microbiology research

MDPI

Review

COPD Pathogenesis and Alterations in the Oral, Lung, and Gut Microbiomes

Nobuhiro Asai [1,2,3,*], Yoshihiro Ohkuni [1], Hideo Kato [2,4,5,6], Mao Hagihara [2], Hiroshige Mikamo [2] and Norihiro Kaneko [1]

1 Department of Pulmonology, Kameda Medical Center, Kamogawa 296-0041, Japan
2 Department of Clinical Infectious Diseases, Aichi Medical University Hospital, Nagakute 480-1195, Japan
3 Department of Pathology, University of Michigan, Ann Arbor, MI 48105, USA
4 Department of Pharmacy, Mie University Hospital, Tsu 514-8507, Japan
5 Department of Clinical Pharmaceutics, Division of Clinical Medical Science, Mie University Graduate School of Medicine, Tsu 514-0001, Japan
6 Department of Molecular Epidemiology and Biomedical Sciences, Aichi Medical University Hospital, Nagakute 480-1195, Japan
* Correspondence: nobuhiro0204@gmail.com

Abstract: Chronic obstructive pulmonary disease (COPD) is a respiratory and systemic disease affecting more than 300 million people globally every year, and it also becomes a substantial economic burden. COPD is commonly comorbid with various underlying diseases such as cancer, cardiovascular diseases, cerebrovascular diseases, diabetes mellitus, osteoporosis, etc. It has been shown that statins can improve a significant decline in pulmonary function among COPD patients due to their pleiomorphic effect. Some systematic reviews also reported that statins reduced the risk of COPD-related events such as cancer and cardiovascular events, eventually resulting in more favorable outcomes than for non-statin user COPD patients. However, the physiological mechanism is still elucidated. Recently, it has been reported that statins influence the gut microbial composition with increased relative abundance of *Akkermansia muciniphila* and *Faecalibacterium prausnitzii* and act with pleiomorphic effects such as anti-inflammatory and anti-cancer effects through modulating gut dysbiosis. We described this review to focus on whether statins can be a useful preventive option for COPD.

Keywords: chronic obstructive pulmonary disease; microbiome; statin; dysbiosis; gut–lung axis

Citation: Asai, N.; Ohkuni, Y.; Kato, H.; Hagihara, M.; Mikamo, H.; Kaneko, N. COPD Pathogenesis and Alterations in the Oral, Lung, and Gut Microbiomes. *Microbiol. Res.* **2024**, *15*, 1605–1615. https://doi.org/10.3390/microbiolres15030106

Academic Editor: Juan Ayala

Received: 28 June 2024
Revised: 4 August 2024
Accepted: 12 August 2024
Published: 20 August 2024

1. Introduction

"Chronic obstructive pulmonary disease (COPD) is a life-threatening lung disease that causes an economic and health burden worldwide" [1], and there are approximately 300 million cases reported globally, with 3.2 million COPD-related deaths, which is ranked as the third leading cause of death in 2017 [2]. In addition, in the USA, COPD-related medical costs increased from 32.1 billion US dollars in 2010 to 49.0 billion US dollars in 2020 in direct healthcare costs, which became a substantial economic burden [3].

COPD is a progressive and systemic disease characterized by dyspnea, persistent cough, sputum, and weight loss due to airflow limitation and various systemic manifestations such as nutritional, musculoskeletal, and cardiovascular impairments, mood disorders, and malignancy [4–6]. It has been shown that COPD patients have various comorbid diseases, and comorbidities cause poor outcomes in COPD patients [4–6]. Thus, physicians need to care for the comorbidities as well. Hyperlipidemia is one of the most common comorbidities in COPD patients [4]. Statin is commonly used to reduce the risk of a cardiovascular event [7–9]. As COPD patients progress to lung function impairment yearly, the prognosis worsens [10]. Previous studies have shown that statin use can significantly improve lung function after introducing a bronchodilator [11,12]. Several pleiotropic

effects of statins can contribute to favorable outcomes in cardiovascular diseases, various cancer patients as well as COPD patients. The pathogenesis of chronic respiratory disorders correlates with lung and gut microbiome, and dysbiosis can affect disease progression in COPD patients. Recently, statins have been reported to have an effect modulating the gut microbiome to keep homeostasis, which is one of its pleiotropic effects, such as anti-inflammatory, antioxidant, and antitumor effects. This review focuses on the modulating microbiome composition caused by statin intake and the possibility of a new therapeutic strategy for COPD.

1.1. Alternation of Lung and Gut Microbiome Gut Correlate with Lung Diseases

Lungs were considered to be sterile organs. Recent studies have documented that alternations of lung and gut microbiomes were associated with the development and progression of chronic lung diseases [1,13,14]. Patients with bronchial asthma have different respiratory microbiomes compared to healthy people [1]. Moreover, various types of asthma can show different altered microbiomes in the lungs and gut [15–17]. We also reported that steroid-resistant asthma differed extremely from naïve control using a cockroach allergen asthma mouse model [18]. Lung and gut microbiomes among patients with advanced lung cancer are significantly different from early-stage lung cancer [19]. Furthermore, patients with non-small cell lung cancer, which is the most common cancer type of lung cancer, showed different microbiomes from those with small-cell lung cancer [20]. Some taxa are considered to correlate with disease progression. "*Streptococcus* was significantly lower in metastatic adenocarcinoma than that in non-metastatic adenocarcinoma, and *Veillonella* and *Rothia* were higher in metastatic SCC compared to non-metastatic SCC using bronchial washing fluid samples" [1,21]. Concerning COPD, its development and progression are affected by altered microbiome in the lung and gut. Details are to be described in the later session.

1.2. Comorbidities Accelerate the Severity of COPD

It is well-known that COPD patients commonly have several comorbidities, which can impact outcomes such as reduced quality of life (QOL) and physical activity, increased frequency of hospital admissions, and worse therapeutic response [22–25]. A systematic review reported that there are 13 of the most common comorbidities, such as hypertension, coronary artery disease, diabetes, osteoarthritis, psychiatric conditions, asthma, gastroesophageal reflux (GERD), chronic heart failure, chronic kidney disease, arrhythmia, osteoporosis, obesity, and atrial fibrillation. Among the 13 comorbidities, coronary artery diseases, DM, psychiatric disorders, chronic heart failure, atrial fibrillation, and other arrhythmias are associated with increased mortality among COPD patients [22]. Benson et al. demonstrated that GERD correlates with increased acute exacerbation and hospitalization [26]. Sleep quality and psychiatric symptoms such as depression and anxiety were associated with physical activity in severe-grade COPD patients [27]. Asthma is also one of the most prevalent respiratory diseases, which overlaps with COPD. Also, asthma can cause more severe respiratory conditions and acute exacerbation of COPD, resulting in impaired lung function and lower QOL. Therefore, it is crucial to recognize the co-existence of asthma and consider using an inhaled corticosteroid in COPD with asthma patients [28,29].

