

Review

Mechanisms Linking COPD to Type 1 and 2 Diabetes Mellitus: Is There a Relationship between Diabetes and COPD?

Sangmi S. Park ¹, Jessica L. Perez Perez ¹, Brais Perez Gandara ¹, Christina W. Agudelo ¹, Romy Rodriguez Ortega ¹, Huma Ahmed ¹, Itsaso Garcia-Arcos ¹, Cormac McCarthy ² and Patrick Geraghty ^{1,*}

- ¹ Department of Medicine, State University of New York Downstate Health Sciences University, Brooklyn, NY 11203, USA; sangmi.park01@downstate.edu (S.S.P.); jessica.perezperez@downstate.edu (J.L.P.P.); brais.perezgandara@downstate.edu (B.P.G.); christina.agudelo@downstate.edu (C.W.A.); romy.rodriguezortega@downstate.edu (R.R.O.); huma.ahmed@downstate.edu (H.A.); itsaso.garcia-arcos@downstate.edu (I.G.-A.)
- ² University College Dublin School of Medicine, Education and Research Centre, St. Vincent's University Hospital, D04 T6F4 Dublin, Ireland; cormac.mccarthy@ucd.ie
- * Correspondence: patrick.geraghty@downstate.edu; Tel.: +1-718-270-3141

Abstract: Chronic obstructive pulmonary disease (COPD) patients frequently suffer from multiple comorbidities, resulting in poor outcomes for these patients. Diabetes is observed at a higher frequency in COPD patients than in the general population. Both type 1 and 2 diabetes mellitus are associated with pulmonary complications, and similar therapeutic strategies are proposed to treat these conditions. Epidemiological studies and disease models have increased our knowledge of these clinical associations. Several recent genome-wide association studies have identified positive genetic correlations between lung function and obesity, possibly due to alterations in genes linked to cell proliferation; embryo, skeletal, and tissue development; and regulation of gene expression. These studies suggest that genetic predisposition, in addition to weight gain, can influence lung function. Cigarette smoke exposure can also influence the differential methylation of CpG sites in genes linked to diabetes and COPD, and smoke-related single nucleotide polymorphisms are associated with resting heart rate and coronary artery disease. Despite the vast literature on clinical disease association, little direct mechanistic evidence is currently available demonstrating that either disease influences the progression of the other, but common pharmacological approaches could slow the progression of these diseases. Here, we review the clinical and scientific literature to discuss whether mechanisms beyond preexisting conditions, lifestyle, and weight gain contribute to the development of COPD associated with diabetes. Specifically, we outline environmental and genetic confounders linked with these diseases.

Keywords: chronic obstructive pulmonary disease; diabetes; hyperglycemia; inflammation; oxidative stress; insulin; metabolism



Citation: Park, S.S.; Perez Perez, J.L.; Perez Gandara, B.; Agudelo, C.W.; Rodriguez Ortega, R.; Ahmed, H.; Garcia-Arcos, I.; McCarthy, C.; Geraghty, P. Mechanisms Linking COPD to Type 1 and 2 Diabetes Mellitus: Is There a Relationship between Diabetes and COPD? *Medicina* **2022**, *58*, 1030. <https://doi.org/10.3390/medicina58081030>

Academic Editor: Brian Oliver

Received: 24 June 2022

Accepted: 27 July 2022

Published: 1 August 2022

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Copyright: © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

Lifestyle risk factors are considered central to the development of type 1 and 2 diabetes mellitus (T1D and T2D) and chronic obstructive pulmonary disease (COPD) [1]. The daily physical activity of COPD patients is reduced in the early phases of the disease, as compared with healthy age-matched controls, and worsens over time [2]. Poor medication adherence is described in patients with these diseases, resulting in increased hospitalization rates. However, a series of clinical studies described herein link COPD and T1D and T2D. Equally, studies in disease models provide mechanistic evidence to suggest that comorbid diabetes and COPD feedback influence the progression of the other disease. This review will focus on the epidemiology, physiology, molecular data, and disease models linking diabetes and COPD.

2. Evidence linking COPD to Diabetes

2.1. Epidemiological Evidence Linking COPD to T1D

The prevalence of T1D was previously reported to be increasing over the past decade [3]. Reduced total lung capacity (TLC), diffusing capacity of the lung for carbon monoxide (DLCO), pulmonary elastic recoil, and end-expiratory lung volume are detected in patients with T1D. This impaired lung physiology is inversely correlated with glycated hemoglobin levels [4]. Changes in collagen glycation of lung parenchyma and alveolar microangiopathy may contribute to this altered pulmonary dysfunction. In a small comparative study, T1D patients exhibited normal spirometry and pleural pressure, but a higher dynamic elastance during hypoxia, possibly indicating peripheral airway involvement [5].

2.2. Epidemiological Evidence Linking COPD to T2D

T2D is a leading comorbidity in COPD [6,7]. A population-based retrospective study from Italy demonstrated a higher prevalence of T2D in COPD patients (18.7%) compared to the general population (10.5%) [6]. In this study, women with COPD were significantly more likely to develop T2D compared to women without COPD [6]. Another population-based study in Taiwan [7] showed that T2D was present in 16% of patients with COPD, and within a 10-year follow-up period, T2D was newly diagnosed in 19% of COPD patients, showing increased prevalence and incidence of the disease. Additionally, the association between diabetes and pulmonary disease did not extend to asthma, according to one prospective cohort study [8], suggesting a specific interplay between COPD and diabetes.

Hyperglycemia is an independent predictor of poor outcomes in patients admitted to the hospital and intensive care unit (ICU) [9]. In a study looking at patients admitted with acute decompensated respiratory failure complicating COPD, baseline hyperglycemia upon presentation was identified as a good predictor of clinical outcomes, determined by the Acute Physiology and Chronic Health Evaluation II (APACHE II) score [10]. Mortality rates are high in patients with COPD, as demonstrated by death in almost 80% of patients within nine years of hospital admission due to acute exacerbation of COPD, and diabetes was associated with decreased long-term survival in these patients [11]. Diabetes and cardiovascular diseases were associated with increased mortality in a cohort of COPD patients, when adjusted for age, gender, and smoking pack-year history [12].

2.3. T1D Affects Specific Lung Function Parameters

T1D is associated with decreased TLC, lung elastic recoil, diffusion capacity to transport carbon monoxide (DLCO), and pulmonary capillary volume [13,14]. These changes in pulmonary function were present, even in the absence of established pulmonary disease. Non-smokers with T1D who were not previously diagnosed with the pulmonary disease had decreased distance in the 6-minute walk test, forced expiratory volume in one second (FEV1), TLC, and DLCO [15]. Poor glycemic control, duration, and severity of diabetes were associated with worsening lung function, observed by changes in forced vital capacity (FVC) and FEV1 [16–18]. Patients with higher hemoglobin A1c (HbA1c) have lower FVC, FEV1, vital capacity, and peak expiratory flow (PEF) [19]. These abnormalities can be mitigated in just three months after correction of hyperglycemia [20].

Systemic inflammation plays a significant role in the pathogenesis and progression of COPD and diabetes. C-Reactive Protein (CRP) levels are inversely associated with FEV1 and FVC at baseline [21]. These changes are present in both sexes and are independent of smoking, obesity, and the presence of other respiratory pathologies, such as asthma [22]. Lung responses appear to be altered by complications of diabetes, with impaired autonomic nerve function in the lungs of T1D patients [23]. In a study testing the responses of diabetic subjects and non-diabetic controls to hypoxia, hypercapnia, and exercise, approximately 25% of diabetic subjects had evidence of impaired sensitivity to hypoxia or decreased ventilatory response to hypercapnia [24]. More recently, the approach to evaluating autonomic dysfunction using assessing cardiorespiratory function has created a body of

evidence that proposes that these abnormalities could potentially be corrected with new interventions [25].

2.4. T2D Affects Specific Lung Function Parameters

The alveolar microvascular function is impaired in T2D non-smokers compared to controlled subjects, as demonstrated by decreased DLCO [26]. When using the German COPD and Systemic Consequences–Comorbidities Network (COSYCONET) cohort, hyperlipidemia (prevalence of 42.9%) is associated with lower intrathoracic gas volume and higher FEV1, when adjusting for risk factors and other comorbidities [27].

2.5. Metabolic Syndrome in COPD

Metabolic syndrome (MetS) represents a major public health challenge and confers a five-fold increase in the risk of T2D and a two-fold increase in the risk of developing cardiovascular disease (CVD) within five to ten years [28]. MetS is defined by a constellation of closely related cardiovascular risk factors, including obesity, altered lipids, increased blood pressure, and impaired fasting glucose [28]. A recent cohort of 7358 adults described the association between MetS and pulmonary function. The risk of MetS was higher in patients with airway obstruction than in those without (odds ratio (OR) 1.47; confidence interval (CI) 1.12–1.92), and after adjusting for body mass index (BMI), central obesity was significantly associated with airflow obstruction (OR 1.43; 95% CI 1.09–1.88) [29].

According to the International Diabetes Confederation, neither COPD nor cigarette smoking was included as fundamental risk factors of MetS. However, an increased prevalence of MetS is observed in COPD patients compared to the general population (21–62%) [29–33]. In particular, patients with earlier stages of COPD exhibit the highest prevalence of MetS [30,31]. In the general population, MetS becomes more prevalent with increasing age [34]. COPD patients with MetS often display worsened courses of the disease, as observed by greater percent-predicted FEV1 reduction, increased dyspnea, and greater use of inhaled steroids [35]. Two COPDGene studies found that diabetes is more frequent in subjects with airway disease than emphysema on CT [36,37]. Therefore, it is warranted to monitor COPD patients without emphysema for diabetes, hypertension, and hyperlipidemia.

2.6. Cigarette Smoking in Diabetics

In a cohort study detailed by George et al., after calculating the attributable risk of COPD, cigarette smoke (CS) accounted for 19% of cases in T1D and 30% of cases in T2D, compared to 26% of cases in non-diabetics [38]. While it is important to note that MetS and hyperglycemia are also described as risk factors for reduced lung function in healthy non-smoking subjects [39], CS may nonetheless play a role in the pathophysiology of COPD in diabetics. A recent large-scale cross-trait GWAS paper investigating genetic overlap between COPD and several cardiac traits (resting heart rate, high blood pressure, coronary artery disease, and stroke) from the UK Biobank, the CARDIoGRAMplusC4D Consortium, and the International Stroke Genetics Consortium demonstrated smoke-related single nucleotide polymorphisms (SNPs) located in the 15q25.1 region that were associated with cigarette smoke usage, resting heart rate, and coronary artery disease [40]. This region was also linked to COPD in a separate study [41]. It is suggested that this smoke-related 15q25.1 region may play a role in the severity of nicotine, alcohol, and opioid dependence [42], partially due to it containing three nicotinic cholinergic receptor genes (*CHRNA5-B4*). A non-synonymous single-nucleotide polymorphism of *CHRNA5*, rs16969968, can result in impaired ciliogenesis and the altered production of inflammatory mediators in airway epithelial cells [43]. Cigarette smoke exposure can also influence differential methylation of CpG sites on genes linked to T2D, such as *ANPEP*, *KCNQ1*, and *ZMIZ1* [44].

2.7. Alpha-1 Antitrypsin and Diabetes

Several clinical trials were undertaken to investigate the potential for alpha-1 antitrypsin (AAT) infusions as a treatment for diabetes [45–47], specifically T1D. Raising blood levels of AAT with augmentation therapy is reported to prevent T1D development, prolong islet allograft survival [48], increase insulin release capacity [49], and inhibit pancreatic β -cell apoptosis [50]. AAT treatment also significantly reduces HbA1c levels [51]. There is an association between AAT deficiency with an increased risk of developing T2D [52]. High levels of degraded AAT are observed in the urine of T2D patients with diabetic kidney disease [53]. We recently published a review focusing on AAT and diabetes, which can be accessed for further reading on this topic [54].

3. Animal Models of T1D and T2D in COPD

There are many studies investigating obesity and pulmonary diseases, but here, we will only discuss T1D and T2D models with noted pulmonary involvement. Alloxan-induced T1D rats are more susceptible to emphysematous lesions in response to porcine pancreatic elastase (PPE) instillation compared to nondiabetic control mice [55]. The diabetic rats had a reduced number of neutrophils in the bronchoalveolar lavage fluid (BALF) and diminished repair of the alveolar walls in response to emphysema. Insulin treatment restored these changes in neutrophil numbers and the magnitude of emphysematous lesions [55]. Mice with cystic fibrosis-related diabetes (CFRD) have increased blood glucose concentration, which is associated with impairment in bacterial clearance from the lung in diabetic mice [56]. Streptozotocin (STZ)-induced hyperglycemia in rats results in lung oxidative stress, as well as changes in lung structure and gas exchange [57]. The same pathomorphological modifications of the lungs, including thickening of the alveolar-capillary barrier, collapsed alveolar epithelium, and destruction of the matrix, are observed in STZ-induced hyperglycemia in hamsters [58]. The structural modifications were more pronounced and developed at a faster rate in hamster models of diabetes associated with hyperlipidemia. Other research groups demonstrated that STZ-induced T1D in rats results in a pulmonary fibrosis phenotype [59,60]. Therefore, hyperglycemia associated with diabetes likely contributes to the pathophysiology of lung diseases.

4. Mechanistic Link between COPD and T1D

Diabetic patients exhibit thickening of the pulmonary basal lamina [61]. Furthermore, T1D patients who have never smoked exhibited thickening of the alveolar-capillary membrane [62]. These morphological features are commonly found in diabetic microangiopathy and hence, may explain the decrease in DLCO in T1D. Similar histopathological pulmonary changes are also observed in experimental models of T1D [63]. Aside from morphological changes, fibrotic changes in the small airways due to chronic inflammation can progressively result in COPD. TGF- β can trigger fibrotic changes in the lungs in human patients and experimental T1D models [59,60]. While T1Ds are more susceptible to impaired lung function and structural changes leading to COPD [17,38,64], the exact mechanisms underlying the association between the two diseases are not yet known. Here, we will outline possible mechanistic links between these diseases (see Figure 1).

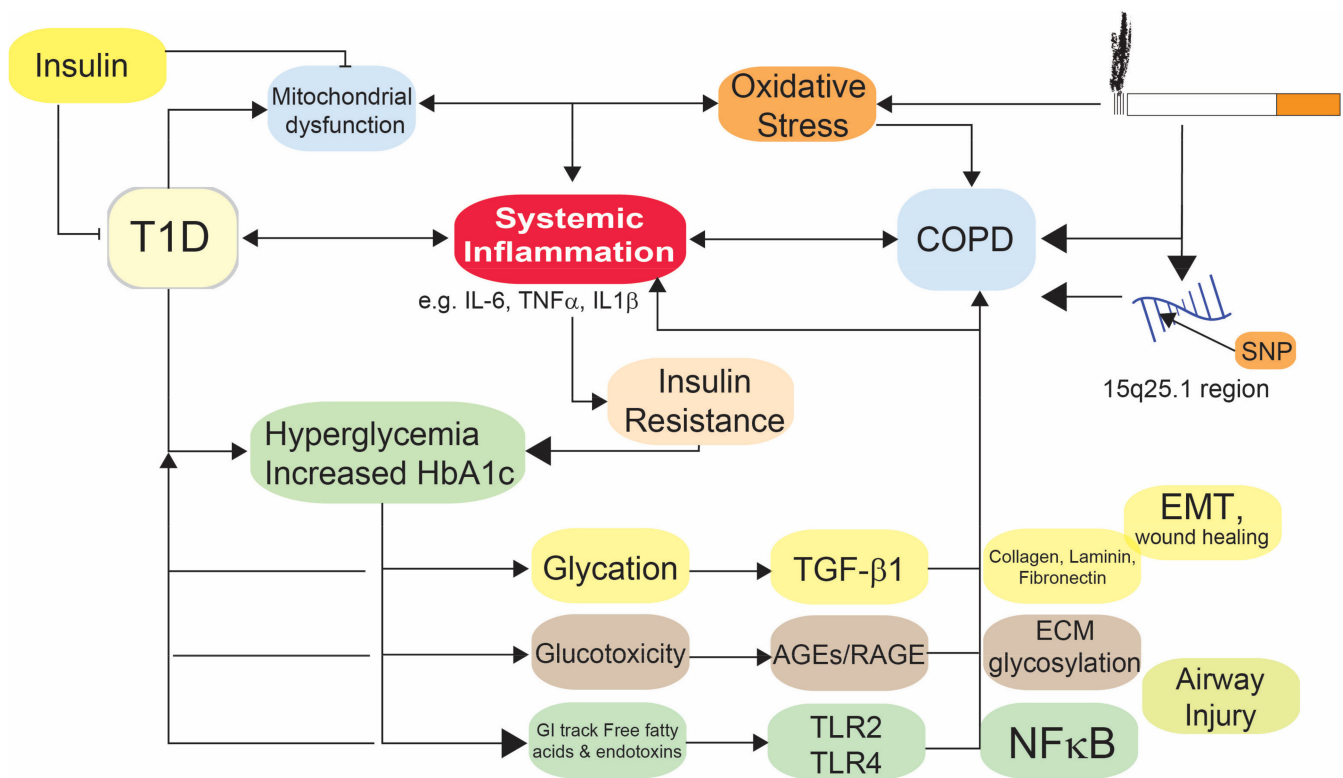


Figure 1. Possible mechanisms resulting in the increased prevalence of T1D in COPD.

