Contemporary perspectives in COPD: Patient burden, the role of gender and trajectories of multimorbidity

SARA C. BUTTERY, MAÉVA ZYSMAN, SIGRID A.A. VIJKJORD, NICHOLAS S. HOPKINSON, CHRISTINE JENKINS AND LOWIE E.G.W. VANFLETEREN

ABSTRACT

An individual’s experience of COPD is determined by many factors in addition to the pathological features of chronic bronchitis and emphysema and the symptoms that derive directly from them. Multimorbidity is the norm rather than the exception, so most people with COPD are living with a range of other medical problems which can decrease overall quality of life. COPD is caused by the inhalation of noxious particles or gases, in particular tobacco smoke, but also by early life disadvantage impairing lung development and by occupations where inhaled exposures are common (e.g. industrial, farming and cleaning work). Wealthy people are therefore relatively protected from developing COPD and people who do develop the condition may have reduced resources to cope.

COPD is also no longer a condition that predominantly affects men. The prevalence of COPD among women has equalled that of men since 2008 in many high-income countries, due to increased exposure to tobacco, and in low-income countries due to biomass fuels. COPD is one of the leading causes of death in women in the USA, and death rates attributed to COPD in women in some countries are predicted to overtake those of men in the next decade. Many factors contribute to this phenomenon, but in addition to socioeconomic and occupational factors, there is increasing evidence of a higher susceptibility of females to smoking and pollutants. Quality of life is also more significantly impaired in women. Although most medications (bronchodilators and inhaled corticosteroids) used to treat COPD demonstrate similar trends for exacerbation prevention and lung function improvement in men and women, this is an understudied area and clinical trials frequently have a predominance of males. A better understanding of gender-based predictors of efficacy of all therapeutic interventions is crucial for comprehensive patient care. There is an urgent need to recognize the increasing burden of COPD in women and to facilitate global improvements in disease prevention and management in this specific population.

Many individuals with COPD follow a trajectory of both lung function decline and also multimorbidity. Unfavourable lung function trajectories throughout life have implications for later development of other chronic diseases. An enhanced understanding of the temporal associations underlying the development of coexisting diseases is a crucial first step in unravelling potential common disease pathways. Lessons can be learned from exploring disease trajectories of other NCD as well as multimorbidity development. Further research will be essential to explain how early life risk factors commonly influence trajectories of COPD and other diseases, how different diseases develop in relation to each other in a temporal way and how this ultimately leads to different multimorbidity patterns in COPD.

This review integrates new knowledge and ideas pertaining to three broad themes (i) the overall burden of disease in COPD, (ii) an unappreciated high burden in women and (iii) the contrast of COPD trajectories and different multimorbidity patterns with trajectories of other NCD. The underlying pathology of COPD is largely irreversible, but many factors noted in the review are potentially amenable to intervention. Health and social care systems need to ensure that effective treatment is accessible to all people with the condition. Preventive strategies and treatments that alter the course of
INTRODUCTION

The health impact of chronic obstructive pulmonary disease (COPD) is substantial and increasing. COPD is responsible for 2.6% of global disability-adjusted life years (DALY) lost and 3.2 million deaths annually. An increasing proportion of the burden of COPD now falls in low- and middle-income countries, as progress in tackling infectious diseases and conditions in childhood mean that non-communicable diseases (NCD) are becoming more prominent. The tobacco industry is seeking to expand markets in these areas even as smoking rates fall in Europe and North America. Factors related to socioeconomic inequality, including poor indoor and outdoor air quality, also contribute.

Despite these figures, COPD receives less attention and less funding than other long-term conditions which have a similar impact. For example, respiratory disease was acknowledged as a priority area for the first time in the 2019 Long Term Plan for the English National Health Service (NHS) whereas a National Service Framework for Coronary Artery Disease was established in 2000. Although COPD is considered preventable and treatable, those with the disease are often left undiagnosed, misdiagnosed or undertreated.

The diagnosis of COPD is typically considered in the presence of dyspnoea, chronic cough with or without sputum production and a history of exposure to one or more risk factors for the disease. However, the reality of living with the disease often includes symptoms beyond the lung, including fatigue, muscle wasting, osteoporosis, anxiety and depression (Box 1). Although the underlying pathology of COPD is largely irreversible, many factors relevant to the physical, social, psychological and cultural experience of the condition are potentially amenable to intervention to reduce the burden of the condition. For most people with COPD, it is only one of the several long-term conditions they experience with symptoms that may be additive or multiplicative.

In the past, attention has largely focused on treatment of airflow obstruction and exacerbation management, with pharmacological symptom control being the mainstay of treatment. More holistic and person-centred approaches acknowledge the importance of pulmonary rehabilitation (PR) and self-management. The development of patient-reported outcome and experience measures is helping to improve recognition and management of the burden of COPD.

In this narrative review, we outline the current understanding of the burden of COPD for people with the condition, focusing on (i) the burden of symptoms and (ii) the psychological and social impact of the disease, with a particular focus on patient perspective and (iii) structural ways in which the burden of COPD is not adequately addressed.

Symptom burden in COPD

The most commonly recognized symptoms that characterize COPD are shortness of breath, cough and sputum production but many other symptoms such as wheeze, chest tightness, fatigue and sleep disturbances can also be prominent. The COPD assessment test (CAT) score, developed as a patient-reported outcome measure, symptoms.

Key words: frailty, inequality, patient perspective, patient-reported outcome measure, symptoms.

ADDRESSING THE BURDEN OF COPD

Symptom burden in COPD

The most commonly recognized symptoms that characterize COPD are shortness of breath, cough and sputum production but many other symptoms such as wheeze, chest tightness, fatigue and sleep disturbances can also be prominent. The COPD assessment test (CAT) score, developed as a patient-reported outcome measure, symptoms.

Key words: frailty, inequality, patient perspective, patient-reported outcome measure, symptoms.

ADDRESSING THE BURDEN OF COPD

Symptom burden in COPD

The most commonly recognized symptoms that characterize COPD are shortness of breath, cough and sputum production but many other symptoms such as wheeze, chest tightness, fatigue and sleep disturbances can also be prominent. The COPD assessment test (CAT) score, developed as a patient-reported outcome measure, symptoms.

Key words: frailty, inequality, patient perspective, patient-reported outcome measure, symptoms.
outcome measure (PROM) provides a simple, plain-language tool to measure symptom burden. More than half of the COPD patients report that they experience symptoms throughout an entire 24-h period and symptoms are the main driver for physician visits. The management of symptoms and their impact on everyday life may be considered of equal or greater importance, from the patient’s perspective, than the prevention of less frequently occurring exacerbations (Fig. 1).

**Breathlessness**

Breathlessness or dyspnoea is one of the core features of COPD, yet it is often under-acknowledged by clinicians. Typically, in a routine clinic environment, doctors are observing patients who have adjusted their everyday lifestyle to minimize the burden of breathlessness. This adjustment behaviour is common in COPD and results in further deterioration, represented in the ‘vicious cycle of inactivity’ (Fig. 2). Physical activity levels are strongly associated with mortality in the general population, a finding confirmed in people with COPD. Early recognition that breathlessness may be a symptom of respiratory illness is important to prevent disease progression and late presentation. Breathlessness in COPD may also be due to coexisting cardiac disease or other medical problems such as anaemia. Therapies that improve breathlessness include PR and inhaled pharmacotherapy, but despite medical management many patients remain significantly limited by it.

Considering the impact of breathlessness on individuals and with a global prevalence comparable to that of pain, it has been suggested that breathlessness continuing despite treatment should be delineated as ‘chronic breathlessness syndrome’ (CBS). CBS commonly exists alongside or as a consequence of other conditions causing significant limitation, distress, emotional burden and poorer quality of life to its sufferer,
as well as increased healthcare utilization and decreased survival. Effective approaches to breathlessness include the use of handheld fans and low doses of oral morphine. \cite{38-40} Recognizing breathlessness as a syndrome should increase awareness among key stakeholders and emphasize its burden to the individual sufferer and healthcare services alike. \cite{37} For example, developing systematic pathways to ensure that medications that are available to help alleviate breathlessness are utilized in an appropriate manner as well as breathlessness management techniques.

Recent National Institute for Clinical Excellence (NICE) guidance advises clinicians to ‘ask people with COPD if they experience breathlessness they find frightening. If they do, consider including a cognitive behavioural component in their self-management plan to help them manage anxiety and cope with breathlessness.’ \cite{21}

Different dyspnoea profiles require specialized management and a recent review of the literature concludes that dyspnoea management should be an individualized, combined intervention with a multidisciplinary approach. \cite{41} Approaches are needed that use multimodal intervention (pharmacotherapy, exercise training and behavioural programme) which can be tailored to patient needs, achieving optimal patient outcomes without increasing treatment burden leading to non-adherence. \cite{42-45}

Cough
Cough with or without sputum production is a common feature of COPD and is the most frequently recorded symptom in people with mild disease. \cite{46} A recent study evaluating patient-reported data on the burden of cough found that among 5286 subjects, those who more frequently reported cough and phlegm of greater severity also reported worse overall disease severity and quality of life. \cite{47} Although cough is often a primary indicator of COPD, failure to recognize this is common, representing a missed opportunity for timely diagnosis and management. \cite{11}

Coughing can affect a person’s life in a number of ways. Patients often describe a cough or sputum worsening at night, posing significant impacts on sleep, or first thing in the morning, causing knock-on effects on energy levels and mood for the rest of the day. Cough worsening during physical exertion may deter patients from participating in exercise or general daily activities, negatively impacting social interaction. Productive cough is also associated with a worse prognosis in COPD. \cite{48,49} Cough incontinence is common in COPD but under-identified and under-researched. \cite{50} The Leicester Cough Questionnaire has been validated in COPD to assess the impact of cough on quality of life. \cite{51}

Interventions to improve cough in COPD include smoking cessation and inhaled pharmacotherapy as well as physiotherapy techniques to aid sputum clearance. It is notable that although mucolytic therapies are widely prescribed, adjuncts to assist sputum clearance such as oscillatory positive expiratory pressure (OPEP) are much less commonly prescribed. \cite{52} The evidence base to support the latter remains strikingly limited, given how common productive cough is in COPD. \cite{53}

Fatigue and sleep disturbance
Fatigue management has received much more attention and evolution of services in the context of cancer care \cite{54} than COPD care. Defined as the subjective feeling of tiredness or exhaustion, \cite{55} fatigue is a commonly reported symptom in the wider population \cite{56} and more so in those with chronic diseases. \cite{57} Goertz et al. \cite{58} reported that fatigue levels were more prevalent in COPD subjects compared with elderly non-COPD subjects and the severity of fatigue was also greater. \cite{59} However, their findings show that fatigue was poorly correlated with airflow obstruction, indicating that it should receive attention as a discrete symptom and be evaluated independent of the severity of COPD patients’ lung disease.

Although fatigue is one of the key components in COPD associated with worse quality of life and an accelerated decline in physical functioning, \cite{58} insufficient attention is given to its burden on the individual. Furthermore, although anxiety and depression are widely acknowledged as coexisting conditions in patients with COPD, one study showed that, comparatively, fatigue affects a greater proportion of patients (50–70%) while also being one of the major contributing factors to either anxiety or depression. \cite{59} A recent study exploring the patient’s perspective of COPD-related fatigue draws upon additional important themes such as associated limitations on daily life and treatment options, as well as factors that contribute to fluctuations in the burden of fatigue such as weather conditions or seasonal change and periods of over or inactivity. \cite{58}

The onset of fatigue, which in clinical care can be difficult to distinguish from the impact of exercise limitation, is most often gradual in nature but may be precipitated by a single episode such as a severe exacerbation or hospital admission. \cite{58} This is an important consideration for clinical management but is often overlooked, perhaps due to its subjective nature, the lack of biomarkers and the limited evidence-based treatment options available. \cite{57}

Frequently associated with fatigue in COPD patients is sleep disturbance. This affects up to 40% of COPD patients \cite{60} but is again largely under-reported by patients and poorly captured and investigated in clinical care. \cite{61} Poor sleep in COPD is associated with decreased health-related quality of life (HRQoL), \cite{62} increased exacerbations, hospitalization, severity of symptoms and mortality. \cite{63} A 2018 meta-review examining data on obstructive sleep apnoea and sleep disturbances reported that cognitive deficits, including memory and attention impairments, were found to be linked to disturbances in sleep. \cite{64} These in turn may impair the ability to self-manage \cite{65} with potentially serious consequences as self-management has been shown to improve HRQoL and reduce the risk of respiratory-related hospital admissions. \cite{65}

Although these consequences are acknowledged, a 2017 systematic review of the literature found that no specific recommendations exist for the treatment
of sleep disturbances in COPD. According to the European Respiratory Society/American Thoracic Society (ERS/ATS) guidelines, all COPD patients should be questioned regarding sleep arousals and prolonged latency, with referral for a diagnostic sleep study or to a specialist arranged where appropriate. But for the patient suffering from poor sleep, the course of treatment is unclear. Diagnosis of OSA and sleep disorders in COPD requires specialist clinical experience to recognize distinct phenotypes that predispose to these comorbidities and provide effective management for the future. Leg cramps are a further common symptom in COPD which can disturb sleep, but for which treatment options are limited.

