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REVIEW

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Tobacco and COPD: presenting the World Health Organization (WHO) Tobacco Knowledge Summary

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Abstract

The WHO recently published a Tobacco Knowledge Summary (TKS) synthesizing current evidence on tobacco and COPD, aiming to raise awareness among a broad audience of health care professionals. Furthermore, it can be used as an advocacy tool in the fight for tobacco control and prevention of tobacco-related disease. This article builds on the evidence presented in the TKS, with a greater level of detail intended for a lung-specialist audience. Pulmonologists have a vital role to play in advocating for the health of their patients and the wider population by sharing five key messages: (1) Smoking is the leading cause of COPD in high-income countries, contributing to approximately 70% of cases. Quitting tobacco is an essential step toward better lung health. (2) People with COPD face a significantly higher risk of developing lung cancer. Smoking cessation is a powerful measure to reduce cancer risk. (3) Cardiovascular disease, lung cancer and type-2 diabetes are common comorbidities in people with COPD. Quitting smoking not only improves COPD management, but also reduces the risk of developing these coexisting conditions. (4) Tobacco smoke also significantly impacts children's lung growth and development, increasing the risk of respiratory infections, asthma and up to ten other conditions, and COPD later in life. Governments should implement effective tobacco control measures to protect vulnerable populations. (5) The tobacco industry's aggressive strategies in the marketing of nicotine delivery systems and all tobacco products specifically target children, adolescents, and young adults. Protecting our youth from these harmful tactics is a top priority.

Keywords Chronic obstructive pulmonary disease, Smoking, Tobacco control, Smoking cessation

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What is COPD?

Chronic obstructive pulmonary disease (COPD) is a progressive and largely irreversible respiratory condition that causes poorly reversible airflow obstruction and an abnormal inflammatory response in the lungs, associated with overall poor lung health [1–3]. It affects the airways, lung parenchyma, and pulmonary vasculature as well as having extra-pulmonary effects. COPD mechanisms include mucus hypersecretion (chronic bronchitis), tissue destruction (emphysema), and small airway inflammation with fibrosis. Emphysema usually develops later, and chronic bronchitis is diagnosed if a productive cough persists for at least three months in at least two consecutive years. The main pathological changes are found in the small airways with epithelial remodeling including goblet cell metaplasia, basal cell hyperplasia, leading to thickening of small airway walls and obliteration [4]. The large airways are also affected with remodeling changes, inflammation, squamous metaplasia, and there can be associated bronchiectasis (Fig. 1). Emphysema of the peri-bronchial lung parenchyma can occur more than 10 years after small airway obstruction can be detected, and predominantly in the areas initially affected by air trapping. The pathological changes in the small airways lead to increased airflow resistance, and air trapping [3, 5]. People with COPD are at risk of developing both infections and lung cancer [6, 7]. The 5-year mortality rate for COPD is estimated at 25% [8, 9].

Development of COPD

COPD is considered a preventable and manageable disease, and it is possible to prevent or reduce its individual and population burden by dealing, among other, with social determinants of health. These social determinants are tobacco and tobacco products, indoor and outdoor pollution, occupational exposures, infections, low education and socioeconomic status, and poverty. COPD is a major global health problem and the third leading cause of death worldwide. In 2019, there were 392 million cases of COPD globally [10], associated with 3.23 million deaths [1] and 74.4 million disability-adjusted life years [11]. Three-quarters of people with COPD live in low- and middle-income countries [1, 10, 11]. Smoking is still the primary, causal risk factor leading to COPD, but environmental exposures, such as exposure to biomass fuel combustion, air pollution, and occupational exposures, and poor lung development (both pre- and post-natal) are increasingly recognized as important causes of COPD [3, 12]. Children's exposure to tobacco constituents during fetal development, and environmental tobacco smoke exposure are also risk factors associated with poor lung development. Second- and third-hand tobacco smoke exposure are also risk factors for ill-health during childhood, including asthma, respiratory infections, otitis media, sudden infant death syndrome (SIDS), low birth weight and premature birth, cognitive and behavioral problems, and likely an increased cancer risk. It is estimated that approximately 70% of COPD cases in high income countries are caused by tobacco smoking [1], and the burden is growing in low- and middle-income countries. When burned, cigarette smoke contains over seven thousand chemicals, some with toxic and carcinogenic effects [13, 14]. The inhaled complex cigarette smoke particles can adhere to and affect the respiratory tract, and the deposition varies depending on their particles size. Larger particles tend to settle in the upper airways (large airways), while smaller particles are deposited in the lower airways (small airways < 2 mm) and alveoli, leading to chronic inflammation, oxidative stress and damage to the airways and lung parenchymal structures [15]. Substantial evidence indicates that exposure to household air pollution, particularly from indoor sources such as biomass cooking fuel, firewood heating, and candles [16], is also associated with an increased risk of developing COPD [17], especially in low- and middle-income countries [18] where children and women are predominantly exposed [19]. Household air pollution is recognized as a major risk factor for COPD, with chronic respiratory diseases in women being associated with the use of solid fuel for cooking [20]. Moreover, the detrimental effects of household air pollution exposure on lung development during early life are also evident [19, 20].