4.1. Oxidative Stress

Oxidative stress is a common feature of COPD and T1D pathogenesis and is caused by an imbalance in oxidant-antioxidant levels. Chronic exposure to CS and other particulate pollutants induces oxidative stress in the lungs [65]. Alveolar macrophages from individuals with COPD generate increased superoxide radicals and hydrogen peroxide compared to those without COPD [66]. Lipid peroxidation (a marker of oxidative stress) and its by-products are elevated in both lung tissue and exhaled breath condensate in individuals with COPD [67]. In addition, BALF concentrations of the antioxidant glutathione are lower in exacerbators compared with individuals with stable COPD [68]. Increased reactive oxygen species (ROS) and oxidative stress can result in impaired efferocytosis, or immune cell-mediated clearance of apoptotic cells, as CS exposure decreases the clearance of apoptotic cells by alveolar macrophages through activation of Rho GTPases [69].

Oxidative stress is reported primarily in the early stages of T1D and is a suggested mechanism that contributes to glucose autooxidation, glycation of proteins, consumption of NADPH through the polyol pathway, and activation of protein kinase C [70]. Superoxide dismutase (SOD) activity and increase in nitric oxide (NO) are decreased in the lungs of animal models of T1D. Oxidative stress appears to remain, even when hyperglycemia is controlled [71], suggesting that oxidative stress may be an important factor early on in the development of T1D.

4.2. Metabolic Changes in T1D and COPD

T1D involves multiple metabolic alterations and their associations with pulmonary disease, and specifically with COPD, have been the subject of intense study. However, the complexity of in vivo metabolism poses an intrinsic difficulty for the interpretation of the available data. Serum concentrations of triglycerides and major choline-containing phospholipids, such as sphingomyelins, phosphatidylcholines, and phosphatidylethanolamines, are reduced in infants who later develop T1D [72], likely reflecting defects in lipoprotein and glucose metabolism in hepatic and peripheral tissues. Plasma sphingomyelin is

negatively correlated with COPD, while glycosphingolipids are associated with COPD exacerbations [73].

Thus far, 168 sphingolipids and 36 phosphatidylethanolamine lipid levels are reportedly elevated in the sputum of smokers with COPD compared to smokers without COPD [74]. Among these, the expression of 13 lipids involved in the sphingolipid pathway (4 ceramides, 5 dihydroceramide, 1 sphingomyelin, and 3 glycosphingolipids) was increased by 2.5-fold or more and showed an inverse correlation with lung function. Because the lipids collected in sputum originate mostly in the upper airways, these data may reflect the increased production of ceramides associated with inflammation. Indeed, ceramides are involved in the destruction of the alveolar integrity in emphysema [75]. Among the lipids detectable in the distal areas of the lung, the alveolar availability of surfactant PC and of sphingomyelin correlates with FEV1 in COPD patients [76].

Furthermore, lysoPC is decreased in rats subjected to CS and LPS instillation, and this alteration was associated with the onset and development of COPD [77]. LysoPC also amplifies PPE-induced emphysema in hamsters [78]. LysoPC may have the potential to activate inflammatory responses [79], which might explain the changes in lysoPC levels observed in inflammatory diseases, including T1D and COPD. For further reading on lipids in pulmonary diseases, see this recent review from our group [80].

4.3. Immune Responses in COPD and T1D

Several immune responses are implicated in the pathogenesis of COPD and T1D, particularly Toll-like receptors (TLR) [81–83]. The respiratory tract is vulnerable to infections and exposure to environmental factors, such as CS, modulates immune responses to infections [84]. TLR2, TLR3, and TLR4 are frequently implicated in the pathogenesis of diabetes, T1D-related vascular complications, and CS-induced inflammation and COPD [83,85].

Circulating levels of endotoxin and monocytes expressing TLR2 and TLR4 are elevated in T1D patients [86,87], possibly due to high glucose and low insulin levels in T1D patients [88]. Likewise, TLR2 and TLR4 expressions are increased in alveolar macrophages of COPD patients [89] and the airways of CS-exposed mice [90]. Biobreeding diabetes-prone rats, a genetic model of T1D, have increased diabetogenicity upon infection with the Kilham rat virus in combination with a TLR3 ligand [91]. In T1D, nuclear factor kappa B (NF- κ B) activation in the β -cells is triggered by TLR-mediated pathways [92]. Equally, *Tlr2* knockout mice are resistant to STZ-induced autoimmune diabetes. Non-obese diabetic (NOD) mice (a T1D model), deficient in TLR2 or treated with agonistic TLR4 monoclonal antibody, are resistant to new-onset T1D due to antigen-presenting cell tolerance and compromised adaptive T cell response [93]. CS exposed animals exhibited airway fibrosis, alveolar enlargement, and decreased lung function, and these changes are attenuated in *Tlr4*^{-/-} mice [90]. TLR2 expression is increased in monocytes in smokers [94].

Hypoxia enhances systemic inflammation through diffuse activation of NF- κ B [95]. Plasma concentrations of inflammatory markers, including serum CRP, IL-6, IL-1 β , and TNF- α , are elevated in T1D patients, which contribute to pathological processes of diabetic complications, such as microvascular complications [96]. Similarly, COPD exacerbates systemic inflammation in smokers, as indicated by elevated circulating concentrations of leukocytes, CRP, fibrinogen, and TNF- α , and these inflammatory processes continued, even after smoking cessation [97]. Importantly, CRP is associated with a decline in lung function in young adults [22]. This alteration in the inflammation factor may cause tissue damage, which may explain lower pulmonary DLCO observed in children with T1D [98]. DLCO impairment may be an early marker of T1D-related complications, such as microangiopathy [98,99]. T1D and its complications, particularly microangiopathy, are associated with pulmonary function changes. Similarly, the presence of systemic inflammation in COPD is linked with a variety of comorbidities, such as cardiovascular diseases [100]. The increased serum levels of IL-6 and plasma fibrinogen concentrations observed in COPD exacerbation predispose individuals to cardiovascular disease development [101]. Finally, the 15q25.1 region contains the cathepsin H gene (*CTSH*), and *CTSH* expression is suppressed by cy-

tokines in islets and β -cells [102]. However, if CTSH is overexpressed in insulin-producing β -cells (INS-1 cell line), it protects the β -cells against cytokine-induced apoptosis [102]. CTSH is also a positive regulator of insulin transcription, and the *CTSH* SNP, rs3825932, affects the expression level of CTSH linked to β -cell function in T1D.

4.4. Impaired Wound Healing

Exposure to CS can alter the repair mechanisms within the lungs, leading to small airway remodeling [103]. Likewise, wound healing is compromised in T1D. Repetitive injury of the airway epithelium by CS also upregulates TGF- β in COPD patients, which subsequently leads to persistent activation of epithelial to mesenchymal transition (EMT) and airway remodeling [104]. Airway epithelial cell senescence may also contribute to the pathogenesis of COPD by inhibiting wound repair and increasing the release of pro-inflammatory cytokines involved in p38-MAPK activation [105]. Fibroblasts from COPD patients are less capable of sustaining tissue repair, which may be due to decreased synthesis and deposition of extracellular matrix (ECM) components, as well as decreased sensitivity to TGF- β 1 [106]. Additionally, the loss of regenerative capability of the bronchial progenitor cells in CS-induced COPD could contribute to airway remodeling and impaired wound repair [107,108].

Studies in T1D patients and animal models demonstrated decreased collagen deposition and delayed wound repair responses [109]. This decreased reparative collagen accumulation in response to wounds coincides with decreased nitric oxide (NO) synthesis in wounds [110], decreased fibroblast proliferation [109,111], and the elevated plasma level of glucocorticoids [112]. Decreased tensile strength [113], reduced expression of IGF-1 and TGF- β in wound fluid [114], and dysregulated late inflammatory response [115] are also suggested to contribute to the impairment of wound healing in T1D in parallel with decreased collagen deposition. Decreased proliferative potential and migration of adipose tissue-derived stem cells (ASCs) may also lead to inefficient wound healing in T1D [116].

4.5. Glucose and COPD

Hyperglycemia can also contribute to airway inflammation [64]. Experimental rat models of T1D have decreased glucose oxidation and a decreased rate of glucose incorporation into neutral lipids and phospholipids [117,118]. Glucose metabolism also plays an important role in surfactant metabolism. The dysregulation of glucose observed in the T1D rat model may potentially lead to the dysregulation of pulmonary surfactant synthesis [119], as there are reduced lamellar inclusion bodies in type II alveolar epithelial cells in the T1D rat model, which are a source of pulmonary surfactant [119]. While studies have looked at the transport of glucose in lung cells [120], in vitro models studying the effect of extracellular glucose on airway cell responses may serve as useful tools for delineating the association between hyperglycemia and COPD. Finally, pancreas and kidney transplantation ameliorated the decline in lung function, in particular FEV1 and FVC, in a T1D population [121]. This suggests that the reversal of T1D influences pulmonary outcomes. In a longitudinal study where 7055 participants were followed over 3.9 years, a longitudinal change in HbA1c was associated with a longitudinal change in FVC. Participants with new-onset diabetes had a higher decline in FVC over time [122]. Equally, diet quality is associated with better FEV1, FVC, and restriction [123].

5. Mechanistic Links between COPD and T2D

5.1. Oxidative Stress

T2D subjects show increased ROS generation and markers of oxidative stress, as well as decreased antioxidant levels compared to non-diabetics [124]. At the cellular level, oxidative stress negatively regulates insulin signaling via interactions with serine/threonine kinases [124], contributing to insulin insensitivity. Systemically, oxidative stress decreases pancreatic β -cell insulin secretion and subsequently impairs insulin signaling in peripheral tissues [125]. Furthermore, pancreatic β -cells are uniquely susceptible to oxidative

stress [125]. CS exposure decreases β -cell insulin production, processing, and secretion, and decreases β -cell enrichment and proliferation. CS increases β -cell oxidative and endoplasmic reticulum stress and induces ceramide accumulation [126].

5.2. Inflammation

Similar to T1D, chronic inflammation is observed in T2D. Individuals with obstructive lung diseases have significantly elevated abdominal adipose tissue [127], and obesity is common in the early stages of COPD [128]. Adipose tissue inflammation is also present in individuals with mild-to-moderate COPD [129]. Furthermore, individuals with COPD have higher levels of plasma CRP compared to control subjects, and CRP levels positively correlate with macrophage infiltration of adipose tissue upon biopsy [129]. Various adipokines, including adiponectin, are associated with worse outcomes in COPD [130]. However, this study had significant confounding factors, with differences in sex, age, pack-years, BMI, methacholine responsiveness, and ethnicity among its group. Obesity increases levels of adipokines and alters cellular immunity. A recent cross-trait genome-wide association study (GWAS), using 457,822 subjects of European ancestry from the UK Biobank, found a positive genetic correlation between BMI and later-onset asthma, with onset at or after 16 years of age [131]. They identified 34 shared loci among 3 obesity-related traits and 2 asthma subtypes and, utilizing an obesity mouse model, identified 2 genes (acyl-coenzyme A oxidase-like (ACOXL) and myosin light chain 6 (MYL6)) playing a significant role in both diseases. Equally, a recent GWAS study utilizing data on 100,285 subjects from the China Kadoorie Biobank (and the UK Biobank) identified 9 novel loci for FEV1, 6 for FVC, and 3 for FEV1/FVC linking lung function to obesity [132]. The biological pathways linking lung function to obesity were cell proliferation; embryo, skeletal, and tissue development; and regulation of gene expression. This study also suggested that BMI had a negative effect on lung function over an eight-year follow-up [132]. These studies suggest that genetic predisposition, in addition to weight gain, can influence lung function. In addition, individuals with T2D are more susceptible to infection, possibly due to the increased risk of skin barrier disruption from diabetic neuropathy and diminished cellular immunity, including suppressed cytokine production and defective phagocytosis [133].

Insulin resistance could contribute to this diminished cellular immunity in T2D, as insulin administration decreases infection and complication rates in T2D populations [134]. Insulin has anti-inflammatory effects and suppresses ROS production [135]. Insulin also acts through PI3 kinase and ERK pathways to increase the secretion of IL-6 and TNF- α from activated LPS-treated macrophages [136]. Insulin therapy also has direct effects on the lung, inducing prostaglandin-mediated airway smooth muscle contraction [135]. Furthermore, the incretin glucagon-like peptide 1 (GLP-1), responsible for raising insulin during meals, may play a role in ROS and influence the responses for the receptor for advanced glycation end-products (RAGE). GLP-1 receptor agonists have anti-inflammatory benefits in the treatment of bronchial hyperresponsiveness [137] and obesity-related asthma [138]. Additionally, the nod-like receptor, containing a pyrin domain 3 (NLRP3) inflammasome, is linked to the development of COPD and other pulmonary conditions [139]. NLRP3 is significantly upregulated in an in vitro model of COPD exacerbation [140]. NLRP3 also participates in obesity-induced inflammation and induces insulin resistance [141].

Inflammation in the lung affects peripheral energy utilization. For instance, NF- κ B-activation in the lung attenuates the suppression of hepatic glucose production by insulin and induces insulin resistance in peripheral tissues [142]. Inflammation in the lung may negatively affect systemic glucose homeostasis by decreasing the recruitment of skeletal muscle capillaries that deliver glucose and insulin to myocytes, thereby increasing blood glucose levels [143].

5.3. Immunometabolism in COPD and T2D

While the exact mechanism by which CS induces insulin sensitivity is not known, metabolic changes that may lead to insulin sensitivity are observed in smokers. Serum

glucose, insulin, and C-peptide levels increase in response to glucose tests in cigarette smokers compared to nonsmokers [144]. Moreover, smokers with T2D have increased plasma insulin and triglyceride levels and decreased HDL cholesterol, [144]. Hypertriglyceridemia is associated with insulin resistance [145] and could be one of the contributing factors to developing insulin resistance in smokers. CS is suggested to impair insulin sensitivity in healthy and T2D subjects [144].

There are conflicting results on the effects of CS on adipokine regulation. While some studies demonstrated a direct association between alveolar and plasma adiponectin with CS [146,147], other studies showed that serum adiponectin levels are negatively associated with CS [148], or are not affected by CS status [130]. These differences in adiponectin associations may be due to multiple differences between study groups, such as sex, age, pack-years, BMI, methacholine responsiveness, and ethnicity. Likewise, some studies reported reduced leptin levels in smokers compared to nonsmokers [149,150], whereas another study suggested that nicotine may have a direct effect on insulin resistance by increasing circulating leptin levels [151]. Whether CS directly affects adipokine secretion in COPD patients remains to be elucidated.

