patients from grades C and D to categories A and B. The new grading system equalizes the Charlson comorbidity score in all groups and minimizes the differences in BODE between groups B and D, making the risk of death similar between them.

Callahan, C. L., P. A. Stewart, et al. (2019). **"Extended Mortality Follow-up of a Cohort of Dry Cleaners."** Epidemiology **30**(2): 285-290.

BACKGROUND: Dry cleaning workers are commonly exposed to tetrachloroethylene, a suspected bladder carcinogen, and other organic solvents. The health risks associated with solvent exposures in this industry are unclear. METHODS: We extended mortality follow-up of 5,369 dry cleaning union members in St. Louis to further investigate solvent-related risks. We added 22 years of follow-up, from 1993 through 2014, via linkage to the National Death Index. Using Cox proportional hazards modeling, we computed hazard ratios (HRs) and 95% confidence intervals (CIs) relating cause-specific mortality with levels of a solvent exposure index previously developed by an industrial hygienist based on workers' job titles from union records. The models were fit adjusting for age, sex, and decade of union enrollment, and assuming different exposure lags. RESULTS: In internal analyses of estimated solvent exposure with a 20-year lag, we observed exposure-response relationships for bladder cancer (HR medium exposure = 4.2; 95% CI = 0.7, 24.5 and HR high exposure = 9.2; 95% CI = 1.1, 76.7 vs. no exposure; Ptrend = 0.08) and kidney cancer (HR = 4.1; 95% CI = 0.7, 22.5 and 24.4; 2.9, 201.6; Ptrend = 0.004). High exposure was also associated with heart disease (HR = 1.6; 95% CI = 1.1, 2.2) and lymphatic/hematopoietic malignancies (HR = 4.3; 95% CI = 1.4, 13.6). CONCLUSIONS: These findings are, to the best of our knowledge, the first cohort evidence relating solvent exposure levels among dry cleaners to elevated risks of selected cancers and heart disease. Additional studies employing solvent-specific exposure assessment are needed to clarify cancer risks associated with tetrachloroethylene.

Campos, M. A., M. C. Runken, et al. (2018). **"Impact of a Health Management Program on Healthcare Outcomes among Patients on Augmentation Therapy for Alpha 1-Antitrypsin Deficiency: An Insurance Claims Analysis."** Adv Ther **35**(4): 467-481.

INTRODUCTION: Alpha 1-antitrypsin deficiency (AATD) is a genetic disorder which reduces serum alpha 1-antitrypsin (AAT or alpha1-proteinase inhibitor, A1PI) and increases the risk of chronic obstructive pulmonary disease (COPD). Management strategies include intravenous A1PI augmentation, and, in some cases, a health management program (Prolastin Direct((R)); PD). OBJECTIVES: This study compared clinical and economic outcomes between patients with and without PD program participation. METHODS: This retrospective study included commercial and Medicare Advantage health insurance plan members with >/= 1 claim with diagnosis codes for COPD and >/= 1 medical or pharmacy claim including A1PI (on index date). Outcomes were compared between patients receiving only Prolastin((R)) or Prolastin((R))-C (PD cohort) and patients who received a different brand without PD (Comparator cohort). Demographic and clinical characteristics were captured during 6 months pre-index. Post-index exacerbation episodes and healthcare utilization and costs were compared between cohorts. RESULTS: The study sample comprised 445 patients (n = 213 in PD cohort; n = 232 in Comparator cohort), with a mean age 55.5 years, 50.8% male, and 78.9% commercially insured. The average follow-up was 822 days (2.25 years), and the average time on A1PI was 747 days (2.04 years). Few differences were observed in demographic or clinical characteristics. Adjusting for differences in patient characteristics, the rate of severe exacerbation episodes was reduced by 36.1% in the PD cohort. Adjusted total annual all-cause costs were 11.4% lower, and adjusted mean respiratory-related costs were 10.6% lower in the PD cohort than the Comparator cohort. Annual savings in all-cause total costs in the PD cohort relative to the Comparator cohort was US$25,529 per patient, largely due to significantly fewer and shorter hospitalizations. CONCLUSIONS: These results suggest that comprehensive health management services may improve both clinical and economic outcomes among patients with COPD and AATD who receive augmentation therapy. FUNDING: Grifols Shared Services of North America, Inc.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5910458/pdf/12325_2018_Article_690.pdf

Cappa, V., A. Marcon, et al. (2019). **"Health-related quality of life varies in different respiratory disorders: a multi-case control population based study."** BMC Pulm Med **19**(1): 32.

BACKGROUND AND OBJECTIVE: Health-related quality of life (HRQL) in respiratory diseases has been generally investigated in clinical settings, focusing on a single disorder. In this study on a general population sample, we assessed the relationship between HRQL and several respiratory diseases studied simultaneously (COPD, current (CA) and past (PA) asthma, allergic (AR) and non-allergic (NAR) rhinitis and chronic bronchitis (CB). METHODS: Controls (n = 328) and cases of NAR (n = 95), AR (n = 163), CB (n = 48), CA (n = 224), PA (n = 126) and COPD (n = 28) were recruited in the centre of Verona in the frame of the Italian multi-case control GEIRD (Gene Environment Interactions in Respiratory Diseases) study; HRQL was measured through the SF-36 questionnaire. The relationships between HRQL (in terms of Physical (PCS) and Mental Component Scores (MCS)), respiratory diseases, and covariates were evaluated. RESULTS: With respect to controls, the adjusted PCS median score was worse in subjects suffering from current asthma (- 1.7; 95%CI:-2.8;-0.6), CB (- 3.8; 95%CI:-5.7;-1.9), and COPD (- 5.6; 95%CI:-8.1;-3.1). MCS was worse in current asthmatics (- 2.2; 95%CI:-4.1;-0.3), CB (- 5.5; 95%CI:-8.7;-2.2), and COPD cases (- 4.6; 95%CI:-8.8;-0.5) as well. CONCLUSIONS: To our knowledge, this is the first study in the general population that analyzed HRQL performing a simultaneous comparison of HRLQ in several respiratory disorders. We found that subjects suffering from COPD, CA, and CB had the poorest HRQL. Clinicians should carefully consider the possible impact of respiratory disorders as CB and not only that of CA and COPD.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6367788/pdf/12890_2019_Article_796.pdf

Chan, H. F., N. J. Stewart, et al. (2018). **"3D diffusion-weighted (129) Xe MRI for whole lung morphometry."** Magn Reson Med **79**(6): 2986-2995.

PURPOSE: To obtain whole lung morphometry measurements from (129) Xe in a single breath-hold with 3D multiple b-value (129) Xe diffusion-weighted MRI (DW-MRI) with an empirically optimized diffusion time and compressed sensing for scan acceleration. METHODS: Prospective three-fold undersampled 3D

multiple b-value hyperpolarized (129) Xe DW-MRI datasets were acquired, and the diffusion time (Delta) was iterated so as to provide diffusive length scale (LmD) estimates from the stretched exponential model (SEM) that are comparable to those from (3) He. The empirically optimized (129) Xe diffusion time was then implemented with a four-fold undersampling scheme and was prospectively benchmarked against (3) He measurements in a cohort of five healthy volunteers, six ex-smokers, and two chronic obstructive pulmonary disease patients using both SEM-derived LmD and cylinder model (CM)-derived mean chord length (Lm). RESULTS: Good agreement between the mean (129) Xe and (3) He LmD (mean difference, 2.2%) and Lm (mean difference, 1.1%) values was obtained in all subjects at an empirically optimized (129) Xe Delta = 8.5 ms. CONCLUSION: Compressed sensing has facilitated single-breath 3D multiple b-value (129) Xe DW-MRI acquisitions, and results at (129) Xe Delta = 8.5 ms indicate that (129) Xe provides a viable alternative to (3) He for whole lung morphometry mapping with either the SEM or CM. Magn Reson Med 79:2986-2995, 2018. (c) 2017 The Authors Magnetic Resonance in Medicine published by Wiley Periodicals, Inc. on behalf of International Society for Magnetic Resonance in Medicine. This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5888195/pdf/MRM-79-2986.pdf

Chen, Y. C., M. C. Lin, et al. (2018). **"Defective formyl peptide receptor 2/3 and annexin A1 expressions associated with M2a polarization of blood immune cells in patients with chronic obstructive pulmonary disease."** J Transl Med **16**(1): 69.

BACKGROUND: Controversy exists in previous studies on macrophage M1/M2 polarization in chronic obstructive pulmonary disease (COPD). We hypothesized that formyl peptide receptor (FPR), a marker of efferocytosis and mediator of M1/M2 polarization, may be involved in the development of COPD. METHODS: We examined FPR 1/2/3 expressions of blood M1/M2a monocyte, neutrophil, natural killer (NK) cell, NK T cell, T helper (Th) cell, and T cytotoxic (Tc) cell by flowcytometry method in 40 patients with cigarette smoking-related COPD and 16 healthy non-smokers. Serum levels of five FPR ligands were measured by ELISA method. RESULTS: The COPD patients had lower M2a percentage and higher percentages of NK, NK T, Th, and Tc cells than the healthy non-smokers. FPR2 expressions on Th/Tc cells, FPR3 expressions of M1, M2a, NK, NK T, Th, and Tc cells, and serum annexin A1 (an endogenous FPR2 ligand) levels were all decreased in the COPD patients as compared with that in the healthy non-smokers. FPR1 expression on neutrophil was increased in the COPD patient with a high MMRC dyspnea scale, while FPR2 expression on neutrophil and annexin A1 were both decreased in the COPD patients with a history of frequent moderate exacerbation (>/= 2 events in the past 1 year). In 10 COPD patients whose blood samples were collected again after 1-year treatment, M2a percentage, FPR3 expressions of M1/NK/Th cells, FPR2 expression on Th cell, and FPR1 expression on neutrophil were all reversed to normal, in parallel with partial improvement in small airway dysfunction. CONCLUSIONS: Our findings provide evidence for defective FPR2/3 and annexin A1 expressions that, associated with decreased M2a polarization, might be involved in the development of cigarette smoking induced persistent airflow limitation in COPD.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5856198/pdf/12967_2018_Article_1435.pdf

Christensen, C. H., B. Rostron, et al. (2018). **"Association of Cigarette, Cigar, and Pipe Use With Mortality Risk in the US Population."** JAMA Intern Med **178**(4): 469-476.

Importance: Tobacco products have changed in recent years. Contemporary mortality risk estimates of combustible tobacco product use are needed. Objective: To investigate the mortality risks associated with current and former use of cigars, pipes, and cigarettes. Design, Setting, and Participants: The National Longitudinal Mortality Study is a longitudinal population-based, nationally representative health survey with mortality follow-up that includes demographic and other information from the Current Population Survey, tobacco product use information from the Tobacco Use Supplement, and

mortality data from the National Death Index. In this study, participants provided tobacco use information at baseline in surveys starting from 1985 and were followed for mortality through the end of 2011. The study includes 357420 participants who reported exclusively using cigar, pipes, or cigarettes or reported never using any type of tobacco product. Exposures: Current or former exclusive use of any cigar (little cigar, cigarillos, large cigar), traditional pipe, or cigarette and never tobacco use. Information on current daily and nondaily use was also collected. Estimates adjusted for age, sex, race/ethnicity, education, and survey year. Main Outcomes and Measures: All-cause and cause-specific mortality as identified as the primary cause of death from death certificate information. Results: Of the 357420 persons included in the analysis, the majority of current and former cigar and pipe smokers were male (79.3%-98.0%), and smokers were more evenly divided by sex (46% of current daily smokers were male). There were 51 150 recorded deaths during follow-up. Exclusive current cigarette smokers (hazard ratio [HR], 1.98; 95% CI, 1.93-2.02) and exclusive current cigar smokers (HR, 1.20; 95% CI, 1.03-1.38) had higher all-cause mortality risks than never tobacco users. Exclusive current cigarette smokers (HR, 4.06; 95% CI, 3.84-4.29), exclusive current cigar smokers (HR, 1.61; 95% CI, 1.11-2.32), and exclusive current pipe smokers (HR, 1.58; 95% CI, 1.05-2.38) had an elevated risk of dying from a tobacco-related cancer (including bladder, esophagus, larynx, lung, oral cavity, and pancreas). Among current nondaily cigarette users, statistically significant associations were observed with deaths from lung cancer (HR, 6.24; 95% CI, 5.17-7.54), oral cancer (HR, 4.62; 95% CI, 1.84-11.58), circulatory death (HR, 1.43; 95% CI, 1.30-1.57), cardiovascular death (HR, 1.24; 95% CI, 1.11-1.39), cerebrovascular death (stroke) (HR, 1.39; 95% CI, 1.12-1.74), and chronic obstructive pulmonary disease (HR, 7.66; 95% CI, 6.09-9.64) as well as for daily smokers. Conclusions and Relevance: This study provides further evidence that exclusive use of cigar, pipes, and cigarettes each confers significant mortality risks.

https://jamanetwork.com/journals/jamainternalmedicine/articlepdf/2672576/jamainternal_christensen_2018_oi_170133.pdf

Cleutjens, F., M. A. Spruit, et al. (2018). **"Cognitive impairment and clinical characteristics in patients with chronic obstructive pulmonary disease."** Chron Respir Dis **15**(2): 91-102.

