

Respiratory

RESEARCH REVIEW™

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Issue 167 – 2019

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Abbreviations used in this issue

BMI = body mass index
COPD = chronic obstructive pulmonary disease
CV = cardiovascular
FEV = forced expiratory volume
FVC = forced vital capacity
MACE = major adverse cardiac event
MMT = million metric tonne
MoCA = Montreal Cognitive Assessment

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Welcome

to issue 167 of **Respiratory Research Review**. Given the season, it may be appropriate to start this review with the good news that tobacco control policies and declining poverty are having a positive effect on reducing overall COPD death rates. Actually, since 2006, COPD mortality rates may have decreased by 26% ([Eur Respir J; published online Nov 19, 2019](#)).

By far the highest burden of COPD is carried by low- and middle-income countries. The highest COPD mortality rates are in Hungary and Kyrgyzstan with 141 and 135 deaths, respectively, per 100,000 person-years. Numerically, the largest number of people living with COPD reside in India or China ([BMJ 2019;365:i2231](#)). *Lancet Respir Med* pointed out the profound unmet need for rehabilitation for people living with chronic lung disease in low- and middle-income countries ([Lancet Respir Med 2019;7:1002-4](#)). Maybe embracing the 'Opportunities and challenges in expanding pulmonary rehabilitation into the home and community' is the way forward ([Am J Respir Crit Care Med 2019;200:822-7](#)); we are certainly part of exploring this in NZ.

The *Lancet* also highlighted NZ's current efforts to address health inequities by revisiting deep-rooted historical, cultural and systemic issues. Although the authors also admit that redistribution, decolonisation and power sharing remain somewhat aspirational for indigenous people ([Lancet 2019;394:1613-4](#)). Bart Celli and Jadwiga Wedzicha provide a precise, easy to read 'Update on clinical aspects of chronic obstructive pulmonary disease' ([N Engl J Med 2019;381:1257-66](#)). With falling smoking rates ([BMJ 2019;365:i2231](#)), we need to keep an open mind of alternative causes, and the changing picture of COPD. Maybe up to half of patients with COPD may have never smoked; however, they may have lung disease because of prematurity ([Lancet Respir Med 2019;7:677-86](#)), occupational exposure ([Thorax 2019;74:650-8](#)), ambient particulate air pollution ([N Engl J Med 2019;381:705-15](#)) or possibly, in the future, secondary to e-cigarettes ([Am J Respir Crit Care Med 2019;200:1134-45](#)).

This year, our colleague Dr Maureen Swanney passed away. She was the scientific director of our local respiratory laboratory, a Fellow of the Thoracic Society of Australia and New Zealand and a lifetime member of the Australian New Zealand Society of Respiratory Scientists. It was pleasing to see that her contribution to respiratory physiology and quality control has been honoured by acknowledging her authorship to the official American Thoracic Society and European Thoracic Society technical statement – standardisation of spirometry 2019 update' ([Am J Respir Crit Care Med 2019;200:e70-88](#)). It is a sensible read with new relative contraindications, medication withholding times and many quality assurance improvements. If you are inclined to be interested in respiratory physiology, you may also enjoy the 'ERS statement on respiratory muscle testing at rest and during exercise' ([Eur Respir J 2019;53:1801214](#)) or the short review on 'measuring lung functions in airways diseases: current and emerging techniques' ([Thorax 2019;74:797-805](#)).

Thank you for your readership, interest and emails/comments during the year. Best wishes to you and your whānau for this season and for the brave new world of 2020.

Kind regards,

Professor Lutz Beckert

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FROM THE TEAM AT



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Occupational exposure to solvents and lung function decline

Authors: Alif SM et al.

Summary: Using data from 767 individuals aged 45–50 years enrolled in the population-based Tasmanian Longitudinal Health Study, these researchers examined associations between occupational exposures and longitudinal lung function decline. The researchers also investigated whether the relationships were modified by sex, smoking and asthma status. Compared with those without exposure, ever exposures to aromatic solvents and metals were associated with greater declines in FEV₁ (aromatic solvents 15.5 mL/year; metals 11.3 mL/year) and FVC (aromatic solvents 14.1 mL/year; metals 17.5 mL/year). Cumulative exposure (unit years) to aromatic solvents was also associated with greater declines in FEV₁ and FVC. While women had less cumulative exposure to aromatic solvents than men (mean 9.6 vs. 16.6 years), women had a greater lung function decline than men. The analyses also identified associations between ever exposures to gases/fumes or mineral dust and greater decline in lung function.