Up to late-20th century, COPD was considered solely a smoking-related disease [21], and most research focused on the pathological and physiological changes in the airways and lungs caused by smoking. As discussed above, it is now recognized that many patients with COPD are people who never smoked, but there is relatively little data on the pathological changes seen in these patients. There is some evidence that the deposition of the particles produced by cigarette smoking is different to that due to biomass or occupational exposures as these are mostly inhaled nasally where the filtration efficiency is higher, whereas tobacco smoke is inhaled through the mouth at a high flow rate leading to greater deposition in the lower airways and alveoli [22]. In susceptible subjects, cigarette smoke triggers a complex cascade of inflammation, with oxidative stress, accelerated cellular senescence and aberrant repair processes. There is evidence that women, especially after menopause, are more susceptible to the effects of tobacco smoke and develop a different pattern of disease with more severe small airway obstruction and less emphysema [23–27].

Tobacco smoke

Tobacco products and tobacco smoke contain a complex mixture of over 9500 compounds, such as nicotine, tar, and chemicals, many of which have been recognized as

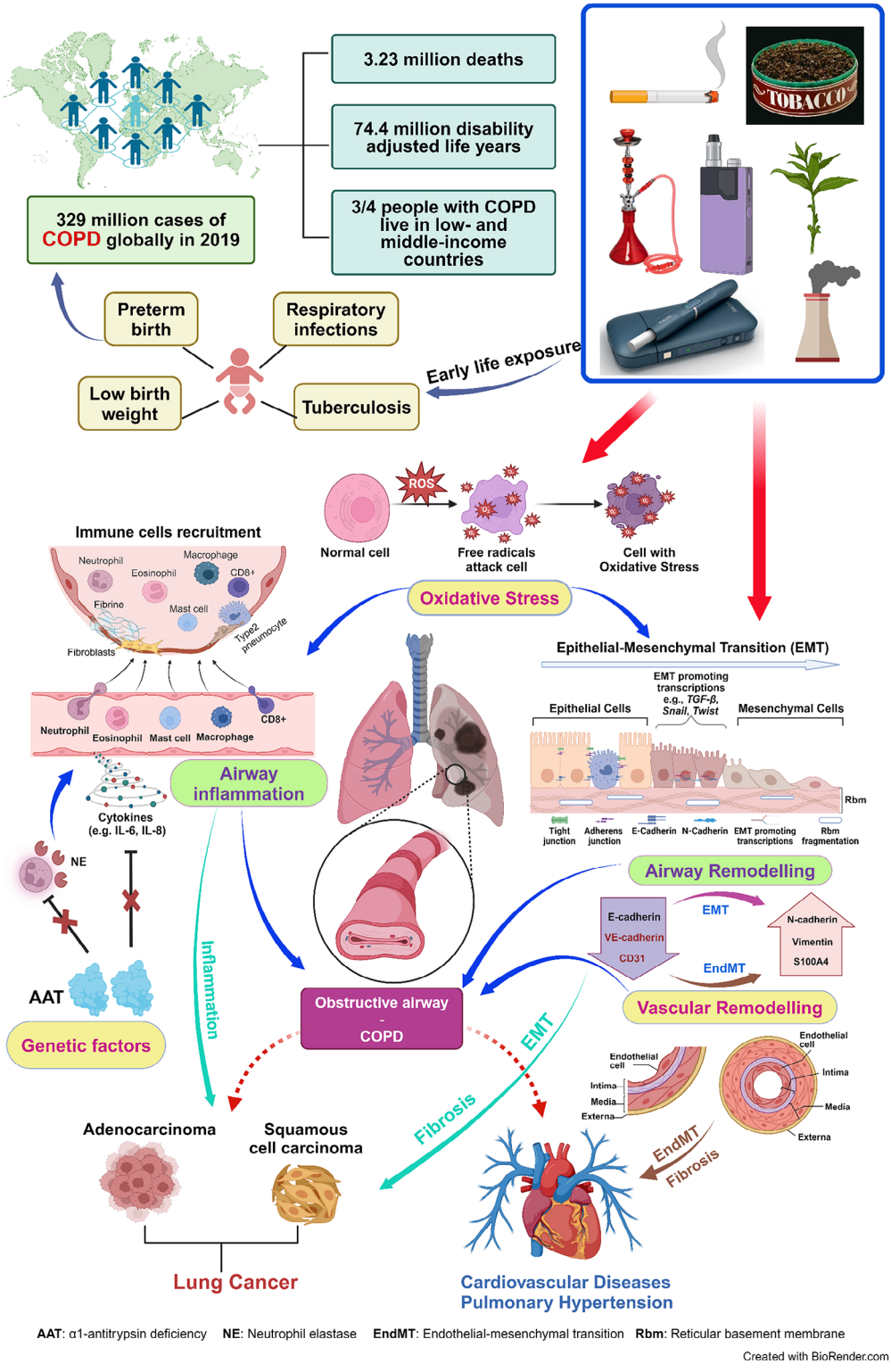

Fig. 1 Tobacco smoking and development of Chronic Obstructive Pulmonary Disease (COPD). There were 329 million cases of COPD globally in 2019, with high rates of mortality and morbidity. The leading risk factor for developing COPD is smoking, including early life exposure. The pathogenesis of COPD involves various factors such as airway inflammation, oxidative stress, genetic factors, epithelial-mesenchymal transition (EMT) mediated airway remodeling, and endothelial-mesenchymal transition (EndMT) mediated vascular remodeling. COPD often coexists with other conditions such as lung cancer, cardiovascular diseases, and pulmonary hypertension as common comorbidities