We aimed to investigate (1) the relationship between cognitive impairment (CI) and disease severity and (2) the potential differences in exercise performance, daily activities, health status, and psychological well-being between patients with and without CI. Clinically stable chronic obstructive pulmonary disease (COPD) patients, referred for pulmonary rehabilitation, underwent a neuropsychological examination. Functional exercise capacity (6-minute walk test [6MWT]), daily activities (Canadian Occupational Performance Measure [COPM]), health status (COPD Assessment Test [CAT]) and St George's Respiratory Questionnaire-COPD specific [SGRQ-C]), and psychological well-being (Hospital Anxiety and Depression Scale [HADS], Beck Depression Inventory [BDI], and Symptom Checklist 90 [SCL-90]) were compared between patients with and without CI. Of 183 COPD patients (mean age 63.6 (9.4) years, FEV1 54.8 (23.0%) predicted), 76 (41.5%) patients had CI. The prevalence was comparable across Global Initiative for Chronic Obstructive Lung Disease (GOLD) grades 1-4 (44.8%, 40.0%, 41.0%, 43.5%, respectively, p = 0.97) and GOLD groups A-D (50.0%, 44.7%, 33.3%, 40.2%, respectively, p = 0.91). Patients with and without CI were comparable for demographics, smoking status, FEV1% predicted, mMRC, 6MWT, COPM, CAT, HADS, BDI, and SCL-90 scores. Clinical characteristics of COPD patients with and without CI are comparable. Assessment of CI in COPD, thus, requires an active case-finding approach.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5958463/pdf/10.1177_1479972317709651.pdf

Cuthbert, J. J., J. W. Kearsley, et al. (2019). **"The impact of heart failure and chronic obstructive pulmonary disease on mortality in patients presenting with breathlessness."** Clin Res Cardiol **108**(2): 185-193.

BACKGROUND: Differentiating heart failure from chronic obstructive pulmonary disease (COPD) in a patient presenting with breathlessness is difficult but may have implications for outcome. We investigated the prognostic impact of diagnoses of COPD and/or heart failure in consecutive patients presenting to a secondary care clinic with breathlessness. METHODS: In patients with left ventricular systolic dysfunction

(LVSD) by visual estimation, N-terminal pro B-type natriuretic peptide (NTproBNP) levels and spirometry were evaluated (N = 4986). Heart failure was defined as either LVSD worse than mild (heart failure with reduced ejection fraction) or LVSD mild or better and raised NTproBNP levels (> 400 ng/L) (heart failure with normal ejection fraction). COPD was defined as forced expiratory volume in 1 s (FEV1) to forced vital capacity (FVC) ratio < 0.7. The primary outcome was all-cause mortality. RESULTS: 1764 (35%) patients had heart failure alone, 585 (12%) had COPD alone, 1751 (35%) had heart failure and COPD, and 886 (18%) had neither. Compared to patients with neither diagnosis, those with COPD alone [hazard ratio (HR) = 1.84 95% confidence interval (CI) 1.40-2.43], heart failure alone [HR = 4.40 (95% CI 3.54-5.46)] or heart failure and COPD [HR = 5.44 (95% CI 4.39-6.75)] had a greater risk of death. COPD was not associated with increased risk of death in patients with heart failure on a multivariable analysis. CONCLUSION: While COPD is associated with increased risk of death compared to patients with neither heart failure nor COPD, it has a negligible impact on prognosis amongst patients with heart failure.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6510798/pdf/392_2018_Article_1342.pdf

De Miguel-Diez, J., A. Lopez-De-Andres, et al. (2019). **"Chronic obstructive pulmonary disease is not associated with worse in-hospital outcomes after surgical aortic valve replacement in Spain (2001-2015)."** J Cardiovasc Surg (Torino) **60**(3): 413-421.

BACKGROUND: The aims of this study were: 1) to examine incidence, characteristics and in-hospital outcomes of surgical aortic valve replacement (SAVR) among patients with or without COPD; 2) to compare both groups matched by sex, age, year hospitalized for SAVR and implanted valve type; and 3) to identify factors associated with in-hospital mortality (IHM) among chronic obstructive pulmonary disease (COPD) patients. METHODS: We used the Spanish National Hospital Discharge Database for patients aged >/=40 years from 2001 to 2015. We selected patients whose medical procedures included SAVR. We grouped hospitalizations by COPD status. Main outcomes were incidences and IHM. Covariates included comorbidities and concomitant procedures. RESULTS: We identified 78,223 hospitalizations with SAVR and COPD accounted for 9.14% (6028 men and 1125 women). Incidence of hospitalizations for SAVR increased overtime in patients without COPD, but not in COPD sufferers. COPD patients were more likely to receive bioprosthetic valves than those without COPD. The proportion of mechanical valves implanted decreased as the bioprosthetic valves increased overtime in both groups. Crude IHM was 6.77% for COPD patients and 6.48% for non-COPD (P=0.17). IHM decreased significantly over time in both groups of patients. After matching no differences were found in IHM between COPD and matched not-COPD patients who received a mechanical or bioprosthetic SAVR. Among COPD patients, IHM was associated with older age, more comorbidities and concomitant coronary artery bypass graft. CONCLUSIONS: Our analysis suggest that COPD per se should not represent a contraindication to SAVR. No differences were found for IHM between patients with and without COPD beside the type of valve used.

Dunican, E. M., B. M. Elicker, et al. (2018). **"Mucus plugs in patients with asthma linked to eosinophilia and airflow obstruction."** J Clin Invest **128**(3): 997-1009.

BACKGROUND: The link between mucus plugs and airflow obstruction has not been established in chronic severe asthma, and the role of eosinophils and their products in mucus plug formation is unknown. METHODS: In clinical studies, we developed and applied a bronchopulmonary segment-based scoring system to quantify mucus plugs on multidetector computed tomography (MDCT) lung scans from 146 subjects with asthma and 22 controls, and analyzed relationships among mucus plug scores, forced expiratory volume in 1 second (FEV1), and airway eosinophils. Additionally, we used airway mucus gel models to explore whether oxidants generated by eosinophil peroxidase (EPO) oxidize cysteine thiol groups to promote mucus plug formation. RESULTS: Mucus plugs occurred in at least 1 of 20 lung segments in 58% of subjects with asthma and in only 4.5% of controls, and the plugs in subjects with asthma persisted in the same segment for years. A high mucus score (plugs in >/= 4 segments) occurred in 67% of subjects with asthma with FEV1 of less than 60% of predicted volume, 19% with FEV1 of 60%-80%,

and 6% with FEV1 greater than 80% (P < 0.001) and was associated with marked increases in sputum eosinophils and EPO. EPO catalyzed oxidation of thiocyanate and bromide by H2O2 to generate oxidants that crosslink cysteine thiol groups and stiffen thiolated hydrogels. CONCLUSION: Mucus plugs are a plausible mechanism of chronic airflow obstruction in severe asthma, and EPO-generated oxidants may mediate mucus plug formation. We propose an approach for quantifying airway mucus plugging using MDCT lung scans and suggest that treating mucus plugs may improve airflow in chronic severe asthma. TRIAL REGISTRATION: Clinicaltrials.gov NCT01718197, NCT01606826, NCT01750411, NCT01761058, NCT01761630, NCT01759186, NCT01716494, and NCT01760915. FUNDING: NIH grants P01 HL107201, R01 HL080414, U10 HL109146, U10 HL109164, U10 HL109172, U10 HL109086, U10 HL109250, U10 HL109168, U10 HL109257, U10 HL109152, and P01 HL107202 and National Center for Advancing Translational Sciences grants UL1TR0000427, UL1TR000448, and KL2TR000428.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5824874/pdf/jci-128-95693.pdf

Durmus, U., N. O. Dogan, et al. (2018). **"The value of lactate clearance in admission decisions of patients with acute exacerbation of COPD."** Am J Emerg Med **36**(6): 972-976.

BACKGROUND: Lactate and lactate clearance are being used as biomarkers in several critical conditions. The aim of this study was to examine the value of sixth hour lactate clearance in patients who were hospitalized with chronic obstructive pulmonary disease (COPD) exacerbations. METHODS: This single-center, cross-sectional study was conducted in a tertiary emergency department (ED) on patients who presented with acute exacerbation of COPD. Discharge or admission decisions were specified according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria and the clinician's decision. In the study, lactate clearance was defined as the percent decrease in lactate from the time of presentation to the ED to the sixth hour. RESULTS: A total of 495 patients were evaluated and 397 patients were excluded. Among included patients, 53 (54.1%) were admitted to the hospital and 45 (45.9%) were discharged. The median lactate clearance was found to be -11.8% (95% CI: -50.0 to 34.5) in the admitted group and 14.7% (95% CI: -11.3 to 42.3) in the discharged group. Between the two groups, the median difference of lactate clearance was found to be 26.5% (95% CI: 0.6 to 52.4). Multivariate logistic regression analysis revealed that the delta lactate value can determine the hospitalization need of patients (OR: 0.91, 95% CI: 0.85 to 0.97). CONCLUSION: Lactate clearance can be evaluated as a useful marker in patients with COPD exacerbations. This study suggests that lactate monitoring in the ED has clinical benefits in addition to GOLD guidelines when deciding whether to discharge or hospitalize a patient.

https://www.ajemjournal.com/article/S0735-6757(17)30910-5/fulltext

Evans, R. A. and M. C. Steiner (2017). **"Pulmonary Rehabilitation: The Lead Singer of COPD Therapy but Not a "One-Man Band"."** Chest **152**(6): 1103-1105.

https://journal.chestnet.org/article/S0012-3692(17)31250-3/pdf

Farahani, P., R. Halabian, et al. (2017). **"Increased Genes Expression Levels of Cytokines Related to Th17/Treg Cells in Peripheral Blood Mononuclear Cell Correlate with Clinical Severity in COPD and Mustard Gas-exposed Patients."** Iran J Allergy Asthma Immunol **16**(5): 396-403.

The long lasting inflammation and immune dysregulation is one of the main mechanisms involved in lung complication of veterans exposed to sulfur mustard (SM) gas. Th17/Treg cells have an important role in immunopathogenesis of chronic obstructive pulmonary disease (COPD) and mustard lung disease. In this study, expression of cytokines genes levels related to Th17/Treg cells was determined in peripheral blood mononuclear (PBMC) of mustard lung patients and was compared with COPD patients and healthy controls (HC). Real time-polymerase chain reaction was used to assay genes expression levels of

Th17 related cytokines (IL-17, IL-6 and TGF-beta) and Treg related cytokines (IL-10, TGF-beta). IL-17 gene expression level considerably was higher in SM patients (9.98+/-0.65, p<0.001), and COPD (4.75+/-0.71, p<0.001), compare to HC group. Also, gene expression level of IL-6 in the SM group (3.31+/-0.93, p<0.001) and COPD group (2.93+/-0.21, p<0.001) were significantly higher than the HC group. The IL-10 gene expression level showed a high increase in SM patients (4.12+/-0.91, p<0.01), and COPD (2.1+/-0.45, p<0.01). Finally, the TGF-beta gene expression level was increased in SM patients (4.91+/-0.69, p<0.001) as well as in COPD group (5.41+/-0.78, p<0.001). In SM patients, IL-17 (R=-0.721, p<0.05), IL-6 (R=-0.621, p<0.05) and TGF-beta (R=-0.658, p<0.05) had significant negative association with FEV1 (%). Inversely, Il-10 showed positive correlation (R=0.673) with FEV1 (%). Th17/Treg cells related cytokines genes were highly expressed and imbalanced in peripheral blood mononuclear cells of SM and COPD patients which correlated with pulmonary dysfunction.

http://ijaai.tums.ac.ir/index.php/ijaai/article/download/1236/765

Fernandes, L. and A. M. Mesquita (2017). **"The success and safety profile of sputum induction in patients with chronic obstructive pulmonary disease: An Indian experience."** Indian J Tuberc **64**(3): 201-205.