PA limitation, frailty and multimorbidity
PA limitation is a common feature of COPD, occurring even at an early stage and associated with skeletal muscle impairment which is also present even with mild airflow obstruction and in smokers without airflow limitation. Locomotor muscles have a reduced endurance capacity. People with the condition will often describe a long history of having reduced their daily activity prior to the diagnosis being made. The PROactive Physical Activity in COPD (PPAC) instruments are valid and reliable tools to capture the patient experience of PA. This has been shown to incorporate two domains: amount and difficulty. Hybrid Patient Reported Outcome (PRO) tools such as these which combine objective measurement (activity monitors) with PROM provide a more comprehensive assessment, appreciating the role that patient experience of PA has on the reality of management approaches. Of note, difficulty scores improve after pharmacological treatment and PR, while amount scores improve after behavioural PA interventions.

Frailty can impact access to effective treatment. Qualitative work in PR identified four frailty-related themes: (i) striving to adapt to multidimensional loss, having to adapt to their changing health and resulting multidimensional losses (e.g. functional abilities, relationships and confidence); (ii) tensions of balancing support with independence; (iii) PR as a challenge worth facing; and (iv) overcoming unpredictable disruptions to participation; due to their changeable health, many had to overcome multiple unpredictable disruptions to complete it. As COPD is a progressive disorder, it is also associated with an ageing and socio-economically disadvantaged population. The accumulation of multimorbidity and indeed frailty is common, although not inevitable. The way in which these extrapulmonary components are approached can significantly shape the patient’s experience and progression of COPD. Multimorbidity should therefore be an explicit area of concern in COPD research and management.

Burden of acute exacerbations
Acute exacerbations of COPD (AECOPD) can have considerable impact, not only for the period that the exacerbation lasts but also on longer term prognosis; fewer than half of patients suffering an AECOPD requiring hospitalization survive greater than 5 years. AECOPD can also be a source of anxiety about future symptoms, hospital admission and risk of death. Improving patient education on exacerbation recognition and self-management plans has been a key focus of COPD care in an attempt to reduce the number of exacerbations requiring hospitalization. However, recognizing an exacerbation can be challenging even for a specialist, due to the heterogeneity of symptom patterns and the patient’s perception of them, ‘usual’ day-to-day variability, the presence of comorbidities and a lack of objective measure or biomarker to define a true exacerbation. Although patients are experts in their own condition, expectations of accurate recognition, diagnosis and management of exacerbations may only add to the burden of living with this disease. It is important that people with COPD have an accurate understanding of what may happen during a hospital admission and that issues such as non-invasive and invasive ventilation as well as advance care plans are discussed in a timely way. Hospital-at-home schemes, which are one approach to avoid the burden of hospital admission, should be developed and utilized where appropriate.

Psychological and social burden of COPD
People with COPD are confronted with a condition that limits their ability to achieve day-to-day activities that they value and to reach longer term goals, as well as shortening their life expectancy. The socioeconomic distribution of COPD means that patients often face this situation with less social and cultural capital. Psychological comorbidities are common and anxiety and depression have a high prevalence in COPD, comparable to cancer, AIDS and heart disease. A 2019 review of psychological therapies for the treatment of depression found that treatment of COPD-related depression was erratic and unsatisfactory. Interestingly, untreated depression appeared to result in worse compliance with medical treatments and, as a consequence, poorer health outcomes for patients including more time spent in hospital, reduced quality of life and increased mortality. Furthermore, anxious COPD patients with significant comorbidities may be more likely to decline surgical treatments to address other conditions due to the fear of potential side effects or increased risk of mortality. This can cause significant psychological burden in terms of increased anxiety or consequential depression due to the burden of multimorbidity. The emotional impact that patients may face due to the responsibility placed on family members who often take on a ‘carer’ role must also be considered. The financial burden from having to give up work or withdrawal from social activities can have an enormous influence on relationships and generate feelings of guilt.

Cognitive behavioural therapy (CBT) has been proposed as a strategy to help people to manage the psychological burden of long-term conditions. There is evidence to suggest that, in COPD, CBT-based interventions may be effective in addressing anxiety and depression and improving HRQoL as well as reducing visits to emergency departments (ED). PR has
similarly been shown to reduce anxiety and depression for up to 6 months after the completion of a programme \(^{48,49}\) but ironically the presence of these psychological comorbidities can also serve as barriers to patients accessing and completing PR. \(^{86}\)

A systematic literature review addressing COPD patients’ support needs highlights the psychological burden of COPD from the patient’s perspective. There is an important emphasis on ‘thinking about the future’ and end of life care. \(^{17}\) Considering the poor prognosis following hospitalized AECOPD, \(^{76}\) this is a key moment requiring careful consideration to support patients’ emotional needs. Although individuals differ as to how and when they wish to learn how their condition may progress, many express a need to understand their prognosis. \(^{17}\) Unfortunately, predicting this in COPD is not easy and questions still remain on how to best provide end of life care. Access to palliative care services is often limited and where they do exist, were typically developed based on traditional cancer models. This may be an unhelpful pathway for the COPD patient who does not follow a predictable course. It is crucial that this is addressed as from the patient’s perspective ‘sometimes the journey is more important than the destination’. \(^{87}\)

Isolation (reduced frequency of social interactions) and loneliness (the subjective consequence of reduced social interaction) \(^{88}\) are recognized problems in COPD and have received more attention in COPD research in recent years, perhaps due to the strong associations with increased morbidity and mortality. \(^{89,90}\) Social isolation and the subjective feeling of loneliness are more commonly experienced in an ageing population. One reason for this may be due to reduced physical function or mobility that is highly prevalent in COPD, restricting individuals from attending social events or even leaving their house. In addition, symptoms such as cough and dyspnoea may cause sufferers to withdraw from social occasions due to embarrassment or discomfort and this may be reinforced further by low energy levels or fatigue that are common in COPD.

COVID-19 social isolation and remote care

The present coronavirus disease 2019 (COVID-19) pandemic has increased the burden on COPD patients as they are at an increased risk from the virus \(^{91,92}\) and are advised to take additional precautions to reduce their exposure. This has interfered with the delivery of routine care including clinic appointments and especially PR, as group exercise indoors is considered particularly risky. Remote provision is one possibility. Step count targets can be effective \(^{45}\) and telecoaching has been used successfully in the past to increase PA \(^{93,94}\) but limited research has been conducted into the feasibility of web-based models of PR delivery. Existing studies do not reliably address the barriers in providing such a service. Polgar et al. recognized the need to understand digital access and preferences around use of digital platforms of current service users for PR delivery. Their results highlighted the lack of confidence and desire to access digital platforms in a large proportion of their cohort, with as many as 31% of patients reporting they had never accessed the internet. \(^{95}\) A digital by default service may increase exclusion particularly among poorer and older groups, and may also aggravate social isolation with adverse consequences. \(^{96}\)

Pathways of care: Addressing failures to relieve the burden of COPD

There is considerable scope for the patients’ experience of COPD to be improved. Many people with significant breathlessness delay seeking health care, and many who do find that their treatment is unsatisfactory. \(^{10}\)

The UK NICE underlines the ‘Five Fundamentals of COPD Care’—smoking cessation, PR, vaccination, self-management and identifying and treating multimorbidity—in its recent guideline on managing the condition. \(^{21}\) However, a 2019 study of patients’ experience of COPD care found a substantial disparity between recommended care standards and care that had actually been received. The study also found no evidence that the situation had improved over the 5 years of data available. \(^{9}\)

Gaps identified in patients’ understanding of COPD and exacerbation recognition, smoking cessation support and discussions around self-management and PR are indicative of systemic failings to deliver these ‘five fundamentals’. \(^{21}\) This patient experience is supported by clinical audit data showing low levels of smoking cessation support and PR as well as a substantial proportion of individuals missing out on flu vaccination. \(^{12}\)

Patients’ understanding of the support available and accessibility to educational resources is vital to ensure benefits to those who need it most. To guarantee this happens, self-management plans must be built into care pathways \(^{13}\) as knowledge increases patients’ confidence and empowerment. In addition, patients may value the presence of a ‘key worker’ who is easy to contact and ensures that they benefit from all of the appropriate interventions available to them. This is reported to be beneficial in patients with lung cancer but less likely to be available for people with COPD. \(^{9}\)

It is well documented that social deprivation is a powerful determinant of health status and this is especially true for COPD. \(^{14}\) Through the cutting of services in austerity programmes, those who are the most deprived are denied adequate support to manage their disease which may lead to more frequent exacerbations and acceleration in disease progression, consequently increasing the burden of COPD on healthcare systems. \(^{97}\) In addition, the failure to give COPD due priority compared to other diseases such as cardiovascular disease and cancer further impedes progress in research, treatment and management (Fig. 3). \(^{25}\)

Recently, more holistic, person-centred \(^{15}\) approaches have been set out to improve delivery of care beyond pharmacotherapy and ensure that the highest value \(^{98}\) items are delivered systematically. The Breathing SPACE (smoking pulmonary disease, anxiety, cardiac disease and exercise) approach to the breathless patients developed by the London Respiratory Network \(^{99}\) is another strategy to promote a holistic approach. Initiatives such as the British Lung Foundation Patient Passport \(^{13}\) enable people with COPD to assess their care against what they should expect to receive, encouraging them to be more assertive where
IS GENDER IMPORTANT IN COPD?

COPD epidemiology

COPD is no longer a respiratory disease that predominantly affects men. A meta-analysis performed with 194 eligible studies reports that summary prevalence is 9.23% (8.16–10.36) in men and 6.16% (5.41–6.95) in women. However, gender prevalence varied widely by regions, with the highest male prevalence occurring in South East Asia (11.34%) and female prevalence found in North America (8.07%). Higher COPD prevalence occurred in urban dwellers (13.03%) compared to rural and mixed populations (8.34%), but this may reflect greater access to health care and diagnosis in urban centres.108

Heightened prevalence of COPD among women in different countries is due to a range of different exposures and settings, varying from increased exposure to tobacco, biomass fuels and household air pollution. COPD is the third highest cause of death in women in the USA.109 In some regions, such as North America, the prevalence of COPD is almost as high in women as in men110 and is increasing more rapidly in women, particularly in younger women.111

In addition, women are more likely to be misdiagnosed,112 typically as having asthma rather than COPD. Cigarette smoking increases the possibility of developing COPD among people who have asthma, and as there is a higher prevalence of asthma among women than men, smoking may be an additional factor predisposing them to develop COPD or asthma–COPD overlap.

It must be remembered that non-smokers can develop COPD. In 14 countries participating in the Burden of Obstructive Lung Disease (BOLD) study, never-smokers comprised 23% of those classified with the Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage II+ COPD.113 Predictors of COPD in never-smokers included age, education, occupational exposure, childhood respiratory diseases and body mass index (BMI) either above or below normal range. COPD in non-smokers was milder (GOLD I–II) than in smokers and in men increased risk was associated with lower education levels and passive smoking. In moderate to severe COPD, a history of hospitalization in childhood for respiratory illness (which could be a surrogate marker of childhood asthma) was a risk factor, while exposure to passive smoke and biomass fuel for heating was discriminative for women. These differing risk factors clearly indicate that men and women may have different environmental and genetic inputs to developing COPD.

Whether gender confers a particular susceptibility to develop COPD is controversial114–117 but there is increasing evidence suggesting that women are more susceptible to the effects of smoking.118 Individual risk
for developing COPD is based on both personal susceptibility and environmental risk factors. Although not fully understood, there is indirect evidence suggesting that for a given level of risk exposure, women are more susceptible to developing COPD or have more rapid disease progression than men. For example, female smokers are at greater risk of airflow obstruction than male smokers.

Data from the UK Biobank study showed a stronger association between cigarettes smoked and airflow obstruction in women, but the association was not linear and there was a greater increase in risk at lower doses for women than men. Many studies have shown that for equal number of cigarettes per day and years of smoking, women have greater severity of airflow obstruction than men. In the UK Biobank study, women were at increased risk of airflow obstruction after only 15 years of smoking and five cigarettes per day. Consistent with this, two longitudinal Danish studies, the Copenhagen City Heart Study and the Glostrup Population Study combined found that for each pack-year of smoking, women had greater excess loss of forced expiratory volume in 1 s (FEV1) in mL per year compared to men. In another study, women were disproportionately represented in the subset of patients with COPD with severe disease despite minimal tobacco smoke exposure (defined as <20 pack-years). Women were also more likely to present with COPD before the age of 60 years.

In a retrospective longitudinal cohort study using population-based health administrative data from Ontario, Canada, roughly 13 million people were monitored for the development of COPD for up to 14 years. Lifetime risk was higher in men than in women, and higher (29.7% vs 25.6%) for individuals of lower socioeconomic status (32.1% vs 23.0%) and those who lived in a rural setting than in those who lived in an urban setting (32.4% vs 26.7%). While it is most likely that socio-demographic factors interplay differently at an individual level, susceptibility due to gender also plays a role.