hazardous to human health by regulatory agencies [28]. Tobacco smoke is a complex aerosol which includes condensed liquid droplets (the particulate matter (PM) or tar) suspended in a mixture of volatile and semi-volatile compounds and combustion gases (the gas fraction). The gas phase of cigarette smoke include traces of acetaldehyde, methane, hydrogen cyanide, nitric acid, acetone, acrolein, ammonia, methanol, hydrogen sulfide, hydrocarbons, gas phase nitrosamines, carbonyl compounds and toxic metals including sodium, mercury, iron, arsenic, cadmium, and cobalt [29]. Constituents in the particulate phase include carboxylic acids, phenols, water, nicotine, terpenoids, tobacco-specific nitrosamines, polycyclic aromatic hydrocarbons, and catechol. Some toxic effects induced by tobacco smoke, result from direct genetic or epigenetic effects resulting in altered gene functions (for example, cell cycle, DNA repair, and tumor suppressor genes). Many components of tobacco smoke also have the potential to drive the inflammatory response and impaired healing. Depending on the size of the inhaled complex smoke particles, they can be deposited throughout the airway. Larger particles favor the larger and more central airways, while smaller particles are deposited in the smaller peripheral airways and sacs, leading to chronic inflammation, infections, oxidative stress and damage to the airways and gas exchange areas of the lung [15]. Combustion also produces reactive oxidative substances such as superoxide anion (O2–), hypochlorite (ClO–), peroxynitrite (ONOO–), and hydroxyl (•OH) [30] that are not present in the leaf. Nicotine levels vary in different types of tobacco leaves [31]. Additives, chemicals, and flavorings are usually added to increase the palatability, attractiveness, and addictiveness of tobacco products [32, 33]. Combined with other substances, such additives can become toxic during combustion of these products [33, 34]. These contribute to oxidative stress and damage epithelial cells by inducing peroxidation of lipids and other cell membrane constituents, activate oxidative-sensitive cellular pathways, and induce DNA damage [35]. Other forms of smoked tobacco products, for example, hookah or water-pipe, burn tobacco leaves with other additives [36, 37]. These forms of smoking are at least as detrimental to lung health as smoking cigarettes and should not be considered as a safe alternatives of cigarette smoking [38]. Moreover, nicotine, a highly addictive substance, is deposited in the lung and rapidly absorbed, stimulating the central nervous system, and causing increase in heart rate and blood pressure [39, 40].