There may be an association between metabolism and immunity when linking obesity and low-grade inflammation [152]. Immune cells, such as mononuclear cells of COPD patients and the mouse macrophage RAW264.7 cell line exposed to CS condensate (CSC), show impaired glycolysis and fatty acid oxidation [153]. Furthermore, mitochondrial ROS production is increased in CSC-exposed RAW264.7 cells in a dose-dependent manner. Immunometabolic changes are likely due to mitochondrial damage induced by CS exposure, which may participate in the progression of COPD [153]. Dysfunctional mitochondria with increased production of ROS are also observed in T2D [154]. Alveolar macrophages in COPD patients exhibit mitochondrial dysfunction [155], and macrophages with such metabolic impairment show reduced ability to migrate, phagocytose, and clear bacterial load [156], emphasizing the importance of metabolic regulation by immune cells to maintain lung homeostasis.

The role of adipose tissue in inducing systemic inflammation in obese COPD patients may contribute to insulin resistance [129,157]. Adipose tissue is proposed to actively participate in enhancing low-grade systemic inflammation in the lungs by producing adipokines, such as leptin and adiponectin, that regulate energy metabolism and inflammatory signaling. Leptin and adiponectin levels in adipose tissue positively correlated with circulating levels of the two adipokines and inflammatory markers in obese individuals, suggesting that adipocytokine secretion in obesity can contribute to systemic inflammation [158]. The circulating levels of adiponectin are increased in COPD patients compared to healthy subjects and are inversely associated with lung function, in particular FEV1 and FEV1/FVC, in COPD patients [146,147].

Increased adipose tissue mass is associated with susceptibility to pulmonary infection [157]. Adipose-derived proinflammatory cytokines, such as TNF- α , could inhibit insulin receptor signaling [159]. Circulating leptin levels positively correlate with adipose mass [129]. Leptin, is present in the induced sputum of COPD patients and is proposed to be involved in the regulation of the innate immune system of the lungs [160]. Leptin is also elevated in the sub-mucosa of COPD patients and negatively correlates with FEV1 and FEV1/FVC [161]. Plasma leptin, CRP, and Hb1Ac levels are elevated in COPD patients and are associated with cardiometabolic complications [162]. COPD patients exhibit increased ectopic fat accumulation, which is reported to cause insulin resistance and T2D [162].

5.4. Hyperglycemia and Hyperinsulinemia

High sucrose intake negatively affects lung mechanics and alveolar septal composition in mice, causing pulmonary extracellular matrix remodeling and reduced elasticity [163]. Hyperglycemic individuals exhibit elevated glucose concentrations in nasal secretions compared to normoglycemic individuals [164]. High airway glucose may foster a favorable environment for microbial colonization, with glucose in bronchial aspirates

increasing the risk of respiratory methicillin-resistant *Staphylococcus aureus* in intubated patients [165]. Hyperglycemia can enhance the contractility of airway smooth muscle via the Rho-associated-coil-containing protein kinase pathway, intracellular calcium releases, and phosphorylation of myosin-targeting subunit-1 [166].

AGEs are formed as a consequence of chronic hyperglycemia via non-specific glycation and deposited throughout the body, leading to serious complications, such as endothelial cell disruption with subsequent micro- and microvasculature damage and, ultimately, organ failure [167]. In the lung, microvascular and parenchymal changes induce systemic hypoxia and dysregulate energy metabolism. AGEs also exert potent signaling activity when bound to RAGEs. AGE-RAGE complexing induces the expression of inflammatory genes in target cells via the NF- κ B pathway [168]. Similar to T1D, sustained activation of the NF- κ B pathway is observed in T2D [169]. In addition, AGEs also increase plasma CRP and TNF α secretion from mononuclear cells in individuals with T2D [170]. RAGE is overexpressed in the airway epithelium and smooth muscle of patients with COPD [171]. The role of AGE and RAGE in T2D and COPD require further exploration, but represents mechanistic areas of interaction for both diseases. Recently, a meta-analysis suggested that lower soluble RAGE is a biomarker for the presence of emphysema and airflow obstruction [172].

5.5. Autonomic Dysregulation

Autonomic dysregulation may be attributed to genetic factors independent of glucose and insulin levels, impacting both COPD and T2D pathogenesis. The B2-adrenergic receptor gene (*ADRB2*) encodes a multifunctional protein important for smooth muscle relaxation in the lung [173] and insulin secretion from the pancreas [174]. Specific polymorphisms in *ADRB2* may lead to the co-occurrence of COPD and T2D. The R16G *ADRB2* polymorphism correlated with decreased FEV1 and COPD severity [175], and also correlated with insulin sensitivity in an obese postmenopausal cohort of women in another study [176]. Other polymorphisms of the *ADRB2*, including T164I, are also known to have systemic consequences, including poor cardiovascular health and outcomes [177], which could affect COPD and T2D pathogenesis. Thus, *ADRB2* may present a unique candidate for investigation of the mechanistic link between COPD and T2D co-occurrence in a subset of individuals (see Figure 2).

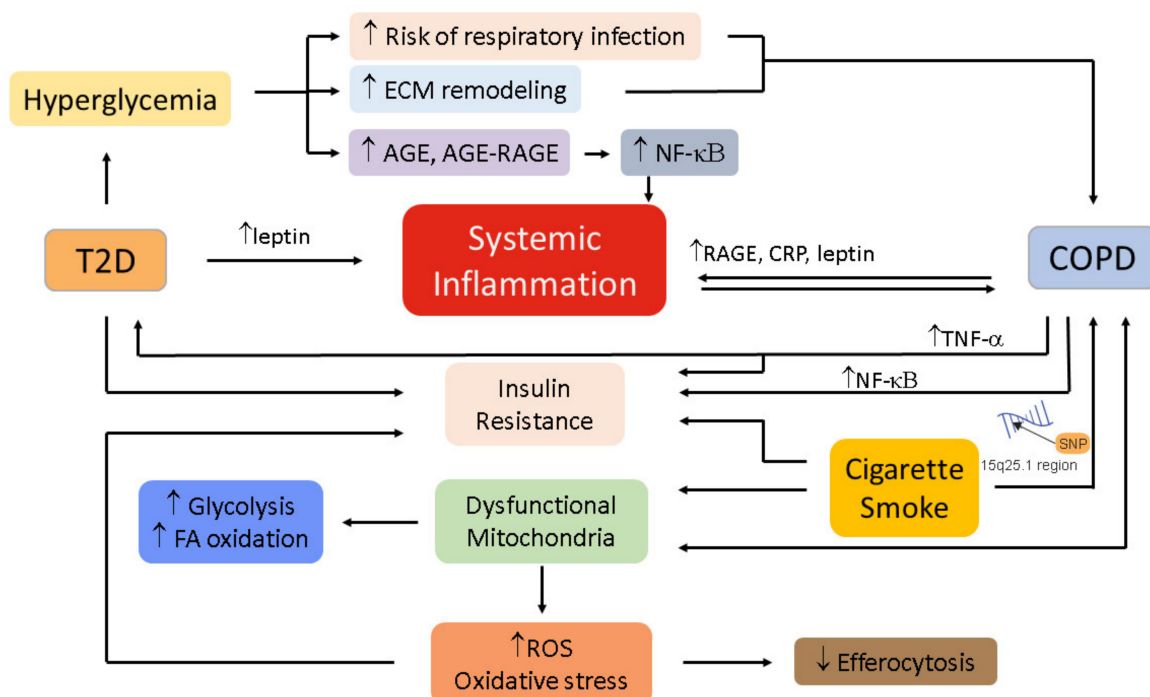


Figure 2. Possible mechanisms linking T2D to COPD.

6. Therapy

There are several potential therapeutic strategies common for COPD and diabetes treatment. Here, we briefly discuss these treatment options, such as metformin, corticosteroids, thiazolidinediones, and AAT augmentation therapy (see Table 1 for a summary).

Table 1. Summary of therapeutic strategies for COPD and diabetes.

Therapy	Mechanism of Action	Outcomes in Patients with T2D	Outcomes in Patients with COPD	Outcomes in Patients with COPD and T2D
Metformin	Inhibits proinflammatory NF-κB signaling in human vascular cells [178].	Reduces the formation of AGEs by improving glycemic control [179]. Reduces CV mortality, all-cause mortality, and CV events in T2D patients with CAD [180]. Changes the composition of gut microbiota, improves insulin resistance, and decrease tissue inflammation [181].	Reduces inflammation in the elastase-induced emphysema mouse model [179]. The reduction in lung infections modifies glucose flow across the lung tissue [182,183]. Improves survival rates in COPD patients with T2D [184]. Reduces loss of CO diffusing capacity [185].	Improves health, symptoms, hospitalizations, and mortality in patients with COPD and T2D [186]. Reduces the likelihood of T2D developing COPD [187] T2D with moderate to severe COPD with symptomatic improvement measured in SGRQ and TDI [188]. COPD patients with T2D are at higher risk of pneumonia, COPD exacerbation, and need for mechanical ventilation [189].
Inhaled corticosteroids	Lower the migration of inflammatory cells; reverse capillary permeability and lysosomal stabilization [190].	Dose-dependent elevation in serum glucose concentration [191] and increase in HbA1C [192].	Increased risk of new-onset T2D [193,194]. 34% increase in the rate of diabetes and increased rate of diabetes progression [195]. No increased risk of diabetes among current users [196].	
Thiazolidinediones	Increase insulin sensitivity by binding and activating PPARs, altering the transcription of glucose and lipid metabolism-related genes [197].	Increase glucose utilization in the tissues by increasing insulin sensitivity [198].	Associated with reduced risk of COPD exacerbations [199]	
AAT augmentation	Physiologic AAT inactivates proteolytic enzymes secreted during inflammation and has anti-apoptotic properties [200].	Safe and well-tolerated in stage 3 T1D [45]. Reduced HbA1c levels in adolescents with recently diagnosed T1D [47]. Children with AAT infusions showed fewer IL-1β producing monocytes and dendritic cells [45].	AAT augmentation slows the progression of emphysema [201].	

AGEs: Advanced glycation end products; SGRQ: St. George’s Respiratory Questionnaire; TDI: transitional dyspnea index.

6.1. Metformin

Metformin, a biguanide antidiabetic drug, is recommended as the first-line therapy for T2D [202] due to its efficacy, relative safety, and beneficial effects of reducing HbA1C levels and weight, in addition to its general tolerability and favorable cost [202]. Moreover, it reduces cardiovascular (CV) mortality, all-cause mortality, and CV events in T2D patients with coronary artery disease (CAD), but not in non-diabetic patients with CAD or with a history of myocardial infarction (MI) [180]. Interestingly, a recent retrospective study demonstrated that metformin treatment for 2 years improved survival rates in COPD patients with T2D [184]. Equally, Mendy et al. found a reduction in mortality of patients with chronic lower respiratory diseases treated with metformin [203]. Metformin was piloted as therapy for many conditions outside of diabetes, including treatment of severe COPD exacerbations [187]. Metformin inhibits proinflammatory NF- κ B signaling in human vascular wall cells [204], potentially dampening lung microvascular complications of T2D. Metformin improves glycemic control in T2D patients and therefore, reduces the formation of AGEs, but additionally, it is an effective scavenger of AGEs [205]. Another recent animal study suggested that activation of 5'-adenosine monophosphate-activated protein kinase (AMPK) by metformin could reduce abnormal inflammatory responses in mice with elastase-induced emphysema, as well as cellular senescence [179].

In COPD, changes to the aero-digestive microbiome are apparent and are associated with disease progression and exacerbations [206]. Metformin is known to change the composition of gut microbiota, induce improved insulin resistance, and decreased tissue inflammation [181]. Additionally, metformin reduces the frequency of lung infections, as demonstrated by the reduction in the glucose-induced growth of *Staphylococcus aureus* [207]. A study by Wishwanath et al. [182] highlighted the potential use of metformin to reduce the hyperglycemia-induced growth of *Pseudomonas aeruginosa*. Metformin was also found to enhance the macrophage bactericidal activity and improve survival in *Legionella pneumonia* [183]. Osteoporosis is more prevalent in patients with advanced COPD due to the direct effect of inhaled or oral corticosteroids. Metformin has anti-inflammatory properties and can decrease the prevalence of osteoporosis in patients with GOLD group D COPD [208].

Metformin may improve health status, symptoms, hospitalizations, and mortality in patients with COPD and T2D [188]. In an unmatched cohort study in Taiwan, T2D patients who had used metformin as an antidiabetic agent were less likely to develop COPD, with a hazard ratio (HR) of 0.56 (95% CI 0.537–0.584) [209]. In a prospective open-label trial of patients with moderate and severe COPD who also had T2D, the use of metformin showed improvement in symptoms and transitional dyspnea index scores compared to the baseline [186]. However, physiological outcomes, including PFTs and exhaled nitric oxide, were unchanged in this study [186]. Metformin was also studied regarding COPD exacerbations in patients without T2D, but failed to demonstrate any improvement in blood glucose control, nor effects on CRP or clinical outcomes in the non-diabetic population [187]. A recent study in Taiwan suggested that metformin use in patients with T2D and COPD was associated with higher risks of pneumonia, hospitalization for COPD, and invasive mechanical ventilation [189]. However, a recent observational study demonstrated that metformin use was associated with lesser emphysema progression over time in humans [185,210], possibly due to metformin protecting against smoke-induced lung, renal, and muscle injury, mitochondrial dysfunction, and ER stress in mice [210].

6.2. Additional Therapeutic Approaches

Inhaled corticosteroids are among the first line of treatments for COPD exacerbation, which leads to rapid loss of lung function and hospitalization. In patients with diabetes, inhaled corticosteroid use is associated with a dose-dependent elevation in serum glucose concentration [191] and an increase in HbA1c [192]. While systemic corticosteroid use is a known risk factor for the development of T2D, the risks harbored by inhaled corticosteroid use, which involves more localized administration, remain debatable. An increased risk of new-onset diabetes was reported in patients taking inhaled corticosteroids [193,194]. The

current use of inhaled corticosteroids in patients with pulmonary disease was associated with a 34% increase in the rate of diabetes and an increased rate of diabetes progression [195]. This risk was greatest with the highest inhaled corticosteroid doses, equivalent to fluticasone 1000 mg per day, or more. However, another study investigating the effect of inhaled corticosteroid treatment did not find an increased risk of diabetes among current users [196]. Another cross-sectional, single-center study was performed in adults with established COPD to determine the prevalence of dysglycemia in COPD patients. The study utilized the oral glucose tolerance test to detect dysglycemia in COPD patients and revealed a near doubling of dysglycemia. The incidence of newly diagnosed diabetes was 21.7% and prediabetes was 30.9% in patients admitted for COPD exacerbation [211].

Other oral hyperglycemic drugs, such as thiazolidines (TZDs), act on master transcriptional inflammation regulators, namely PPAR γ , and function as anti-inflammatory and anti-atherogenic agents [212]. PPAR γ agonists have shown promising results in the treatment of airway neutrophilia [213] and COPD [214], in addition to their management of diabetes. TZDs are associated with a reduced risk of COPD exacerbations [199]. The use of another anti-inflammatory diabetes therapy, PDE4 inhibitors, was also tested for the treatment of COPD exacerbation frequency [215].

6.3. Dietary Links and Lung Function

The pattern of dietary intake is an important factor in the pathogenesis and prevention of COPD and diabetes, especially since obesity is a risk factor and a comorbidity of both. Dietary factors could indirectly alter the impact of adverse environmental exposures or genetic predisposition in COPD and diabetes, and may also directly affect biological processes associated with lung function, disease development, inflammation, and outcomes. Studies using self-reported data on dietary intake are informally known to be significantly inaccurate, and the collected data may be associated with additional lifestyle choices that can impact the outcome of the study. Therefore, it is difficult to propose mechanistic links for the available data. Lower energy intake, with varying intake of macro and micro nutrients, are observed in COPD patients [216] in combination with obesity [217]. Several recent large population-based prospective studies showed an inverse and independent association between the long-term consumption of fruits and vegetables and the incidence of COPD [218,219]. Fiber intake is also observed as a risk factor for COPD [220]. Equally, dietary intakes of vitamin C, a hydrophilic antioxidant, was reported to be associated with FEV1 preservation [221]. Similarly, vitamin D supplementation trials to prevent COPD exacerbation suggest that it may only benefit patients with low baseline vitamin D levels [222]. In a recent randomized trial in COPD patients, supplementation with flavonoids (oligomeric pro-anthocyanidins extracted from grape seeds) improved oxidative stress and lipid profile, but not lung function [223]. A case-control study in Japanese adults observed a positive association between the intake of calcium, phosphorus, iron, potassium, and selenium with FEV1 measurements [224]. Polyunsaturated fatty acids of the omega-3 family, such as α -linolenic acid, eicosapentaenoic acid, and docosahexaenoic acid, may play an anti-inflammatory role in COPD and diabetes, but randomized controlled trials are needed to confirm any relationships between the intake of polyunsaturated fatty acids and COPD, with or without diabetes. A comprehensive review of the role of dietary metabolites and dietary treatment in pulmonary function in COPD is outlined in the cited review paper [225]. Several recent studies also suggest a role of extracellular cholesterol and impaired cholesterol efflux in pulmonary outcomes [226]. This topic will be an exciting area for further research in COPD, diabetes, and other comorbidities.

