

Pathobiological mechanisms underlying metabolic syndrome (MetS) in chronic obstructive pulmonary disease (COPD): clinical significance and therapeutic strategies



Stanley M.H. Chan, Stavros Selemidis, Steven Bozinovski, Ross Vlahos *

School of Health and Biomedical Sciences, RMIT University, Bundoora, VIC 3083, Australia

ARTICLE INFO

Keywords:

Smoking
obesity
COPD comorbidities
oxidants
metabolic dysregulation
immunometabolism

ABSTRACT

Chronic obstructive pulmonary disease (COPD) is a major incurable global health burden and is currently the 4th largest cause of death in the world. Importantly, much of the disease burden and health care utilisation in COPD is associated with the management of its comorbidities (e.g. skeletal muscle wasting, ischemic heart disease, cognitive dysfunction) and infective viral and bacterial acute exacerbations (AECOPD). Current pharmacological treatments for COPD are relatively ineffective and the development of effective therapies has been severely hampered by the lack of understanding of the mechanisms and mediators underlying COPD. Since comorbidities have a tremendous impact on the prognosis and severity of COPD, the 2015 American Thoracic Society/European Respiratory Society (ATS/ERS) Research Statement on COPD urgently called for studies to elucidate the pathobiological mechanisms linking COPD to its comorbidities. It is now emerging that up to 50% of COPD patients have metabolic syndrome (MetS) as a comorbidity. It is currently not clear whether metabolic syndrome is an independent co-existing condition or a direct consequence of the progressive lung pathology in COPD patients. As MetS has important clinical implications on COPD outcomes, identification of disease mechanisms linking COPD to MetS is the key to effective therapy. In this comprehensive review, we discuss the potential mechanisms linking MetS to COPD and hence plausible therapeutic strategies to treat this debilitating comorbidity of COPD.

© 2019 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

Contents

1. Introduction	160
2. Metabolic syndrome (MetS) in COPD.	162
3. Development of metabolic syndrome in COPD.	167
4. Clinical implications of MetS and COPD.	172
5. Perspectives and conclusions	179
Assurance	180
Conflict of interest statement.	180
Acknowledgments.	180
References	180

Abbreviations: AECOPD, Acute exacerbation of chronic obstructive pulmonary disease; AM, Alveolar macrophages; AMPK, Adenosine monophosphate-activated protein kinase; COPD, Chronic obstructive pulmonary disease; CRP, C-reactive protein; CVD, Cardiovascular disease; FEV₁, Forced expiratory volume in the first second; GOLD, Global initiative for chronic obstructive lung disease; HIF, Hypoxia-inducible factor; IL-8, Interleukin 8; LDL, Low density lipoprotein; MetS, Metabolic syndrome; NAFLD, Non-alcoholic fatty liver disease; ROS, Reactive oxygen species; SREBP-1c, Sterol response element binding protein-1c; TNF- α , Tumour necrosis factor- α ; VLDL, Very low density lipoprotein.

* Corresponding author at: School of Health and Biomedical Sciences, RMIT University, PO Box 71, Bundoora, VIC 3083, Australia.

E-mail address: ross.vlahos@rmit.edu.au (R. Vlahos).

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a major incurable global health burden and is currently the 4th largest cause of death in the world (Vogelmeier et al., 2017). In 2010, COPD incurred a total of \$50 billion in economic cost to the US community (Guarascio, Ray, Finch, & Self, 2013). Importantly, much of the disease burden and health care utilisation in COPD is associated with the management of its comorbidities (e.g. skeletal muscle wasting, ischemic heart disease, cognitive dysfunction) and infectious viral and bacterial acute exacerbations (AECOPD) (Vogelmeier et al., 2017). Many patients with COPD also present with metabolic syndrome (MetS) a cluster of conditions including diabetes and prediabetes (insulin resistance), abdominal obesity, high cholesterol and high blood pressure. It is estimated that over a quarter of the world's adult population have metabolic syndrome (International Diabetes Federation, 2017) and they are twice as likely to die from and three times as likely to have a heart attack or stroke compared with people without the syndrome (Alberti et al., 2009). The morbidity and motility rate are amplified when MetS is coupled with COPD (Alberti et al., 2005; Sin & Man, 2003b). In this review, we discuss the mechanisms of cross-talk, clinical significance and therapeutic strategies for COPD and MetS.

1.1. Definition of COPD

COPD is a disease characterised by persistent respiratory symptoms and poorly-reversible airflow limitation that is usually progressive. The airflow limitation is associated with a chronic inflammatory response in the airways and the lungs to noxious particles and gases. Cigarette smoking is the major cause of COPD and accounts for more than 95% of cases in developed countries (Vogelmeier et al., 2017). COPD encompasses large airways bronchitis with mucus plugging, chronic obstructive bronchiolitis with fibrosis and obstruction of small airways, and emphysema with enlargement of airspaces and destruction of lung parenchyma, loss of lung elasticity, and closure of small airways. Many patients with COPD have all three pathological conditions (i.e. bronchitis, chronic obstructive bronchiolitis and emphysema), but the relative extent of emphysema, obstructive bronchiolitis and overall disease manifestation can vary within individual patients. Airflow limitation is diagnosed using spirometry according to The Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2018 and the World Health Organization (WHO) criteria. Based on the calculated forced expiratory volume in one second (FEV₁), the severity of COPD is classified into four stages (GOLD 1–4) with respect to deterioration lung function and symptoms (Global Strategy for the Diagnosis, Management and Prevention of COPD: 2018 Report). The ABCD GOLD assessment tool combines spirometry, patient symptoms (assessed using modified British Medical Research Council [mMRC] questionnaire and the COPD assessment test score [CAT]) and history of exacerbations to facilitate therapeutic strategies at an individual patient level (Vogelmeier et al., 2017; Global Strategy for the Diagnosis, Management and Prevention of COPD: 2018 Report). Alternative assessments, such as the BODE Index (Body mass index, airflow Obstruction, Dyspnoea and Exercise capacity index in COPD), have been proposed and may offer a more comprehensive measure of severity as they also take into account systemic manifestations that are not reflected by the FEV₁ (Celli et al., 2004).

1.2. Health burden of COPD: an escalating problem with limited treatment options

Patients with COPD develop a myriad of symptoms such as cough, sputum production, and progressive exertion breathlessness. As the disease progresses, patients at intermediate (GOLD 2) disease stage or beyond tend to experience more frequent and severe worsening of the respiratory symptoms (i.e. exacerbations), which are largely attributed to bacterial and viral chest infections, as well as pollutants (Barnes

& Celli, 2009). These exacerbations not only constitute a major cost in patient care, but also greatly increase the rate of mortality and morbidity. Over the past decade, there has been a growing body of evidence suggesting COPD as a systemic disease and that its pathological manifestations are not restricted to pulmonary inflammation and airway remodelling (Barnes, 2010; Barnes & Celli, 2009; Decramer et al., 2008). In fact, the majority of patients with COPD die of non-respiratory disorders making them co-morbidities to COPD (McGarvey et al., 2007). The best recognized systemic manifestations of COPD include systemic inflammation, cardiovascular diseases (CVD), muscle wasting and dysfunction, osteoporosis, anaemia, and clinical depression and anxiety (Barnes & Celli, 2009; Wouters, 2005). Importantly, there is increasing evidence to suggest metabolic syndrome (MetS) as a critical clinical component associated with COPD, as one or more features of MetS, such as obesity and diabetes are frequently found in those individuals admitted for hospitalisation (Crisafulli et al., 2010; Fabbri, Luppi, Beghe, & Rabe, 2008).

1.3. Causes and pathophysiology of COPD

Cigarette smoking is the major risk factor for COPD (Vogelmeier et al., 2017) and is one of the most important risk factors for the chronic diseases and COPD-associated comorbidities (Fabbri & Rabe, 2007). Other reported causes for COPD include occupational factors (e.g. miners and workers of the textile industry), respiratory infections, atmospheric pollution and passive smoking (Salvi & Barnes, 2009). Repeated exposure to these irritants promotes local inflammation of the airways leading to obstruction and reduction in FEV₁, which is not completely reversible even with bronchodilator treatment (Qureshi, Sharafkhaneh, & Hanania, 2014). If unresolved, chronic inflammation of the airways may be amplified and gives rise to more severe conditions limiting airflow. Chronic bronchitis is a condition characterized by inflammation of the bronchial wall, associated with hyperplasia of the goblet cells, enlargement of the tracheobronchic submucosa and the mucus hypersecretion (Lahousse et al., 2017). The development of emphysema is due to destruction of the walls of the terminal bronchiole driven by an imbalanced proteases and anti-proteases in the lung by cigarette smoking (Abboud & Vimalanathan, 2008; Kersul et al., 2011). Bronchiolitis is another lung pathology that may develop when small airways in the lungs become permanently damaged and persistently inflamed from repeated exposure to cigarette smoking or irritant fumes. As the disease progresses, a variety of cell types including macrophages, neutrophils and T-cells become hyper-activated and release pro-inflammatory mediators including tumour necrosis factor- α (TNF- α), monocyte chemoattractant protein-1 (MCP-1), reactive oxygen species (ROS), and neutrophil chemoattractant factors, such as leukotriene B₄ (LTB₄) and interleukin-8 (IL-8) in response to the irritants, in particular cigarette smoke (Vlahos & Bozinovski, 2014). These mediators serve to perpetuate the inflammatory response through the recruitment of peripheral blood monocytes, neutrophils and CD8⁺ cytotoxic T-cells into the airways. These recruited cells, particularly activated macrophages and neutrophils, release proteases resulting in tissue destruction and emphysema (Barnes, 2017; Fabbri & Rabe, 2007). Simultaneously, ROS generated by the macrophages constitute an oxidative insult that causes lung inflammation and tissue injury. COPD patients are also susceptible to viral and bacterial infections, which amplifies lung inflammation and ROS production that causes a rapid decline in lung function during repeated episodes of acute exacerbation COPD (AECOPD) (Barnes & Celli, 2009; Decramer et al., 2008).

Recent genome-wide association studies have also identified genetic predisposition, in particular alpha-1 antitrypsin deficiency, as an important factor in the development of COPD (Ding et al., 2015; Jiang et al., 2016; Siedlinski et al., 2013). There is clear heterogeneity in the clinical manifestations of COPD, which are greatly attributed to these environmental and genetic cues. For example, small airway limitations are more commonly found in COPD patients with cigarette smoking history,

whereas non-smokers mainly develop emphysema-dominant phenotypes characterized by increased alveolar space and destruction (Burgel et al., 2010; Castaldi et al., 2014). Other factors that might impact on disease presentation and progression include age, gender, other pre-existing conditions (e.g. asthma) and ethnicity. It is well established that lung function declines with increasing age (Fletcher & Peto, 1977). Moreover, female COPD patients tend to be more susceptible to the toxic effects of cigarette smoking (Han et al., 2007). Asthma appears to be a major underlying risk factor for COPD evidenced by the finding that up to 30% of COPD patients are asthmatics (Soriano et al., 2003) and that a more rapid decline in lung function is observed in smokers with asthma than those without (Lange, Parner, Vestbo, Schnohr, & Jensen, 1998). Finally, population groups with poorer social-economic status tend to have a greater risk of developing COPD and its complications than their wealthier counterparts (Fragoso, 2016; Lawlor, Ebrahim, & Davey Smith, 2004; Sahni, Talwar, Khanijo, & Talwar, 2017; Shohaimi et al., 2004), which is likely to be related to poor nutritional status, living standard, exposure to pollutants and high smoking rate along with poor access to health care.

1.4. Comorbidities of COPD

Cardiovascular disease (CVD), skeletal muscle wasting, and metabolic abnormalities are classic comorbidities that are found in COPD patients (Austin, Crack, Bozinovski, Miller, & Vlahos, 2016; Vogelmeier et al., 2017). The co-existence of these conditions not only contributes to ill health but also greatly increases the risk of mortality at all stages of COPD, as well as incidence of hospitalisation (Franssen & Rochester, 2014). Hypertension and peripheral vascular disease are likely to be the most frequently occurring CVD-related comorbidities in COPD, which affects up to 50% of the patients (Divo et al., 2012). With the progression of the disease, COPD patients are at increasing risk of developing arrhythmias, ischemic myocardial damage and even heart failure (Bhatt & Dransfield, 2013). Hence, impaired FEV₁ has been demonstrated to be a powerful predictor of cardiovascular mortality (Young, Hopkins, & Eaton, 2007). Meanwhile, the severity of airflow obstruction has been reported to promote arterial stiffness (Sabit et al., 2007) which in turns can exacerbate cardiovascular-related comorbidities in COPD.

Skeletal muscle wasting and dysfunction is another common condition associated with COPD, which severely impacts on patient quality of life and survival (Passey et al., 2016). Loss of muscle mass is found in up to 40% of COPD patients, the prevalence as well as the extent of the wasting are worsened in patients with advanced COPD (Schols, Broekhuizen, Weling-Scheepers, & Wouters, 2005; Sergi et al., 2006; Vestbo et al., 2006). Skeletal muscle wasting is a powerful predictor of mortality in COPD, independent of lung function impairment (Schols, Slangen, Volovics, & Wouters, 1998). Patients with severe COPD who have reduced mid-thigh cross-sectional area (less than 70cm²) have an approximately 4-times higher odds ratio for mortality than patients with a similar degree of airflow limitation but with preserved muscle size (Marquis et al., 2002). Low Fat Free Mass Index (FFMI) and reduced quadriceps strength have been identified as predictors of COPD mortality, independent of lung function decline (Schols, 2010; Swallow et al., 2007), highlighting the importance of muscle mass and function in the overall pathology of COPD. Clinically, rapid deteriorations in lean muscle mass have been described following acute exacerbations causing both loss of strength and endurance (Allaire et al., 2004; Gosker et al., 2002). In addition to loss of muscle mass and strength, phenotypic changes occur in the muscle of COPD patients. A shift in the fibre types has been observed, with an increase in the proportion of fast glycolytic Type II fibres and a reduction in slow, oxidative Type I fibres (Debigare, Cote, Hould, LeBlanc, & Maltais, 2003; Jobin et al., 1998; Vogiatzis et al., 2011; Whittom et al., 1998). While the lung pathology in COPD is largely irreversible, the inherent adaptability of muscle tissue offers therapeutic opportunities to tackle muscle wasting and

potentially reverse or delay the progression of this aspect of the disease, to improve patients' quality of life.

Patients with COPD often have one or more physiological abnormalities that are features of the metabolic syndrome (Cebon Lipovec et al., 2016). Obesity has emerged to be an important feature of the MetS found in early stages of COPD (GOLD 1 and 2) (ten Hacken, 2009), and that abdominal obesity was found to be a reliable predictor of lung function impairment (Leone et al., 2009). More importantly the presence of MetS imposes further limitation on exercise capacity which could in turn hamper lung function and general wellbeing of COPD patients, predisposing them to more severe comorbidities and/or clinical complications such as lung cancer (Hartman, Boezen, de Greef, Bossenbroek, & ten Hacken, 2010).

2. Metabolic syndrome (MetS) in COPD

MetS is a complex disorder that is recognised clinically by the presence of a cluster of risk factors including excess abdominal obesity or body mass index (BMI) >30 kg/m², elevated blood pressure, pro-atherogenic blood lipid profile, impaired fasting blood glucose with or without insulin resistance (Alberti et al., 2005; Saltiel & Olefsky, 2017). Each metabolic risk factor is associated with one another, and together these risk factors promote atherosclerosis (Hutcheson & Rocic, 2012). According to the International Diabetes Federation (IDF), the general consensus is that neither cigarette smoke nor COPD are canonical risk factors for MetS and *vice versa*, and that there is no clear mechanistic data for the causal relationship. However, recent clinical findings suggest a strong association of COPD and MetS.

Firstly, MetS is found to be twice more common in COPD patients when compared to the general population. Several studies have demonstrated a prevalence of 21–62% (see Table 1). Notably, almost 50% of patients with COPD manifest with one or more components of the MetS (Marquis et al., 2005). MetS confers a 5-fold increase in the risk of type 2 diabetes mellitus (T2DM) and double the risk of developing CVD over the next 5 to 10 years (Alberti et al., 2009). Moreover, MetS increases the risk of stroke by 2- to 4-fold, risk of myocardial infarction by up to 4-fold, and doubles the risk of mortality compared with those without the syndrome (Alberti et al., 2005). When both COPD and MetS coexist, the occurrence of these comorbidities and complications are amplified (Sin & Man, 2003b). COPD patients with MetS present with a more severe form of the disease reflected by more dyspnoea, a lower FEV₁ and require more medication (e.g. inhalation of glucocorticoids) to control the disease (Diez-Manglano, Barquero-Romero, Almagro, et al., 2014). The prevalence of MetS and its comorbidities were originally thought to be associated with COPD severity and age (Hildrum, Mykletun, Hole, Midtjell, & Dahl, 2007). However, recent data demonstrated that MetS is present in a large proportion of COPD patients of younger age groups and in those with a less severe form of COPD (Minas et al., 2011). COPD patients with MetS have greater insulin resistance which favours the development of T2DM (Minas et al., 2011). Currently, the exact cause of MetS in COPD patients remains poorly understood triggering an urgent call by both the American Thoracic Society and European Respiratory Society for further studies to elucidate the pathobiological mechanisms linking COPD to its comorbidities (Celli et al., 2015).

Development of MetS in COPD is multifactorial in origin, but shares several common contributing factors including oxidative stress, inflammatory cytokines, and physical inactivity (Clini, Crisafulli, Radaeli, & Malerba, 2013) (Fig. 1). There is compelling evidence that increased oxidative stress in COPD and the 'spill over' of lung inflammation into the systemic circulation plays an important role in the pathophysiology of COPD and its comorbidities such as MetS (Barnes & Celli, 2009; Bernardo, Bozinovski, & Vlahos, 2015). Lung inflammation during COPD leads to a rise in a number of biomarkers associated with neutrophilic inflammation (MMP9, elastase, calprotectin, and bronchoalveolar lavage neutrophils) and pro-inflammatory cytokines (IL-6, IL-1β, IFNα,

Table 1
Reported prevalence of metabolic syndromes amongst COPD patients

Subject characteristics	Prevalence	Feature(s) of MetS found	Ref	Note
114 male current/past smokers with COPD without significant co-morbidities	Overall prevalence was 21%, more prevalent in earlier stages of COPD	BMI >30 Fasting hyperglycaemia Hypertriglyceridemia ↑plasma leptin ↓plasma adiponectin Insulin resistance	(Minas et al., 2011)	Not age-matched
38 COPD patients and 34 controls	47% in COPD patients, 21% in controls	Abdominal obesity Hypertension Hypertriglyceridemia	(Marquis et al., 2005)	Controls are age- and gender- matched Small sample size
170 COPD patients and 30 controls	Overall prevalence was 47.5%, GOLD stages I, II, III, and IV, were 53%, 50%, 53%, 37%, and 44%, respectively	Abdominal obesity Fasting hyperglycaemia Hypertension Hypertriglyceridemia	(Watz et al., 2009)	Age- and gender-matched COPD patients with MetS had increased systemic inflammation and reduced physical activity independent of pulmonary function impairment
7,358 adults aged > or =50 years	22.6% in COPD patients, 19.8% in controls	BMI >30 Abdominal obesity Hypertriglyceridemia	(Lam et al., 2010)	Subjects are age-adjusted and gender-matched
70 Stable COPD patients and 20 control subjects	32.9% in COPD patients, 5% in the controls	Fasting hyperglycaemia Hypertriglyceridemia ↓HDL	(Ameen, Mohamed, Abd El Mageed, & Abd El Wahab, 2016)	Gender-matched but not age matched
98 consecutive stable COPD patients	Overall prevalence was 37.8%, GOLD stages I, II, III, and IV were 33.3 %, 48.8 %, 31.6 %, and 23.1 %, respectively	BMI >30 Abdominal obesity Hypertension Hypertriglyceridemia Fasting hyperglycaemia ↓HDL	(Vujic, Nagorni, Maric, Popovic, & Jankovic, 2016)	Age- and gender-matched COPD patients with MetS had higher systemic inflammatory markers (↑leukocyte count and CRP) than patients without MetS
28 male patients with stable COPD	50% in COPD patients	BMI >30 Abdominal obesity Hypertension Fasting hyperglycaemia Fasting hyperinsulinaemia Insulin resistance ↓HDL Coronary artery disease Cerebrovascular accident	(Poulain et al., 2017)	Age-matched COPD patients with MetS had higher systemic inflammatory markers (↑TNFα, IL-6, leptin & ↑adiponectin) than patients without MetS Small sample size
228 clinically stable COPD patients and 156 controls	57% in COPD patients, 40% in controls.	Abdominal obesity ↓HDL Fasting hyperglycaemia Hypertriglyceridemia	(Breyer et al., 2014)	Groups were stratified for BMI and gender
76 consecutive COPD patients	62% in COPD	BMI >30 Abdominal obesity Hypertension Fasting hyperglycaemia Fasting hyperglycaemia Insulin resistance ↓HDL Hypertriglyceridemia	(Piazzolla et al., 2017)	Age- and gender-matched

C-reactive protein (CRP) and TNF- α) in the peripheral blood (Ropcke et al., 2012). Chronic elevation of inflammatory molecules in the circulation constitutes low-grade systemic inflammation which is the key mediator of MetS. For example, IL-6, IL-1 β , TNF- α and CRP promotes whole-body insulin resistance, a central feature of MetS (de Luca & Olefsky, 2008). Moreover, continued systemic inflammation promotes the formation of atherosclerotic plaques, giving rise to cardiovascular comorbidity in COPD patients (Fabbri et al., 2008; Mizuno, Jacob, & Mason, 2011). Adipose tissue inflammation has been proposed to be another important mechanism linking COPD to MetS. In obese COPD patients, the expansion of adipose tissue leads to adipocyte hypertrophy and hyperplasia and that large adipocytes outstrip the local oxygen supply leading to cell autonomous hypoxia with activation of local

inflammation within the adipose tissue (Clini et al., 2013; Diez-Mangano, Barquero-Romero, Almagro, et al., 2014). Strikingly, several markers of inflammation such as IL-6, CRP and TNF- α are further elevated when COPD and obesity coexist (Rana et al., 2004) suggesting the adipose tissue may be another major contributor of inflammation during COPD.

2.1. COPD and obesity

The prevalence of obesity in COPD patients was first reported by Steuten, Creutzberg, Vrijhoef, & Wouters (2006) to be 18% in the Netherlands population with the highest prevalence in subjects with mild to moderate COPD (16–24% in GOLD stages 1 and 2) and the lowest

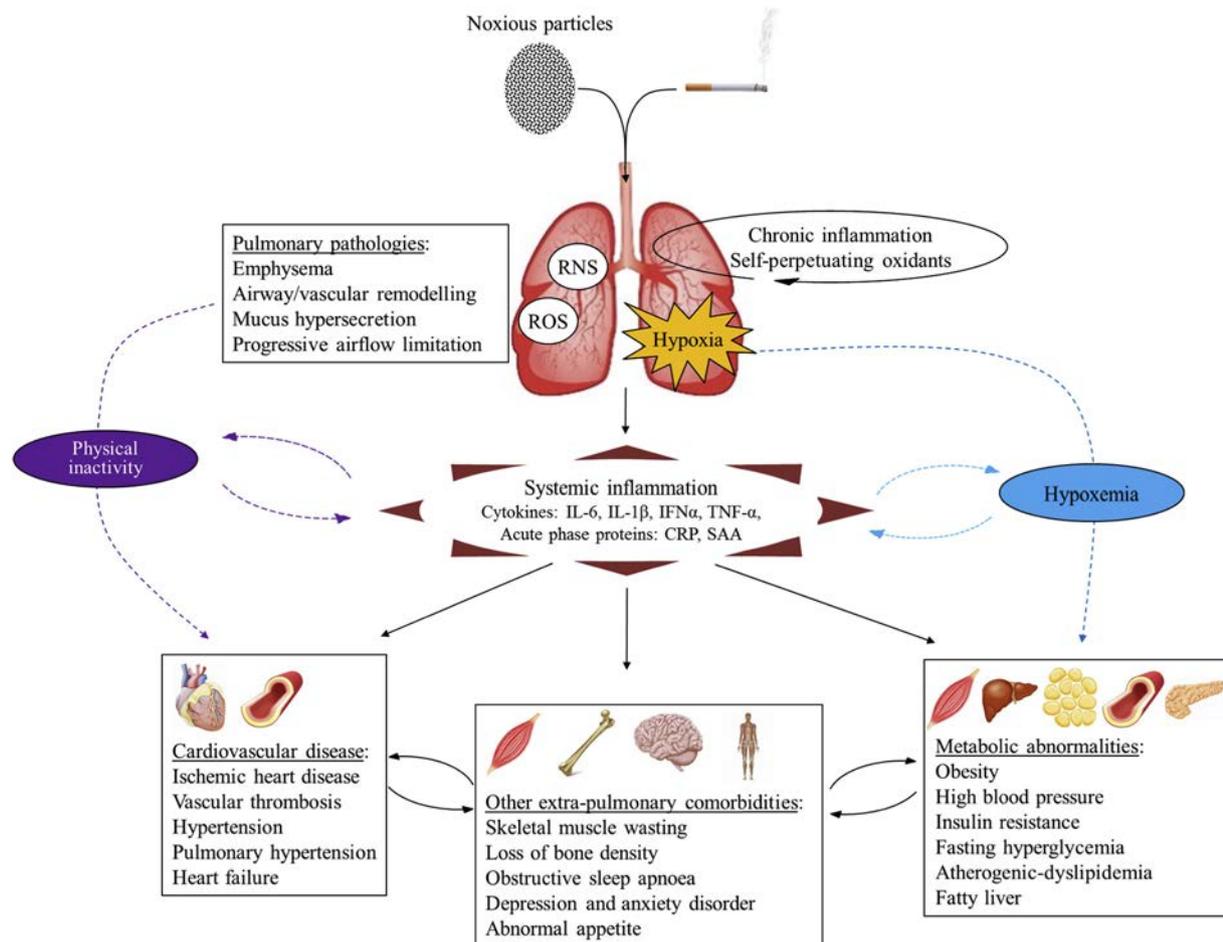


Fig. 1. Development of metabolic syndrome (MetS) in COPD. Repeated cigarette smoking and/or exposure to noxious particles (e.g. occupational dust, air pollution, biomass combustion) evoke an inflammatory response with increased macrophage and neutrophil infiltration into the lungs. Meanwhile, oxidants may also enter the pulmonary compartment via direct inhalation of cigarette smoke and noxious particles. The combination of endogenous and inhaled oxidants causes oxidative damage to DNA, lipids, carbohydrates and proteins, and thereby mediates an array of downstream processes that contribute to the development and progression of COPD. Oxidative damage activates resident cells in the lung (e.g. epithelial cells and alveolar macrophages), to generate chemotactic molecules that recruit additional inflammatory cells and perpetuate oxidative stress in the lung. Collectively, these events lead to a vicious cycle of persistent inflammation, accompanied by chronic oxidative stress, which lead to disturbances in the protease-anti-protease balance, defects in tissue repair mechanisms, accelerated apoptosis and tissue destruction resulting in the spill over of pro-inflammatory mediators into the systemic circulation. Systemic inflammation promotes the manifestation of cardiovascular disease, metabolic abnormalities and other extra-pulmonary comorbidities which are interconnected in nature. Impaired pulmonary function decreases oxygen-exchange efficiency which in turn would trigger hypoxemia and limit physical activity. Both hypoxemia and physical inactivity *per se* are capable of directly and indirectly promoting the development of metabolic syndrome and other comorbidities.

in severe COPD (5.9% in GOLD stage 4). A subsequent study by [Eisner et al. \(2007\)](#) in a multi-ethnic cohort of patients found 54% of the COPD patients were found to also suffer from obesity, which is defined as a BMI of greater than 30 kg/m². In patients with COPD, obesity is generally associated with increased risk of mortality, however, surprisingly a number of studies have demonstrated that being overweight or obese may confer a survival advantage over a leaner phenotype ([Bonsaksen, Fagermoen, & Lerdal, 2016](#); [Cebon Lipovec et al., 2016](#); [Maatman et al., 2016](#)). In fact, COPD patients with a lower BMI tend to have a higher mortality rate when compared with patients of normal BMI, and that subjects who were overweight or obese had a lower risk of mortality ([Cao et al., 2012](#)), which constitute the “obesity paradox”. However, it is important to view this paradox in reference with the progression of COPD, as the majority of patients suffering from lung disorders have a progressive loss of muscle mass ([Vestbo et al., 2006](#)) which is a likely result of physical inactivity. BMI is a simple indicator of weight for height and cannot differentiate between lean muscle mass that are metabolically and functionally active, and fat mass. Therefore, BMI can be a misleading indicator for survival or health outcomes in COPD patients. On this note, a study by [Marquis et al. \(2002\)](#) have demonstrated increased mortality risk in COPD patients with low mid-thigh cross-sectional area which is indicative of loss of lean muscle mass. In line

with this, a subsequent study by [Schols et al. \(2005\)](#) on 412 patients with moderate-to-severe COPD also confirmed that lean mass can serve as an independent predictor of mortality irrespective of fat mass. Muscle is an important tissue not only for the mechanical contraction to produce movement, but it is also an active metabolic tissue responsible for energy storage and utilization. Moreover, muscles are capable of secreting systemic factors (i.e. myokines) which act on distal target tissues including the lungs. Disruption to such tissue cross-talk as a result of muscle wasting has been postulated to negatively impact on lung function ([Cheung, Joham, Marks, & Teede, 2017](#); [Zhi, Xin, Ying, Guohong, & Shuying, 2016](#)). Given the capacity of physical activity is directly related to the amount of lean muscle mass, and increased fat mass is known to negatively impact on respiratory mechanics and lung volumes ([DeLorey, Wyrick, & Babb, 2005](#); [Hedenstierna & Santesson, 1976](#); [Pelosi, Croci, Ravagnan, Vicardi, & Gattinoni, 1996](#)), it is possible that the protective effect of obesity may be coming from the lean muscle mass. This highlights the importance of body composition assessment in the clinical management of COPD patients.

The concomitant increase in fat mass and loss of muscle mass represent two arms of metabolic abnormalities that may be relate to systemic inflammation ([Tkacova, 2010](#)). Systemic inflammation not only is the hallmark of COPD but it is also a key mechanism responsible for disease

progression and the consequential increased rate of comorbidities (Wouters, 2005). There are two main sources of pro-inflammatory mediators that are considered to be important for the systemic inflammation seen during COPD: the lungs and peripheral organs in particular adipose tissue (Akpınar, Akpınar, Ertek, Sayin, & Gulhan, 2012; Magnussen & Watz, 2009; Sin & Man, 2003b; Tkacova, 2010). As COPD is increasingly recognized as a more complex systemic disease rather than solely an airway and lung disease, the source of systemic inflammation in COPD patients has been a subject of intense discussion (Chung & Adcock, 2008; Kim, Rogers, & Criner, 2008; Vogelmeier et al., 2017). The critical points of discussion are whether systemic inflammation is due to spill over from inflammation arising predominantly in the lungs or to an up regulated production of inflammatory mediators in non-pulmonary tissue(s) as well. In support of the “spill over” concept, studies have demonstrated that cigarette smoke and COPD are associated with increased permeability of pulmonary vessels, the leakiness of which contributes directly to the spill over of the local pro-inflammatory mediators from the lungs into the systemic compartment. In human bronchial epithelium, Olivera et al. (Olivera, Boggs, Beenhouwer, Aden, & Knall, 2007) demonstrated transient loss of epithelial barrier function upon exposure to cigarette smoke which resulted in macromolecular permeability. In murine models of lung injury, similar loss of epithelial barrier function was observed which resulted in increased leak of surfactant protein D, a lung specific protein (Fujita et al., 2005) as well as the pro-inflammatory cytokine IL-6 (Tamagawa et al., 2009) into the circulation favouring the development of systemic inflammation. In humans, increased alveolar-capillary membrane permeability was observed in cigarette smoke compared to nonsmokers (Kennedy, Elwood, Wiggs, Pare, & Hogg, 1984). Improvements of FEV₁ by steroid therapy was associated with restoration of alveolar-capillary membrane permeability (Chou, Chen, Chuang, Kao, & Huang, 2006), as well as reduction of systemic surfactant protein D levels in COPD patients (Antoniu, 2008; Man et al., 2009).

At a glance, the findings from the above studies are suggesting pulmonary inflammation as a prevailing mechanism for the systemic inflammation during COPD. However, upon closer examination, the inverse relationship between FEV₁ and pulmonary vessel permeability demonstrated by these studies is also indicative that this lung-to-circulation spill over of pro-inflammatory mediators may not be prominent in patients with early stages of COPD or prior to the onset of severe pulmonary dysfunction. Indeed, the coexistence of obesity and metabolic syndrome have been demonstrated to positively correlate with increased systemic inflammation as well as reduced physical activity independent of lung function impairment (Watz et al., 2009). Meanwhile, the decline in pulmonary function with COPD limits physical activity which increases the propensity for weight gain exacerbating obesity. To make matters worse, excess obesity not only accelerates pulmonary function loss but together they pose further restriction on physical activity (Franssen, O'Donnell, Goossens, Blaak, & Schols, 2008) forming a vicious cycle.

2.2. COPD and dyslipidaemia

Cigarette smoking is known to cause an increase in circulating levels of very low density lipoprotein (VLDL), low density lipoprotein (LDL), and triglycerides and low levels of high density lipoprotein (HDL) (Craig, Palomaki, & Haddow, 1989). While the alteration of this panel of circulatory factors is generally believed to be pro-atherosclerotic, studies on dyslipidaemia in COPD are limited and the lipid profile has yet to be well characterized in COPD. A study conducted in a Spanish population involving 1500 subjects found dyslipidaemia in 48.3% of COPD patients with various stages of the disease (de Lucas-Ramos et al., 2012). A more recent study has reported the detection of elevated levels of oxidised LDL in current smokers (Wada et al., 2012) and that the levels of oxidised LDL were rapidly reduced upon smoking cessation (Komiya et al., 2015). Lipoprotein particles like VLDL and LDL are

prone to oxidative modifications, which are inhibited by HDL under healthy state. Oxidised LDL is predominant at sites of atherosclerotic lesions, and the levels of oxidised LDL in the blood is reflective of the activity of foam cells in atherosclerotic lesions (Mashiba et al., 2001). On one hand, the altered circulatory profile in COPD patients renders LDL more easily oxidized. On the other hand, a number of steps in the reverse cholesterol transport pathway have been found to be impaired by systemic inflammation (Athysos, Katsiki, Doulas, Karagiannis, & Mikhailidis, 2013; Goldklang et al., 2012). Of interest, treatment of the underlying disease leading to a reduction in inflammation results in the return of the lipid profile towards normal (Dessi et al., 2013) indicating dyslipidaemia might be a key mediator for comorbidities stemming from systemic inflammation.