Airway inflammation

The immune response to inhaled tobacco smoke leads to the recruitment of inflammatory cells, such as neutrophils, lymphocytes and alveolar macrophages [41]. COPD is a heterogeneous condition, with between-individual variation in the nature and severity of airway inflammation [42] and the inflammatory cell profile also varies in large and small airways and with severity of COPD, hence careful appraisal is needed [43]. Both neutrophil-associated COPD with T1 and T17 type immune responses and eosinophil-associated T2-mediated immunity are found in different patients, as well as autoimmunity in more severe disease [42]. Studies have also shown increase in M1/M2 macrophages and mast cells in people who smoke and patients with COPD [44–46].

Genetic factors

Genetic factors also play a role in the development of COPD and may accelerate a decline in lung function. The well-known genetic factor related to COPD is the deficiency of serine protease α1-antitrypsin (AATD), a hereditary disorder, which increases the risk of 1–3% of individuals developing COPD, especially in those who smoke [47]. Genetic variants could strongly predict COPD in independent populations, and these variants are higher in those who smoke [48]. In addition, the enrichment of lung developmental pathways was observed in lung function-associated genetic variants, which altered lung gene expression [49]. The study also showed that although the heritability of lung function and COPD was estimated to be between 38 and 50%, individual genetic variants only account for a small fraction of the overall risk associated with COPD [50].

Tobacco smoking, COPD and multimorbidity

People with COPD also have a higher risk for other health problems, both because of shared risk factors and due to the systemic effects of COPD [3, 51]. Multimorbidity can impact negatively on symptoms, quality of life, complication rates, disease management and life expectancy [2]. The most common multi-morbid conditions include coronary artery disease, atrial fibrillation, congestive heart failure, skeletal muscle wasting, metabolic syndromes including diabetes mellitus, osteoporosis, depression, anxiety, gastro-esophageal reflux disease (GERD) and lung cancer [3]. Nearly half of all COPD patients have three or more other long-term conditions, underscoring the importance of a holistic person-centered approach to the overall management of COPD [51]. (Fig. 2)

Cardiovascular diseases

Individuals with COPD often share cardiovascular risk factors, such as smoking, sedentary lifestyle, and hypertension [52]. Chronic inflammation in COPD can also contribute to atherosclerosis and vascular thrombosis [51]. Impaired lung function or oxygen exchange can increase strain on the heart in people with COPD. Cardiovascular diseases can have a negative impact on individuals with COPD, causing pulmonary hypertension