7. Conclusions

There appears to be mounting evidence of common signaling and genetic signature links between COPD, T1D, and T2D. Promisingly, treatments for these isolated conditions seem to have broad-acting effects that ameliorate COPD and diabetes symptoms and slow disease progression. Given the alarmingly increasing burden of COPD and diabetes world-

wide, identification of modifiable risk factors, intervention options, and novel therapeutic options are of interest.

Author Contributions: Conceptualization, S.S.P., J.L.P.P., B.P.G., C.W.A., C.M., and P.G.; writing—original draft preparation, S.S.P., J.L.P.P., B.P.G., C.W.A., R.R.O., H.A., C.M., and P.G.; writing—review and editing, S.S.P., J.L.P.P., B.P.G., C.W.A., R.R.O., H.A., I.G.-A., C.M., and P.G. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported by grants made available to P.G. (the Alpha-1 Foundation, 493373 and 614218).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Owen, N.; Healy, G.N.; Matthews, C.E.; Dunstan, D.W. Too much sitting: The population health science of sedentary behavior. *Exerc. Sport Sci. Rev.* **2010**, *38*, 105–113. [[CrossRef](#)] [[PubMed](#)]
2. Waschki, B.; Kirsten, A.M.; Holz, O.; Mueller, K.C.; Schaper, M.; Sack, A.L.; Meyer, T.; Rabe, K.F.; Magnussen, H.; Watz, H. Disease Progression and Changes in Physical Activity in Patients with Chronic Obstructive Pulmonary Disease. *Am. J. Respir. Crit. Care Med.* **2015**, *192*, 295–306. [[CrossRef](#)] [[PubMed](#)]
3. Lin, X.; Xu, Y.; Pan, X.; Xu, J.; Ding, Y.; Sun, X.; Song, X.; Ren, Y.; Shan, P.F. Global, regional, and national burden and trend of diabetes in 195 countries and territories: An analysis from 1990 to 2025. *Sci. Rep.* **2020**, *10*, 14790. [[CrossRef](#)] [[PubMed](#)]
4. Niranjana, V.; McBrayer, D.G.; Ramirez, L.C.; Raskin, P.; Hsia, C.C. Glycemic control and cardiopulmonary function in patients with insulin-dependent diabetes mellitus. *Am. J. Med.* **1997**, *103*, 504–513. [[CrossRef](#)]
5. Scano, G.; Filippelli, M.; Romagnoli, I.; Mancini, M.; Misuri, G.; Duranti, R.; Rosi, E. Hypoxic and hypercapnic breathlessness in patients with type I diabetes mellitus. *Chest* **2000**, *117*, 960–967. [[CrossRef](#)]
6. Cazzola, M.; Bettoncelli, G.; Sessa, E.; Cricelli, C.; Biscione, G. Prevalence of comorbidities in patients with chronic obstructive pulmonary disease. *Respiration* **2010**, *80*, 112–119. [[CrossRef](#)] [[PubMed](#)]
7. Ho, T.W.; Huang, C.T.; Ruan, S.Y.; Tsai, Y.J.; Lai, F.; Yu, C.J. Diabetes mellitus in patients with chronic obstructive pulmonary disease—The impact on mortality. *PLoS ONE* **2017**, *12*, e0175794. [[CrossRef](#)]
8. Rana, J.S.; Mittleman, M.A.; Sheikh, J.; Hu, F.B.; Manson, J.E.; Colditz, G.A.; Speizer, F.E.; Barr, R.G.; Camargo, C.A., Jr. Chronic obstructive pulmonary disease, asthma, and risk of type 2 diabetes in women. *Diabetes Care* **2004**, *27*, 2478–2484. [[CrossRef](#)] [[PubMed](#)]
9. Capes, S.E.; Hunt, D.; Malmberg, K.; Pathak, P.; Gerstein, H.C. Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: A systematic overview. *Stroke* **2001**, *32*, 2426–2432. [[CrossRef](#)]
10. Chakrabarti, B.; Angus, R.M.; Agarwal, S.; Lane, S.; Calverley, P.M. Hyperglycaemia as a predictor of outcome during non-invasive ventilation in decompensated COPD. *Thorax* **2009**, *64*, 857–862. [[CrossRef](#)]
11. Gudmundsson, G.; Ulrik, C.S.; Gislason, T.; Lindberg, E.; Brøndum, E.; Bakke, P.; Janson, C. Long-term survival in patients hospitalized for chronic obstructive pulmonary disease: A prospective observational study in the Nordic countries. *Int. J. Chron. Obstruct. Pulmon. Dis.* **2012**, *7*, 571–576. [[CrossRef](#)] [[PubMed](#)]
12. Miller, J.; Edwards, L.D.; Agustí, A.; Bakke, P.; Calverley, P.M.; Celli, B.; Coxson, H.O.; Crim, C.; Lomas, D.A.; Miller, B.E.; et al. Comorbidity, systemic inflammation and outcomes in the ECLIPSE cohort. *Respir. Med.* **2013**, *107*, 1376–1384. [[CrossRef](#)] [[PubMed](#)]
13. Sandler, M.; Bunn, A.E.; Stewart, R.I. Cross-section study of pulmonary function in patients with insulin-dependent diabetes mellitus. *Am. Rev. Respir. Dis.* **1987**, *135*, 223–229. [[CrossRef](#)]
14. Schuyler, M.R.; Niewoehner, D.E.; Inkley, S.R.; Kohn, R. Abnormal lung elasticity in juvenile diabetes mellitus. *Am. Rev. Respir. Dis.* **1976**, *113*, 37–41. [[CrossRef](#)] [[PubMed](#)]
15. Kuziemska, K.; Słomiński, W.; Jassem, E. Impact of diabetes mellitus on functional exercise capacity and pulmonary functions in patients with diabetes and healthy persons. *BMC Endocr. Disord.* **2019**, *19*, 2. [[CrossRef](#)] [[PubMed](#)]
16. Walter, R.E.; Beiser, A.; Givelber, R.J.; O'Connor, G.T.; Gottlieb, D.J. Association between glycemic state and lung function: The Framingham Heart Study. *Am. J. Respir. Crit. Care Med.* **2003**, *167*, 911–916. [[CrossRef](#)] [[PubMed](#)]
17. Yeh, H.C.; Punjabi, N.M.; Wang, N.Y.; Pankow, J.S.; Duncan, B.B.; Cox, C.E.; Selvin, E.; Brancati, F.L. Cross-sectional and prospective study of lung function in adults with type 2 diabetes: The Atherosclerosis Risk in Communities (ARIC) study. *Diabetes Care* **2008**, *31*, 741–746. [[CrossRef](#)]

18. Kinney, G.L.; Black-Shinn, J.L.; Wan, E.S.; Make, B.; Regan, E.; Lutz, S.; Soler, X.; Silverman, E.K.; Crapo, J.; Hokanson, J.E. Pulmonary function reduction in diabetes with and without chronic obstructive pulmonary disease. *Diabetes Care* **2014**, *37*, 389–395. [[CrossRef](#)]
19. Davis, W.A.; Knuiman, M.; Kendall, P.; Grange, V.; Davis, T.M. Glycemic exposure is associated with reduced pulmonary function in type 2 diabetes: The Fremantle Diabetes Study. *Diabetes Care* **2004**, *27*, 752–757. [[CrossRef](#)]
20. Gutiérrez-Carrasquilla, L.; Sánchez, E.; Barbé, F.; Dalmases, M.; López-Cano, C.; Hernández, M.; Rius, F.; Carmona, P.; Hernández, C.; Simó, R.; et al. Effect of Glucose Improvement on Spirometric Maneuvers in Patients With Type 2 Diabetes: The Sweet Breath Study. *Diabetes Care* **2019**, *42*, 617–624. [[CrossRef](#)]
21. Ahmadi-Abhari, S.; Kaptoge, S.; Luben, R.N.; Wareham, N.J.; Khaw, K.T. Longitudinal association of C-reactive protein and lung function over 13 years: The EPIC-Norfolk study. *Am. J. Epidemiol.* **2014**, *179*, 48–56. [[CrossRef](#)] [[PubMed](#)]
22. Hancox, R.J.; Poulton, R.; Greene, J.M.; Filsell, S.; McLachlan, C.R.; Rasmussen, F.; Taylor, D.R.; Williams, M.J.; Williamson, A.; Sears, M.R. Systemic inflammation and lung function in young adults. *Thorax* **2007**, *62*, 1064–1068. [[CrossRef](#)]
23. Antonelli Incalzi, R.; Fuso, L.; Giordano, A.; Pitocco, D.; Maiolo, C.; Calcagni, M.L.; Ghirlanda, G. Neuroadrenergic denervation of the lung in type I diabetes mellitus complicated by autonomic neuropathy. *Chest* **2002**, *121*, 443–451. [[CrossRef](#)]
24. Williams, J.G.; Morris, A.I.; Hayter, R.C.; Ogilvie, C.M. Respiratory responses of diabetics to hypoxia, hypercapnia, and exercise. *Thorax* **1984**, *39*, 529–534. [[CrossRef](#)]
25. Bernardi, L.; Bianchi, L. Integrated Cardio-Respiratory Control: Insight in Diabetes. *Curr. Diabetes Rep.* **2016**, *16*, 107. [[CrossRef](#)] [[PubMed](#)]
26. Chance, W.W.; Rhee, C.; Yilmaz, C.; Dane, D.M.; Pruneda, M.L.; Raskin, P.; Hsia, C.C. Diminished alveolar microvascular reserves in type 2 diabetes reflect systemic microangiopathy. *Diabetes Care* **2008**, *31*, 1596–1601. [[CrossRef](#)] [[PubMed](#)]
27. Kahnert, K.; Lucke, T.; Huber, R.M.; Behr, J.; Biertz, F.; Vogt, A.; Watz, H.; Alter, P.; Fahndrich, S.; Bals, R.; et al. Relationship of hyperlipidemia to comorbidities and lung function in COPD: Results of the COSYCONET cohort. *PLoS ONE* **2017**, *12*, e0177501. [[CrossRef](#)] [[PubMed](#)]
28. Alberti, K.G.; Eckel, R.H.; Grundy, S.M.; Zimmet, P.Z.; Cleeman, J.I.; Donato, K.A.; Fruchart, J.C.; James, W.P.; Loria, C.M.; Smith, S.C., Jr. 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* **2009**, *120*, 1640–1645. [[CrossRef](#)]
29. Lam, K.B.; Jordan, R.E.; Jiang, C.Q.; Thomas, G.N.; Miller, M.R.; Zhang, W.S.; Lam, T.H.; Cheng, K.K.; Adab, P. Airflow obstruction and metabolic syndrome: The Guangzhou Biobank Cohort Study. *Eur. Respir. J.* **2010**, *35*, 317–323. [[CrossRef](#)]
30. Watz, H.; Waschki, B.; Kirsten, A.; Müller, K.C.; Kretschmar, G.; Meyer, T.; Holz, O.; Magnussen, H. The metabolic syndrome in patients with chronic bronchitis and COPD: Frequency and associated consequences for systemic inflammation and physical inactivity. *Chest* **2009**, *136*, 1039–1046. [[CrossRef](#)]
31. Vujic, T.; Nagorni, O.; Maric, G.; Popovic, L.; Jankovic, J. Metabolic syndrome in patients with chronic obstructive pulmonary disease: Frequency and relationship with systemic inflammation. *Hippokratia* **2016**, *20*, 110–114. [[PubMed](#)]
32. Breyer, M.K.; Spruit, M.A.; Hanson, C.K.; Franssen, F.M.; Vanfleteren, L.E.; Groenen, M.T.; Bruijnzeel, P.L.; Wouters, E.F.; Rutten, E.P. Prevalence of metabolic syndrome in COPD patients and its consequences. *PLoS ONE* **2014**, *9*, e98013. [[CrossRef](#)] [[PubMed](#)]
33. Piazzolla, G.; Castrovilli, A.; Liotino, V.; Vulpi, M.R.; Fanelli, M.; Mazzocca, A.; Candigliota, M.; Berardi, E.; Resta, O.; Sabbà, C.; et al. Metabolic syndrome and Chronic Obstructive Pulmonary Disease (COPD): The interplay among smoking, insulin resistance and vitamin D. *PLoS ONE* **2017**, *12*, e0186708. [[CrossRef](#)]
34. Hildrum, B.; Mykletun, A.; Hole, T.; Midthjell, K.; Dahl, A.A. 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* **2007**, *7*, 220. [[CrossRef](#)]
35. Díez-Manglano, J.; Barquero-Romero, J.; Almagro, P.; Cabrera, F.J.; López García, F.; Montero, L.; Soriano, J.B. COPD patients with and without metabolic syndrome: Clinical and functional differences. *Intern. Emerg. Med.* **2014**, *9*, 419–425. [[CrossRef](#)]
36. Hersh, C.P.; Make, B.J.; Lynch, D.A.; Barr, R.G.; Bowler, R.P.; Calverley, P.M.; Castaldi, P.J.; Cho, M.H.; Coxson, H.O.; DeMeo, D.L.; et al. Non-emphysematous chronic obstructive pulmonary disease is associated with diabetes mellitus. *BMC Pulm. Med.* **2014**, *14*, 164. [[CrossRef](#)] [[PubMed](#)]
37. Han, M.K.; Kazerooni, E.A.; Lynch, D.A.; Liu, L.X.; Murray, S.; Curtis, J.L.; Criner, G.J.; Kim, V.; Bowler, R.P.; Hanania, N.A.; et al. Chronic obstructive pulmonary disease exacerbations in the COPD Gene study: Associated radiologic phenotypes. *Radiology* **2011**, *261*, 274–282. [[CrossRef](#)] [[PubMed](#)]
38. George, C.; Ducatman, A.M.; Conway, B.N. Increased risk of respiratory diseases in adults with Type 1 and Type 2 diabetes. *Diabetes Res. Clin. Pract.* **2018**, *142*, 46–55. [[CrossRef](#)] [[PubMed](#)]
39. Lim, S.Y.; Rhee, E.J.; Sung, K.C. Metabolic syndrome, insulin resistance and systemic inflammation as risk factors for reduced lung function in Korean nonsmoking males. *J. Korean Med. Sci.* **2010**, *25*, 1480–1486. [[CrossRef](#)] [[PubMed](#)]
40. Zhu, Z.; Wang, X.; Li, X.; Lin, Y.; Shen, S.; Liu, C.L.; Hobbs, B.D.; Hasegawa, K.; Liang, L.; International, C.G.C.; et al. Genetic overlap of chronic obstructive pulmonary disease and cardiovascular disease-related traits: A large-scale genome-wide cross-trait analysis. *Respir. Res.* **2019**, *20*, 64. [[CrossRef](#)]