Comment: As a community we tend to forget lessons from the past from time to time; the really hot topic at the moment is the re-emergence of silicosis in workers polishing artificial stones ([Respirology 2019;24:1165–75](#)). Another potential overlooked occupational course for chronic obstructive airways disease may be exposure to aromatic, chlorinated and other solvents or pesticides. These Australian researchers use the Tasmanian Longitudinal Health Study to explore the impact of occupational exposure on lung function decline over 45–50 years. **Bottom line: exposure to aromatic solvents, metals and mineral dust accelerates lung function decline. Women appear to be more greatly affected by aromatic solvents than men.**

Reference: *Thorax* 2019;74:650–8

[Abstract](#)

Each month we highlight a particularly excellent paper with our butterfly symbol.



Cigarette consumption estimates for 71 countries from 1970 to 2015

Authors: Hoffman SJ et al.

Summary: This study reports on the systematic collection of national cigarette consumption data from 71 countries (95% of global cigarette consumption) from 1970 to 2015. In most countries, cigarette consumption fell over three decades, but country-specific consumption trends were highly variable. In 2013, China consumed 2.5 MMTs (million metric tonnes) of cigarettes, more than the next 35 highest consuming countries combined, including Russia (0.36 MMTs), the US (0.28 MMTs), Indonesia (0.28 MMTs) and Japan (0.20 MMTs). Japan and the US experienced reductions of >0.1 MMTs from a decade earlier, Russian consumption plateaued, while Chinese consumption increased by 0.75 MMTs and Indonesian consumption increased by 0.1 MMTs.

Comment: The message may not be all that new; however, the authors' rigour to create an open-access database covering 71 countries overarching private company data and national statistics is admirable and the graphs are sobering. China consumes more cigarettes than the US, Russia, Indonesia, Japan and the next 35 countries combined. Although the smoking rates have declined, with an increase in the population, the total number of smokers has increased from 720 million in 1980, to more than a billion in 2012. It is fascinating, open-access reading with a silver lining. **Bottom line: the better the implementation of the WHO Framework Convention on Tobacco Control, the lower the smoking rates. The authors suggest mandatory biennial reports to protect present and future generations.**

Reference: *BMJ* 2019;365:12231

[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 with particular clinical interests in interstitial lung disease, pulmonary vascular disease, respiratory physiology and COPD (chronic obstructive pulmonary disease). Lutz is happy to be contacted to discuss research ideas either as a sounding board or with the view of future collaborations.

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Reference: 1. PHARMAC, 2019. Decision to fund oncology, multiple sclerosis and respiratory treatments.

Available at <https://www.pharmac.govt.nz/news/notification-2019-10-07-various/>. Accessed 07 October 2019. FVC = Forced Vital Capacity

PM-NZ-0569/TAPSN11401/20190CT

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Electronic cigarette vapor with nicotine causes airway mucociliary dysfunction preferentially via TRPA1 receptors

Authors: Chung S et al.

Summary: The effects of nicotine-containing e-cigarette vapours on airway mucociliary function were investigated in differentiated human bronchial epithelial cells isolated from never-smokers and also in an ovine airways model. The human bronchial epithelial cells showed dose-dependent reductions in airway surface liquid hydration and increases in mucus viscosity on exposure to e-cigarette vapour. Acute nicotine exposure also increased intracellular calcium levels, an effect that is primarily TRPA1 (transient receptor potential ankyrin 1)-dependent; nicotine-mediated impairment of mucociliary parameters was restored by TRPA1 inhibition with A967079. In the ovine experiments, exposure to e-cigarette vapour was associated with reduced tracheal mucus velocity (an *in vivo* measure of mucociliary clearance). Nebulised nicotine-containing e-cigarette liquid was also associated with a dose-dependent reduction in tracheal mucus velocity along with an increase in plasma cotinine levels. These effects of e-cigarette liquid on tracheal mucus velocity were reversed with nebulised A967079.

Comment: The debate on e-cigarettes is rather fierce at the moment. There is the ability to assist in smoking cessation (Respiratory Research Review, [issue 161](#)), and the emergence of e-cigarette-associated lung disease ([N Engl J Med. Published online Sept 6, 2019](#)). The final verdict is not out yet on the future of e-cigarettes, and now we need evidence more than ever. In the last review, we reported on the positive impact in smoking cessation; in this review, we draw attention to a laboratory study on human bronchial epithelial cells. The [editorial title/bottom line: 'high nicotine content in electronic cigarettes disrupts mucociliary clearance, the essential defense mechanism of the lung'](#).