Another important aspect of dyslipidaemia lies in the pro-inflammatory properties of certain lipid species. First of all, elevating levels of circulating non-esterified lipids (NEFA) have been demonstrated to promote inflammation (Gordon, 2007; Johnson, Milner, & Makowski, 2012; Kosteli et al., 2010). Like triglycerides, NEFA is transported out of the liver into the circulation in the form of lipoprotein. Uptake of these lipid-rich VLDL and LDL particles by macrophages leads to lipid deposition which triggers a cascade of intracellular signalling mediated by mitogen activated protein kinases (MAPK; ERK1/2, JNK & p38) resulting in the production of inflammatory proteins (Saraswathi & Hasty, 2006). In line with this, VLDL has been shown to trigger pro-inflammatory response in vascular endothelial cells (Dichtl et al., 1999). This evidence suggested that apart from spill over of pro-inflammatory mediators from the lungs, systemic inflammation may also arise from dyslipidaemia. In support of this, diets rich in cholesterol and fat have been demonstrated to promote pulmonary inflammation (Tilton et al., 2013) and emphysema development (Goldklang et al., 2012). Cigarette smoke exposure is also known to impact on key organs including liver, muscle, and white and brown adipose tissue, that are important in lipid and lipoprotein metabolism (Hutcheson & Rocić, 2012). Hence, dyslipidaemia arising from MetS or cigarette smoke may serve as an important mechanistic link not only to COPD but also its comorbidities.

2.3. COPD and non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease (NAFLD) is recognized as a hepatic manifestation of MetS (Fargion, Porzio, & Fracanzani, 2014). NAFLD is a collective term that encompasses non-alcoholic hepatic steatosis (modest lipid accumulation within the liver) to non-alcoholic steatohepatitis (NASH), which often precedes liver fibrosis, cirrhosis, and hepatocellular carcinoma (Fargion et al., 2014). NAFLD has also been identified as an independent risk factor for atherosclerosis and CVD (Hamaguchi et al., 2007; Targher et al., 2005). To date, the molecular mechanism underlying the conversion from the modest fatty liver to NASH remains poorly understood. However, experimental evidence indicates cigarette smoking may be a major risk factor for such pathological conversion. Firstly, increased serum cholesterol and lipid levels arising from cigarette smoke has been shown to be a risk factor for liver disease (Corey & Cohen, 2000; Mizoue, Ueda, Hino, & Yoshimura, 1999) in which elevation of serum lipids greater than 5% of normal level is a dividing line between simple steatosis to more severe forms of NAFLD (Tannapfel et al., 2011). Secondly, cigarette smoking has been shown to exacerbate hepatocellular lipid accumulation in laboratory rodent and cell culture by modulating the activity of adenosine monophosphate-activated protein kinase (AMPK) and sterol response element binding protein-1c (SREBP-1c) (Yuan, Shyy, & Martins-Green, 2009). AMPK is a master regulator of energy metabolism, while SREBP-1c is a basic-helix-loop-helix-leucine zipper transcription factor responsible for transcriptional activation of lipogenic genes (Postic & Girard, 2008). Activation of AMPK inhibits SREBP-1c thereby blocking energy-consuming biosynthetic pathways such as lipogenesis and activates energy-producing catabolic pathways such as fatty acid oxidation

(Long & Zierath, 2006). Exposure to cigarette smoke rapidly inhibits AMPK phosphorylation, and its function, leading to the activation of lipogenesis driven by SREBP-1c (Yuan et al., 2009). Thirdly, cigarette smoke exposure has also been demonstrated to perturb the cellular pro-oxidant to anti-oxidant balance giving rise to oxidative stress. Data from our laboratory showed increased oxidative stress in response to cigarette smoke (Duong et al., 2010).

In the liver, cigarette smoke stimulates the production of hepatocellular ROS which induces DNA damage (Chen et al., 2015) and liver injury that worsens the severity of NAFLD in the setting of obesity (Azzalini et al., 2010). In addition to inducing oxidative stress, cigarette smoke may contain high levels of chemical toxins which could have profound effects on NAFLD and are linked to the formation of hepatocellular carcinoma. For example, benzopyrene has been shown to cause oxidative stress and apoptotic cell death in primary rat hepatocytes (Collin et al., 2014). Aldehydes found in cigarette smoke have been shown to increase histone 3 phosphorylation via the hyper-activation of proliferative pathways including the phosphatidylinositol-3 kinase (PI3K) / protein kinase B (PKB/Akt) (Ibuki, Toyooka, Zhao, & Yoshida, 2014) and MAPK pathway (Lee & Shukla, 2007). Histone modifications are an important mechanism in chromatin remodelling which regulates gene expression. Histone 3 phosphorylation has been reported to promote malignant transformation and cancer development (Choi et al., 2005; Kim et al., 2008). In an obesity mouse model, nicotine has additive effects on the severity of hepatic steatosis induced by high fat feeding (Friedman et al., 2012). The liver tissue of these mice had greater lipid deposition, level of oxidative stress, incidence of hepatocellular apoptosis than those fed a high fat diet alone, which may be attributed to the negative impact of nicotine on AMPK activation (Friedman et al., 2012). Collectively, these findings suggest cigarette smoking is capable of causing liver injury by driving excessive oxidative stress, dysregulated lipid metabolism and hyperactivation of growth signals which may serve as an important trigger for the pathological conversion of fatty liver to NASH.

Despite the consistency, the clinical relevance of these experimental findings is more controversial. A randomized, placebo-controlled trial conducted on a cohort in Israel reported no significant relationship between cigarette smoking and liver function (Sofer, Boaz, Matas, Mashavi, & Shargorodsky, 2011). Moreover, post hoc analysis of the GREek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) study also revealed no association between cigarette smoking and NAFLD (Athysros, Tziomalos, et al., 2013). Paradoxically, a cross-sectional study involving 8,500 participants demonstrated both passive smoking and active smoking are positively correlated with prevalent NAFLD in middle-aged and elderly populations (Liu et al., 2013). The apparent controversy is likely to be explained by a number of concurrent factors such as obesity, smoke history, gender, age and genetic predisposition. Hence these factors should be taken into consideration in future clinical studies. Of interest, cigarette smoking has been reported to accelerate NAFLD pathology and liver injury only when obesity is present (Azzalini et al., 2010) suggesting the deleterious effects of CS in the liver may require additional metabolic insults, which further strengthens the connection between cigarette smoking and metabolic derangement in COPD.

2.4. COPD and diabetes

Although the exact prevalence varies between studies (Bitar, Ghoto, Dayo, Arain, & Parveen, 2017; Makarevich, Valevich, & Pochtavtsev, 2007; Parappil, Depczynski, Collett, & Marks, 2010), patients with COPD in general tend to have a greater chance of developing diabetes (type 2) with a prevalence of 18.7% in COPD patients versus 10.5% in the general population (Cazzola, Bettoncelli, Sessa, Cricelli, & Biscione, 2010; Yin et al., 2017). Persistent systemic inflammation appears to be an important mechanistic factor responsible for the progression of the two diseases (Akpınar et al., 2012; Tkacova, 2010; Yanbaeva,

Dentener, Creutzberg, & Wouters, 2006), greatly increasing an individual's risk for comorbidities such as cardiovascular complications (Barnes & Celli, 2009; Cazzola et al., 2010; Vogelmeier et al., 2017). Noteworthy is the mutual relationship that existed between these two diseases, in that not only patients with COPD are at risk of developing diabetes, but that COPD is also found to be a common comorbidity of diabetes (Cazzola et al., 2017). First of all, cigarette smoking doubles the risk of developing diabetes which is likely to be attributed to the worsened insulin resistance driven by systemic inflammation and/or oxidative stress by cigarette smoke (Oh & Sin, 2012). Moreover, the risk of developing diabetes is further increased in overweight/obese subjects (Cravo & Esquinas, 2017; Lambert et al., 2017). Secondly, experimental evidence demonstrated that airway inflammation blunts the metabolic actions of insulin on liver (suppress glucose production) and peripheral tissues (glucose uptake) such as muscle and adipose tissue leading to impairment of glucose metabolism (Cyphert et al., 2015). Importantly, the blunted insulin action in these tissues occurred without detectable defects in insulin receptor signalling. In line with this, inflammation of the airway epithelium has been shown to negatively regulate glucose metabolism via limitation of muscle blood flow and microvascular recruitment without impairment of insulin signalling (Clerk et al., 2006). Thirdly, the use of corticosteroid therapy for COPD has been reported to be associated with increased blood glucose levels (Barnes, 2010) and this association appears to be dose-dependent (Price et al., 2016). However, controversy exists regarding the adverse effects of corticosteroid therapy on diabetes as several studies have reported no evidence of such an association (Dendukuri, Blais, & LeLorier, 2002; Flynn, MacDonald, Hapca, MacKenzie, & Schembri, 2014; O'Byrne et al., 2012).

On the contrary, impaired lung function is one of the most common comorbidities found in diabetic patients (Cazzola et al., 2017). There is a strong correlation between severity of diabetes and decline in FEV₁ and forced vital capacity (FVC) (Kinney et al., 2014), particular in the elderly population (Caughey et al., 2010) which is likely to be a result of reductions in activity-related quality of life (Cecere et al., 2011; Mekov et al., 2016). The consequences of a reduced FEV₁ goes far beyond the effects of hyperglycaemia on lung function as recently demonstrated. In a 10-year follow up study involving 27,000+ non-smokers, Zaigham, Nilsson, Wollmer, and Engstrom (2016) reported that low FEV₁ precedes and significantly predicts the onset of diabetes. This heightens the notion that reduced FEV₁ could pose significant risk on an individual for developing diabetes which could arise many years following the initial decline in lung function independent of smoking history.

The association of diabetes and decline in lung function are linked at multiple levels namely systemic inflammation, glucotoxicity and insulin resistance. A large body of evidence has demonstrated systemic inflammation to be the major culprit underlying the impairment of lung function by diabetes (Akpınar et al., 2012). Diabetes is associated with a persistent elevation of inflammatory mediators such as IL-6, TNF- α , and CRP (Saltiel & Olefsky, 2017), which in turn could act to increase vascular permeability in the lung (Sedgwick, Menon, Gern, & Busse, 2002). In addition to the induction of inflammatory mediators, the hyperglycaemia and insulin resistance play important roles in lung pathology. On one hand, the increased blood glucose levels may lead to a rise in glucose concentration in the airway secretion lining fluid (Wood, Brennan, Philips, & Baker, 2004). It has been shown that glucose remains at undetectable levels under normoglycaemic conditions, but can be as high as 9 mM in airways secretions isolated under conditions of hyperglycaemia indicating an airway glucose threshold may exist (Wood et al., 2004). Moreover, the increased glucose levels in airway secretions has been shown to contribute to impairment of lung function (McKeever, Weston, Hubbard, & Fogarty, 2005). On the other hand, hyperglycaemia may also result in the formation of glycosylation end-products (AGEs) which are pro-inflammatory in nature and may accelerate complications in the lungs (Sparvero et al., 2009).

Insulin resistance is predominant at the onset of diabetes resulting in a chronic elevation of circulating basal insulin levels, to overcome the

reduced sensitivity. Over time, the hypersecretion of insulin exhausts pancreatic β -cells leading to a decline in cell mass. Type 2 diabetes manifests when the β -cell is no longer able to hypersecrete insulin to maintain a normal concentration of glucose in the blood (euglycemia) (de Luca & Olefsky, 2008). Hence, insulin resistance is an important feature of the MetS which marks pre-diabetes. In the pulmonary compartment, insulin exerts a number of remodelling effects on airway smooth muscle cells by stimulating proliferation, collagen release, as well as their contractions via β -catenin signalling contributing to airway hyperresponsiveness (Singh et al., 2016). In the context of COPD, a decline in pulmonary function as the disease progresses increases the risk of alveolar hypoxia and consequential hypoxemia (systemic hypoxia) (Vogelmeier et al., 2017). Tissue hypoxia has been proposed to be responsible for many of the maladaptive processes and extra-pulmonary comorbidities that characterize COPD (Kent, Mitchell, & McNicholas, 2011). Indeed, chronic hypoxia produces profound changes in cellular metabolism and insulin sensitivity (Gileles-Hillel, Kheirandish-Gozal, & Gozal, 2016). In adipose tissues, hypoxia creates a state of insulin resistance via the action of hypoxia-inducible factor (HIF), which is a basic helix-loop-helix transcription factor composed of α - and β -subunits (Wang, Jiang, Rue, & Semenza, 1995). Under normoxic conditions, HIF- α is subjected to proline hydroxylation, leading to degradation by the proteasome. Hypoxia inactivates the proline hydroxylases, leading to HIF- α accumulation and formation of a functional heterodimeric transcription factor (Kim, Tchernyshyov, Semenza, & Dang, 2006). HIF activation by hypoxia decreases the phosphorylation of the insulin receptor which subsequently blunts the downstream signalling mediated by Akt, resulting in a reduced glucose transport in response to insulin stimulation (Regazzetti et al., 2009).

In the liver, the role of hypoxia appears to be more complex. Activation of HIF has been reported to increase hepatic insulin sensitivity via induction of insulin receptor substrate 2 (IRS2) (Wei et al., 2013), despite exacerbated hepatic lipid accumulation attributable to induction of lipogenic genes (Qu et al., 2011; Taniguchi et al., 2013). In skeletal muscle, exposure to hypoxia tends to have differential outcomes on insulin sensitivity. Intermittent hypoxia has been demonstrated to induce insulin resistance (Thomas et al., 2017) but chronic hypoxia tends to increase insulin action (Gamboa, Garcia-Cazarin, & Andrade, 2011). The apparent differences are likely to be related to the severity of hypoxia (Lecoultre et al., 2013) and muscle composition (Gamboa et al., 2011) which may determine the adaptation outcome of skeletal muscle. On this note, augmentation of the skeletal muscle AMPK pathway has been shown to counteract the detrimental effects of intermittent hypoxia on whole-body glucose tolerance (Thomas et al., 2017) suggesting the AMPK pathway may be a key adaptation mechanism. Taken together, these findings offer an explanation, at least in part, to the positive correlation observed on insulin sensitivity and lung function (Forno, Han, Muzumdar, & Celedon, 2015).

2.5. COPD and CVD

CVD is one of the most common comorbidities of chronic inflammatory diseases and it is regarded as the leading cause of morbidity and mortality in COPD patients (Divo et al., 2012; Schols et al., 2005; Sin, Anthonisen, Soriano, & Agusti, 2006). Coronary artery disease, hypertension, pulmonary hypertension, and heart failure are probably the most frequently occurring cardiovascular disorders amongst patients with COPD (Bhatt & Dransfield, 2013). These conditions can sometimes overlap and the presence of one or more of these conditions greatly impacts on quality-of-life as well as the survivability of COPD patients accounting for 20%–30% of death in patients with mild to moderate COPD (Bhatt & Dransfield, 2013; Dalal, Shah, Lunacsek, & Hanania, 2011; de Lucas-Ramos et al., 2012).

Although different in their clinical manifestations, CVD conditions are related to atherosclerosis which is the stiffening of the vasculature due to the build up of plaques. The oxidised LDL that is deposited in

the plaques is taken up by macrophages, turning them into lipid-laden foam cells resulting in the stabilization of a collagen-rich fibrous cap with large lipid core on the vessel wall (Dessi et al., 2013; Mizuno et al., 2011). Over time, the fibrous cap encapsulating the enlarged lipid-rich thrombogenic core becomes vulnerable to rupture. Rupture of an atherosclerotic plaque leads to formation of a thrombus which is associated with partial or complete vessel occlusion in a coronary artery resulting in a heart attack or stroke (Bhatt & Dransfield, 2013).

Cigarette smoke exposure is an important risk factor for atherosclerosis initiation and progression due to its oxidative stress-inducing and pro-inflammatory characteristics (Athysros, Katsiki, et al., 2013). Chronic low grade systemic inflammation is present in both COPD and CVD, meanwhile oxidative stress is a major contributor to COPD progression, has also been shown to implicate in CVD (Zampetaki, Dudek, & Mayr, 2013). Indeed, the increased systemic inflammation due to cigarette smoking has been demonstrated to disrupt the stability of vulnerable plaques shifting the vasculature towards a pro-thrombotic state (Man, Van Eeden, & Sin, 2012; Mirrakhimov & Mirrakhimov, 2013). Importantly, cigarette smoking not only promotes systemic inflammation but also promotes dyslipidaemia as aforementioned. Both dyslipidaemia and inflammation are key events for the pathogenesis of atherosclerosis, dyslipidaemia results in increased availability of oxidised LDL for the development of atherosclerotic plaques, sustained systemic inflammation and pulmonary impairment, while in turn systemic inflammation favours the exacerbation of dyslipidaemia forming yet another viscous cycle (Athysros, Katsiki, et al., 2013; Dessi et al., 2013). To make matters worse, hypoxia may arise from cigarette smoking, decline in pulmonary function and/or vessel occlusion due to atherosclerosis which has been shown to alter pulmonary blood flow, resulting in right ventricle hypertrophy and left ventricular diastolic dysfunction which impacts on cardiac function (Larsen et al., 2006). On this note, acute exacerbations of COPD due to secondary infections or exposure to airborne irritants have also been reported to promote myocardial ischemia (Mills et al., 2007).

3. Development of metabolic syndrome in COPD

Both cross-sectional and longitudinal studies have demonstrated that MetS in people with COPD worsens respiratory symptoms and lung function and that this is due to amplified systemic inflammation (Cebon Lipovec et al., 2016; Price et al., 2016; Stanciu et al., 2009). This amplified systemic inflammation can feed forward to exacerbate metabolic abnormalities such as dyslipidaemia and insulin resistance (Saltiel & Olefsky, 2017). It is likely that MetS is a consequence of COPD based on the following observations: 1) MetS is a life style and dietary related disorder and no experimental evidence so far exists to support that dietary and/or life style factors can directly cause COPD in the absence of smoking or airborne irritants; 2) cigarette smoking is an important modifiable risk factor for MetS where smoking cessation has been shown to exert beneficial effects on MetS and its individual components (Chen et al., 2008; Heggen, Svendsen, & Tonstad, 2017; Ishizaka et al., 2005). The next part of this review will focus on the most plausible pathogenic mechanisms linking COPD to MetS.

3.1. Systemic inflammation: the spill over hypothesis

In a multicentre 3-year observational study, the ECLIPSE study investigated systemic inflammation as a distinct phenotype amongst 2164 clinically stable COPD patients (Faner et al., 2014). The study found that COPD is a complex and heterogeneous disease in which not all patients with COPD display elevated markers of inflammation. In fact, about one-third of these patients manifested with no evidence of systemic inflammation during the follow up (Faner et al., 2014). For the majority of the patients manifested with systemic inflammation, the systemic elevation of IL-8 and TNF- α were better correlated with cigarette smoking rather than COPD (Vestbo et al., 2008). The study also

identified a distinctive pattern of systemic inflammation termed “inflammome” which is consisted of elevated white blood cell count, plasma CRP, IL-6 and fibrinogen, that may be used as good biomarkers for mortality and exacerbations in COPD (Agusti et al., 2012). Importantly, 16% of patients with COPD from the study had persistent systemic inflammation, and this was associated with much worse outcomes reflected by a six-fold increase in all-cause mortality in the 3 year of follow up (Agusti et al., 2012). Taken together, the findings from the ECLIPSE study support systemic inflammation as an important driver for the extra-pulmonary complications.

Several theories have been proposed regarding the underlying mechanisms driving the systemic inflammation during COPD. The predominating theory is that the inflammatory process originates in the airways and lung parenchyma, then “spill over” into the systemic circulation (Bernardo et al., 2015; Oh & Sin, 2012). Indeed, several studies have reported an association between COPD and low-grade systemic inflammation. A meta-analysis of these studies (Gan, Man, Senthilselvan, & Sin, 2004) has found that patients with stable COPD have an increased number of activated leukocytes, increased levels of CRP, cytokines (IL-6, TNF- α and their soluble receptors), as well as fibrinogen. The intensity of this systemic manifestation is further augmented during exacerbations (Gan et al., 2004; Wedzicha et al., 2000). While this spill over of the local inflammation into the circulation is primarily attributed to the increased membrane permeability as mentioned previously, direct damage can also occur in the pulmonary compartment due to the oxidants found in cigarette smoke and from excessive levels of ROS and reactive nitrogen species (RNS) produced as a result of both pulmonary and systemic inflammation (Bernardo et al., 2015).

As cellular inflammation is an important cue for the manifestation of systemic inflammation (Editorial, 2017), hence identifying the cellular source of inflammation may be a key to arrest the systemic pathologies. An important cellular source of inflammatory mediators in COPD are resident and recruited macrophage populations in COPD. The monocyte-macrophage lineage is a heterogeneous population of cells with significant phenotypic plasticity to acquire the functional phenotypes depending on the microenvironment (Vlahos & Bozinovski, 2014). The M1 phenotype produces pro-inflammatory cytokines (eg. IL-6, TNF- α & IL-1 β), and RNS and ROS that exhibit strong microbicidal and tumoricidal activity. In contrast, the M2 phenotype induces the expression of anti-inflammatory cytokines (eg. IL-10 & IL-1ra), and molecules (eg. VEGF & MMP9) implicated in tissue repair and remodeling (Gordon & Taylor, 2005). In general, glycolytic metabolism supports M1 polarization, whereas M2 macrophage predominantly rely on mitochondrial oxidative phosphorylation for energy metabolism. For this reason, changes in metabolism have been proposed to govern the phenotype of immune cells by controlling transcriptional and post-transcriptional events that are central to activation (O'Neill & Pearce, 2016). At a glance, this may lead us to think that cigarette smoking may be driving systemic inflammation by predominantly influencing glycolytic metabolism in immune cells residing in the lung, particularly the alveolar macrophages (AM). However, AM isolated from smokers exhibit a coordinated down-regulation of a considerable number of genes typical for M1 polarization, with a concomitant induction of a panel of genes that are typical of the M2 phenotype (Shaykhiev et al., 2009), suggesting cigarette smoke may induce reprogramming of AM toward M1-deactivated, and M2-polarized. In line with this, experimental evidence in a rodent COPD model found increased deposition of M2 AM (He, Xie, Lu, & Sun, 2017). Intriguingly, a recent study also observed attenuated glycolytic reserve and spare respiratory capacity in AM from smokers leading to impairment of glycolytic response to infection (Gleeson et al., 2018). Although counter intuitive, the findings are not entirely surprising particularly from a host defence perspective. As suppression of M1-activation and glycolytic metabolism in smokers is consistent with the epidemiologic data that smokers with/without COPD are more susceptible to respiratory tract infection than non-smokers (Murin & Bilello, 2005). It is therefore possible that persistent lung

infection might develop in smokers with advanced COPD, due to deactivation of the M1 polarization program in AM. This in turn may trigger a compensatory inflammatory response that is maladaptive in nature, leading to excessive production of pro-inflammatory mediators and chronic inflammation.

Chronic low-grade inflammation is a hallmark feature of obesity, dyslipidaemia, insulin resistance and type 2 diabetes, which are key features of the MetS (Fabbri & Rabe, 2007; Saltiel & Olefsky, 2017). Over the past decade, it has become increasingly evident that systemic inflammation is a major contributor to the pathogenesis of MetS leading to more life-threatening diseases such as CVD and cancer (Hotamisligil, Budavari, Murray, & Spiegelman, 1994; Pothiwala, Jain, & Yaturu, 2009; Roytblat et al., 2000; Sartipy & Loskutoff, 2003; Serino et al., 2007; Straczkowski et al., 2002). Elevated levels of TNF- α , IL-6, IL-8 and CRP have all been reported in COPD patients with various degrees of MetS (Cazzola et al., 2017; Kupeli et al., 2010; Stanciu et al., 2009). Systemic elevation of TNF- α (Uysal, Wiesbrock, Marino, & Hotamisligil, 1997) and IL-6 (Cai et al., 2005) have been shown to promote insulin resistance particularly in the context of obesity. IL-8 is a chemotactic cytokine responsible for amplification of inflammation via the recruitment and activation of mononuclear cells. Similar to TNF- α and IL-6, IL-8 has been demonstrated to directly attenuate the metabolic actions of insulin by inhibiting its receptor signal transduction (Kobashi et al., 2009). Moreover, IL-8 is a chemotactic cytokine responsible for amplification of inflammation via the recruitment and activation of mononuclear cells which could also result in the worsening of insulin resistance states (de Luca & Olefsky, 2008). The release of pro-inflammatory cytokines like TNF- α and IL-6 into systemic compartments can mediate distal inflammatory effects, including activation of hepatic genes encoding acute phase reactants including fibrinogen, CRP, and serum amyloid A which constitute an important cue for the onset of systemic inflammation (Gabay & Kushner, 1999). CRP is probably the best characterised acute phase reactants of all and is commonly reported to be elevated under conditions of MetS (de Luca & Olefsky, 2008). CRP stimulates further cytokine release, as well as the synthesis of cell adhesion molecules and tissue factors in monocytes and endothelial cells which in turn could activate the extrinsic coagulation cascade (Koh, 2002). Meanwhile, our laboratory has shown that serum amyloid A is highly elevated during AECOPD which is capable of causing skeletal muscle atrophy by eliciting a robust pro-inflammatory response driven by Toll-like receptor 2 (TLR2) which may explain the common metabolic and CVD comorbidities of these two diseases. On the contrary, improvement of pulmonary function (Zhang et al., 2017), regular physical activity (Balducci et al., 2010), recovery from events of exacerbation (Perera et al., 2007), as well as improvements in body mass index (McDonald et al., 2016) via dietary and exercise interventions are associated with a reduction of systemic inflammation and better disease outcomes for both COPD and MetS patients.

3.2. Adipose tissue: a critical source of inflammatory mediators

As described above, elevated inflammatory markers such as IL-6, TNF- α , and CRP are a common feature of both COPD and MetS. However, these markers are elevated to a greater extent in obese patients (Rana et al., 2004) which heightens the importance of obesity in the process of inflammation. Indeed, abdominal obesity has been shown to have the strongest association with lung function impairment (Leone et al., 2009). Obesity is regarded as a state of inflammation characterized by low-grade, chronic inflammation orchestrated by metabolic tissues/cells in response to excess nutrients and energy (Gregor & Hotamisligil, 2011; Hotamisligil, 2010). Adipose tissue can respond rapidly and dynamically to nutrient availability particularly in the condition of excess, through adipose tissue expansion, thereby fulfilling its major role in whole-body energy homeostasis.

Adipose tissue is not just a fat depot, but rather an endocrine organ that is actively involved in a wide range of metabolic processes

including inflammation, insulin sensitivity, lipid metabolism and blood pressure regulation (Kajimura, 2017). The adipose tissue is comprised of adipocytes, macrophages and endothelial cells which are capable of synthesizing and secreting proteins (i.e. adipokines) such as pro-inflammatory cytokines (TNF- α , IL-6, IFN γ), metabolic hormones (adiponectin, resistin, adipisin, leptin), growth factors (vascular endothelial growth factor [VEGF]) and blood pressure regulators (Plasminogen activator inhibitor-1 [PAI-1] and components of the renin-angiotensin system) which may exert local and systemic effects (Kajimura, 2017). Adipose tissue expansion is an important physiological process in response to nutritional surplus allowing for the storage of excess energy as fat. Healthy adipose tissue expansion is a highly orchestrated process with effective recruitment of precursor cells, adequate angiogenesis and appropriate remodelling of the extracellular matrix. However, rapid weight gain seen in obesity can lead to pathological adipose tissue expansion characterised by massive enlargement (hypertrophy) of existing adipocytes (Sun, Kusminski, & Scherer, 2011). This rapid rate of expansion often outpaces the rate of angiogenesis resulting in poor oxygenation and local hypoxia within deeper parts of the tissue (Halberg et al., 2009; Kabon et al., 2004). Adipose tissue hypoxia is a form of cellular stress which stimulates the production of pro-inflammatory mediators IL-6, TNF- α , macrophage migration inhibitory factor, VEGF, tissue inhibitor of metalloproteinases-1, leptin, and monocyte chemotactic proteins, while concomitantly downregulating the expression of adiponectin, a renowned anti-inflammatory adipokine resulting in an overall shift of balance towards inflammation (Hosogai et al., 2007; Lolmede, Durand de Saint Front, Galitzky, Lafontan, & Bouloumie, 2003). In line with this concept, acute exacerbations of COPD have been reported to associate with increased levels of serum leptin and an increased ratio of leptin to adiponectin, as well as elevations of the classic pro-inflammatory markers such as IL-6, TNF- α and their soluble receptors in the circulation (Krommidas et al., 2010; Yamauchi et al., 2001). On the contrary, increased circulatory levels of adiponectin were detected upon resolution of the exacerbation (Krommidas et al., 2010) suggesting adipose tissue might be an important source of inflammation in COPD patients with weight gain issues.

In addition to promoting systemic inflammation, these adipocyte-released cytokines may exert negative effects on metabolism. For example, TNF- α may increase systemic insulin resistance by promoting the release of fatty acids from adipose tissue into the bloodstream to act on tissues such as muscle and liver (Gregor & Hotamisligil, 2011; Hotamisligil, Shargill, & Spiegelman, 1993). TNF- α is also a potent stimulus for the production and release of IL-6 and IL-8 from adipocytes (Bruun, Pedersen, Kristensen, & Richelsen, 2002) which in turn promotes further release of fatty acids from adipose tissue lipolysis (Greenberg et al., 1992). Furthermore, TNF- α has also been demonstrated to promote the synthesis of leptin from adipose tissue (Zumbach et al., 1997). Leptin has strong immunoregulatory activity which up-regulates expression of pro-inflammatory cytokines (Loffreda et al., 1998). On this note, increased circulatory leptin levels correlate with impairment of lung function (Sin & Man, 2003a). Previous experimental and clinical research indicates the involvement of leptin in body weight homeostasis. Leptin is a hormone produced by the adipose tissue responsible for regulating energy balance in a feedback mechanism involving the hypothalamus. The normal leptin feedback mechanism can be disturbed by several factors. In rodents, administration of endotoxin or pro-inflammatory cytokines like TNF- α resulted in a dose-dependent up-regulation of leptin mRNA in adipose tissue and elevation of circulating leptin concentrations (Grunfeld et al., 1996; Sarraf et al., 1997). In stable patients with emphysema, leptin was found to be positively associated with soluble TNF receptor-55 (Schols et al., 1999). Hence, a disturbed leptin feedback mechanism might offer an explanation, at least in part for the augmented leptin levels particularly during episodes of exacerbation where the systemic inflammatory response may be more pronounced than in stable patients (Saetta et al., 1994).

In contrast to leptin, adiponectin is probably the only adipocyte-derived factor with demonstrated anti-inflammatory properties. Adiponectin reduces the production and activity of TNF- α , inhibits IL-6 production, and induces the production of anti-inflammatory cytokines in epithelial cells and monocytes/macrophages (Takeda, Nakanishi, Tachibana, & Kumanogoh, 2012; Wolf, Wolf, Rumpold, Enrich, & Tilg, 2004). In human and animal models, adiponectin promotes whole-body insulin sensitivity and glucose homeostasis (Kadowaki et al., 2006). The angiogenic effect of adiponectin also helps to improve vascularization during adipose tissue expansion, preventing the onset of inflammation due to local hypoxia (Kim et al., 2007). A growing body of evidence demonstrates that adiponectin may also act on the endothelial cells to maintain vascular homeostasis and offer protection against vascular dysfunction commonly associated with COPD and MetS (Kim et al., 2007). Indeed, adiponectin is inversely associated with both smoking and diabetes incidence and that it may also be the most probable mediator for the association between current smoking and MetS (Hilawe et al., 2015).

Of interest, several animal studies have detected the expression of the leptin receptor in lung tissue (Chelikani, Glimm, & Kennelly, 2003; Henson et al., 2004; Hoggard et al., 1997). In humans, the different leptin receptor isoforms are found to be expressed in airway smooth muscle cells (Nair et al., 2008), epithelial cells and submucosa of the lung (Bruno et al., 2005). Although the functional significance of these receptors is presently unknown, the existence of leptin receptors indicates that the lung may also be a target organ for leptin signalling (Malli, Papaioannou, Gourgoulis, & Daniil, 2010). In support of this, not just leptin, but receptors for adiponectin have been found to be expressed in the lung (Miller, Cho, Pham, Ramsdell, & Broide, 2009). Importantly, leptin expression is increased in the bronchial mucosa of COPD patients and a functional leptin signalling pathway has been demonstrated to exist in lung epithelial cells (Vernooy et al., 2009). Moreover, experimental evidence indicates that adiponectin may attenuate airway inflammation and airway hyperresponsiveness in mice following allergen exposure (Shore, Terry, Flynt, Xu, & Hug, 2006). These findings suggest the existence of a cross-talk between adipose tissue and lungs which may serve as a mechanistic link for the inflammatory basis of COPD and MetS.