BACKGROUND: Neutrophilic inflammation is common in chronic obstructive pulmonary disease while Asthma COPD overlap syndrome has eosinophilic predominance. Identifying the type of inflammation will aid in better management of COPD, but published studies show that induced sputum examination is more frequently used in asthma than COPD, with safety being the limiting factor. We aimed to determine the success and safety of sputum induction (SI) in COPD patients. METHODS: 116 stable COPD patients underwent SI. Success was defined as adequate sputum sample resulting in a cytospin sufficient to assess differential count while safety by the fall in FEV1. RESULTS: The mean (SD) FEV1% predicted post bronchodilator was 58.8 (17.8) and 59 (51.8%) patients had moderate COPD. Success was 98.28%. The procedure was safe with overall fall in FEV1 of 11.1% (5.1, 15.2). >/=20% fall was noted in 13 (11.4%) patients, 10-20% in 24 (21.0%) patients, and less than 10% in 29 (25.4%) patients while 48 (42.1%) had no fall. There was an inverse correlation between reversibility in FEV1 and percentage fall in FEV1; r=-0.437 and p=0.001. Stepwise multivariate linear regression showed reversibility as an independent predictor of fall in FEV1; R(2)=0.137. CONCLUSIONS: Sputum induction is successful and safe in COPD. Even a fall in FEV1>20% is reversible.

https://www.sciencedirect.com/science/article/pii/S0019570716302426?via%3Dihub

Frenkel, A., E. Kachko, et al. (2018). **"Estimations of a degree of steroid induced leukocytosis in patients with acute infections."** Am J Emerg Med **36**(5): 749-753.

BACKGROUND: Glucocorticosteroids (GCS) are known to cause the hematologic effect of leukocytosis and neutrophilia. Leukocytosis is a key parameter in establishing the diagnosis of sepsis and in the estimation of its severity. OBJECTIVE: To quantify the effect of chronic or acute GCS treatment on the level of leukocytosis in patients with acute infectious process. METHODS: We conducted a retrospective cohort study of patients with an acute infection hospitalized in tertiary medical center between the years 2003-2014. Patients were classified into three categories: chronic GCS treatment, acute GCS treatment, no GCS treatment. The primary outcome was the maximal WBC count within the first 24h from admission. RESULTS: We identified 5468 patients with acute infection: 333 of them with chronic GCS treatment, 213 with acute GCS treatment and 4922 with no GCS treatment. The overall maximal leukocytes count was higher in GCS therapy groups: 15.4+/-8.3x10(9)/L for the acute GCS treatment, 14.9+/-7.4x10(9)/L for chronic GCS treatment and 12.9+/-6.4x10(9)/L for the no GCS group (P<0.001). CONCLUSION: In patients with acute infections chronically treated with GCS, an increase in the WBC is at average of 5x10(9)/L. These data must be taken into consideration while using the level of leukocytosis as a parameter in the diagnosis of the infectious process.

https://www.ajemjournal.com/article/S0735-6757(17)30805-7/fulltext

Frykholm, E., P. Klijn, et al. (2019). **"Effect and feasibility of non-linear periodized resistance training in people with COPD: study protocol for a randomized controlled trial."** Trials **20**(1): 6.

BACKGROUND: In people with chronic obstructive pulmonary disease (COPD), limb-muscle dysfunction is one of the most troublesome systemic manifestations of the disease, which at the functional level is evidenced by reduced strength and endurance of limb muscles. Improving limb-muscle function is an important therapeutic goal of COPD management, for which resistance training is recommended. However, current guidelines for resistance training in COPD mainly focus on improving muscle strength which only reflects one aspect of limb-muscle function and does not address the issue of reduced muscle endurance. The latter is of importance considering that the reduction in limb-muscle endurance often is greater than that of muscle weakness, and also, limb-muscle endurance seems to be closer related to walking capacity as well as arm function than to limb-muscle strength within this group of people. Thus, strategies targeting multiple aspects of the decreased muscle function are warranted to increase the possibility for an optimal effect for the individual patient. Periodized resistance training, which represents a planned variation of resistance training variables (i.e., volume, intensity, frequency, etc.), is one strategy that could be used to target limb-muscle strength as well as limb-muscle endurance within the same exercise regimen. METHODS: This is an international, multicenter, randomized controlled trial comparing the effect and feasibility of non-linear periodized resistance training to traditional non-periodized resistance training in people with COPD. Primary outcomes are dynamic limb-muscle strength and endurance. Secondary outcomes include static limb-muscle strength and endurance, functional performance, quality of life, dyspnea, intramuscular adaptations as well as the proportion of responders. Feasibility of the training programs will be assessed and compared on attendance rate, duration, satisfaction, drop-outs as well as occurrence and severity of any adverse events. DISCUSSION: The proposed trial will provide new knowledge to this research area by investigating and comparing the feasibility and effects of non-linear periodized resistance training compared to traditional non-periodized resistance training. If the former strategy produces larger physiological adaptations than non-periodized resistance training, this project may influence the prescription of resistance training in people with COPD. TRIAL REGISTRATION: ClinicalTrials.gov, ID: NCT03518723 . Registered on 13 April 2018.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6318913/pdf/13063_2018_Article_3129.pdf

Galizia, G., G. Balestrieri, et al. (2018). **"Role of rehabilitation in the elderly after an acute event: insights from a real-life prospective study in the subacute care setting."** Eur J Phys Rehabil Med **54**(6): 934-938.

BACKGROUND: Any acute event, either primary or secondary to a chronic disease, is generally followed by some degree of physical impairment. Subacute care (SAC) represents one of the inpatient intermediate care settings aimed at completing recovery and restoring functional capacity. Debate exists on the role of the rehabilitation treatment in the SAC setting. AIM: The aim of this study was to compare the outcomes of patients managed in two different SAC Units where A) patients undergo an individualized rehabilitation program on top of optimal medical therapy (OMT) B) patients receive OMT only. DESIGN: Real-life prospective study. SETTING: SAC units. POPULATION: Seventy-five chronic heart failure (CHF) and chronic obstructive pulmonary disease (COPD) patients transferred after an acute hospitalization. METHODS: Upon SAC admission, the following scales were obtained: cumulative illness rating scale comorbidity and severity (CIRSC and CIRSS), mini mental state examination (MMSE), Performance-Oriented Mobility Assessment (POMA), Barthel Index (BI), the 10-meter walking test (10MWT). Pre-admission BI was also collected based on history. Upon SAC discharge, BI, POMA, and 10MWT were repeated. RESULTS: Patients (44 in Group A, 31 in Group B) were similar with regard to age, gender, MMSE, clinical complexity, pre-admission BI, admission 10MWT, POMA, and bedrest conditions. Admission BI was lower in Group A. In both groups BI was lower when compared to the respective pre-admission score. Upon discharge, Group A patients were characterized by a higher BI and POMA compared to Group B. Indeed, BI and POMA improved at discharge only in Group A patients. Only this latter group reached the pre-morbid BI. Upon discharge the number of bedrest patients decreased only in Group A. The percentage of patients discharged home was also much higher in Group A, while a

greater number of Group B patients were transferred to a rehabilitation ward or were enrolled in an integrated home care assistance program. CONCLUSIONS: In a real-life prospective experience, a better outcome is demonstrated in elderly CHF and COPD patients undergoing a rehabilitative approach during their in-hospital SAC stay. CLINICAL REHABILITATION IMPACT: An individualized rehabilitation program should integrate medical treatment of CHF and BPCO patients in the SAC setting. This approach demonstrates a better cost-effectiveness management of these patients.

Grigoryeva, N. Y., C. Maiorova capital Em, et al. (2019). **"capital ES, Cyrillicomorbidity and polymorbidity of the patient with chronic obstructive pulmonary disease and cardiovascular diseases."** Ter Arkh **91**(1): 44-47.

AIM: the study of comorbid status and characteristics of clinical course of ischemic heart disease (IHD) in patients with chronic obstructive pulmonary disease (COPD). MATERIALS AND METHODS: We conducted a retrospective analysis of case histories of 958 IHD patients aged 32 to 93 years (mean age of 60.8+/-10.2 years), including men - 525 (54.8%), women - 433 (45.2%) who were treated in the cardiology Department of city clinical hospital numero sign5 of Nizhny Novgorod. Related COPD was diagnosed in 251 patients (26.3%). We compared two groups patients: with IHD and COPD, and the second - persons suffering from only IHD (without COPD). RESULTS: Myocardial infarction was transferred by 62.2% of patients in Group 1, which is 16.3% more than in Group 2 (p<0.05). Arterial hypertension in patients with COPD was 13.6% more frequent than in patients without COPD (p<0.05), and 6.4% more often (p<0.05), with comorbid pathology there was a chronic and paroxysmal forms of atrial fibrillation. In patients with IHD in combination with COPD it is 21.5% more often (p<0.05) than in IHD without COPD, there was shortness of breath and 32.1% more often (p<0.05) of the heartbeat. In patients with IHD with COPD, a higher level of was C-reactive protein detected (p<0.05) and more pronounced violations of the lipid profile (p<0.05). CONCLUSION: COPD makes a significant contribution to the development of the cardiovascular continuum, modifying its course. A modern patient with COPD is a high-risk patient with severe cardiovascular comorbidity and various polymorbidity.

Hamad, G. A., W. Cheung, et al. (2018). **"Eosinophils in COPD: how many swallows make a summer?"** Eur Respir J **51**(1)
https://erj.ersjournals.com/content/51/1/1702177

Hassan, T., C. de Santi, et al. (2017). **"Alpha-1 antitrypsin augmentation therapy decreases miR-199a-5p, miR-598 and miR-320a expression in monocytes via inhibition of NFkappaB."** Sci Rep **7**(1): 13803.

Alpha-1 antitrypsin (AAT) augmentation therapy involves infusion of plasma-purified AAT to AAT deficient individuals. Whether treatment affects microRNA expression has not been investigated. This study's objectives were to evaluate the effect of AAT augmentation therapy on altered miRNA expression in monocytes and investigate the mechanism. Monocytes were isolated from non-AAT deficient (MM) and AAT deficient (ZZ) individuals, and ZZs receiving AAT. mRNA (qRT-PCR, microarray), miRNA (miRNA profiling, qRT-PCR), and protein (western blotting) analyses were performed. Twenty one miRNAs were differentially expressed 3-fold between ZZs and MMs. miRNA validation studies demonstrated that in ZZ monocytes receiving AAT levels of miR-199a-5p, miR-598 and miR-320a, which are predicted to be regulated by NFkappaB, were restored to levels similar to MMs. Validated targets co-regulated by these miRNAs were reciprocally increased in ZZs receiving AAT in vivo and in vitro. Expression of these miRNAs could be increased in ZZ monocytes treated ex vivo with an NFkappaB agonist and decreased by NFkappaB inhibition. p50 and p65 mRNA and protein were significantly lower in ZZs receiving AAT than

untreated ZZs. AAT augmentation therapy inhibits NFkappaB and decreases miR-199a-5p, miR-598 and miR-320a in ZZ monocytes. These NFkappaB-inhibitory properties may contribute to the anti-inflammatory effects of AAT augmentation therapy.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5653852/pdf/41598_2017_Article_14310.pdf

Hernandez Zenteno, R. J., D. F. Lara, et al. (2018). **"Varenicline for long term smoking cessation in patients with COPD."** Pulm Pharmacol Ther **53**: 116-120.

