Respiratory Research Review™

Making Education Easy

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In this issue:

Abbreviations used in this issue
COPD = chronic obstructive pulmonary disease
CV = cardiovascular
FEV = forced expiratory volume
FVC = forced vital capacity
HR = hazard ratio
ICS = inhaled corticosteroid
LABA = long-acting β-agonist
LAMA = long-acting muscarinic antagonist

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Welcome to this Christmas issue of Respiratory Research Review with the topic of COPD (chronic obstructive pulmonary disease).

In addition to our selection of ten articles, we are offering a slightly longer list for further reading, which is driven by the number of publications in the last few months. Also, eventually the work will slow down, and you may wish to read a little deeper into one topic or another; there is plenty of excellent reading to choose from.

'Skeletal muscle dysfunction in chronic obstructive pulmonary disease. What we know and can do for our patients' is the top suggestion. It is a concise clinical review written by our colleagues in Barcelona where they remind us of three principal forces that contribute to skeletal muscle dysfunction: i) signals and stimuli that initiate muscle loss and wasting like immobilisation, malnutrition, smoking, infections, hypoxia, hypercapnia and steroid use; ii) intrinsic cellular processes that mediate muscle dysfunction like anabolic suppression, muscle injury and oxidative stress and mitochondrial dysfunction; and iii) extrinsic processes like hyperinflation-associated diaphragmatic dysfunction, bony thoracic remodeling and lactate hyperproduction. The principal treatment is exercise training best delivered as part of a pulmonary rehabilitation course. Participation in a rehabilitation course has been shown to reduce hospital admissions, reduce unscheduled healthcare visits, increase exercise capacity, reduce symptoms of dyspnoea and improve quality of life, emotional function, self-efficacy, self-management and activities of daily living. Here may also be a good time to highlight the great work of my local colleagues, who have managed to use the earthquake to change the model of care for COPD, such that despite the disruptions, hospital admissions for COPD were reduced.

We are going through a paradigm shift in our understanding of COPD in that we now realise that only half of our patients are presenting with smoking-induced accelerated lung loss and associated comorbidities (Am J Respir Crit Care Med). The remainder never reach full lung capacity and end up presenting with COPD following a normal or even accelerated decline in lung function due to other causes. Here lies a possible mechanism for halting the progression towards COPD as articulated by some of our key opinion leaders in an article covering early detection of COPD, the burden of early COPD, possible mechanism of the progression of early COPD, the role of the lung microbiome and reflections on possible future therapeutic trials.

It was 1999 when the US Department of Justice sued several major US tobacco companies for making false and deceptive statements about: i) the risk of smoking; ii) the health risk of secondhand smoke; iii) the addictiveness of nicotine; and iv) cigarettes marketed as low tar or light and the manipulation of the delivery of nicotine. Yet it took until 2016 before the companies were held responsible by Judge Gladys Keller under the Racketeer Influenced and Corrupt Organisation Act: *"Defendants have marketed and sold their lethal products with zeal, with deception, with a single-minded focus on their financial success, and without regard for the human tragedy and social cost that success exacted"* (Chest). It took another 11 years of fighting the court ruling before these statements are being published. In this context and also in the context of confusing statements by the tobacco industry, this ATS document is most helpful: 'Recommendation for the appropriate structure, communication, and investigations of tobacco harm reduction claims'.

Three short recommendations for further reading are also provided: i) Donald Tashkin has published an authoritative review on 'Marijuana and lung disease'; ii) Am J Respir Crit Care Med published a concise clinical review on 'Home oxygen in chronic obstructive pulmonary disease' and one of the best editorials on high flow nasal therapy: 'Not just oxygen? Mechanisms of benefit from high-flow nasal cannula in hypoxemic respiratory failure'; and iii) while we are getting ready for Christmas, you may wish to spend two minutes reflecting on the 'Dangers of COPD and asthma under-recognised among Hajj pilgrims' (Lancet Respir Med).

Thank you for your readership over the year. Please provide feedback on how we can improve this edition, and a Merry Christmas and Prosperous New Year for 2019 (the last 'teen year in our lifetime).

Kind regards

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Lung function trajectories from pre-school age to adulthood and their associations with early life factors

Authors: Belgrave DCM et al.