In addition to local adipose tissue hypoxia, systemic hypoxia resulting from reduced pulmonary function is also believed to be an important cue for pro-inflammatory cytokine expression (Bernardo et al., 2015). It is however presently unclear whether systemic hypoxia exerts additional or multiplicative effects on adipose tissue in patients with COPD and concurrent obesity (Tkacova, 2010). Perhaps experimental evidence derived from sleep apnoea may shed light upon this. It is well-established that intermittent systemic hypoxia resulting from sleep apnoea is associated with systemic inflammation (da Rosa et al., 2012; Gileles-Hillel et al., 2017; Perrini et al., 2017). More importantly, intermittent systemic hypoxia may profoundly impact on metabolic homeostasis. Chronic intermittent hypoxia promotes dysregulation of lipid (Li et al., 2005) and cholesterol biosynthesis (Li et al., 2007), impairment of insulin sensitivity (Murphy et al., 2017), as well as disruption to the normal diurnal rhythm leading to hyperglycaemia and raising susceptibility of pancreatic β -cells to hypoxia-induced death (Yokoe et al., 2008). There is also evidence to suggest that adipose tissue becomes inflamed in response to intermittent hypoxia which in turn drives the onset of insulin resistance (Murphy et al., 2017). These findings are suggestive of adipose tissue dysfunction as an important mechanism for disease development and that further studies are warranted to analyse adipose tissue inflammation during stable COPD and acute exacerbations.

3.3. Oxidative stress: an under recognized link between COPD and MetS

Oxidative stress is an imbalance between the oxidant and antioxidant levels in favour of a pro-oxidant environment in cells and tissues

(Srinivasan et al., 2013). In COPD patients, oxidative stress may arise from inhalation of oxidants by cigarette smoke or airborne irritants, or as a result of the host inflammatory response where activated leukocytes release ROS (Bernardo et al., 2015). If uncontrolled, these oxidants can cause direct damage to the lung through oxidation of cellular components and molecules. This can lead to the activation of signalling pathways such as those mediated by NF κ B, resulting in the production of pro-inflammatory mediators as aforementioned which favours the development of systemic inflammation (Cyphert et al., 2015; Man et al., 2012; Oh & Sin, 2012). Oxidative stress is also apparent in MetS. Unlike COPD, oxidative stress in this context mainly arises from activation of specific biochemical pathways (e.g. oxidative metabolism in mitochondria), increased cellular production as a result of inflammation, exhaustion of cellular antioxidant mechanisms, as well as lipid peroxidation which is typically seen during obesity (Furukawa et al., 2004). Due to its pro-inflammatory nature, the presence of oxidative stress has been suggested to be the most probable link for the increased cardiovascular comorbidity risk in COPD and MetS (Hutcheson & Rocic, 2012).

On one hand, a prolonged increase in oxidative stress due to cigarette smoking has been shown to promote the development of diabetes via the upsurge of insulin resistance. On the other hand, oxidative stress by MetS may cause further impairment of pulmonary function by activating inflammation (Cyphert et al., 2015; Kim et al., 2010; Kobashi et al., 2009; Minas et al., 2011). The close inter-relationship between COPD and MetS discussed this far may be in favour of cigarette smoking being a link for these diseases. Indeed, the oxidative properties of cigarette smoke is crucial for the initiation of COPD (Vogelmeier et al., 2017) and at the same time, cigarette smoking is also an independent and modifiable risk factor for MetS (Willi, Bodenmann, Ghali, Faris, & Cornuz, 2007). However, cigarette smoking itself is currently not a recognized link between COPD and MetS (Cazzola et al., 2010) indicating further work is needed in this area.

3.4. Physical inactivity: a cause or a consequence?

Regular physical activity offers many health benefits and reduces the risk of various comorbidities (Dietz, Douglas, & Brownson, 2016). However, COPD patients are reported to have reduced physical activity, which is further hampered in the presence of concurrent MetS (Clini et al., 2013). It is well recognised that loss of fat-free mass contributes to muscle weakness and reduced exercise capacity, a condition known as muscle wasting in patients with moderate to severe COPD (Passey et al., 2016). In obese patients with COPD, increased contractile muscle effort is required to sustain ventilation during exercise to overcome the serious mechanical constraints from airflow obstructions. As a result of this, these patients present with more severe incapacitating dyspnoea when they exercise compared to non-obese patients with COPD (Monteiro et al., 2012). Therefore, having COPD may increase the propensity of weight gain and obesity by limiting physical activity thus predisposing the patients to develop MetS. In return, MetS can place further constraint on physical activity which in turn would contribute to a decline in pulmonary function and promote the progression of COPD severity (Hartman et al., 2010).

On the contrary, regular physical activity is well documented to counteract systemic inflammation, pulmonary dysfunction and muscle wasting (Passey et al., 2016). Increasing levels of physical activity are associated with reduced levels of CRP, a negative prognostic factor for the development of cardiovascular comorbidities in COPD patients (Abramson & Vaccarino, 2002; Ford, 2002). Furthermore, in patients with MetS, modest exercise can reduce peripheral markers of inflammation namely MCP-1 and IL-8 (Troseid et al., 2004). Importantly, exercise training has been proven to be beneficial in COPD patients in terms of pulmonary function and quality of life owing to, at least in part by the improved peripheral muscle function (Passey et al., 2016). From the perspective of glucose homeostasis, muscle is a major organ for glucose

utilization and energy expenditure. Increased exercise capacity due to improved muscle function restores glucose metabolism via means of insulin-dependent and -independent mechanisms (Holloszy, 2005). Regular physical activity has been demonstrated to exert protective effects against oxidative stress via induction of antioxidant pathways (de Sousa et al., 2017). When combined with proper dietary regime, exercise training is also effective in combating obesity, achieving better weight-control, as well as restoring endothelial function which greatly reduces individual's risk of cardiovascular comorbidities (Johansson, Neovius, & Hemmingsson, 2014; Moien-Afshari et al., 2008). Meanwhile, better weight-control also confers better quality of life in COPD patients. Taken together, both experimental and epidemiological evidence demonstrates that impaired physical activity is a key factor in the pathogenesis of MetS in COPD patients.

3.5. Inadequacy of steroids for COPD management

Inhaled and oral glucocorticoids are used frequently but are inadequate to treat patients with COPD.

In a multicentre study involving 912 mild COPD patients, the EUROSCOP (Pauwels et al., 1999) demonstrated inhaled glucocorticoids offer no long-term benefits on lung function decline over the three year follow up, despite small short-term benefits. In the 751 moderate-severe COPD cohort, the ISOLDE study (Burge et al., 2000) reported glucocorticoids did not affect the rate of FEV₁ decline but was associated with fewer exacerbations and a slower decline in health status. On the contrary, the TORCH study (Calverley et al., 2007) conducted on 6,112 patients with moderate-severe COPD patients, found that glucocorticoid therapy was associated with a slower decline in FEV₁. However, such benefit did not translate into better survival rate, and that patients receiving glucocorticoid medication containing fluticasone were at greater risk of having pneumonia.

Overall, the short-term improvement in lung function may help shorten hospital stays which may provide support for the use of glucocorticoid therapy on patients experiencing AECOPD. However, excessive use of glucocorticoids has profound effects on most of the parameters of the metabolic syndrome (Di Dalmazi, Pagotto, Pasquali, & Vicennati, 2012). Firstly, glucocorticoids can impair pancreatic β -cell function by disrupting the uptake and the metabolism of glucose (van Raalte, Ouwens, & Diamant, 2009). Secondly, glucocorticoids have been shown to exert anti-insulin action in liver, skeletal muscle and adipose tissue (Mazziotti, Gazzaruso, & Giustina, 2011) which are key organs for maintaining metabolic homeostasis. Disruption of insulin's actions in these organs has profound metabolic consequences particularly in the postprandial states. Insulin promotes the uptake and storage of glucose as glycogen in muscle and triglycerides in adipose tissue, while lipolysis is concomitantly repressed via the inhibition of fatty acid releasing enzymes. Importantly, insulin also suppresses hepatic gluconeogenesis and glycogenolysis to aid glycaemic control under fed states (Petersen, Vatner, & Shulman, 2017). Failure to do so will render the development of insulin resistance. The anti-insulin action of glucocorticoids on one hand dampens the activity of key signalling molecules upon insulin receptor activation namely the insulin receptor substrate-1 (IRS-1), PI3K/Akt pathway resulting in impaired translocation of glucose transporters to the cell surface and a decrease in glucose uptake by these tissues (Mazziotti et al., 2011; Petersen et al., 2017). While on the other hand, glucocorticoids stimulate activation of rate-limiting enzymes involved in gluconeogenesis, such as phosphoenolpyruvate carboxykinase (PEPCK) (Cassuto et al., 2005).

Thirdly, glucocorticoids oppose the suppressive effect of insulin and stimulate lipolysis in adipose tissues causing elevation of free fatty acids which contribute to the impairment of glucose uptake into peripheral tissues contributing to hyperglycaemia (Mazziotti et al., 2011). The lipolytic effect of glucocorticoids also promotes the abnormal distribution of body fat towards the visceral depot (Mazziotti et al., 2011) creating central/abdominal-obesity. Central-obesity is the most prevalent

manifestation of MetS and reflective of dysfunctional adipose tissue which favours the development of insulin resistance (Despres & Lemieux, 2006). Strikingly, cigarette smoking itself is linked to the preferential deposition of visceral fat in that smokers often have more abdominal adipose mass than non-smokers even after adjustments for total adiposity (Barrett-Connor & Khaw, 1989; Shimokata, Muller, & Andres, 1989). Finally, glucocorticoids may interfere with the expression and activity profiles of adipose tissue-derived cytokines (i.e. adipokines) such as adiponectin, leptin which in turn may impair insulin sensitivity (Bianco et al., 2013; Mazziotti et al., 2011; Takeda et al., 2012).

In addition to exogenous administration, endogenous biosynthesis and degradation of steroid hormones also appear to play a role in the development of MetS. Tobacco contains 11 β -hydroxysteroid dehydrogenase type 2 inhibitor - glycyrrhizic acid which can inhibit the conversion of cortisol to inactive cortisone (Gilbert & Lim, 2008) leading to a prolonged bioavailability and extended activity. Moreover, persistent hypoxia may increase catecholamine output (Kanstrup et al., 1999) leading to the development of hyperglycaemia via inhibition of the actions of insulin (Barth et al., 2007). Regardless of the source, hypercortisolism resulting from either exogenous or endogenous origins causes proximal muscle weakness (Mazziotti et al., 2011) which may pose additional constraints on an individual's daily activity levels, increasing the propensity of further complications. As a whole, this evidence suggest abnormalities in steroid hormone metabolism and action are likely to be the missing links connecting COPD to MetS.

3.6. Hyperglycaemia: an intersection for COPD and MetS

Hyperglycaemia is a condition characterized by an elevated blood glucose concentration >11.1 mmol·L⁻¹ and a diagnostic feature of type 2 diabetes. The first evidence to suggest the concept that alterations in pulmonary function may precede the onset of MetS come from a prospective study on lung function in diabetic adults (Yeh et al., 2008). Following that, using a mouse model in which the pro-inflammatory cytokine IL-18 was specifically overexpressed in the lung, Takenaka et al. (Takenaka et al., 2014) observed severe emphysematous changes, pulmonary hypertension and pulmonary dysfunction in these mice, features which are seen in human COPD. Importantly, these mice went on to develop glucose intolerance later in life which provides compelling evidence to support a direct causal relationship between pulmonary inflammation and metabolic disturbance. Essentially, all of the afore-described mechanisms can directly cause or contribute to the manifestation of hyperglycaemia. Pro-inflammatory cytokines, leptin, oxidative stress, use of steroid medications and endogenous hormonal imbalance disrupts glucose homeostasis by interfering with insulin actions (Mirrahimov, 2012). In fact, hyperglycaemia is a major side effect of glucocorticoid medications use in AECOPD (Baker et al., 2006). While diminished physical activity arising from these conditions may offer another plausible mechanism for the continuation of hyperglycaemia, as regular physical activity and less sedentary time are associated with reduced risk of such comorbidities (Park & Larson, 2014).

Hyperglycaemia is the golden hallmark for the onset of diabetes (WHO, 2006). Moreover, persistent hyperglycaemia can give rise to more serious complications such as CVD, neuropathy and nephropathy resulting in mortality. The impact does not end here, once developed, hyperglycaemia may in turn potentiate the pathogenesis and clinical course of COPD. Experimental evidence in humans demonstrated that hyperglycaemia stimulates pro-inflammatory cytokines, including TNF- α , IL-6 and IL-18 in the circulation (Esposito et al., 2002). In separate studies, increased levels of CRP were detected in individuals with impaired fasting glucose levels (Andreozzi et al., 2007; Choi et al., 2004) which is suggestive of systemic inflammation by hyperglycaemia. In line with this, diabetic patients with AECOPD are reported to frequently display hyperglycaemia (up to 80% of the studied cases) during their hospital stay, which is also associated with extended length of

hospitalization and mortality when compared to non-diabetic patients (Baker et al., 2006; Parappil et al., 2010). Moreover, blood glucose levels of ≥ 7 mM have been found to significantly correlate with adverse AECOPD outcomes (Chakrabarti, Angus, Agarwal, Lane, & Calverley, 2009). Moreover, this relationship is marked by a 15% increase in risk of death and/or long inpatient stay for every 1 mmol·L⁻¹ increment in blood glucose (Baker et al., 2006). A retrospective study of administrative claims data from the Australian Government Department of Veterans' Affairs also revealed that COPD patients with diabetes are at significantly increased risk of diabetes-related hospitalizations upon high-dose corticosteroid therapy (Caughey, Preiss, Vitry, Gilbert, & Roughead, 2013).

In addition to systemic inflammation, *in vivo* studies have demonstrated that chronic hyperglycaemia can trigger endothelial dysfunction in blood vessels of diabetic patients via the excessive generation of ROS (Ceriello, 2006). Nevertheless, the most significant consequence of hyperglycaemia still lies with its impact on pulmonary function. The increased levels of ROS induced by hyperglycaemia can lead to the activation of cellular stress pathways such as those mediated by MAPK and NF κ B to impair pulmonary function (Tiengo, Fadini, & Avogaro, 2008). In isolated human bronchi, high glucose concentrations can lead to enhance responsiveness of airway smooth muscle cells to a contractile agent via a specific cellular pathway mediated by Rho-kinase (Cazzola et al., 2012). Enhanced airway hyperresponsiveness is a major risk factor for the accelerated decline in pulmonary function seen in COPD patients. Furthermore, hyperglycaemia may also increase the risk of pulmonary infections by rendering the appearance of glucose in airway secretion, making the respiratory tracts vulnerable to infectious exacerbations (Cazzola et al., 2012; McKeever et al., 2005). Finally, hyperglycaemia may also target the diaphragm which is a major respiratory muscle. The oxidative stress and inflammation inflicted by hyperglycaemia can result in sarcomeric injury via activation of proteolytic machinery, leading to contractile protein wasting and, consequently, a loss of force generating capacity of diaphragm fibers in patients with COPD (Ottenheijm, Heunks, & Dekhuijzen, 2008). This finding is strengthened by the striking observation that, pulmonary function impairment is more prominent in patients with poorly controlled blood glucose levels independent of obesity and age (Rogliani, Calzetta, Segreti, Barrile, & Cazzola, 2014).

3.7. Aging and hypogonadism

Hypogonadism is a condition of androgen deficiency combined with otherwise unexplained fatigue or diminished energy, a diminished sense of vitality, or a diminished sense of well-being which are commonly experienced by patients with COPD (Laghi et al., 2005). Hypogonadism arises from a decline in serum testosterone which is frequently associated with aging and chronic illness (Rhoden & Morgentaler, 2004). The prevalence of hypogonadism in COPD patients ranges from 22% to 69% and has been associated with several other systemic manifestations including osteoporosis, depression, and muscle weakness (Balasubramanian & Naing, 2012). In addition to aging, the potential causes of hypogonadism in COPD includes systemic hypoxia, hypercapnia and glucocorticoid therapy (Balasubramanian & Naing, 2012) with systemic inflammation being the underlying driver (Agusti, 2007; Barnes & Celli, 2009) indicating COPD conditions might give rise to hypogonadism. However, a lack of correlation was reported between testosterone levels and severity of airway obstruction suggesting hypogonadism may not directly contribute to respiratory symptoms (Van Vliet et al., 2005). As aging, muscle weakness, systemic hypoxia, glucocorticoid use and systemic inflammation are all pathogenic cues for MetS, it is possible that MetS might serve as a connecting piece to this puzzle. In a longitudinal study involving 1,296 male patients with various stages of the disease and without additional intervention for three years found that low testosterone levels strongly correlated with higher BMI (Spearman's $r = -0.47$) meanwhile no correlation was

found between testosterone level and FEV₁ (Wang et al., 2012). In a separate study involving 101 middle-aged men with stable COPD, greater BMI was also observed in patients with hypogonadism when compared to those without (Laghi et al., 2005). Moreover, it has been reported that hypogonadism is closely linked to MetS. Hypogonadal individuals are at risk of diabetes due to the unfavourable change in body composition which promotes the accumulation of body fat while decreasing muscle mass with a concomitant decrease in insulin sensitivity, muscle strength and oxygen consumption capacity (Bojesen, Host, & Gravholt, 2010). Meanwhile, MetS has also been shown to promote the development of hypogonadism (Gautier et al., 2013). For this reason, hypogonadism has been proposed to be a fundamental component of MetS. Indeed, testosterone therapies have been shown to have great potential in slowing or halting the progression of metabolic syndrome to more overt complications such as full-blown diabetes or cardiovascular disease via beneficial effects on insulin regulation, lipid profile and blood pressure (Makhsida, Shah, Yan, Fisch, & Shabsigh, 2005). This evidence suggests that the level of testosterone may play a pivotal role in the development of MetS, particularly in aging patient with COPD. On the contrary, female sex-hormones also appear to impact on lung physiology as chronic exposure of mice to cigarette smoke has been reported to induce emphysematous-like changes in the alveolar structure more rapidly in females than in males (Carey et al., 2007). This was partly explained by an observation that estradiol may up-regulate cytochrome P450 enzymes which in turns makes the female lungs more susceptible to oxidant damage in response to cigarette smoke (Van Winkle, Gunderson, Shimizu, Baker, & Brown, 2002).

4. Clinical implications of MetS and COPD

Several key pieces of evidence have recently suggested that the co-existence of MetS can worsen the progression and prognosis of COPD. First of all, the negative impact of diabetes on COPD was clearly demonstrated by the ECLIPSE study, which is a large multi-centre investigation that sought to define distinct phenotypes and identify biomarkers that predict the progression of COPD. In a cohort consisting of 2,164 clinically stable COPD subjects, as well as 337 smokers and 245 non-smokers with normal lung function, the study identified that diabetes increased the odds of mortality when coexistent with COPD (Faner et al., 2014). Moreover, diabetes was also found to be associated with greater dyspnoea scores and reduced 6-min walking distance which are indicative of pulmonary function decline. On this note, pulmonary function decline evidenced by reduced FEV₁ is also related to increased requirement for inhalational glucocorticoids to control the disease (Cecere et al., 2011) which in turns favours the continuation of MetS. Moreover, pulmonary hypertension has been found to be more severe in patients with concurrent COPD and diabetes (Makarevich et al., 2007). The coexistence of MetS, particularly hyperglycaemia that is typically seen in poorly controlled diabetes greatly increases the length of hospitalization and risk of mortality in patients with AECOPD (Baker et al., 2006; Parappil et al., 2010) and this association is exacerbated with advancing age (Stojkovicj et al., 2016; Vogelmeier et al., 2017). Importantly, there is an increasing prevalence of MetS amongst the younger population (Zimmet & Alberti, 2008). Despite having less severe COPD, these younger patients with MetS had higher circulating levels of leptin, lower

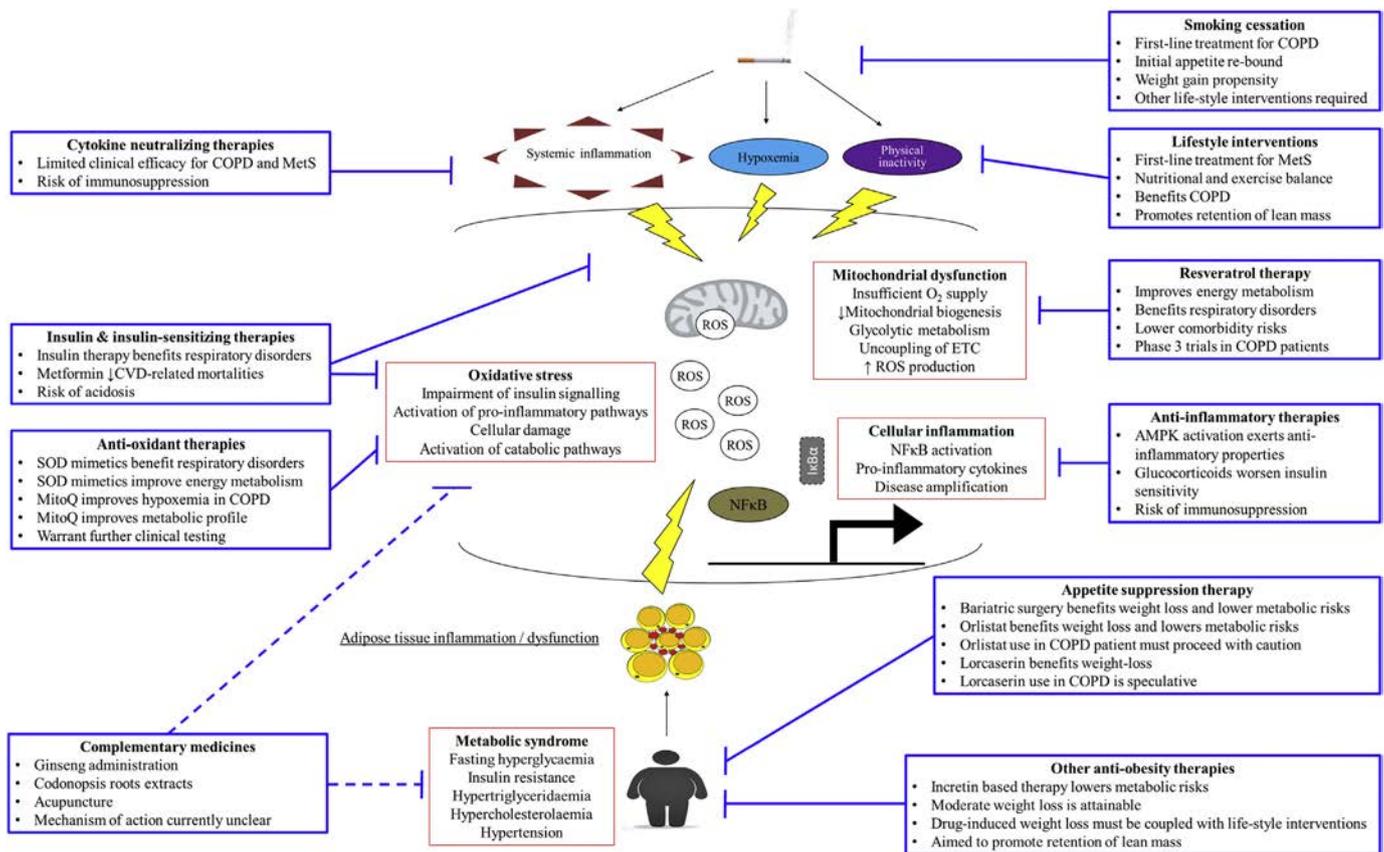


Fig. 2. Summary of therapeutic strategies that may benefit MetS and COPD outcomes. Systemic inflammation, hypoxemia, physical inactivity resulting from cigarette smoking may have a profound impact on metabolic homeostasis. At the cellular level, these events promote impairment of mitochondrial function and biogenesis, leading to the excessive production of ROS which depletes cellular antioxidant defence giving rise to oxidative stress. Oxidative stress i) inhibits major metabolic pathways such as glucose metabolism by insulin, ii) activates cellular pro-inflammatory pathways mediated by NFκB, iii) damages cells by oxidative modification of protein, DNA and lipids, and iv) activates adaptive pathways which are generally catabolic in nature. The NFκB-driven inflammation generates cytokines which exacerbate systemic inflammation, causing amplification of the disease. The coexistence of obesity may enforce the onset of metabolic derangements which may accelerate the systemic manifestation of COPD and related comorbidities. Hence, a number of strategies have been developed to target the various contributory aspects of COPD and MetS. So far, experimental and clinical evidence support the reversal of metabolic derangement as a viable therapeutic strategy for treating COPD comorbidities which may benefit the outcome of COPD.

levels of adiponectin and increased insulin resistance reflected by Homeostatic Model Assessment (HOMA) index, compared with patients without MetS (Minas et al., 2011). Conversely, the literature also indicated COPD may be an important risk factor for the onset and continuation of MetS (Breyer et al., 2014; Cebon Lipovec et al., 2016). Taken together, MetS represents an important mechanism for the negative outcomes seen in COPD patients, and for this reason patients with concurrent existence of these conditions should be treated as “high-risk” and should be placed under close monitoring.

4.1. Therapeutic strategies that may benefit MetS and COPD outcomes: targeting smoking

As cigarette smoking is a recognized modifiable risk factor for MetS (Harris, Zopey, & Friedman, 2016) and COPD (Vogelmeier et al., 2017), early smoking cessation should in theory address much of the pathologies arising from these diseases. Indeed, smoking cessation is regarded as the first-line of treatment for avoiding or reducing the progression of COPD (Vogelmeier et al., 2017). Smoking cessation is most effective at lowering the risk for cardiovascular comorbidities and lung cancer (Fig. 2). The benefits on CVD are almost immediate. Within 24 hours of smoking cessation, there are significant improvements in blood pressure and heart rate. Within one year of abstinence, the risk of cardiovascular events such as myocardial infarction and stroke is reduced by half when compared to those continuing smoking. Between 5 and 15 years post-smoking, the risk of stroke and coronary heart disease is “normalized” to that of never smokers (Wu & Sin, 2011). However, the full benefits of tobacco treatment may not be realized until many years of abstinence. For example, the benefits of smoking cessation on the risk of lung cancer might not be evidenced until after about 10 years of abstinence (Anthonisen et al., 2005). This is probably partly explained by the presence of ongoing airway inflammation in ex-smokers (Godtfredsen et al., 2008). Indeed, controversy exists whether the pathologies of airway inflammation may benefit from smoking cessation due to opposing findings in the literature (Gamble et al., 2007; Turato et al., 1995; Willemse et al., 2005) which are likely to be influenced by smoking history, cessation compliance, ethnicity, and other underlying factors such as genetic susceptibility (Yang, Holloway, & Fong, 2013). Nonetheless, smoking cessation in COPD patients is generally associated with slower rate of pulmonary function decline, lung inflammation and oxidative stress (Anthonisen et al., 2005; Athyros, Katsiki, et al., 2013; Godtfredsen et al., 2008) which in turns leads to improved survival rate compared with continuing smokers (Godtfredsen et al., 2008).

On the metabolic front, smoking cessation is known to have beneficial effects on insulin sensitivity. However, this is often accompanied by a paradoxical body weight gain which could render the subsequent re-emergence of insulin resistance (Harris et al., 2016). This is due to the profound effects of nicotine exposure on metabolism. Nicotine stimulates the activation of lipoprotein lipase that breaks down triglycerides to form free fatty acids. At the same time, nicotine promotes energy expenditure and the production of leptin from adipose tissue by stimulating the release of catecholamines (Liu, Mizuta, & Matsukura, 2003). Nicotine also activates $\alpha 3\beta 4$ nicotinic acetylcholine receptors in the hypothalamus leading to activation of pro-opiomelanocortin (POMC) neurons. POMC neurons and subsequent activation of melanocortin 4 receptors lead to suppression of appetite (Mineur et al., 2011). The appetite suppressive effect of nicotine is reinforced by the high level of leptin in the circulation (Wynne, Stanley, McGowan, & Bloom, 2005). Weight loss is generally associated with improved metabolic parameters such as insulin sensitivity (Gregor & Hotamisligil, 2011; Monteiro et al., 2012; Sun et al., 2011), however, the weight loss mediated by nicotine is attributed to a loss of skeletal muscle mass (Passey et al., 2016) and redistribution of fat mass in favour of visceral accumulation (Audrain-McGovern & Benowitz, 2011) resulting in metabolic disturbances. During smoking cessation, the withdrawal of nicotine decreases metabolic expenditure and restores appetite leading to a positive

energy balance which increases the propensity of post-cessation weight gain (Harris et al., 2016). Although undesirable, post-cessation weight gain is manageable by dietary and exercise interventions that emphasize on caloric control and energy expenditure (Johansson et al., 2014; Maatman et al., 2016). Despite its impact on metabolism, it must be pointed out that post-cessation weight gain is still far less harmful than smoking, the benefits associated with individual's health and social economy of quitting clearly outweigh that of the counterpart (U.S. Department of Health and Human Services, 2014).

4.2. Targeting local and systemic inflammation

The inflammatory nature of both MetS and COPD had attracted much interest in cytokine-neutralisation therapy as a possible treatment for these diseases. In genetically obese rats, neutralization of TNF- α restored insulin-stimulated glucose uptake (Hotamisligil et al., 1993) and insulin sensitivity in peripheral tissues (Hotamisligil et al., 1994). TNF neutralization in humans was associated with reduced systemic inflammation, however its efficacy on insulin sensitivity appears to be inconclusive with some studies reporting improvement (Kiortsis, Mavridis, Vasakos, Nikas, & Drosos, 2005; Oguz, Oguz, & Uzunlulu, 2007; Stagakis et al., 2012; Stavropoulos-Kalinoglou et al., 2012; Tam, Tomlinson, Chu, Li, & Li, 2007), while others showed little or no effect (Ferraz-Amaro et al., 2011; Rosenvinge, Krogh-Madsen, Baslund, & Pedersen, 2007; Seriola, Ferrone, & Cutolo, 2008). The reasons behind such discrepancies are not fully-understood, however it is likely to be influenced by the degree and severity of insulin resistance before the onset of therapy, as well as the co-existence of other underlying conditions such as obesity (Wascher et al., 2011). In the COPD context, TNF- α neutralization therapy by infliximab failed to improve the disease outcomes for patients including symptom score, pulmonary function, exercise capacity, dyspnoea score, health status, and rate of acute exacerbations (Rennard et al., 2007), despite the marked efficacy demonstrated in experimental cigarette smoke models (Churg et al., 2004). Moreover, TNF- α neutralization therapies have been shown to be ineffective at reducing local and systemic inflammation in COPD patients (Loza, Watt, Baribaud, Barnathan, & Rennard, 2012) with a lack of overall clinical benefit on lung pathology (Rennard et al., 2007). This lack of clinical efficacy on one hand may be related to the timing of the therapeutic intervention in relation to disease severity (Passey et al., 2016). Meanwhile, TNF- α appears to be more of a marker of cigarette smoking rather than COPD (Faner et al., 2014) suggesting TNF- α may not be a suitable target for treating COPD. Noteworthy, chronic TNF- α neutralization was also associated with an increased risk for pneumonia and lung malignancies in COPD patients (Durham, Caramori, Chung, & Adcock, 2016).

While not currently used for treatment of MetS or COPD, IL-6 neutralisation therapies have shown promise in the treatment of cancer cachexia. Bayliss et al. (Bayliss, Smith, Schuster, Dragnev, & Rigas, 2011) reported the use of a humanised anti-IL-6 monoclonal antibody, ALD518, which has a high affinity for binding IL-6 in clinical trials focused on non-small cell lung cancer. The antibody therapy was well tolerated and ameliorates key pathologies arising from the disease such as anaemia and cachexia which contributed to better survival rate. Meanwhile, an IL-6 receptor antibody, Tocilizumab has been shown to be beneficial for cachexia in cancer patients (Ando et al., 2013). Given IL-6 has been demonstrated to be a *bona fide* biomarker for COPD and AECOPD, neutralisation of this cytokine should benefit COPD and MetS (Fig. 2). Likewise, neutralising antibody for IL-1 α has also been developed and tested in clinical trial. Hong et al. (2014) demonstrated that the anti-IL-1 α antibody therapy was effective in reducing markers of systemic inflammation with no dose-limiting toxicities experienced amongst the test subjects. Importantly, 70% of the cancer patients receiving the therapy had a gradual increase in lean body mass with a concomitant reduction in fat mass assessed by dual energy X-ray absorptiometry (DEXA) scan. These patients also experienced

improvements in overall energy levels and general quality of life scores which indicate that the therapy may benefit muscle mass and function. As both muscle mass and function are of critical importance in maintaining metabolic homeostasis and pulmonary physiology, these findings strengthen the rationale for the use of IL-1 α neutralising therapy in patients with MetS or COPD. In support of this, IL-1 α neutralising therapy has been shown to be effective in attenuating inflammation resulting from virus-induced exacerbations in cigarette smoke-exposed mice (Botelho et al., 2011).

Metformin is the recommended first-line treatment for type 2 diabetic patients (American Diabetes Association, 2017; Sonne & Hemmingsen, 2017). Metformin is an anti-hyperglycaemic agent, which improves glucose tolerance in patients with type 2 diabetes by lowering both basal and postprandial plasma glucose levels. It belongs to the biguanides class and its pharmacological mechanisms of action include suppression of hepatic glucose production, reduction of intestinal absorption of glucose, and improvement in insulin sensitivity by increasing peripheral glucose uptake and utilization (Viollet et al., 2012). In addition, the use of this drug has also been found to reduce risk of cardiovascular events and mortalities (Holman, Paul, Bethel, Matthews, & Neil, 2008), despite the occurrence of lactic acidosis in rare cases (Frid et al., 2010). Given that pulmonary function decline in COPD may promote poor oxygenation to metabolic tissues which favours the production of lactic acid from anaerobic metabolism of glucose (Hitchings, Archer, Srivastava, & Baker, 2015), this raised safety concerns for the use of metformin in COPD. The British National Formulary and the US Federal Drug Administration advised that metformin should be withheld promptly in the presence of any conditions associated with hypoxemia. In light of this, a recent study conducted by Hitchings et al. (Hitchings et al., 2015) investigated the safety of metformin in a COPD retrospective cohort with 130 patients. The study found that metformin therapy among patients with COPD at high risk for lactate accumulation was associated with a minor elevation of lactate concentration of doubtful clinical significance suggesting the safety of metformin use in COPD.