41. Hobbs, B.D.; de Jong, K.; Lamontagne, M.; Bosse, Y.; Shrine, N.; Artigas, M.S.; Wain, L.V.; Hall, I.P.; Jackson, V.E.; Wyss, A.B.; et al. Genetic loci associated with chronic obstructive pulmonary disease overlap with loci for lung function and pulmonary fibrosis. *Nat. Genet.* **2017**, *49*, 426–432. [[CrossRef](#)] [[PubMed](#)]
42. Erlich, P.M.; Hoffman, S.N.; Rukstalis, M.; Han, J.J.; Chu, X.; Linda Kao, W.H.; Gerhard, G.S.; Stewart, W.F.; Boscarino, J.A. Nicotinic acetylcholine receptor genes on chromosome 15q25.1 are associated with nicotine and opioid dependence severity. *Hum. Genet.* **2010**, *128*, 491–499. [[CrossRef](#)] [[PubMed](#)]
43. Diabasana, Z.; Perotin, J.M.; Belgacemi, R.; Ancel, J.; Mulette, P.; Launois, C.; Delepine, G.; Dubernard, X.; Merol, J.C.; Ruaux, C.; et al. Chr15q25 Genetic Variant rs16969968 Alters Cell Differentiation in Respiratory Epithelia. *Int. J. Mol. Sci.* **2021**, *22*, 6657. [[CrossRef](#)] [[PubMed](#)]
44. Ligthart, S.; Steenaard, R.V.; Peters, M.J.; van Meurs, J.B.; Sijbrands, E.J.; Uitterlinden, A.G.; Bonder, M.J.; Consortium, B.; Hofman, A.; Franco, O.H.; et al. Tobacco smoking is associated with DNA methylation of diabetes susceptibility genes. *Diabetologia* **2016**, *59*, 998–1006. [[CrossRef](#)]
45. Gottlieb, P.A.; Alkanani, A.K.; Michels, A.W.; Lewis, E.C.; Shapiro, L.; Dinarello, C.A.; Zipris, D. alpha1-Antitrypsin therapy downregulates toll-like receptor-induced IL-1beta responses in monocytes and myeloid dendritic cells and may improve islet function in recently diagnosed patients with type 1 diabetes. *J. Clin. Endocrinol. Metab.* **2014**, *99*, E1418–E1426. [[CrossRef](#)]
46. Weir, G.C.; Ehlers, M.R.; Harris, K.M.; Kanaparthi, S.; Long, A.; Phippard, D.; Weiner, L.J.; Jepson, B.; McNamara, J.G.; Koulmanda, M.; et al. Alpha-1 antitrypsin treatment of new-onset type 1 diabetes: An open-label, phase I clinical trial (RETAIN) to assess safety and pharmacokinetics. *Pediatr Diabetes* **2018**, *19*, 945–954. [[CrossRef](#)]
47. Lebenthal, Y.; Brener, A.; Hershkovitz, E.; Shehadeh, N.; Shalitin, S.; Lewis, E.C.; Elias, D.; Haim, A.; Barash, G.; Loewenthal, N.; et al. A Phase II, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study Evaluating the Efficacy and Safety of Alpha-1 Antitrypsin (AAT) (Glassia((R))) in the Treatment of Recent-Onset Type 1 Diabetes. *Int. J. Mol. Sci.* **2019**, *20*, 6032. [[CrossRef](#)]
48. Lewis, E.C.; Shapiro, L.; Bowers, O.J.; Dinarello, C.A. Alpha1-antitrypsin monotherapy prolongs islet allograft survival in mice. *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 12153–12158. [[CrossRef](#)]
49. Kalis, M.; Kumar, R.; Janciauskiene, S.; Salehi, A.; Cilio, C.M. alpha 1-antitrypsin enhances insulin secretion and prevents cytokine-mediated apoptosis in pancreatic beta-cells. *Islets* **2010**, *2*, 185–189. [[CrossRef](#)]
50. Zhang, B.; Lu, Y.; Campbell-Thompson, M.; Spencer, T.; Wasserfall, C.; Atkinson, M.; Song, S. Alpha1-antitrypsin protects beta-cells from apoptosis. *Diabetes* **2007**, *56*, 1316–1323. [[CrossRef](#)]
51. Rachmiel, M.; Strauss, P.; Dror, N.; Benzaquen, H.; Horesh, O.; Tov, N.; Weintrob, N.; Landau, Z.; Ben-Ami, M.; Haim, A.; et al. Alpha-1 antitrypsin therapy is safe and well tolerated in children and adolescents with recent onset type 1 diabetes mellitus. *Pediatr Diabetes* **2016**, *17*, 351–359. [[CrossRef](#)] [[PubMed](#)]
52. Sandstrom, C.S.; Ohlsson, B.; Melander, O.; Westin, U.; Mahadeva, R.; Janciauskiene, S. An association between Type 2 diabetes and alpha-antitrypsin deficiency. *Diabet Med.* **2008**, *25*, 1370–1373. [[CrossRef](#)] [[PubMed](#)]
53. Brondani, L.A.; Soares, A.A.; Recamonde-Mendoza, M.; Dall’Agnol, A.; Camargo, J.L.; Monteiro, K.M.; Silveiro, S.P. Urinary peptidomics and bioinformatics for the detection of diabetic kidney disease. *Sci. Rep.* **2020**, *10*, 1242. [[CrossRef](#)]
54. Park, S.S.; Rodriguez Ortega, R.; Agudelo, C.W.; Perez Perez, J.; Perez Gandara, B.; Garcia-Arcos, I.; McCarthy, C.; Geraghty, P. Therapeutic Potential of Alpha-1 Antitrypsin in Type 1 and Type 2 Diabetes Mellitus. *Medicina* **2021**, *57*, 397. [[CrossRef](#)] [[PubMed](#)]
55. Di Petta, A.; Greco, K.V.; Castro, E.O.; Lopes, F.D.; Martins, M.A.; Capelozzi, V.L.; Moreira, L.F.; Sannomiya, P. Insulin modulates inflammatory and repair responses to elastase-induced emphysema in diabetic rats. *Int. J. Exp. Pathol.* **2011**, *92*, 392–399. [[CrossRef](#)] [[PubMed](#)]
56. Hunt, W.R.; Zughaier, S.M.; Guentert, D.E.; Shenep, M.A.; Koval, M.; McCarty, N.A.; Hansen, J.M. Hyperglycemia impedes lung bacterial clearance in a murine model of cystic fibrosis-related diabetes. *Am. J. Physiol. Lung Cell. Mol. Physiol.* **2014**, *306*, L43–L49. [[CrossRef](#)] [[PubMed](#)]
57. Forgiarini, L.A., Jr.; Kretzmann, N.A.; Porawski, M.; Dias, A.S.; Marroni, N.A. Experimental diabetes mellitus: Oxidative stress and changes in lung structure. *J. Bras. Pneumol.* **2009**, *35*, 788–791. [[CrossRef](#)] [[PubMed](#)]
58. Popov, D.; Simionescu, M. Alterations of lung structure in experimental diabetes, and diabetes associated with hyperlipidaemia in hamsters. *Eur. Respir. J.* **1997**, *10*, 1850–1858. [[CrossRef](#)]
59. Hu, Y.; Ma, Z.; Guo, Z.; Zhao, F.; Wang, Y.; Cai, L.; Yang, J. Type 1 diabetes mellitus is an independent risk factor for pulmonary fibrosis. *Cell Biochem. Biophys* **2014**, *70*, 1385–1391. [[CrossRef](#)]
60. Talakatta, G.; Sarikhani, M.; Muhamed, J.; Dhanya, K.; Somashekar, B.S.; Mahesh, P.A.; Sundaresan, N.; Ravindra, P.V. Diabetes induces fibrotic changes in the lung through the activation of TGF-beta signaling pathways. *Sci. Rep.* **2018**, *8*, 11920. [[CrossRef](#)]
61. Weynand, B.; Jonckheere, A.; Frans, A.; Rahier, J. Diabetes mellitus induces a thickening of the pulmonary basal lamina. *Respiration* **1999**, *66*, 14–19. [[CrossRef](#)] [[PubMed](#)]
62. Minette, P.; Buyschaert, M.; Rahier, J.; Veriter, C.; Frans, A. Pulmonary gas exchange in life-long nonsmoking patients with diabetes mellitus. *Respiration* **1999**, *66*, 20–24. [[CrossRef](#)] [[PubMed](#)]
63. Ofulue, A.F.; Kida, K.; Thurlbeck, W.M. Experimental diabetes and the lung. I. Changes in growth, morphometry, and biochemistry. *Am. Rev. Respir. Dis.* **1988**, *137*, 162–166. [[CrossRef](#)] [[PubMed](#)]
64. Glaser, S.; Kruger, S.; Merkel, M.; Bramlage, P.; Herth, F.J. Chronic obstructive pulmonary disease and diabetes mellitus: A systematic review of the literature. *Respiration* **2015**, *89*, 253–264. [[CrossRef](#)]

65. Kirkham, P.A.; Caramori, G.; Casolari, P.; Papi, A.A.; Edwards, M.; Shamji, B.; Triantaphyllopoulos, K.; Hussain, F.; Pinart, M.; Khan, Y.; et al. Oxidative stress-induced antibodies to carbonyl-modified protein correlate with severity of chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* **2011**, *184*, 796–802. [[CrossRef](#)]
66. Schaberg, T.; Klein, U.; Rau, M.; Eller, J.; Lode, H. Subpopulations of alveolar macrophages in smokers and nonsmokers: Relation to the expression of CD11/CD18 molecules and superoxide anion production. *Am. J. Respir. Crit. Care Med.* **1995**, *151*, 1551–1558. [[CrossRef](#)] [[PubMed](#)]
67. Paredi, P.; Kharitonov, S.A.; Leak, D.; Ward, S.; Cramer, D.; Barnes, P.J. Exhaled ethane, a marker of lipid peroxidation, is elevated in chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* **2000**, *162*, 369–373. [[CrossRef](#)] [[PubMed](#)]
68. Drost, E.M.; Skwarski, K.M.; Sauleda, J.; Soler, N.; Roca, J.; Agusti, A.; MacNee, W. Oxidative stress and airway inflammation in severe exacerbations of COPD. *Thorax* **2005**, *60*, 293–300. [[CrossRef](#)]
69. Richens, T.R.; Linderman, D.J.; Horstmann, S.A.; Lambert, C.; Xiao, Y.Q.; Keith, R.L.; Boe, D.M.; Morimoto, K.; Bowler, R.P.; Day, B.J.; et al. Cigarette smoke impairs clearance of apoptotic cells through oxidant-dependent activation of RhoA. *Am. J. Respir. Crit. Care Med.* **2009**, *179*, 1011–1021. [[CrossRef](#)]
70. VanderJagt, D.J.; Harrison, J.M.; Ratliff, D.M.; Hunsaker, L.A.; Vander Jagt, D.L. Oxidative stress indices in IDDM subjects with and without long-term diabetic complications. *Clin. Biochem.* **2001**, *34*, 265–270. [[CrossRef](#)]
71. Tang, W.H.W.; McGee, P.; Lachin, J.M.; Li, D.Y.; Hoogwerf, B.; Hazen, S.L.; Grp, D.E.R. Oxidative Stress and Cardiovascular Risk in Type 1 Diabetes Mellitus: Insights From the DCCT/EDIC Study. *J. Am. Heart Assoc.* **2018**, *7*, e008368. [[CrossRef](#)]
72. Beyersdorf, N.; Muller, N. Sphingomyelin breakdown in T cells: Role in activation, effector functions and immunoregulation. *Biol. Chem.* **2015**, *396*, 749–758. [[CrossRef](#)] [[PubMed](#)]
73. Bowler, R.P.; Jacobson, S.; Cruickshank, C.; Hughes, G.J.; Siska, C.; Ory, D.S.; Petrache, I.; Schaffer, J.E.; Reisdorph, N.; Kechris, K. Plasma sphingolipids associated with chronic obstructive pulmonary disease phenotypes. *Am. J. Respir. Crit. Care Med.* **2015**, *191*, 275–284. [[CrossRef](#)] [[PubMed](#)]
74. Telenga, E.D.; Hoffmann, R.F.; Ruben, T.K.; Hoonhorst, S.J.; Willemse, B.W.; van Oosterhout, A.J.; Heijink, I.H.; van den Berge, M.; Jorge, L.; Sandra, P.; et al. Untargeted lipidomic analysis in chronic obstructive pulmonary disease. Uncovering sphingolipids. *Am. J. Respir. Crit. Care Med.* **2014**, *190*, 155–164. [[CrossRef](#)]
75. Petrache, I.; Natarajan, V.; Zhen, L.; Medler, T.R.; Richter, A.T.; Cho, C.; Hubbard, W.C.; Berdyshev, E.V.; Tudor, R.M. Ceramide upregulation causes pulmonary cell apoptosis and emphysema-like disease in mice. *Nat. Med.* **2005**, *11*, 491–498. [[CrossRef](#)]
76. Agudelo, C.W.; Kumley, B.K.; Area-Gomez, E.; Xu, Y.; Dabo, A.J.; Geraghty, P.; Campos, M.; Foronjy, R.; Garcia-Arcos, I. Decreased surfactant lipids correlate with lung function in chronic obstructive pulmonary disease (COPD). *PLoS ONE* **2020**, *15*, e0228279. [[CrossRef](#)] [[PubMed](#)]
77. Fang, W.; Li, C.; Wu, Q.; Yao, Z.; Wu, J.; Huang, P.; Wang, D.; Li, Z. Metabolic profiling of chronic obstructive pulmonary disease model rats and the interventional effects of HuaTanJiangQi decoction using UHPLC-Q-TOF/MS(E). *J. Pharm. Biomed. Anal.* **2020**, *180*, 113078. [[CrossRef](#)]
78. Rice, K.L.; Duane, P.G.; Niewoehner, D.E. Lysophosphatidylcholine augments elastase-induced alveolar epithelial permeability and emphysema in the hamster. *Am. Rev. Respir. Dis.* **1987**, *136*, 941–946. [[CrossRef](#)]
79. Van Belle, T.L.; Coppieters, K.T.; von Herrath, M.G. Type 1 diabetes: Etiology, immunology, and therapeutic strategies. *Physiol. Rev.* **2011**, *91*, 79–118. [[CrossRef](#)] [[PubMed](#)]
80. Agudelo, C.W.; Samaha, G.; Garcia-Arcos, I. Alveolar lipids in pulmonary disease. A review. *Lipids Health Dis.* **2020**, *19*, 122. [[CrossRef](#)]
81. Zipris, D. Epidemiology of type 1 diabetes and what animal models teach us about the role of viruses in disease mechanisms. *Clin. Immunol.* **2009**, *131*, 11–23. [[CrossRef](#)] [[PubMed](#)]
82. Rewers, M.; Zimmet, P. The rising tide of childhood type 1 diabetes—What is the elusive environmental trigger? *Lancet* **2004**, *364*, 1645–1647. [[CrossRef](#)]
83. Bezemer, G.F.; Sagar, S.; van Bergenhenegouwen, J.; Georgiou, N.A.; Garssen, J.; Kraneveld, A.D.; Folkerts, G. Dual role of Toll-like receptors in asthma and chronic obstructive pulmonary disease. *Pharmacol. Rev.* **2012**, *64*, 337–358. [[CrossRef](#)] [[PubMed](#)]
84. Foronjy, R.F.; Dabo, A.J.; Taggart, C.C.; Weldon, S.; Geraghty, P. Respiratory syncytial virus infections enhance cigarette smoke induced COPD in mice. *PLoS ONE* **2014**, *9*, e90567. [[CrossRef](#)] [[PubMed](#)]
85. Devaraj, S.; Jialal, I.; Yun, J.M.; Bremer, A. Demonstration of increased toll-like receptor 2 and toll-like receptor 4 expression in monocytes of type 1 diabetes mellitus patients with microvascular complications. *Metabolism* **2011**, *60*, 256–259. [[CrossRef](#)] [[PubMed](#)]
86. Devaraj, S.; Dasu, M.R.; Park, S.H.; Jialal, I. Increased levels of ligands of Toll-like receptors 2 and 4 in type 1 diabetes. *Diabetologia* **2009**, *52*, 1665–1668. [[CrossRef](#)]
87. Devaraj, S.; Dasu, M.R.; Rockwood, J.; Winter, W.; Griffen, S.C.; Jialal, I. Increased toll-like receptor (TLR) 2 and TLR4 expression in monocytes from patients with type 1 diabetes: Further evidence of a proinflammatory state. *J. Clin. Endocrinol. Metab.* **2008**, *93*, 578–583. [[CrossRef](#)] [[PubMed](#)]
88. Dandona, P.; Ghanim, H.; Green, K.; Sia, C.L.; Abuaysheh, S.; Kuhadiya, N.; Batra, M.; Dhindsa, S.; Chaudhuri, A. Insulin infusion suppresses while glucose infusion induces Toll-like receptors and high-mobility group-B1 protein expression in mononuclear cells of type 1 diabetes patients. *Am. J. Physiol. Endocrinol. Metab.* **2013**, *304*, E810–E818. [[CrossRef](#)]