Reference: *Am J Respir Crit Care Med* 2019;200:1134–45
[Abstract](#)

Cognitive function during exacerbations of chronic obstructive pulmonary disease

Authors: Poot B et al.

Summary: This NZ study evaluated the prevalence of cognitive impairment in 25 patients hospitalised for an acute COPD exacerbation; the patients were assessed using the MoCA (Montreal Cognitive Assessment) tool, COPD Assessment Test and modified Borg dyspnoea scale within 24 hours of admission, 48–72 hours after admission and again 6 weeks after discharge. Cognitive impairment was evident in 76% of the patients at the initial evaluation, in 76% at the second evaluation and in 66% at the final evaluation. Overall, 88% of patients had cognitive impairment within 72 hours of a COPD exacerbation. Mean MoCA score tended to improve with time (22.6 at admission, 23.6 at 48–72h after admission and 24.4 at 6 weeks postdischarge).

Comment: Congratulations to our colleagues from Wellington and the Hutt for this real-life study on the cognitive function in 25 patients during an acute COPD exacerbation. Cognitive impairment reduced the efficacy of self-management plans, and the ability to judge symptoms, act on them and follow through with interventions like smoking cessation. The researchers used the validated MoCA instrument to assess for mild cognitive impairment. **Bottom line: more than three-quarters of patients had cognitive impairment that didn't fully resolve after the acute phase. This needs to be considered when planning education, rehabilitation and long-term management plans.**

Reference: *Intern Med J* 2019;49:1307–12
[Abstract](#)

Chronic obstructive pulmonary disease and breathlessness in older workers predict economic inactivity

Authors: Schofield SJ et al.

Summary: This prospective longitudinal study investigated the impact of COPD or breathlessness on employment outcomes for a cohort of 1656 individuals aged 50–59 years who completed follow-up questionnaires at 18 months. Full-time employment was continued by 78.5% of respondents at follow-up, 10.6% were in part-time employment and 10.9% were no longer in paid employment. Respondents with moderate or severe COPD at baseline were more likely to experience loss of employment (risk ratio 2.89 [95% CI 1.80, 4.65]), as were those who reported breathlessness (3.07 [2.16, 4.37]); these associations did not appear to be modified by sex or by manual versus nonmanual work.

Comment: This article is relevant to many of us who continue to work beyond the age of 50 years. With the falling birth rate, the economic incentive is high; the state gains tax revenue and remaining at work is good for physical and mental health. UK researchers followed a group of 2000 workers aged in their 50s for 18 months to find that most continued in fulltime employment, 10% went to part time and 10% left paid employment. The risk of losing employment doubled with evidence of airway disease or breathlessness. The [editorial](#) gives us the **bottom line: the ability to work should be seen as an important objective for COPD management.**

Reference: *Am J Respir Crit Care Med* 2019;200:1228–33
[Abstract](#)

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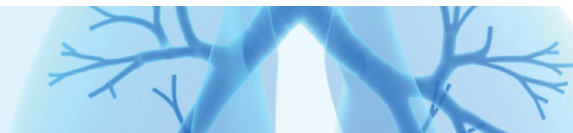
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Behaviour change techniques to optimise participation in physical activity or exercise in adolescents and young adults with chronic cardiorespiratory conditions

Authors: Sawyer A et al.

Summary: Interventions for optimising physical activity participation in patients aged 15–45 years with chronic cardiorespiratory conditions were classified and their behaviour change techniques categorised in this systematic review. A literature search yielded six studies reporting objective measures of physical activity pre- and post-intervention for inclusion (n=396), for which 19 of 93 behaviour change techniques were described. Three of the studies had interventions that the authors classified as 'promising'. The most commonly used behaviour change technique consisted of goal setting, action planning and social support. Five behaviour change techniques were used only in 'promising' interventions.