Summary: These researchers set out to identify distinct lung function trajectories during childhood and if they extend to adulthood and infancy. Latent profile modelling was applied to retrospective spirometry data from childhood into early adulthood from two population-based birth cohort studies, which included 1046 participants from 5 to 16 years of age and 1390 from 8 to 24 years of age, and a third cohort of 196 participants from 1 month to 18 years of age with repeat lung function measures in infancy (maximal expiratory flow; V'_{maxFRC}) and childhood (FEV_1). An allele score was derived to investigate genetic associations of the trajectories, and early-life predictors were detected using a multivariable model. Four childhood FEV_1 trajectories were identified: persistently high, normal, below average and persistently low. Individuals from the persistently low trajectory (n=129) had persistent wheezing and asthma throughout follow-up. The genetic analysis revealed that compared with the normal trajectory, the respective pooled relative risk ratios per allele for the persistently high, below average and persistently low trajectories were 0.96 (95% CI 0.92, 1.01), 1.01 (0.99, 1.02) and 1.05 (0.98, 1.13). Most children in the low maximal expiratory flow trajectory during infancy did not progress to the low FEV_1 trajectory in childhood. Recurrent wheeze with severe wheezing exacerbations, early allergic sensitisation and tobacco smoke exposure during early life were associated with the persistently low trajectory.

Comment: About half of all patients with COPD don't have a significant birth history, and only 20–25% of smokers develop COPD. This article from our colleagues in Melbourne and Tasmania and an article from Perth examine, as Erika von Mutius puts it in her comment, the 'Childhood origins of COPD'. Combined, these articles encourage us to look after young lungs to reduce smoke exposure, pollution and early-life sensitisation to enable the best possible lung function in early adulthood. **Bottom line: childhood asthma, bronchitis, pneumonia, allergic rhinitis, eczema, parental asthma and maternal smoking predict below average lung growth trajectories.**

Reference: Lancet Respir Med 2018;6:526–34
Abstract

Chronic obstructive pulmonary disease in China

Authors: Fang L et al.

Summary: A cross-sectional survey of a nationally representative sample of 66,752 individuals aged ≥40 years from mainland China was undertaken to estimate the country's COPD prevalence according to the 2017 GOLD (Global Initiative for Chronic Obstructive Lung Disease) criteria. The estimated standardised prevalence of COPD was 13.6%, and was higher in men than women (19.0% vs. 8.1% [p<0.0001]) driven by a significant difference in the proportions of current smokers between genders (58.2% vs. 4.0%). COPD prevalence was greatest in southwest China (20.2%) and lowest in central China (10.2%). Mild disease (GOLD stage I) accounted for 56.4% of COPD cases among adults, while 36.3% had moderate COPD (GOLD stage II), 6.5% had severe COPD (GOLD stage III) and 0.9% had very severe disease (GOLD stage IV).

Comment: Liwen Fang presents data on more than 60,000 adults from China including spirometry, smoking history and symptom exploration. Over the last 10 years, the incidence of COPD has increased from 8% to almost 14%. China has more than 300 million smokers; 58% of men and 4% of women smoke. Actually, the prevalence of COPD in men is now 19%; and most patients with GOLD stage III and IV COPD are symptomatic and have had an admission with an exacerbation. Yilan Sun and Don Sin synthesise the information in their editorial and give us their **bottom line: each year tobacco accounts for 1.4 million deaths and 30 million disability life-years lost in China.**

Reference: Lancet Respir Med 2018;6:421–30
Abstract

A pragmatic trial of e-cigarettes, incentives, and drugs for smoking cessation

Authors: Halpern SD et al.

Summary: In this trial, 6006 smoking employees from 54 US companies were randomised to usual care, consisting of information on the benefits of smoking cessation and motivational text messages, with or without one of the following smoking cessation interventions: i) nicotine-replacement therapy or pharmacotherapy, with e-cigarettes on failure; ii) e-cigarettes with no requirement for a prior standard therapy; iii) cessation aids plus a monetary reward (US$600) for sustained abstinence; or iv) free cessation aids plus US$600 in redeemable funds with deductions when cessation milestones were not met. The 6-month sustained abstinence rate (primary outcome) was 0.1% in the usual-care arm, 0.5% in the free cessation aids arm, 1.0% in the free e-cigarettes arm, 2.0% in the rewards arm and 2.9% in the redeemable funds arm, with the redeemable funds and rewards groups showing significant superiority over the free cessation aids group and the redeemable funds group significantly superior to the free e-cigarettes group. There was no significant difference between the free e-cigarettes group and the usual care group or the free cessation aids group. Sustained abstinence rates were 4–6 times greater among 1191 participants who were deemed to be actively engaged in the trial compared with those who weren't.