In addition to smoking, the role of the workplace in COPD causation is often under-recognized. In women, several different occupational factors as compared to men may warrant particular consideration. For example, regular use of chemical disinfectants among nurses may be a risk factor for developing COPD, while men may be more exposed to agricultural insecticides and biologic dusts. However, there is evidence, as with tobacco exposure, that women with lower cumulative exposure years to aromatic solvents than men have a greater lung function decline than men. On the other hand, men are more likely to work in dusty jobs, more often unprotected, be concurrently smoking tobacco and have occupational and recreational exposure to dusts that are known to increase the prevalence of COPD. Men more commonly work in construction, mining, warehouses, spray painting, manufacturing and welding, with subsequent exposure to the associated hazards.

Exposure to smoke from biomass burning is a strong risk factor for the development of COPD. It has been reported that women exposed to biomass have clinical characteristics and prognosis similar to that of smokers, although there are data to suggest that an airway-predominant phenotype may be more common than an emphysema phenotype. Women’s exposure to smoke from biomass fuel burning particularly occurs indoors, when they are cooking and caring for children in small and poorly ventilated houses.

COPD pathophysiology

Developmentally, even prenatally, there are significant differences between the growth of male and female lungs, numbers of bronchioles and alveoli, and size of the lungs at birth. Sex steroids have effects on airway smooth muscle and mucus-secreting cells, can modulate the effects of toxic exposures and potentiate the effects of cigarette smoke and other insults on airway and alveolar epithelial cells. This may predispose women to bronchitis while men are more prone to develop emphysematous disease.

Clinical presentation for stable disease

The clinical manifestation of COPD can differ by gender, with women experiencing worse lung function and HRQoL than men. In addition, women tend to report more symptoms given the same disease severity. As measured by FEV1 or GOLD stage, women are more likely to present early in the course of COPD and more likely to be admitted to hospital.

Presentation and diagnosis

Important limitations to the treatment of females with COPD include greater under-diagnosis than in men in some countries, but not in others, and a tendency of health professionals to diagnose asthma rather than COPD in women. There is a greater prevalence of females among those with early onset of COPD.

Course of disease

Disease progression and outcomes appear different among women and men with COPD.

Faster lung function decline. Progressive lung function decline is the hallmark of COPD. Prescott et al. examined the interaction of gender and smoking on development of COPD through lung function and hospital admission caused by COPD in two independent population samples. Among more than 13 000 subjects, they estimated that the excess loss of FEV1 per pack-year of smoking was between 7.4 and 10.5 mL in female smokers compared to 6.0 and 8.4 mL in male smokers.

Respiratory symptoms are associated with reduced baseline FEV1 in men with COPD as compared to women and more severe airway obstruction is associated with accelerated decline. The annual decline in lung density is more rapid in women.

Gender difference in symptoms. For a given age and level of airflow obstruction, women with COPD have higher BOD (Body mass, Obstruction, Dyspnoea) scores due to more pronounced dyspnoea. Quality
of life [St George’s Respiratory Questionnaire (COPD) (SGRQ-C)] is also more impaired in women than in men (scores: 50.6 vs 45.4; P < 0.02).140 A higher burden of the disease with higher levels of dyspnoea has been confirmed even after matching on age and FEV1.142 This observation was confirmed several times with younger women with COPD having a greater likelihood of more severe dyspnoea and airflow limitation.145

**Higher risk of exacerbation.** Moderate or severe exacerbations are more frequent in women compared with men.142,144 Recently, the risk of first moderate or severe exacerbation was estimated to be 17% greater in women than in men (hazard ratio: 1.17; 95% CI: 1.12–1.23), with a median time to first exacerbation of 504 days for women and 637 days for men. As previously mentioned, COPD starts earlier in women explaining why these differences were more prominent in the younger age group from 40 to 65 years.146

**Higher risk of hospitalization.** Females have an increased risk of hospitalization for COPD compared with males [relative risk (RR) = 1.5 (1.2–2.1) to 3.6 (1.4–9)].143 Female representation among patients hospitalized for COPD exacerbation is increasing over time147 and females are at higher risk of readmission.148

**Gender differences in COPD mortality.** Vestbo et al. examined survival after admission due to COPD in 267 men and 220 women after discharge. The 5-year survival rate after COPD admission was higher in women (52%) than in men (37%). However, age-adjusted COPD mortality rates in the USA increased more in women (+126%) than in men (+17%).149

**Gender differences in comorbidities associated with COPD.** For a given age and level of airflow obstruction, women with COPD are more likely to exhibit anxiety,142 with the anxiety score being higher (score: 9.8 vs 7.1).140 In a Swedish study of patients aged 50 years or older, starting long-term oxygen therapy for COPD, men had significantly more arrhythmias, cancer, ischaemic heart disease and renal failure, and less hypertension, mental disorders and osteoporosis (P < 0.05 for all odds ratios (OR)). Comorbidity was an independent predictor of mortality, and the effect was similar for both sexes.150

**Clinicians’ responses.** In several studies, male patients with COPD have been shown to be more likely to be prescribed more than one maintenance treatment, and a have greater likelihood of receiving antimuscarinic and dual long-acting bronchodilators for COPD.151,152 However, specific treatments targeting smoking may be prescribed more often for women.153 In one study, COPD was more frequently the most likely diagnosis for the male patients in primary care even though men and women presented with identical COPD symptoms. This bias towards making a COPD diagnosis in men was seen to a greater extent in female compared to male physicians.155

There is a greatly concerning, consistent trend in low- to middle-income countries of women receiving fewer classes of medications and non-pharmacological interventions for COPD than men.154–156 Treatment differences and the range of treatments offered to men and women with COPD in high-income settings do not appear as marked and have been reported as sometimes greater in women than men.157–159 These observations should be interpreted in context and not generalized to all countries.

**Clinical presentation of exacerbations**

**Presentation and diagnosis**

Women and men appear to experience a different spectrum and severity of symptoms for a given severity of spirometric abnormality during stable periods of COPD care. A different spectrum of symptom presentation in exacerbations is also evident. First, women appear to experience more exacerbations than men by the current treatment-defined criteria.160 In a Spanish study, although women were younger, smoked less and had better resting oxygenation, they experienced more exacerbations in the last year.161 Comorbidities, which may also contribute to symptom burden in exacerbations, are different between men and women in several studies,159,162 with a greater predominance of anxiety, depression, osteoporosis and sleep disturbance in women but a lower prevalence of cardiovascular diagnoses compared to men.162 Apart from anxiety and osteoporosis, in most studies, men with COPD have a higher prevalence of comorbidities than women.

The higher rate of exacerbations in women versus men with COPD, identified in some studies, may contribute to the overall higher death rate in women observed in some countries such as the USA.166 This is not a universal finding167,168 and is changing in countries where it has been the case.169 In the ECLIPSE COPD cohort (n = 2,164), the rate of exacerbations was found to be significantly higher in women than men at each GOLD stage.170 Similarly, in a post hoc analysis from the POET-COPD trial, the risk of first exacerbation was higher for women compared with men (hazard ratio (HR): 1.31; 95% CI: 1.19–1.43).171 Data from the TORCH study also showed that the time to first exacerbation was shorter and the rate of exacerbations was 25% higher in women than in men (P < 0.001; 95% CI: 16–34), although the number of hospital admissions caused by exacerbations was similar in both sexes.172

There may be more powerful determinants of exacerbation frequency than gender. Productive cough is strongly associated with exacerbation risk and mortality. Men with COPD have a higher prevalence of productive cough and higher mortality, even compared to women with COPD and productive cough.49,173,174 On the other hand, particular combinations of symptoms in women are associated with greater mortality risk. In one study, differences in dyspnoea and BMI contributed to poorer prognostic scores demonstrated by a worse Body mass index, airflow Obstruction, Dyspnoea and Exercise capacity (BODE) score in women compared with men matched for lung function and age.174 In a large primary care-based UK study, female patients with high dyspnoea scores, more severely impaired lung function and comorbidities were at greatest risk of being frequent exacerbators.175
Course and outcomes of exacerbations

Although women may more frequently report some symptoms such as dyspnoea and wheeze, this is not the case for all symptoms. Women have been noted to be less likely to report cough and sputum but for a given level of airflow obstruction, experience a greater impact on exercise capacity, breathlessness and quality of life.

As COPD progresses, exacerbations leading to hospitalization become more frequent. Although some studies show similar outcomes in general men who require hospital admission for acute exacerbations tend to do worse than women, with higher in-hospital and 30- and 90-day mortality rates as well as a higher rate of readmission. Many factors determine hospital admission, including the severity of symptoms, respiratory failure, age, capacity to manage at home and the impact of comorbidities. In a Canadian study, a higher likelihood of admission was associated with older age, female gender (OR: 2.13; 95% CI: 1.2–3.78), more pack-years of smoking, recent use of inhaled corticosteroid, self-reported activity limitation in the past 24 h, higher respiratory rate at ED presentation and a concomitant diagnosis of pneumonia. Subsequently, other Canadian authors have shown that COPD hospitalizations and ED visit rates for people with COPD were forecast to remain stable up to 2024, including the observation of approximately equal sex ratios.

Clinicians’ responses

Women with COPD are likely to have more frequent interactions with healthcare providers and use more healthcare resources than men, but under-recognition of COPD in women may lead to suboptimal treatment. Although the gender bias in diagnosis is reduced by the use of spirometry, this tool in general remains underused, particularly in women. There is some evidence to suggest that there may be differences in men and women’s perception of the COPD care they receive. In addition, coping strategies may differ between men and women. There is a need for further work in this area to determine how women with COPD can best be supported.

Treatment responses

Smoking cessation is the most important initial step in COPD management, and in some studies this appears to be more often offered to women. The Lung Health Study suggests that women may benefit more from smoking cessation than men, even though other studies suggest they may have more difficulty giving up. There are no studies designed to examine sex-related differences in the effects of nicotine replacement therapy and smoking cessation medications (such as bupropion and varenicline) appear to be equally effective in men and women. As women may have greater levels of anxiety and greater smoking dependence than men, they may also benefit from a tailored behavioural approach; however, men and women need to be encouraged to access these strategies. PR is also a key non-pharmacological intervention for patients with COPD, but very few studies report any differences between men and women and most enrol more males than females.

There are also gender-related differences on treatment and the utilization of healthcare resources by women, evident in relation to care-seeking behaviour at the time of an exacerbation. As the definition of an exacerbation requires an interaction with a healthcare provider in order to receive antibiotics or corticosteroids for worsening symptoms, it may be that women seek medical help more readily and/or present earlier in an exacerbation, and not necessarily the case that exacerbations are worse in women. However, studies have reported more frequent and/or more severe exacerbations and higher levels of dyspnoea in women compared with men. A higher prevalence of airway hyperresponsiveness in women than men may, at least partially, account for some of the variability between genders in symptoms such as dyspnoea, although further studies are required.

In pharmacological trials, gendered analyses are very rarely undertaken. Studies are underpowered for analyses based on sex, particularly when women are underrepresented. In the EUROSOP study, the improvement in sputum production on budesonide was limited to men. Longitudinally, men showed a greater response based on their symptom reporting to cigarette exposure (worsening) and treatment (improvement). Women initially reported greater remission of symptoms in the first year of follow-up but over the 3-year period the symptom prevalence differences between men and women disappeared. Little is known about gender differences with respect to response to treatment. There are no consistent findings to suggest that inhaled steroids act differently in males and females, but gender differences in plasma albuterol concentrations have been found. The concentration at which maximal bronchodilation is observed (C50) is nearly double in males compared with females (median: 6.4 vs 3.3 ng/mL) suggesting that females are more sensitive to albuterol in their FEV1 response.

Post hoc analyses of clinical trials assessing long-acting bronchodilators have shown similar reductions in exacerbation prevention and lung function improvement in men and women.

The principal focus of treatment for COPD patients must be smoking cessation, as it alters the course of disease. In addition, prevention of further decline in physical functioning and enhancement of HRQoL is a prime focus of attention. Symptomatic treatment is part of the management of COPD, including bronchodilators. Female smokers with COPD who became sustained quitters had an average improvement in FEV1 during the first year that was 2.5 times as great as the improvement in males. However, another study reported that in quitters, males had a greater reduction in FEV1 decline than females (20.6 vs 15.7 mL, respectively).

Males and females do not always have the same success with smoking cessation. A gender analysis on sustained quit rates observed that males had higher sustained quit rates at 12 and 36 months. After controlling for other variables that confound for sustained abstinence, such as educational level and marital status, the effect was lost at 12 months but remained
significant at 36 months. This implies that women have greater difficulty in sustaining long-term abstinence from tobacco than men. This could be due to less commitment to quitting and gender differences in physical response to nicotine resulting in greater withdrawal symptoms in women.\textsuperscript{192}

Some nicotine-replacement therapies may not be as effective in women. For instance, nicotine replacement therapy has been shown to reduce craving for cigarettes less effectively in women than in men, resulting in larger weight gain in females. Women may do better with antidepressant medications for smoking cessation. However, a study showed that bupropion was equally effective in females and males with COPD.\textsuperscript{193} In relation to non-pharmacological interventions, PR has been shown to have beneficial effects, specifically improving quality of life and exercise capacity. PR also reduces hospital admissions, both in the long run and after short-term exercise training. Men and women differ with regard to decline in functional aerobic capacity, even at equivalent levels of pulmonary dysfunction. Women report more gains than men in the dyspnoea domain, namely 0.85 versus 0.4 unit improvements and fatigue domain 0.55 versus 0.3 of the chronic respiratory questionnaire.\textsuperscript{194} These benefits and the specific interventions that can maximize gains for men and women require further research.