BACKGROUND: Quitting smoking is key for patients with Chronic Obstructive Pulmonary Disease (COPD). Standard recommendations for quitting smoking are implemented for COPD as well. Varenicline Tartrate (VT) is the most effective drug to help quit smoking, but few studies have analysed its effectiveness. AIM OF THE STUDY: To determine the Abstinence Rate (AR) at 12 months, in COPD and non-COPD smokers. METHODS: Observational study in 31 COPD (post bronchodilator-BD FEV1/FVC <0.70) and in 63 non-COPD smokers, were invited to receive treatment with Varenicline Tartrate (VT). Fourteen subjects with COPD and 46 non-COPD subjects received additionally Cognitive-Behavioral Therapy (CBT). Abstinence rate (AR) was validated by exhaled carbon monoxide CO (COe), in addition to a phone or face-to-face interview. Motivation score was measured with a visual analogue scale (MS). RESULTS: Differences between COPD and non-COPD, mean FEV1/FVC ratio 0.52+/-0.10 vs. 0.90+/-0.15, age 60+/-10 vs. 47+/-10 years, smoking pack-years 37+/-3.5 vs. 22+/-12, and COe 16+/-11 vs. 12+/-9ppm were statistically significant ($p<0.05$); for MS the score was 93+/-11 vs. 93+/-11 and for attempts to quit (AQ) 2+/-2 vs. 2+/-3 were not. AR was not significantly different at 12 months (61.2 vs. 42.8% $p=0.072$). Motivation was the only significant one-year AR predictor. CONCLUSIONS: COPD smokers had a similar response (higher tendency) to VT regardless of the presence of airflow obstruction and stronger nicotine addiction.

https://www.sciencedirect.com/science/article/pii/S1094553918300427?via%3Dihub

Hsu, A. C., K. Dua, et al. (2017). **"MicroRNA-125a and -b inhibit A20 and MAVS to promote inflammation and impair antiviral response in COPD."** JCI Insight **2**(7): e90443.

Influenza A virus (IAV) infections lead to severe inflammation in the airways. Patients with chronic obstructive pulmonary disease (COPD) characteristically have exaggerated airway inflammation and are more susceptible to infections with severe symptoms and increased mortality. The mechanisms that control inflammation during IAV infection and the mechanisms of immune dysregulation in COPD are unclear. We found that IAV infections lead to increased inflammatory and antiviral responses in primary bronchial epithelial cells (pBECs) from healthy nonsmoking and smoking subjects. In pBECs from COPD patients, infections resulted in exaggerated inflammatory but deficient antiviral responses. A20 is an important negative regulator of NF-kappaB-mediated inflammatory but not antiviral responses, and A20 expression was reduced in COPD. IAV infection increased the expression of miR-125a or -b, which directly reduced the expression of A20 and mitochondrial antiviral signaling (MAVS), and caused exaggerated inflammation and impaired antiviral responses. These events were replicated in vivo in a mouse model of experimental COPD. Thus, miR-125a or -b and A20 may be targeted therapeutically to inhibit excessive inflammatory responses and enhance antiviral immunity in IAV infections and in COPD.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5374076/pdf/jciinsight-2-90443.pdf

Huang, T. H., T. R. Hsiue, et al. (2018). **"Comparison of different staging methods for COPD in predicting outcomes."** Eur Respir J **51**(3)Chronic obstructive pulmonary disease (COPD) is commonly staged according to the percentage of predicted forced expiratory volume in 1 s (FEV1 % pred), but other methods have been proposed. In this study we compared the performance of seven staging methods in

predicting outcomes.We retrospectively studied 296 COPD outpatients. For each patient the disease severity was staged by separately applying the following methods: the criteria proposed by the Global Initiative for Chronic Obstructive Lung Disease (GOLD), quartiles of FEV1 % pred and z-score of FEV1, quartiles and specified cut-off points of the ratio of FEV1 over height squared ((FEV1.Ht(-2))A and (FEV1.Ht(-2))B, respectively), and quartiles of the ratio of FEV1 over height cubed (FEV1.Ht(-3)) and of FEV1 quotient (FEV1Q). We evaluated the performance of these methods in predicting the risks of severe acute exacerbation and all-cause mortality.Overall, staging based on the reference-independent FEV1Q performed best in predicting the risks of severe acute exacerbation (including frequent exacerbation) and mortality, followed by (FEV1.Ht(-2))B The performance of staging methods could also be influenced by the choice of cut-off values. Future work using large and ethnically diverse populations to refine and validate the cut-off values would enhance the prediction of outcomes.

https://erj.ersjournals.com/content/51/3/1700577

Jaen-Moreno, M. J., N. Feu, et al. (2019). **"Smoking cessation opportunities in severe mental illness (tobacco intensive motivational and estimate risk - TIMER-): study protocol for a randomized controlled trial."** Trials **20**(1): 47.

BACKGROUND: There is an increased risk of premature death in people with severe mental illness (SMI). Respiratory disorders and cardiovascular disease are leading causes of increased mortality rates in these patients, and tobacco consumption remains the most preventable risk factor involved. Developing new tools to motivate patients towards cessation of smoking is a high priority. Information on the motivational value of giving the lung age and prevention opportunities is unknown in this high-risk population. METHODS/DESIGN: This article describes in detail a protocol developed to evaluate an intensive motivational tool, based on the individual risks of pulmonary damage and prevention opportunities. It is designed as a randomized, 12-month, follow-up, multicenter study. A minimum of 204 smokers will be included, aged 40 years and older, all of whom are patients diagnosed with either schizophrenia or bipolar disorder (BD). Chronic obstructive pulmonary disease (COPD) will be evaluated using spirometry, and the diagnosis will then be validated by a pneumologist and the lung age estimated. Based on this value, a motivational message about prevention will be issued for the intervention group, which will be reinforced by individualized text messages over a period of 3 months. The efficacy of the method and the pulmonary damage variables will be evaluated: smoking cessation at the end of follow-up will be confirmed by cooximetry, and the COPD diagnosis and the severity of the staging for disease will be assessed. DISCUSSION: In the context of community care, screening and early detection of lung damage could potentially be used, together with mobile technology, in order to produce a prevention message, which may provide patients with SMI with a better chance of quitting smoking. TRIAL REGISTRATION: ClinicalTrials.gov, ID: NCT03583203 . Registered on 11 July 2018. Trial status: recruitment.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6332915/pdf/13063_2018_Article_3139.pdf

Jia, Q., J. Chang, et al. (2018). **"MiR-212-5p exerts a protective effect in chronic obstructive pulmonary disease."** Discov Med **26**(144): 173-183.

Chronic obstructive pulmonary disease (COPD) is a common respiratory tract disease with an incompletely understood pathogenesis. According to previous reports, miRNAs play a crucial pathophysiological role in COPD. MiR-212 was reported to be downregulated in COPD patients; however, the role of miR-212 in COPD remains unknown. In this study, the expression level of miR-212-5p and miR-223 decreased significantly in COPD patients compared to healthy controls. In vitro experiments showed that cigarette smoke extract (CSE) induced NCI-H292 cell apoptosis and inhibited cell proliferation. Inflammation and COPD related genes were also upregulated by CSE, while miR-212-5p inhibited the overexpression of these genes. Furthermore, miR-212-5p promoted cell proliferation and inhibited IGFBP3 expression which was induced by CSE. The expression of p-Akt was also inhibited by CSE, while miR-212-5p significantly promoted the phosphorylation of Akt. In summary, our data suggest that miR-212-5p exerts

a protective effect in COPD, and may serve as a prognostic biomarker and potential therapeutic target for COPD.

Kalchiem-Dekel, O. and R. M. Reed (2017). **"Statins in COPD: Life After STATCOPE."** Chest **152**(3): 456-457.

https://journal.chestnet.org/article/S0012-3692(17)30731-6/pdf

Khan, N., J. Vestbo, et al. (2018). **"The Manchester Respiratory-related Sleep Symptoms scale for patients with COPD: development and validation."** Int J Chron Obstruct Pulmon Dis **13**: 3885-3894.

Background: In COPD disturbed sleep is related to exacerbation frequency, poor quality of life, and early mortality. We developed the Manchester Respiratory-related Sleep Symptoms scale (MaRSS) to assess sleep-time symptoms in COPD. Methods: Focus groups including COPD and age-matched controls were used to develop an item-list, which was then administered to COPD patients and age-matched controls in a cross-sectional study. Hierarchical and Rasch analysis informed item selection and scale unidimensionality. Construct validity was examined using Pearson's correlation with the Sleep Problems Index, St George's Respiratory Questionnaire (SGRQ), and FACIT-Fatigue scale. MaRSS change scores from baseline (stable) to exacerbation were assessed in a separate sub-study of COPD patients. Results: Thirty-six COPD patients and nine age-matched controls produced an initial 26-item list. The cross-sectional study involved 203 COPD patients (male: 63%, mean age 64.7 years) and 50 age-matched controls (male: 56%, mean age 65.8 years). Eighteen items were removed to develop an eight-item unidimensional scale covering breathlessness, chest tightness, cough, sputum production, lack of sleep, and medication use. MaRSS scores significantly correlated with sleep problems, SGRQ Total, and FACIT-Fatigue (r=0.58-0.62) and demonstrated a good fit to the Rasch model (chi-squared=29.2; P=0.04). In the substudy, MaRSS scores demonstrated a moderate effect size from baseline to exacerbation visit in 27 patients with 32 exacerbation episodes (Cohen's d=0.6). Conclusion: The MaRSS is a reliable, valid, and clinically responsive measure of respiratory-related symptoms that disturb sleep. It is simple to use and score, making it suitable for research and clinical practice.

https://www.dovepress.com/getfile.php?fileID=46620

Kisialiou, A., G. Prinzi, et al. (2019). **"Pharmacological Management of Chronic Obstructive Lung Disease (COPD). Evidence from a Real-World Perspective - Part 2."** Curr Med Chem **26**(10): 1734-1745.

BACKGROUND: We report a comprehensive overview of current COPD therapies from a real-world experience. OBJECTIVE: Critically review the opportunities and the challenges occurring in the real-world treatment of COPD. METHODS: This is a review that also report results from COPD patients treated with standardized therapy including pulmonary rehabilitation (Real World Data - RWD). CONCLUSION: Comprehensive assessment of COPD management requires strategies able to evaluate efficacy and usefulness in a real-world population, that take into account the interaction between experience and academic training, research, adherence to guidelines and judgments in order to plan the appropriate and optimum use of available strategies.

http://www.eurekaselect.com/166776/article

Koo, H. K., D. M. Vasilescu, et al. (2018). **"Small airways disease in mild and moderate chronic obstructive pulmonary disease: a cross-sectional study."** Lancet Respir Med **6**(8): 591-602.