Comment: This US trial is arguably not too relevant for the NZ healthcare setting; however, a little tentatively, we thought it may be worth including this trial exploring standard advice on smoking cessation including nicotine replacement or pharmacotherapy with standard advice plus a $600 financial incentive and free e-cigarettes. Probably due to the rather idiosyncratic setting of this trial, the 6-month abstinence rates were all very low: 0.5% for standard advice, 1% for e-cigarettes and 2–2.9% in the two rewards groups. **Bottom line: a financial incentive added to free cessation aids resulted in a higher abstinence rate. Free cessation aids or e-cigarettes did not provide a benefit.**

Reference: N Engl J Med 2018;378:2302–10
Abstract

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Natural history of chronic obstructive pulmonary disease exacerbations in a general practice-based population with chronic obstructive pulmonary disease

Authors: Rothnie KJ et al.

Summary: This study evaluated the course of acute COPD exacerbations over a 10-year period in a general practice COPD population of 99,574 patients from the UK. Moderate acute COPD exacerbations were defined as those managed out of hospital, and severe exacerbations were defined as those requiring hospitalisation. Approximately one-quarter of patients with COPD did not experience an exacerbation during a mean 4.9 years of follow-up. Compared with no acute COPD exacerbations at baseline, the number of exacerbations in the first year predicted the future rate in a graduated manner (HRs 1.71–3.41 for 1–≥5 events). The risk of death was also increased by ≥2 moderate acute COPD exacerbations during the first year (HRs 1.10–1.57 for 2–≥5 moderate acute COPD exacerbations). The risk of death was even greater for severe acute COPD exacerbations (HR 1.79 [CI 1.65, 1.94]).

Comment: This article is based on almost 100,000 COPD patients from the UK Clinical Practice Research Datalink, who were observed for a maximum of 10 years. This study has a number of surprising results; three of them are: i) more than half of all COPD patients are current smokers; ii) about 50% had no exacerbations in the first year, and about a quarter had no exacerbations during the follow-up; and iii) changing the prescription to a new class of inhaler therapy was associated with fewer exacerbations in the first year of follow-up. **Bottom line: a reduction of exacerbation rate is possible in patients who respond well to therapy.**

Reference: Am J Respir Crit Care Med 2018;198:464–71
Abstract

Independent commentary by Professor Lutz Beckert.
Professor Lutz Beckert is the Head of Department of Medicine of the University of Otago, Christchurch. He is also a Respiratory Physician at Canterbury District Health Board. **FOR FULL BIO CLICK HERE**

Time spent reading this publication has been approved for CME for Royal New Zealand College of General Practitioners (RNZCGP) General Practice Educational Programme Stage 2 (GPEP2) and the Maintenance of Professional Standards (MOPS) purposes, provided that a Learning Reflection Form is completed. Please **CLICK HERE** to download your CPD MOPS Learning Reflection Form. One form per review read would be required.

Time spent reading this publication has been approved for CNE by The College of Nurses Aotearoa (NZ) for RNs and NPs. For more information on how to claim CNE hours please **CLICK HERE**.

Health services burden of undiagnosed and overdiagnosed COPD

Authors: Gershon AS et al., for the Canadian Respiratory Research Network

Summary: The health services burden of undiagnosed and overdiagnosed COPD was quantified for a real-world cohort of 1403 participants from the COLD (Canadian Obstructive Lung Disease) study who underwent spirometry to detect COPD; linked health administrative data were queried to identify pre-existing physician diagnoses of COPD. Undiagnosed COPD was detected in 13.7% of the participants, 5.1% were overdiagnosed and 3.7% had been correctly diagnosed. Compared with participants without COPD, those with overdiagnosed COPD had significantly more hospitalisations, ED visits and ambulatory care visits, and those with moderate-to-severe undiagnosed COPD also had more hospitalisations.