**FROM LUNG FUNCTION TO MULTIMORBIDITY: TRAJECTORIES IN COPD**

**Introduction**

There is an increasing interest in the early origins of obstructive lung diseases, and patients with COPD in older age might have followed different lung function trajectories.\textsuperscript{195} A recent review pointed to the fact that some of the trajectories may have substantial implications for morbidity and mortality.\textsuperscript{196} Indeed, it has been shown that low lung function in early adulthood is associated with higher incidence of respiratory, cardiovascular and metabolic diseases later in life,\textsuperscript{185} or with an increased risk of premature cardiovascular mortality.\textsuperscript{197} FEV\textsubscript{1} is not just a lung function test, but is a marker of premature death from all causes.\textsuperscript{198}

Previous studies have shown that in utero and early life factors, including low birth weight and alterations in insulin response,\textsuperscript{199,200} and abnormal acquisition of body fat and peak bone mass,\textsuperscript{201} may influence the development of comorbidities later in life. Low attained lung function in childhood and adolescence may affect exercise capacity and cardiovascular fitness, which, are themselves risk factors for the development of comorbid diseases later in life.\textsuperscript{202} Furthermore, established risk factors for disease such as tobacco smoking, ageing and sedentary lifestyle probably play an important role in both suboptimal lung function trajectories and development of other diseases.\textsuperscript{203} Patients with COPD therefore follow not only a trajectory of lung function decline, but also a trajectory of multimorbidity. This is complex, as a life course perspective on the development of NCD does not follow a simplistic health model where an individual is healthy until disease occurs. Currently, little is known about these temporal associations between lung function and comorbidity trajectories.

The aim of this narrative review is to integrate the knowledge of lung growth, lung function trajectories and trajectories of other NCD in the context of COPD and its different multimorbidity patterns.

**Lung function trajectories and COPD**

**Normal lung function development**

Normal lung function development is essential for lung health. Development of lung function starts in utero and may continue until adulthood.\textsuperscript{204} A number of factors are known to interfere with normal lung development in different stages of life.\textsuperscript{196} Failure to develop optimal lung function may influence an individual’s health and could also affect morbidity and mortality. It is now evident that suboptimal lung function development early in life may result in chronic obstructive lung disease in adulthood.\textsuperscript{117,205–207} Although we have substantial knowledge on determinants of lung development, we do not know how we can reverse or halt lung function decline and established disease, and currently no curative treatment exists.

The development of the human lungs happens from the fourth week in the embryonic period. During organogenesis, organs form from the three primary germ tissues. The endodermal lung buds originate as an outgrowth from the ventral wall of the foregut at the tracheal anlage. Epithelial tubes form from week 5 during the pseudo-glandular stage of lung growth, followed by extensive airway branching in the canalicular stage from week 16. Alveolarization of surrounding mesenchymal cells occurs in the saccular and alveolar stages, the latter stage continuing during the first two decades of life. Alveolarization and microvascular maturation are parallel processes that continue until early adulthood.\textsuperscript{208} All these phases are sensitive to development influences, including well-known factors such as maternal smoking and nutrition, as well as genetic and epigenetic mechanisms.

**The impact of low maximally attained lung function on COPD**

Low attained lung function in childhood and early adulthood is associated with increased risk of COPD later in life.\textsuperscript{117,204,206} The normal lung function trajectory throughout the life course has three phases: a growth phase lasting from birth to early adulthood, a plateau phase lasting from around 20 years of age and a phase of decline resulting from normal ageing of the lungs. All these phases can be altered by several environmental, clinical and genetic factors. Recent studies have shown that there are several potential trajectories in these phases, and that some of them may have substantial implications for morbidity and mortality.\textsuperscript{196} Burrows et al. identified a period from late childhood through adolescence in which maturation significantly increased forced vital capacity (FVC) and FEV\textsubscript{1}, independent of body growth, and a plateau phase from late adolescence to the early or mid-30s with relatively little change in these parameters.\textsuperscript{209}
They found that the physiological decline in FVC and FEV₁ may not start before the mid-30s.²⁰⁹ Further low maximally attained lung function in early adulthood is likely to be relevant in almost half of all COPD cases, and hence accelerated decline of FEV₁ is not needed for the development of COPD.¹¹⁷ These findings are confirmed in several longitudinal studies.¹³⁶ An Australian study identified six distinct trajectories, in which three trajectories contributed to 75% of COPD burden.²⁰⁵

The impact of low maximally attained lung function on comorbidity
A recent observational study by Agusti et al. following individuals from two independent US cohorts as well as their offspring examined how low lung function impacts the risk of later adult chronic disease. They found that individuals with FEV₁ of less than 80% predicted at the age of 25–40 years had higher prevalence of respiratory, cardiovascular and metabolic abnormalities in early adulthood; higher incidence of comorbidities and at a younger age; and higher mortality compared to individuals with normal lung function.¹⁹⁶ These findings were also supported by another observational study, where low FEV₁ in young adulthood predicted the risk of premature cardiovascular mortality.¹⁹⁷

Why are there differences in lung function development?
Environmental and lifestyle determinants cannot fully explain the heterogeneity of lung function development and COPD. In recent years, researchers have been unravelling the underlying genetic mechanisms of lung function indices and pathophysiology, which adds to our understanding of individual susceptibility for the development of obstructive lung disease. Advances in fields such as genome-wide association studies (GWAS), Mendelian randomization and epigenetics give us further clues in the search for causative mechanisms behind COPD. The emergence of state-of-the-art biobanks, large cohorts and improved analysis techniques have paved the way for new insights in the genetic determinants of lung function development and decline. However, these insights are only valuable for clinical practice if they are coupled with disease phenotypes, patient characteristics and longitudinal data, which is a promising area of further research.

Genetic determinants of lung function development
Genetic determinants of lung function development have been assessed in several large GWAS.²¹⁰ A recent study on almost 50,000 subjects from the UK Biobank has identified 97 independent genetic associations with lung function parameters in both children and adults.²¹¹ Genes influencing lung development, elastic fibres and epigenetic regulation pathways were among these.²¹¹ Furthermore, a genetic risk score was developed showing a clear association with COPD susceptibility, and that there is an overlap in certain genetic variants between lung function and COPD.²¹¹ Heritability of FEV₁ was estimated to be 9.6%.²¹¹ However, few studies have investigated the role of genetic variants on longitudinal lung function development. A GWAS on almost 600 individuals classified into pre-defined trajectories found that a genetic polymorphism on chromosome 8 was associated with a pattern of normal growth and early decline.³⁷ However, in another study with a slightly larger sample, previously identified genetic variants were not found to affect the rate of lung function decline.³⁷ Future studies exploring the genetic variants associated with lung function trajectories, including new methods like Mendelian randomization-phenome-wide association studies (MR-phenWAS), will possibly tell us more about the causative mechanisms behind lung function development.

Epigenetic influence of lung function development
Beyond the nucleotide variations explored by GWAS and related studies, the emerging role of epigenetics as an explanatory model for lung function development has gained increasing interest in recent years. Epigenetic modification mechanisms regulating gene activity and expression, including DNA methylation, histone modification and non-coding RNA-associated gene silencing, are being extensively explored. Several methylation sites have been associated with both childhood lung function and later-life COPD,²¹² as well as lung function properties like FEV₁.²¹³ However, despite exciting prospects, it is too early to extend these results to current clinical practice.²¹⁴

Lung function catch-up
Some individuals with low attained lung function in childhood seem to go through a period of catch-up lung growth, with recovery of deficits observed during childhood occurring during adolescence and early adulthood.²⁰⁷,²⁰⁸ Agusti and Faner propose a window of opportunity for catch-up, as evidence of catch-up has been found in observational studies of adolescents but not in children.¹⁹⁶ This theory is strengthened by the fact that lung function continues to increase for years after body height plateaus are reached,²¹⁵ indicating that lung function development is not only part of general body growth. Little is known about the underlying mechanisms for such catch-up, probably due to the lack of suitable cohorts to study this phenomenon.

Trajectorial studies highlight the possibility and importance of early detection of risk factors known to predispose for important contributors to multimorbidity later in life. Further exploration of the catch-up phenomenon and its association to later disease development would be of great interest, in order to increase our understanding of the development of—and thereby prevention of—multimorbidity.

© 2021 Asian Pacific Society of Respirology.

Respirology (2021) 26, 419–441
From common risk factors to developmental influence

In the last decade, attention has shifted from adult lifestyle and risk factors as a cause for NCD to early life experiences that influence adult health and mortality risk.\(^{215}\)

On a yearly global basis, approximately 15 million infants are born prematurely. Improvement in intensive care for premature infants and increased knowledge of neonatal physiology have increased survival. However, the lifetime morbidity remains high for these individuals. It is well known that individuals with extremely low birth weight (<1000 g) or those born extremely pre-term (<28 weeks) have an increased risk of reduced respiratory function and exercise capacity later in life,\(^{216}\) predisposing to increased morbidity. Immature lung growth could lead to later respiratory problems, including COPD and other chronic lung diseases.\(^{117}\) However, prematurity and low birth weight also affect other organs such as the kidneys, heart and blood vessels. A systematic review found that even individuals born at late preterm (34–36 weeks) or early term (37–38 weeks) had an increased risk of stroke, type 2 diabetes and asthma.\(^{217}\) In two systematic reviews and meta-analyses, those born preterm (<37 weeks) also had a higher risk of increased low-density lipoprotein (LDL) levels and high blood pressure in adulthood, factors predisposing to atherosclerosis and cardiovascular disease.\(^{218,219}\) In a large population-based study including more than 2.5 million individuals from a Swedish cohort, those born at <32 weeks of gestation were found to have an increased risk of heart failure in childhood and young adulthood.\(^{220}\) Prematurity also increases the risk of future chronic kidney disease (CKD).\(^{221}\)

Some of the factors increasing the risk of being born prematurely, such as maternal smoking and low socioeconomic status, show a strong degree of ‘heritability’; hence, such ‘traits’ are passed along to the offspring, further adding to the risk of disease. Established risk factors such as smoking, hyperglycaemia and hypertension are well-known players in the development of NCD. However, even after removing these risk factors, some individuals still seem to have an increased risk of developing such degenerative diseases.\(^{222}\) Parts of the explanation have developmental causes, considering that prematurely born individuals start their growth trajectory at a lower level.

The ‘Barker Hypothesis’\(^{223}\) and later the Developmental Origins of Health and Disease (DOHaD) approach\(^{224}\) have focused on the foetal origins of adult disorders. The latter set of hypotheses focuses on developmental plasticity or ‘foetal programming’, including the effects of maternal nutrition, psycho-neuroendocrine and epigenetic processes, explaining how early life factors influence adult morbidity.\(^{224}\) Several studies have shown that maternal diet regulates blood flow to the developing foetal organs, and one study showed that foetuses of women with poor diet or abdominal obesity had increased hepatic blood flow.\(^{225}\) Such redirection of blood flow to other organs could cause impaired alveolar growth, low nephron count and hepatic endocrine dysfunction,\(^{225}\) predisposing for later disease development.

Other disease trajectories: What is known?

Several studies have been conducted on patterns of disease progression of isolated conditions such as cancer, frailty, dementia and sudden death.\(^{226}\) Such studies have focused on functional decline during the last stages of life and illustrate the highly variable trajectories expected from different index conditions (Fig. 4). Of special interest for this review are the trajectories of chronic organ diseases or NCD that are commonly seen in COPD, including chronic heart failure (CHF), hypertension, diabetes, alterations in body composition and CKD. A pattern of stepwise decline preceded by disease exacerbations are typical for such chronic degenerative diseases. However, few studies have looked at such trajectorial patterns from a lifetime perspective. Here, we summarize what is known on these disease trajectories and on possible temporal interactions with other diseases, with regard to lung function or COPD.

Trajectories of blood pressure

Despite an association between increasing age and systolic blood pressure, experimental data on the nematode Caenorhabditis elegans have shown that the onset of development of hypertension might be delayed by biological resilience.\(^{228,229}\) A study on the Framingham cohort supported this paradigm, as distinct change points of blood pressure trajectories were seen, identifying individuals with higher or lower risk of developing hypertension based on the timing of their change point.\(^{230}\) The timing of the onset of overt hypertension, whether it occurred during middle age or older age, could reflect the rate and onset of underlying vascular remodelling.\(^{228}\) However, several studies have highlighted the importance of even earlier recognition of trajectories leading to hypertension. Higher blood pressure trajectories in children and young adults have
been found to correlate with coronary atherosclerosis and subclinical atherosclerosis in middle age. A 23-year follow-up study of children aged 5–16 years in the Georgia Stress and Heart (GSH) Study found that subgroup blood pressure trajectories could predict subclinical cardiovascular risk factors (including intima-media thickness and left ventricular mass index) as early as in young adulthood.