BACKGROUND: The concept that small conducting airways less than 2 mm in diameter become the major site of airflow obstruction in chronic obstructive pulmonary disease (COPD) is well established in the scientific literature, and the last generation of small conducting airways, terminal bronchioles, are known to be destroyed in patients with very severe COPD. We aimed to determine whether destruction of the terminal and transitional bronchioles (the first generation of respiratory airways) occurs before, or in parallel with, emphysematous tissue destruction. METHODS: In this cross-sectional analysis, we applied a novel multiresolution CT imaging protocol to tissue samples obtained using a systematic uniform sampling method to obtain representative unbiased samples of the whole lung or lobe of smokers with normal lung function (controls) and patients with mild COPD (Global Initiative for Chronic Obstructive Lung Disease [GOLD] stage 1), moderate COPD (GOLD 2), or very severe COPD (GOLD 4). Patients with GOLD 1 or GOLD 2 COPD and smokers with normal lung function had undergone lobectomy and pneumonectomy, and patients with GOLD 4 COPD had undergone lung transplantation. Lung tissue samples were used for stereological assessment of the number and morphology of terminal and transitional bronchioles, airspace size (mean linear intercept), and alveolar surface area. FINDINGS: Of the 34 patients included in this study, ten were controls (smokers with normal lung function), ten patients had GOLD 1 COPD, eight had GOLD 2 COPD, and six had GOLD 4 COPD with centrilobular emphysema. The 34 lung specimens provided 262 lung samples. Compared with control smokers, the number of terminal bronchioles decreased by 40% in patients with GOLD 1 COPD (p=0.014) and 43% in patients with GOLD 2 COPD (p=0.036), the number of transitional bronchioles decreased by 56% in patients with GOLD 1 COPD (p=0.0001) and 59% in patients with GOLD 2 COPD (p=0.0001), and alveolar surface area decreased by 33% in patients with GOLD 1 COPD (p=0.019) and 45% in patients with GOLD 2 COPD (p=0.0021). These pathological changes were found to correlate with lung function decline. We also showed significant loss of terminal and transitional bronchioles in lung samples from patients with GOLD 1 or GOLD 2 COPD that had a normal alveolar surface area. Remaining small airways were found to have thickened walls and narrowed lumens, which become more obstructed with increasing COPD GOLD stage. INTERPRETATION: These data show that small airways disease is a pathological feature in mild and moderate COPD. Importantly, this study emphasises that early intervention for disease modification might be required by patients with mild or moderate COPD. FUNDING: Canadian Institutes of Health Research.

https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(18)30196-6/fulltext

Kubota, Y., A. R. Folsom, et al. (2018). **"Prospective study of lung function and abdominal aortic aneurysm risk: The Atherosclerosis Risk in Communities study."** Atherosclerosis **268**: 225-230.

BACKGROUND AND AIMS: No prospective study has investigated whether individuals with respiratory impairments, including chronic obstructive pulmonary disease (COPD) and restrictive lung disease (RLD), are at increased risk of abdominal aortic aneurysm (AAA). We aimed to prospectively investigate whether those respiratory impairments are associated with increased AAA risk. METHODS: In 1987-1989, the Atherosclerosis Risk in Communities (ARIC) study followed 14,269 participants aged 45-64 years, without a history of AAA surgery, through 2011. Participants were classified into four groups, "COPD" [forced expiratory volume in 1 s (FEV1)/forced vital capacity (FVC) <lower limit of normal (LLN)], "RLD" (FEV1/FVC >/= LLN and FVC < LLN), "respiratory symptoms with normal spirometry" (without RLD or COPD), and "normal" (without respiratory symptoms, RLD or COPD, reference group). RESULTS: During the 284,969 person-years of follow-up, 534 incident AAA events were documented. In an age, sex, and race-adjusted proportional hazards model, individuals with respiratory impairments had a significantly higher risk of AAA than the normal reference group. After adjustment for AAA risk factors, including smoking status and pack-years of smoking, AAA risk was no longer significant in the respiratory symptoms with normal spirometry group [HR (95% CI), 1.25 (0.98-1.60)], but was still increased in the other two groups [RLD: 1.45 (1.04-2.02) and COPD: 1.66 (1.34-2.05)]. Moreover, continuous measures of FEV1/FVC, FEV1 and FVC were associated inversely with risk of AAA. CONCLUSIONS: In the prospective population-based cohort study, obstructive and restrictive spirometric patterns were associated with increased risk of AAA independent of smoking, suggesting that COPD and RLD may increase the risk of AAA.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5785925/pdf/nihms935283.pdf

Lai, T., Y. Li, et al. (2018). **"Heparin-binding epidermal growth factor contributes to COPD disease severity by modulating airway fibrosis and pulmonary epithelial-mesenchymal transition."** Lab Invest **98**(9): 1159-1169.

Although airway fibrosis and epithelial-mesenchymal transition (EMT) contribute to airway remodeling in chronic obstructive pulmonary disease (COPD), the mechanisms underlying their development have not been fully elucidated. In the present study, we aimed to assess heparin-binding epidermal growth factor (HB-EGF) expression in the airways of patients with COPD and to elucidate the possible role of HB-EGF in the pathology of COPD. Sputum and lung tissue HB-EGF expression was evaluated in control subjects and patients with COPD. The relationships between HB-EGF expression, disease severity, collagen deposition (fibrosis), and EMT were investigated. In vitro, human bronchial epithelial (HBE) cells and lung fibroblast cells exposed to the recombinant HB-EGF, collagen deposition and EMT were assessed. We found that sputum HB-EGF expression was significantly increased in patients with COPD compared with non-smokers and smokers without COPD. There was a significant positive correlation between sputum HB-EGF and COPD assessment test (CAT) score. HB-EGF expression was significantly increased in the lung tissue samples of patients with COPD and associated with collagen deposition and N- and E-cadherin, and vimentin expression. In vitro, HB-EGF promoted collagen production in lung fibroblasts. Moreover, HB-EGF induced the EMT process through induction of N-and E-cadherin, and vimentin expression in HBE cells. Collectively, HB-EGF induces airway remodeling by modulating airway fibrosis and pulmonary EMT, and contributes to the COPD severity. The current data may provide insight into the underlying pathogenesis of COPD, in which HB-EGF has an important pathogenic role.

https://www.nature.com/articles/s41374-018-0049-0

Landis, S., R. Suruki, et al. (2018). **"Demographic and Clinical Characteristics of COPD Patients at Different Blood Eosinophil Levels in the UK Clinical Practice Research Datalink."** Copd **15**(2): 177-184.

Blood eosinophil count may be a useful biomarker for predicting response to inhaled corticosteroids and exacerbation risk in chronic obstructive pulmonary disease (COPD) patients. The optimal cut point for categorizing blood eosinophil counts in these contexts remains unclear. We aimed to determine the distribution of blood eosinophil count in COPD patients and matched non-COPD controls, and to describe demographic and clinical characteristics at different cut points. We identified COPD patients within the UK Clinical Practice Research Database aged >/=40 years with a FEV1/FVC <0.7, and >/=1 blood eosinophil count recorded during stable disease between January 1, 2010 and December 31, 2012. COPD patients were matched on age, sex, and smoking status to non-COPD controls. Using all blood eosinophil counts recorded during a 12-month period, COPD patients were categorized as "always above," "fluctuating above and below," and "never above" cut points of 100, 150, and 300 cells/muL. The geometric mean blood eosinophil count was statistically significantly higher in COPD patients versus matched controls (196.6 cells/microL vs. 182.1 cells/microL; mean difference 8%, 95% CI: 6.8, 9.2), and in COPD patients with versus without a history of asthma (205.0 cells/microL vs. 192.2 cells/microL; mean difference 6.7%, 95%, CI: 4.9, 8.5). About half of COPD patients had all blood eosinophil counts above 150 cells/muL; this persistent higher eosinophil phenotype was associated with being male, higher body mass index, and history of asthma. In conclusion, COPD patients demonstrated higher blood eosinophil count than non-COPD controls, although there was substantial overlap in the distributions. COPD patients with a history of asthma had significantly higher blood eosinophil count versus those without.

https://www.tandfonline.com/doi/full/10.1080/15412555.2018.1441275

Liao, K. M. and C. Y. Chen (2019). **"The association between adherence and dementia in chronic obstructive pulmonary disease."** Medicine (Baltimore) **98**(20): e15646.

Our previous studies have shown that patients with chronic obstructive pulmonary disease (COPD) have an increased risk of dementia and that COPD combined with dementia confers an increased risk of acute respiratory dysfunction, severe sepsis, and hospital mortality. The aim of this study was to investigate whether medication adherence can decrease the risk of dementia in COPD.This retrospective study enrolled COPD patients from 1 million beneficiaries randomly sampled from all beneficiaries in Taiwan. We excluded COPD patients not prescribed a bronchodilator or those using theophylline or short-acting beta2-agonists for <1 year. To ensure a sufficient observation period, we excluded patients diagnosed with dementia within 1 year after the diagnosis of COPD or those prescribed bronchodilators after the diagnosis of dementia. Patients with COPD and a history of severe mental disorders were also excluded.There was a total of 13,015 first diagnoses of COPD from 1998 to 2012, of whom 9,489 had a proportion of days covered (PDC) <80% and 1,206 had a PDC >/=80% before matching. In the high PDC group, 226 (18.74%) patients had acute exacerbations of COPD and were hospitalized within 1 year after diagnosis. Compared with the PDC <80% group, the PDC >/=80% group had a risk of dementia with an adjusted hazard ration of 0.88, but there were no statistically significant differences (95% confidence interval, 0.57-1.35).Medication adherence to bronchodilators may not modify the risk of dementia in patients with COPD.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6531282/pdf/medi-98-e15646.pdf

Makino, Y., Y. Shimada, et al. (2018). **"Assessment of emphysema severity as measured on three-dimensional computed tomography images for predicting respiratory complications after lung surgery."** Eur J Cardiothorac Surg **54**(4): 671-676.

OBJECTIVES: Emphysema is one of the main causes of respiratory complications in patients operated on for lung cancer. We have used three-dimensional computed tomography (3D CT) for surgical simulations, as well as for depicting emphysematous areas as low attenuation areas (LAAs) and visual scores based on the Goddard classification (Goddard score), which is a visual scale of the area of vascular disruption and LAA for each lung field. This study aimed to investigate the effectiveness of the 3D CT function for assessing emphysema severity and its association with respiratory complications. METHODS: The study included 504 lung cancer patients who had preoperative 3D CT from October 2010 to March 2015. Goddard score and LAA% (LAA/total lung volume) were measured using 3D CT data. The relationship between respiratory complications and independent variables was investigated. RESULTS: Postoperative respiratory complications were observed in 69 (13.6%) patients. The receiver operating characteristic curves for respiratory complications determined using the Goddard score and LAA% dichotomized at each cut-off level (1 and 0.7%, respectively) showed that the events were observed in 32% of the patients with a Goddard score >/=1 and in 25% of the patients with an LAA% >/=0.7. On multivariable analyses, the Goddard score was significantly correlated with postoperative respiratory complications (P < 0.001). CONCLUSIONS: Preoperative measurement of the Goddard score and LAA% using 3D CT in patients with lung cancer, particularly with the coexistence of emphysema, was beneficial for predicting postoperative respiratory complications.

https://academic.oup.com/ejcts/article-abstract/54/4/671/4930723?redirectedFrom=fulltext

Maniscalco, M., D. Paris, et al. (2018). **"Differential diagnosis between newly diagnosed asthma and COPD using exhaled breath condensate metabolomics: a pilot study."** Eur Respir J **51**(3)

https://erj.ersjournals.com/content/51/3/1701825

Miyamoto, A., A. Kurosaki, et al. (2019). **"Reduced area of the normal lung on high-resolution computed tomography predicts poor survival in patients with lung cancer and combined pulmonary fibrosis and emphysema."** Respir Investig **57**(2): 140-149.

BACKGROUND: This study aimed to determine the radiologic predictors and clarify the clinical features related to survival in patients with combined pulmonary fibrosis and emphysema (CPFE) and lung cancer. METHODS: We retrospectively reviewed the medical chart data and high-resolution computed tomography (HRCT) findings for 81 consecutive patients with CPFE and 92 primary lung cancers (70 men, 11 women; mean age, 70.9 years). We selected 8 axial HRCT images per patient, and visually determined the normal lung, modified Goddard, and fibrosis scores. Multivariate analysis was performed using the Cox proportional hazards regression model. RESULTS: The major clinical features were a high smoking index of 54.8 pack-years and idiopathic pulmonary fibrosis (n = 44). The major lung cancer profile was a peripherally located squamous cell carcinoma (n = 40) or adenocarcinoma (n = 31) adjacent to emphysema in the upper/middle lobe (n = 27) or fibrosis in the lower lobe (n = 26). The median total normal lung, modified Goddard, and fibrosis scores were 10, 8, and 8, respectively. TNM Classification of malignant tumors (TNM) stage I, II, III, and IV was noted in 37, 7, 26, and 22 patients, respectively. Acute exacerbation occurred in 20 patients. Multivariate analysis showed that a higher normal lung score and TNM stage were independent radiologic and clinical predictors of poor survival at the time of diagnosis of lung cancer. CONCLUSIONS: A markedly reduced area of normal lung on HRCT was a relevant radiologic predictor of survival.

https://www.sciencedirect.com/science/article/abs/pii/S2212534518301503?via%3Dihub

Mohamed Hoesein, F. A. A. and P. Zanen (2017). **"Don't Forget Symptomatic Smokers without Airflow Obstruction."** Ann Am Thorac Soc **14**(5): 615-616.