1.3. COPD Pathogenesis and Microbiome

The lung has been considered a sterile organ for a long time [1,30]. However, increasing evidence suggests that a microbiome exists in the lung, and the lung microbiome plays an essential role in the pathogenesis of COPD [1,13,30,31]. Previous studies documented that the respiratory microbiome detected by Bronchoalveolar lavage fluid (BALF) and sputum in COPD patients were quite different from that of healthy control, with an increased relative abundance of *Moraxella*, *Streptococcus*, *Proteobacteria*, *Veillonella*, *Eubacterium*, and *Prevotella* spp. [32,33]. Conversely, Sze et al. compared GOLD stage 4 COPD patients with a

control group using explanted lung tissue and reported an increase in *Proteobacteria* phylum organisms and a decrease in *Firmicutes*, *Bacteroidetes* phylum, *Streptococcus*, *Haemophilus infuenzae*, and *Prevotella* spp. have also been documented [34]. This discrepancy can happen due to the different methods of analyzing the microbiome [35,36]. In terms of an event of acute exacerbation, the fecal microbiome has also been shown to display a lower relative abundance of *Firmicutes* and *Actinobacteria*, with an associated increase in *Bacteroidetes* and *Proteobacteria* [37,38]. These results suggest that the gut–lung axis can influence disease progression in COPD patients, and modulating the lung and gut microbiome can be targeted and potentially become a proper preventive strategy for COPD.

1.4. A Link with Respiratory Syncytial Virus Infection and COPD

Respiratory syncytial virus (RSV) is a single-stranded negative-sense RNA virus that belongs to the Paramyxoviridae family, predominantly recognized as a pediatric pathogen causing acute respiratory failure and persistent wheezing, resulting in bronchial asthma in children [39,40]. Numerous studies reported that lower tract infection due to RSV was associated with impairment of lung function and the development of bronchial asthma. "Susceptibility to persistent RSV infection could involve both host and viral factors. Cigarette smoking and COPD are likely to result in impaired antiviral immunity, and RSV is capable of evading immune responses by inducing skewed type 2 T-helper cell responses, antagonizing antiviral cytokines, mimicking chemokines, inhibiting apoptosis, and entering immune-privileged cells such as pulmonary neurons" [41]. It can also escape an established immune response through antigenic drift. It has been estimated that children with a history of LRTI due to RSV infection have a 2- to 12-fold higher risk of developing asthma. The correlation between RSV infection and impairment and decline of function remains throughout adolescence and early adulthood, suggesting a possible role for RSV even in the inception of chronic obstructive pulmonary disease. Lukacs et al. performed a study by using an early-life mouth model and demonstrated that long-term effects due to a secondary RSV infection 3 months following initial early-life RSV infection led to significant lung dysfunction [42]. They previously reported that the altered PFT and structural changes induced by early-life RSV were alleviated in TSLPR-/- mice. Despite these, the mechanisms by which RSV contributes to the onset of wheezing/asthma and lung function impairment are not fully understood but appear to relate to injury caused directly by the virus and/or to pre-existing predisposing factors. A possible explanation of the mechanism that RSV can cause the development of bronchial asthma and COPD is that RSV alters lung and gut microbiomes. Some documented that 16S rRNA gene sequencing analysis showed an increase in the relative abundance of *Haemophilus*, *Streptococcus*, and *Moraxella* in the lung following RSV infection [43]. Interestingly, these taxonomic changes in the lung microbiome are similar to those of patients with asthma [17,44,45]. These alternations in the lung and gut microbiomes can cause altered metabolomics, leading to focal lung impairment and systemic inflammations.

1.5. Acute Excarbation Event and RSV Infections

Acute exacerbation event is a critical event showing a high mortality rate in COPD patients. RSV has been known as an important pathogen which induces acute respiratory failure. Recent studies documented that RSV could impact respiratory conditions in adults with comorbidity, including cancer, heart disease, and chronic respiratory disease. A previous study performed in the United States between 1999 and 2003 showed that 3–7% of healthy older adults, 4–10% of high-risk patients, and 8–13% of hospitalized patients had RSV infections [3]. A prospective observational cohort in the EU reported that RSV had been found in 2 to 5% of community-acquired pneumonia in adults [9]. We also previously performed a prospective cohort to examine the exact frequency of acute exacerbation of COPD and to detect a causative pathogen by multiplex polymerase chain reaction (PCR) using sputum in Japan. The results showed that 20% of the patients who were admitted to our institute had RSV, which was the second most frequent virus isolated, followed

by influenza virus and adenovirus [46]. While demanding a deeper understanding and clearing the pathophysiological mechanism between RSV infections and the development of chronic respiratory diseases, the essential role of physicians is to establish a preventive strategy against RSV infections to prevent children and young adults from developing worsened respiratory conditions in the future.

A Vaccine against RSV in adults was approved first in the USA in 2022 [47]. The randomized control trial (RCT) demonstrated the efficacy and safety of the RSV vaccine for elderly patients with comorbidities. While the study showed a high prevention rate for RSV-associated infections, most participants were healthy without any comorbidities, or the comorbidities were well controlled. In addition, there was the RCT showing the efficacy and safety of the vaccine for pregnant women and infants, although most of the participants were healthy people without unstable comorbidity [22]. A meta-analysis of RCTs for RSV maternal vaccine showed lower significant differences in the incidence of LRTI [risk ratio (RR): 0.64; 95% confidence interval (CI): 0.43, 0.96; $p = 0.03$)] and severe LRTI (RR: 0.37; 95% CI: 0.18, 0.79; $p = 0.01$) between the vaccine group and the placebo group for newborns and infants. These differences were observed at 90, 120, and 150 days after birth, respectively ($p = 0.003$, $p = 0.05$, $p = 0.02$, $p = 0.03$, $p = 0.009$, $p = 0.05$). At 180 days after birth, there was a significant difference observed in the incidence of LRTI between the two groups (RR: 0.43; 95% CI: 0.21, 0.90; $p = 0.02$). The analysis concluded that the RSV maternal vaccine is effective and safe for preventing LRTI in postpartum infants [48]. These results suggest that the RSV vaccine would be a useful preventive method for RSV infections in children in early life, resulting in a reduction of bronchial asthma COPD occurrence. INSPIRE trial, which is a large, population-based birth cohort of healthy infants with non-low birthweight born during 2012 and 2013 in Tennessee, USA, revealed that the estimated proportion of 5-year current asthma cases that could be prevented by avoiding RSV infection during infancy was 15% (95% CI 22–26.8) [49]. Despite a huge demand for a new drug to treat effectively and safely against RSV infections, Palivizumab, a monoclonal antibody, has been currently approved [50]. Another monoclonal antibody with a long half-life, Nirsevimab, will soon be approved for clinical use [51]. However, the long-term efficacy of these drugs to prevent the development of chronic respiratory diseases in the future is not clear. Prevention against RSV infection would be an essential strategy for adult patients with COPD to avoid events of acute exacerbation and to reduce the development of bronchial asthma and COPD in children.

1.6. Statin Can Improve COPD Outcomes

"Statins are competitive inhibitors of 3-hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) reductases, which catalyze the rate-limiting step in cholesterol biosynthesis" [52]. They are also one of the most prescribed drugs worldwide, with a high volume of solid evidence of having a significant reduction in morbidity and mortality associated with cardiovascular diseases. Statins have shown anti-inflammatory, antithrombotic, antitumor, and antioxidant effects [53]. Due to these pleiotropic effects, statin use leads to a favorable outcome in several diseases such as cancers, COPD, etc. A systematic review showed that statins reduce the risk of mortality and hospitalization and some cytokine levels, such as C-reactive protein (CRP) and interleukin (IL)-6 among COPD patients [54]. A recent case–control study published in Korea reported that statin use decreased the risk of acute exacerbation in COPD patients [55]. Additionally, a meta-analysis of randomized control trials showed statins improved exercise tolerance and lung function among COPD patients with hyperlipidemia [56]. As illustrated below, our study also reproduced the result of the meta-analysis.