Trajectories of BMI and body composition
In the last 5 years, there have been several publications on the relationship between BMI trajectories and adult cardiovascular risk. Latent class growth mixture modelling and other related methods are applied to identify subgroup patterns in large samples. Commonly, three to six distinct trajectories have been identified, depending on the definition of BMI categories and naming conventions. Not surprisingly, these studies uniformly identify the overweight/obese trajectories as being associated with higher cardiovascular risk.

An observational study of more than 5000 individuals over the life course in the China Health and Nutrition Survey found that individuals following a normal-overweight or overweight-obese pattern had higher risk of developing hypertension, hyperglycaemia and dyslipidaemia, compared to individuals maintaining a low or normal body weight. A recent German study following individuals from 4–18 years similarly found that males following an overweight trajectory from young age had higher levels of high-density lipoprotein (HDL) and the pro-inflammatory interleukin-18, whereas women following the same trajectory had significantly higher blood pressure compared to other trajectories.

Similarly, a recently published Swedish study collected birth weight as well as measurements of height and weight from centrally archived School Health Care records and from military conscription tests for all men born between 1945 and 1961 in Gothenburg, Sweden. Interestingly, men who became overweight during puberty (i.e. normal weight at 8 years and overweight at 20 years) had a substantially increased risk of COPD later in life, compared with men who were never overweight.

Recent findings from the UK population-based Avon Longitudinal Study of Parents and Children (ALSPAC) study, examining trajectories of lean and fat body mass in association with lung function parameters in children between 7 and 15 years, showed interesting differences in lung function development. Children of both sexes with higher lean BMI had consistently higher levels and growth rates of FVC and FEV1, whereas children with higher fat BMI had lower levels and growth rates of FEV1 and FEV1/FVC. These findings were adjusted for important confounders including smoking, PA, pubertal status and diet.

On the other hand, obesity might be protective against the development of emphysema. Multiple studies suggest that malnutrition and starvation may contribute to the development of emphysema. In a rat model, induced starvation was associated with aggravated elastase-induced injury, which was reversed with refedding. Autopsies undertaken by Jewish physicians documenting the effect of Nazi starvation policies in the Warsaw Ghetto found signs of emphysema in relatively young individuals. In addition, early levels of emphysema have been detected after chronic malnutrition, such as in patients with anorexia nervosa. Together, these data suggest that more pronounced fat deposition may potentially protect against the development of emphysema during the life course.

Trajectories of diabetes mellitus
Few studies have examined lifetime trajectories of diabetes mellitus. Large-scale data analysis of electronic health records including 70,000 individuals aged 46 years (±16) years identified a typical trajectory developing from hyperlipidaemia to hypertension, impaired fasting glucose and type II diabetes mellitus. An Australian study of 210 individuals followed up for 20 years found that blood glucose levels in the upper normal range at baseline were associated with lower grey/white matter volumes in the frontal cortices, associated with poorer cognitive functions and cerebral health later in life.

A Japanese study of non-diabetic individuals followed up for a mean of almost 10 years saw a steady increase in average blood glucose before a sharp increase followed by development of overt diabetes.

Unfavourable trajectories of fasting glucose and insulin resistance during young adulthood, >25 years before the development of diabetes, were associated with poorer cardiac function, including changes in diastolic function and left ventricular structure. These changes could not solely be explained by levels of fasting glucose and insulin resistance, indicating that unfavourable glucose trajectories not only predicted the development of diabetes, but also affected cardiac health later in life.

In line with this, the presence of diabetes has been shown to adversely affect respiratory function, resulting in a restrictive lung function pattern. Furthermore, subclinical impairment of lung function was seen in children with type 1 diabetes mellitus and was associated with disease duration and the degree of metabolic control. This might not surprise as the large vascular network and high collagen and elastin composition of the pulmonary system is prone to microvascular damage and non-enzymatic glycation in diabetes.

Trajectories of CKD
Foetal stressors are thought to result in a reduced number of nephrons at birth. As nephrons cannot regenerate, these numbers are lifelong. The number of functioning nephrons decreases with time, leading to a physiological decrease in glomerular filtration rate upon advancing age. As a response to this, the surface area of the remaining nephrons increase in a compensatory manner, so-called ‘nephron under-dosing’. This maladaptive response may cause systemic hypertension, increasing nephron destruction, albuminuria and later CKD through several mechanisms.

Multimorbidity trajectories
Clusters of comorbidities
It is evident that certain diseases tend to occur together in the same individual. Recent studies have
shown that COPD comorbidities tend to appear in clusters, identifying distinct disease phenotypes.\textsuperscript{198,250} A wide range of co-occurring diseases in an individual and the resulting complex data make it difficult to disentangle such patterns. Advanced techniques such as machine learning\textsuperscript{251} and a variety of clustering algorithms allow grouping of similar conditions in large data sets, allowing us to group patient characteristics, diseases and even genetic data into interpretable patterns.

Cluster analysis is increasingly popular in medical literature the last decade, and has increased our knowledge of disease patterns in both general cohorts and disease subgroups. A systematic review by Prados-Torres \textit{et al.} identified 97 clusters of multimorbidity, with three distinct clusters, namely a cardiometabolic, a mental health and a musculoskeletal cluster being the most prominent.\textsuperscript{252} Several heterogenous clusters without a clear pattern were also identified among the included studies.\textsuperscript{252} However, due to the cross-sectional nature of most of these studies, we still do not know much about the trajectories of the clusters, interactions of different disease expressions over time that define the clusters, temporal change of individuals from one cluster to another (Fig. 5), influences of lifestyle changes and pharmacotherapy on disease coexistence and how this affects later morbidity and mortality. Hopefully, future advances in this field could help us extract the possible causal underlying mechanisms of related diseases.

In a population-wide registry study, Danish researchers found that among almost 1200 significant disease trajectories, a few key diagnoses including COPD were central to disease progression.\textsuperscript{254} In the COPD cluster of diseases, a subsequent diagnosis of COPD was highly associated with an existing diagnosis of angina pectoris or atherosclerosis.\textsuperscript{254} These findings suggested a common pathophysiological pathway between the diseases, as well as a strong temporal pattern. A rapid progression to severe outcomes such as bacterial pneumonia, septicaemia, respiratory failure and death was seen when a diagnosis of COPD was established.\textsuperscript{254} Of further interest is the association with a later diagnosis of osteoporosis. Interestingly, the same study also identified asthma as the index disorder of a cluster network highly connected to later diabetes mellitus, renal and cardiovascular disorders.\textsuperscript{254}

Most studies on multimorbidity clusters have been conducted on individuals in their sixth decade of life and onwards. In this age group, many chronic diseases are already overt, and although such studies add valuable information about disease patterns, it tells us less about the dynamics of preclinical disease and how these are associated with premorbid risk factors. Following a well-defined cohort from the first decades of life and throughout the lifespan would be an ideal platform to study such lifetime disease trajectories. However, few existing cohorts are suitable for such extensive study designs. A 70-year follow-up study on the National Survey of Health and Development (NSHD) birth cohort following disease clusters and trajectories of 5000 individuals is ongoing,\textsuperscript{255} but is currently unpublished.

\textbf{CONCLUSIONS AND FUTURE IMPLICATIONS: BURDEN OF DISEASE, THE ROLE OF GENDER AND PATTERNS AND TRAJECTORIES OF MULTIMORBIDITY}

The burden of COPD depends on a complex interaction of both physical and psychological symptoms, the presence of other chronic conditions, and the influence of lifestyle and environmental factors. Understanding these patterns can help in developing personalized treatment strategies to improve outcomes and quality of life for individuals with multitudes of chronic conditions. Further research is needed to explore the temporal dynamics of these clusters and their impact on long-term outcomes and can be instrumental in guiding future clinical and policy decisions.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{multimorbidity_clusters.png}
\caption{Evolution of multimorbidity clusters and clinical trajectories of older adults with multimorbidity.\textsuperscript{253} Cluster analysis were done at baseline and after 6 and 12 years, and the change in cluster configuration was visualized using an alluvial plot, showing the temporal flow between the clusters. Open access was provided by https://creativecommons.org/licenses/by/4.0/ and no changes were made to the original content.}
\end{figure}

Respirology (2021) 26, 419–441 © 2021 Asian Pacific Society of Respirology.
of multimorbidity, the socioeconomic factors that increase the risk of COPD while reducing capacity to cope with its effects and structural issues that impede the delivery of adequate care to people with this condition across the health and social care system. Adopting a systematic approach to assessment and diagnosis allows clinicians to provide individualized management plans that address patient-specific needs. The use of COPD PROMs may help to develop a greater understanding of individual symptom burden, as will the availability of more treatment options which will depend on ongoing and innovative research. Early assessment and diagnosis may alter the course and impact individual symptoms have on a patient’s quality of life, but equally important are the development of management plans and pathways of care that reflect the complex and multicomponent nature of the disease. Multimodal interventions and therapies such as PR and active self-management plans are vital in empowering patients to reduce the burden of their disease, but clinicians and commissioners of care need to listen to patient voices, raise their expectations and ensure that the resources are provided to allow all people with COPD to access high quality care.

Many areas of the effects of gender on COPD pathogenesis, progression, presentation, treatment and outcomes are still very poorly understood, in particular the interactions between gender, genes and environment. There are significant differences between countries and exposures which variably influence airway disease development, phenotypes, diagnosis, interventions and impact in women. Across the world, these factors require much more detailed analysis and carefully performed prospective studies to fully assess the effects of treatment in real-world settings, in addition to carefully conducted in vitro studies to understand mechanisms. There is a great deal more to do in understanding the effect of gender in the evolution and outcomes of COPD.

Finally, COPD is inevitably associated with comorbidity and multimorbidity, which impacts importantly on overall morbidity and mortality. The characterization of extrapulmonary manifestations and comorbidity in an individual with COPD partly defines the clinical COPD phenotype. Abnormal lung development early in life increases the risk of COPD, but also the incidence for other diseases later in life. When exploring the early origins of COPD and studying lung function trajectories that lead to COPD, this leads inherently to the interaction with development or non-development of comorbidities. Multiorgan disease trajectories have been described as well as interactions between organ trajectories. We need to increase our understanding on (i) How early life risk factors commonly influence trajectories of COPD and other diseases; (ii) How different diseases develop in relation to each other in a temporal way; and (iii) How this ultimately leads to different multimorbidity patterns, commonly seen in COPD. This knowledge could lead to common preventive strategies, as well as the development of treatment strategies that alter the course of disease, not only for COPD, but also for a patient with COPD as one of the problems.

The Authors:
S.C.B. is a specialist respiratory physiotherapist in her first year of an NIHR fellowship at the National Heart and Lung Institute, Imperial College London. She has worked in COPD research for 6 years at the Royal Brompton Hospital and her PhD is focused on improving patient access and selection for lung volume reduction therapies. Other research interests include PA, PR and patient experience. N.S.H. is a Reader in Respiratory Medicine at the National Heart and Lung Institute, Imperial College London and the Royal Brompton Hospital where he runs the advanced COPD service. His research focuses on addressing exercise and activity limitation in COPD in areas including pulmonary physiology and lung volume reduction, skeletal muscle impairment and PR. He is also active in tobacco control advocacy and is Chair of Action on Smoking and Health. K.W. is a Researcher at the British Lung Foundation. M.Z. is respiratory physician at Bordeaux University Hospital, France, and member of the COPD-Center which focuses on physiopathology of COPD, Centre de Recherche cardio-thoracique de Bordeaux. She is member of the managing committee of the French Respiratory Society (SPLF) and the ERS. C.J. is an academic respiratory physician, Head of the Respiratory Group at the George Institute for Global Health and Professor, Respiratory Medicine, UNSW Sydney. Her research interests focus on best management of airways diseases, assessing pharmacological and non-pharmacological interventions. She chairs the Lung Foundation Australia which is a patient facing organisation raising funds, supporting research and providing patient and health professional resources for people with lung disease. S.A.A.V. is a resident doctor in respiratory medicine at Levanger Hospital, Norway. She recently defended her PhD on COPD and comorbidities at the Norwegian University of Science and Technology, NTNU. Research interests include obstructive lung diseases and their association with comorbidity and multimorbidity, with an emphasis on osteoporosis, anxiety and depression. L.E.G.W.V. is respiratory physician at Sahlgrenska University Hospital and the head of the COPD-Center which focuses on novel patient-centred and multi-disciplinary treatment of patients with COPD and COPD-related research. He is university lecturer at the University of Gothenburg (GU) with focus on COPD. He is member of the managing committee of the Swedish National Airway Register and the management committee of the Krefting Research Center at Gothenburg University.

Acknowledgements: We thank Prentis Hancock and Moira Van Biene for their input describing their experience of COPD and for helpful comments to improve this manuscript.

Disclosure statement: M.Z. has acted as a paid consultant to Novartis, Boehringer Ingelheim, Chiesi, GSK and fondation pour la recherche médicale, and has received funding for research carried out in this work from Astra Zeneca and Novartis.