In addition to the pro-inflammation, hyperglycaemia also mediates increased glucose in airway surface liquid, making the respiratory tracts of COPD patients vulnerable to infectious exacerbations (Cazzola et al., 2012; McKeever et al., 2005). Metformin treatment has been shown to have a direct effect on glucose flux across the airway epithelium to limit hyperglycaemia-induced bacterial growth that is responsible for respiratory infections (Garnett et al., 2013). In a retrospective investigation involving patients with concurrent COPD and MetS, treatment with hypoglycaemic agents was independently associated with improvements in FVC (Kim et al., 2010). Moreover, in a prospective observational study, metformin administration improves dyspnoea and respiratory muscle strength in COPD patients with diabetes (Sexton, Metcalf, & Kolbe, 2014). Metformin has also been found to possess important anti-inflammatory and anti-oxidative properties which may account for some of the efficacies observed. At a cellular level, metformin has been shown to directly inhibit TNF- α mediated NF κ B signalling and IL-6 production via the activation of AMPK (Huang et al., 2009). In type 2 diabetic subjects, metformin administration reduced the appearance of urinary 8-iso-PGF(2 α), a biomarker for oxidative stress (Formoso et al., 2008). Metformin might, therefore, be of additional benefit in the prevention and treatment of respiratory disorders (Fig. 2).

Given the observation that newly diagnosed diabetic patients, characterised by diminishing endogenous insulin production and frequently having impaired pulmonary function (Tiengo et al., 2008), and that insulin therapy has been demonstrated to improve alveolar-capillary membrane gas conductance (Guazzi, Oreglia, & Guazzi, 2002), the possibility of insulin administration for the treatment of respiratory disorders has been explored. Disappointingly, inhalation of human insulin was associated with respiratory symptoms, including cough and mild dyspnoea, along with reductions in FEV₁ and diffusing capacity of the lung for carbon monoxide, a surrogate marker for the alveolar-capillary membrane function (Ceglia, Lau, & Pittas, 2006).

This mode of insulin delivery itself also presented with a number of undesirable effects including difficulties in dosage control and tendency of hypoglycaemia, which could be fatal. Hence, more research is needed to determine the safety and benefits of inhaled insulin therapy for diabetic patients with COPD.

Since the abnormal inflammatory response from cigarette smoke may arise from the reprogramming of AM toward M2 polarization, and that the M1/M2 phenotype polarization is closely dependent on the state of cellular metabolism, metabolic reprogramming of macrophages and other immune cells may be a plausible therapeutic strategy to disconnect COPD from MetS and other comorbidities. On this note, modulation of glycolysis (Tan et al., 2015) and mitochondrial oxidative phosphorylation (Vats et al., 2006) via genetic manipulations have been demonstrated to be sufficient to produce a phenotypic switch of macrophages. In addition to the conventional genetic and pharmacological approaches, a more recent study by Saborano et al. (Saborano et al., 2017) demonstrated metabolic reprogramming of macrophages is achievable with nanoparticles of specific diameters. However, the benefits of these manipulations on systemic inflammation and COPD comorbidities remain to be determined.

4.3. Targeting oxidative stress

As oxidative stress is attributed to the imbalance between the oxidants and antioxidants, restoring this balance offers hope in preventing and treating multiple diseases. For this reason, therapeutic approaches are aimed at: replenishing the depleted non-enzymatic defences through dietary or pharmacological means or increasing the endogenous antioxidant enzyme activity via enzyme modulators/mimetics (Bernardo et al., 2015). Given the renowned radical scavenging properties of vitamins, vitamins have been extensively studied. However, disappointing results were obtained on vitamin supplementation and other alike dietary antioxidants which demonstrated little-to-no effects on metabolic parameters including body weight, glycaemia and plasma lipid profiles in patients with MetS (Avignon, Hokayem, Bisbal, & Lambert, 2012; Manning et al., 2013). Vitamin supplementation also appears to be insufficient to have benefits on cardiovascular complications associated with MetS (Debrececi & Debrececi, 2012). Likewise, administration of vitamins and other dietary antioxidants have also shown minimal improvements in either COPD or its comorbidities (Rahman & MacNee, 2012).

In contrast to vitamins, flavonoids and polyphenols supplementation have been shown to be efficacious in counteracting metabolic abnormalities as well as cardiovascular dysfunction in human or animals with the MetS. Resveratrol is a naturally-occurring polyphenol found in red wine and grape skin/seed. Administration of resveratrol or its derivative (S17834) to mice normalised left ventricular hypertrophy, interstitial fibrosis, and diastolic dysfunction induced by diet high in fat and sugar. These beneficial effects were associated with decreases in oxidant-mediated protein modifications and hyperinsulinemia with a concomitant increase in plasma adiponectin which are indicative of improved insulin sensitivity (Qin et al., 2012). Similarly, resveratrol supplementation lowered adiposity, serum cholesterol, and C-reactive protein levels, along with improved glucose tolerance and endothelial function in a swine model for MetS and myocardial ischemia (Robich et al., 2011). Moreover, eight weeks administration of resveratrol to high-fructose fed rats resulted in a remarkable improvement in glucose tolerance, plasma insulin and lipid levels, as well as enhanced hepatic catalase and superoxide dismutase (SOD) enzyme activities which are reflective of attenuated oxidative stress in these animals (Bagul et al., 2012). Importantly, the attenuated oxidative stress was only found in the resveratrol-treated group but not the metformin-treated group (Bagul et al., 2012) suggesting a different mode of action, despite both agents appearing to activate AMPK. In humans, moderate red-wine consumption has been suggested to have protective effects against the development of MetS and its related cardiovascular complications (Liu,

Wang, Lam, & Xu, 2008). In obese individuals with MetS, 30 days of resveratrol supplementation markedly enhanced energy metabolism, restoring insulin sensitivity and glycaemic control, while normalising blood pressure and plasma lipid profile. This was accompanied by an enhanced mitochondrial function in skeletal muscle as a result of increased AMPK activity and expression of the NAD⁺-dependent deacetylase, SIRT1 resembling that in calorie restriction (Timmers et al., 2011). The beneficial effects of resveratrol appear to be AMPK-dependent, as mice deficient of this metabolic sensor are no longer protected from metabolic derangement induced by high fat feeding despite the administration of resveratrol (Um et al., 2010). In the context of COPD, resveratrol administration to mice has been shown to alleviate *Haemophilus influenzae*-induced inflammation of the airway by up-regulating the negative regulator of inflammation MyD88 short (MyD88s) (Andrews, Matsuyama, Lee, & Li, 2016). In a separate study, treatment with resveratrol reduced the expression of pro-inflammatory cytokines (IL-17, IL-6, TNF- α , and TGF- β) in the bronchoalveolar lavage fluid (BALF) of mice exposed to cigarette smoke. Along with this, resveratrol treatment also attenuated the cigarette smoke-induced fibrotic response and mucus hypersecretion in the lungs (Andrews et al., 2016). A recent study in rats also confirmed the efficacy of resveratrol in COPD, and that the beneficial effect of resveratrol may be exerted via the SIRT1 and PGC-1 α axis (Wang, Li, Li, Miao, & Xiao, 2017). Resveratrol therapy is currently in phase 3 clinical trials for use in COPD patients (CARMENS-trial; [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02245932) Identifier NCT02245932). Overall, human and animal studies suggest a great potential for resveratrol use to treat MetS, and possibly COPD comorbidities (Fig. 2). Flavonoids like anthocyanin was shown to have anti-oxidative stress properties (Guo et al., 2008) which may lower LDL cholesterol and other metabolic parameters in dyslipidemic patients (Qin et al., 2009). Quercetin is another flavonoid that has been shown to benefit cardiovascular health by lowering blood pressure and plasma oxidized LDL concentrations in overweight subjects (Egert et al., 2009). Other natural agents such as genistein, triterpenoid, naringenin and curcumin have also displayed potent *in vitro* activity against various aspects of MetS (Xia & Weng, 2010), however further studies are needed to verify their benefits on COPD.

Although short-lived, free-radicals like hydroxyl-radicals and peroxynitrite are extremely reactive and indiscriminate to a point that they would attack the first substrate they come into contact with resulting in impairment of cellular functions and damage (Bernardo et al., 2015). Since the mitochondria is a major site for substrate metabolism, this means that it is also a major source of ROS during MetS when substrate availability is in excess. For this reason, mitochondria-targeted antioxidant compounds have been developed and examined for efficacy in animal models of MetS. Pharmacological mimetics of SOD such as Tempol, has been shown to be effective in attenuating oxidative stress, restoring mitochondrial function and metabolic derangement (Ahmed, Shehata, Abdelkader, & Khattab, 2014; Mariappan, Soorappan, Haque, Sriramula, & Francis, 2007). Likewise, administration of the SOD mimetics in animal models of COPD also appears to be beneficial. Treatment with SOD mimetic M40419 in rats reduced the expression of markers for oxidative stress and the development of emphysema (Tuder et al., 2003). In a similar COPD model, administration of a different SOD mimetic AEOL 10150 was found to reduce airway inflammation by cigarette smoke evidenced by the significant reduction in BALF cell number (Smith et al., 2002). In line with this, Gongora et al. (Gongora et al., 2008) have demonstrated that acute ablation of SOD3 via gene deletion results in severe respiratory distress syndrome resembling that of advanced COPD with high risk of mortality (Gongora et al., 2008). On the contrary, overexpression of SOD attenuates airway inflammation and respiratory disorders following hyperoxia, which in turn may reduce the risk of mortality highlighting the exciting potential of SOD as a therapeutic agent. Metalloporphyrin (MnTBAP) is another SOD mimetic with peroxynitrite scavenging properties. Treatment of genetically obese (ob/ob) mice with MnTBAP improved glucose tolerance

and insulin sensitivity with a maximum effect comparable to that of animals treated with the anti-diabetic agent rosiglitazone (Houstis, Rosen, & Lander, 2006). Administration of MnTBAP in mice has been shown to antagonize the detrimental effects of cigarette smoke partly by inhibiting the RhoA–Rho kinase pathway which ultimately resulted in enhanced clearance of apoptotic cells by alveolar macrophage (Richens et al., 2009).

CoenzymeQ₁₀ (CoQ₁₀) is a vitamin-like lipid-soluble component of the mitochondrial electron transport chain (ETC). Due to its role as an electron carrier in the mitochondrial ETC, CoQ₁₀ possesses potent redox properties which can be utilised as an antioxidant (Lenaz, Fato, Formiggin, & Genova, 2007). In contrast to vitamin E, exogenous supplementation of CoQ₁₀ is readily taken up by cells leading to its mitochondrial localization and enrichment (Saito et al., 2009) where free-radicals are generated. Along this line, diabetic animals are found to have increased oxidative stress from lipid peroxidation and reduced levels of CoQ₁₀ in key metabolic tissues such as heart, liver and skeletal muscle (Kucharska, Braunova, Ulicna, Zlatos, & Gvozdzakova, 2000). In genetically obese mice, treatment of CoQ₁₀ reduced the elevated plasma lipid profiles and decreased the expression of pro-inflammatory cytokines, while enhancing the expression of the anti-inflammatory and insulin-sensitizing adipokine, adiponectin (Carmona et al., 2009). The same study also demonstrated additional benefits of CoQ₁₀ therapy in neutralising the unwanted side-effects of rosiglitazone on body weight and adiposity. In diabetic rats, CoQ₁₀ supplementation markedly increases antioxidant enzyme activity of SOD, catalase, and glutathione in the liver of diabetic rats along with reduced lipid peroxidation (Modi, Santani, Goyal, & Bhatt, 2006). This is accompanied by improved hyperglycaemia and glucose intolerance without noticeable changes in circulating insulin levels (Modi et al., 2006) suggesting enhancement of insulin sensitivity and its potential in treating MetS in humans. However, 6 months CoQ₁₀ therapy did not have apparent benefits on glycaemic control or plasma lipid profiles of overweight type-2 diabetic subjects (Eriksson, Forsen, Mortensen, & Rohde, 1999). Likewise, in type-1 diabetics, 3 months CoQ₁₀ therapy resulted in no improvements on glycated haemoglobin (HbA1c), mean daily blood glucose concentrations, insulin requirement, number of hypoglycaemic episodes or circulatory cholesterol concentrations compared to the control group (Henriksen et al., 1999). There is also a lack of evidence to substantiate its role in cardiovascular health, as the CoQ₁₀ supplementation was unable to ameliorate hypertension in patients with MetS (Bjelakovic, Nikolova, Gluud, Simonetti, & Gluud, 2012; Young et al., 2012). The apparent discrepancy in efficacy of CoQ₁₀ supplementation remains unknown, however the poor water solubility and lipophilic nature of CoQ₁₀ (Alam & Rahman, 2014) might constitute poor oral bioavailability. Given this, future studies may wish to explore the use of CoQ₁₀ as an adjunct therapy to existing medications. This notion is supported by the finding that addition of CoQ₁₀ to regular medications improved diastolic function in children with dilated cardiomyopathy (Kocharian, Shabanian, Rafiel-Khorgami, Kiani, & Heidari-Bateni, 2009).

Limited studies have assessed pulmonary benefits of CoQ₁₀ supplementation. Eight weeks of CoQ₁₀ administration to patients with COPD was associated with significantly elevated serum CoQ₁₀ levels and improvement in hypoxemia at rest. These subjects displayed no differences in oxygen consumption during exercise, however, their arterial oxygen saturation was markedly improved with a lower heart rate when exercised. In line with this, CoQ₁₀ administration also resulted in a trend of enhanced exercise performance and lactate production was concomitantly suppressed (Fujimoto, Kurihara, Hirata, & Takeda, 1993). A more recent study demonstrated that dietary supplementation with creatine and CoQ₁₀ increased lean body mass and exercise tolerance, while reducing dyspnoea and exacerbations associated with COPD which in turn improves quality of life for the patients (Marinari, Manigrasso, & De Benedetto, 2013). These data suggested that CoQ₁₀ may exert favourable effects on cardiovascular system and energy

metabolism in patients with COPD via the attenuation of hypoxemia (Fig. 2).

In attempt to overcome the limitations, derivatives of CoQ₁₀ have been developed and explored. MitoQ is a triphenylphosphonium-conjugated antioxidant with improved oral bioavailability, cell-permeability with several hundred-fold enhanced localization affinity to the mitochondria than its parental molecule, CoQ₁₀ (Murphy & Smith, 2000). MitoQ also displays protective effects against mitochondrial oxidative damage with no effects in laboratory rodents (Rodriguez-Cuenca et al., 2010). In rodents, oral administration of MitoQ decreased adiposity, hypercholesterolemia and hypertriglyceridemia associated with MetS. MitoQ administration also corrected hyperglycaemia and plasma lipid profiles in these rodents, while minimising DNA oxidative damage in multiple organs (Mercer et al., 2012). Thus far, the use of MitoQ has been tested in patients with Parkinson's disease and chronic hepatitis C (Smith & Murphy, 2011) with no reported adverse effects which suggests potential suitability of this agent and alike mitochondrial antioxidants such as MitoTempol (Prakash, Pabelick, & Sieck, 2017) to be used in clinical studies for treating MetS and COPD. In addition, novel mitochondria-targeted antioxidants have also been identified including those derived from natural products such as berberine and palmatine (Lyamzaev et al., 2011), as well as synthetic antioxidant peptides (Chen, Liu, Gao, Zhuo, & Ge, 2011) which exhibits potent radical-scavenging properties in isolated mitochondria and in human cells. However, their use in the context of MetS and COPD are yet to be explored.

4.4. Targeting obesity with lifestyle and pharmacotherapies

The strong association between obesity and pulmonary health has prompted therapeutic interventions targeting adiposity and/or restoring adipose tissue dysfunction. However, the existence of the 'obesity paradox' had raised doubts regarding the appropriateness of targeting obesity in COPD patients. This is because weight loss in obese COPD patients, on one hand may improve cardiovascular outcomes, but on the contrary may worsen respiratory outcomes and even increase their risk of mortality (Cao et al., 2012; Pi-Sunyer, 2009; Vestbo et al., 2006). Moreover, it is also possible that the reduced lung volumes caused by obesity may protect against hyperinflation in moderate to severe COPD which in turn may benefit lung function. In a follow-up study involving 190 patients with stable COPD (GOLD 3–4), the overweight/obese cohort indeed had better lung function and survival rate than those with normal BMI despite a significantly higher peak work rate (Galesanu et al., 2014). However, such benefits were diminished or worsened when adjusted for midhigh muscle cross-sectional area suggesting the speculated benefits of having greater BMI is likely to be coming from the muscle mass rather than fat. A recent study by Orfanos et al. (2018) also demonstrated that obesity induces airway smooth muscle hyperresponsiveness in human which provides another pathogenic link between obesity and COPD, further substantiating the detrimental effects of obesity on lung function. These findings provide a good rationale for targeting obesity as a plausible therapeutic strategy to better COPD outcomes. However, a therapeutic approach that targets obesity can be problematic, as weight loss interventions particularly in the elderly group result not only in loss of fat mass but also loss of skeletal muscle mass, which is very detrimental in the COPD context (Passey et al., 2016). For this reason, clinicians are faced with the dilemma of whether to recommend weight loss in obese COPD patients. To make matters worse, there is insufficient evidence to guide the management of COPD patients with concurrent weight issues at the present time which has raised an urgent call from international experts for research in this area (Schols et al., 2014). In light of this, a recent study by McDonald et al. (2016) involving 28 obese COPD patients who underwent strict dietary calorie restriction regime coupled with resistance exercise training resulted in clinically significant improvements in body mass index, exercise tolerance and health status, whilst

preserving skeletal muscle mass. The findings in the study are consistent with results obtained from an obese asthmatic cohort, where modest weight loss (between 5% and 10%) can lead to significant clinical improvements in health status and disease control (Lv, Xiao, & Ma, 2015). Although not assessed in these studies, a reduction of excess weight in general correlates with significantly lowered risk of comorbid conditions arising from metabolic derangement (Pi-Sunyer, 2009). Together, these findings provide a proof-of-concept for the feasibility and benefits of weight loss intervention in obese COPD patients (Fig. 2). Future work should place emphasis on treatment interventions that would preserve and/or enhance skeletal muscle mass as a core consideration for the management of obese COPD patients.

Nutritional and exercise are lifestyle interventions that are commonly used as a first-line treatment of obesity. However, lifestyle interventions are not always satisfactory. In fact, it is recommended that if adequate weight loss by lifestyle intervention is not achieved within 3–6 months, pharmacotherapy should be commenced (Srivastava & Apovian, 2017). It is important to note that, the primary goals of pharmacotherapy on obesity are to improve or prevent complications arising from MetS such as hypertension, dyslipidaemia and diabetes, rather than weight loss *per se* (Srivastava & Apovian, 2017). Currently, several Food and Drug Administration (FDA, USA) approved drugs are used for the long- and short-term management of obesity. A number of sympathomimetic drugs such as Phentermine and Diethylpropion are approved only in the USA for short-term (less than 3 months) treatment due to safety concerns (Manning, Pucci, & Finer, 2014) and thus do not appear to fit the rational paradigm for treating chronic disorders such as COPD and MetS. Even for drugs approved for long-term use, if 3% mean weight loss is not attained during the first 3 months of medication, alternative treatment modalities should be considered (Manning et al., 2014).

Orlistat is a potent and selective inhibitor of pancreatic lipase required for the hydrolysis of dietary fat in the gastrointestinal tract into fatty acids and monoacylglycerol. Orlistat is approved by the FDA (USA) for the long-term management of obesity in conjunction with dieting (Lucas & Kaplan-Machlis, 2001) which is mainly attributed to its negligible systemic absorption profile (Zhi, Melia, Eggers, Joly, & Patel, 1995). In a 4-year, double-blind, prospective study, administration of Orlistat in overweight patients resulted in a significant reduction in weight with a mean loss of 5.8 kg from baseline (i.e. before treatment) (Torgerson, Hauptman, Boldrin, & Sjostrom, 2004). Compared to lifestyle intervention alone, the incidence of type 2 diabetes was also found to be significantly reduced over the course of the 4 years (Torgerson et al., 2004). Moreover, Orlistat treatment also demonstrated beneficial effects on cardiovascular risk by lowering blood pressure, fasting glucose levels, as well as serum cholesterol and lipid profiles (Broom et al., 2002). Orlistat use in overweight/obese patients with concurrent COPD must be proceeded with caution. This is largely because of the "obesity paradox" and that weight loss of more than 10% over a period of 3–6 months has been shown to have profound negative impacts on COPD prognosis (Qureshi et al., 2014; Shavelle, Paculdo, Kush, Mannino, & Strauss, 2009). This precaution should not impede the use of Orlistat or similar weight loss agents in this population, but therapeutic interventions should be coupled with dietary and exercise rehabilitation to maintain the lean body mass. Meanwhile, signs of any unintentional weight losses and/or side effects should be closely monitored and promptly acted upon accordingly.

Lorcaserin is another FDA-approved agent that is used in the long-term management of obesity. In the hypothalamus, Lorcaserin activates serotonin 5-HT_{2C} receptors leading to suppression of appetite, reducing caloric intake without a direct impact on energy expenditure (Halford, Harrold, Boyland, Lawton, & Blundell, 2007). Clinical administration of Lorcaserin demonstrated effective weight loss along with a favourable safety profile with no signs of heart-valve problems, unlike that of 5-HT_{2B} receptor agonists (Fidler et al., 2011; O'Neil et al., 2012; Smith et al., 2010). Administration of Lorcaserin to obese diabetic subjects

exerted significant improvements on glycaemic control evidenced by reduction in mean HbA1c levels and fasting blood glucose (O'Neil et al., 2012). So far, there is no experimental evidence or clinical data to suggest benefits of Lorcaserin administration on respiratory disorders. Given that pre-clinical and clinical studies have indicated that Lorcaserin is well-tolerated and not associated with cardiac valvulopathy or pulmonary hypertension (Redman & Ravussin, 2010), then it is possible that COPD patients with weight control issues may benefit from Lorcaserin therapy especially when use in conjunction with lifestyle interventions. Noteworthy, similar weight loss precautions also apply to the use of Lorcaserin, and signs of serotonin syndrome should also be closely monitored with the use of serotonergic medications (Halford et al., 2007).

Phentermine is another sympathomimetic drug which stimulates the release of synaptic noradrenaline, dopamine and serotonin release leading to appetite-suppression (Manning et al., 2014). As described above, Phentermine alone is only recommended for short-term use, however by combining with Topiramate, Phentermine is suitable for long-term use (Allison et al., 2012; Gadde et al., 2011). The synergistic effects of Phentermine and extended-release Topiramate (marketed as Qnexa/Qsiva/Qsymia) allows a dose reduction of each drug and thus less toxicity without a loss in efficacy (Gadde et al., 2011). Topiramate is an anti-convulsant drug that was originally used in epileptic patients when its weight loss-inducing properties was accidentally discovered (Astrup & Toubro, 2004). Phentermine/Topiramate therapy for 56 weeks was reported to be well-tolerated and resulted in dose-dependent weight loss of up to 11% from baseline (Allison et al., 2012; Gadde et al., 2011). The weight loss was associated with various improvements of metabolic parameters including systolic and diastolic blood pressure, fasting glucose, triglycerides, total cholesterol, LDL, and HDL (Allison et al., 2012). Despite the demonstrated safety and efficacies in treating obesity and metabolic derangement, no studies to-date have examined the effect of Phentermine/Topiramate on respiratory diseases exposing the need for research in this area.

In light of the relative lack of prospects for novel anti-obesity therapy and the high attrition rate associated with drug development (Chan & Ye, 2013), more recently, researchers and clinicians have begun to turn to drug repurposing strategies in an attempt to broaden therapeutic options (Shih, Zhang, & Aronov, 2017). Glucagon-like peptide-1 (GLP-1) based therapy represents one of the best examples of anti-obesity therapy deriving from this strategy. GLP-1 belongs to a group of hormones called incretins which are secreted from the enteroendocrine cells of the gut into the bloodstream shortly following food consumption. GLP-1 is responsible for enhancing the insulin secretory response by the pancreas to the products (e.g. glucose) within the nutrients in the food (Garber, 2011). In addition, more recent research has indicated that GLP-1 mediates satiation by acting on peripheral and central pathways (Holst, 2013) in which the appetite-suppressant properties may be of therapeutic application in the fight against obesity. Two classes of GLP-1 based therapy have been developed: i) GLP-1R agonists (Exenatide and Liraglutide) which exhibit increased resistance to dipeptidyl peptidase 4 (DPP-4) degradation and thus provide pharmacological levels of GLP-1; ii) DPP-4 inhibitors (Sitagliptin, Vildagliptin, Saxagliptin) which reduce endogenous GLP-1 degradation, thereby providing physiological levels of GLP-1 (Garber, 2011). GLP-1R belongs to the family B subclass of G protein-coupled receptors (GPCRs). Activation of this receptor results in the amplification of intracellular signalling via protein kinase A (PKA) which in turn drive the expression, biosynthesis, and secretion of insulin from pancreatic β -cells in a glucose-dependent manner (Drucker, Philippe, Mojsov, Chick, & Habener, 1987). GLP-1R agonists are well-tolerated with demonstrated efficacy as a monotherapy or combination-therapy. Both Exenatide (DeFronzo et al., 2005) and Liraglutide (Garber et al., 2009; Zinman et al., 2009) demonstrated moderate but significant weight loss especially when administered in concert with insulin-sensitizing agents like metformin with

minimal adverse effects such as hypoglycaemia. GLP-1R agonists effectively improved glycaemic control in obese patient with concurrent diabetes evidenced by reduction in mean HbA1c levels (DeFronzo et al., 2005; Garber et al., 2009; Zinman et al., 2009). In an experimental mice model of AECOPD induced by inhalation of ovalbumin and lipopolysaccharide, administration of GLP-1R agonists significantly improved pulmonary function, reduced the severity of exacerbations and enhanced survival rate independent of changes in the mRNA expression of pro-inflammatory cytokines and surfactant proteins in the lung (Viby et al., 2013). Moreover, not only are functional GLP-1R expressed in lung tissue (Romani-Perez et al., 2013; Viby et al., 2013), but they appear to have an important role in regulating surfactant-protein production and lung development in an experimental rat model (Romani-Perez et al., 2013). As a whole, these evidence indicated that GLP-1R agonists appear to be safe and effective against obesity and various parameters of metabolic derangements in patients with no negative effects on the cardiovascular risk on patients (Filippatos, Panagiotopoulou, & Elisaf, 2014). Thus, GLP-1R agonists appear to have a favourable safety profile, but ongoing trials will further assess their effects on the pulmonary components, as well as the mechanism of action.

On the contrary, the effect of DPP-4 inhibitors on weight loss appears to be variable and controversial. Meta-analysis of 29 clinical studies verified that the efficacy of all three DPP-4 inhibitors on weight loss to be insignificant (Amori, Lau, & Pittas, 2007). Despite the neutral effect on body weight, all three DPP-4 inhibitors display similar efficacy on glycaemic control reflected by reduction of HbA1c levels along with good safety profile and patient tolerance (Amori et al., 2007). Noteworthy, the same study also suggested DPP-4 inhibitors were only slightly less effective than Sulfonylureas and as effective as Metformin and Thiazolidinediones, which are the standard drugs for treating diabetes, in terms of reducing blood glucose. In addition to glycaemic control, DPP-4 inhibitors also appear to exert beneficial effects on the vasculature. In diabetic patients with concurrent coronary heart disease, Sitagliptin treatment improved heart function and coronary artery perfusion (Read, Khan, Heck, Hoole, & Dutka, 2010). A separate study showed that Sitagliptin treatment resulted in a moderate but significant reduction in diastolic blood pressure in non-diabetic hypertensive patients (Mistry et al., 2008). Finally, 4 weeks of Vildagliptin administration on drug-naïve patients with type 2 diabetes was associated with improvement of postprandial plasma triglyceride and apolipoprotein B-48-containing triglyceride-rich lipoprotein particle metabolism following a fat-rich meal (Matikainen et al., 2006). Similar effects of Vildagliptin on postprandial lipid mobilization and oxidation were reported in a more recent study which is likely to be mediated via the sympathetic activation rather than a direct effect on metabolic status (Boschmann et al., 2009). Unlike that of GLP-1R agonists, so far, no experimental or clinical studies have examined the pulmonary aspects of DPP-4 inhibitor therapy. However, it is noteworthy that DPP-4 inhibitor therapy has been shown to coincide with an increased risk of upper respiratory tract infection (Amori et al., 2007; Willemen et al., 2011), which may limit its experimental and clinical use in COPD.

Evidence from previous weight loss research indicates that life style rehabilitation and pharmacotherapy are often ineffective in patients with severe obese issues to lose enough weight to improve their health and quality of life in the long term (Pi-Sunyer, 2009). Meanwhile, a growing body of evidence indicates that bariatric surgery is effective in attaining sustained weight control, improving comorbidities, and prolonging survival (Sjostrom et al., 2004). In addition to reversing obesity, bariatric surgery has been shown to improve other parameters of the MetS including abnormal plasma lipid and cholesterol profile, elevated blood pressure and fasting glucose (Batsis et al., 2008) which in turn may reduce cardiovascular risk (Batsis et al., 2007). A recent study conducted on 481 obese patients with COPD in the US has found bariatric surgery remarkably reduced the incidence of emergency visits and hospitalization related to AECOPD in patients with concurrent obesity (Goto, Tsugawa, Faridi, Camargo Jr., & Hasegawa, 2017). As

obesity profoundly impinges on respiratory mechanics which can contribute to the manifestation of deteriorating symptoms, it is possible that surgical weight loss may contribute to the alleviation of COPD symptoms by lowering systemic inflammation (Fig. 2). In line with this, reduced systemic CRP level has been observed in morbidly obese patients following surgical weight loss (Chen et al., 2009). Moreover, the systemic appearance of soluble intercellular adhesion molecule-1 (sICAM-1), a key mediator of atherosclerotic plaque formation, was also found to be dramatically reduced following surgical weight loss (Orea Soler et al., 2010) which may explain the associated cardiovascular benefit.

4.5. The use of natural products and complementary medicines

Natural products derived from plants, microbes, and animals are an invaluable source of molecular diversity in drug discovery and have greatly contributed to the identification of new drugs or drug derivatives (Chan & Ye, 2013; Li & Vederas, 2009). Using fish oil as an example, which is enriched in omega-3 (ω -3) fatty acids namely eicosapentaenoic acid (EPA; 20:5n-3) and docosahexaenoic acid (DHA; 22:6n-3) (Calder, 2015), experimental evidence demonstrated that these ω -3 fatty acids restore metabolism and functions of adipose tissue by promoting oxidative metabolism via mitochondrial biogenesis and fatty acid oxidation (Flachs et al., 2005). EPA and DHA promote glucose utilization and insulin sensitivity in key metabolic tissues including the liver, skeletal muscle and adipose tissue through the activation of Peroxisome Proliferator-Activated Receptor gamma (PPAR γ) and AMPK (Neschen et al., 2007; Oh et al., 2010; Storlien et al., 1987; Storlien et al., 1991). Moreover, EPA and DHA also appear to suppress the production of pro-inflammatory chemokines and cytokines, while increasing the expression of anti-inflammatory cytokines and adipokines such as adiponectin in adipose tissue which in turn may reduce inflammation (Kalupahana, Claycombe, & Moustaid-Moussa, 2011; Oh et al., 2010). Although yet to be fully elucidated, the mechanisms underlying the anti-inflammatory actions of these ω -3 fatty acids may be related to their ability to alter cellular membrane phospholipid composition and disruption of the lipid rafts, suppression of the pro-inflammatory transcription factor NF κ B to reduce transcription of pro-inflammatory genes, activation of the anti-inflammatory transcription factor PPAR γ and inhibition of TLR4 signalling via binding to G protein coupled receptor 120 (GPR120) in adipocytes, macrophages, and hepatic stellate cells (Calder, 2015). Disappointingly, data from clinical trials do not support the link between either EPA or DHA to restoring insulin sensitivity. A meta-analysis of 11 randomized controlled trials (RCTs) with 618 participants concluded that ω -3 fatty acids consumption did not affect insulin sensitivity (Akinkuolie, Ngwa, Meigs, & Djousse, 2011). Another systematic review involving 17 RCTs and at least 3 months continuous administration of ω -3 fatty acids also found no clear effects on various risk factors of MetS, despite significant improvement in blood pressure and lipid profile with no adverse effects reported (Lopez-Huertas, 2012). Of note, data from a dose-response study in healthy subjects have demonstrated the existence of a threshold for the anti-inflammatory effects of EPA (Rees et al., 2006). This implies that the daily intake of these ω -3 fatty acids must exceed a certain level in order to exert any health benefits. In summary, human studies have largely failed to recapitulate the protective effect of EPA and DHA on glucose metabolism and insulin sensitivity that have been observed in rodents. Besides the obvious interspecies genetic and phenotypical differences, it is also noteworthy that the majority of the intervention studies in rodents were conducted in parallel of the disease development (preventative protocol) whereas intervention studies in humans are typically administered after establishment of the disease (reversal protocol). Hence, further clinical trials properly taking into account the aforementioned discrepancies are needed before any conclusions of the systemic use of ω -3 fatty acids on MetS can be made.

Laboratory evidence suggest that ω -3 fatty acids also exert beneficial anti-inflammatory effects on arachidonic acid metabolic pathways and the downstream balance of eicosanoids, including prostaglandins and leukotrienes which may influence neutrophil recruitment and bronchoconstriction (Calder, 2017). Moreover, fish intake (rich source of ω -3 fatty acids) in children has been associated with reduced wheeze and asthma in majority of epidemiologic cohort studies (Wendell, Baffi, & Holguin, 2014). Currently, an ancillary study is ongoing on a subset of participants in Vitamin D and Omega-3 Hypertension Trial (VITAL Hypertension) with an aim to examine whether ω -3 fatty acids supplementation (Omacor® 1 g/day) may improve respiratory symptoms or reduce the risk of lung infections or the decline of pulmonary function. The sub-cohort from VITAL-Hypertension is composed of 1,973 participants of both gender, 50 years or older from 11 continental US locations. These subjects were randomized and 1,924 had lung function tests of acceptable quality, among these 27.3% had mild to moderate COPD and 5.9% displayed obstructive spirometry evidenced by FEV₁ < 80% normal. Moreover, the mean BMI was 29.9 (>30 = obesity) suggesting the subjects entering the study are either overweight or borderline obese (Gold et al., 2016). The outcome of this trial would undoubtedly advance our understandings regarding the therapeutic potentials of ω -3 fatty acids for COPD.