Comment: We have already touched on the challenge to provide appropriate pulmonary rehabilitation opportunities for our patients, particularly in low- and middle-income countries ([Lancet Respir Med 2019;7:1002–4](#)). Another issue is that according to the infographic, only a quarter of us get the recommended aerobic and strength-based exercise each week ([MMWR 2019;68:513–8](#)); this is worse in younger people and people living with chronic conditions. In this well-researched systematic review, the authors draw out the most commonly used behaviour changing strategies. **Bottom line: the most promising behaviour changing strategy tools are problem solving, information about previous circumstances, health consequences, pros and cons, and comparative imagining of future outcomes.**

Reference: *Intern Med J 2019;49:1209–20*

[Abstract](#)



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It's more than low BMI: prevalence of cachexia and associated mortality in COPD

Authors: McDonald M-LN et al.

Summary: This analysis of the ECLIPSE study evaluated the association between cachexia and mortality in 1483 patients with COPD, with cachexia defined using both a consensus definition (weight loss >5% in 12 months or low BMI, in addition to three of five of decreased muscle strength, fatigue, anorexia, low fat-free mass index and inflammation) and a weight-loss definition (weight loss >5%, or >2% if BMI is low, within 12 months); according to these definitions, cachexia was present in 4.7% and 10.4% of patients, respectively. Over 3 years of follow-up, patients with cachexia, by either definition, had >3-fold increased mortality, independent of BMI and lung function.

Comment: Christmas time is not a traditional time to worry about cachexia; however, this article confirms it is a marker of adverse outcome and poor survival. The author argues that cachexia in chronic conditions is not only reflected by a low BMI but also by any BMI with a weight loss of >5%, in addition to three of the five criteria of 1) decreased muscle strength, 2) fatigue, 3) anorexia 4) low fat-free mass and 5) evidence of increased inflammatory markers. **Bottom line: evidence of cachexia independent of BMI was associated with a 3-fold increased risk of death.**

Reference: *Respir Res 2019;20:100*

[Abstract](#)

Increased risk of major adverse cardiac events following the onset of acute exacerbations of COPD

Authors: Reilev M et al.

Summary: This research included 118,807 registrants who experienced a MACE (major adverse cardiac event; acute myocardial infarction, stroke or CV-related death) following an acute COPD exacerbation over the period 1997–2014. Compared with periods without exacerbations, these individuals had a higher MACE risk following the onset of an acute COPD exacerbation (odds ratio 3.70 [95% CI 3.60, 3.80]), with increased risks for each MACE (3.57, 4.33 and 2.78 for acute myocardial infarction, CV-related death and stroke, respectively) and strong associations for severe exacerbations (5.92) and older patients (4.18).

Comment: The last two articles in this issue span a spectrum of discussion, almost as fiercely debated as e-cigarettes, on whether we can address the cardiac mortality of patients with COPD. This nationwide study from Denmark identified that a 'MACE' is about 3–5 times more likely following an acute exacerbation of COPD. The editorial cautions us about jumping to 'causality'; however, both the authors and the [editorialists](#), T Mkorombindo and M Dransfield, offer us essentially the same **bottom line: the strong association between exacerbation of COPD and MACE should lead to particular vigilance for signs or symptoms of CV events.**

Reference: *Respirology 2019;24:1183–90*

[Abstract](#)

Metoprolol for the prevention of acute exacerbations of COPD

Authors: Dransfield MT et al., for the BLOCK COPD Trial Group

Summary: Patients aged 40–85 years with COPD (n=532) were randomised to receive extended-release metoprolol or placebo in this trial. There was no significant difference between the metoprolol and placebo arms for median time to first exacerbation (primary endpoint; 202 vs. 222 days [p=0.66]), and metoprolol recipients had a greater risk of exacerbation requiring hospital admission (hazard ratio 1.91 [95% CI 1.29, 2.83]). Adverse events possibly related to treatment and nonrespiratory serious adverse events were similar for the two groups. There were 11 deaths in the metoprolol arm and five in the placebo arm. The trial was terminated prematurely due to both futility regarding the primary endpoint and safety.

Comment: BLOCK COPD (Beta-Blockers for the Prevention of Acute Exacerbations of Chronic Obstructive Pulmonary Disease) was stopped because of futility after randomising 500 patients. Metoprolol was well tolerated; however, there was no difference in mortality or exacerbation rate, but there was an increase of severe exacerbations of COPD. William MacNee is making the case in the accompanying [editorial](#) that we haven't solved the key issue yet on whether β -blockers may improve MACE. **The bottom line: COPD patients without a therapeutic indication to treat cardiac disease should not be offered β -blockers currently.**

Reference: *N Engl J Med 2019;381:2304–14*

[Abstract](#)

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