Comment: About 1400 participants in the COLD study had spirometry performed and the results were linked to their clinical records. A total of 244 participants had COPD by spirometric criteria. Of these, only 52 were diagnosed by their physician, and 192 patients had no clinical diagnosis of COPD. In addition, 72 participants had a diagnostic label of COPD not confirmed by spirometry. The authors argue that patients underdiagnosed were deprived of appropriate management and that the patients wrongly diagnosed took unnecessary medication and often had restrictive lung disease or CV disease. **Bottom line: under- and overdiagnosis of COPD was more common than correctly diagnosed COPD.**

Reference: Chest 2018;153:1336–46
Abstract

Exacerbations of chronic obstructive pulmonary disease and cardiac events

Authors: Kunisaki KM et al., on behalf of the SUMMIT Investigators

Summary: This *post hoc* analysis of the SUMMIT trial investigated whether acute COPD exacerbations are associated with an increased risk of subsequent CV disease in current/former smokers with moderate COPD. Among 16,485 SUMMIT participants, 4704 of them had ≥1 acute COPD exacerbation and 688 had at least one CV disease event. Cox proportional hazards models found that the risk of a CV disease event was increased in the first 30 days after an acute COPD exacerbation (HR 3.8 [95% CI 2.7, 5.5]) and the risk remained elevated for up to 1 year. Participants who had been hospitalised with an acute COPD exacerbation were at even greater risk for CV disease (HR 9.9 [95% CI 6.6, 14.9]).

Comment: Between 30% and 60% of COPD patients have CV comorbidities; indeed many studies suggest that about 30–50% of deaths are driven by underlying CV disease. We have commented on the SUMMIT trial before (Respiratory Research Review, issue 101), which had enrolled more than 16,000 participants. These international authors present a secondary analysis, which showed that 30 days after a hospital admission for an exacerbation, our patients have a 10-fold higher risk of a CV event. John Hurst and Don Sin publish the authoritative editorial and suggest in their **bottom line: this trial raises the possibility of using cardioprotective medications like aspirin, statins and β-blockers following acute exacerbations of COPD.**

Reference: Am J Respir Crit Care Med 2018;198:51–7
Abstract

Under-utilisation of β-blockers in patients with acute coronary syndrome and comorbid chronic obstructive pulmonary disease

Authors: Kratzer L et al.

Summary: This retrospective research evaluated under-prescribing of β-blockers at discharge for the first 245 evaluable patients hospitalised for acute coronary syndrome at an Australian hospital, comparing those with versus without a COPD diagnosis. Compared with patients without COPD, a smaller proportion of those with COPD received β-blockers at discharge (66.7% vs. 86.2% [p<0.05]); presence of COPD was the only significant predictor associated with receiving a β-blocker at discharge after controlling for clinically meaningful confounding factors.

Comment: This study is from our colleagues in Perth, who identified 250 consecutive patients with an admission for acute coronary syndrome, encompassing ST-elevation myocardial infarction, non-ST elevation myocardial infarction and ischaemic heart disease. Of these, 27 also had a diagnosis of COPD. These patients were older, had more pre-existing ischaemic heart disease and were more likely to be taking statins or antiplatelet therapy. However, despite the strong evidence base for β-blocker use, patients with COPD were less likely to be discharged on β-blockers. **Bottom line: β-blockers remain under-prescribed in COPD despite good evidence of safety and efficacy.**

Reference: Intern Med J 2018;48:931–6
Abstract

Comparative effectiveness of LABA-ICS versus LAMA as initial treatment in COPD targeted by blood eosinophils

Authors: Suissa S et al.