Plants have traditionally been a tremendous source of natural products with beneficial effects on several types of diseases including MetS and COPD. The use of ginseng dates back to about five thousand years ago, by the legendary Emperor Shennong in ancient China who as reported in the literature, was the first to classify hundreds of medicinal and poisonous herbs, giving rise to the bedrock of the oldest Pharmacopoeia in the world (Yun, 2001). Thirteen species of ginseng have been identified, with *Panax ginseng* (Korean ginseng), *Panax quinquefolius* (American ginseng) being the most commonly used (Baeg & So, 2013). Administration of ginseng has been demonstrated to have a number of positive effects on glucose and lipid metabolism in humans. Eight week-oral administration of heat-processed *Panax ginseng* decreased fasting blood glucose level, increased serum insulin and glucose tolerance in streptozotocin-induced diabetic mice (Jang et al., 2017). In high-fructose fed rats, *Panax ginseng* administration for eight weeks significantly reduced increments of body weight and adiposity. This is associated with reduced hyperlipidemia and hypertension, together with ameliorated endothelial dysfunction and marked upregulation of IRS-1 and glucose transporter type 4 (Glut4) in the muscle suggestive of enhanced insulin sensitivity (Kho et al., 2016). Similar results were also obtained in ob/ob mice with 16 weeks of *Panax ginseng* administration in drinking water (Cheon, Kim, & Kim, 2015). Moreover, *Panax ginseng* also appears to enhance islet function and attenuated cytokine-induced apoptosis (Kim et al., 2016) which may explain its beneficial effects on glucose metabolism (Luo, Dong, Liu, & Zhou, 2015). The metabolic benefits of *Panax ginseng* may be extended into the cardiovascular system. Long-term consumption of ginseng extract has been shown to reduce the susceptibility to acute ischemia reperfusion heart injury in rats by up-regulating the actions of Sirtuins (Luo et al., 2015). In a clinical setting, *Panax ginseng* has been shown to exert positive effects on glucose metabolism reflected by an improved glucose tolerance (Shergis, Zhang, Zhou, & Xue, 2013). A meta-analysis of 16 randomized controlled trials of moderate duration (≥ 30 days) assessing the glycaemic effects of ginseng in diabetic patients have found that ginseng modestly yet significantly improved fasting blood glucose in people with and without diabetes (Shishtar et al., 2014). It must be noted that most of these studies were of short duration (67% trials < 12 wks), and that participants included also have a relatively stable glycaemic control (median HbA1c non-diabetes = 5.4% [2 trials]; median HbA1c diabetes = 7.1% [7 trials]). Hence, larger and longer duration randomized controlled trials using standardized preparations are needed to validate ginseng's anti-diabetic and metabolic efficacy.

In addition to glucose metabolism, *Panax ginseng* also appears to modulate immune response which may have important implications in chronic inflammatory diseases such as COPD (Shergis et al., 2013). Delivery of *Panax ginseng* in the form of 200 mg G115 to patients with chronic bronchitis have demonstrated enhanced bacterial clearance rate following acute attacks compared to those receiving antibacterials alone (Scaglione, Cogo, Cocuzza, Arcidiacono, & Beretta, 1994; Scaglione, Weiser, & Alessandria, 2001). On a similar note, both *Panax ginseng* and *Panax quinquefolius* have also been shown to offer protection against upper respiratory tract infections by rhinovirus and coronavirus in a randomized, double-blind, placebo controlled trial involving 100 healthy volunteers (Lee et al., 2012). Administration of 200 mg G115 to patients with moderate to severe COPD for 12 weeks was associated with increased FEV₁ and FVC, as well as VO_{2max} which correlates with exercise capacity (Gross et al., 2002). Although these improvements gradually subsided 8 weeks post-treatment, this piece of clinical evidence provided proof-of-concept for the therapeutic use of *Panax ginseng* in COPD. In line with this, a systematic review also concluded promising benefits of *Panax ginseng* for improving FEV₁ and quality of life of patients evidenced by St. Georges Respiratory Questionnaire when compared with no treatment or when administered in combination with pharmacotherapy and compared with pharmacotherapy alone. Wu et al. have recently conducted a pilot study based on a full-scale 52 weeks trial protocol (Wu et al., 2014) comparing *Panax ginseng* with placebo for treating moderate to very severe COPD. In a feasibility study involving nine participants with COPD, it was found that P. ginseng (200mg G115, twice daily) was well tolerated with no adverse events reported. Based on this success, the full-scale trial has been approved and has been registered with the ANZCTR (ACTRN: 12613000382774) for implementation in the Guangdong Provincial Hospital of Chinese Medicine in China. Overall, the use of natural products such as ginseng appears to be well-tolerated in healthy subjects and patients. The meta-analysis results indicate that the addition of natural products to routine pharmacotherapies may produce additional benefits in terms of decreasing the BODE Index and increasing the 6-min walking distance in stable COPD patients when used for up to six months (Chen et al., 2014).

Another natural product which has proven be effective in treating various diseases is the *Codonopsis* species (Dang shen) which belongs to the *Campanulaceae* family. The root extracts of *Codonopsis* species have been demonstrated to possess pharmacological efficacies, such as antioxidant, anti-tumor, anti-microbial and immune-boosting properties (Luo et al., 2007. The pharmacological; Wang, Ng, Yeung, & Xu, 1996). The efficacy of the *Codonopsis* roots is likely due to be attributed to the enriched constituents, including polysaccharides, saponins, alkaloids and phytosteroids (Li, Xu, Han, & Wu, 2009; Yongxu & Jicheng, 2008). *Codonopsis* roots is commonly used in combination with other natural product formulations to treat stable COPD. Meta-analysis of 48 randomized controlled trials found that clinical therapy with *Codonopsis* roots exerts a number of positive effects on pulmonary function with minimal adverse events (Shergis et al., 2015) In these COPD patients, *Codonopsis* roots therapy improved FEV₁ and 6-min walking distance compared with conventional pharmacotherapy such as bronchodilators and mucolytics. These patients also had reduced exacerbations and a better quality of life reflected by St. Georges Respiratory Questionnaire compared with placebo. The systematic review highlighted that there is sufficient evidence to support the routine use of *Codonopsis* roots as a standard clinical therapy.

In the metabolic disease context, administration of *Codonopsis* root extracts to fructose-fed rats significantly attenuated weight gain and fasting hyperinsulinemia accompanied by an improved glucose tolerance. In these rats, *Codonopsis* root extracts was also protected from oxidative damage resulting from lipid peroxidation which is likely to be due to improved antioxidant enzyme activities, including superoxide dismutase, glutathione peroxidase and glutathione reductase in the liver (Chen et al., 2013). Moreover, in non-obese diabetic rats

consumption of *Codonopsis* root extracts effectively reduced serum glucose levels and the urinary appearance of glucose compared to control. The treated rats also displayed greater glucose infusion rates together during hyperinsulinemic euglycaemic clamp and lower hepatic glucose output under basal and hyperinsulinemic conditions indicative of restored insulin sensitivity (Jeong, Kang, Kim, & Park, 2017). Likewise, oral supplementation of *Codonopsis* root extracts resulted in lowered fasting blood glucose and insulin in high-fat diet induced obese mice. This was associated with improved serum profiles for triglycerides, total cholesterol and LDL compared to high-fat diet fed mice. In addition, the supplementation also exerts benefits on adiposity and liver function in these obese mice (Lee et al., 2014). Overall, experimental evidence indicates therapeutic potential of *Codonopsis* roots for treating MetS which may be exerted via obesity-dependent and -independent mechanisms. However, its efficacy in treating MetS in humans is still awaiting clinical verification.

A review of the medical records from Australian clinics has revealed that acupuncture is the most frequent form of complementary medicine use for respiratory disorders (Nik Nabil et al., 2015). A systematic review of 16 RCTs that examined the benefits of acupuncture or other related therapies for treatment of COPD has revealed that acupuncture therapies improved health-related quality of life in patients with mild to severe forms of COPD (Coyle et al., 2014). Despite being associated with improvement in St George's Respiratory Questionnaire score, Medical Research Council's dyspnoea scale, dyspnoea visual analogue scale and greater 6-min walking distance when compared to placebo control, acupuncture therapies reportedly had no additional effects on pulmonary function when compared to either placebo or pharmacotherapy. Although not directly benefiting pulmonary function, emerging evidence suggests that ear-acupuncture/-acupressure may help individuals to maintain smoking cessation which warrants further investigation. In the metabolic context, acupuncture interventions have recently been explored (Martinez & Peplow, 2016). The authors concluded that electro-acupuncture (a modern form of acupuncture) at low intensity and low frequency may ameliorate insulin resistance and enhance insulin sensitivity in experimental models and human insulin-resistant conditions, thus highlighting its potential use as a monotherapy or as an add-on therapy to diet-exercise interventions for treating chronic diseases like COPD and MetS (Fig. 2).

5. Perspectives and conclusions

A growing body of research indicates correlative links between MetS and pulmonary dysfunction during COPD. The correlation implies that components of the MetS particularly hyperglycaemia can give rise to pulmonary function impairment in COPD and *vice versa*. Regardless of the direction of the drive, the concurrent existence of MetS and COPD amplifies an individual's risk of cardiovascular comorbidity which is a major cause of mortality in these patients. Although the causal relationship and the underlying mechanisms for the development of these two chronic diseases are intertwined in nature, it is apparent that the major risk factor for the onset of COPD is cigarette smoking, while that for MetS is obesity. Both systemic inflammation and oxidative stress are emerging to be important links connecting COPD to MetS and extra-pulmonary pathologies such as CVD. In COPD, systemic inflammation may result from the spill over of lung-derived pro-inflammatory mediators including white blood cells, CRP, IL-6 and fibrinogen. In COPD patients with weight gain issues, adipose tissue may also release a panel of adipokines such as IL-6 and leptin which may potentiate the spill over inflammation from the lung. Parallel to this, loss of skeletal muscle mass associated with physical inactivity may negate the homeostatic effects of myokines which further exacerbates systemic inflammation. The altered oxidant balance during COPD may deplete the endogenous antioxidant defence leading to oxidation of cellular components and molecules within the lung, adipose tissue and skeletal muscle sustaining their roles in systemic inflammation. Polypharmacy is a major issue

commonly encountered in COPD patients, as all the comorbidities and syndromes are treated in isolation (Diez-Mangano et al., 2014; Franssen, Spruit, & Wouters, 2011). This means that the risk of adverse events due to combining drugs is increased and compliance may become difficult particularly in elderly/frail group of patients. Therefore, identifying convergent mechanisms that can treat the lung/systemic inflammation and comorbidities such as MetS concurrently should be a key focus for future therapeutic interventions.

Assurance

This is to declare that the present manuscript has not been published and is not under consideration for publication elsewhere

Conflict of interest statement

The authors declare no conflict of interest

Acknowledgments

The authors would like to acknowledge the support of the National Health and Medical Research Council of Australia (Project Grant Numbers APP1084627 and APP1138915) over this work.

References

- Abboud, R. T., & Vimalanathan, S. (2008). Pathogenesis of COPD. Part I. The role of protease-antiprotease imbalance in emphysema. *The International Journal of Tuberculosis and Lung Disease* 12, 361–367.
- Abramson, J. L., & Vaccarino, V. (2002). Relationship between physical activity and inflammation among apparently healthy middle-aged and older US adults. *Archives of Internal Medicine* 162, 1286–1292.
- Agusti, A. (2007). Systemic effects of chronic obstructive pulmonary disease: what we know and what we don't know (but should). *Proceedings of the American Thoracic Society* 4, 522–525.
- Agusti, A., Edwards, L. D., Rennard, S. I., MacNee, W., Tal-Singer, R., Miller, B. E., ... Evaluation of ClTIPSEI (2012). Persistent systemic inflammation is associated with poor clinical outcomes in COPD: a novel phenotype. *PLoS One* 7, e37483.
- Ahmed, L. A., Shehata, N. I., Abdelkader, N. F., & Khattab, M. M. (2014). Tempol, a superoxide dismutase mimetic agent, ameliorates cisplatin-induced nephrotoxicity through alleviation of mitochondrial dysfunction in mice. *PLoS One* 9, e108889.
- Akinkuolie, A. O., Ngwa, J. S., Meigs, J. B., & Djousse, L. (2011). Omega-3 polyunsaturated fatty acid and insulin sensitivity: a meta-analysis of randomized controlled trials. *Clinical Nutrition* 30, 702–707.
- Akpinar, E. E., Akpinar, S., Ertek, S., Sayin, E., & Gulhan, M. (2012). Systemic inflammation and metabolic syndrome in stable COPD patients. *Tüberküloz ve Toraks* 60, 230–237.
- Alam, M. A., & Rahman, M. M. (2014). Mitochondrial dysfunction in obesity: potential benefit and mechanism of Co-enzyme Q10 supplementation in metabolic syndrome. *Journal of Diabetes and Metabolic Disorders* 13.
- Alberti, K. G., Eckel, R. H., Grundy, S. M., Zimmet, P. Z., Cleeman, J. I., Donato, K. A., ... International Diabetes Federation Task Force on E, Prevention, National Heart L, Blood I, American Heart A, World Heart F, International Atherosclerosis S and International Association for the Study of O (2009). Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation* 120, 1640–1645.
- Alberti, K. G., Zimmet, P., Shaw, J., & Group IDFETFC (2005). The metabolic syndrome—a new worldwide definition. *Lancet* 366, 1059–1062.
- Allaire, J., Maltais, F., Doyon, J. F., Noel, M., LeBlanc, P., Carrier, G., ... Jobin, J. (2004). Peripheral muscle endurance and the oxidative profile of the quadriceps in patients with COPD. *Thorax* 59, 673–678.
- Allison, D. B., Gadde, K. M., Garvey, W. T., Peterson, C. A., Schwiers, M. L., Najarian, T., ... Day, W. W. (2012). Controlled-release phentermine/topiramate in severely obese adults: a randomized controlled trial (EQUIP). *Obesity (Silver Spring)* 20, 330–342.
- Ameen, N. M., Mohamed, R. S. E., Abd El Mageed, N. I., & Abd El Wahab, M. H. (2016). The metabolic syndrome in patients with chronic obstructive pulmonary disease. *Egypt Journal of Chest Disease Tuberculosis* 65, 593–596.
- Amori, R. E., Lau, J., & Pittas, A. G. (2007). Efficacy and safety of incretin therapy in type 2 diabetes: systematic review and meta-analysis. *JAMA* 298, 194–206.
- Ando, K., Takahashi, F., Motojima, S., Nakashima, K., Kaneko, N., Hoshi, K., & Takahashi, K. (2013). Possible role for tocilizumab, an anti-interleukin-6 receptor antibody, in treating cancer cachexia. *Journal of Clinical Oncology* 31, e69–e72.
- Andreozzi, F., Succurro, E., Mancuso, M. R., Perticone, M., Sciacqua, A., Perticone, F., & Sesti, G. (2007). Metabolic and cardiovascular risk factors in subjects with impaired fasting glucose: the 100 versus 110 mg/dL threshold. *Diabetes/Metabolism Research and Reviews* 23, 547–550.
- Andrews, C. S., Matsuyama, S., Lee, B. C., & Li, J. D. (2016). Resveratrol suppresses NTH1-induced inflammation via up-regulation of the negative regulator MyD88 short. *Scientific Reports* 6, 34445.
- Anthonsen, N. R., Skeans, M. A., Wise, R. A., Manfreda, J., Kanner, R. E., Connett, J. E., & Lung Health Study Research G (2005). The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. *Annals of Internal Medicine* 142, 233–239.
- Antoniu, S. A. (2008). Inhaled corticosteroids in COPD: systemic effects of a local therapy? *Expert Opinion on Pharmacotherapy* 9, 3271–3273.
- American Diabetes Association (2017). Diabetes Care in the Hospital. Sec. 14. In Standards of Medical Care in Diabetes-2017. *Diabetes Care* 40, 986.
- Astrup, A., & Toubro, S. (2004). Topiramate: a new potential pharmacological treatment for obesity. *Obesity Research* 12(Suppl), 167S–173S.
- Athyros, V. G., Katsiki, N., Doulas, M., Karagiannis, A., & Mikhailidis, D. P. (2013). Effect of tobacco smoking and smoking cessation on plasma lipoproteins and associated major cardiovascular risk factors: a narrative review. *Current Medical Research and Opinion* 29, 1263–1274.
- Athyros, V. G., Tziomalos, K., Katsiki, N., Gossios, T. D., Gioulema, O., Anagnostis, P., ... Group GSC (2013). The impact of smoking on cardiovascular outcomes and comorbidities in statin-treated patients with coronary artery disease: a post hoc analysis of the GREACE study. *Current Vascular Pharmacology* 11, 779–784.
- Audrain-McGovern, J., & Benowitz, N. L. (2011). Cigarette smoking, nicotine, and body weight. *Clinical Pharmacology and Therapeutics* 90, 164–168.
- Austin, V., Crack, P. J., Bozinovski, S., Miller, A. A., & Vlahos, R. (2016). COPD and stroke: are systemic inflammation and oxidative stress the missing links? *Clinical Science (London, England)* 130, 1039–1050.
- Avignon, A., Hokayem, M., Bisbal, C., & Lambert, K. (2012). Dietary antioxidants: Do they have a role to play in the ongoing fight against abnormal glucose metabolism? *Nutrition* 28, 715–721.
- Azzalini, L., Ferrer, E., Ramalho, L. N., Moreno, M., Dominguez, M., Colmenero, J., ... Bataller, R. (2010). Cigarette smoking exacerbates nonalcoholic fatty liver disease in obese rats. *Hepatology* 51, 1567–1576.
- Baeg, I. H., & So, S. H. (2013). The world ginseng market and the ginseng (Korea). *Journal of Ginseng Research* 37, 1–7.
- Bagul, P. K., Middela, H., Matapally, S., Padiya, R., Bastia, T., Madhusudana, K., ... Banerjee, S. K. (2012). Attenuation of insulin resistance, metabolic syndrome and hepatic oxidative stress by resveratrol in fructose-fed rats. *Pharmacological Research* 66, 260–268.
- Baker, E. H., Janaway, C. H., Philips, B. J., Brennan, A. L., Baines, D. L., Wood, D. M., & Jones, P. W. (2006). Hyperglycaemia is associated with poor outcomes in patients admitted to hospital with acute exacerbations of chronic obstructive pulmonary disease. *Thorax* 61, 284–289.
- Balasubramanian, V., & Naing, S. (2012). Hypogonadism in chronic obstructive pulmonary disease: incidence and effects. *Current Opinion in Pulmonary Medicine* 18, 112–117.
- Balducci, S., Zanuso, S., Nicolucci, A., Fernando, F., Cavallo, S., Cardelli, P., ... Pugliese, G. (2010). Anti-inflammatory effect of exercise training in subjects with type 2 diabetes and the metabolic syndrome is dependent on exercise modalities and independent of weight loss. *Nutrition, Metabolism, and Cardiovascular Diseases: NMCD* 20, 608–617.
- Barnes, P. J. (2010). Chronic obstructive pulmonary disease: effects beyond the lungs. *PLoS Medicine* 7, e1000220.
- Barnes, P. J. (2017). Cellular and molecular mechanisms of asthma and COPD. *Clinical Science (London, England)* 131, 1541–1558.
- Barnes, P. J., & Celli, B. R. (2009). Systemic manifestations and comorbidities of COPD. *The European Respiratory Journal* 33, 1165–1185.
- Barrett-Connor, E., & Khaw, K. T. (1989). Cigarette smoking and increased central adiposity. *Annals of Internal Medicine* 111, 783–787.
- Barth, E., Albuszies, G., Baumgart, K., Matejovic, M., Wachter, U., Vogt, J., ... Calzia, E. (2007). Glucose metabolism and catecholamines. *Critical Care Medicine* 35, S508–S518.
- Batsis, J. A., Romero-Corral, A., Collazo-Clavell, M. L., Sarr, M. G., Somers, V. K., Brekke, L., & Lopez-Jimenez, F. (2007). Effect of weight loss on predicted cardiovascular risk: change in cardiac risk after bariatric surgery. *Obesity (Silver Spring)* 15, 772–784.
- Batsis, J. A., Romero-Corral, A., Collazo-Clavell, M. L., Sarr, M. G., Somers, V. K., & Lopez-Jimenez, F. (2008). Effect of bariatric surgery on the metabolic syndrome: a population-based, long-term controlled study. *Mayo Clinic Proceedings* 83, 897–907.
- Bayliss, T. J., Smith, J. T., Schuster, M., Dragnev, K. H., & Rigas, J. R. (2011). A humanized anti-IL-6 antibody (ALD518) in non-small cell lung cancer. *Expert Opinion on Biological Therapy* 11, 1663–1668.
- Bernardo, I., Bozinovski, S., & Vlahos, R. (2015). Targeting oxidant-dependent mechanisms for the treatment of COPD and its comorbidities. *Pharmacology & Therapeutics* 155, 60–79.
- Bhatt, S. P., & Dransfield, M. T. (2013). Chronic obstructive pulmonary disease and cardiovascular disease. *Translational Research* 162, 237–251.
- Bianco, A., Mazzarella, G., Turchiarelli, V., Nigro, E., Corbi, G., Scudiero, O., ... Daniele, A. (2013). Adiponectin: An Attractive Marker for Metabolic Disorders in Chronic Obstructive Pulmonary Disease (COPD). *Nutrients* 5, 4115–4125.
- Bitar, A. N., Ghoto, M. A., Dayo, A., Arain, M. I., & Parveen, R. (2017). Pathophysiological correlation between diabetes mellitus type-II and chronic obstructive pulmonary diseases. *Journal of the Liaquat University of Medical and Health Sciences* 16, 41–48.
- Bjelakovic, G., Nikolova, D., Gluud, L. L., Simonetti, R. G., & Gluud, C. (2012). Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases. *Cochrane Database Syst. Rev.* 3, CD007176.
- Bojesen, A., Host, C., & Grønholt, C. H. (2010). Klinefelter's syndrome, type 2 diabetes and the metabolic syndrome: the impact of body composition. *Molecular Human Reproduction* 16, 396–401.

- Bonsaksen, T., Fagermoen, M. S., & Lerdal, A. (2016). Trajectories of physical and mental health among persons with morbid obesity and persons with COPD: a longitudinal comparative study. *Journal of Multidisciplinary Healthcare* 9, 191–200.
- Boschmann, M., Engeli, S., Dobberstein, K., Budziatek, P., Strauss, A., Boehnke, J., ... Jordan, J. (2009). Dipeptidyl-peptidase-IV inhibition augments postprandial lipid mobilization and oxidation in type 2 diabetic patients. *The Journal of Clinical Endocrinology and Metabolism* 94, 846–852.
- Botelho, F. M., Bauer, C. M., Finch, D., Nikota, J. K., Zavitz, C. C., Kelly, A., ... Stampfli, M. R. (2011). IL-1alpha/IL-1R1 expression in chronic obstructive pulmonary disease and mechanistic relevance to smoke-induced neutrophilia in mice. *PLoS One* 6 e28457.
- Breyer, M. K., Spruit, M. A., Hanson, C. K., Franssen, F. M., Vanfleteren, L. E., Groenen, M. T., ... Rutten, E. P. (2014). Prevalence of metabolic syndrome in COPD patients and its consequences. *PLoS One* 9 e98013.
- Broom, I., Wilding, J., Stott, P., Myers, N., & Group UKMS (2002). Randomised trial of the effect of orlistat on body weight and cardiovascular disease risk profile in obese patients: UK Multimorbidity Study. *International Journal of Clinical Practice* 56, 494–499.
- Bruno, A., Chanez, P., Chiappara, G., Siena, L., Giammanco, S., Gjomarkaj, M., ... Vignola, A. M. (2005). Does leptin play a cytokine-like role within the airways of COPD patients? *The European Respiratory Journal* 26, 398–405.
- Bruun, J. M., Pedersen, S. B., Kristensen, K., & Richelsen, B. (2002). Opposite regulation of interleukin-8 and tumor necrosis factor-alpha by weight loss. *Obesity Research* 10, 499–506.
- Burge, P. S., Calverley, P. M., Jones, P. W., Spencer, S., Anderson, J. A., & Maslen, T. K. (2000). Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. *BMJ* 320, 1297–1303.
- Burgel, P. R., Paillasseur, J. L., Caillaud, D., Tillie-Leblond, I., Chanez, P., Escamilla, R., ... Initiatives, B. S. C. (2010). Clinical COPD phenotypes: a novel approach using principal component and cluster analyses. *The European Respiratory Journal* 36, 531–539.
- Cai, D., Yuan, M., Frantz, D. F., Melendez, P. A., Hansen, L., Lee, J., & Shoelson, S. E. (2005). Local and systemic insulin resistance resulting from hepatic activation of IKK-beta and NF-kappaB. *Nature Medicine* 11, 183–190.
- Calder, P. C. (2015). Marine omega-3 fatty acids and inflammatory processes: Effects, mechanisms and clinical relevance. *Biochimica et Biophysica Acta* 1851, 469–484.
- Calder, P. C. (2017). Omega-3 fatty acids and inflammatory processes: from molecules to man. *Biochemical Society Transactions* 45, 1105–1115.
- Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, Yates JC, Vestbo J and investigators T (2007) Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *The New England Journal of Medicine* 356: 775–789.
- Cao, C., Wang, R., Wang, J., Bunjhoo, H., Xu, Y., & Xiong, W. (2012). Body mass index and mortality in chronic obstructive pulmonary disease: a meta-analysis. *PLoS One* 7 e43892.
- Carey, M. A., Card, J. W., Voltz, J. W., Germolec, D. R., Korach, K. S., & Zeldin, D. C. (2007). The impact of sex and sex hormones on lung physiology and disease: lessons from animal studies. *American Journal of Physiology. Lung Cellular and Molecular Physiology* 293, L272–L278.
- Carmona, M. C., Lefebvre, P., Lefebvre, B., Galinier, A., Benani, A., Jeanson, Y., ... Technology M and New Therapeutic T (2009). Coadministration of coenzyme Q prevents rosiglitazone-induced adipogenesis in ob/ob mice. *International Journal of Obesity* 33, 204–211.
- Cassuto, H., Kochan, K., Chakravarty, K., Cohen, H., Blum, B., Olszwang, Y., ... Reshef, L. (2005). Glucocorticoids regulate transcription of the gene for phosphoenolpyruvate carboxykinase in the liver via an extended glucocorticoid regulatory unit. *The Journal of Biological Chemistry* 280, 33873–33884.
- Castaldi, P. J., Dy, J., Ross, J., Chang, Y., Washko, G. R., Curran-Everett, D., ... Cho, M. H. (2014). Cluster analysis in the COPDGenes study identifies subtypes of smokers with distinct patterns of airway disease and emphysema. *Thorax* 69, 415–422.
- Caughy, G. E., Preiss, A. K., Vitry, A. I., Gilbert, A. L., & Roughead, E. E. (2013). Comorbid diabetes and COPD: impact of corticosteroid use on diabetes complications. *Diabetes Care* 36, 3009–3014.
- Caughy, G. E., Roughead, E. E., Vitry, A. I., McDermott, R. A., Shakib, S., & Gilbert, A. L. (2010). Comorbidity in the elderly with diabetes: Identification of areas of potential treatment conflicts. *Diabetes Research and Clinical Practice* 87, 385–393.
- Cazzola, M., Bettoncelli, G., Sessa, E., Cricelli, C., & Biscione, G. (2010). Prevalence of comorbidities in patients with chronic obstructive pulmonary disease. *Respiration* 80, 112–119.
- Cazzola, M., Calzetta, L., Rogliani, P., Lauro, D., Novelli, L., Page, C. P., ... Matera, M. G. (2012). High glucose enhances responsiveness of human airways smooth muscle via the Rho/ROCK pathway. *American Journal of Respiratory Cell and Molecular Biology* 47, 509–516.
- Cazzola, M., Rogliani, P., Calzetta, L., Lauro, D., Page, C., & Matera, M. G. (2017). Targeting Mechanisms Linking COPD to Type 2 Diabetes Mellitus. *Trends Pharmacol Sci* 38, 940–951.
- Ceborn Lipovec, N., Beijers, R. J., van den Borst, B., Doehner, W., Lainscak, M., & Schols, A. M. (2016). The Prevalence of Metabolic Syndrome In Chronic Obstructive Pulmonary Disease: A Systematic Review. *COPD* 13, 399–406.
- Cecere, L. M., Littman, A. J., Slatore, C. G., Udris, E. M., Bryson, C. L., Boyko, E. J., ... Au, D. H. (2011). Obesity and COPD: associated symptoms, health-related quality of life, and medication use. *COPD* 8, 275–284.
- Ceglia, L., Lau, J., & Pittas, A. G. (2006). Meta-analysis: efficacy and safety of inhaled insulin therapy in adults with diabetes mellitus. *Annals of Internal Medicine* 145, 665–675.
- Celli, B. R., Cote, C. G., Marin, J. M., Casanova, C., Montes de Oca, M., Mendez, R. A., ... Cabral, H. J. (2004). The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *The New England Journal of Medicine* 350, 1005–1012.
- Celli BR, Decramer M, Wedzicha JA, Wilson KC, Agusti A, Criner GJ, MacNee W, Make BJ, Rennard SI, Stockley RA, Vogelmeier C, Anzueto A, Au DH, Barnes PJ, Burgel PR, Calverley PM, Casanova C, Clini EM, Cooper CB, Coxson HO, Dusser DJ, Fabbri LM, Fahy B, Ferguson GT, Fisher A, Fletcher MJ, Hayot M, Hurst JR, Jones PW, Mahler DA, Maltais F, Mannino DM, Martinez FJ, Miravittles M, Meek PM, Papi A, Rabe KF, Roche N, Sciruba FC, Sethi S, Siafakas N, Sin DD, Soriano JB, Stoller JK, Tashkin DP, Troosters T, Verleden GM, Verschakelen J, Vestbo J, Walsh JW, Washko GR, Wise RA, Wouters EF, ZuWallack RL and Research AETFC (2015) An Official American Thoracic Society/European Respiratory Society Statement: Research questions in chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine* 191:e4–e27.
- Ceriello, A. (2006). Oxidative stress and diabetes-associated complications. *Endocrine Practice* 12(Suppl. 1), 60–62.
- Chakrabarti, B., Angus, R. M., Agarwal, S., Lane, S., & Calverley, P. M. (2009). Hyperglycaemia as a predictor of outcome during non-invasive ventilation in decompensated COPD. *Thorax* 64, 857–862.
- Chan, S. M. H., & Ye, J. M. (2013). Strategies for the Discovery and Development of Anti-Diabetic Drugs from the Natural Products of Traditional Medicines. *Journal of Pharmacy & Pharmaceutical Sciences* 16, 207–216.
- Chelikani, P. K., Glimm, D. R., & Kennelly, J. J. (2003). Short communication: Tissue distribution of leptin and leptin receptor mRNA in the bovine. *Journal of Dairy Science* 86, 2369–2372.
- Chen, C. C., Li, T. C., Chang, P. C., Liu, C. S., Lin, W. Y., Wu, M. T., ... Lin, C. C. (2008). Association among cigarette smoking, metabolic syndrome, and its individual components: the metabolic syndrome study in Taiwan. *Metabolism* 57, 544–548.
- Chen, K. N., Peng, W. H., Hou, C. W., Chen, C. Y., Chen, H. H., Kuo, C. H., & Korivi, M. (2013). Codonopsis javanica root extracts attenuate hyperinsulinemia and lipid peroxidation in fructose-fed insulin resistant rats. *Journal of Food and Drug Analysis* 21, 347–355.
- Chen, M., Liu, B., Gao, Q., Zhuo, Y., & Ge, J. (2011). Mitochondria-targeted peptide MTP-131 alleviates mitochondrial dysfunction and oxidative damage in human trabecular meshwork cells. *Investigative Ophthalmology & Visual Science* 52, 7027–7037.
- Chen, S. B., Lee, Y. C., Ser, K. H., Chen, J. C., Chen, S. C., Hsieh, H. F., & Lee, W. J. (2009). Serum C-reactive protein and white blood cell count in morbidly obese surgical patients. *Obesity Surgery* 19, 461–466.
- Chen, X., May, B., Di, Y. M., Zhang, A. L., Lu, C., Xue, C. C., & Lin, L. (2014). Oral Chinese herbal medicine combined with pharmacotherapy for stable COPD: a systematic review of effect on BODE index and six minute walk test. *PLoS One* 9 e91830.
- Chen, Z., Wang, D., Liu, X., Pei, W., Li, J., Cao, Y., ... Tong, J. (2015). Oxidative DNA damage is involved in cigarette smoke-induced lung injury in rats. *Environmental Health and Preventive Medicine* 20, 318–324.
- Cheon, J. M., Kim, D. I., & Kim, K. S. (2015). Insulin sensitivity improvement of fermented Korean Red Ginseng (Panax ginseng) mediated by insulin resistance hallmarks in old-aged ob/ob mice. *Journal of Ginseng Research* 39, 331–337.
- Cheung, Y. M., Joham, A., Marks, S., & Teede, H. (2017). The obesity paradox: an endocrine perspective. *Internal Medicine Journal* 47, 727–733.
- Choi, H. S., Choi, B. Y., Cho, Y. Y., Mizuno, H., Kang, B. S., Bode, A. M., & Dong, Z. (2005). Phosphorylation of histone H3 at serine 10 is indispensable for neoplastic cell transformation. *Cancer Research* 65, 5818–5827.
- Choi, K. M., Lee, J., Lee, K. W., Seo, J. A., Oh, J. H., Kim, S. G., ... Baik, S. H. (2004). Comparison of serum concentrations of C-reactive protein, TNF-alpha, and interleukin 6 between elderly Korean women with normal and impaired glucose tolerance. *Diabetes Research and Clinical Practice* 64, 99–106.
- Chou, S. H., Chen, Y. W., Chuang, H. Y., Kao, E. L., & Huang, M. F. (2006). Alveolar-capillary membrane permeability for early prediction of response of inhaled steroid on patients with chronic obstructive pulmonary disease. *Journal of Clinical Pharmacy and Therapeutics* 31, 363–368.
- Chung, K. F., & Adcock, I. M. (2008). Multifaceted mechanisms in COPD: inflammation, immunity, and tissue repair and destruction. *The European Respiratory Journal* 31, 1334–1356.
- Churg, A., Wang, R. D., Tai, H., Wang, X., Xie, C., & Wright, J. L. (2004). Tumor necrosis factor-alpha drives 70% of cigarette smoke-induced emphysema in the mouse. *American Journal of Respiratory and Critical Care Medicine* 170, 492–498.
- Clerk, L. H., Vincent, M. A., Jahn, L. A., Liu, Z., Lindner, J. R., & Barrett, E. J. (2006). Obesity blunts insulin-mediated microvascular recruitment in human forearm muscle. *Diabetes* 55, 1436–1442.
- Clini, E., Crisafulli, E., Radaeli, A., & Malerba, M. (2013). COPD and the metabolic syndrome: an intriguing association. *Internal and Emergency Medicine* 8, 283–289.
- Collin, A., Hardonniere, K., Chevanne, M., Vuillemin, J., Pouchard, N., Burel, A., ... Sergent, O. (2014). Cooperative interaction of benzo[a]pyrene and ethanol on plasma membrane remodeling is responsible for enhanced oxidative stress and cell death in primary rat hepatocytes. *Free Radical Biology & Medicine* 72, 11–22.
- Corey KE and Cohen DE (2000) Lipid and lipoprotein metabolism in liver disease, in *Endotext* (De Groot LJ, Chrousos G, Dungan K, Feingold KR, Grossman A, Hershman JM, Koch C, Korbonits M, McLachlan R, New M, Purnell J, Rebar R, Singer F and Vinik A eds), South Dartmouth (MA).
- Coyle, M. E., Shergis, J. L., Huang, E. T., Guo, X., Di, Y. M., Zhang, A., & Xue, C. C. (2014). Acupuncture therapies for chronic obstructive pulmonary disease: a systematic review of randomized, controlled trials. *Alternative Therapies in Health and Medicine* 20, 10–23.
- Craig, W. Y., Palomaki, G. E., & Haddow, J. E. (1989). Cigarette smoking and serum lipid and lipoprotein concentrations: an analysis of published data. *BMJ* 298, 784–788.
- Cravo, J., & Esquinas, A. M. (2017). Obesity and COPD exacerbations - it's not that simple. *Respiratory Medicine* 125, 103.