Abbreviations: AIDS, acquired immune deficiency syndrome; CBT, cognitive behavioural therapy; CBS, chronic breathlessness syndrome; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; ED, emergency department; ERS, European Respiratory Society; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; GWAS, genome-wide association study; HRQoL, health-related quality of life; NCD, non-communicable disease; NICE, National Institute for Clinical Excellence; PA, physical activity; PR, pulmonary rehabilitation; PROM, patient-reported outcome measure

REFERENCES

1. GBD 2015 Chronic Respiratory Disease Collaborators. Global, regional, and national deaths, prevalence, disability-adjusted life
Contemporary perspectives in COPD

years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet Respir. Med. 2017; 5: 691–706.

2 Burney P. Chronic respiratory disease – the acceptable epidemic? Clin. Med. 2017; 17: 29–32.

3 World Health Organization. Global progress report on implementation of the WHO Framework Convention on Tobacco Control 2018. 2018. [Accessed 1 Feb 2021]. Available from URL: https://www.who.int/tct/reporting/WHO-FCTC-2018_global_progress_report.pdf

4 Doiron D, de Hoogh K, Probst-Hensch N, Fortier I, Cai Y, De Matteis S, Hansell AL. Air pollution, lung function and COPD: results from the population-based UK Biobank study. Eur. Respir. J. 2019; 54: 1802140.

5 Kurmi OP, Semple S, Simkhada P, Smith WCS, Ayres JG. COPD and chronic bronchitis risk of indoor air pollution from solid fuel: a systematic review and meta-analysis. Thorax 2010; 65: 221–8.

6 Quaderi SA, Hurst JR. The unmet global burden of COPD. Glob. Health Epidemiol. Genom. 2018; 3: e4.

7 Williams S, Sheikh A, Campbell H, Fitch N, Griffiths C, Hewittman PM, Jordan RE, Katikedi SV, Tsiligianni I, Obaşi A. Respiratory research funding is inadequate, inequitable, and a missed opportunity. Lancet Respir. Med. 2020; 8: e67–8.

8 Hopkinson N. Respiratory disease is in the long term plan. BMJ 2019; 364: l1413.

9 Philip K, Gaduzo S, Rogers J, Laffan M, Hopkinson NS. Patient experience of COPD care: outcomes from the British Lung Foundation Patient Passport. BMJ Open Respir. Res. 2019; 6: e000478.

10 Elbeheiry AF, Quint JK, Rogers J, Laffan M, Polkey MI, Hopkinson NS. Patterns of breathlessness and associated consulting behaviour: results of an online survey. Thorax 2019; 74: 814–7.

11 Jones RCM, Price D, Ryan D, Griffiths C, Hewittman PM, Jordan RE, Katikedi SV, Tsiligianni I, Obaşi A. Opportunities to diagnose chronic obstructive pulmonary disease in routine care in the UK: a retrospective study of a clinical cohort. Lancet Respir. Med. 2014; 2: 267–76.

12 Royal College of Physicians. National COPD primary care audit 2014–15 national report (Wales). 2017. [Accessed 24 Mar 2017]. Available from URL: https://www.rcplondon.ac.uk/projects/outputs/primary-care-time-take-breath.

13 Whittaker HB, Connell O, Campbell J, Elbeheiry AF, Hopkinson NS, Quint JK. Eligibility for lung volume reduction surgery in patients with COPD identified in a UK primary care setting. Chest 2020; 157: 276–85.

14 Buttery SC, Lewis A, Oey I, Hargrave J, Waller D, Steiner M, Shah PL, Kemp SV, Jordan S, Hopkinson NS. Patient experience of lung volume reduction procedures for emphysema: a qualitative service improvement project. ERI Open Res. 2017; 3: 00031-2017.

15 Buxton SC, Lewis A, Kemp SV, Banya W, Quint JK, Steiner MC, Hopkinson NS. Lung volume reduction eligibility in patients with COPD completing pulmonary rehabilitation: results from the UK National Asthma and COPD Audit Programme. BMJ Open 2020; 10: e040942.

16 Miravitlles M, Ribera A. Understanding the impact of symptoms on the burden of COPD. Respir. Res. 2017; 18: 67.

17 Gardener AC, Ewing G, Kuhn I, Farquhar M. Support needs of patients with COPD: a systematic literature search and narrative review. Int. J. Chron. Obstruct. Pulmon. Dis. 2016; 13: 1021–35.

18 Gershon AS, Dolmage TE, Stephenson A, Jackson B. Chronic obstructive pulmonary disease and socioeconomic status: a systematic review. COPD 2012; 9: 216–26.

19 Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. Lancet 2012; 380: 37–43.

20 Vanleteren LE, Spruit MA, Groenen M, Gaaffron S, van Empel VP, Bruijnzeel PL, Rutter EP, Op ’t Roodt J, Wouters EF, Franssen FM. Clusters of comorbidities based on validated objective measurements and systemic inflammation in patients with chronic obstructive pulmonary disease. Am. J. Respir. Crit. Care Med. 2013; 187: 728–35.

21 Hopkinson NS, Molyneux A, Pink J, Harrissngic M. Chronic obstructive pulmonary disease: diagnosis and management: summary of updated NICE guidance. BMJ 2019; 369: i4486.

22 Hodson M, Roberts CM, Andrew S, Graham L, Jones PW, Yorke J. Development and first validation of a patient-reported experience measure in chronic obstructive pulmonary disease (PREM-C9). Thorax 2019; 74: 600–3.

23 Gimeno-Santos E, Raste Y, Demeyer H, Louvaris Z, de Jong C, Rabinovich RA, Hopkinson NS, Polkey ML, Vogiatzis I, Tabberer M et al; PROactive Consortium. The PROactive instruments to measure physical activity in patients with chronic obstructive pulmonary disease. Eur. Respir. J. 2015; 46: 988–1000.

24 Dodd JW, Hogg L, Nolan J, Jefferd H, Grant A, Lord VM, Falzon C, Garrad R, Lee C, Polkey MI et al. The COPD assessment test (CAT): response to pulmonary rehabilitation. A multi-centre, prospective study. Thorax 2011; 66: 425–9.

25 Kelly JL, Ramsay O, Smith C, Lord VM, Shrikrisilna D, Jones PW, Polkey MI, Hopkinson NS. Health status assessment in routine clinical practice: the chronic obstructive pulmonary disease assessment test score in outpatients. Respiration 2012; 84: 193–9.

26 Miravitlles M, Worth H, Soler Cataluna JJ, Price D, De Benedetto F, Roche N, Godtfredsen NS, van der Molen T, Löfdahl C-G, Padullés L et al. Observational study to characterise 24-hour COPD symptoms and their relationship with patient-reported outcomes: results from the ASSESS study. Respir. Res. 2014; 15: 122–2.

27 Babe KF. Improving dyspnea in chronic obstructive pulmonary disease: optimal treatment strategies. Proc. Am. Thorac. Soc. 2006; 3: 270–5.

28 Kardos P, Vogelmeier C, Worth H, Buhl R, Lossi NS, Malländer C, Crieé C-P. A two-year evaluation of the ‘real life’ impact of COPD on patients in Germany: the DACCORD observational study. Respir. Med. 2013; 124: 57–64.

29 Shrikrisilna D, Hopkinson NS. Chronic obstructive pulmonary disease: consequences beyond the lung. Clin. Med. (Lond.) 2012; 12: 71–4.

30 Gimeno-Santos E, Frei A, Steurer-Stey C, de Battile J, Rabinovich RA, Raste Y, Hopkinson NS, Polkey MI, van Remoortel H, Troosters T et al; PROactive Consortium. Determinants and outcomes of physical activity in patients with COPD: a systematic review. Thorax 2014; 69: 731–9.

31 Hopkinson NS, Polkey MI. Does physical inactivity cause chronic obstructive pulmonary disease? Clin. Sci. (Lond.) 2010; 118: 565–72.

32 Shrikrisilna D, Patel M, Tanner RJ, Seymour JM, Connolly BA, Puthucheary ZA, Walsh SL, Bloch SA, Sidhu PS, Hart N et al. Quadriceps wasting and physical inactivity in patients with COPD. Eur. Respir. J. 2012; 40: 1115–22.

33 Strain T, Wijnlaade K, Dempsey PC, Sharp SJ, Pearce M, Jeon J, Lindsay T, Wareham N, Brage S. Wearable-device-measured physical activity and future health risk. Nat. Med. 2020; 26: 1385–91.

34 Waschki B, Kirsten A, Holz O, Müller KC, Meyer T, Watz H, Magnussen H. Physical activity is the strongest predictor of all-cause mortality in patients with COPD: a prospective cohort study. Chest 2011; 140: 331–42.

35 Aitsi-Selmi A, Hopkinson NS. Breathlessness, physical activity and sustainability of healthcare. Eur. Respir. J. 2015; 45: 284–5.

36 Boutou AK, Karrar S, Hopkinson NS, Polkey MI. Anemia and survival in chronic obstructive pulmonary disease: a dichotomous rather than a continuous predictor. Respiration 2013; 85: 126–31.

37 Johnson MJ, Yorke J, Hansen-Flaschen J, Lansing R, Ekström M, Löfdahl C-G, Padullés L et al. Observational study to characterise 24-hour COPD symptoms and their relationship with patient-reported outcomes: results from the ASSESS study. Respir. Res. 2014; 15: 122–2.

38 Galbraith S, Fagan P, Perkins P, Lynch A, Booth S. Does the use of a handheld fan improve chronic dyspnea? A randomized, controlled, crossover trial. J. Pain Symptom Manage. 2010; 39: 831–8.
39 Luckett T, Phillips J, Johnson MJ, Farquhar M, Swan F, Assen T, Bhattachar J, Boob S. Contributions of a hand-held fan to self-management of chronic breathlessness. Eur. Respir. J. 2017; 50: 1700262.

40 Smallwood N, Le B, Currow D, Irving L, Philip J. Management of refractory breathlessness with morphine in patients with chronic obstructive pulmonary disease. Intern. Med. J. 2015; 45: 898–904.

41 O’Donnell DE, Milne KM, James MD, de Torres JP, Neder JA. Dyspnea in COPD: new mechanistic insights and management implications. Adv. Ther. 2020; 37: 41–60.

42 Harb N, Foster JM, Dohler CC. Patient-perceived treatment burden of chronic obstructive pulmonary disease. Int. J. Chron. Obstruct. Pulmon. Dis. 2017; 12: 1641–52.

43 Bourbeau J, Lavoie KL, Sedeno M, De Sousa D, Erzen D, Hamilton A, Maltais F, Troosters T, Leidy N. Behaviour-change intervention in a multicentre, randomised, placebo-controlled COPD study: methodological considerations and implementation. BMJ Open 2016; 6: e010109.

44 Troosters T, Bourbeau J, Maltais F, Leidy N, Erzen D, De Sousa D, Korducki L, Hamilton A. Enhancing exercise tolerance and physical activity in COPD with combined pharmacological and non-pharmacological interventions. PHYSACTO randomised, placebo-controlled study design. BMJ Open 2016; 6: e010106.

45 Mendoza L, Horta P, Espinoza J, Aguilera M, Balmaceda N, Castro A, Ruiz M, Diaz O, Hopkinson NS. Pedometers to enhance physical activity in COPD: a randomised controlled trial. Eur. Respir. J. 2015; 45: 347–54.

46 Jones PW, Brusselle G, Dal Negro RW, Ferrer M, Dal Negro R, Ferrer M, Kardos P, Durack J, Maltais F, Lavoie KL, Sedeno M, De Sousa D, Erzen D, Hamilton A, Maltais F, Troosters T, Leidy N. Behaviour-change intervention in a multicentre, randomised, placebo-controlled COPD study: methodological considerations and implementation. BMJ Open 2016; 6: e010109.

47 Williams RL, Morgan MR, Brown MJ, Morley SA. Impact of physical activity in COPD: a systematic review and meta-analysis. BMJ Open 2016; 6: e010106.
Contemporary perspectives in COPD

Ayermer I et al. Progression of physical inactivity in COPD patients: the effect of time and climate conditions – a multicenter prospective cohort study. Int. J. Chron. Obstruct. Pulmon. Dis. 2019; 14: 1979–92.

García-Ayermer I, Puhlan MA, Corriol-Rohou S, de Jong C, Demeyer H, Dobbels F, Erzen D, Frei A, Gimeno-Santos E, Hopkinson NS et al. Validity and responsiveness of the Daily- and Clinical visit-PRoActive Physical Activity in COPD (D-PPAC and C-PPAC) instruments. Thorax 2021; 76: 228–38.

Patel MS, Mohan D, Andersson YM, Baz M, Samantha Kon SC, Brighton LJ, Bristowe K, Bayly J, Ogden M, Farquhar M, Evans CJ, Boutou AK, Tanner RJ, Lord VM, Hogg L, Nolan J, Jefford H, Zhang WZ. The origins of chronic obstructive pulmonary disease: Bu F, Philip K, Fancourt D. Social isolation and loneliness as risk factors for anxiety and depression in adults with chronic obstructive pulmonary disease. Docherty AB, Harrison EM, Green CA, Hardwick HE, Pius R, Norman L, Holden KA, Read JM, Dondelinger F, Carson G et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. BMJ 2020; 369: m1985.