Murakami, J., K. Ueda, et al. (2018). **"Grading of Emphysema Is Indispensable for Predicting Prolonged Air Leak After Lung Lobectomy."** Ann Thorac Surg **105**(4): 1031-1037.

BACKGROUND: The aim of this study was to assess the utility of quantitative computed tomography-based grading of emphysema for predicting prolonged air leak after thoracoscopic lobectomy. METHODS: A consecutive series of 284 patients undergoing thoracoscopic lobectomy for lung cancer was retrospectively reviewed. Prolonged air leak was defined as air leaks lasting 7 days or longer. The grade of emphysema (emphysema index) was defined by the proportion of the emphysematous lung volume (less than -910 HU) to the total lung volume (-600 to -1,024 HU) by a computer-assisted histogram analysis of whole-lung computed tomography scans. RESULTS: The mean length of chest tube drainage was 1.5 days. Fifteen patients (5.3%) presented with prolonged air leak. According to a receiver-operating characteristics curve analysis, the emphysema index was the best predictor of prolonged air leak, with an area under the curve of 0.85 (95% confidence interval: 0.73 to 0.98). An emphysema index of 35% or greater was the best cutoff value for predicting prolonged air leak, with a negative predictive value of 0.99. The emphysema index was the only significant predictor for the length of postoperative chest tube drainage among conventional variables, including the pulmonary function and resected lobe, in both univariate and multivariate analyses. Prolonged air leak resulted in an increased duration of hospitalization ($p < 0.001$) and was frequently accompanied by pneumonia or empyema ($p < 0.001$). CONCLUSIONS: The grade of emphysema on computed tomography scan is the best predictor of prolonged air leak that adversely influences early postoperative outcomes. We must take new measures against prolonged air leak in quantitative computed tomography-based high-risk patients.

https://www.annalsthoracicsurgery.org/article/S0003-4975(17)31631-4/pdf

Nagatani, Y., M. Hashimoto, et al. (2018). **"Continuous quantitative measurement of the main bronchial dimensions and lung density in the lateral position by four-dimensional dynamic-ventilation CT in smokers and COPD patients."** Int J Chron Obstruct Pulmon Dis **13**: 3845-3856.

Purpose: The purpose of this study was to measure changes in lung density and airway dimension in smokers in the lateral position using four-dimensional dynamic-ventilation computed tomography (CT) during free breathing and to evaluate their correlations with spirometric values. Materials and methods: Preoperative pleural adhesion assessments included dynamic-ventilation CT of 42 smokers (including 22 patients with COPD) in the lateral position, with the unoperated lung beneath (dependent lung). The scanned lungs' mean lung density (MLD) and the bilateral main bronchi's luminal areas (Ai) were measured automatically (13-18 continuous image frames, 0.35 seconds/frame). Calculations included cross-correlation coefficients (CCCs) between the MLD and Ai time curves, and correlations between the quantitative measurements and spirometric values were evaluated by using Spearman's rank coefficient. Results: The DeltaMLD1.05 (from the peak inspiration frame to the third expiratory frame, 1.05 seconds later) in the nondependent lung negatively correlated with FEV1/FVC ($r=-0.417$, $P<0.01$), suggesting that large expiratory movement of the nondependent lung would compensate limited expiratory movement of the dependent lung due to COPD. The DeltaAi1.05 negatively correlated with the FEV1/FVC predicted in both the lungs ($r=-0.465$ and -0.311, $P<0.05$), suggesting that early expiratory collapses of the main bronchi indicate severe airflow limitation. The CCC correlated with FEV1/FVC in the dependent lung ($r=-0.474$, $P<0.01$), suggesting that reduced synchrony between the proximal airway and lung occurs in patients with severe airflow limitation. Conclusion: In COPD patients, in the lateral position, the following abnormal dynamic-ventilation CT findings are associated with airflow limitation: enhanced complementary ventilation in the nondependent lung, early expiratory airway collapses, and reduced synchrony between airway and lung movements in the dependent lung.

https://www.dovepress.com/getfile.php?fileID=46548

Nagy, P., C. Antony, et al. (2018). **"Same-day Routine Chest-X Ray After Thoracic Surgery is Not Necessary!"** Zentralbl Chir **143**(1): 96-101.

INTRODUCTION: Performing a routine postoperative chest X-ray (CXR) after general thoracic surgery is daily practice in many thoracic surgery departments. The quality, frequency of pathological findings and the clinical consequences have not been well evaluated. Furthermore, exposure to ionising radiation should be restricted to a minimum and therefore routine practice can be questioned. METHODS: As a hospital standard, each patient was given a routine CXR after opening of the pleura and inserting a chest tube. From October 2015 to March 2016, each postoperative patient with a routine CXR was included in a prospective database, including film quality, pathological findings, clinical and laboratory results and cardiorespiratory monitoring, as well as clinical consequences. RESULTS: 546 patients were included. Risk factors for postoperative complications were obesity in 50 patients (9.2%), emphysema in 127 patients (23.3%), coagulopathy in 34 patients (6.2%), longer operation time (more than two hours) in 242 patients (44.3%) and previous lung irradiation in 29 (5.3%) of patients. Major lung resections were performed in 191 patients (35.9%). 263 (48.2%) patients had procedures with minimally invasive access. The quality of the X-ray film was insufficient in 8.2% of patients. 90 (16.5%) of CXRs were found to show pathological findings, with a trend for more pathological findings after open surgery (55/283; 19.4%) compared to minimally invasive surgery (35/263; 13.3%) ($p = 0.064$). 11 (2.0%) patients needed a surgical or clinical intervention during postoperative observation; this corresponds to 12.2% of patients with a pathological finding on CXR. Nine of these 11 patients were clinically symptomatic and only two (0.37%) patients were asymptomatic with a relevant pneumothorax. CONCLUSIONS: Our study cannot support routine postoperative CXR after general thoracic procedures and we believe that restriction to clinically symptomatic cases should be a safe option.

https://www.thieme-connect.com/products/ejournals/abstract/10.1055/s-0043-117174

Ngo, C. Q., T. Thi Bui, et al. (2018). **"Direct Hospitalization Cost of Patients with Acute Exacerbation of Chronic Obstructive Pulmonary Disease in Vietnam."** Int J Environ Res Public Health **16**(1)Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) have been found to contribute, predominantly, to increasing costs of COPD-a major public health issue. This study aimed to fill the gap in literature concerning costs of AECOPD in Vietnam, by examining the direct cost of AECOPD hospitalization and determining potentially associated factors. A cross-sectional study was conducted at the Respiratory Center of Bach Mai Hospital, Hanoi. A total of 57 participants were selected. Information regarding sociodemographic features, clinical characteristics, and hospitalization costs were collected. A multivariate generalized linear regression model was utilized to determine the factors associated with hospitalization costs. The mean total and daily hospitalization cost were 18.3 million VND (SD = 12.9) and 2.5 million VND (SD = 3.2), respectively. Medication cost accounted for 53.9% of hospitalization cost (from 44.0% in the Global Initiative for Chronic Obstructive Lung Disease Classification A (GOLD A) to 55.3% in GOLD C). Patients having GOLD D COPD (Coef. = 5.78; 95% CI = 0.73(-)10.83), higher age (Coef. = 0.37; 95% CI = 0.13(-)0.61), and higher duration of hospitalization (Coef. = 1.91; 95% CI = 1.28(-)2.53) had higher hospitalization costs ($p < 0.05$). This study suggested that interventions to screen COPD patients as well as provide timely treatment should be conducted widely in the community in order to avoid any unnecessary hospitalization cost, consequently reducing the economic burden of COPD.

https://res.mdpi.com/ijerph/ijerph-16-00088/article_deploy/ijerph-16-00088.pdf?filename=&attachment=1

Novotna, B., M. Abdel-Hamid, et al. (2018). **"A pilot data analysis of a metabolomic HPLC-MS/MS study of patients with COPD."** Adv Clin Exp Med **27**(4): 531-539.

BACKGROUND: Chronic obstructive pulmonary disease (COPD) is a heterogeneous condition with multiple clinical faces. Metabolomic profiling studies small molecules present in biological samples by combined use of chromatography with mass spectrometry. OBJECTIVES: The goal of our work was to perform a high performance liquid chromatography combined with tandem mass spectrometry (HPLC-MS/MS) metabolomic study to compare the concentrations of metabolites in COPD patients and in controls. MATERIAL AND METHODS: Participants were recruited at the University Hospital, Hradec Kralove, Czech Republic, with the approval of the ethics committee. The analysis of blood samples was performed at Health Sciences Center (HSC) in Kuwait. The blood samples were analyzed for concentrations of acylcarnitines and amino acids by high performance liquid chromatography (Waters 2690 HPLC; Waters, Milford, USA) and a triple-quadruple tandem mass spectrometer (Quattro LC, Micromass, Manchester, United Kingdom). RESULTS: Groups of 10 subjects with COPD and 10 healthy controls were analyzed. Carnitine analysis showed that the free carnitine to acylcarnitine ratio (C0/AC ratio) was significantly lower in COPD (0.58 muM/L) compared to the controls (0.73 muM/L; $p = 0.002$). The mean C8/C2 ratio in the COPD group was significantly higher (0.03 muM/L) - in the control group it was 0 muM/L ($p = 0.03$). Amino acid analysis showed lower levels of phenylalanine in the COPD group (22.05 muM/L) compared to the controls (30.05 muM/L; $p = 0.008$). The alanine concentrations were significantly lower in the COPD group (173 muM/L) than in the control group (253 muM/L; $p = 0.001$). The pyroglutamate levels were higher in COPD (1.58 muM/L) than in the controls (1 muM/L; $p = 0.040$). CONCLUSIONS: The carnitine and acylcarnitine levels in COPD subjects in this study possibly indicate a predisposition to atherosclerosis as a result of inadequate beta-oxidation of fatty acids and show the presence of oxidative stress. Furthermore, the high sensitivity to changes in circulating amino acid levels may allow us to detect subclinical malnutrition and take early preventative interventions such as nutritional supplementation and patient education.

Olivares, A., M. Vitacca, et al. (2018). **"Combining the Pulmonary Rehabilitation Decisional Score with the Bode Index and Clinical Opinion in Assigning Priority for Pulmonary Rehabilitation."** Copd **15**(3): 238-244.

Combining objective tools with clinical decision (CD) may help clinicians identify the priority for pulmonary rehabilitation (PR) in patients with COPD. We aimed to assess the specificity, sensitivity and efficiency of a new tool, the Pulmonary Rehabilitation Decisional Score (PRDS), and its correlation with the BODE index (BI) and CD in assigning PR priority. We retrospectively compared the three methods (CD vs. PRDS vs. BI) in 124 patients. We assigned low priority (LP), high priority (HP) and very high priority (VHP) to PR based on a priori scores of PRDS (LP = 0-10; HP = 11-17; VHP >/=18) and BI (LP = 0-2; HP = 3-5; VHP >/=6) and compared these with CD. PR priority assigned by the different methods was similar among groups, but did not often refer to the same subjects. PRDS and BI showed very high concordance with CD in defining VHP (97.8% and 95.6% for PRDS and BI, respectively), but were less concordant with CD in assigning LP and HP. Both PRDS and BI differently evaluated 38/124 cases compared to CD (PRDS underprescribed 18 and overprescribed 20; BI underprescribed 19 and overprescribed 19). However, a direct comparison between PRDS and BI showed that the discordance decreased to 8 underprescriptions and 10 overprescriptions (efficiency approximately 85%). An objective instrument such as the PRDS can enhance CD with additional information on new aspects such as disability and fragility. PRDS and BI are nonetheless equally efficient at detecting discrepancies versus CD alone, especially when the priority for PR is defined as low or very high.

https://www.tandfonline.com/doi/full/10.1080/15412555.2018.1531389

Paschos, K. A. and A. Chatzigeorgiadis (2019). **"Cervicofacial Emphysema, Pneumomediastinum and Pneumothorax Caused by a Dental Procedure."** J Coll Physicians Surg Pak **29**(2): 191-192.