1.7. Do Statins Affect the Gut Microbiome?

Some statins influence the bacterial gut microbiome in both human and murine studies [57–60]. Sun and Liu documented that individuals with statins showed a higher relative abundance of Firmicutes by phylum level and an increased proportion of *Lactobacillus*

and *Bifidobacterium* genera. In addition, both studies found that a better response to statin treatment correlated with diversity in the gut microbiome [57,58]. As for the mechanism of how statins affect the gut microbiome, Khan reported that atorvastatin-treated hypercholesterolemic patients showed a higher relative abundance of anti-inflammatory gut microbial profile with increased proportions of *Faecalibacterium prausnitzii* and *Akkermansia muciniphila*, a lower relative abundance of proinflammatory species, *Desulfovibrio* sp. than the untreated hypercholesterolemic patients did [59]. Schneeberger et al. performed a murine study and reported that "levels of *Akkermansia muciniphila* were strongly and positively correlated with the levels of almost all the parameters involved in fatty acid oxidation and fat browning. Conversely, the levels of *Akkermansia muciniphila* were inversely associated with inflammatory markers, lipid synthesis, and several plasma markers of insulin resistance, cardiovascular risk and adiposity" [61]. Concomitantly, *F. prausnitzii* is a butyrogenic bacteria that has the potential to decrease TNF-α and IL-12 and increase IL-10, acting as anti-inflammatory effects [62].

1.8. Oral Microbiome and COPD Pathogenesis

"The balance of oral bacterial composition can keep the oral ecosystem healthy. The resident bacteria in a healthy mouth are divided into six broad phyla. *Firmicutes*, *Proteobacteria*, *Fusobacteria*, *Actinobacteria*, *Bacteroidetes*, and *Spirochaetes* constitute 96% of total bacteria. They maintain a dynamic balance to maintain oral health" [63]. However, the imbalance of the oral ecosystem can cause the development of oral diseases as well as cardiovascular disease, pancreatic cancer, rheumatic arthritis, and pulmonary diseases [64–66]. The alternation of the oral microbiome affects the pathogenesis of COPD.

A possible mechanism by which the oral microbiome affects COPD is the entry of oral pathogenic bacteria into the airways to induce lung injury. *Porphyromonas gingivalis*, a Gram-negative, anaerobic, rod-shaped bacterium, is an important causative pathogen of periodontitis. *P. gingivalis* can alter the oral microbiome [67]. Watanabe et al. reported that *P. gingivalis* is a potent inflammatory stimulant for human bronchial and pharyngeal epithelial cells and can stimulate TLR2-mediated cytokine production [15 Watanabe]. "*P. gingivalis* causes lung injury by activating toll-like receptor-2 (TLR2) in respiratory epithelial cells, promoting the secretion of inflammatory factors such as TNF-α, IL-6, and IL-17 and causing a large number of neutrophils to accumulate in the lungs" [66]. Besides, *P. gingivalis* can collaborate with the influenza virus to accelerate lung injury, and the co-infection of *P. gingivalis* with influenza virus H1N1 in the lung epithelial cells can activate the Bcl-2/Bax/caspase-3 pathway to increase the level of apoptosis, promoting lung epithelial injury [68]. *P. gingivalis* also accelerates the invasive ability of *Pseudomonas aeruginosa* and regulates the apoptotic mechanism of *P. aeruginosa* by activating the STAT3 signaling pathway. Compared with simple infection with *P. aeruginosa*, co-infection of *P. gingivalis* with *P. aeruginosa* resulted in more cell death, leading to AE-COPD [67,69]. *Fusobacterium nucleatum*, an anaerobic bacillus, is an essential causative pathogen of periodontitis. It has been reported that *F. nucleatum* can induce proinflammatory cytokines IL-6 and IL-8 in bronchial and pharyngeal respiratory epithelial cells in vitro and in vivo, leading to AE-COPD. Co-existence with *F. nucleatum* and *P. aeruginosa* can aggregate the severity of AE-COPD. Li et al. documented that *F. nucleatum* co-existed with P. aeruginosa in the respiratory tract, and the number of *F. nucleatum* was negatively correlated with the lung function of AE-COPD patients in human cell lines. In addition, *F. nucleatum* interacts with *P. aeruginosa* to induce the formation of *P. aeruginosa* biofilm to antibiotic tolerance in vitro via *Fusobacterium* adhesin A [70].

Some have already documented that oral dysbiosis is associated with the prevalence of COPD [71–73]. A previous meta-analysis reported that periodontal disease was an independent risk factor for COPD [71]. Takeuchi et al. conducted a 5-year prospective follow-up study in Japan and concluded that the severity of periodontitis positively correlated with the risk of COPD [72]. A case–control study of COPD and periodontitis in China displayed a strong correlation between periodontitis and COPD. Participants with more severe COPD

were more likely to have severe periodontal disease. Also, they concluded that the plaque index can be a major periodontal factor for predicting COPD among Chinese adults [74]. Although accumulated evidence shows the correlation between periodontitis and the development of COPD, there is a debate about whether both periodontitis and COPD contribute mutually or whether periodontitis promotes COPD unilaterally [66]. Some studies indicated that certain oral microorganisms were associated with a decline in lung function. A large prospective cohort study performed in Germany found that periodontal diseases were significantly correlated with reduced lung volumes and airflow limitation in the general adult population [75]. Tan et al. reported that the increase of specific microorganisms such as *P. gingivalis, Klebsiella pneumonia*, *P. aeruginosa*, and *Streptococcus pneumonia* was found in COPD patients than in control patients. Additionally, a significant negative association was noted between the relative content of *P. gingivalis* and FEV1% in participants with COPD. Yang et al. conducted a multicenter cohort study among HIV patients with lung diseases. The results showed that oral dysbiosis in HIV patients with lung diseases was related to impaired pulmonary function and systemic inflammation [76]. Beck et al. conducted a comparative study to examine the oral and lung microbiome in patients HIV-uninfected, those HIV-infected without antiviral therapy, and those HIV-infected who received antiviral therapy. "Microbial populations differed in the oral washes among the subject groups (*Streptococcus*, *Actinomyces, Rothia*, and *Atopobium*), but there were no individual taxa that differed among the BALs" [77]. Interestingly, CD4 cells did not affect the oral or lung microbial composition microbiome. These concluded that the oral microbiome might be a biomarker of lung function among HIV patients with lung diseases [76,77].