Summary: This population-based study involved a real-world cohort of 539,643 patients aged ≥55 years with COPD initiating LAMA or LABA/ICS therapy, comparing the effectiveness and safety of these initial treatments as a function of blood eosinophilia, a potential biomarker of ICS effectiveness. After propensity score matching, data from 12,366 patients starting LAMAs (mainly tiotropium) and 12,366 starting LABA/ICS therapy were extracted for analyses. There was no significant difference between patients who started LABA/ICS therapy versus those who started a LAMA for COPD exacerbations (HR 0.95 [95% CI 0.90, 1.01]), and this lack of a significant difference persisted in patients with blood eosinophil levels <2% and 2–4% (1.03 [0.93, 1.13] and 1.00 [0.91, 1.10], respectively), but LABA/ICS initiators with eosinophil levels >4% had a lower risk (0.79 [0.70, 0.88]). Patients who started LABA/ICS therapy had a higher incidence of pneumonia than those starting a LAMA (HR 1.37 [95% CI 1.17, 1.60]), irrespective of eosinophil level. These findings were consistent in sensitivity analyses, except for a marginally lower exacerbation risk for LABA/ICS therapy initiators among the subgroup of 2766 patients who had experienced ≥2 COPD exacerbations during the baseline year (HR 0.87 [95% CI 0.79, 0.97]).

Comment: These Canadian authors used the UK Clinical Practice Research Datalink to explore whether the modest effect of ICSs may actually be a moderate effect in a subset of COPD patients. They matched about 12,000 COPD patients who started on a LAMA with 12,000 who started on an ICS/LABA. Overall, both cohorts had a similar risk of exacerbations; however, the patients taking an ICS/LABA had about a 40% increased risk of pneumonia. The subgroup with a high baseline eosinophil count of ≥4% had reduced exacerbations when taking an ICS/LABA. **Bottom line: in COPD patients with ≥4% eosinophilia, an ICS/LABA may be more effective than a LAMA.**

Reference: Lancet Respir Med 2018;6:855–62
Abstract

Effect of theophylline as adjunct to inhaled corticosteroids on exacerbations in patients with COPD

Authors: Devereux G et al.

Summary: The TWICS trial randomised patients with COPD, who had an FEV_1/FVC ratio <0.7 and had experienced ≥2 exacerbations in the prior year, to receive theophylline 200mg once or twice daily (evaluable n=772) or placebo (evaluable n=764) added to ICS therapy for 1 year. There was no significant difference between the theophylline and placebo arms for the number of COPD exacerbations during the 1-year treatment period (1727 vs. 1703; adjusted incidence rate ratio 0.99 [95% CI 0.91, 1.08]).

Comment: According to the accompanying editorial in Lancet Respir Med, it was in 1951 that the first negative trial of theophylline in COPD was published. However, despite this theophylline has been widely used because of its mild bronchodilatory effect, possible support of the diaphragmatic muscle, and its synergistic anti-inflammatory effect when used in combination with ICSs. These British authors report a randomised controlled trial of theophylline 200/100mg or placebo in around 1500 COPD patients. Patients taking theophylline experienced more nausea, headaches and GI side effects. **Bottom line: low-dose theophylline did not reduce exacerbations. Is this the death of theophylline?**

Reference: JAMA 2018;320:1548–59
Abstract

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Missed opportunity? Worsening breathlessness as a harbinger of death

Authors: Currow DC et al.

Summary: This prospective cohort study obtained point-of-care data for 6801 consecutive patients from an Australian palliative care centre over the 2011–2014 period to analyse trajectories of breathlessness intensity by function and life-limiting illness diagnosis during the final 3 weeks of life. The patients' mean age was 71.5 years and most had cancer. The last recorded AKPS (Australia-modified Karnofsky Performance Status) physical function score was >40 for 26.8% of the patients. Breathlessness was worst in individuals with cardiorespiratory disease and an AKPS score >40, with breathlessness numerical rating scores increasing during the final week of life for most of this group compared with others (adjusted mean 2.92 vs. 1.51 [p=0.0001]).

Comment: As death approaches, many symptoms become less prominent; however, fatigue and breathlessness are dominant. These international researchers followed almost 7000 patients referred to a community palliative care service. Patients with better functional status and patients with underlying cardiorespiratory illness experienced more breathlessness. Increased breathlessness appears to be a biomarker of approaching death in patients with cardiorespiratory disease. However, it also raises the question, are we missing treatable pathology like cardiac arrhythmias, pulmonary embolism or infections, which may reduce suffering? **Bottom line: breathlessness is more intense and increases more in patients with better function and background cardiorespiratory illness immediately before death.**

Reference: Eur Respir J 2018;52:1800684
Abstract