89. Lea, S.R.; Reynolds, S.L.; Kaur, M.; Simpson, K.D.; Hall, S.R.; Hessel, E.M.; Singh, D. The effects of repeated Toll-like receptors 2 and 4 stimulation in COPD alveolar macrophages. *Int. J. Chron. Obstruct. Pulmon. Dis.* **2018**, *13*, 771–780. [[CrossRef](#)]
90. Haw, T.J.; Starkey, M.R.; Pavlidis, S.; Fricker, M.; Arthurs, A.L.; Nair, P.M.; Liu, G.; Hanish, I.; Kim, R.Y.; Foster, P.S.; et al. Toll-like receptor 2 and 4 have opposing roles in the pathogenesis of cigarette smoke-induced chronic obstructive pulmonary disease. *Am. J. Physiol. Lung Cell. Mol. Physiol.* **2018**, *314*, L298–L317. [[CrossRef](#)]
91. Zipris, D.; Lien, E.; Xie, J.X.; Greiner, D.L.; Mordes, J.P.; Rossini, A.A. TLR activation synergizes with Kilham rat virus infection to induce diabetes in BBDR rats. *J. Immunol.* **2005**, *174*, 131–142. [[CrossRef](#)] [[PubMed](#)]
92. Zhao, Y.; Krishnamurthy, B.; Mollah, Z.U.; Kay, T.W.; Thomas, H.E. NF-kappaB in type 1 diabetes. *Inflamm. Allergy Drug Targets* **2011**, *10*, 208–217. [[CrossRef](#)] [[PubMed](#)]
93. Bednar, K.J.; Tsukamoto, H.; Kachapati, K.; Ohta, S.; Wu, Y.; Katz, J.D.; Ascherman, D.P.; Ridgway, W.M. Reversal of New-Onset Type 1 Diabetes With an Agonistic TLR4/MD-2 Monoclonal Antibody. *Diabetes* **2015**, *64*, 3614–3626. [[CrossRef](#)] [[PubMed](#)]
94. Pons, J.; Sauleda, J.; Regueiro, V.; Santos, C.; Lopez, M.; Ferrer, J.; Agusti, A.G.; Bengoechea, J.A. Expression of Toll-like receptor 2 is up-regulated in monocytes from patients with chronic obstructive pulmonary disease. *Respir. Res.* **2006**, *7*, 64. [[CrossRef](#)]
95. Kent, B.D.; Mitchell, P.D.; McNicholas, W.T. Hypoxemia in patients with COPD: Cause, effects, and disease progression. *Int. J. Chron. Obstruct. Pulmon. Dis.* **2011**, *6*, 199–208. [[CrossRef](#)]
96. Devaraj, S.; Cheung, A.T.; Jialal, I.; Griffen, S.C.; Nguyen, D.; Glaser, N.; Aoki, T. Evidence of increased inflammation and microcirculatory abnormalities in patients with type 1 diabetes and their role in microvascular complications. *Diabetes* **2007**, *56*, 2790–2796. [[CrossRef](#)]
97. Gan, W.Q.; Man, S.F.; Senthilselvan, A.; Sin, D.D. Association between chronic obstructive pulmonary disease and systemic inflammation: A systematic review and a meta-analysis. *Thorax* **2004**, *59*, 574–580. [[CrossRef](#)] [[PubMed](#)]
98. Scaramuzza, A.E.; Morelli, M.; Rizzi, M.; Borgonovo, S.; De Palma, A.; Mameli, C.; Giani, E.; Beretta, S.; Zuccotti, G.V. Impaired diffusing capacity for carbon monoxide in children with type 1 diabetes: Is this the first sign of long-term complications? *Acta Diabetol.* **2012**, *49*, 159–164. [[CrossRef](#)] [[PubMed](#)]
99. Strojek, K.; Ziara, D.; Sroczynski, J.W.; Oklek, K. Pulmonary complications of type 1 (insulin-dependent) diabetic patients. *Diabetologia* **1992**, *35*, 1173–1176. [[CrossRef](#)] [[PubMed](#)]
100. Schunemann, H.J.; Dorn, J.; Grant, B.J.; Winkelstein, W., Jr.; Trevisan, M. Pulmonary function is a long-term predictor of mortality in the general population: 29-year follow-up of the Buffalo Health Study. *Chest* **2000**, *118*, 656–664. [[CrossRef](#)] [[PubMed](#)]
101. Wedzicha, J.A.; Seemungal, T.A.; MacCallum, P.K.; Paul, E.A.; Donaldson, G.C.; Bhowmik, A.; Jeffries, D.J.; Meade, T.W. Acute exacerbations of chronic obstructive pulmonary disease are accompanied by elevations of plasma fibrinogen and serum IL-6 levels. *Thromb. Haemost.* **2000**, *84*, 210–215. [[PubMed](#)]
102. Floyel, T.; Brorsson, C.; Nielsen, L.B.; Miani, M.; Bang-Berthelsen, C.H.; Friedrichsen, M.; Overgaard, A.J.; Berchtold, L.A.; Wiberg, A.; Poulsen, P.; et al. CTSH regulates beta-cell function and disease progression in newly diagnosed type 1 diabetes patients. *Proc. Natl. Acad. Sci. USA* **2014**, *111*, 10305–10310. [[CrossRef](#)] [[PubMed](#)]
103. Perotin, J.M.; Adam, D.; Vella-Boucaud, J.; Delepine, G.; Sandu, S.; Jonvel, A.C.; Prevost, A.; Berthiot, G.; Pison, C.; Lebagry, F.; et al. Delay of airway epithelial wound repair in COPD is associated with airflow obstruction severity. *Respir. Res.* **2014**, *15*, 151. [[CrossRef](#)] [[PubMed](#)]
104. Takizawa, H.; Tanaka, M.; Takami, K.; Ohtoshi, T.; Ito, K.; Satoh, M.; Okada, Y.; Yamasawa, F.; Nakahara, K.; Umeda, A. Increased expression of transforming growth factor-beta1 in small airway epithelium from tobacco smokers and patients with chronic obstructive pulmonary disease (COPD). *Am. J. Respir. Crit. Care Med.* **2001**, *163*, 1476–1483. [[CrossRef](#)] [[PubMed](#)]
105. Zhou, F.; Onizawa, S.; Nagai, A.; Aoshiba, K. Epithelial cell senescence impairs repair process and exacerbates inflammation after airway injury. *Respir. Res.* **2011**, *12*, 78. [[CrossRef](#)]
106. Togo, S.; Holz, O.; Liu, X.; Sugiura, H.; Kamio, K.; Wang, X.; Kawasaki, S.; Ahn, Y.; Fredriksson, K.; Skold, C.M.; et al. Lung fibroblast repair functions in patients with chronic obstructive pulmonary disease are altered by multiple mechanisms. *Am. J. Respir. Crit. Care Med.* **2008**, *178*, 248–260. [[CrossRef](#)]
107. Van Winkle, L.S.; Brown, C.D.; Shimizu, J.A.; Gunderson, A.D.; Evans, M.J.; Plopper, C.G. Impaired recovery from naphthalene-induced bronchiolar epithelial injury in mice exposed to aged and diluted sidestream cigarette smoke. *Toxicol. Lett.* **2004**, *154*, 1–9. [[CrossRef](#)]
108. Ganesan, S.; Sajjan, U.S. Repair and Remodeling of airway epithelium after injury in Chronic Obstructive Pulmonary Disease. *Curr. Respir. Care Rep.* **2013**, *2*, 145–154. [[CrossRef](#)]
109. Black, E.; Vibe-Petersen, J.; Jorgensen, L.N.; Madsen, S.M.; Agren, M.S.; Holstein, P.E.; Perrild, H.; Gottrup, F. Decrease of collagen deposition in wound repair in type 1 diabetes independent of glycemic control. *Arch. Surg.* **2003**, *138*, 34–40. [[CrossRef](#)]
110. Schaffer, M.R.; Tantry, U.; Efron, P.A.; Ahrendt, G.M.; Thornton, F.J.; Barbul, A. Diabetes-impaired healing and reduced wound nitric oxide synthesis: A possible pathophysiologic correlation. *Surgery* **1997**, *121*, 513–519. [[CrossRef](#)]
111. Hehenberger, K.; Kratz, G.; Hansson, A.; Brismar, K. Fibroblasts derived from human chronic diabetic wounds have a decreased proliferation rate, which is recovered by the addition of heparin. *J. Dermatol. Sci.* **1998**, *16*, 144–151. [[CrossRef](#)]
112. Bitar, M.S.; Farook, T.; Wahid, S.; Francis, I.M. Glucocorticoid-dependent impairment of wound healing in experimental diabetes: Amelioration by adrenalectomy and RU 486. *J. Surg. Res.* **1999**, *82*, 234–243. [[CrossRef](#)]
113. Goodson, W.H., 3rd; Hung, T.K. Studies of wound healing in experimental diabetes mellitus. *J. Surg. Res.* **1977**, *22*, 221–227. [[CrossRef](#)]

114. Bitar, M.S.; Labbad, Z.N. Transforming growth factor-beta and insulin-like growth factor-I in relation to diabetes-induced impairment of wound healing. *J. Surg. Res.* **1996**, *61*, 113–119. [[CrossRef](#)] [[PubMed](#)]
115. Fahey, T.J., 3rd; Sadaty, A.; Jones, W.G., 2nd; Barber, A.; Smoller, B.; Shires, G.T. Diabetes impairs the late inflammatory response to wound healing. *J. Surg. Res.* **1991**, *50*, 308–313. [[CrossRef](#)]
116. Cianfarani, F.; Toietta, G.; Di Rocco, G.; Cesareo, E.; Zambruno, G.; Odorisio, T. Diabetes impairs adipose tissue-derived stem cell function and efficiency in promoting wound healing. *Wound Repair Regen.* **2013**, *21*, 545–553. [[CrossRef](#)]
117. Morishige, W.K.; Uetake, C.A.; Greenwood, F.C.; Akaka, J. Pulmonary insulin responsiveness: In vivo effects of insulin on the diabetic rat lung and specific insulin binding to lung receptors in normal rats. *Endocrinology* **1977**, *100*, 1710–1722. [[CrossRef](#)]
118. Moxley, M.A.; Longmore, W.J. Studies on the effects of alloxan and streptozotocin induced diabetes on lipid metabolism in the isolated perfused rat lung. *Life Sci.* **1975**, *17*, 921–925. [[CrossRef](#)]
119. Sugahara, K.; Ushijima, K.; Morioka, T.; Usuku, G. Studies of the lung in diabetes mellitus. I. Ultrastructural studies of the lungs in alloxan-induced diabetic rats. *Virchows. Arch. A Pathol. Anat. Histol.* **1981**, *390*, 313–324. [[CrossRef](#)]
120. De Prost, N.; Saumon, G. Glucose transport in the lung and its role in liquid movement. *Respir. Physiol. Neurobiol.* **2007**, *159*, 331–337. [[CrossRef](#)]
121. Dieterle, C.D.; Schmauss, S.; Arbogast, H.; Domsch, C.; Huber, R.M.; Landgraf, R. Pulmonary function in patients with type 1 diabetes before and after simultaneous pancreas and kidney transplantation. *Transplantation* **2007**, *83*, 566–569. [[CrossRef](#)]
122. Lee, W.H.; Wu, D.W.; Chen, Y.C.; Liu, Y.H.; Liao, W.S.; Chen, S.C.; Hung, C.H.; Kuo, C.H.; Su, H.M. Association of Pulmonary Function Decline over Time with Longitudinal Change of Glycated Hemoglobin in Participants without Diabetes Mellitus. *J. Pers. Med.* **2021**, *11*, 994. [[CrossRef](#)] [[PubMed](#)]
123. Ducharme-Smith, K.; Mora-Garcia, G.; de Castro Mendes, F.; Ruiz-Diaz, M.S.; Moreira, A.; Villegas, R.; Garcia-Larsen, V. Lung function, COPD and Alternative Healthy Eating Index in US adults. *ERJ Open Res.* **2021**, *7*, 927–2020. [[CrossRef](#)] [[PubMed](#)]
124. Rains, J.L.; Jain, S.K. Oxidative stress, insulin signaling, and diabetes. *Free Radic. Biol. Med.* **2011**, *50*, 567–575. [[CrossRef](#)] [[PubMed](#)]
125. Evans, J.L.; Goldfine, I.D.; Maddux, B.A.; Grodsky, G.M. Are oxidative stress-activated signaling pathways mediators of insulin resistance and beta-cell dysfunction? *Diabetes* **2003**, *52*, 1–8. [[CrossRef](#)]
126. Tong, X.; Chaudhry, Z.; Lee, C.C.; Bone, R.N.; Kanojia, S.; Maddatu, J.; Sohn, P.; Weaver, S.A.; Robertson, M.A.; Petrache, I.; et al. Cigarette smoke exposure impairs beta-cell function through activation of oxidative stress and ceramide accumulation. *Mol. Metab.* **2020**, *37*, 100975. [[CrossRef](#)]
127. Van den Borst, B.; Gosker, H.R.; Koster, A.; Yu, B.; Kritchevsky, S.B.; Liu, Y.; Meibohm, B.; Rice, T.B.; Shlipak, M.; Yende, S.; et al. The influence of abdominal visceral fat on inflammatory pathways and mortality risk in obstructive lung disease. *Am. J. Clin. Nutr.* **2012**, *96*, 516–526. [[CrossRef](#)]
128. Vozoris, N.T.; O'Donnell, D.E. Prevalence, risk factors, activity limitation and health care utilization of an obese, population-based sample with chronic obstructive pulmonary disease. *Can. Respir. J.* **2012**, *19*, 732618. [[CrossRef](#)] [[PubMed](#)]
129. Van den Borst, B.; Gosker, H.R.; Wesseling, G.; de Jager, W.; Hellwig, V.A.; Snelvangers, F.J.; Schols, A.M. Low-grade adipose tissue inflammation in patients with mild-to-moderate chronic obstructive pulmonary disease. *Am. J. Clin. Nutr.* **2011**, *94*, 1504–1512. [[CrossRef](#)] [[PubMed](#)]
130. Yoon, H.I.; Li, Y.; Man, S.F.P.; Tashkin, D.; Wise, R.A.; Connett, J.E.; Anthonisen, N.A.; Churg, A.; Wright, J.L.; Sin, D.D. The complex relationship of serum adiponectin to COPD outcomes COPD and adiponectin. *Chest* **2012**, *142*, 893–899. [[CrossRef](#)]
131. Zhu, Z.; Guo, Y.; Shi, H.; Liu, C.L.; Panganiban, R.A.; Chung, W.; O'Connor, L.J.; Himes, B.E.; Gazal, S.; Hasegawa, K.; et al. Shared genetic and experimental links between obesity-related traits and asthma subtypes in UK Biobank. *J. Allergy Clin. Immunol.* **2020**, *145*, 537–549. [[CrossRef](#)] [[PubMed](#)]
132. Zhu, Z.; Li, J.; Si, J.; Ma, B.; Shi, H.; Lv, J.; Cao, W.; Guo, Y.; Millwood, I.Y.; Walters, R.G.; et al. A large-scale genome-wide association analysis of lung function in the Chinese population identifies novel loci and highlights shared genetic aetiology with obesity. *Eur. Respir. J.* **2021**, *58*, 2100199. [[CrossRef](#)] [[PubMed](#)]
133. Berbudi, A.; Rahmadika, N.; Tjahjadi, A.I.; Ruslami, R. Type 2 Diabetes and its Impact on the Immune System. *Curr. Diabetes Rev.* **2020**, *16*, 442–449. [[CrossRef](#)] [[PubMed](#)]
134. American Diabetes, A. 1. Strategies for Improving Care. *Diabetes Care* **2016**, *39* (Suppl. S1), S6–S12. [[CrossRef](#)] [[PubMed](#)]
135. Dandona, P.; Mohanty, P.; Chaudhuri, A.; Garg, R.; Aljada, A. Insulin infusion in acute illness. *J. Clin. Investig.* **2005**, *115*, 2069–2072. [[CrossRef](#)]
136. Tessaro, F.H.G.; Ayala, T.S.; Nolasco, E.L.; Bella, L.M.; Martins, J.O. Insulin Influences LPS-Induced TNF-alpha and IL-6 Release Through Distinct Pathways in Mouse Macrophages from Different Compartments. *Cell Physiol. Biochem.* **2017**, *42*, 2093–2104. [[CrossRef](#)]
137. Rogliani, P.; Calzetta, L.; Capuani, B.; Facciolo, F.; Cazzola, M.; Lauro, D.; Matera, M.G. Glucagon-Like Peptide 1 Receptor: A Novel Pharmacological Target for Treating Human Bronchial Hyperresponsiveness. *Am. J. Respir. Cell. Mol. Biol.* **2016**, *55*, 804–814. [[CrossRef](#)]
138. Nguyen, D.V.; Linderholm, A.; Haczku, A.; Kenyon, N. Glucagon-like peptide 1: A potential anti-inflammatory pathway in obesity-related asthma. *Pharm. Ther.* **2017**, *180*, 139–143. [[CrossRef](#)]
139. Yang, W.; Ni, H.; Wang, H.; Gu, H. NLRP3 inflammasome is essential for the development of chronic obstructive pulmonary disease. *Int. J. Clin. Exp. Pathol.* **2015**, *8*, 13209–13216. [[PubMed](#)]