Oral dysbiosis influences the occurrence of acute exacerbation of COPD (AE-COPD) [78,79]. A large longitudinal cohort study performed in Taiwan showed a positive correlation between the risk of periodontitis and the times of COPD exacerbations [80]. Another case–control study displayed that median antibody levels for *H1N1* and *Prevotella intermedia* in patients with AE-COPD were higher than in the control group [81]. Baldeoro et al. researched the relationship between AE-COPD occurrence and dental health. The results displayed that "oral health status was not related to COPD exacerbations but was associated with self-reported respiratory health. Non-exacerbators were more likely to be edentate or have $\leq$4 teeth compared to exacerbators" [82]. "Extensive plaque biofilm attached to the affected teeth can be aspirated into the lungs, leading to AE-COPD, forming a vicious cycle" [66]. Brushing reduces the accumulation of plaque, removing oral pathogens, decreasing the incidence of periodontitis, and restoring the balance of the oral microbiome. In addition, it is beneficial in reducing the frequency of AE-COPD [82]. Good periodontal health can contribute to a reduction of the decline of lung function, resulting in acute exacerbation of COPD and frequent hospitalization. Therefore, frequent brushing with dental floss can be a preventive method for AE-COPD. Another possible mechanism for aggravating the severity of COPD is gut–oral axis. It has been well-known that the gut microbiome mutually correlates with the oral microbiome. In addition, oral dysbiosis can exaggerate the severity of COPD via the gut–oral axis and the gut–lung axis [1,83,84]. Oral care can be one of the proper preventive methods for accelerating the pathogenesis of COPD.

2. Perspective

COPD is not only a respiratory but a systemic inflammatory disease with various manifestations. COPD causes systemic inflammation, leading to multiple comorbidities. Strong evidence suggests that systemic inflammation can increase the risk of developing cardiovascular disease, malignancy, diabetes mellitus, osteoporosis, etc., resulting in poor outcomes, while the pathophysiological mechanism is still unclear. It has been shown that statins have a potent anti-inflammatory, antithrombotic, and antitumor effect and improve clinical outcomes in breast cancer, liver cirrhosis, COVID-19, cardiovascular disease, etc. [85–89]. We hypothesize that the anti-inflammatory effect of statins can contribute to

decreasing the risk of COPD development and the occurrence of various events, resulting in a favorable outcome compared to those not taking statins.

There is a sufficient volume of evidence regarding microbiome studies that have suggested that the alternation of the gut microbiome (gut dysbiosis) involves various disease progression and pathogenesis [1,14,30]. The progression and pathogenesis of COPD are linked to the altered respiratory microbiome, which correlates with gut dysbiosis (Figure 1).

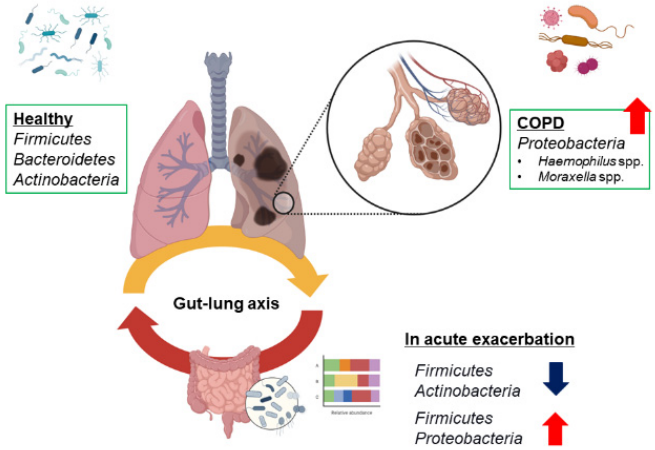

Figure 1. Correlation between the gut–lung axis and microbiomes in COPD. Figure 1 shows the comparison of microbial composition between healthy control (HC) and COPD patients. COPD patients show different microbial compositions in the airway microbiome than those of HCs.

It has been reported that some species with anti-inflammatory effects, such as *Faecalibacterium prausnitzii* and *Akkermansia muciniphila,* were decreased in chronic respiratory diseases and cancer patients [60]. A meta-analysis showed that *Acinetobacter baumannii* and *P. aeruginosa* were more prevalent in patients with COPD and asthma than healthy control [90]. *A. baumannii* can induce the production of proinflammatory cytokines, such as TNF-α, type I IFN, and IL-1β, which mediates lung immune response and lead to cell death [91–93]. "*P. aeruginosa* is the leading cause of a decline in lung infections" [90]. It also attaches to different solid surfaces and forms biofilms to enable bacteria to resist the host's innate immune system and antibiotic treatment [94] and can induce acute host inflammatory response [90], leading to a significant decline in lung function. As statin intakes result in the increased relative abundance of *F. prausnitzii* and *A. muciniphila* in humans [60], it is reasonable that statins help to increase anti-inflammatory bacteria, leading to favorable outcomes.

In conclusion, statins can be a helpful option as a preventive treatment, even though there are several limitations regarding the studies evaluating statins' efficacy for COPD. Simultaneously, modulating the altered respiratory and gut microbiome can be one of the helpful treatment options, which should be examined in further studies.

Author Contributions: Conception, N.A.; writing, N.A.; editing, N.A., Y.O., H.K., M.H., H.M. and N.K.; supervision, N.K. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: All data generated or analyzed during this study are included in this published article.

Acknowledgments: We are grateful for the diligent and thorough critical reading of our manuscript by John Wocher, Advisor, Kameda Medical Center (Japan).

Conflicts of Interest: The authors declare that they have no conflicts of interest.