Respirology (2021) 26, 419–441 © 2021 Asian Pacific Society of Respirology.
Chapman KR, Tashkin DP, Pye DJ. Gender bias in the diagnosis of COPD. *Chest* 2001; 119: 1691–5.

Lamprecht B, McBurnie MA, Vollmer WM, Gudmundsson G, Welte T, Nizankowska-Mogilnicka E, Studnicka M, Bateman E, Anto JM, Burney P et al. COPD in never smokers: results from the population-based burden of obstructive lung disease study. *Chest* 2011; 139: 752–63.

Buist AS, McBurnie MA, Vollmer WM, Gillespie S, Burney P, Mannino DM, Menezes AM, Sullivan SD, Lee TA, Weiss KB et al. International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. *Lancet* 2007; 370: 741–50.

Watson L, Vonk JM, Löfdahl CG, Pride NB, Pauwels RA, Laitinen LA, Schouten JP, Postma DS. Predictors of lung function and its decline in mild to moderate COPD in association with gender: results from the Eosuroc study. *Respir. Med.* 2006; 100: 746–53.

Silverman M, Pedersen S, Grigg J. Measurement of airflow in children. *Introduction*. Am. J. Respir. Crit. Care Med. 2000; 162: S1.

Lange P, Celli B, Agusti A, Boje Jensen G, Divo M, Faner R, Gershon AS, Warner L, Cascagnette P, Victor JC, To T. Lifetime risk of developing chronic obstructive pulmonary disease: the effect of different diagnostic criteria. Analysis of the SAPALDIA 2 cohort study. *Thorax* 2012; 67: 600–5.

Wang S, Gong W, Tian Y. Voluntary pulmonary function screening in children. *Introduction*. Am. J. Respir. Crit. Care Med. 2009; 180: S1.

DeMeo DL. Gender differences in COPD: are women more susceptible to smoking effects than men? *Thorax* 2010; 65: 480–5.

Jordan RE, Miller MR, Lam KB, Cheng KK, Marsh J, Adab P. Sex, gender and chronic obstructive pulmonary disease: the effect of different diagnostic criteria. Analysis of the Health Survey for England. *Thorax* 2012; 67: 600–5.

Ulrick C. Smoking and mortality in women: “smoke like a man, die (at least) like a man”. *Eur. Respir. Monogr.* 2003; 25: DOI: 10.1183/1025488x.00025009.

Downs SH, Brändli O, Zellweger J-P, Schindler C, Künzli N, Gerkase MB, Burdett L, Betschart R, Zemp E, Frey M et al.; SAPALDIA Team. Accelerated decline in lung function in smoking women with airway obstruction: SAPALDIA 2 cohort study. *Respir. Res.* 2005; 6: 45.

Gershon AS, Warner L, Cascagnette P, Victor JC, To T. Lifetime risk of developing chronic obstructive pulmonary disease: a longitudinal population study. *Lancet* 2011; 378: 991–6.

Blanc PD, Iribarren C, Trupin L, Earnest G, Katz PP, Balles M, Sidney S, Eisner MD. Occupational exposures and the risk of COPD: dusty trades revisited. *Thorax* 2009; 64: 6–12.

Dumas O, Varraso R, Boggs KM, Quinot C, Zock J-P, Hennepker PK, Speizer FE, Le Moual N, Camargo CA Jr. Association of occupational exposure to disinfectants with incidence of chronic obstructive pulmonary disease among US female nurses. *JAMA Netw. Open*; 2019; 2:e1913563.

Eduard W, Pearce N, Douwes J. Chronic bronchitis, COPD, and lung function in farmers: the role of biological agents. *Chest* 2009; 136: 716–25.

Rinsky JL, Richardson DB, Kreiss K, Nylander-French I, Beane Freeman LE, London SJ, Hennepker PK, Hoppin JA. Animal production, insecticide use and self-reported symptoms and diagnoses of COPD, including chronic bronchitis, in the Agricultural Health Study. *Environ. Int.* 2019; 127: 764–72.

Alif SM, Dharmage S, Benke G, Dennekamp M, Burgess J, Perret JL, Lodge C, Morrison S, Johns DP, Giles G et al. Occupational exposure to solvents and lung function decline: a population based study. *Thorax* 2019; 74: 650–8.

Torek K, Järvelin M. Effect of occupational exposure to vapors, gases, dusts, and fumes on COPD mortality risk among Swedish construction workers: a longitudinal cohort study. *Chest* 2014; 145: 992–7.

Siddharthan T, Grigsby MR, Goodman D, Chowdhury M, Rubinstein A, Irazola V, Gutierrez L, Miranda JJ, Bernabe-Urrea A, Alam D et al. Association between household air pollution exposure and chronic obstructive pulmonary disease outcomes in 13 low- and middle-income country settings. *Am. J. Respir. Crit. Care Med.* 2018; 197: 611–20.

Ramírez-Venegas A, Velázquez- Uncal M, Pérez-Hernández R, Guzmán-Boulloud NE, Falfán-Valencia RA, Mayar-Mayra ME, Aranda-Chávez A, Sansores RH. Prevalence of COPD and respiratory symptoms associated with biomass smoke exposure in a sub-urban area. *Int. J. Chron. Obstruct. Pulmon. Dis.* 2018; 13: 1727–34.

Camp PG, Ramírez-Venegas A, Sansores RH, Alva LF, McDougal JE, Sin DD, Paré PD, Müller NL, Silva CIS, Rojas CE et al. COPD phenotypes in biomass smoke- versus tobacco smoke-exposed Mexican women. *Eur. Respir. J.* 2014; 43: 725–34.

Tom A, Cheung A, Wright JL, Zhou S, Kirby M, Coxson HO, Lam S, Man SF, Sin DD. Sex differences in airway remodeling in a mouse model of chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* 2018; 193: 825–32.

Roberts NJ, Patel IS, Partridge MR. The diagnosis of COPD in primary care: gender differences and the role of spirometry. *Respir. Med.* 2011; 111: 60–3.

Wheaton AG, Pleasants RA, Croft JB, Obar JA, Heldair K, Mannino DM, Liu Y, Strange C. Gender and asthma-chronic obstructive pulmonary disease overlap syndrome. *J. Asthma* 2016; 53: 720–31.

Nabaran K, Azpeitia A, Cantoni J, Miravitlles M. Impairment of quality of life in women with chronic obstructive pulmonary disease. *Eur. Respir. Med.* 2012; 106: 367–73.

Raherison C, Tillie-Leblond I, Prudhomme A, Taillé C, Biron E, Noencent-Ejnaini C, Mathieu B, Ostinelli J. Clinical characteristics and quality of life in women with COPD: an observational study. *RMC Women’s Health 2014*: 14: 31.

Zyaman M, Burgel P-R, Court-Fortune I, Brinchault-Rabin G, Nesme-Meyer P, Surpas P, Deslée G, Perez T, Le Rouzic O, Jebrak G et al.; Initiatives BPCO Scientific Committee and Investigators. Relationship between gender and survival in a real-life cohort of patients with COPD. *Respir. Res.* 2019; 20: 191.

Roche N, Deslée G, Caillaud D, Brinchault G, Court-Fortune I, Nesme-Meyer P, Surpas P, Escamilla R, Perez T, Chanez P et al.; INITIATIVES BPCO Scientific Committee. Impact of gender on COPD expression in a real-life cohort. *Respir. Res.* 2014; 15: 20.

Prescott E, Bjerg AM, Andersen PK, Lange P, Vestbo J. Gender difference in smoking effects on lung function and risk of hospitalization for COPD: results from a Danish longitudinal population study. *Eur. Respir. J.* 1997; 10: 822–7.

Coxson HO, Dirksen A, Edwards LD, Yates JC, Agusti A, Bakke P, Calverley PM, Celli B, Crim C, Duvoix A et al. The presence and progression of emphysema in COPD as determined by CT scanning and biomarker expression: a prospective analysis from the ECLIPSE study. *Lancet Respir. Med.* 2013; 1: 129–36.

DeMeo DL, Ramagopalan S, Kavati A, Vegesna A, Han MK, Yadao A, Wilcox TK, Make BJ. Women manifest more severe COPD symptoms across the life course. *Int. J. Chron. Obstruct. Pulmon. Dis.* 2018; 13: 3021–9.

Stoldt D, Kostikas K, Loeefroth E, Fogel R, Gutzwiller FS, Conti V, Cao H, Clemens A. Differences in COPD exacerbation risk between women and men: analysis from the UK clinical practice research datalink data. *Chest* 2019; 156: 674–84.
Molinari N, Chanez P, Roche N, Ahmed E, Vachieri I, Bourdin A. Rising total costs and mortality rates associated with admissions due to COPD exacerbations. Respir. Res. 2016; 17: 149.

Goto T, Yoshida K, Faridi MK, Camargo CA Jr, Hasegawa K. Contribution of social factors to readmissions within 30 days after hospitalization for COPD exacerbation. BMC Pulm. Med. 2020; 20: 107.

Vestbo J, Prescott E, Lange P, Schnohr P, Jensen G. Vital prognosis after hospitalization for COPD: a study of a random population sample. Respir. Med. 1998; 92: 772-6.

Ekström MP, Jogrèus C, Ström KE. Comorbidity and sex-related differences in mortality in oxygen-dependent chronic obstructive pulmonary disease. PLoS One 2012; 7: e35066.

Bade BC, DeLycke EC, Ramsey C, Skanderson M, Crothers K, Bennett BC, DeRycke EC, Ramsey C, Skanderson M, Crothers K, Haskell S, Bean-Mayberry B, Brandt C, Bastian LA, Akgün KM. Sex differences in veterans admitted to the hospital for chronic obstructive pulmonary disease exacerbation. Ann. Am. Thorac. Soc. 2019; 16: 707-14.

Roche N, Antoniadis A, Hess D, Li PZ, Kelkel E, Leroy S, Pison C, Burgel PR, Aguilaniu B. Are there specific clinical characteristics associated with physician’s treatment choices in COPD? Respir. Med. 2019; 149: 189-97.

Delgado A, Saletti-Cuesta L, López-Fernández LA, Gil-Garrido N, Mosteiro-Añón M, Mouronte-Roibas C, Fernández-Villar A. Social inequalities of patients hospitalized for COPD exacerbations. A gender analysis. Arch. Bronconeumol. 2020; 56: 84-9.

Castañ-Abad MT, Montserrat-Cardapleva J, Godoy P, Marsal JR, Ortega M, Alsedà M, Barbé F. Diabetes as a risk factor for severe exacerbation and death in patients with COPD: a prospective cohort study. Eur. J. Public Health 2020; 30: 822-7.

de Torres JP, Casanova C, Montijo de Garçini A, Aguirre-Jaime A, Celli BR. Gender and respiratory factors associated with dyspnea in chronic obstructive pulmonary disease. Respir. Rev. 2007; 8: 18.

Doucet M, Rochette I, Hamel D. Incidence, prevalence, and mortality trends in severe obstructive pulmonary disease over 2001 to 2011: a public health point of view of the burden. Can. Respir. J. 2016; 2016: 7518287.

Jain NK, Thakkar MS, Jain N, Rohan KA, Sharma M. Chronic obstructive pulmonary disease: does gender really matter? Lung India 2011; 28: 258-62.

Gershon A, Hjee V, Victor JC, Wilton A, Wu R, Day A, To T. Mortality trends in women and men with COPD in Ontario, Canada, 1996-2012. Thorax 2015; 70: 121-6.

Müllerova H, Maselli DJ, Locantore N, Vestbo J, Hurst JR, Wedzicha JA, Bakke P, Agusti A, Anzueto A. Hospitalized exacerbations of COPD: risk factors and outcomes in the ECLIPSE cohort. Chest 2015; 147: 999-1007.

Beeth KM, Glaab T, Stowasser S, Schmidt H, Fabbri LM, Rabe KF, Vogelmeier CF. Characterisation of exacerbation risk and exacerbator phenotypes in the POET-COPD trial. Respir. Res. 2013; 14: 116.

Celli B, Vestbo J, Jenkins CR, Jones PW, Ferguson GT, Calverley PM, Yates JC, Anderson JA, Willits LR, Wise RA. Sex differences in mortality and clinical expressions of patients with chronic obstructive pulmonary disease. The TORCH experience. Am. J. Respir. Crit. Care Med. 2011; 183: 317-22.

Sundh J, Johansson G, Larsson K, Lindén A, Löfdahl CG, Sandström T, Janson C. The phenotype of concurrent chronic bronchitis and frequent exacerbations in patients with severe COPD attending Swedish secondary care units. Int. J. Chron. Obstruct. Pulmon. Dis. 2015; 10: 2327-34.

Golpe R, Mengual-Macenlle N, Martín-Robles I, Sanjuán-López P, Pérez de Llano LA. Prognostic value of multidimensional indices in ambulatory COPD patients. Eur. J. Intern. Med. 2015; 26: e389-e9.

McGarvey L, Lee AJ, Roberts J, Gruffydd-Jones K, McKnight E, Haughney J. Characterisation of the frequent exacerbator phenotype in COPD patients in a large UK primary care population. Respir. Med. 2015; 109: 328-37.

Fuhrmann C, Moutengou E, Roche N, Delmas MC. Prognostic factors after hospitalization for COPD exacerbation. Rev. Mal. Respir. 2017; 34: 1-18.