140. Nachmias, N.; Langier, S.; Brzezinski, R.Y.; Siterman, M.; Stark, M.; Etkin, S.; Avriel, A.; Schwarz, Y.; Shenhar-Tsarfaty, S.; Bar-Shai, A. NLRP3 inflammasome activity is upregulated in an in-vitro model of COPD exacerbation. *PLoS ONE* **2019**, *14*, e0214622. [[CrossRef](#)] [[PubMed](#)]
141. Vandanmagsar, B.; Youm, Y.H.; Ravussin, A.; Galgani, J.E.; Stadler, K.; Mynatt, R.L.; Ravussin, E.; Stephens, J.M.; Dixit, V.D. The NLRP3 inflammasome instigates obesity-induced inflammation and insulin resistance. *Nat. Med.* **2011**, *17*, 179–188. [[CrossRef](#)] [[PubMed](#)]
142. Cyphert, T.J.; Morris, R.T.; House, L.M.; Barnes, T.M.; Otero, Y.F.; Barham, W.J.; Hunt, R.P.; Zaynagetdinov, R.; Yull, F.E.; Blackwell, T.S.; et al. NF-kappaB-dependent airway inflammation triggers systemic insulin resistance. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **2015**, *309*, R1144–R1152. [[CrossRef](#)] [[PubMed](#)]
143. Clerk, L.H.; Vincent, M.A.; Jahn, L.A.; Liu, Z.; Lindner, J.R.; Barrett, E.J. Obesity blunts insulin-mediated microvascular recruitment in human forearm muscle. *Diabetes* **2006**, *55*, 1436–1442. [[CrossRef](#)] [[PubMed](#)]
144. Targher, G.; Alberiche, M.; Zenere, M.B.; Bonadonna, R.C.; Muggeo, M.; Bonora, E. Cigarette smoking and insulin resistance in patients with noninsulin-dependent diabetes mellitus. *J. Clin. Endocrinol. Metab.* **1997**, *82*, 3619–3624. [[CrossRef](#)]
145. Widen, E.; Ekstrand, A.; Saloranta, C.; Franssila-Kallunki, A.; Eriksson, J.; Schalin-Jantti, C.; Groop, L. Insulin resistance in type 2 (non-insulin-dependent) diabetic patients with hypertriglyceridaemia. *Diabetologia* **1992**, *35*, 1140–1145. [[CrossRef](#)]
146. Yazdani, R.; Gholamrezapour, M.; Hassanaghahi, T. Adiponectin Level in Serum and BAL Sample of Patients with Chronic Obstructive Pulmonary Disease. *Tanaffos* **2013**, *12*, 53–57.
147. Sato, K.; Shibata, Y.; Abe, S.; Inoue, S.; Igarashi, A.; Yamauchi, K.; Aida, Y.; Nunomiya, K.; Nakano, H.; Sato, M.; et al. Association between plasma adiponectin levels and decline in forced expiratory volume in 1 s in a general Japanese population: The Takahata study. *Int. J. Med. Sci.* **2014**, *11*, 758–764. [[CrossRef](#)]
148. Kawamoto, R.; Tabara, Y.; Kohara, K.; Miki, T.; Ohtsuka, N.; Kusunoki, T.; Abe, M. Smoking status is associated with serum high molecular adiponectin levels in community-dwelling Japanese men. *J. Atheroscler. Thromb.* **2010**, *17*, 423–430. [[CrossRef](#)]
149. Hodge, A.M.; Westerman, R.A.; de Courten, M.P.; Collier, G.R.; Zimmet, P.Z.; Alberti, K.G. Is leptin sensitivity the link between smoking cessation and weight gain? *Int. J. Obes. Relat. Metab. Disord.* **1997**, *21*, 50–53. [[CrossRef](#)]
150. Wei, M.; Stern, M.P.; Haffner, S.M. Serum leptin levels in Mexican Americans and non-Hispanic whites: Association with body mass index and cigarette smoking. *Ann. Epidemiol.* **1997**, *7*, 81–86. [[CrossRef](#)]
151. Eliasson, B.; Smith, U. Leptin levels in smokers and long-term users of nicotine gum. *Eur. J. Clin. Investig.* **1999**, *29*, 145–152. [[CrossRef](#)] [[PubMed](#)]
152. Wellen, K.E.; Hotamisligil, G.S. Inflammation, stress, and diabetes. *J. Clin. Investig.* **2005**, *115*, 1111–1119. [[CrossRef](#)] [[PubMed](#)]
153. Agarwal, A.R.; Kadam, S.; Brahme, A.; Agrawal, M.; Apte, K.; Narke, G.; Kekani, K.; Madas, S.; Salvi, S. Systemic Immunometabolic alterations in chronic obstructive pulmonary disease (COPD). *Respir. Res.* **2019**, *20*, 171. [[CrossRef](#)] [[PubMed](#)]
154. Czajka, A.; Ajaz, S.; Gnudi, L.; Parsade, C.K.; Jones, P.; Reid, F.; Malik, A.N. Altered Mitochondrial Function, Mitochondrial DNA and Reduced Metabolic Flexibility in Patients With Diabetic Nephropathy. *EBioMedicine* **2015**, *2*, 499–512. [[CrossRef](#)]
155. O’Beirne, S.L.; Kikkers, S.A.; Oromendia, C.; Salit, J.; Rostmai, M.R.; Ballman, K.V.; Kaner, R.J.; Crystal, R.G.; Cloonan, S.M. Alveolar Macrophage Immunometabolism and Lung Function Impairment in Smoking and Chronic Obstructive Pulmonary Disease. *Am. J. Respir. Crit. Care Med.* **2020**, *201*, 735–739. [[CrossRef](#)]
156. Taylor, A.E.; Finney-Hayward, T.K.; Quint, J.K.; Thomas, C.M.; Tudhope, S.J.; Wedzicha, J.A.; Barnes, P.J.; Donnelly, L.E. Defective macrophage phagocytosis of bacteria in COPD. *Eur. Respir. J.* **2010**, *35*, 1039–1047. [[CrossRef](#)] [[PubMed](#)]
157. Mancuso, P. Obesity and lung inflammation. *J. Appl. Physiol.* **2010**, *108*, 722–728. [[CrossRef](#)] [[PubMed](#)]
158. Maachi, M.; Pieroni, L.; Bruckert, E.; Jardel, C.; Fellahi, S.; Hainque, B.; Capeau, J.; Bastard, J.P. Systemic low-grade inflammation is related to both circulating and adipose tissue TNFalpha, leptin and IL-6 levels in obese women. *Int. J. Obes. Relat. Metab. Disord.* **2004**, *28*, 993–997. [[CrossRef](#)] [[PubMed](#)]
159. Barnes, P.J.; Celli, B.R. Systemic manifestations and comorbidities of COPD. *Eur. Respir. J.* **2009**, *33*, 1165–1185. [[CrossRef](#)]
160. Broekhuizen, R.; Vernooij, J.H.; Schols, A.M.; Dentener, M.A.; Wouters, E.F. Leptin as local inflammatory marker in COPD. *Respir. Med.* **2005**, *99*, 70–74. [[CrossRef](#)]
161. Bruno, A.; Chanez, P.; Chiappara, G.; Siena, L.; Giammanco, S.; Gjomarkaj, M.; Bonsignore, G.; Bousquet, J.; Vignola, A.M. Does leptin play a cytokine-like role within the airways of COPD patients? *Eur. Respir. J.* **2005**, *26*, 398–405. [[CrossRef](#)] [[PubMed](#)]
162. Coats, V.; Després, J.P.; Alméras, N.; Martin, M.; Sin, D.D.; Rabasa-Lhoret, R.; Larose, É.; Tan, W.C.; Bourbeau, J.; Maltais, F. Ectopic adiposity and cardiometabolic health in COPD. *Int. J. Chron. Obstruct. Pulmon. Dis.* **2018**, *13*, 3331–3340. [[CrossRef](#)] [[PubMed](#)]
163. Hollenbach, J.; Lopez-Rodriguez, E.; Muhlfeld, C.; Schipke, J. Voluntary Activity Modulates Sugar-Induced Elastic Fiber Remodeling in the Alveolar Region of the Mouse Lung. *Int. J. Mol. Sci.* **2019**, *20*, 2438. [[CrossRef](#)] [[PubMed](#)]
164. Wood, D.M.; Brennan, A.L.; Philips, B.J.; Baker, E.H. Effect of hyperglycaemia on glucose concentration of human nasal secretions. *Clin. Sci.* **2004**, *106*, 527–533. [[CrossRef](#)] [[PubMed](#)]
165. Philips, B.J.; Redman, J.; Brennan, A.; Wood, D.; Holliman, R.; Baines, D.; Baker, E.H. Glucose in bronchial aspirates increases the risk of respiratory MRSA in intubated patients. *Thorax* **2005**, *60*, 761–764. [[CrossRef](#)] [[PubMed](#)]
166. Cazzola, M.; Calzetta, L.; Rogliani, P.; Lauro, D.; Novelli, L.; Page, C.P.; Kanabar, V.; Matera, M.G. High glucose enhances responsiveness of human airways smooth muscle via the Rho/ROCK pathway. *Am. J. Respir. Cell. Mol. Biol.* **2012**, *47*, 509–516. [[CrossRef](#)] [[PubMed](#)]

167. Gasparotto, J.; Ribeiro, C.T.; da Rosa-Silva, H.T.; Bortolin, R.C.; Rabelo, T.K.; Peixoto, D.O.; Moreira, J.C.F.; Gelain, D.P. Systemic Inflammation Changes the Site of RAGE Expression from Endothelial Cells to Neurons in Different Brain Areas. *Mol. Neurobiol.* **2019**, *56*, 3079–3089. [[CrossRef](#)] [[PubMed](#)]
168. Sparvero, L.J.; Asafu-Adjei, D.; Kang, R.; Tang, D.; Amin, N.; Im, J.; Rutledge, R.; Lin, B.; Amoscato, A.A.; Zeh, H.J.; et al. RAGE (Receptor for Advanced Glycation Endproducts), RAGE ligands, and their role in cancer and inflammation. *J. Transl. Med.* **2009**, *7*, 17. [[CrossRef](#)]
169. Bierhaus, A.; Schiekofe, S.; Schwaninger, M.; Andrassy, M.; Humpert, P.M.; Chen, J.; Hong, M.; Luther, T.; Henle, T.; Klöting, I.; et al. Diabetes-associated sustained activation of the transcription factor nuclear factor-kappaB. *Diabetes* **2001**, *50*, 2792–2808. [[CrossRef](#)] [[PubMed](#)]
170. Vlassara, H.; Cai, W.; Crandall, J.; Goldberg, T.; Oberstein, R.; Dardaine, V.; Peppas, M.; Rayfield, E.J. Inflammatory mediators are induced by dietary glycotoxins, a major risk factor for diabetic angiopathy. *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 15596–15601. [[CrossRef](#)]
171. Ferhani, N.; Letuve, S.; Kozhich, A.; Thibaudeau, O.; Grandsaigne, M.; Maret, M.; Dombret, M.C.; Sims, G.P.; Kolbeck, R.; Coyle, A.J.; et al. Expression of high-mobility group box 1 and of receptor for advanced glycation end products in chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* **2010**, *181*, 917–927. [[CrossRef](#)] [[PubMed](#)]
172. Pratte, K.A.; Curtis, J.L.; Kechris, K.; Couper, D.; Cho, M.H.; Silverman, E.K.; DeMeo, D.L.; Sciruba, F.C.; Zhang, Y.; Ortega, V.E.; et al. Soluble receptor for advanced glycation end products (sRAGE) as a biomarker of COPD. *Respir. Res.* **2021**, *22*, 127. [[CrossRef](#)] [[PubMed](#)]
173. Snyder, E.M.; Beck, K.C.; Dietz, N.M.; Joyner, M.J.; Turner, S.T.; Johnson, B.D. Influence of beta2-adrenergic receptor genotype on airway function during exercise in healthy adults. *Chest* **2006**, *129*, 762–770. [[CrossRef](#)]
174. Ahren, B.; Schersten, B. Beta 2-adrenoceptor induced increase of plasma insulin levels in man: Evidence of direct and indirect B-cell stimulation and liver effects. *Diabetes Res.* **1986**, *3*, 443–445. [[PubMed](#)]
175. Papatheodorou, A.; Latsi, P.; Vrettou, C.; Dimakou, A.; Chroneou, A.; Makrythanasis, P.; Kaliakatsos, M.; Orfanidou, D.; Roussos, C.; Kanavakis, E.; et al. Development of a novel microarray methodology for the study of SNPs in the promoter region of the TNF-alpha gene: Their association with obstructive pulmonary disease in Greek patients. *Clin. Biochem.* **2007**, *40*, 843–850. [[CrossRef](#)] [[PubMed](#)]
176. Prior, S.J.; Goldberg, A.P.; Ryan, A.S. ADRB2 haplotype is associated with glucose tolerance and insulin sensitivity in obese postmenopausal women. *Obesity* **2011**, *19*, 396–401. [[CrossRef](#)]
177. Thomsen, M.; Dahl, M.; Tybjaerg-Hansen, A.; Nordestgaard, B.G. beta2 -adrenergic receptor Thr164Ile polymorphism, blood pressure and ischaemic heart disease in 66 750 individuals. *J. Intern. Med.* **2012**, *271*, 305–314. [[CrossRef](#)]
178. Hattori, Y.; Suzuki, K.; Hattori, S.; Kasai, K. Metformin inhibits cytokine-induced nuclear factor kappaB activation via AMP-activated protein kinase activation in vascular endothelial cells. *Hypertension* **2006**, *47*, 1183–1188. [[CrossRef](#)]
179. Cheng, X.Y.; Li, Y.Y.; Huang, C.; Li, J.; Yao, H.W. AMP-activated protein kinase reduces inflammatory responses and cellular senescence in pulmonary emphysema. *Oncotarget* **2017**, *8*, 22513–22523. [[CrossRef](#)]
180. Han, Y.; Xie, H.; Liu, Y.; Gao, P.; Yang, X.; Shen, Z. Effect of metformin on all-cause and cardiovascular mortality in patients with coronary artery diseases: A systematic review and an updated meta-analysis. *Cardiovasc. Diabetol.* **2019**, *18*, 96. [[CrossRef](#)]
181. Hur, K.Y.; Lee, M.S. New mechanisms of metformin action: Focusing on mitochondria and the gut. *J. Diabetes Investig.* **2015**, *6*, 600–609. [[CrossRef](#)] [[PubMed](#)]
182. Patkee, W.R.; Carr, G.; Baker, E.H.; Baines, D.L.; Garnett, J.P. Metformin prevents the effects of *Pseudomonas aeruginosa* on airway epithelial tight junctions and restricts hyperglycaemia-induced bacterial growth. *J. Cell. Mol. Med.* **2016**, *20*, 758–764. [[CrossRef](#)] [[PubMed](#)]
183. Kajiwar, C.; Kusaka, Y.; Kimura, S.; Yamaguchi, T.; Nanjo, Y.; Ishii, Y.; Udono, H.; Standiford, T.J.; Tateda, K. Metformin Mediates Protection against *Legionella Pneumonia* through Activation of AMPK and Mitochondrial Reactive Oxygen Species. *J. Immunol.* **2018**, *200*, 623–631. [[CrossRef](#)] [[PubMed](#)]
184. Ho, T.W.; Huang, C.T.; Tsai, Y.J.; Lien, A.S.; Lai, F.; Yu, C.J. Metformin use mitigates the adverse prognostic effect of diabetes mellitus in chronic obstructive pulmonary disease. *Respir. Res.* **2019**, *20*, 69. [[CrossRef](#)]
185. Kahnert, K.; Andreas, S.; Kellerer, C.; Lutter, J.I.; Lucke, T.; Yildirim, O.; Lehmann, M.; Seissler, J.; Behr, J.; Frankenberger, M.; et al. Reduced decline of lung diffusing capacity in COPD patients with diabetes and metformin treatment. *Sci. Rep.* **2022**, *12*, 1435. [[CrossRef](#)]
186. Sexton, P.; Metcalf, P.; Kolbe, J. Respiratory effects of insulin sensitisation with metformin: A prospective observational study. *Copd* **2014**, *11*, 133–142. [[CrossRef](#)]
187. Hitchings, A.W.; Lai, D.; Jones, P.W.; Baker, E.H. Metformin in severe exacerbations of chronic obstructive pulmonary disease: A randomised controlled trial. *Thorax* **2016**, *71*, 587–593. [[CrossRef](#)]
188. Zhu, A.; Teng, Y.; Ge, D.; Zhang, X.; Hu, M.; Yao, X. Role of metformin in treatment of patients with chronic obstructive pulmonary disease: A systematic review. *J. Thorac. Dis.* **2019**, *11*, 4371–4378. [[CrossRef](#)]
189. Yen, F.S.; Wei, J.C.; Yang, Y.C.; Hsu, C.C.; Hwu, C.M. Respiratory outcomes of metformin use in patients with type 2 diabetes and chronic obstructive pulmonary disease. *Sci. Rep.* **2020**, *10*, 10298. [[CrossRef](#)]
190. Skubitz, K.M.; Craddock, P.R.; Hammerschmidt, D.E.; August, J.T. Corticosteroids block binding of chemotactic peptide to its receptor on granulocytes and cause disaggregation of granulocyte aggregates in vitro. *J. Clin. Investig.* **1981**, *68*, 13–20. [[CrossRef](#)]