References

1. Yagi, K.; Huffnagle, G.B.; Lukacs, N.W.; Asai, N. The Lung Microbiome during Health and Disease. *Int. J. Mol. Sci.* **2021**, *22*, 10872. [CrossRef]
2. Chronic Obstructive Pulmonary Disease Website. Available online: https://www.cdc.gov/copd/index.html (accessed on 10 August 2022).
3. Chronic Obstructive Pulmonary Disease (COPD). Available online: https://www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-(copd) (accessed on 10 August 2022).
4. Schwab, P.; Dhamane, A.D.; Hopson, S.D.; Moretz, C.; Annavarapu, S.; Burslem, K.; Renda, A.; Kaila, S. Impact of comorbid conditions in COPD patients on health care resource utilization and costs in a predominantly Medicare population. *Int. J. Chron. Obstr. Pulm. Dis.* **2017**, *12*, 735–744. [CrossRef]
5. Holguin, F.; Folch, E.; Redd, S.C.; Mannino, D.M. Comorbidity and mortality in COPD-related hospitalizations in the United States, 1979 to 2001. *Chest* **2005**, *128*, 2005–2011. [CrossRef]
6. Menzin, J.; Boulanger, L.; Marton, J.; Guadagno, L.; Dastani, H.; Dirani, R.; Phillips, A.; Shah, H. The economic burden of chronic obstructive pulmonary disease (COPD) in a U.S. Medicare population. *Respir. Med.* **2008**, *102*, 1248–1256. [CrossRef] [PubMed]
7. Catapano, A.L.; Graham, I.; De Backer, G.; Wiklund, O.; Chapman, M.J.; Drexel, H.; Hoes, A.W.; Jennings, C.S.; Landmesser, U.; Pedersen, T.R.; et al. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. *Eur. Heart J.* **2016**, *37*, 2999–3058. [CrossRef]
8. Grundy, S.M.; Stone, N.J.; Bailey, A.L.; Beam, C.; Birtcher, K.K.; Blumenthal, R.S.; Braun, L.T.; de Ferranti, S.; Faiella-Tommasino, J.; Forman, D.E.; et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* **2019**, *139*, e1082–e1143.
9. Davies, J.T.; Delfino, S.F.; Feinberg, C.E.; Johnson, M.F.; Nappi, V.L.; Olinger, J.T.; Schwab, A.P.; Swanson, H.I. Current and Emerging Uses of Statins in Clinical Therapeutics: A Review. *Lipid Insights* **2016**, *9*, 13–29. [CrossRef] [PubMed]
10. Jo, Y.S. Long-term outcome of chronic obstructive pulmonary disease: A review. *Tuberc. Respir. Dis.* **2022**, *85*, 289. [CrossRef] [PubMed]
11. Janda, S.; Park, K.; FitzGerald, J.M.; Etminan, M.; Swiston, J. Statins in COPD: A systematic review. *Chest* **2009**, *136*, 734–743. [CrossRef]
12. Keddissi, J.I.; Younis, W.G.; Chbeir, E.A.; Daher, N.N.; Dernaika, T.A.; Kinasewitz, G.T. The use of statins and lung function in current and former smokers. *Chest* **2007**, *132*, 1764–1771. [CrossRef]
13. Asai, N.; Kato, H.; Mikamo, H. The pathophysiological mechanisms of COVID-19 and host immunity, with emphasis on the dysbiosis of the lung and gut microbiomes and pregnancy. *Respir. Investig.* **2022**, *60*, 496–502. [CrossRef]
14. Asai, N.; Mikamo, H. COVID-19 disease severity is linked to host immunity as well as lung and gut dysbiosis: A narrative review. *J. Glob. Antimicrob. Resist.* **2021**, *27*, 282–283. [CrossRef]
15. Huang, Y.J.; Nariya, S.; Harris, J.M.; Lynch, S.V.; Choy, D.F.; Arron, J.R.; Boushey, H. The airway microbiome in patients with severe asthma: Associations with disease features and severity. *J. Allergy Clin. Immunol.* **2015**, *136*, 874–884. [CrossRef] [PubMed]
16. Begley, L.; Madapoosi, S.; Opron, K.; Ndum, O.; Baptist, A.; Rysso, K.; Erb-Downward, J.R.; Huang, Y.J. Gut microbiota relationships to lung function and adult asthma phenotype: A pilot study. *BMJ Open Respir. Res.* **2018**, *5*, e000324. [CrossRef]
17. Barcik, W.; Boutin, R.C.T.; Sokolowska, M.; Finlay, B.B. The Role of Lung and Gut Microbiota in the Pathology of Asthma. *Immunity* **2020**, *52*, 241–255. [CrossRef]
18. Asai, N.; Ethridge, A.D.; Fonseca, W.; Yagi, K.; Rasky, A.J.; Morris, S.B.; Falkowski, N.R.; Huang, Y.J.; Huffnagle, G.B.; Lukacs, N.W. A steroid-resistant cockroach allergen model is associated with lung and cecal microbiome changes. *Physiol. Rep.* **2023**, *11*, e15761. [CrossRef]
19. Perrone, F.; Belluomini, L.; Mazzotta, M.; Bianconi, M.; Di Noia, V.; Meacci, F.; Montrone, M.; Pignataro, D.; Prelaj, A.; Rinaldi, S.; et al. Exploring the role of respiratory microbiome in lung cancer: A systematic review. *Crit. Rev. Oncol. Hematol.* **2021**, *164*, 103404. [CrossRef]
20. Gomes, S.; Cavadas, B.; Ferreira, J.C.; Marques, P.I.; Monteiro, C.; Sucena, M.; Sousa, C.; Vaz Rodrigues, L.; Teixeira, G.; Pinto, P.; et al. Profiling of lung microbiota discloses differences in adenocarcinoma and squamous cell carcinoma. *Sci. Rep.* **2019**, *9*, 12838. [CrossRef]
21. Huang, D.; Su, X.; Yuan, M.; Zhang, S.; He, J.; Deng, Q.; Qiu, W.; Dong, H.; Cai, S. The characterization of lung microbiome in lung cancer patients with different clinicopathology. *Am. J. Cancer Res.* **2019**, *9*, 2047–2063.
22. Santos, N.C.D.; Miravitlles, M.; Camelier, A.A.; Almeida, V.D.C.; Maciel, R.; Camelier, F.W.R. Prevalence and Impact of Comorbidities in Individuals with Chronic Obstructive Pulmonary Disease: A Systematic Review. *Tuberc. Respir. Dis.* **2022**, *85*, 205–220. [CrossRef]
23. Divo, M.J.; Casanova, C.; Marin, J.M.; Pinto-Plata, V.M.; de-Torres, J.P.; Zulueta, J.J.; Cabrera, C.; Zagaceta, J.; Sanchez-Salcedo, P.; Berto, J.; et al. COPD comorbidities network. *Eur. Respir. J.* **2015**, *46*, 640–650. [CrossRef] [PubMed]
24. Crisafulli, E.; Costi, S.; Luppi, F.; Cirelli, G.; Cilione, C.; Coletti, O.; Fabbri, L.M.; Clini, E.M. Role of comorbidities in a cohort of patients with COPD undergoing pulmonary rehabilitation. *Thorax* **2008**, *63*, 487–492. [CrossRef] [PubMed]