- Crisafulli, E., Gorgone, P., Vagaggini, B., Pagani, M., Rossi, G., Costa, F., ... Clini, E. M. (2010). Efficacy of standard rehabilitation in COPD outpatients with comorbidities. *The European Respiratory Journal* 36, 1042–1048.
- Cyphert, T. J., Morris, R. T., House LM, Barnes, T. M., Otero, Y. F., Barham, W. J., ... McGuinness, O. P. (2015). NF-kappaB-dependent airway inflammation triggers systemic insulin resistance. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology* 309, R1144–R1152.
- Dalal, A. A., Shah, M., Lunacek, O., & Hanania, N. A. (2011). Clinical and economic burden of patients diagnosed with COPD with comorbid cardiovascular disease. *Respiratory Medicine* 105, 1516–1522.
- Debigare, R., Cote, C. H., Hould, F. S., LeBlanc, P., & Maltais, F. (2003). In vitro and in vivo contractile properties of the vastus lateralis muscle in males with COPD. *The European Respiratory Journal* 21, 273–278.
- Debrececi, B., & Debrececi, L. (2012). Why do homocysteine-lowering B vitamin and antioxidant E vitamin supplementations appear to be ineffective in the prevention of cardiovascular diseases? *Cardiovascular Therapeutics* 30, 227–233.
- Decramer, M., Rennard, S., Troosters, T., Mapel, D. W., Giardino, N., Mannino, D., ... Cooper, C. B. (2008). COPD as a lung disease with systemic consequences—clinical impact, mechanisms, and potential for early intervention. *COPD* 5, 235–256.
- DeFronzo, R. A., Ratner, R. E., Han, J., Kim, D. D., Fineman, M. S., & Baron, A. D. (2005). Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. *Diabetes Care* 28, 1092–1100.
- DeLorey, D. S., Wyrick, B. L., & Babb, T. G. (2005). Mild-to-moderate obesity: implications for respiratory mechanics at rest and during exercise in young men. *International Journal of Obesity* 29, 1039–1047.
- Dendukuri, N., Blais, L., & LeLorier, J. (2002). Inhaled corticosteroids and the risk of diabetes among the elderly. *British Journal of Clinical Pharmacology* 54, 59–64.
- Despres, J. P., & Lemieux, I. (2006). Abdominal obesity and metabolic syndrome. *Nature* 444, 881–887.
- Dessi, M., Noce, A., Bertucci, P., Manca di Villahermosa, S., Zenobi, R., Castagnola, V., ... Di Daniele, N. (2013). Atherosclerosis, dyslipidemia, and inflammation: the significant role of polyunsaturated Fatty acids. *ISRN Inflammation* 2013, 191823.
- Di Dalmazi, G., Pagotto, U., Pasquali, R., & Vicennati, V. (2012). Glucocorticoids and type 2 diabetes: from physiology to pathology. *Journal of Nutrition and Metabolism* 2012, 525093.
- Dichtl, W., Nilsson, L., Goncalves, I., Ares, M. P., Banfi, C., Calara, F., ... Nilsson, J. (1999). Very low-density lipoprotein activates nuclear factor-kappaB in endothelial cells. *Circulation Research* 84, 1085–1094.
- Dietz, W. H., Douglas, C. E., & Brownson, R. C. (2016). Chronic Disease Prevention: Tobacco Avoidance, Physical Activity, and Nutrition for a Healthy Start. *JAMA* 316, 1645–1646.
- Diez-Manglano, J., Barquero-Romero, J., Almagro, P., Cabrera, F. J., Lopez Garcia, F., Montero, L., ... Working Group on C and Spanish Society of Internal M (2014). COPD patients with and without metabolic syndrome: clinical and functional differences. *Internal and Emergency Medicine* 9, 419–425.
- Diez-Manglano, J., Barquero-Romero, J., Mena, P. A., Recio-Iglesias, J., Cabrera-Aguilar, J., Lopez-Garcia, F., ... Researchers, E. S. (2014). Polypharmacy in patients hospitalised for acute exacerbation of COPD. *The European Respiratory Journal* 44, 791–794.
- Ding, Y., Niu, H., Zhou, L., Zhou, W., Chen, J., Xie, S., ... Jin, T. (2015). Association of multiple genetic variants with chronic obstructive pulmonary disease (COPD) susceptibility in Hainan region. *The Clinical Respiratory Journal* 11, 727–732.
- Divo, M., Cote, C., de Torres, J. P., Casanova, C., Marin, J. M., Pinto-Plata, V., ... Group BC (2012). Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine* 186, 155–161.
- Drucker, D. J., Philippe, J., Mojsov, S., Chick, W. L., & Habener, J. F. (1987). Glucagon-like peptide I stimulates insulin gene expression and increases cyclic AMP levels in a rat islet cell line. *Proceedings of the National Academy of Sciences of the United States of America* 84, 3434–3438.
- Duong, C., Seow, H. J., Bozinovski, S., Crack, P. J., Anderson, G. P., & Vlahos, R. (2010). Glutathione peroxidase-1 protects against cigarette smoke-induced lung inflammation in mice. *American Journal of Physiology. Lung Cellular and Molecular Physiology* 299, L425–L433.
- Durham, A. L., Caramori, G., Chung, K. F., & Adcock, I. M. (2016). Targeted anti-inflammatory therapeutics in asthma and chronic obstructive lung disease. *Translational Research* 167, 192–203.
- Editorial, N. I. (2017). A current view on inflammation. *Nature Immunology* 18, 825.
- Egert, S., Bosity-Westphal, A., Seiberl, J., Kurbitz, C., Settler, U., Plachta-Danielzik, S., ... Muller, M. J. (2009). Quercetin reduces systolic blood pressure and plasma oxidised low-density lipoprotein concentrations in overweight subjects with a high-cardiovascular disease risk phenotype: a double-blinded, placebo-controlled crossover study. *The British Journal of Nutrition* 102, 1065–1074.
- Eisner, M. D., Blanc, P. D., Sidney, S., Yelin, E. H., Lathon, P. V., Katz, P. P., ... Iribarren, C. (2007). Body composition and functional limitation in COPD. *Respiratory Research* 8, 7.
- Eriksson, J. G., Forsen, T. J., Mortensen, S. A., & Rohde, M. (1999). The effect of coenzyme Q10 administration on metabolic control in patients with type 2 diabetes mellitus. *Biofactors* 9, 315–318.
- Esposito, K., Nappo, F., Marfella, R., Giugliano, G., Giugliano, F., Ciotola, M., ... Giugliano, D. (2002). Inflammatory cytokine concentrations are acutely increased by hyperglycemia in humans: role of oxidative stress. *Circulation* 106, 2067–2072.
- Fabbri, L. M., Luppi, F., Beghe, B., & Rabe, K. F. (2008). Complex chronic comorbidities of COPD. *The European Respiratory Journal* 31, 204–212.
- Fabbri, L. M., & Rabe, K. F. (2007). From COPD to chronic systemic inflammatory syndrome? *Lancet* 370, 797–799.
- Faner, R., Tal-Singer, R., Riley, J. H., Celli, B., Vestbo, J., MacNee, W., ... Investigators, E. S. (2014). Lessons from ECLIPSE: a review of COPD biomarkers. *Thorax* 69, 666–672.
- Fargion, S., Porzio, M., & Fracanzani, A. L. (2014). Nonalcoholic fatty liver disease and vascular disease: state-of-the-art. *World Journal of Gastroenterology* 20, 13306–13324.
- Ferraz-Amaro, L., Arce-Franco, M., Muniz, J., Lopez-Fernandez, J., Hernandez-Hernandez, V., Franco, A., ... Diaz-Gonzalez, F. (2011). Systemic blockade of TNF-alpha does not improve insulin resistance in humans. *Hormone and Metabolic Research* 43, 801–808.
- Fidler, M. C., Sanchez, M., Raether, B., Weissman, N. J., Smith, S. R., Shanahan, W. R., ... Group BCT (2011). A one-year randomized trial of lorcaserin for weight loss in obese and overweight adults: the BLOSSOM trial. *The Journal of Clinical Endocrinology and Metabolism* 96, 3067–3077.
- Filippatos, T. D., Panagiopoulou, T. V., & Elisaf, M. S. (2014). Adverse effects of GLP-1 receptor agonists. *The Review of Diabetic Studies: RDS* 11, 202–230.
- Flachs, P., Horakova, O., Brauner, P., Rossmeisl, M., Pecina, P., Franssen-van Hal, N., ... Kopecky, J. (2005). Polyunsaturated fatty acids of marine origin upregulate mitochondrial biogenesis and induce beta-oxidation in white fat. *Diabetologia* 48, 2365–2375.
- Fletcher, C., & Peto, R. (1977). The natural history of chronic airflow obstruction. *British Medical Journal* 1, 1645–1648.
- Flynn, R. W., MacDonald, T. M., Hapca, A., MacKenzie, I. S., & Schembri, S. (2014). Quantifying the real life risk profile of inhaled corticosteroids in COPD by record linkage analysis. *Respiratory Research* 15, 141.
- Ford, E. S. (2002). Does exercise reduce inflammation? Physical activity and C-reactive protein among U.S. adults. *Epidemiology* 13, 561–568.
- Formoso, G., De Filippis, E. A., Michetti, N., Di Fulvio, P., Pandolfi, A., Bucciarelli, T., ... Consoli, A. (2008). Decreased in vivo oxidative stress and decreased platelet activation following metformin treatment in newly diagnosed type 2 diabetic subjects. *Diabetes/Metabolism Research and Reviews* 24, 231–237.
- Forno, E., Han, Y. Y., Muzumdar, R. H., & Celedon, J. C. (2015). Insulin resistance, metabolic syndrome, and lung function in US adolescents with and without asthma. *The Journal of Allergy and Clinical Immunology* 136(304–311), e308.
- Fragoso, C. A. (2016). Epidemiology of Chronic Obstructive Pulmonary Disease (COPD) in Aging Populations. *COPD* 13, 125–129.
- Franssen, F. M., O'Donnell, D. E., Goossens, G. H., Blaak, E. E., & Schols, A. M. (2008). Obesity and the lung: 5. Obesity and COPD. *Thorax* 63, 1110–1117.
- Franssen, F. M., & Rochester, C. L. (2014). Comorbidities in patients with COPD and pulmonary rehabilitation: do they matter? *European Respiratory Review* 23, 131–141.
- Franssen, F. M., Spruit, M. A., & Wouters, E. F. (2011). Determinants of polypharmacy and compliance with GOLD guidelines in patients with chronic obstructive pulmonary disease. *International Journal of Chronic Obstructive Pulmonary Disease* 6, 493–501.
- Frid, A., Sterner, G. N., Londahl, M., Wiklander, C., Cato, A., Vinge, E., & Andersson, A. (2010). Novel assay of metformin levels in patients with type 2 diabetes and varying levels of renal function: clinical recommendations. *Diabetes Care* 33, 1291–1293.
- Friedman, T. C., Sinha-Hikim, I., Parveen, M., Najjar, S. M., Liu, Y., Mangubat, M., ... Sinha-Hikim, A. P. (2012). Additive effects of nicotine and high-fat diet on hepatic steatosis in male mice. *Endocrinology* 153, 5809–5820.
- Fujimoto, S., Kurihara, N., Hirata, K., & Takeda, T. (1993). Effects of Coenzyme-Q(10) Administration on Pulmonary-Function and Exercise Performance in Patients with Chronic Lung-Diseases. *The Clinical Investigator* 71, S162–S166.
- Fujita, M., Shannon, J. M., Ouchi, H., Voelker, D. R., Nakanishi, Y., & Mason, R. J. (2005). Serum surfactant protein D is increased in acute and chronic inflammation in mice. *Cytokine* 31, 25–33.
- Furukawa, S., Fujita, T., Shimabukuro, M., Iwaki, M., Yamada, Y., Nakajima, Y., ... Shimomura, I. (2004). Increased oxidative stress in obesity and its impact on metabolic syndrome. *The Journal of Clinical Investigation* 114, 1752–1761.
- Gabay, C., & Kushner, I. (1999). Acute-phase proteins and other systemic responses to inflammation. *The New England Journal of Medicine* 340, 448–454.
- Gadde, K. M., Allison, D. B., Ryan, D. H., Peterson, C. A., Troupin, B., Schwiens, M. L., & Day, W. W. (2011). Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomised, placebo-controlled, phase 3 trial. *Lancet* 377, 1341–1352.
- Galesanu, R. G., Bernard, S., Marquis, K., Lacasse, Y., Poirier, P., Bourbeau, J., & Maltais, F. (2014). Obesity in chronic obstructive pulmonary disease: is fatter really better? *Canadian Respiratory Journal* 21, 297–301.
- Gamble, E., Grootendorst, D. C., Hattotuwa, K., O'Shaughnessy, T., Ram, F. S., Qiu, Y., ... Barnes, N. C. (2007). Airway mucosal inflammation in COPD is similar in smokers and ex-smokers: a pooled analysis. *The European Respiratory Journal* 30, 467–471.
- Gamboa, J. L., Garcia-Cazarin, M. L., & Andrade, F. H. (2011). Chronic hypoxia increases insulin-stimulated glucose uptake in mouse soleus muscle. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology* 300, R85–R91.
- Gan, W. Q., Man, S. F., Senthilselvan, A., & Sin, D. D. (2004). Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis. *Thorax* 59, 574–580.
- Garber, A., Henry, R., Ratner, R., Garcia-Hernandez, P. A., Rodriguez-Pattzi, H., Olvera-Alvarez, I., ... Group L-S (2009). Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomised, 52-week, phase III, double-blind, parallel-treatment trial. *Lancet* 373, 473–481.
- Garber, A. J. (2011). Long-acting glucagon-like peptide 1 receptor agonists: a review of their efficacy and tolerability. *Diabetes Care* 34(Suppl. 2), S279–S284.
- Garnett, J. P., Baker, E. H., Naik, S., Lindsay, J. A., Knight, G. M., Gill, S., ... Baines, D. L. (2013). Metformin reduces airway glucose permeability and hyperglycaemia-induced Staphylococcus aureus load independently of effects on blood glucose. *Thorax* 68, 835–845.
- Gautier, A., Bonnet, F., Dubois, S., Massart, C., Grosheny, C., Bachelot, A., ... Ducluzeau, P. H. (2013). Associations between visceral adipose tissue, inflammation and sex steroid concentrations in men. *Clinical Endocrinology* 78, 373–378.
- Gilbert, R., & Lim, E. M. (2008). The diagnosis of Cushing's syndrome: an endocrine society clinical practice guideline. *Clinical Biochemist Reviews* 29, 103–106.

- Gileles-Hillel, A., Almendros, I., Khalyfa, A., Nigdelioglu, R., Qiao, Z., Hamanaka, R. B., ... Gozal, D. (2017). Prolonged exposures to intermittent hypoxia promote visceral white adipose tissue inflammation in a murine model of severe sleep apnea: effect of normoxic recovery. *Sleep*, 40.
- Gileles-Hillel, A., Kheirandish-Gozal, L., & Gozal, D. (2016). Biological plausibility linking sleep apnoea and metabolic dysfunction. *Nature Reviews. Endocrinology* 12, 290–298.
- Gleeson, L. E., Ryan, D., O'Leary, S. M., McLaughlin, A. M., Sheedy, F. J., & Keane, J. M. (2018). Cigarette smoking impairs the bioenergetic immune response to mycobacterium tuberculosis infection. *American Journal of Respiratory Cell and Molecular Biology* 59, 572–579.
- Global Initiative for Chronic Obstructive Lung Disease (GOLD) (2018). *Global Strategy for the Diagnosis, Management and Prevention of chronic obstructive pulmonary disease: 2018 Report*.
- Godtfredsen, N. S., Lam, T. H., Hansel, T. T., Leon, M. E., Gray, N., Dresler, C., ... Vestbo, J. (2008). COPD-related morbidity and mortality after smoking cessation: status of the evidence. *The European Respiratory Journal* 32, 844–853.
- Gold, D. R., Litonjua, A. A., Carey, V. J., Manson, J. E., Buring, J. E., Lee, I. M., ... Luttmann-Gibson, H. (2016). Lung VITAL: Rationale, design, and baseline characteristics of an ancillary study evaluating the effects of vitamin D and/or marine omega-3 fatty acid supplements on acute exacerbations of chronic respiratory disease, asthma control, pneumonia and lung function in adults. *Contemporary Clinical Trials* 47, 185–195.
- Goldklang, M., Golovatch, P., Zelonina, T., Trischler, J., Rabinowitz, D., Lemaitre, V., & D'Armiento, J. (2012). Activation of the TLR4 signaling pathway and abnormal cholesterol efflux lead to emphysema in ApoE-deficient mice. *American Journal of Physiology. Lung Cellular and Molecular Physiology* 302, L1200–L1208.
- Gongora, M. C., Lob, H. E., Landmesser, U., Guzik, T. J., Martin, W. D., Ozumi, K., ... Harrison, D. G. (2008). Loss of extracellular superoxide dismutase leads to acute lung damage in the presence of ambient air: a potential mechanism underlying adult respiratory distress syndrome. *The American Journal of Pathology* 173, 915–926.
- Gordon, S. (2007). Macrophage heterogeneity and tissue lipids. *The Journal of Clinical Investigation* 117, 89–93.
- Gordon, S., & Taylor, P. R. (2005). Monocyte and macrophage heterogeneity. *Nature Reviews. Immunology* 5, 953–964.
- Gosker, H. R., Engelen, M. P., van Mameren, H., van Dijk, P. J., van der Vusse, G. J., Wouters, E. F., & Schols, A. M. (2002). Muscle fiber type IIX atrophy is involved in the loss of fat-free mass in chronic obstructive pulmonary disease. *The American Journal of Clinical Nutrition* 76, 113–119.
- Goto, T., Tsugawa, Y., Faridi, M. K., Camargo, C. A., Jr., & Hasegawa, K. (2017). Reduced Risk of Acute Exacerbation of COPD After Bariatric Surgery: A Self-Controlled Case Series Study. *Chest*. 153, 611–617.
- Greenberg, A. S., Nordan, R. P., McIntosh, J., Calvo, J. C., Scow, R. O., & Jablons, D. (1992). Interleukin 6 reduces lipoprotein lipase activity in adipose tissue of mice in vivo and in 3T3-L1 adipocytes: a possible role for interleukin 6 in cancer cachexia. *Cancer Research* 52, 4113–4116.
- Gregor, M. F., & Hotamisligil, G. S. (2011). Inflammatory mechanisms in obesity. *Annual Review of Immunology* 29, 415–445.
- Gross, D., Shenkman, Z., Bleiberg, B., Dayan, M., Gittelson, M., & Efrat, R. (2002). Ginseng improves pulmonary functions and exercise capacity in patients with COPD. *Monaldi Archives for Chest Disease* 57, 242–246.
- Grunfeld, C., Zhao, C., Fuller, J., Pollack, A., Moser, A., Friedman, J., & Feingold, K. R. (1996). Endotoxin and cytokines induce expression of leptin, the ob gene product, in hamsters. *The Journal of Clinical Investigation* 97, 2152–2157.
- Guarascio, A. J., Ray, S. M., Finch, C. K., & Self, T. H. (2013). The clinical and economic burden of chronic obstructive pulmonary disease in the USA. *Clinicoecon Outcomes Research* 5, 235–245.
- Guazzi, M., Oreglia, I., & Guazzi, M. D. (2002). Insulin improves alveolar-capillary membrane gas conductance in type 2 diabetes. *Diabetes Care* 25, 1802–1806.
- Guo, H., Ling, W., Wang, Q., Liu, C., Hu, Y., & Xia, M. (2008). Cyanidin 3-glucoside protects 3T3-L1 adipocytes against H2O2- or TNF-alpha-induced insulin resistance by inhibiting c-Jun NH2-terminal kinase activation. *Biochemical Pharmacology* 75, 1393–1401.
- Halberg, N., Khan, T., Trujillo, M. E., Wernstedt-Asterholm, I., Attie, A. D., Sherwani, S., ... Scherer, P. E. (2009). Hypoxia-inducible factor 1alpha induces fibrosis and insulin resistance in white adipose tissue. *Molecular and Cellular Biology* 29, 4467–4483.
- Halford, J. C., Harrold, J. A., Boyland, E. J., Lawton, C. L., & Blundell, J. E. (2007). Serotonergic drugs : effects on appetite expression and use for the treatment of obesity. *Drugs* 67, 27–55.
- Hamaguchi, M., Kojima, T., Takeda, N., Nagata, C., Takeda, J., Sarui, H., ... Yoshikawa, T. (2007). Nonalcoholic fatty liver disease is a novel predictor of cardiovascular disease. *World Journal of Gastroenterology* 13, 1579–1584.
- Han, M. K., Postma, D., Mannino, D. M., Giardino, N. D., Buist, S., Curtis, J. L., & Martinez, F. J. (2007). Gender and chronic obstructive pulmonary disease: why it matters. *American Journal of Respiratory and Critical Care Medicine* 176, 1179–1184.
- Harris, K. K., Zopey, M., & Friedman, T. C. (2016). Metabolic effects of smoking cessation. *Nature Reviews. Endocrinology* 12, 299–308.
- Hartman, J. E., Boezen, H. M., de Greef, M. H., Bossenbroek, L., & ten Hacken, N. H. (2010). Consequences of physical inactivity in chronic obstructive pulmonary disease. *Expert Review of Respiratory Medicine* 4, 735–745.
- He, S., Xie, L., Lu, J., & Sun, S. (2017). Characteristics and potential role of M2 macrophages in COPD. *International Journal of Chronic Obstructive Pulmonary Disease* 12, 3029–3039.
- Hedenstierna, G., & Santesson, J. (1976). Breathing mechanics, dead space and gas exchange in the extremely obese, breathing spontaneously and during anaesthesia with intermittent positive pressure ventilation. *Acta Anaesthesiologica Scandinavica* 20, 248–254.
- Heggen, E., Svendsen, M., & Tonstad, S. (2017). Smoking cessation improves cardiometabolic risk in overweight and obese subjects treated with varenicline and dietary counseling. *Nutrition, Metabolism, and Cardiovascular Diseases: NMCD* 27, 335–341.
- Henriksen, J. E., Andersen, C. B., Hother-Nielsen, O., Vaag, A., Mortensen, S. A., & Beck-Nielsen, H. (1999). Impact of ubiquinone (coenzyme Q10) treatment on glycaemic control, insulin requirement and well-being in patients with Type 1 diabetes mellitus. *Diabetic Medicine* 16, 312–318.
- Henson, M. C., Swan, K. F., Edwards, D. E., Hoyle, G. W., Purcell, J., & Castracane, V. D. (2004). Leptin receptor expression in fetal lung increases in late gestation in the baboon: a model for human pregnancy. *Reproduction* 127, 87–94.
- Hilawe, E. H., Yatsuya, H., Li, Y., Uemura, M., Wang, C., Chiang, C., ... Aoyama, A. (2015). Smoking and diabetes: is the association mediated by adiponectin, leptin, or C-reactive protein? *Journal of Epidemiology* 25, 99–109.
- Hildrum, B., Mykletun, A., Hole, T., Midthjell, K., & Dahl, A. A. (2007). Age-specific prevalence of the metabolic syndrome defined by the International Diabetes Federation and the National Cholesterol Education Program: the Norwegian HUNT 2 study. *BMC Public Health* 7, 220.
- Hitchings, A. W., Archer, J. R., Srivastava, S. A., & Baker, E. H. (2015). Safety of metformin in patients with chronic obstructive pulmonary disease and type 2 diabetes mellitus. *COPD* 12, 126–131.
- Hoggard, N., Hunter, L., Duncan, J. S., Williams, L. M., Trayhurn, P., & Mercer, J. G. (1997). Leptin and leptin receptor mRNA and protein expression in the murine fetus and placenta. *Proceedings of the National Academy of Sciences of the United States of America* 94, 11073–11078.
- Holloszy JO (2005) Exercise-induced increase in muscle insulin sensitivity. *Journal of Applied Physiology* (Bethesda, MD: 1985) n.d. 99:338–343.
- Holman, R. R., Paul, S. K., Bethel, M. A., Matthews, D. R., & Neil, H. A. (2008). 10-year follow-up of intensive glucose control in type 2 diabetes. *The New England Journal of Medicine* 359, 1577–1589.
- Holst, J. J. (2013). Incretin hormones and the satiation signal. *International Journal of Obesity* 37, 1161–1168.
- Hong, D. S., Hui, D., Bruera, E., Janku, F., Naing, A., Falchook, G. S., ... Kurzrock, R. (2014). MABp1, a first-in-class true human antibody targeting interleukin-1alpha in refractory cancers: an open-label, phase 1 dose-escalation and expansion study. *The Lancet Oncology* 15, 656–666.
- Hosogai, N., Fukuhara, A., Oshima, K., Miyata, Y., Tanaka, S., Segawa, K., ... Shimomura, I. (2007). Adipose tissue hypoxia in obesity and its impact on adipocytokine dysregulation. *Diabetes* 56, 901–911.
- Hotamisligil, G. S. (2010). Endoplasmic reticulum stress and the inflammatory basis of metabolic disease. *Cell* 140, 900–917.
- Hotamisligil, G. S., Budavari, A., Murray, D., & Spiegelman, B. M. (1994). Reduced tyrosine kinase activity of the insulin receptor in obesity-diabetes. Central role of tumor necrosis factor-alpha. *The Journal of Clinical Investigation* 94, 1543–1549.
- Hotamisligil, G. S., Shargill, N. S., & Spiegelman, B. M. (1993). Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. *Science* 259, 87–91.
- Houstis, N., Rosen, E. D., & Lander, E. S. (2006). Reactive oxygen species have a causal role in multiple forms of insulin resistance. *Nature* 440, 944–948.
- Huang, N. L., Chiang, S. H., Hsueh, C. H., Liang, Y. J., Chen, Y. J., & Lai, L. P. (2009). Metformin inhibits TNF-alpha-induced IkkappaB kinase phosphorylation, IkkappaB-alpha degradation and IL-6 production in endothelial cells through PI3K-dependent AMPK phosphorylation. *International Journal of Cardiology* 134, 169–175.
- Hutcheson, R., & Rocic, P. (2012). The metabolic syndrome, oxidative stress, environment, and cardiovascular disease: the great exploration. *Experimental Diabetes Research* 2012, 271028.
- Ibuki, Y., Toyooka, T., Zhao, X., & Yoshida, I. (2014). Cigarette sidestream smoke induces histone H3 phosphorylation via JNK and PI3K/Akt pathways, leading to the expression of proto-oncogenes. *Carcinogenesis* 35, 1228–1237.
- International Diabetes Federation (2006). *The IDF consensus worldwide definition of the metabolic syndrome*. Accessed 21 January 2019.
- Ishizaka, N., Ishizaka, Y., Toda, E., Hashimoto, H., Nagai, R., & Yamakado, M. (2005). Association between cigarette smoking, metabolic syndrome, and carotid arteriosclerosis in Japanese individuals. *Atherosclerosis* 181, 381–388.
- Jang, S. H., Park, J., Kim, S. H., Choi, K. M., Ko, E. S., Cha, J. D., ... Jang, Y. S. (2017). Red ginseng powder fermented with probiotics exerts antidiabetic effects in the streptozotocin-induced mouse diabetes model. *Pharmaceutical Biology* 55, 317–323.
- Jeong, S. Y., Kang, S., Kim, D. S., & Park, S. (2017). Codonopsis lanceolata Water extract increases hepatic insulin sensitivity in rats with experimentally-induced type 2 diabetes. *Nutrients* 9.
- Jiang, S., Yang, Z. H., Chen, Y. Y., He, Z., Zhou, Y., Gao, Y., ... Tan, M. Q. (2016). MMP-9 genetic polymorphism may confer susceptibility to COPD. *Genetics and Molecular Research* 15.
- Jobin, J., Maltais, F., Doyon, J. F., LeBlanc, P., Simard, P. M., Simard, A. A., & Simard, C. (1998). Chronic obstructive pulmonary disease: capillary and fiber-type characteristics of skeletal muscle. *Journal of Cardiopulmonary Rehabilitation* 18, 432–437.
- Johansson, K., Neovius, M., & Hemmingsson, E. (2014). Effects of anti-obesity drugs, diet, and exercise on weight-loss maintenance after a very-low-calorie diet or low-calorie diet: a systematic review and meta-analysis of randomized controlled trials. *The American Journal of Clinical Nutrition* 99, 14–23.
- Johnson, A. R., Milner, J. J., & Makowski, L. (2012). The inflammation highway: metabolism accelerates inflammatory traffic in obesity. *Immunological Reviews* 249, 218–238.
- Kabon, B., Nagele, A., Reddy, D., Eagon, C., Fleshman, J. W., Sessler, D. I., & Kurz, A. (2004). Obesity decreases perioperative tissue oxygenation. *Anesthesiology* 100, 274–280.