191. Barnes, P.J. Inflammatory mechanisms in patients with chronic obstructive pulmonary disease. *J. Allergy Clin. Immunol.* **2016**, *138*, 16–27. [[CrossRef](#)] [[PubMed](#)]
192. Price, D.B.; Russell, R.; Mares, R.; Burden, A.; Skinner, D.; Mikkelsen, H.; Ding, C.; Brice, R.; Chavannes, N.H.; Kocks, J.W.; et al. Metabolic Effects Associated with ICS in Patients with COPD and Comorbid Type 2 Diabetes: A Historical Matched Cohort Study. *PLoS ONE* **2016**, *11*, e0162903. [[CrossRef](#)] [[PubMed](#)]
193. Caughey, G.E.; Roughead, E.E.; Vitry, A.I.; McDermott, R.A.; Shakib, S.; Gilbert, A.L. Comorbidity in the elderly with diabetes: Identification of areas of potential treatment conflicts. *Diabetes Res. Clin. Pract.* **2010**, *87*, 385–393. [[CrossRef](#)] [[PubMed](#)]
194. O’Byrne, P.M.; Rennard, S.; Gerstein, H.; Radner, F.; Peterson, S.; Lindberg, B.; Carlsson, L.G.; Sin, D.D. Risk of new onset diabetes mellitus in patients with asthma or COPD taking inhaled corticosteroids. *Respir. Med.* **2012**, *106*, 1487–1493. [[CrossRef](#)] [[PubMed](#)]
195. Suissa, S.; Kezouh, A.; Ernst, P. Inhaled corticosteroids and the risks of diabetes onset and progression. *Am. J. Med.* **2010**, *123*, 1001–1006. [[CrossRef](#)]
196. Dendukuri, N.; Blais, L.; LeLorier, J. Inhaled corticosteroids and the risk of diabetes among the elderly. *Br. J. Clin. Pharmacol.* **2002**, *54*, 59–64. [[CrossRef](#)]
197. Forman, B.M.; Tontonoz, P.; Chen, J.; Brun, R.P.; Spiegelman, B.M.; Evans, R.M. 15-Deoxy-delta 12, 14-prostaglandin J2 is a ligand for the adipocyte determination factor PPAR gamma. *Cell* **1995**, *83*, 803–812. [[CrossRef](#)]
198. Way, J.M.; Harrington, W.W.; Brown, K.K.; Gottschalk, W.K.; Sundseth, S.S.; Mansfield, T.A.; Ramachandran, R.K.; Willson, T.M.; Kliewer, S.A. Comprehensive messenger ribonucleic acid profiling reveals that peroxisome proliferator-activated receptor gamma activation has coordinate effects on gene expression in multiple insulin-sensitive tissues. *Endocrinology* **2001**, *142*, 1269–1277. [[CrossRef](#)]
199. Rinne, S.T.; Liu, C.F.; Feemster, L.C.; Collins, B.F.; Bryson, C.L.; O’Riordan, T.G.; Au, D.H. Thiazolidinediones are associated with a reduced risk of COPD exacerbations. *Int. J. Chron. Obstruct. Pulmon. Dis.* **2015**, *10*, 1591–1597. [[CrossRef](#)]
200. Petrache, I.; Fijalkowska, I.; Zhen, L.; Medler, T.R.; Brown, E.; Cruz, P.; Choe, K.H.; Taraseviciene-Stewart, L.; Scerbavicius, R.; Shapiro, L.; et al. A novel antiapoptotic role for alpha1-antitrypsin in the prevention of pulmonary emphysema. *Am. J. Respir. Crit. Care Med.* **2006**, *173*, 1222–1228. [[CrossRef](#)]
201. Chapman, K.R.; Burdon, J.G.; Piitulainen, E.; Sandhaus, R.A.; Seersholm, N.; Stocks, J.M.; Stoel, B.C.; Huang, L.; Yao, Z.; Edelman, J.M.; et al. Intravenous augmentation treatment and lung density in severe alpha1 antitrypsin deficiency (RAPID): A randomised, double-blind, placebo-controlled trial. *Lancet* **2015**, *386*, 360–368. [[CrossRef](#)]
202. Maruthur, N.M.; Tseng, E.; Hutfless, S.; Wilson, L.M.; Suarez-Cuervo, C.; Berger, Z.; Chu, Y.; Iyoha, E.; Segal, J.B.; Bolen, S. Diabetes Medications as Monotherapy or Metformin-Based Combination Therapy for Type 2 Diabetes: A Systematic Review and Meta-analysis. *Ann. Intern. Med.* **2016**, *164*, 740–751. [[CrossRef](#)] [[PubMed](#)]
203. Mendy, A.; Gopal, R.; Alcorn, J.F.; Forno, E. Reduced mortality from lower respiratory tract disease in adult diabetic patients treated with metformin. *Respirology* **2019**, *24*, 646–651. [[CrossRef](#)]
204. Isoda, K.; Young, J.L.; Zirlik, A.; MacFarlane, L.A.; Tsuboi, N.; Gerdes, N.; Schonbeck, U.; Libby, P. Metformin inhibits proinflammatory responses and nuclear factor-kappaB in human vascular wall cells. *Arterioscler. Thromb. Vasc. Biol.* **2006**, *26*, 611–617. [[CrossRef](#)] [[PubMed](#)]
205. Bonnefont-Rousselot, D. Antioxidant and anti-AGE therapeutics: Evaluation and perspectives. *J. Soc. Biol.* **2001**, *195*, 391–398. [[CrossRef](#)] [[PubMed](#)]
206. Mammen, M.J.; Sethi, S. COPD and the microbiome. *Respirology* **2016**, *21*, 590–599. [[CrossRef](#)] [[PubMed](#)]
207. Garnett, J.P.; Baker, E.H.; Naik, S.; Lindsay, J.A.; Knight, G.M.; Gill, S.; Tregoning, J.S.; Baines, D.L. Metformin reduces airway glucose permeability and hyperglycaemia-induced Staphylococcus aureus load independently of effects on blood glucose. *Thorax* **2013**, *68*, 835–845. [[CrossRef](#)] [[PubMed](#)]
208. Kahnert, K.; Jorres, R.A.; Lucke, T.; Trudzinski, F.C.; Mertsch, P.; Bickert, C.; Ficker, J.H.; Behr, J.; Bals, R.; Watz, H.; et al. Lower Prevalence of Osteoporosis in Patients with COPD Taking Anti-Inflammatory Compounds for the Treatment of Diabetes: Results from COSYCONET. *Int. J. Chron. Obstruct. Pulmon. Dis.* **2021**, *16*, 3189–3199. [[CrossRef](#)] [[PubMed](#)]
209. Tseng, C.H. Metformin and risk of chronic obstructive pulmonary disease in diabetes patients. *Diabetes Metab.* **2019**, *45*, 184–190. [[CrossRef](#)] [[PubMed](#)]
210. Polverino, F.; Wu, T.D.; Rojas-Quintero, J.; Wang, X.; Mayo, J.; Tomchaney, M.; Tram, J.; Packard, S.; Zhang, D.; Cleveland, K.H.; et al. Metformin: Experimental and Clinical Evidence for a Potential Role in Emphysema Treatment. *Am. J. Respir. Crit. Care Med.* **2021**, *204*, 651–666. [[CrossRef](#)]
211. Zulkifli, K.K.; Mohamed Shah, F.Z.; Ismail, A.I.; Abdul Rahman, T.H.; Ghani, R.A. Prevalence and associated factors of dysglycemia among patients with chronic obstructive pulmonary disease. *Chron. Respir. Dis.* **2021**, *18*, 1–8. [[CrossRef](#)]
212. Ceriello, A. Thiazolidinediones as anti-inflammatory and anti-atherogenic agents. *Diabetes Metab. Res. Rev.* **2008**, *24*, 14–26. [[CrossRef](#)] [[PubMed](#)]
213. Birrell, M.A.; Patel, H.J.; McCluskie, K.; Wong, S.; Leonard, T.; Yacoub, M.H.; Belvisi, M.G. PPAR-gamma agonists as therapy for diseases involving airway neutrophilia. *Eur. Respir. J.* **2004**, *24*, 18–23. [[CrossRef](#)] [[PubMed](#)]
214. Lea, S.; Plumb, J.; Metcalfe, H.; Spicer, D.; Woodman, P.; Fox, J.C.; Singh, D. The effect of peroxisome proliferator-activated receptor-gamma ligands on in vitro and in vivo models of COPD. *Eur. Respir. J.* **2014**, *43*, 409–420. [[CrossRef](#)] [[PubMed](#)]
215. Wedzicha, J.A.; Rabe, K.F.; Martinez, F.J.; Bredenkroter, D.; Brose, M.; Goehring, U.M.; Calverley, P.M.A. Efficacy of roflumilast in the COPD frequent exacerbator phenotype. *Chest* **2013**, *143*, 1302–1311. [[CrossRef](#)] [[PubMed](#)]

216. Laudisio, A.; Costanzo, L.; Di Gioia, C.; Delussu, A.S.; Traballese, M.; Gemma, A.; Antonelli Incalzi, R. Dietary intake of elderly outpatients with chronic obstructive pulmonary disease. *Arch. Gerontol. Geriatr.* **2016**, *64*, 75–81. [[CrossRef](#)]
217. Van de Bool, C.; Mattijssen-Verdonschot, C.; van Melick, P.P.; Spruit, M.A.; Franssen, F.M.; Wouters, E.F.; Schols, A.M.; Rutten, E.P. Quality of dietary intake in relation to body composition in patients with chronic obstructive pulmonary disease eligible for pulmonary rehabilitation. *Eur. J. Clin. Nutr.* **2014**, *68*, 159–165. [[CrossRef](#)]
218. Kaluza, J.; Larsson, S.C.; Orsini, N.; Linden, A.; Wolk, A. Fruit and vegetable consumption and risk of COPD: A prospective cohort study of men. *Thorax* **2017**, *72*, 500–509. [[CrossRef](#)] [[PubMed](#)]
219. Kaluza, J.; Harris, H.R.; Linden, A.; Wolk, A. Long-term consumption of fruits and vegetables and risk of chronic obstructive pulmonary disease: A prospective cohort study of women. *Int. J. Epidemiol.* **2018**, *47*, 1897–1909. [[CrossRef](#)] [[PubMed](#)]
220. Varraso, R.; Willett, W.C.; Camargo, C.A., Jr. Prospective study of dietary fiber and risk of chronic obstructive pulmonary disease among US women and men. *Am. J. Epidemiol.* **2010**, *171*, 776–784. [[CrossRef](#)]
221. Ochs-Balcom, H.M.; Grant, B.J.; Muti, P.; Sempos, C.T.; Freudenheim, J.L.; Browne, R.W.; McCann, S.E.; Trevisan, M.; Cassano, P.A.; Iacoviello, L.; et al. Antioxidants, oxidative stress, and pulmonary function in individuals diagnosed with asthma or COPD. *Eur. J. Clin. Nutr.* **2006**, *60*, 991–999. [[CrossRef](#)] [[PubMed](#)]
222. Jolliffe, D.A.; Greenberg, L.; Hooper, R.L.; Mathyssen, C.; Rafiq, R.; de Jongh, R.T.; Camargo, C.A.; Griffiths, C.J.; Janssens, W.; Martineau, A.R. Vitamin D to prevent exacerbations of COPD: Systematic review and meta-analysis of individual participant data from randomised controlled trials. *Thorax* **2019**, *74*, 337–345. [[CrossRef](#)] [[PubMed](#)]
223. Lu, M.C.; Yang, M.D.; Li, P.C.; Fang, H.Y.; Huang, H.Y.; Chan, Y.C.; Bau, D.T. Effect of Oligomeric Proanthocyanidin on the Antioxidant Status and Lung Function of Patients with Chronic Obstructive Pulmonary Disease. *In Vivo* **2018**, *32*, 753–758. [[CrossRef](#)] [[PubMed](#)]
224. Hirayama, F.; Lee, A.H.; Oura, A.; Mori, M.; Hiramatsu, N.; Taniguchi, H. Dietary intake of six minerals in relation to the risk of chronic obstructive pulmonary disease. *Asia Pac. J. Clin. Nutr.* **2010**, *19*, 572–577. [[PubMed](#)]
225. Scoditti, E.; Massaro, M.; Garbarino, S.; Toraldo, D.M. Role of Diet in Chronic Obstructive Pulmonary Disease Prevention and Treatment. *Nutrients* **2019**, *11*, 1357. [[CrossRef](#)]
226. Li, L.; Liu, Y.; Liu, X.; Zheng, N.; Gu, Y.; Song, Y.; Wang, X. Regulatory roles of external cholesterol in human airway epithelial mitochondrial function through STARD3 signalling. *Clin. Transl. Med.* **2022**, *12*, e902. [[CrossRef](#)] [[PubMed](#)]