Pedraza-Serrano, F., R. Jimenez-Garcia, et al. (2019). **"Characteristics and outcomes of patients hospitalized with interstitial lung diseases in Spain, 2014 to 2015."** Medicine (Baltimore) **98**(21): e15779.

To assess characteristics and outcomes of patients hospitalized with interstitial lung diseases (ILD) and to analyze patient's comorbidities, procedures, and in-hospital outcomes.We identified patients hospitalized with idiopathic pulmonary fibrosis and others ILD such as hypersensitivity pneumonitis, cryptogenic organizing pneumonia, lymphangioleiomyomatosis, pulmonary Langerhans cell histiocytosis, and sarcoidosis in Spain during 2014 and 2015.We identified 14,565 discharges among patients admitted for ILD in Spain during the study period: idiopathic pulmonary fibrosis (IPF) in 42.32% (n = 6164), sarcoidosis in 37.65% (n = 5484), hypersensitivity pneumonitis in 10.55% (n = 1538), cryptogenic organizing pneumonia in 7.06% (n = 1028), pulmonary Langerhans cell histiocytosis in 1.48% (n = 215), and lymphangioleiomyomatosis in 0.94% (n = 136). The most common associated comorbidities according to those included in the Charlson Comorbidity Index (CCI) were COPD, diabetes, and congestive heart disease. The presence of pulmonary hypertension increased the probability of dying in patients with idiopathic pulmonary fibrosis (OR 1.36; 95%CI 1.06-1.73). Patients with cryptogenic organizing pneumonia had the longest length of hospital stay and the highest percentage of hospital readmissions (23.64%). The highest IHM corresponded to the idiopathic pulmonary fibrosis (14.94%). Computed tomography of the chest was the procedure more used during admissions for ILD.IPF was responsible for larger percentage of hospital admission among ILD in our study. In addition, the IHM were higher in IPF patients in comparison with those with other ILD. The most common associated comorbidity in ILD according to those included in the CCI was COPD. Computed tomography of the chest was the procedure more frequently used.

Pornsuriyasak, P., M. Rambod, et al. (2018). **"Oxygen Uptake and Lactate Kinetics in Patients with Chronic Obstructive Pulmonary Disease during Heavy Intensity Exercise: Role of Pedaling Cadence."** Copd **15**(3): 283-293.

Oxygen uptake slow component ([Formula: see text]sc) is associated with lactate accumulation, likely a contribution of poorly oxidative muscle fibers. We aimed to test the hypothesis that higher muscle tension during slow pedaling rates would yield more prominent [Formula: see text]sc in healthy subjects, but not in COPD patients. Eight severe COPD patients and 8 age-matched healthy individuals performed 4 rest-heavy exercise transitions at 40 and 80 RPM. Work rates at the two cadences were balanced. Venous blood was sampled for measurement of lactate concentration at rest and every 2 minutes until the end of exercise. [Formula: see text] kinetics were analyzed utilizing nonlinear regression. [Formula: see text] phase II amplitudes at the two cadences were similar in both groups. In healthy individuals, [Formula: see text]sc was steeper at 40 than 80 RPM (46.6 +/- 12.0 vs. 29.5 +/- 11.7 mL/min(2), p = 0.002) but not in COPD patients (16.2 +/- 14.7 vs. 13.3 +/- 7.6 mL/min(2)). End-exercise lactate concentration did not differ between cadences in either group. In healthy individuals, greater slow-cadence [Formula: see text]sc seems likely related to oxidative muscle fiber recruitment at higher muscular tension. COPD patients, known to have fast-twitch fiber predominance, might be unable to recruit oxidative fibers at high muscle tension, blunting [Formula: see text]sc response.

https://www.tandfonline.com/doi/full/10.1080/15412555.2018.1487391

Prokopenko, D., P. Sakornsakolpat, et al. (2018). **"Whole-Genome Sequencing in Severe Chronic Obstructive Pulmonary Disease."** Am J Respir Cell Mol Biol **59**(5): 614-622.

Genome-wide association studies have identified common variants associated with chronic obstructive pulmonary disease (COPD). Whole-genome sequencing (WGS) offers comprehensive coverage of the entire genome, as compared with genotyping arrays or exome sequencing. We hypothesized that WGS in subjects with severe COPD and smoking control subjects with normal pulmonary function would allow us to identify novel genetic determinants of COPD. We sequenced 821 patients with severe COPD and 973 control subjects from the COPDGene and Boston Early-Onset COPD studies, including both non-Hispanic white and African American individuals. We performed single-variant and grouped-variant analyses, and in addition, we assessed the overlap of variants between sequencing- and array-based imputation. Our most significantly associated variant was in a known region near HHIP (combined P = 1.6 x 10(-9)); additional variants approaching genome-wide significance included previously described regions in CHRNA5, TNS1, and SERPINA6/SERPINA1 (the latter in African American individuals). None of our associations were clearly driven by rare variants, and we found minimal evidence of replication of genes identified by previously reported smaller sequencing studies. With WGS, we identified more than 20 million new variants, not seen with imputation, including more than 10,000 of potential importance in previously identified COPD genome-wide association study regions. WGS in severe COPD identifies a large number of potentially important functional variants, with the strongest associations being in known COPD risk loci, including HHIP and SERPINA1. Larger sample sizes will be needed to identify associated variants in novel regions of the genome.

Qin, J., X. Deng, et al. (2019). **"Correlation between hypocalcemia and acute exacerbation of chronic obstructive pulmonary disease in the elderly."** Postgrad Med **131**(5): 319-323.

Introduction: Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is an important disease of hospitalized elderly patients, who often have electrolyte imbalances. This study was performed to analyze total serum calcium levels in elderly patients with AECOPD and identify the correlation between hypocalcemia and AECOPD. Methods: 153 elderly patients with AECOPD served as the observation group, and 115 healthy elderly people undergoing physical examinations served as the control group. Differences in the corrected serum calcium, albumin (ALB), and neutrophil/lymphocyte ratio (NLR) were analyzed between the observation and control groups before and after treatment. The incidence of

hypocalcemia was compared among patients at different ages and with different pulmonary function classifications before treatment. The relationship between hypocalcemia and respiratory infection was analyzed. Differences in the pretreatment NLR, ALB, logarithm of the serum C-reactive protein level (LogCRP), and hospital stay were compared between patients with and without hypocalcemia. Results: The corrected serum calcium level ($P < 0.001$), NLR ($P = 0.001$) and albumin level ($P < 0.001$) were significantly different among the pretreatment group, post-treatment group, and control group. The serum calcium level, LogCRP, and NLR were significantly lower after than before treatment ($P < 0.05$). Significant differences in the incidence of hypocalcemia were found among patients of different ages ($P = 0.002$). The respiratory infection rate ($P < 0.001$), hospital stay ($P < 0.001$), NLR ($P = 0.007$), and LogCRP ($P < 0.001$) was higher in patients with than without hypocalcemia. However, the albumin level was lower in patients with than without hypocalcemia ($P < 0.001$). Conclusions: In elderly patients with AECOPD, hypocalcemia may be related to the disease progression, respiratory infection rate, and hospital stay of patients with AECOPD.

https://www.tandfonline.com/doi/full/10.1080/00325481.2019.1585689

Ronit, A., T. Kristensen, et al. (2018). **"Computed tomography quantification of emphysema in people living with HIV and uninfected controls."** Eur Respir J **52**(1)People living with HIV (PLWH) may be more susceptible to the development of emphysema than uninfected individuals. We assessed prevalence and risk factors for emphysema in PLWH and uninfected controls. Spirometry and chest computed tomography scans were obtained in PLWH from the Copenhagen Comorbidity in HIV Infection (COCOMO) study and in uninfected controls from the Copenhagen General Population Study (CGPS) who were >40 years. Emphysema was quantified using a low attenuation area < -950 Hounsfield units (%LAA-950) and the 15th percentile density index (PD15) and assessed by semi-quantitative visual scales. Of 742 PLWH, 21.2% and 4.7% had emphysema according to the %LAA-950 threshold with cut-offs at 5% and 10%, respectively. Of 470 uninfected controls, these numbers were 24.3% (p=0.23) and 4.0% (p=0.68). HIV was not associated with emphysema (adjusted OR 1.25, 95% CI 0.68-2.36 for %LAA-950 >10%) by PD15 or by visually assessed emphysema. We found no interaction between HIV and cumulative smoking. Breathlessness and sputum production were more common in PLWH with emphysema, and emphysema seemed to be more prevalent in PLWH with airflow limitation. HIV was therefore not independently associated with emphysema, but the clinical impact of emphysema was greater in PLWH than in uninfected controls.

https://erj.ersjournals.com/content/52/1/1800296

Sandri, B. J., A. Kaplan, et al. (2018). **"Multi-omic molecular profiling of lung cancer in COPD."** Eur Respir J **52**(1)Chronic obstructive pulmonary disease (COPD) is a known risk factor for developing lung cancer but the underlying mechanisms remain unknown. We hypothesise that the COPD stroma contains molecular mechanisms supporting tumourigenesis.We conducted an unbiased multi-omic analysis to identify gene expression patterns that distinguish COPD stroma in patients with or without lung cancer. We obtained lung tissue from patients with COPD and lung cancer (tumour and adjacent non-malignant tissue) and those with COPD without lung cancer for profiling of proteomic and mRNA (both cytoplasmic and polyribosomal). We used the Joint and Individual Variation Explained (JIVE) method to integrate and analyse across the three datasets.JIVE identified eight latent patterns that robustly distinguished and separated the three groups of tissue samples (tumour, adjacent and control). Predictive variables that associated with the tumour, compared to adjacent stroma, were mainly represented in the transcriptomic data, whereas predictive variables associated with adjacent tissue, compared to controls, were represented at the translatomic level. Pathway analysis revealed extracellular matrix and phosphatidylinositol-4,5-bisphosphate 3-kinase-protein kinase B signalling pathways as important signals in the tumour adjacent stroma.The multi-omic approach distinguishes tumour adjacent stroma in lung cancer and reveals two stromal expression patterns associated with cancer.

https://erj.ersjournals.com/content/52/1/1702665

Satici, C., B. Arpinar Yigitbas, et al. (2018). **"Does Adherence to Domiciliary NIMV Decrease the Subsequent Hospitalizations Rates and Cost for Patients Diagnosed with COPD?"** Copd **15**(3): 303-309.

Domiciliary noninvasive mechanical ventilation (NIMV) is used for treating patients with hypercapnic chronic obstructive pulmonary disease (COPD). We aimed to evaluate the association between adherence to the treatment and subsequent hospitalizations and costs. Data from 54 (27 adherent; 27 non-adherent) patients with COPD who were undergoing NIMV treatment at home for 6 months. We assessed adherence based on digitally recorded data and checked hospital records for clinical and laboratory data, rehospitalization rates, and costs during the following 6 months. Nocturnal NIMV usage, mean daily usage of the device, and time to first hospitalization were higher in the treatment-adherent group ($p < .001$, $p < .001$, and $p=.006$, respectively). The percentage of active smokers, device leaks above 30 L/min, length of hospital stay, rehospitalization rates, and costs were significantly higher in the treatment-non-adherent group ($p = 05$, $p = 006$, $p = 004$, $p = 006$, and $p = 01$, respectively). The most frequent reasons for not using NIMV in the treatment-non-adherent group were a decreased need, dry mouth, mask incompatibility, and gastrointestinal complaints. Adherence to NIMV treatment decreases the subsequent hospitalizations rates and noncompliance leads to complications. Findings of this study may help physicians in convincing patients diagnosed with COPD of the need for correct NIMV use to prevent hospitalizations and reduce the costs of COPD treatment.

https://www.tandfonline.com/doi/full/10.1080/15412555.2018.1500532

Seijo, L. M., J. B. Soriano, et al. (2019). **"New evidence on the chemoprevention of inhaled steroids and the risk of lung cancer in COPD."** Eur Respir J **53**(6)

https://erj.ersjournals.com/content/erj/53/6/1900717.full.pdf

Shevcova, V. I., A. A. Zujkova, et al. (2018). **"Verification of zinc role in pathophysiology of chronic obstructive pulmonary disease."** Ter Arkh **90**(3): 33-37.