25. Pasquale, M.K.; Xu, Y.; Baker, C.L.; Zou, K.H.; Teeter, J.G.; Renda, A.M.; Davis, C.C.; Lee, T.C.; Bobula, J. COPD exacerbations associated with the modified Medical Research Council scale and COPD assessment test among Humana Medicare members. *Int. J. Chron. Obstr. Pulm. Dis.* **2016**, *11*, 111–121. [CrossRef] [PubMed]
26. Benson, V.S.; Mullerova, H.; Vestbo, J.; Wedzicha, J.A.; Patel, A.; Hurst, J.R.; Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) Investigators. Associations between gastro-oesophageal reflux, its management and exacerbations of chronic obstructive pulmonary disease. *Respir. Med.* **2015**, *109*, 1147–1154. [CrossRef]
27. Neale, C.D.; Christensen, P.E.; Dall, C.; Ulrik, C.S.; Godtfredsen, N.; Hansen, H. Sleep Quality and Self-Reported Symptoms of Anxiety and Depression Are Associated with Physical Activity in Patients with Severe COPD. *Int. J. Environ. Res. Public. Health* **2022**, *19*, 16804. [CrossRef]
28. Chalmers, J.D.; Laska, I.F.; Franssen, F.M.E.; Janssens, W.; Pavord, I.; Rigau, D.; McDonnell, M.J.; Roche, N.; Sin, D.D.; Stolz, D.; et al. Withdrawal of inhaled corticosteroids in COPD: A European Respiratory Society guideline. *Eur. Respir. J.* **2020**, *55*, 2000351. [CrossRef]
29. Singh, D.; Wedzicha, J.A.; Siddiqui, S.; de la Hoz, A.; Xue, W.; Magnussen, H.; Miravitlles, M.; Chalmers, J.D.; Calverley, P.M.A. Blood eosinophils as a biomarker of future COPD exacerbation risk: Pooled data from 11 clinical trials. *Respir. Res.* **2020**, *21*, 240. [CrossRef]
30. Huffnagle, G.B.; Dickson, R.P.; Lukacs, N.W. The respiratory tract microbiome and lung inflammation: A two-way street. *Mucosal Immunol.* **2017**, *10*, 299–306. [CrossRef]
31. Huang, Y.J.; Boushey, H.A. The microbiome in asthma. *J. Allergy Clin. Immunol.* **2015**, *135*, 25–30. [CrossRef]
32. Haldar, K.; George, L.; Wang, Z.; Mistry, V.; Ramsheh, M.Y.; Free, R.C.; John, C.; Reeve, N.F.; Miller, B.E.; Tal-Singer, R.; et al. The sputum microbiome is distinct between COPD and health, independent of smoking history. *Respir. Res.* **2020**, *21*, 183. [CrossRef]
33. Sze, M.A.; Dimitriu, P.A.; Suzuki, M.; McDonough, J.E.; Campbell, J.D.; Brothers, J.F.; Erb-Downward, J.R.; Huffnagle, G.B.; Hayashi, S.; Elliott, W.M.; et al. Host Response to the Lung Microbiome in Chronic Obstructive Pulmonary Disease. *Am. J. Respir. Crit. Care Med.* **2015**, *192*, 438–445. [CrossRef]
34. Clooney, A.G.; Fouhy, F.; Sleator, R.D.; O'Driscoll, A.; Stanton, C.; Cotter, P.D.; Claesson, M.J. Comparing Apples and Oranges?: Next Generation Sequencing and Its Impact on Microbiome Analysis. *PLoS ONE* **2016**, *11*, e0148028. [CrossRef]
35. Hahn, A.; Sanyal, A.; Perez, G.F.; Colberg-Poley, A.M.; Campos, J.; Rose, M.C.; Perez-Losada, M. Different next generation sequencing platforms produce different microbial profiles and diversity in cystic fibrosis sputum. *J. Microbiol. Methods* **2016**, *130*, 95–99. [CrossRef] [PubMed]
36. Wu, Y.; Luo, Z.; Liu, C. Variations in fecal microbial profiles of acute exacerbations and stable chronic obstructive pulmonary disease. *Life Sci.* **2021**, *265*, 118738. [CrossRef] [PubMed]
37. Jang, Y.O.; Lee, S.H.; Choi, J.J.; Kim, D.H.; Choi, J.M.; Kang, M.J.; Oh, Y.M.; Park, Y.J.; Shin, Y.; Lee, S.W. Fecal microbial transplantation and a high fiber diet attenuates emphysema development by suppressing inflammation and apoptosis. *Exp. Mol. Med.* **2020**, *52*, 1128–1139. [CrossRef] [PubMed]
38. Yagi, K.; Asai, N.; Huffnagle, G.B.; Lukacs, N.W.; Fonseca, W. Early-Life Lung and Gut Microbiota Development and Respiratory Syncytial Virus Infection. *Front. Immunol.* **2022**, *13*, 877771. [CrossRef]
39. Malinczak, C.A.; Lukacs, N.W.; Fonseca, W. Early-Life Respiratory Syncytial Virus Infection, Trained Immunity and Subsequent Pulmonary Diseases. *Viruses* **2020**, *12*, 505. [CrossRef] [PubMed]
40. Sikkel, M.B.; Quint, J.K.; Mallia, P.; Wedzicha, J.A.; Johnston, S.L. Respiratory syncytial virus persistence in chronic obstructive pulmonary disease. *Pediatr. Infect. Dis. J.* **2008**, *27*, S63–S70. [CrossRef]
41. Malinczak, C.A.; Fonseca, W.; Hrycaj, S.M.; Morris, S.B.; Rasky, A.J.; Yagi, K.; Wellik, D.M.; Ziegler, S.F.; Zemans, R.L.; Lukacs, N.W. Early-life Pulmonary Viral Infection Leads to Long-term Functional and lower airway Structural changes in the lungs. *Am. J. Physiol. Lung Cell Mol. Physiol.* **2024**, *326*, L280–L291. [CrossRef]
42. Yagi, K.; Lukacs, N.W.; Huffnagle, G.B.; Kato, H.; Asai, N. Respiratory and Gut Microbiome Modification during Respiratory Syncytial Virus Infection: A Systematic Review. *Viruses* **2024**, *16*, 220. [CrossRef]
43. Durack, J.; Lynch, S.V.; Nariya, S.; Bhakta, N.R.; Beigelman, A.; Castro, M.; Dyer, A.M.; Israel, E.; Kraft, M.; Martin, R.J.; et al. Features of the bronchial bacterial microbiome associated with atopy, asthma, and responsiveness to inhaled corticosteroid treatment. *J. Allergy Clin. Immunol.* **2017**, *140*, 63–75. [CrossRef] [PubMed]
44. Huang, C.; Ni, Y.; Du, W.; Shi, G. Effect of inhaled corticosteroids on microbiome and microbial correlations in asthma over a 9-month period. *Clin. Transl. Sci.* **2022**, *15*, 1723–1736. [CrossRef] [PubMed]
45. Asai, N.; Ohkuni, Y.; Ohashi, W.; Kaneko, N. Modified MRC assessment and FEV1.0 can predict frequent acute exacerbation of COPD: An observational prospective cohort study at a single-center in Japan. *Respir. Med.* **2023**, *212*, 107218. [CrossRef] [PubMed]
46. Walsh, E.E.; Perez Marc, G.; Zareba, A.M.; Falsey, A.R.; Jiang, Q.; Patton, M.; Polack, F.P.; Llapur, C.; Doreski, P.A.; Ilangovan, K.; et al. Efficacy and Safety of a Bivalent RSV Prefusion F Vaccine in Older Adults. *N. Engl. J. Med.* **2023**, *388*, 1465–1477. [CrossRef]
47. Ma, J.; Chen, L.; Tang, S.; Shi, Y. Efficacy and safety of respiratory syncytial virus vaccination during pregnancy to prevent lower respiratory tract illness in newborns and infants: A systematic review and meta-analysis of randomized controlled trials. *Front. Pediatr.* **2023**, *11*, 1260740. [CrossRef]
48. Rosas-Salazar, C.; Chirkova, T.; Gebretsadik, T.; Chappell, J.D.; Peebles, R.S., Jr.; Dupont, W.D.; Jadhao, S.J.; Gergen, P.J.; Anderson, L.J.; Hartert, T.V. Respiratory syncytial virus infection during infancy and asthma during childhood in the USA (INSPIRE): A population-based, prospective birth cohort study. *Lancet* **2023**, *401*, 1669–1680. [CrossRef]