- Kadowaki, T., Yamauchi, T., Kubota, N., Hara, K., Ueki, K., & Tobe, K. (2006). Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. *The Journal of Clinical Investigation* 116, 1784–1792.
- Kajimura, S. (2017). Adipose tissue in 2016: Advances in the understanding of adipose tissue biology. *Nature Reviews. Endocrinology* 13, 69–70.
- Kalupahana, N. S., Claycombe, K. J., & Moustaid-Moussa, N. (2011). (n-3) Fatty acids alleviate adipose tissue inflammation and insulin resistance: mechanistic insights. *Advances in Nutrition* 2, 304–316.
- Kanstrup, I. L., Poulsen, T. D., Hansen, J. M., Andersen, L. J., Bestle, M. H., Christensen, N. J., & Olsen, N. V. (1999). Blood pressure and plasma catecholamines in acute and prolonged hypoxia: effects of local hypothermia. *Journal of Applied Physiology* 87, 2053–2058.
- Kennedy, S. M., Elwood, R. K., Wiggs, B. J., Pare, P. D., & Hogg, J. C. (1984). Increased airway mucosal permeability of smokers. Relationship to airway reactivity. *The American Review of Respiratory Disease* 129, 143–148.
- Kent, B. D., Mitchell, P. D., & McNicholas, W. T. (2011). Hypoxemia in patients with COPD: cause, effects, and disease progression. *International Journal of Chronic Obstructive Pulmonary Disease* 6, 199–208.
- Kersul, A. L., Iglesias, A., Rios, A., Noguera, A., Forteza, A., Serra, E., ... Cosio, B. G. (2011). Molecular mechanisms of inflammation during exacerbations of chronic obstructive pulmonary disease. *Archivos de Bronconeumología* 47, 176–183.
- Kho, M. C., Lee, Y. J., Park, J. H., Kim, H. Y., Yoon, J. J., Ahn, Y. M., ... Lee, H. S. (2016). Fermented red ginseng potentiates improvement of metabolic dysfunction in metabolic syndrome rat models. *Nutrients* 8.
- Kim, H. G., Lee, K. W., Cho, Y. Y., Kang, N. J., Oh, S. M., Bode, A. M., & Dong, Z. (2008). Mitogen- and stress-activated kinase 1-mediated histone H3 phosphorylation is crucial for cell transformation. *Cancer Research* 68, 2538–2547.
- Kim, H. J., Lee, J. Y., Jung, H. S., Kim, D. K., Lee, S. M., Yim, J. J., ... Lee, C. H. (2010). The impact of insulin sensitizers on lung function in patients with chronic obstructive pulmonary disease and diabetes. *The International Journal of Tuberculosis and Lung Disease* 14, 362–367.
- Kim, J. S., Jang, H. J., Kim, S. S., Oh, M. Y., Kim, H. J., Lee, S. Y., ... Han, D. J. (2016). Red ginseng administration before islet isolation attenuates apoptosis and improves islet function and transplant outcome in a syngeneic mouse marginal islet mass model. *Transplantation Proceedings* 48, 1258–1265.
- Kim, J. W., Tchernyshyov, I., Semenza, G. L., & Dang, C. V. (2006). HIF-1-mediated expression of pyruvate dehydrogenase kinase: a metabolic switch required for cellular adaptation to hypoxia. *Cell Metabolism* 3, 177–185.
- Kim, J. Y., van de Wall, E., Laplante, M., Azzara, A., Trujillo, M. E., Hofmann, S. M., ... Scherer, P. E. (2007). Obesity-associated improvements in metabolic profile through expansion of adipose tissue. *The Journal of Clinical Investigation* 117, 2621–2637.
- Kim, V., Rogers, T. J., & Criner, G. J. (2008). New concepts in the pathobiology of chronic obstructive pulmonary disease. *Proceedings of the American Thoracic Society* 5, 478–485.
- Kinney, G. L., Black-Shinn, J. L., Wan, E. S., Make, B., Regan, E., Lutz, S., ... Investigators, C. O. (2014). Pulmonary function reduction in diabetes with and without chronic obstructive pulmonary disease. *Diabetes Care* 37, 389–395.
- Kiortsis, D. N., Mavridis, A. K., Vasakos, S., Nikas, S. N., & Drosos, A. A. (2005). Effects of infliximab treatment on insulin resistance in patients with rheumatoid arthritis and ankylosing spondylitis. *Annals of the Rheumatic Diseases* 64, 765–766.
- Kobashi, C., Asamizu, S., Ishiki, M., Iwata, M., Usui, I., Yamazaki, K., ... Urakaze, M. (2009). Inhibitory effect of IL-8 on insulin action in human adipocytes via MAP kinase pathway. *Journal of Inflammation (London)* 6, 25.
- Kocharian, A., Shabanian, R., Rafiel-Khorgami, M., Khiani, A., & Heidari-Bateni, G. (2009). Coenzyme Q10 improves diastolic function in children with idiopathic dilated cardiomyopathy. *Cardiology in the Young* 19, 501–506.
- Koh, K. K. (2002). Effects of estrogen on the vascular wall: vasomotor function and inflammation. *Cardiovascular Research* 55, 714–726.
- Komiyama, M., Wada, H., Ura, S., Yamakage, H., Satoh-Asahara, N., Shimada, S., ... Hasegawa, K. (2015). The effects of weight gain after smoking cessation on atherogenic alpha1-antitrypsin-low-density lipoprotein. *Heart and Vessels* 30, 734–739.
- Kosteli, A., Sagar, E., Haemmerle, G., Martin, J. F., Lei, J., Zechner, R., & Ferrante, A. W., Jr. (2010). Weight loss and lipolysis promote a dynamic immune response in murine adipose tissue. *The Journal of Clinical Investigation* 120, 3466–3479.
- Krommidas, G., Kostikas, K., Papatheodorou, G., Koutsokera, A., Gourgoulianis, K. I., Roussos, C., ... Loukides, S. (2010). Plasma leptin and adiponectin in COPD exacerbations: associations with inflammatory biomarkers. *Respiratory Medicine* 104, 40–46.
- Kucharska, J., Braunova, Z., Ulicna, O., Zlatos, L., & Gvozdzakova, A. (2000). Deficit of coenzyme Q in heart and liver mitochondria of rats with streptozotocin-induced diabetes. *Physiological Research* 49, 411–418.
- Kupeli, E., Ulubay, G., Ulasli, S. S., Sahin, T., Erayman, Z., & Gursoy, A. (2010). Metabolic syndrome is associated with increased risk of acute exacerbation of COPD: a preliminary study. *Endocrine* 38, 76–82.
- Laghi, F., Antonescu-Turcu, A., Collins, E., Segal, J., Tobin, D. E., Jubran, A., & Tobin, M. J. (2005). Hypogonadism in men with chronic obstructive pulmonary disease: prevalence and quality of life. *American Journal of Respiratory and Critical Care Medicine* 171, 728–733.
- Lahousse, L., Seys, L. J. M., Joos, G. F., Franco, O. H., Stricker, B. H., & Brusselle, G. G. (2017). Epidemiology and impact of chronic bronchitis in chronic obstructive pulmonary disease. *The European Respiratory Journal* 50.
- Lam, K. B., Jordan, R. E., Jiang, C. Q., Thomas, G. N., Miller, M. R., Zhang, W. S., ... Adab, P. (2010). Airflow obstruction and metabolic syndrome: the Guangzhou Biobank Cohort Study. *The European Respiratory Journal* 35, 317–323.
- Lambert, A. A., Putcha, N., Drummond, M. B., Boriek, A. M., Hanania, N. A., Kim, V., ... Investigators, C. O. (2017). Obesity Is Associated With Increased Morbidity in Moderate to Severe COPD. *Chest* 151, 68–77.
- Lange, P., Parner, J., Vestbo, J., Schnohr, P., & Jensen, G. (1998). A 15-year follow-up study of ventilatory function in adults with asthma. *The New England Journal of Medicine* 339, 1194–1200.
- Larsen, K. O., Sjaastad, I., Svindland, A., Krobret, K. A., Skjonsberg, O. H., & Christensen, G. (2006). Alveolar hypoxia induces left ventricular diastolic dysfunction and reduces phosphorylation of phospholamban in mice. *American Journal of Physiology. Heart and Circulatory Physiology* 291, H507–H516.
- Lawlor, D. A., Ebrahim, S., & Davey Smith, G. (2004). Association between self-reported childhood socioeconomic position and adult lung function: findings from the British Women's Heart and Health Study. *Thorax* 59, 199–203.
- Lecoulter, V., Peterson, C. M., Covington, J. D., Ebenezer, P. J., Frost, E. A., Schwarz, J. M., & Ravussin, E. (2013). Ten nights of moderate hypoxia improves insulin sensitivity in obese humans. *Diabetes Care* 36, e197–e198.
- Lee, C. S., Lee, J. H., Oh, M., Choi, K. M., Jeong, M. R., Park, J. D., ... Chae, S. W. (2012). Preventive effect of Korean red ginseng for acute respiratory illness: A randomized and double-blind clinical trial. *Journal of Korean Medical Science* 27, 1472–1478.
- Lee, J. S., Kim, K. J., Kim, Y. H., Kim, D. B., Shin, G. H., Cho, J. H., ... Lee, O. H. (2014). Codonopsis lanceolata extract prevents diet-induced obesity in C57BL/6 mice. *Nutrients* 6, 4663–4677.
- Lee, Y. J., & Shukla, S. D. (2007). Histone H3 phosphorylation at serine 10 and serine 28 is mediated by p38 MAPK in rat hepatocytes exposed to ethanol and acetaldehyde. *European Journal of Pharmacology* 573, 29–38.
- Lenaz, G., Fato, R., Formiggini, G., & Genova, M. L. (2007). The role of Coenzyme Q in mitochondrial electron transport. *Mitochondrion* 7(Suppl), S8–S33.
- Leone, N., Courbon, D., Thomas, F., Bean, K., Jegu, B., Leynaert, B., ... Zureik, M. (2009). Lung function impairment and metabolic syndrome: the critical role of abdominal obesity. *American Journal of Respiratory and Critical Care Medicine* 179, 509–516.
- Li, C. Y., Xu, H. X., Han, Q. B., & Wu, T. S. (2009). Quality assessment of Radix Codonopsis by quantitative nuclear magnetic resonance. *Journal of Chromatography. A* 1216, 2124–2129.
- Li, J., Grigoryev, D. N., Ye, S. Q., Thorne, L., Schwartz, A. R., Smith, P. L., ... Polotsky, V. Y. (2005). Chronic intermittent hypoxia upregulates genes of lipid biosynthesis in obese mice. *Journal of Applied Physiology* 99, 1643–1648.
- Li, J., Savransky, V., Nanayakkara, A., Smith, P. L., O'Donnell, C. P., & Polotsky, V. Y. (2007). Hyperlipidemia and lipid peroxidation are dependent on the severity of chronic intermittent hypoxia. *Journal Applied Physiology* 102, 557–563.
- Li, J. W., & Vederas, J. C. (2009). Drug discovery and natural products: end of an era or an endless frontier? *Science* 325, 161–165.
- Liu, L., Wang, Y., Lam, K. S., & Xu, A. (2008). Moderate wine consumption in the prevention of metabolic syndrome and its related medical complications. *Endocrine, Metabolic & Immune Disorders Drug Targets* 8, 89–98.
- Liu, R. H., Mizuta, M., & Matsukura, S. (2003). Long-term oral nicotine administration reduces insulin resistance in obese rats. *European Journal of Pharmacology* 458, 227–234.
- Liu, Y., Dai, M., Bi, Y., Xu, M., Xu, Y., Li, M., ... Ning, G. (2013). Active smoking, passive smoking, and risk of nonalcoholic fatty liver disease (NAFLD): a population-based study in China. *Journal of Epidemiology* 23, 115–121.
- Loffreda, S., Yang, S. Q., Lin, H. Z., Karp, C. L., Brengman, M. L., Wang, D. J., ... Diehl, A. M. (1998). Leptin regulates proinflammatory immune responses. *The FASEB Journal* 12, 57–65.
- Lolmede, K., Durand de Saint Front, V., Galitzky, J., Lafont, M., & Bouloumie, A. (2003). Effects of hypoxia on the expression of proangiogenic factors in differentiated 3T3-F442A adipocytes. *International Journal of Obesity and Related Metabolic Disorders* 27, 1187–1195.
- Long, Y. C., & Zierath, J. R. (2006). AMP-activated protein kinase signaling in metabolic regulation. *The Journal of Clinical Investigation* 116, 1776–1783.
- Lopez-Huertas, E. (2012). The effect of EPA and DHA on metabolic syndrome patients: a systematic review of randomised controlled trials. *The British Journal of Nutrition* 107(Suppl. 2), S185–S194.
- Loza, M. J., Watt, R., Baribaud, F., Barnathan, E. S., & Rennard, S. I. (2012). Systemic inflammatory profile and response to anti-tumor necrosis factor therapy in chronic obstructive pulmonary disease. *Respiratory Research* 13, 12.
- de Luca, C., & Olefsky, J. M. (2008). Inflammation and insulin resistance. *FEBS Letters* 582, 97–105.
- Lucas, K. H., & Kaplan-Machlis, B. (2001). Orlistat—a novel weight loss therapy. *The Annals of Pharmacotherapy* 35, 314–328.
- de Lucas-Ramos P, Izquierdo-Alonso JL, Rodriguez-Gonzalez Moro JM, Frances JF, Lozano PV, Bellon-Cano JM and group Cs (2012) Chronic obstructive pulmonary disease as a cardiovascular risk factor. Results of a case-control study (CONSISTE study). *International Journal of Chronic Obstructive Pulmonary Disease* 7:679-686.
- Luo, H., Lin, S., Ren, F., Wu, L., Chen, L., & Sun, Y. (2007). Antioxidant and antimicrobial capacity of Chinese medicinal herb extracts in raw sheep meat. *Journal of Food Protection* 70, 1440–1445.
- Luo, P., Dong, G., Liu, L., & Zhou, H. (2015). The Long-Term Consumption of Ginseng Extract Reduces the Susceptibility of Intermediate-Aged Hearts to Acute Ischemia Reperfusion Injury. *PLoS One* 10, e0144733.
- Lv, N., Xiao, L., & Ma, J. (2015). Weight management interventions in adult and pediatric asthma populations: A systematic review. *Journal of Pulmonary and Respiratory Medicine* 5.
- Lyamzaev, K. G., Pustovidko, A. V., Simonyan, R. A., Rokitskaya, T. I., Domnina, L. V., Ivanova, O. Y., ... Skulachev, V. P. (2011). Novel mitochondria-targeted antioxidants: plastoquinone conjugated with cationic plant alkaloids berberine and palmatine. *Pharmacological Research* 28, 2883–2895.
- Maatman, R. C., Spruiell, M. A., van Melick, P. P., Peeters, J. P., Rutten, E. P., Vanfleteren, L. E., ... Franssen, F. M. (2016). Effects of obesity on weight-bearing versus weight-supported exercise testing in patients with COPD. *Respirology* 21, 483–488.

- Magnussen, H., & Watz, H. (2009). Systemic inflammation in chronic obstructive pulmonary disease and asthma: relation with comorbidities. *Proceedings of the American Thoracic Society* 6, 648–651.
- Makarevich, A. E., Valevich, V. E., & Pochtavtsev, A. U. (2007). Evaluation of pulmonary hypertension in COPD patients with diabetes. *Advances in Medical Sciences* 52, 265–272.
- Makhsida, N., Shah, J., Yan, G., Fisch, H., & Shabsigh, R. (2005). Hypogonadism and metabolic syndrome: implications for testosterone therapy. *The Journal of Urology* 174, 827–834.
- Malli, F., Papaioannou, A. I., Gourgoulis, K. I., & Daniil, Z. (2010). The role of leptin in the respiratory system: an overview. *Respiratory Research* 11, 152.
- Man, S. F., Van Eeden, S., & Sin, D. D. (2012). Vascular risk in chronic obstructive pulmonary disease: role of inflammation and other mediators. *The Canadian Journal of Cardiology* 28, 653–661.
- Man, S. F., Xuekui, Z., Vessey, R., Walker, T., Lee, K., Park, D., & Sin, D. D. (2009). The effects of inhaled and oral corticosteroids on serum inflammatory biomarkers in COPD: an exploratory study. *Therapeutic Advances in Respiratory Disease* 3, 73–80.
- Manning, P. J., Sutherland, W. H., Williams, S. M., Walker, R. J., Berry, E. A., De Jong, S. A., & Ryalls, A. R. (2013). The effect of lipoic acid and vitamin E therapies in individuals with the metabolic syndrome. *Nutrition, Metabolism, and Cardiovascular Diseases* 23, 543–549.
- Manning, S., Pucci, A., & Finer, N. (2014). Pharmacotherapy for obesity: novel agents and paradigms. *Therapeutic Advances in Chronic Disease* 5, 135–148.
- Mariappan, N., Soorappan, R. N., Haque, M., Sriramula, S., & Francis, J. (2007). TNF- α -induced mitochondrial oxidative stress and cardiac dysfunction: restoration by superoxide dismutase mimetic Tempol. *American Journal of Physiology. Heart and Circulatory Physiology* 293, H2726–H2737.
- Marinari, S., Manigrasso, M. R., & De Benedetto, F. (2013). Effects of nutraceutical diet integration, with coenzyme Q(10) (Q-Ter multicomposite) and creatine, on dyspnea, exercise tolerance, and quality of life in COPD patients with chronic respiratory failure. *Multidisciplinary Respiratory Medicine* 8.
- Marquis, K., Debigare, R., Lacasse, Y., LeBlanc, P., Jobin, J., Carrier, G., & Maltais, F. (2002). Midthigh muscle cross-sectional area is a better predictor of mortality than body mass index in patients with chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine* 166, 809–813.
- Marquis, K., Maltais, F., Duguay, V., Bezeau, A. M., LeBlanc, P., Jobin, J., & Poirier, P. (2005). The metabolic syndrome in patients with chronic obstructive pulmonary disease. *Journal of Cardiopulmonary Rehabilitation* 25, 226–232 discussion 233–224.
- Martinez, B., & Peplow, P. V. (2016). Treatment of insulin resistance by acupuncture: a review of human and animal studies. *Acupuncture in Medicine* 34, 310–319.
- Mashiba, S., Wada, Y., Takeya, M., Sugiyama, A., Hamakubo, T., Nakamura, A., ... Kodama, T. (2001). In vivo complex formation of oxidized α (1)-antitrypsin and LDL. *Arteriosclerosis, Thrombosis, and Vascular Biology* 21, 1801–1808.
- Matikainen, N., Manttari, S., Schweizer, A., Ulvestad, A., Mills, D., Dunning, B. E., ... Taskinen, M. R. (2006). Vildagliptin therapy reduces postprandial intestinal triglyceride-rich lipoprotein particles in patients with type 2 diabetes. *Diabetologia* 49, 2049–2057.
- Mazziotti, G., Gazzaruso, C., & Giustina, A. (2011). Diabetes in Cushing syndrome: basic and clinical aspects. *Trends in Endocrinology and Metabolism* 22, 499–506.
- McDonald, V. M., Gibson, P. G., Scott, H. A., Baines, P. J., Hensley, M. J., Pretto, J. J., & Wood, L. G. (2016). Should we treat obesity in COPD? The effects of diet and resistance exercise training. *Respirology* 21, 875–882.
- McGarvey, L. P., John, M., Anderson, J. A., Zvarich, M., Wise, R. A., & Committee, T. C. E. (2007). Ascertainment of cause-specific mortality in COPD: operations of the TORCH Clinical Endpoint Committee. *Thorax* 62, 411–415.
- McKeever, T. M., Weston, P. J., Hubbard, R., & Fogarty, A. (2005). Lung function and glucose metabolism: an analysis of data from the Third National Health and Nutrition Examination Survey. *American Journal of Epidemiology* 161, 546–556.
- Mekov, E. V., Slavova, Y. G., Genova, M. P., Tsakova, A. D., Kostadinov, D. T., Minchev, D. D., ... Boyanov, M. A. (2016). Diabetes mellitus type 2 in hospitalized COPD patients: Impact on quality of life and lung function. *Folia Medica (Plovdiv)* 58, 36–41.
- Mercer, J. R., Yu, E., Figg, N., Cheng, K. K., Prime, T. A., Griffin, J. L., ... Bennett, M. R. (2012). The mitochondria-targeted antioxidant MitoQ decreases features of the metabolic syndrome in ATM $^{-/-}$ /ApoE $^{-/-}$ mice. *Free Radical Biology & Medicine* 52, 841–849.
- Miller, M., Cho, J. Y., Pham, A., Ramsdell, J., & Brodie, D. H. (2009). Adiponectin and functional adiponectin receptor 1 are expressed by airway epithelial cells in chronic obstructive pulmonary disease. *Journal of Immunology* 182, 684–691.
- Mills, N. L., Tornqvist, H., Gonzalez, M. C., Vink, E., Robinson, S. D., Soderberg, S., ... Newby, D. E. (2007). Ischemic and thrombotic effects of dilute diesel-exhaust inhalation in men with coronary heart disease. *The New England Journal of Medicine* 357, 1075–1082.
- Minas, M., Kostikas, K., Papaioannou, A. I., Myrstridou, P., Karetis, E., Georgoulis, P., ... Gourgoulis, K. I. (2011). The association of metabolic syndrome with adipose tissue hormones and insulin resistance in patients with COPD without co-morbidities. *COPD* 8, 414–420.
- Mineur, Y. S., Abizaid, A., Rao, Y., Salas, R., DiLeone, R. J., Gundisch, D., ... Picciotto, M. R. (2011). Nicotine decreases food intake through activation of POMC neurons. *Science* 332, 1330–1332.
- Mirrahimov, A. E. (2012). Chronic obstructive pulmonary disease and glucose metabolism: a bitter sweet symphony. *Cardiovascular Diabetology* 11, 132.
- Mirrahimov, A. E., & Mirrahimov, E. M. (2013). Chronic obstructive pulmonary disease and vascular risk: should we account for diabetes mellitus and renal disease? *The Canadian Journal of Cardiology* 29(639) e639.
- Mistry, G. C., Maes, A. L., Lasseter, K. C., Davies, M. J., Gottesdiener, K. M., Wagner, J. A., & Herman, G. A. (2008). Effect of sitagliptin, a dipeptidyl peptidase-4 inhibitor, on blood pressure in nondiabetic patients with mild to moderate hypertension. *Journal of Clinical Pharmacology* 48, 592–598.
- Mizoue, T., Ueda, R., Hino, Y., & Yoshimura, T. (1999). Workplace exposure to environmental tobacco smoke and high density lipoprotein cholesterol among nonsmokers. *American Journal of Epidemiology* 150, 1068–1072.
- Mizuno, Y., Jacob, R. F., & Mason, R. P. (2011). Inflammation and the development of atherosclerosis. *Journal of Atherosclerosis and Thrombosis* 18, 351–358.
- Modi, K., Santani, D. D., Goyal, R. K., & Bhatt, P. A. (2006). Effect of coenzyme Q10 on catalase activity and other antioxidant parameters in streptozotocin-induced diabetic rats. *Biological Trace Element Research* 109, 25–34.
- Moien-Afshari, F., Ghosh, S., Elmi, S., Rahman, M. M., Sallam, N., Khazaei, M., ... Laher, I. (2008). Exercise restores endothelial function independently of weight loss or hyperglycaemic status in db/db mice. *Diabetologia* 51, 1327–1337.
- Monteiro, F., Camillo, C. A., Vitorasso, R., Sant'Anna, T., Hernandez, N. A., Probst, V. S., & Pitta, F. (2012). Obesity and physical activity in the daily life of patients with COPD. *Lung* 190, 403–410.
- Murin, S., & Billello, K. S. (2005). Respiratory tract infections: another reason not to smoke. *Cleveland Clinic Journal of Medicine* 72, 916–920.
- Murphy, A. M., Thomas, A., Crinion, S. J., Kent, B. D., Tambuwala, M. M., Fabre, A., ... Ryan, S. (2017). Intermittent hypoxia in obstructive sleep apnoea mediates insulin resistance through adipose tissue inflammation. *The European Respiratory Journal* 49.
- Murphy, M. P., & Smith, R. A. J. (2000). Drug delivery to mitochondria: the key to mitochondrial medicine. *Advanced Drug Delivery Reviews* 41, 235–250.
- ten Hacken, N. H. (2009). Physical inactivity and obesity: relation to asthma and chronic obstructive pulmonary disease? *Proceedings of the American Thoracic Society* 6, 663–667.
- Nair, P., Radford, K., Fanat, A., Janssen, L. J., Peters-Golden, M., & Cox, P. G. (2008). The effects of leptin on airway smooth muscle responses. *American Journal of Respiratory Cell and Molecular Biology* 39, 475–481.
- Neschen, S., Morino, K., Dong, J., Wang-Fischer, Y., Cline, G. W., Romanelli, A. J., ... Shulman, G. I. (2007). n-3 Fatty acids preserve insulin sensitivity in vivo in a peroxisome proliferator-activated receptor- α -dependent manner. *Diabetes* 56, 1034–1041.
- Nik Nabil, W. N., Zhou, W., Shergis, J. L., Mansu, S., Xue, C. C., & Zhang, A. L. (2015). Management of respiratory disorders in a Chinese medicine teaching clinic in Australia: review of clinical records. *Chinese Medicine* 10, 31.
- O'Byrne, P. M., Rennard, S., Gerstein, H., Radner, F., Peterson, S., Lindberg, B., ... Sin, D. D. (2012). Risk of new onset diabetes mellitus in patients with asthma or COPD taking inhaled corticosteroids. *Respiratory Medicine* 106, 1487–1493.
- Oguz, F. M., Oguz, A., & Uzunlulu, M. (2007). The effect of infliximab treatment on insulin resistance in patients with rheumatoid arthritis. *Acta Clinica Belgica* 62, 218–222.
- Oh, D. Y., Talukdar, S., Bae, E. J., Imamura, T., Morinaga, H., Fan, W., ... Olefsky, J. M. (2010). GPR120 is an omega-3 fatty acid receptor mediating potent anti-inflammatory and insulin-sensitizing effects. *Cell* 142, 687–698.
- Oh, J. Y., & Sin, D. D. (2012). Lung inflammation in COPD: why does it matter? *F1000 Medical Report* 4, 23.
- Olivera, D. S., Boggs, S. E., Beenhouwer, C., Aden, J., & Knall, C. (2007). Cellular mechanisms of mainstream cigarette smoke-induced lung epithelial tight junction permeability changes in vitro. *Inhalation Toxicology* 19, 13–22.
- O'Neil, P. M., Smith, S. R., Weissman, N. J., Fidler, M. C., Sanchez, M., Zhang, J., ... Shanahan, W. R. (2012). Randomized placebo-controlled clinical trial of lorcaserin for weight loss in type 2 diabetes mellitus: the BLOOM-DM study. *Obesity (Silver Spring)* 20, 1426–1436.
- O'Neill, L. A., & Pearce, E. J. (2016). Immunometabolism governs dendritic cell and macrophage function. *The Journal of Experimental Medicine* 213, 15–23.
- Orea Soler, I., Illan Gomez, F., Gonzalez Ortega, M., Alcaraz Tafalla, M. S., Perez Paredes, M., Lozano Almela, M. L., ... Pascual Diaz, M. (2010). Soluble intercellular adhesion molecule-1 and C reactive protein after bariatric surgery. *Endocrinología y Nutrición* 57, 90–94.
- Orfanos, S., Jude, J., Deeney, B. T., Cao, G., Rastogi, D., van Zee, M., ... Panettieri, R., Jr. (2018). Obesity increases airway smooth muscle responses to contractile agonists. *American Journal of Physiology. Lung Cellular and Molecular Physiology* 315, L673–L681.
- Ottenheijm, C. A., Heunks, L. M., & Dekhuijzen, R. P. (2008). Diaphragm adaptations in patients with COPD. *Respiratory Research* 9, 12.
- Parappil, A., Depczynski, B., Collett, P., & Marks, G. B. (2010). Effect of comorbid diabetes on length of stay and risk of death in patients admitted with acute exacerbations of COPD. *Respirology* 15, 918–922.
- Park, S. K., & Larson, J. L. (2014). The relationship between physical activity and metabolic syndrome in people with chronic obstructive pulmonary disease. *The Journal of Cardiovascular Nursing* 29, 499–507.
- Passey, S. L., Hansen, M. J., Bozinovski, S., McDonald, C. F., Holland, A. E., & Vlahos, R. (2016). Emerging therapies for the treatment of skeletal muscle wasting in chronic obstructive pulmonary disease. *Pharmacology & Therapeutics* 166, 56–70.
- Pauwels, R. A., Lofdahl, C. G., Laitinen, L. A., Schouten, J. P., Postma, D. S., Pride, N. B., & Ohlsson, S. V. (1999). Long-term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking. European Respiratory Society Study on Chronic Obstructive Pulmonary Disease. *The New England Journal of Medicine* 340, 1948–1953.
- Pelosi, P., Croci, M., Ravagnan, I., Vicardi, P., & Gattinoni, L. (1996). Total respiratory system, lung, and chest wall mechanics in sedated-paralyzed postoperative morbidly obese patients. *Chest* 109, 144–151.
- Perera, W. R., Hurst, J. R., Wilkinson, T. M., Sapsford, R. J., Mullerova, H., Donaldson, G. C., & Wedzicha, J. A. (2007). Inflammatory changes, recovery and recurrence at COPD exacerbation. *The European Respiratory Journal* 29, 527–534.
- Perrini, S., Signorelli, A., Quaranta, V. N., Falcone, V. A., Kounaki, S., Porro, S., ... Giorgino, F. (2017). Correction of intermittent hypoxia reduces inflammation in obese subjects with obstructive sleep apnea. *JCI Insight* 2.
- Petersen, M. C., Vatner, D. F., & Shulman, G. I. (2017). Regulation of hepatic glucose metabolism in health and disease. *Nature Reviews. Endocrinology* 13, 572–587.

- Piazzolla, G., Castrovilla, A., Liotino, V., Vulpi, M. R., Fanelli, M., Mazzocca, A., ... Tortorella, C. (2017). Metabolic syndrome and Chronic Obstructive Pulmonary Disease (COPD): The interplay among smoking, insulin resistance and vitamin D. *PLoS One* 12, 21–33.
- Pi-Sunyer, X. (2009). The medical risks of obesity. *Postgraduate Medicine* 121, 21–33.
- Postic, C., & Girard, J. (2008). Contribution of de novo fatty acid synthesis to hepatic steatosis and insulin resistance: lessons from genetically engineered mice. *The Journal of Clinical Investigation* 118, 829–838.
- Pothiwala, P., Jain, S. K., & Yaturu, S. (2009). Metabolic syndrome and cancer. *Metabolic Syndrome and Related Disorders* 7, 279–288.
- Poulain, L., Mathieu, H., Thomas, A., Borel, A. L., Remy, C., Levy, P., ... Dematteis, M. (2017). Intermittent hypoxia-induced insulin resistance is associated with alterations in white fat distribution. *Scientific Reports* 7, 11180.
- Prakash, Y. S., Pabelick, C. M., & Sieck, G. C. (2017). Mitochondrial Dysfunction in Airway Disease. *Chest* 152, 618–626.
- Price, D. B., Russell, R., Mares, R., Burden, A., Skinner, D., Mikkelsen, H., ... Haughey, J. (2016). Metabolic Effects Associated with ICS in Patients with COPD and Comorbid Type 2 Diabetes: A Historical Matched Cohort Study. *PLoS One* 11, e0162903.
- Qin, F., Siwik, D. A., Luptak, I., Hou, X., Wang, L., Higuchi, A., ... Colucci, W. S. (2012). The polyphenols resveratrol and S17834 prevent the structural and functional sequelae of diet-induced metabolic heart disease in mice. *Circulation* 125(1757–1764), S1751–S1756.
- Qin, Y., Xia, M., Ma, J., Hao, Y., Liu, J., Mou, H., ... Ling, W. (2009). Anthocyanin supplementation improves serum LDL- and HDL-cholesterol concentrations associated with the inhibition of cholesteryl ester transfer protein in dyslipidemic subjects. *The American Journal of Clinical Nutrition* 90, 485–492.
- Qu, A., Taylor, M., Xue, X., Matsubara, T., Metzger, D., Chambon, P., ... Shah, Y. M. (2011). Hypoxia-inducible transcription factor 2alpha promotes steatohepatitis through augmenting lipid accumulation, inflammation, and fibrosis. *Hepatology* 54, 472–483.
- Qureshi, H., Sharafkhan, A., & Hanania, N. A. (2014). Chronic obstructive pulmonary disease exacerbations: latest evidence and clinical implications. *Ther Adv Chronic Dis* 5, 212–227.
- van Raalte, D. H., Ouwens, D. M., & Diamant, M. (2009). Novel insights into glucocorticoid-mediated diabetogenic effects: towards expansion of therapeutic options? *European Journal of Clinical Investigation* 39, 81–93.
- Rahman, I., & MacNee, W. (2012). Antioxidant pharmacological therapies for COPD. *Current Opinion in Pharmacology* 12, 256–265.
- Rana, J. S., Mittleman, M. A., Sheikh, J., Hu, F. B., Manson, J. E., Colditz, G. A., ... Camargo, C. A., Jr. (2004). Chronic obstructive pulmonary disease, asthma, and risk of type 2 diabetes in women. *Diabetes Care* 27, 2478–2484.
- Read, P. A., Khan, F. Z., Heck, P. M., Hoole, S. P., & Dutka, D. P. (2010). DPP-4 inhibition by sitagliptin improves the myocardial response to dobutamine stress and mitigates stunning in a pilot study of patients with coronary artery disease. *Circulation. Cardiovascular Imaging* 3, 195–201.
- Redman, L. M., & Ravussin, E. (2010). Lorcaserin for the treatment of obesity. *Drugs Today (Barc)* 46, 901–910.
- Rees, D., Miles, E. A., Banerjee, T., Wells, S. J., Roynette, C. E., Wahle, K. W., & Calder, P. C. (2006). Dose-related effects of eicosapentaenoic acid on innate immune function in healthy humans: a comparison of young and older men. *The American Journal of Clinical Nutrition* 83, 331–342.
- Regazzetti, C., Peraldi, P., Gremeaux, T., Najem-Lendom, R., Ben-Sahra, I., Cormont, M., ... Giorgetti-Peraldi, S. (2009). Hypoxia decreases insulin signaling pathways in adipocytes. *Diabetes* 58, 95–103.
- Rennard, S. I., Fogarty, C., Kelsen, S., Long, W., Ramsdell, J., Allison, J., ... Investigators, C. (2007). The safety and efficacy of infliximab in moderate to severe chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine* 175, 926–934.
- Rhoden, E. L., & Morgentaler, A. (2004). Risks of testosterone-replacement therapy and recommendations for monitoring. *The New England Journal of Medicine* 350, 482–492.
- Richens, T. R., Linderman, D. J., Horstmann, S. A., Lambert, C., Xiao, Y. Q., Keith, R. L., ... Vandivier, R. W. (2009). Cigarette smoke impairs clearance of apoptotic cells through oxidant-dependent activation of RhoA. *American Journal of Respiratory and Critical Care Medicine* 179, 1011–1021.
- Robich, M. P., Osipov, R. M., Chu, L. M., Han, Y., Feng, J., Nezafat, R., ... Sellke, F. W. (2011). Resveratrol modifies risk factors for coronary artery disease in swine with metabolic syndrome and myocardial ischemia. *European Journal of Pharmacology* 664, 45–53.
- Rodriguez-Cuenca, S., Cocheme, H. M., Logan, A., Abakumova, I., Prime, T. A., Rose, C., ... Murphy, M. P. (2010). Consequences of long-term oral administration of the mitochondria-targeted antioxidant MitoQ to wild-type mice. *Free Radical Biology & Medicine* 48, 161–172.
- Rogliani, P., Calzetta, L., Segreti, A., Barrile, A., & Cazzola, M. (2014). Diabetes mellitus among outpatients with COPD attending a university hospital. *Acta Diabetologica* 51, 933–940.
- Romani-Perez, M., Outeirino-Iglesias, V., Gil-Lozano, M., Gonzalez-Matias, L. C., Mallo, F., & Vigo, E. (2013). Pulmonary GLP-1 receptor increases at birth and exogenous GLP-1 receptor agonists augmented surfactant-protein levels in litters from normal and nitrofen-treated pregnant rats. *Endocrinology* 154, 1144–1155.
- Ropcke, S., Holz, O., Lauer, G., Muller, M., Rittinghausen, S., Ernst, P., ... Hohlfeil, J. M. (2012). Repeatability of and relationship between potential COPD biomarkers in bronchoalveolar lavage, bronchial biopsies, serum, and induced sputum. *PLoS One* 7, e46207.
- da Rosa, D. P., Forgiarini, L. F., Baronio, D., Feijo, C. A., Martinez, D., & Marroni, N. P. (2012). Simulating sleep apnea by exposure to intermittent hypoxia induces inflammation in the lung and liver. *Mediators of Inflammation* 2012, 879419.
- Rosenvinge, A., Krogh-Madsen, R., Baslund, B., & Pedersen, B. K. (2007). Insulin resistance in patients with rheumatoid arthritis: effect of anti-TNFalpha therapy. *Scandinavian Journal of Rheumatology* 36, 91–96.
- Roytblat, L., Rachinsky, M., Fisher, A., Greemberg, L., Shapira, Y., Douvdevani, A., & Gelman, S. (2000). Raised interleukin-6 levels in obese patients. *Obesity Research* 8, 673–675.
- Sabit, R., Bolton, C. E., Edwards, P. H., Pettit, R. J., Evans, W. D., McEniery, C. M., ... Shale, D. J. (2007). Arterial stiffness and osteoporosis in chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine* 175, 1259–1265.
- Saborano, R., Wongpinyochit, T., Totten, J. D., Johnston, B. F., Seib, F. P., & Duarte, I. F. (2017). Metabolic reprogramming of macrophages exposed to silk, poly(lactic-co-glycolic acid), and silica nanoparticles. *Advanced Healthcare Materials* 6.
- Saetta, M., Di Stefano, A., Maestrelli, P., Turato, G., Ruggieri, M. P., Roggeri, A., ... Fabbri, L. M. (1994). Airway eosinophilia in chronic bronchitis during exacerbations. *American Journal of Respiratory and Critical Care Medicine* 150, 1646–1652.
- Sahni, S., Talwar, A., Khanijo, S., & Talwar, A. (2017). Socioeconomic status and its relationship to chronic respiratory disease. *Advances in Respiratory Medicine* 85, 97–108.
- Saito, Y., Fukuhara, A., Nishio, K., Hayakawa, M., Ogawa, Y., Sakamoto, H., ... Niki, E. (2009). Characterization of cellular uptake and distribution of coenzyme Q10 and vitamin E in PC12 cells. *The Journal of Nutritional Biochemistry* 20, 350–357.
- Saltiel, A. R., & Olefsky, J. M. (2017). Inflammatory mechanisms linking obesity and metabolic disease. *The Journal of Clinical Investigation* 127, 1–4.
- Salvi, S. S., & Barnes, P. J. (2009). Chronic obstructive pulmonary disease in non-smokers. *Lancet* 374, 733–743.
- Saraswathi, V., & Hasty, A. H. (2006). The role of lipolysis in mediating the proinflammatory effects of very low density lipoproteins in mouse peritoneal macrophages. *Journal of Lipid Research* 47, 1406–1415.
- Sarraf, P., Frederich, R. C., Turner, E. M., Ma, G., Jaskowiak, N. T., Rivet, D. J., 3rd, ... Alexander, H. R. (1997). Multiple cytokines and acute inflammation raise mouse leptin levels: potential role in inflammatory anorexia. *The Journal of Experimental Medicine* 185, 171–175.
- Sartipy, P., & Loskutoff, D. J. (2003). Monocyte chemoattractant protein 1 in obesity and insulin resistance. *Proceedings of the National Academy of Sciences of the United States of America* 100, 7265–7270.
- Scaglione, F., Cogo, R., Cocuzza, C., Arcidiacono, M., & Beretta, A. (1994). Immunomodulatory effects of Panax-ginseng Ca Meyer (G115) on alveolar macrophages from patients suffering with chronic-bronchitis. *International Journal of Immunotherapy* 10, 21–24.
- Scaglione, F., Weiser, K., & Alessandria, M. (2001). Effects of the standardised ginseng extract G115 (R) in patients with chronic bronchitis - A nonblinded, randomised, comparative pilot study. *Clinical Drug Investigation* 21, 41–45.
- Schols, A. M. (2010). Body composition in COPD: stepping back or moving forward? *Respiratory Medicine* 104, 157–158.
- Schols, A. M., Broekhuizen, R., Weling-Scheepers, C. A., & Wouters, E. F. (2005). Body composition and mortality in chronic obstructive pulmonary disease. *The American Journal of Clinical Nutrition* 82, 53–59.
- Schols, A. M., Creutzberg, E. C., Buurman, W. A., Campfield, L. A., Saris, W. H., & Wouters, E. F. (1999). Plasma leptin is related to proinflammatory status and dietary intake in patients with chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine* 160, 1220–1226.
- Schols, A. M., Ferreira, I. M., Franssen, F. M., Gosker, H. R., Janssens, W., Muscaritoli, M., ... Singh, S. J. (2014). Nutritional assessment and therapy in COPD: a European Respiratory Society statement. *The European Respiratory Journal* 44, 1504–1520.
- Schols, A. M., Slangen, J., Volovics, L., & Wouters, E. F. (1998). Weight loss is a reversible factor in the prognosis of chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine* 157, 1791–1797.
- Sedgwick, J. B., Menon, I., Gern, J. E., & Busse, W. W. (2002). Effects of inflammatory cytokines on the permeability of human lung microvascular endothelial cell monolayers and differential eosinophil transmigration. *The Journal of Allergy and Clinical Immunology* 110, 752–756.
- Sergi, G., Coin, A., Marin, S., Vianello, A., Manzan, A., Peruzza, S., ... Enzi, G. (2006). Body composition and resting energy expenditure in elderly male patients with chronic obstructive pulmonary disease. *Respiratory Medicine* 100, 1918–1924.
- Serino, M., Menghini, R., Fiorentino, L., Amoroso, R., Mauriello, A., Lauro, D., ... Federici, M. (2007). Mice heterozygous for tumor necrosis factor-alpha converting enzyme are protected from obesity-induced insulin resistance and diabetes. *Diabetes* 56, 2541–2546.
- Seriolo, B., Ferrone, C., & Cutolo, M. (2008). Long-term anti-tumor necrosis factor-alpha treatment in patients with refractory rheumatoid arthritis: relationship between insulin resistance and disease activity. *The Journal of Rheumatology* 35, 355–357.
- Services USDoHaH (2014). *The Health consequences of smoking—50 years of progress: A report of the surgeon general*. Atlanta: U.S. Department of Health and Human Services CDCaP, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health ed.
- Sexton, P., Metcalf, P., & Kolbe, J. (2014). Respiratory effects of insulin sensitisation with metformin: a prospective observational study. *COPD* 11, 133–142.
- Shavelle, R. M., Paculdo, D. R., Kush, S. J., Mannino, D. M., & Strauss, D. J. (2009). Life expectancy and years of life lost in chronic obstructive pulmonary disease: findings from the NHANES III Follow-up Study. *International Journal of Chronic Obstructive Pulmonary Disease* 4, 137–148.
- Shaykhiev, R., Krause, A., Salit, J., Strulovici-Barel, Y., Harvey, B. G., O'Connor, T. P., & Crystal, R. G. (2009). Smoking-dependent reprogramming of alveolar macrophage polarization: implication for pathogenesis of chronic obstructive pulmonary disease. *Journal of Immunology* 183, 2867–2883.
- Shergis, J. L., Liu, S., Chen, X., Zhang, A. L., Guo, X., Lu, C., & Xue, C. C. (2015). Dang shen [Codonopsis pilosula (Franch.) Nannf] herbal formulae for chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Phytotherapy Research* 29, 167–186.
- Shergis, J. L., Zhang, A. L., Zhou, W., & Xue, C. C. (2013). Panax ginseng in randomised controlled trials: a systematic review. *Phytotherapy Research* 27, 949–965.