AIM: Determination of the level of zinc and its fractions, as well as the enzyme neutrophilic elastase and albumin in persons suffering from chronic obstructive pulmonary disease (COPD), as well as smoking actively and passively. MATERIALS AND METHODS: The study involved 30 patients with a diagnosis of COPD and 90 healthy persons (60 of them smoking at the present time, 30 - no) who underwent spirometry and determination of zinc levels and its pools, albumin, and neutrophil elastase. All data are subject to statistical processing. RESULTS: It is determined that the studied parameters differ significantly in the groups of smokers with COPD, healthy smokers and non-smokers, and correlate with the volume of forced exhalation for 1 second as a percentage of the due. CONCLUSION: The revealed regularities make it possible to consider the indicator "share of bound zinc fraction" introduced in the study as a screening criterion in diagnosing COPD in smokers.

Swigris, J. (2017). **"Caution against Extrapolating Results from the Trial of Long-Term Oxygen for Chronic Obstructive Pulmonary Disease."** Ann Am Thorac Soc **14**(2): 296.

Tanabe, N., D. M. Vasilescu, et al. (2018). **"Analysis of airway pathology in COPD using a combination of computed tomography, micro-computed tomography and histology."** Eur Respir J **51**(2)The small conducting airways are the major site of obstruction in chronic obstructive pulmonary disease (COPD). This study examined small airway pathology using a novel combination of multidetector row computed tomography (MDCT), micro-computed tomography (microCT) and histology.Airway branches visible on specimen MDCT were counted and the dimensions of the third- to fifth-generation airways were computed, while the terminal bronchioles (designated TB), preterminal bronchioles (TB-1) and pre-preterminal bronchioles (TB-2) were examined with microCT and histology in eight explanted lungs with end-stage COPD and seven unused donor lungs that served as controls.On MDCT, COPD lungs showed a decrease in the number of 2-2.5 mm diameter airways and the lumen area of fifth-generation airways, while on microCT there was a reduction in the number of terminal bronchioles as well as a decrease in the luminal areas, wall volumes and alveolar attachments to the walls of TB, TB-1 and TB-2 bronchioles. The combination of microCT and histology showed increased B-cell infiltration into the walls of TB-1 and TB-2 bronchioles, and this change was correlated with a reduced number of alveolar attachments in COPD.Small airways disease extends from 2 mm diameter airways to the terminal bronchioles in COPD. Destruction of alveolar attachments may be driven by a B-cell-mediated immune response in the preterminal bronchioles.

https://erj.ersjournals.com/content/51/2/1701245

Ueda, K., J. Murakami, et al. (2018). **"Predicting the response to a bronchodilator in patients with airflow obstruction and lung cancer."** J Surg Res **228**: 20-26.

BACKGROUND: The aim of the present study was to clarify the predictors of the response of patients with resectable lung cancer and untreated airflow obstruction to tiotropium, an antimuscarinic bronchodilator. METHODS: Tiotropium was administered to 29 preoperative patients with untreated airflow obstruction. The forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV1) were measured before and after the introduction of tiotropium. The response to tiotropium was determined based on the percentage gain in the FEV1. The volume of the total lung area (TLV) and the low-attenuation area (LAA) was measured by deep inspiratory computed tomography based on the predefined thresholds for attenuation values. RESULTS: The introduction of tiotropium resulted in a 15% gain in the FEV1 ($P < 0.001$). A univariate regression analysis revealed that the FVC/TLV was the best predictor of the gain in FEV1, followed by the FEV1/FVC. Based on the results of a multiple regression analysis, a regression equation to predict a gain in the FEV1 was generated using the FVC, TLV, and LAA. A receiver operating characteristic curve analysis revealed that this equation led to the highest area under the curve for predicting a major response to tiotropium, followed by the FVC/TLV and FEV1/FVC. Postoperatively, six of the 20 minor responders experienced a progression of dyspnea. In contrast, none of the major responders experienced a progression of dyspnea ($P < 0.05$). CONCLUSIONS: We developed an equation for predicting the response to tiotropium using parameters obtained from spirometry and quantitative computed tomography. A large-scale study to validate the usefulness of this equation is warranted.

https://www.journalofsurgicalresearch.com/article/S0022-4804(18)30102-1/fulltext

Vashi, M. T., J. L. Willoughby, et al. (2019). **"Eosinophilic Chronic Obstructive Pulmonary Disease: Implications for Exacerbations, Readmissions, and Treatment."** Am J Respir Crit Care Med **199**(1): 110-112.

Voskrebenzev, A., M. Gutberlet, et al. (2018). **"Feasibility of quantitative regional ventilation and perfusion mapping with phase-resolved functional lung (PREFUL) MRI in healthy volunteers and COPD, CTEPH, and CF patients."** Magn Reson Med **79**(4): 2306-2314.

PURPOSE: In this feasibility study, a phase-resolved functional lung imaging postprocessing method for extraction of dynamic perfusion (Q) and ventilation (V) parameters using a conventional 1H lung MRI Fourier decomposition acquisition is introduced. METHODS: Time series of coronal gradient-echo MR images with a temporal resolution of 288 to 324 ms of two healthy volunteers, one patient with chronic thromboembolic hypertension, one patient with cystic fibrosis, and one patient with chronic obstructive pulmonary disease were acquired at 1.5 T. Using a sine model to estimate cardiac and respiratory phases of each image, all images were sorted to reconstruct full cardiac and respiratory cycles. Time to peak (TTP), V/Q maps, and fractional ventilation flow-volume loops were calculated. RESULTS: For the volunteers, homogenous ventilation and perfusion TTP maps (V-TTP, Q-TTP) were obtained. The chronic thromboembolic hypertension patient showed increased perfusion TTP in hypoperfused regions in visual agreement with dynamic contrast-enhanced MRI, which improved postpulmonary endaterectomy surgery. Cystic fibrosis and chronic obstructive pulmonary disease patients showed a pattern of increased V-TTP and Q-TTP in regions of hypoventilation and decreased perfusion. Fractional ventilation flow-volume loops of the chronic obstructive pulmonary disease patient were smaller in comparison with the healthy volunteer, and showed regional differences in visual agreement with functional small airways disease and emphysema on CT. CONCLUSIONS: This study shows the feasibility of phase-resolved functional lung imaging to gain quantitative information regarding regional lung perfusion and ventilation without the need for ultrafast imaging, which will be advantageous for future clinical translation. Magn Reson Med 79:2306-2314, 2018. (c) 2017 International Society for Magnetic Resonance in Medicine.

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Wang, J., H. Shang, et al. (2019). **"Procalcitonin, C-reactive protein, PaCO2, and noninvasive mechanical ventilation failure in chronic obstructive pulmonary disease exacerbation."** Medicine (Baltimore) **98**(17): e15171.

It is unclear whether procalcitonin (PCT) is correlated with noninvasive ventilation (NIV) failure. This retrospective case-control study aimed to compare PCT levels, C-reactive protein (CRP) levels, and PaCO2 in patients (05/2014-03/2015 at the Harrison International Peace Hospital, China) with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) and NIV failure/success.This was a retrospective case-control study of patients with AECOPD who required NIV between May 2014 and March 2015. All consecutive patients with AECOPD admitted at the Department of Critical Care Medicine and transferred from the general ward were included in the study. Hemogram, PCT, erythrocyte sedimentation rate (ESR), arterial blood gas (ABG), and CRP levels were measured </=1 hour before NIV was used. NIV was considered to have failed if at least one of the following criteria was met: cardiac arrest or severe hemodynamic instability; respiratory arrest or gasping; mask intolerance; difficulty in clearing bronchial secretions; or worsening of ABGs or sensorium level during NIV. The factors associated with NIV failure were determined.A total of 376 patients were included: 286 with successful NIV and 90 wither NIV failure. The multivariate analysis showed that PCT (OR = 2.0, 95%CI: 1.2-3.2, P = .006), CRP (OR = 1.2, 95%CI: 1.1-1.3, P < .001), and PaCO2 (OR = 1.1, 95%CI: 1.1-1.2, P < .001) </=1 hour before NIV were independently associated with NIV failure. The optimal cutoff were 0.31 ng/mL for PCT (sensitivity, 83.3%; specificity, 83.7%), 15.0 mg/mL for CRP (sensitivity, 75.6%; specificity, 93.0%), and 73.5 mm Hg for PaCO2 (sensitivity, 71.1%; specificity, 100%). The area under the curve (AUC) was 0.854 for PCT, 0.849 for CRP, and 0.828 for PaCO2. PCT, CRP, and PaCO2 were used to obtain a combined prediction factor, which achieved an AUC of 0.978 (95%CI: 0.961-0.995).High serum PCT, CRP, and PaCO2 levels predict NIV failure for patients with AECOPD. The combination of these three parameters might enable even more accurate prediction.

Zeng, S., A. Tham, et al. (2019). **"Lung volume indices predict morbidity in smokers with preserved spirometry."** Thorax **74**(2): 114-124.

BACKGROUND: Abnormal lung volumes that reflect air trapping are common in COPD. However, their significance in smokers with preserved spirometry (normal FEV1 to FVC ratio) is unclear. METHODS: Using the Veterans Administration Informatics and Computing Infrastructure database, we identified 7479 patients at risk for COPD (ever smokers >40 years of age without restrictive lung disease) who had preserved spirometry and concomitant lung volume measurements, and examined their subsequent health records for clinical diagnoses of COPD, healthcare utilisation, follow-up spirometry and mortality. RESULTS: Air trapping was prevalent, with 31% of patients having residual volume to total lung capacity ratio (RV:TLC) greater than the upper limit of normal (ULN). RV:TLC varied widely from 14% to 77% (51% to 204% of predicted) across the normal ranges of FEV1:FVC and FEV1. Patients with RV:TLC greater than the ULN were more likely to receive subsequent clinical diagnoses of COPD (HR (95% CI)=1.55 (1.42 to 1.70), p<0.001) and had higher all-cause mortality (HR (95% CI)=1.41 (1.29 to 1.54), p<0.001). They had higher rates of respiratory medication prescriptions and hospital and intensive care unit admissions. Other air trapping and static hyperinflation indices showed similar associations with health outcomes. Additionally, high-normal RV:TLC was associated with intermediate adverse health outcomes compared with low-normal and abnormal RV:TLC. Abnormal RV:TLC predicted higher likelihood of progression to spirometric COPD (OR (95% CI)=1.30 (1.03 to 1.65), p=0.027). CONCLUSION: In this study of the Veterans Affairs electronic health records, air trapping was common in smokers with preserved spirometry and predicted adverse respiratory outcomes and progression to overt COPD.

https://thorax.bmj.com/content/74/2/114.long

Zinellu, A., A. G. Fois, et al. (2018). **"Increased kynurenine plasma concentrations and kynurenine-tryptophan ratio in mild-to-moderate chronic obstructive pulmonary disease patients."** Biomark Med **12**(3): 229-237.

AIM: Since an increase in kynurenine (Kyn) plasma concentrations has been proposed as marker of immune system activation, we studied the associations between the Kyn levels and presence and severity of chronic obstructive pulmonary disease (COPD). METHODS & RESULTS: Plasma Kyn, tryptophan (Trp) and Kyn/Trp ratio were measured in 43 COPD patients with clinically defined mild (n = 29) or moderate (n = 14) disease and 43 age- and sex-matched healthy controls. When compared with controls, COPD patients had significantly higher plasma Kyn concentrations and Kyn/Trp ratios. In multiple logistic regression analysis, after adjusting for clinical and demographic confounders, the Kyn/Trp ratio was independently associated with COPD severity. DISCUSSION & CONCLUSION: Kyn and Kyn/Trp ratio might represent a new, sensitive, biomarker of systemic inflammation in COPD patients.

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