49. Scotta, M.C.; Stein, R.T. Current strategies and perspectives for active and passive immunization against Respiratory Syncytial Virus in childhood. *J. Pediatr.* **2023**, *99* (Suppl. S1), S4–S11. [CrossRef]
50. Mazur, N.I.; Terstappen, J.; Baral, R.; Bardaji, A.; Beutels, P.; Buchholz, U.J.; Cohen, C.; Crowe, J.E., Jr.; Cutland, C.L.; Eckert, L.; et al. Respiratory syncytial virus prevention within reach: The vaccine and monoclonal antibody landscape. *Lancet Infect. Dis.* **2023**, *23*, e2–e21. [CrossRef] [PubMed]
51. Istvan, E.S.; Deisenhofer, J. Structural mechanism for statin inhibition of HMG-CoA reductase. *Science* **2001**, *292*, 1160–1164. [CrossRef] [PubMed]
52. Tousoulis, D.; Psarros, C.; Demosthenous, M.; Patel, R.; Antoniades, C.; Stefanadis, C. Innate and adaptive inflammation as a therapeutic target in vascular disease: The emerging role of statins. *J. Am. Coll. Cardiol.* **2014**, *63*, 2491–2502. [CrossRef] [PubMed]
53. Xue, X.; Cai, H.; Chai, Z.; Shang, F.; Guan, W.; Zhang, L.; Chen, X.; Zhou, B.; Zhang, L. Efficacy of statin therapy in chronic obstructive pulmonary disease: A systematic review and meta-analysis from 2008–2019. *Panminerva Med.* **2020**, *65*, 376–384. [CrossRef]
54. Kim, J.H.; Choi, H.G.; Kwon, M.J.; Kim, J.H.; Park, J.Y.; Hwang, Y.I.; Jang, S.H.; Jung, K.S. The Influence of Prior Statin Use on the Prevalence and Exacerbation of Chronic Obstructive Pulmonary Disease in an Adult Population. *Front. Med.* **2022**, *9*, 842948. [CrossRef]
55. Zhang, W.; Zhang, Y.; Li, C.W.; Jones, P.; Wang, C.; Fan, Y. Effect of Statins on COPD: A Meta-Analysis of Randomized Controlled Trials. *Chest* **2017**, *152*, 1159–1168. [CrossRef] [PubMed]
56. Sun, B.; Li, L.; Zhou, X. Comparative analysis of the gut microbiota in distinct statin response patients in East China. *J. Microbiol.* **2018**, *56*, 886–892. [CrossRef]
57. Liu, Y.; Song, X.; Zhou, H.; Zhou, X.; Xia, Y.; Dong, X.; Zhong, W.; Tang, S.; Wang, L.; Wen, S.; et al. Gut Microbiome Associates With Lipid-Lowering Effect of Rosuvastatin in Vivo. *Front. Microbiol.* **2018**, *9*, 530. [CrossRef]
58. Khan, T.J.; Ahmed, Y.M.; Zamzami, M.A.; Mohamed, S.A.; Khan, I.; Baothman, O.A.S.; Mehanna, M.G.; Yasir, M. Effect of atorvastatin on the gut microbiota of high fat diet-induced hypercholesterolemic rats. *Sci. Rep.* **2018**, *8*, 662. [CrossRef] [PubMed]
59. Dias, A.M.; Cordeiro, G.; Estevinho, M.M.; Veiga, R.; Figueira, L.; Reina-Couto, M.; Magro, F.; Clinical Pharmacology Unit, São João Hospital University Centre. Gut bacterial microbiome composition and statin intake—A systematic review. *Pharmacol. Res. Perspect.* **2020**, *8*, e00601. [CrossRef]
60. Schneeberger, M.; Everard, A.; Gomez-Valades, A.G.; Matamoros, S.; Ramirez, S.; Delzenne, N.M.; Gomis, R.; Claret, M.; Cani, P.D. Akkermansia muciniphila inversely correlates with the onset of inflammation, altered adipose tissue metabolism and metabolic disorders during obesity in mice. *Sci. Rep.* **2015**, *5*, 16643. [CrossRef]
61. Sokol, H.; Pigneur, B.; Watterlot, L.; Lakhdari, O.; Bermudez-Humaran, L.G.; Gratadoux, J.J.; Blugeon, S.; Bridonneau, C.; Furet, J.P.; Corthier, G.; et al. Faecalibacterium prausnitzii is an anti-inflammatory commensal bacterium identified by gut microbiota analysis of Crohn disease patients. *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 16731–16736. [CrossRef]
62. Verma, D.; Garg, P.K.; Dubey, A.K. Insights into the human oral microbiome. *Arch. Microbiol.* **2018**, *200*, 525–540. [CrossRef]
63. Sampaio-Maia, B.; Caldas, I.M.; Pereira, M.L.; Perez-Mongiovi, D.; Araujo, R. The Oral Microbiome in Health and Its Implication in Oral and Systemic Diseases. *Adv. Appl. Microbiol.* **2016**, *97*, 171–210.
64. Nagata, N.; Nishijima, S.; Kojima, Y.; Hisada, Y.; Imbe, K.; Miyoshi-Akiyama, T.; Suda, W.; Kimura, M.; Aoki, R.; Sekine, K.; et al. Metagenomic Identification of Microbial Signatures Predicting Pancreatic Cancer From a Multinational Study. *Gastroenterology* **2022**, *163*, 222–238. [CrossRef] [PubMed]
65. Wen, S.; Zhang, Z.; Ouyang, Y.; Liu, J.; Liang, Z.; Pi, Y.; Su, Z.; Chen, D.; Guo, L.; Jiang, Q.; et al. The Role of Oral Microbiota in Chronic Obstructive Pulmonary Disease. *Respiration* **2022**, *101*, 859–868. [CrossRef]
66. Bostanci, N.; Belibasakis, G.N. Porphyromonas gingivalis: An invasive and evasive opportunistic oral pathogen. *FEMS Microbiol. Lett.* **2012**, *333*, 1–9. [CrossRef]
67. Chen, Y.; Zhou, R.; Yi, Z.; Li, Y.; Fu, Y.; Zhang, Y.; Li, P.; Li, X.; Pan, Y. Porphyromonas gingivalis induced inflammatory responses and promoted apoptosis in lung epithelial cells infected with H1N1 via the Bcl2/Bax/Caspase3 signaling pathway. *Mol. Med. Rep.* **2018**, *18*, 97–104.
68. Li, Q.; Pan, C.; Teng, D.; Lin, L.; Kou, Y.; Haase, E.M.; Scannapieco, F.A.; Pan, Y. Porphyromonas gingivalis modulates Pseudomonas aeruginosa-induced apoptosis of respiratory epithelial cells through the STAT3 signaling pathway. *Microbes Infect.* **2014**, *16*, 17–27. [CrossRef] [PubMed]
69. Li, Q.; Tan, L.; Wang, H.; Kou, Y.; Shi, X.; Zhang, S.; Pan, Y. Fusobacterium nucleatum Interaction with Pseudomonas aeruginosa Induces Biofilm-Associated Antibiotic Tolerance via Fusobacterium Adhesin A. *ACS Infect. Dis.* **2020**, *6*, 1686–1696. [CrossRef]
70. Shi, Q.; Zhang, B.; Xing, H.; Yang, S.; Xu, J.; Liu, H. Patients with Chronic Obstructive Pulmonary Disease Suffer from Worse Periodontal Health-Evidence from a Meta-Analysis. *Front. Physiol.* **2018**, *9*, 33. [CrossRef] [PubMed]
71. Takeuchi, K.; Matsumoto, K.; Furuta, M.; Fukuyama, S.; Takeshita, T.; Ogata, H.; Suma, S.; Shibata, Y.; Shimazaki, Y.; Hata, J.; et al. Periodontitis Is Associated with Chronic Obstructive Pulmonary Disease. *J. Dent. Res.* **2019**, *98*, 534–540. [CrossRef]
72. Parashar, P.; Parashar, A.; Saraswat, N.; Pani, P.; Pani, N.; Joshi, S. Relationship between Respiratory and Periodontal Health in Adults: A Case-Control Study. *J. Int. Soc. Prev. Community Dent.* **2018**, *8*, 560–564. [CrossRef]
73. Si, Y.; Fan, H.; Song, Y.; Zhou, X.; Zhang, J.; Wang, Z. Association between periodontitis and chronic obstructive pulmonary disease in a Chinese population. *J. Periodontol.* **2012**, *83*, 1288–1296. [CrossRef] [PubMed]