- Shih, H. P., Zhang, X., & Aronov, A. M. (2017). Drug discovery effectiveness from the standpoint of therapeutic mechanisms and indications. *Nature Reviews. Drug Discovery* 17, 19–33.
- Shimokata, H., Muller, D. C., & Andres, R. (1989). Studies in the distribution of body fat. III. Effects of cigarette smoking. *JAMA* 261, 1169–1173.
- Shishtar, E., Sievenpiper, J. L., Djedovic, V., Cozma, A. I., Ha, V., Jayalath, V. H., ... Vuksan, V. (2014). The effect of ginseng (the genus panax) on glycemic control: a systematic review and meta-analysis of randomized controlled clinical trials. *PLoS One* 9, e107391.
- Shohaimi, S., Welch, A., Bingham, S., Luben, R., Day, N., Wareham, N., & Khaw, K. T. (2004). Area deprivation predicts lung function independently of education and social class. *The European Respiratory Journal* 24, 157–161.
- Shore, S. A., Terry, R. D., Flynt, L., Xu, A., & Hug, C. (2006). Adiponectin attenuates allergen-induced airway inflammation and hyperresponsiveness in mice. *The Journal of Allergy and Clinical Immunology* 118, 389–395.
- Siedlinski M, Tingley D, Lipman PJ, Cho MH, Litonjua AA, Sparrow D, Bakke P, Gulsvik A, Lomas DA, Anderson W, Kong X, Rennan SI, Beaty TH, Hokanson JE, Crapo JD, Lange C, Silverman EK, Copdgene and Investigators E (2013) Dissecting direct and indirect genetic effects on chronic obstructive pulmonary disease (COPD) susceptibility. *Human Genetics* 132:431–441.
- Sin, D. D., Anthonisen, N. R., Soriano, J. B., & Agustí, A. G. (2006). Mortality in COPD: Role of comorbidities. *The European Respiratory Journal* 28, 1245–1257.
- Sin, D. D., & Man, S. F. (2003a). Impaired lung function and serum leptin in men and women with normal body weight: a population based study. *Thorax* 58, 695–698.
- Sin, D. D., & Man, S. F. (2003b). Why are patients with chronic obstructive pulmonary disease at increased risk of cardiovascular diseases? The potential role of systemic inflammation in chronic obstructive pulmonary disease. *Circulation* 107, 1514–1519.
- Singh, S., Bodas, M., Bhatraju, N. K., Pattnaik, B., Gheware, A., Parameswaran, P. K., ... Agrawal, A. (2016). Hyperinsulinemia adversely affects lung structure and function. *American Journal of Physiology. Lung Cellular and Molecular Physiology* 310, L837–L845.
- Sjostrom, L., Lindroos, A. K., Peltonen, M., Torgerson, J., Bouchard, C., Carlsson, B., ... Swedish Obese Subjects Study Scientific G (2004). Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. *The New England Journal of Medicine* 351, 2683–2693.
- Smith, K. R., Uyeminami, D. L., Kodavanti, U. P., Crapo, J. D., Chang, L. Y., & Pinkerton, K. E. (2002). Inhibition of tobacco smoke-induced lung inflammation by a catalytic antioxidant. *Free Radical Biology & Medicine* 33, 1106–1114.
- Smith, R. A., & Murphy, M. P. (2011). Mitochondria-targeted antioxidants as therapies. *Discovery Medicine* 11, 106–114.
- Smith, S. R., Weissman, N. J., Anderson, C. M., Sanchez, M., Chuang, E., Stubbe, S., ... Lorcaserin for Obesity Management Study G (2010). Multicenter, placebo-controlled trial of lorcaserin for weight management. *The New England Journal of Medicine* 363, 245–256.
- Sofer, E., Boaz, M., Matas, Z., Mashavi, M., & Shargorodsky, M. (2011). Treatment with insulin sensitizer metformin improves arterial properties, metabolic parameters, and liver function in patients with nonalcoholic fatty liver disease: a randomized, placebo-controlled trial. *Metabolism* 60, 1278–1284.
- Sonne, D. P., & Hemmingsen, B. (2017). Standards of Medical Care in Diabetes-2017. *Diabetes Care* 2017;40(Suppl. 1):S1135. *Diabetes Care* 40, E92–E93.
- Soriano, J. B., Davis, K. J., Coleman, B., Visick, G., Mannino, D., & Pride, N. B. (2003). The proportional Venn diagram of obstructive lung disease: two approximations from the United States and the United Kingdom. *Chest* 124, 474–481.
- de Sousa, C. V., Sales, M. M., Rosa, T. S., Lewis, J. E., de Andrade, R. V., & Simoes, H. G. (2017). The Antioxidant Effect of Exercise: A Systematic Review and Meta-Analysis. *Sports Medicine* 47, 277–293.
- Sparvero, L. J., Asafu-Adjei, D., Kang, R., Tang, D., Amin, N., Im, J., ... Lotze, M. T. (2009). RAGE (Receptor for Advanced Glycation Endproducts), RAGE ligands, and their role in cancer and inflammation. *Journal of Translational Medicine* 7, 17.
- Srinivasan, S., Spear, J., Chandran, K., Joseph, J., Kalyanaraman, B., & Avadhani, N. G. (2013). Oxidative stress induced mitochondrial protein kinase A mediates cytochrome c oxidase dysfunction. *PLoS One* 8, e77129.
- Srivastava, G., & Apovian, C. M. (2017). Current pharmacotherapy for obesity. *Nature Reviews. Endocrinology* 14, 12–24.
- Stagakis, I., Bertias, G., Karvounaris, S., Kavousanaki, M., Virla, D., Raptopoulos, A., ... Sidirooulos, P. I. (2012). Anti-tumor necrosis factor therapy improves insulin resistance, beta cell function and insulin signaling in active rheumatoid arthritis patients with high insulin resistance. *Arthritis Research & Therapy* 14, R141.
- Stanciu, S., Marinescu, R., Iordache, M., Dumitrescu, S., Muresan, M., & Bogdan, M. A. (2009). Are systemic inflammatory profiles different in patients with COPD and metabolic syndrome as compared to those with COPD alone? *Romanian Journal of Internal Medicine* 47, 381–386.
- Stavropoulos-Kalinoglou, A., Metsios, G. S., Panoulas, V. F., Nightingale, P., Koutedakis, Y., & Kitas, G. D. (2012). Anti-tumour necrosis factor alpha therapy improves insulin sensitivity in normal-weight but not in obese patients with rheumatoid arthritis. *Arthritis Research & Therapy* 14, R160.
- Steuten, L. M., Creutzberg, E. C., Vrijhoef, H. J., & Wouters, E. F. (2006). COPD as a multi-component disease: inventory of dyspnoea, underweight, obesity and fat free mass depletion in primary care. *Primary Care Respiratory Journal* 15, 84–91.
- Stojkovič, J., Zafirova-Ivanovska, B., Kaeva, B., Anastasova, S., Angelovska, I., Jovanovski, S., & Stojkovič, D. (2016). The prevalence of diabetes mellitus in COPD patients with severe and very severe stage of the disease. *Open Access Macedonian Journal of Medical Science* 4, 253–258.
- Storlien, L. H., Jenkins, A. B., Chisholm, D. J., Pascoe, W. S., Khouri, S., & Kraegen, E. W. (1991). Influence of dietary fat composition on development of insulin resistance in rats. Relationship to muscle triglyceride and omega-3 fatty acids in muscle phospholipid. *Diabetes* 40, 280–289.
- Storlien, L. H., Kraegen, E. W., Chisholm, D. J., Ford, G. L., Bruce, D. G., & Pascoe, W. S. (1987). Fish oil prevents insulin resistance induced by high-fat feeding in rats. *Science* 237, 885–888.
- Strackowski, M., Dziennis-Strackowska, S., Stepien, A., Kowalska, I., Szelachowska, M., & Kinalska, I. (2002). Plasma interleukin-8 concentrations are increased in obese subjects and related to fat mass and tumor necrosis factor- α system. *The Journal of Clinical Endocrinology and Metabolism* 87, 4602–4606.
- Sun, K., Kusminski, C. M., & Scherer, P. E. (2011). Adipose tissue remodeling and obesity. *The Journal of Clinical Investigation* 121, 2094–2101.
- Swallow, E. B., Reyes, D., Hopkinson, N. S., Man, W. D., Porcher, R., Cetti, E. J., ... Polkey, M. I. (2007). Quadriceps strength predicts mortality in patients with moderate to severe chronic obstructive pulmonary disease. *Thorax* 62, 115–120.
- Takeda, Y., Nakanishi, K., Tachibana, I., & Kumanooh, A. (2012). Adiponectin: A Novel Link Between Adipocytes and COPD. *Vitamins and Hormones* 90, 419–435.
- Takenaka, S., Kawayama, T., Imaoka, H., Sakazaki, Y., Oda, H., Kaku, Y., ... Hoshino, T. (2014). The progression of comorbidity in IL-18 transgenic chronic obstructive pulmonary disease mice model. *Biochemical and Biophysical Research Communications* 445, 597–601.
- Tam, L. S., Tomlinson, B., Chu, T. T., Li, T. K., & Li, E. K. (2007). Impact of TNF inhibition on insulin resistance and lipids levels in patients with rheumatoid arthritis. *Clinical Rheumatology* 26, 1495–1498.
- Tamagawa, E., Suda, K., Wei, Y., Xing, L., Mui, T., Li, Y., ... Sin, D. D. (2009). Endotoxin-induced translocation of interleukin-6 from lungs to the systemic circulation. *Innate Immunity* 15, 251–258.
- Tan, Z., Xie, N., Cui, H., Moellering, D. R., Abraham, E., Thannickal, V. J., & Liu, G. (2015). Pyruvate dehydrogenase kinase 1 participates in macrophage polarization via regulating glucose metabolism. *Journal of Immunology* 194, 6082–6089.
- Taniguchi, C. M., Finger, E. C., Krieg, A. J., Wu, C., Diep, A. N., LaGory, E. L., ... Giaccia, A. J. (2013). Cross-talk between hypoxia and insulin signaling through Phd3 regulates hepatic glucose and lipid metabolism and ameliorates diabetes. *Nature Medicine* 19, 1325–1330.
- Tannapfel, A., Denk, H., Dienes, H. P., Langner, C., Schirmacher, P., Trauner, M., & Flott-Rahmel, B. (2011). Histopathological diagnosis of non-alcoholic and alcoholic fatty liver disease. *Virchows Archiv* 458, 511–523.
- Targher, G., Bertolini, L., Poli, F., Rodella, S., Scala, L., Tessari, R., ... Falezza, G. (2005). Non-alcoholic fatty liver disease and risk of future cardiovascular events among type 2 diabetic patients. *Diabetes* 54, 3541–3546.
- Thomas, A., Belaidi, E., Moulin, S., Horman, S., van der Zon, G. C., Viollet, B., ... Guigas, B. (2017). Chronic intermittent hypoxia impairs insulin sensitivity but improves whole-body glucose tolerance by activating skeletal muscle AMPK. *Diabetes* 66, 2942–2951.
- Tiengo, A., Fadini, G. P., & Avogaro, A. (2008). The metabolic syndrome, diabetes and lung dysfunction. *Diabetes & Metabolism* 34, 447–454.
- Tilton, S. C., Waters, K. M., Karin, N. J., Webb-Robertson, B. J., Zangar, R. C., Lee, K. M., ... Corley, R. A. (2013). Diet-induced obesity reprograms the inflammatory response of the murine lung to inhaled endotoxin. *Toxicology and Applied Pharmacology* 267, 137–148.
- Timmers, S., Konings, E., Bilet, L., Houtkooper, R. H., van de Weijer, T., Goossens, G. H., ... Schrauwen, P. (2011). Calorie restriction-like effects of 30 days of resveratrol supplementation on energy metabolism and metabolic profile in obese humans. *Cell Metabolism* 14, 612–622.
- Tkacova, R. (2010). Systemic inflammation in chronic obstructive pulmonary disease: may adipose tissue play a role? Review of the literature and future perspectives. *Mediators of Inflammation* 2010, 585989.
- Torgerson, J. S., Hauptman, J., Boldrin, M. N., & Sjostrom, L. (2004). XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. *Diabetes Care* 27, 155–161.
- Troscid, M., Lappegard, K. T., Claudi, T., Damas, J. K., Morkrid, L., Brendberg, R., & Mollnes, T. E. (2004). Exercise reduces plasma levels of the chemokines MCP-1 and IL-8 in subjects with the metabolic syndrome. *European Heart Journal* 25, 349–355.
- Tuder, R. M., Zhen, L., Cho, C. Y., Taraseviciene-Stewart, L., Kasahara, Y., Salvemini, D., ... Flores, S. C. (2003). Oxidative stress and apoptosis interact and cause emphysema due to vascular endothelial growth factor receptor blockade. *American Journal of Respiratory Cell and Molecular Biology* 29, 88–97.
- Turato, G., Di Stefano, A., Maestrelli, P., Mapp, C. E., Ruggieri, M. P., Roggeri, A., ... Sietta, M. (1995). Effect of smoking cessation on airway inflammation in chronic bronchitis. *American Journal of Respiratory and Critical Care Medicine* 152, 1262–1267.
- Um, J. H., Park, S. J., Kang, H., Yang, S., Foretz, M., McBurney, M. W., ... Chung, J. H. (2010). AMP-activated protein kinase-deficient mice are resistant to the metabolic effects of resveratrol. *Diabetes* 59, 554–563.
- Uysal, K. T., Wiesbrock, S. M., Marino, M. W., & Hotamisligil, G. S. (1997). Protection from obesity-induced insulin resistance in mice lacking TNF- α function. *Nature* 389, 610–614.
- Van Vliet, M., Spruijt, M. A., Verleden, G., Kasran, A., Van Herck, E., Pitta, F., ... Decramer, M. (2005). Hypogonadism, quadriceps weakness, and exercise intolerance in chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine* 172, 1105–1111.
- Van Winkle, L. S., Gunderson, A. D., Shimizu, J. A., Baker, G. L., & Brown, C. D. (2002). Gender differences in naphthalene metabolism and naphthalene-induced acute lung injury. *American Journal of Physiology. Lung Cellular and Molecular Physiology* 282, L1122–L1134.
- Vats, D., Mukundan, L., Odegaard, J. I., Zhang, L., Smith, K. L., Morel, C. R., ... Chawla, A. (2006). Oxidative metabolism and PGC-1 β attenuate macrophage-mediated inflammation. *Cell Metabolism* 4, 13–24.

- Vernooy, J. H., Drummen, N. E., van Suylen, R. J., Cloots, R. H., Moller, G. M., Bracke, K. R., ... Wouters, E. F. (2009). Enhanced pulmonary leptin expression in patients with severe COPD and asymptomatic smokers. *Thorax* 64, 26–32.
- Vestbo J, Anderson W, Coxson HO, Crim C, Dawber F, Edwards L, Hagan G, Knobil K, Lomas DA, MacNee W, Silverman EK, Tal-Singer R and investigators E (2008) Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE). The European Respiratory Journal 31:869-873.
- Vestbo, J., Prescott, E., Almdal, T., Dahl, M., Nordestgaard, B. G., Andersen, T., ... Lange, P. (2006). Body mass, fat-free body mass, and prognosis in patients with chronic obstructive pulmonary disease from a random population sample: findings from the Copenhagen City Heart Study. *American Journal of Respiratory and Critical Care Medicine* 173, 79–83.
- Viby, N. E., Isidor, M. S., Buggeskov, K. B., Poulsen, S. S., Hansen, J. B., & Kissow, H. (2013). Glucagon-like peptide-1 (GLP-1) reduces mortality and improves lung function in a model of experimental obstructive lung disease in female mice. *Endocrinology* 154, 4503–4511.
- Viollot, B., Guigas, B., Sanz Garcia, N., Leclerc, J., Foretz, M., & Andreelli, F. (2012). Cellular and molecular mechanisms of metformin: an overview. *Clinical Science (London, England)* 122, 253–270.
- Vlahos, R., & Bozinovski, S. (2014). Role of alveolar macrophages in chronic obstructive pulmonary disease. *Frontiers in Immunology* 5, 435.
- Vogelmeier, C. F., Criner, G. J., Martinez, F. J., Anzueto, A., Barnes, P. J., Bourbeau, J., ... Agusti, A. (2017). Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report. GOLD executive summary. *American Journal of Respiratory and Critical Care Medicine* 195, 557–582.
- Vogiatzis, I., Terzis, G., Stratakos, G., Cherouveim, E., Athanasopoulos, D., Spetsioti, S., ... Zakyntinos, S. (2011). Effect of pulmonary rehabilitation on peripheral muscle fiber remodeling in patients with COPD in GOLD stages II to IV. *Chest* 140, 744–752.
- Vujic, T., Nagorni, O., Maric, G., Popovic, L., & Jankovic, J. (2016). Metabolic syndrome in patients with chronic obstructive pulmonary disease: frequency and relationship with systemic inflammation. *Hippokratia* 20, 110–114.
- Wada, H., Ura, S., Satoh-Asahara, N., Kitaoka, S., Mashiba, S., Akao, M., ... Hasegawa, K. (2012). alpha1-Antitrypsin low-density-lipoprotein serves as a marker of smoking-specific oxidative stress. *Journal of Atherosclerosis and Thrombosis* 19, 47–58.
- Wang, C., Clark, R. V., Miller, B. E., Edwards, L. D., Rennard, S. I., Tal-Singer, R. M., ... Casaburi, R. (2012). Impact of testosterone level on long-term outcomes of men with COPD and association with phenotypic characteristics in a longitudinal study, ECLIPSE. *The Endocrine Society's 94th Annual Meeting and Expo*. TX, USA: Endocrine Society's Journals Houston.
- Wang, G. L., Jiang, B. H., Rue, E. A., & Semenza, G. L. (1995). Hypoxia-inducible factor 1 is a basic-helix-loop-helix-PAS heterodimer regulated by cellular O₂ tension. *Proceedings of the National Academy of Sciences of the United States of America* 92, 5510–5514.
- Wang, X. L., Li, T., Li, J. H., Miao, S. Y., & Xiao, X. Z. (2017). The effects of resveratrol on inflammation and oxidative stress in a rat model of chronic obstructive pulmonary disease. *Molecules* 22.
- Wang, Z. T., Ng, T. B., Yeung, H. W., & Xu, G. J. (1996). Immunomodulatory effect of a polysaccharide-enriched preparation of *Codonopsis pilosula* roots. *General Pharmacology* 27, 1347–1350.
- Wascher, T. C., Lindeman, J. H., Sourij, H., Kooistra, T., Pacini, G., & Roden, M. (2011). Chronic TNF-alpha neutralization does not improve insulin resistance or endothelial function in "healthy" men with metabolic syndrome. *Molecular Medicine* 17, 189–193.
- Watz, H., Waschki, B., Kirsten, A., Muller, K. C., Kretschmar, G., Meyer, T., ... Magnussen, H. (2009). The metabolic syndrome in patients with chronic bronchitis and COPD: frequency and associated consequences for systemic inflammation and physical inactivity. *Chest* 136, 1039–1046.
- Wedzicha, J. A., Seemungal, T. A., MacCallum, P. K., Paul, E. A., Donaldson, G. C., Bhowmik, A., ... Meade, T. W. (2000). Acute exacerbations of chronic obstructive pulmonary disease are accompanied by elevations of plasma fibrinogen and serum IL-6 levels. *Thrombosis and Haemostasis* 84, 210–215.
- Wei, K., Pieciewicz, S. M., McGinnis, L. M., Taniguchi, C. M., Wiegand, S. J., Anderson, K., ... Kuo, C. J. (2013). A liver Hif-2alpha-lrs2 pathway sensitizes hepatic insulin signaling and is modulated by Vegf inhibition. *Nature Medicine* 19, 1331–1337.
- Wendell, S. G., Baffi, C., & Holguin, F. (2014). Fatty acids, inflammation, and asthma. *The Journal of Allergy and Clinical Immunology* 133, 1255–1264.
- Whittom, F., Jobin, J., Simard, P. M., Leblanc, P., Simard, C., Bernard, S., ... Maltais, F. (1998). Histochemical and morphological characteristics of the vastus lateralis muscle in patients with chronic obstructive pulmonary disease. *Medicine and Science in Sports and Exercise* 30, 1467–1474.
- WHO (2006). *Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia*.
- Willemens, M. J., Mantel-Teeuwisse, A. K., Straus, S. M., Meyboom, R. H., Egberts, T. C., & Leufkens, H. G. (2011). Use of dipeptidyl peptidase-4 inhibitors and the reporting of infections: a disproportionality analysis in the World Health Organization Vigibase. *Diabetes Care* 34, 369–374.
- Willemse, B. W., ten Hacken, N. H., Rutgers, B., Lesman-Leegte, I. G., Postma, D. S., & Timens, W. (2005). Effect of 1-year smoking cessation on airway inflammation in COPD and asymptomatic smokers. *The European Respiratory Journal* 26, 835–845.
- Willi, C., Bodenmann, P., Ghali, W. A., Faris, P. D., & Cornuz, J. (2007). Active smoking and the risk of type 2 diabetes: a systematic review and meta-analysis. *JAMA* 298, 2654–2664.
- Wolf, A. M., Wolf, D., Rumpold, H., Enrich, B., & Tilg, H. (2004). Adiponectin induces the anti-inflammatory cytokines IL-10 and IL-1RA in human leukocytes. *Biochemical and Biophysical Research Communications* 323, 630–635.
- Wood, D. M., Brennan, A. L., Philips, B. J., & Baker, E. H. (2004). Effect of hyperglycaemia on glucose concentration of human nasal secretions. *Clinical Science (London, England)* 106, 527–533.
- Wouters, E. F. (2005). Local and systemic inflammation in chronic obstructive pulmonary disease. *Proceedings of the American Thoracic Society* 2, 26–33.
- Wu, J., & Sin, D. D. (2011). Improved patient outcome with smoking cessation: when is it too late? *International Journal of Chronic Obstructive Pulmonary Disease* 6, 259–267.
- Wu, L., Zhang, A. L., Di, Y. M., Shergis, J. L., Chen, Y., Guo, X., ... Xue, C. C. (2014). Panax ginseng therapy for chronic obstructive pulmonary disease: a clinical trial protocol and pilot study. *Chinese Medicine* 9, 20.
- Wynne, K., Stanley, S., McGowan, B., & Bloom, S. (2005). Appetite control. *The Journal of Endocrinology* 184, 291–318.
- Xia, X., & Weng, J. (2010). Targeting metabolic syndrome: candidate natural agents. *Journal of Diabetes* 2, 243–249.
- Yamauchi, T., Kamon, J., Waki, H., Terauchi, Y., Kubota, N., Hara, K., ... Kadowaki, T. (2001). The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. *Nature Medicine* 7, 941–946.
- Yanbaeva, D. G., Dentener, M. A., Creutzberg, E. C., & Wouters, E. F. (2006). Systemic inflammation in COPD: is genetic susceptibility a key factor? *COPD* 3, 51–61.
- Yang, I. A., Holloway, J. W., & Fong, K. M. (2013). Genetic susceptibility to lung cancer and co-morbidities. *Journal of Thoracic Disease* 5(Suppl. 5), S454–S462.
- Yeh, H. C., Punjabi, N. M., Wang, N. Y., Pankow, J. S., Duncan, B. B., Cox, C. E., ... Brancati, F. L. (2008). Cross-sectional and prospective study of lung function in adults with type 2 diabetes: the Atherosclerosis Risk in Communities (ARIC) study. *Diabetes Care* 31, 741–746.
- Yin, H. L., Yin, S. Q., Lin, Q. Y., Xu, Y., Xu, H. W., & Liu, T. (2017). Prevalence of comorbidities in chronic obstructive pulmonary disease patients: A meta-analysis. *Medicine (Baltimore)* 96 e6836.
- Yokoe, T., Alonso, L. C., Romano, L. C., Rosa, T. C., O'Doherty, R. M., Garcia-Ocana, A., ... O'Donnell, C. P. (2008). Intermittent hypoxia reverses the diurnal glucose rhythm and causes pancreatic beta-cell replication in mice. *The Journal of Physiology* 586, 899–911.
- Yongxu, S., & Jicheng, L. (2008). Structural characterization of a water-soluble polysaccharide from the roots of *Codonopsis pilosula* and its immunity activity. *International Journal of Biological Macromolecules* 43, 279–282.
- Young, J. M., Florkowski, C. M., Molyneux, S. L., McEwan, R. G., Frampton, C. M., Nicholls, M. G., ... George, P. M. (2012). A randomized, double-blind, placebo-controlled cross-over study of coenzyme Q10 therapy in hypertensive patients with the metabolic syndrome. *American Journal of Hypertension* 25, 261–270.
- Young, R. P., Hopkins, R., & Eaton, T. E. (2007). Forced expiratory volume in one second: not just a lung function test but a marker of premature death from all causes. *The European Respiratory Journal* 30, 616–622.
- Yuan, H., Shyy, J. Y., & Martins-Green, M. (2009). Second-hand smoke stimulates lipid accumulation in the liver by modulating AMPK and SREBP-1. *Journal of Hepatology* 51, 535–547.
- Yun, T. K. (2001). Brief introduction of Panax ginseng C.A. Meyer. *Journal of Korean Medical Science* 16(Suppl), S3–S5.
- Zaigham, S., Nilsson, P. M., Wollmer, P., & Engstrom, G. (2016). The temporal relationship between poor lung function and the risk of diabetes. *BMC Pulmonary Medicine* 16, 75.
- Zampetaki, A., Dudek, K., & Mayr, M. (2013). Oxidative stress in atherosclerosis: the role of microRNAs in arterial remodeling. *Free Radical Biology & Medicine* 64, 69–77.
- Zhang, W., Zhang, Y., Li, C. W., Jones, P., Wang, C., & Fan, Y. (2017). Effect of statins on COPD: A meta-analysis of randomized controlled trials. *Chest* 152, 1159–1168.
- Zhi, G., Xin, W., Ying, W., Guohong, X., & Shuying, L. (2016). "Obesity Paradox" in acute respiratory distress syndrome: A systematic review and meta-analysis. *PLoS One* 11 e0163677.
- Zhi, J., Melia, A. T., Eggers, H., Joly, R., & Patel, I. H. (1995). Review of limited systemic absorption of orlistat, a lipase inhibitor, in healthy human volunteers. *Journal of Clinical Pharmacology* 35, 1103–1108.
- Zimmet, P., & Alberti, G. (2008). The metabolic syndrome: progress towards one definition for an epidemic of our time. *Nature Clinical Practice. Endocrinology & Metabolism* 4, 239.
- Zinman, B., Gerich, J., Buse, J. B., Lewin, A., Schwartz, S., Raskin, P., ... Investigators, L. -S. (2009). Efficacy and safety of the human glucagon-like peptide-1 analog liraglutide in combination with metformin and thiazolidinedione in patients with type 2 diabetes (LEAD-4 Met+TZD). *Diabetes Care* 32, 1224–1230.
- Zumbach, M. S., Boehme, M. W., Wahl, P., Stremmel, W., Ziegler, R., & Nawroth, P. P. (1997). Tumor necrosis factor increases serum leptin levels in humans. *The Journal of Clinical Endocrinology and Metabolism* 82, 4080–4082.