Lindberg A, Larsson LG, Muellerova H, Rönmark E, Lundbäck B. Up-to-date on mortality in COPD – report from the OLIN COPD study. BMC Pulm. Med. 2012; 12: 1.

Johansson G, Mushnikov V, Bäckström T, Engström A, Khalid J, Wall J, Hovi F. Exacerbations and healthcare resource utilization among COPD patients in a Swedish registry-based nation-wide study. BMC Pulm. Med. 2018; 18: 17.

Tsi CL, Clark S, Cylhuka RK, Rowe BH, Camargo CA Jr. Factors associated with hospital admission among emergency department patients with chronic obstructive pulmonary disease exacerbation. Acad. Emerg. Med. 2007; 14: 6-14.

Gershon A, Thruchelvam D, Moineddin R, Zhao XY, Hjee J, To T. Forecasting hospitalization and emergency department visit rates for chronic obstructive pulmonary disease. A time-series analysis. Ann. Am. Thorac. Soc. 2017; 14: 867-73.

Sundh J, Johansson G, Larsson K, Lindén A, Löfdahl CG, Johansson C, Sandström T. Comorbidity and health-related quality of life in patients with severe chronic obstructive pulmonary disease attending Swedish secondary care units. Int. J. Chron. Obstruct. Pulmon. Dis. 2015; 10: 173-83.

Martínez CH, Raparla S, Pauschinat CA, Giardino ND, Rogers B, Beresford J, Bentkover JD, Schachtner-Appel A, Curtis JL, Martinez FJ et al. Gender differences in symptoms and care delivery for chronic obstructive pulmonary disease. J. Women’s Health (Larchmt) 2012; 21: 1267-74.
Mamary AJ, Stewart JJ, Kinney GL, Hokanson JE, Shenoy K, Dransfield MT, Foreman MG, Vance GB, Criner GJ. Race and gender disparities are evident in COPD underdiagnoses across all severities of measured airflow obstruction. *Chronic Obstr. Pulm. Dis.* 2018; 5: 177–84.

Connett JE, Murray RP, Buist AS, Bailey WC, Lindgren PG, Owens GR. Changes in smoking status affect women more than men: results of the Lung Health Study. *Am. J. Epidemiol.* 2003; 157: 973–9.

Tsiligianni I, Rodríguez MR, Lisspers K, LeeTan T, Infantino A. Call to action: improving primary care for women with COPD. *NPJ Prim. Care Respir. Med.* 2017; 27: 11.

Pauwels RA, Lofäld CG, Laitinen NA, Schouten JP, Postma DS, Wedzicha JA, Singh D, Tsiligianni I, Jenkins C, Fucile S, Fogel R, Pomerleau CS, Pomerleau OF, Garcia AW. Biobehavioral research. © 2021 Asian Paci

Barker DJ. The developmental origins of chronic adult disease. *Lancet Respir. Med.* 2018; 6: 535–44.

Youth RP, Hopkins R, Eaton TE. Forced expiratory volume in one second of exacerbating COPD patients by gender: a post-hoc analysis in the FLAME study. *Respir. Res.* 2019; 20: 4.

Tsiligianni I, Mezi K, Fucile S, Kostikas K, Shen S, Banerji D, Fogel R. Response to inhaled glycopyrronium and salmeterol/fluticasone in exacerbating COPD patients by gender: a post-hoc analysis in the FLAME study. *Respir. Res.* 1994; 5: 1056–61.

Pomerleau CS, Pomerleau OF, Garcia AW. Biobehavioral research on nicotine use in women. *Respirology* 1994; 150: 1256–61.

Tashkin D, Kanner R, Bailey W, Buist S, Anderson P, Nides M, Gonzales D, Dozier G, Patel MK, Jamerson B. Smoking cessation in patients with chronic obstructive pulmonary disease: a double-blind, placebo-controlled, randomised trial. *Lancet* 2001; 357: 1571–5.

Moore SM, Kramer FM. Women’s and men’s preferences for cardiac rehabilitation program features. *J. Cardiopulm. Rehabil.* 1996; 16: 163–8.

Agusti A, Noell G, Brugada J, Faner R. Lung function in early adulthood and health in later life: a transgenerational cohort analysis. *Lancet Respir. Med.* 2017; 5: 935–45.

Agusti A, Faner R. Lung function trajectories in health and disease. *Lancet Respir. Med.* 2019; 7: 358–64.

Vasquez MM, Zhou M, Hu C, Martinez FD, Guerra S. Low lung function in young adult life is associated with early mortality. *Am. J. Respir. Crit. Care Med.* 2017; 195: 1399–401.

Young RP, Hopkins R, Eaton TE. Forced expiratory volume in one second: not just a lung function test but a marker of premature death from all causes. *Eur. Respir. J.* 2007; 30: 616–22.

Barker DJ. The developmental origins of chronic adult disease. *Acta Paediatr.* Suppl. 2004; 93: 26–33.

Jornayvaz FR, Selz R, Tappy L, Theinze GC. Metabolism of oral glucose in children born small for gestational age: evidence for an impaired whole body glucose oxidation. *Metabolism* 2004; 53: 847–51.

Cameron N, Demethar EW. Critical periods in human growth and their relationship to diseases of aging. *Am. J. Phys. Anthropol.* 2002; 119(Suppl. 35): 159–84.

Janssen I, Leblanc AG. Systematic review of the health benefits of physical activity and fitness in school-aged children and youth. *Int. J. Behav. Nutr. Phys. Act.* 2010; 7: 40.

Agusti A. 2020. The Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for prevention, diagnosis and management of COPD. 2020. [Accessed 1 Feb 2021]. Available from URL: https://goldcopd.org/gold-reports/

Melen E, Guerra S. Recent advances in understanding lung function development. *F1000Res.* 2017; 6: 726.

Butt SY, Lodge CJ, Burgess JA, Losei AJ, Perret J, Biu MQ, Bowatte G, Gurin L, Johns DP, Thompson BR et al. Childhood predictors of lung function trajectories and future COPD risk: a prospective cohort study from the first to the sixth decade of life. *Lancet Respir. Med.* 2018; 6: 535–44.

Martinez FD. Early-life origins of chronic obstructive pulmonary disease. *N. Engl. J. Med.* 2016; 375: 871–8.

McGeachie MJ, Yates KP, Zhou X, Guo F, Sternberg AL, Van Natta ML, Wise RA, Szefler SJ, Sharma S, Kho AT et al. Patterns of growth and decline in lung function in persistent childhood asthma. *N. Engl. J. Med.* 2016; 374: 1842–52.

Chitk RC. Development of the lung. *Cell Tissue Res.* 2017; 367: 427–44.

Burrows B, Cline MG, Knudson RJ, Taussig LM, Lebowitz MD. A descriptive analysis of the growth and decline of the FVC and FEV1. *Chest* 1983; 83: 717–24.

Hall R, Hall IP, Sayers I. Genetic risk factors for the development of pulmonary disease identified by genome-wide association. *Respiratory* 2019; 24: 204–14.

Wain LV, Shrine N, Artigas MS, Erzurumlougu AM, Norbert V, Bossini-Castillo L, Obediat MD, Henry AP, Portelli MA, Hall RJ et al. Genome-wide association analyses for lung function and chronic obstructive pulmonary disease identify new loci and potential druggable targets. *Nat. Genet.* 2017; 49: 416–25.

Dekker HT, Burrows K, Felix JF, Salas LA, Nedeljkovic I, Yao J, Rivas-Shimman SL, Ruiz-Arenas C, Amin N, Bustamante M et al. Newborn DNA-methylation, childhood lung function, and the risks of asthma and COPD across the life course. *Eur. Respir. J.* 2019; 53: 1801795.

Bermingham ML, Walker RM, Marioni RE, Morris SW, Rawlik K, Zeng Y, Campbell A, Redmond P, Whalley HC, Adams MJ et al. Identification of novel differentially methylated sites with potential as clinical predictors of impaired respiratory function and COPD. *EBioMedicine* 2019; 43: 576–86.

Lahousse L. Epigenetic targets for lung diseases. *EBioMedicine* 2019; 43: 24–5.

Jacob CM, Baird J, Barker M, Cooper C, Hanson M. The importance of life course approach to health: chronic disease risk from preconception through adolescence and adulthood. *WHO.* 2017. [Accessed 1 Feb 2021]. Available from URL: https://www.who.int/life-course/publications/importance-of-life-course-approach-to-health/en/

Gibson AM, Doyle LW. Respiratory outcomes for the tiniest or most immature infants. *Semin. Fetal Neonatal Med.* 2014; 19: 105–11.

Kajantie E, Strang-Karlsson S, Evenens KAI, Haaramo P. Adult outcomes of being born late preterm or early term – what do we know? *Semin. Fetal Neonatal Med.* 2019; 24: 66–83.

Parkinson JR, Hyde MJ, Gale C, Santakhumaran S, Modi N. Preterm birth and the metabolic syndrome in adult life: a systematic review and meta-analysis. *Pediatrics* 2013; 131: e1240–63.

de Jong F, Monuteaux MC, van Elburg RM, Gillman MW, Belfort MB. Systematic review and meta-analysis of preterm birth and later systolic blood pressure. *Hypertension* 2012; 59: 126–34.

Carr H, Cnattingius S, Granath F, Ludvigsson JF, Edstedt-Bonamy AK. Preterm birth and risk of heart failure up to early adulthood. *J. Am. Coll. Cardiol.* 2017; 69: 2634–42.

Starr MC, Hingorani SR. Prematurity and future kidney health: the growing risk of chronic kidney disease. *Curr. Opin. Pediatr.* 2018; 30: 228–35.

Barnes PJ. Mechanisms of development of multimorbidity in the elderly. *Eur. Respir. J.* 2015; 45: 790–806.

© 2021 Asian Pacific Society of Respirology.
229 Stroustrup N, Anthony WE, Nash ZM, Gowda V, Gomez A, Berenson GS. Childhood risk factors predict adult risk associated with cardiovascular risk: results from the 23-year longitudinal Framingham Heart Study Original Cohort. *JAMA Cardiol.* 2018; 3: 427–31.

230 Allen NB, Siddique J, Wilkins JT, Shay C, Lewis CE, Goff DC, Niiranen TJ, Henglin M, Claggett B, Muggeo VMR, McCabe E, Jain M, Wadhwa PD, Buss C, Entringer S, Swanson JM. Developmental trajectories predicting cardiovascular risk in adolescence. *Health and illness trajectories: description and clinical implications.* *J. Palliat. Med.* 2017; 20: 426–7.

231 Luyten P, Lewis CE, Goff DC, Niiranen TJ, Henglin M, Claggett B, Muggeo VMR, McCabe E, Jain M, Wadhwa PD, Buss C, Entringer S, Swanson JM. Developmental trajectories of blood pressure elevation preceding hypertension onset: an analysis of the Framingham Heart Study Original Cohort. *JAMA Cardiol.* 2018; 3: 427–31.

232 Islam MT, Moller J, Zhou X, Liang Y. Life-course trajectories of childhood and mid-life cardiac structure and function. *J. Diabetes Complications* 2019; 33: 356–62.

233 van den Borst B, Gosker HB, Zeegers MP, Schols AM. Pulmonary function in diabetes: a metaanalysis. *Chest* 2010; 138: 393–406.

234 Anik A, Anik A, Uysal P. Assessment of pulmonary function by impulse oscillometry and spirometry in children with type 1 diabetes mellitus. *Pediatr. Pulmonol.* 2020; 55: 3517–24.

235 Luyckx VA, Brenner BM. Low birth weight, nephron number, and kidney disease. *Kidney Int. Suppl.* 2005; 68: S68–77.

236 Triest FJJ, Franssen FME, Reynaert N, Gaffren S, Spruit MA, Janssen DJA, Rutten EPA, Wouters EFM, Vanfleteren L. Disease-specific comorbidity clusters in COPD and accelerated aging. *J. Clin. Med.* 2019; 8: 511.

237 Deo RC. Machine learning in medicine. *Circulation* 2015; 132: 1920–30.

238 Prados-Torres A, Calderon-Larranaga A, Hanco-Saavedra J, Poblador-Plou B, van den Akker M. Multimorbidity patterns: a systematic review. *J. Clin. Epidemiol.* 2014; 67: 254–68.

239 Vetrano DL, Roso-Llorach A, Fernandez S, Guisado-Clavero M, Violan C, Onder G, Fratiglioni L, Calderon-Larranaga A, Marengoni A. Twelve-year clinical trajectories of multimorbidity in a population of older adults. *Nat. Commun.* 2020; 11: 3223.

240 Jensen AB, Moseley PL, Oprea TI, Ellesoe SG, Eriksson R, Schmook H, Jensen PB, Jensen LJ, Brunak S. Temporal disease trajectories condensed from population-wide registry data covering 6.2 million patients. *Nat. Commun.* 2014; 5: 4022.

241 Khandelkar A, Patlay P. Clustering & trajectories of multimorbidity across the lifecycle: a 70 year birth cohort study. *Eur. J. Public Health* 2019; 29: czk186.228. DOI: 10.1093/eurpub/czk186.228