74. Holtfreter, B.; Richter, S.; Kocher, T.; Dorr, M.; Volzke, H.; Ittermann, T.; Obst, A.; Schaper, C.; John, U.; Meisel, P.; et al. Periodontitis is related to lung volumes and airflow limitation: A cross-sectional study. *Eur. Respir. J.* **2013**, *42*, 1524–1535. [CrossRef] [PubMed]
75. Yang, L.; Dunlap, D.G.; Qin, S.; Fitch, A.; Li, K.; Koch, C.D.; Nouraie, M.; DeSensi, R.; Ho, K.S.; Martinson, J.J.; et al. Alterations in Oral Microbiota in HIV Are Related to Decreased Pulmonary Function. *Am. J. Respir. Crit. Care Med.* **2020**, *201*, 445–457. [CrossRef] [PubMed]
76. Beck, J.M.; Schloss, P.D.; Venkataraman, A.; Twigg, H., 3rd; Jablonski, K.A.; Bushman, F.D.; Campbell, T.B.; Charlson, E.S.; Collman, R.G.; Crothers, K.; et al. Multicenter Comparison of Lung and Oral Microbiomes of HIV-infected and HIV-uninfected Individuals. *Am. J. Respir. Crit. Care Med.* **2015**, *192*, 1335–1344. [CrossRef] [PubMed]
77. Kuwal, A.; Joshi, V.; Dutt, N.; Singh, S.; Agarwal, K.C.; Purohit, G. A Prospective Study of Bacteriological Etiology in Hospitalized Acute Exacerbation of COPD Patients: Relationship with Lung Function and Respiratory Failure. *Turk. Thorac. J.* **2018**, *19*, 19–27. [CrossRef] [PubMed]
78. Mayhew, D.; Devos, N.; Lambert, C.; Brown, J.R.; Clarke, S.C.; Kim, V.L.; Magid-Slav, M.; Miller, B.E.; Ostridge, K.K.; Patel, R.; et al. Longitudinal profiling of the lung microbiome in the AERIS study demonstrates repeatability of bacterial and eosinophilic COPD exacerbations. *Thorax* **2018**, *73*, 422–430. [CrossRef]
79. Shen, T.C.; Chang, P.Y.; Lin, C.L.; Chen, C.H.; Tu, C.Y.; Hsia, T.C.; Shih, C.M.; Hsu, W.H.; Sung, F.C.; Kao, C.H. Risk of Periodontal Diseases in Patients With Chronic Obstructive Pulmonary Disease: A Nationwide Population-based Cohort Study. *Medicine* **2015**, *94*, e2047. [CrossRef]
80. Brook, I.; Frazier, E.H. Immune response to Fusobacterium nucleatum and Prevotella intermedia in the sputum of patients with acute exacerbation of chronic bronchitis. *Chest* **2003**, *124*, 832–833. [CrossRef]
81. Baldomero, A.K.; Siddiqui, M.; Lo, C.Y.; Petersen, A.; Pragman, A.A.; Connett, J.E.; Kunisaki, K.M.; Wendt, C.H. The relationship between oral health and COPD exacerbations. *Int. J. Chron. Obstr. Pulm. Dis.* **2019**, *14*, 881–892. [CrossRef]
82. Chen, X.; Wang, N.; Wang, J.; Liao, B.; Cheng, L.; Ren, B. The interactions between oral-gut axis microbiota and Helicobacter pylori. *Front. Cell Infect. Microbiol.* **2022**, *12*, 914418. [CrossRef]
83. de Oliveira, R.C.G.; Gardev, E.; Shaddox, L.M. Dysbiotic relationship between arthritis and the oral-gut microbiome. A critical review. *J. Periodontal Res.* **2022**, *57*, 711–723. [CrossRef] [PubMed]
84. Kronborg, T.M.; Ytting, H.; Hobolth, L.; Moller, S.; Kimer, N. Novel Anti-inflammatory Treatments in Cirrhosis. A Literature-Based Study. *Front Med.* **2021**, *8*, 718896. [CrossRef] [PubMed]
85. Nowakowska, M.K.; Lei, X.; Thompson, M.T.; Shaitelman, S.F.; Wehner, M.R.; Woodward, W.A.; Giordano, S.H.; Nead, K.T. Association of statin use with clinical outcomes in patients with triple-negative breast cancer. *Cancer* **2021**, *127*, 4142–4150. [CrossRef] [PubMed]
86. Manthravadi, S.; Shrestha, A.; Madhusudhana, S. Impact of statin use on cancer recurrence and mortality in breast cancer: A systematic review and meta-analysis. *Int. J. Cancer.* **2016**, *139*, 1281–1288. [CrossRef] [PubMed]
87. Umakanthan, S.; Senthil, S.; John, S.; Madhavan, M.K.; Das, J.; Patil, S.; Rameshwaram, R.; Cintham, A.; Subramaniam, V.; Yogi, M.; et al. The Effect of Statins on Clinical Outcome Among Hospitalized Patients With COVID-19: A Multi-Centric Cohort Study. *Front. Pharmacol.* **2022**, *13*, 742273. [CrossRef] [PubMed]
88. Caputo, F.; Santini, C.; Casadei-Gardini, A.; Cerma, K.; Bardasi, C.; Garajova, I.; Lattanzi, E.; Passardi, A.; Rapposelli, I.G.; Spallanzani, A.; et al. Statins increase pathological response in locally advanced rectal cancer treated with chemoradiation: A multicenter experience. *Future Oncol.* **2022**, *18*, 2651–2659. [CrossRef] [PubMed]
89. Chai, L.; Wang, Q.; Si, C.; Gao, W.; Zhang, L. Potential Association Between Changes in Microbiota Level and Lung Diseases: A Meta-Analysis. *Front Med.* **2021**, *8*, 723635. [CrossRef]
90. Smani, Y.; Docobo-Perez, F.; McConnell, M.J.; Pachon, J. Acinetobacter baumannii-induced lung cell death: Role of inflammation, oxidative stress and cytosolic calcium. *Microb. Pathog.* **2011**, *50*, 224–232. [CrossRef] [PubMed]
91. Asai, N.; Sakanashi, D.; Suematsu, H.; Kato, H.; Watanabe, H.; Shiota, A.; Hagihara, M.; Koizumi, Y.; Yamagishi, Y.; Mikamo, H. Clinical manifestations and risk factors of community-onset Acinetobacter species pneumonia in Japan; case control study in a single institute in Japan. *J. Infect. Chemother.* **2019**, *25*, 639–642. [CrossRef]
92. Kang, M.J.; Jo, S.G.; Kim, D.J.; Park, J.H. NLRP3 inflammasome mediates interleukin-1beta production in immune cells in response to Acinetobacter baumannii and contributes to pulmonary inflammation in mice. *Immunology* **2017**, *150*, 495–505. [CrossRef] [PubMed]
93. Mulcahy, L.R.; Isabella, V.M.; Lewis, K. Pseudomonas aeruginosa biofilms in disease. *Microb. Ecol.* **2014**, *68*, 1–12. [CrossRef] [PubMed]
94. Ghebre, M.A.; Pang, P.H.; Diver, S.; Desai, D.; Bafadhel, M.; Haldar, K.; Kebadze, T.; Cohen, S.; Newbold, P.; Rapley, L.; et al. Biological exacerbation clusters demonstrate asthma and chronic obstructive pulmonary disease overlap with distinct mediator and microbiome profiles. *J. Allergy Clin. Immunol.* **2018**, *141*, 2027–2036.e2012. [CrossRef] [PubMed]