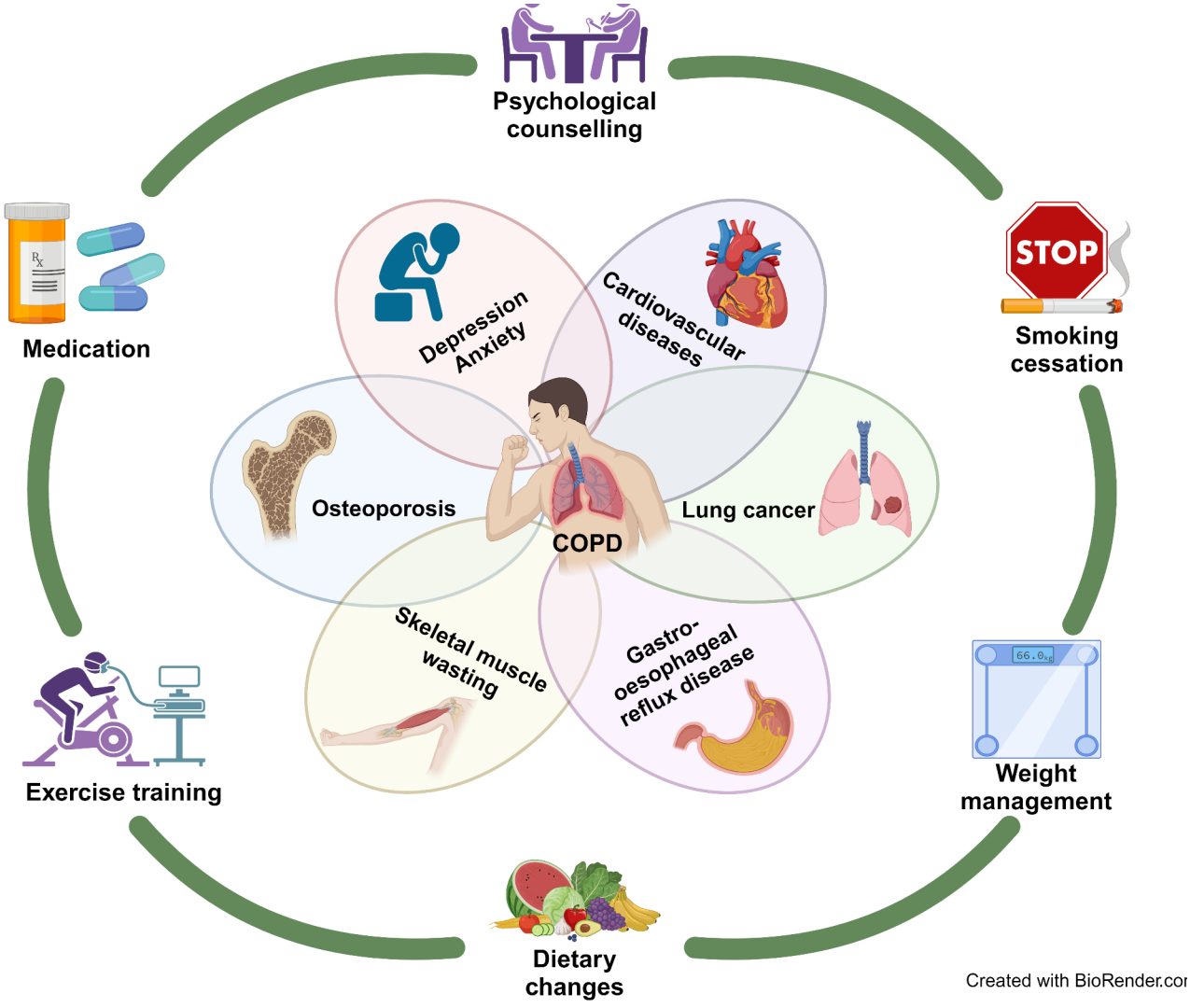

Fig. 2 Chronic obstructive pulmonary disease (COPD) and multimorbidity, and the management strategies. The most common comorbidities in COPD include cardiovascular diseases, lung cancer, gastro-oesophageal reflux disease (GERD), skeletal muscle wasting, osteoporosis, depression and anxiety, which normally affect COPD progression and management. Most COPD patients have three or more comorbidities. Multidisciplinary management strategies, including smoking cessation, weight management, dietary changes, exercise training, medication and psychological counselling, are essential for COPD patients with multimorbidity

(PH) [53]. In addition, coronary artery disease or heart failure can compromise lung function by reducing oxygen supply to the lungs [54]. The co-existence of COPD and cardiovascular diseases is associated with worse outcomes, increased hospitalization, higher death rates and reduced quality of life. PH has also been associated with COPD and cardiovascular abnormalities. Patients with COPD showed noticeable alteration in the pulmonary vasculature, characterized by vascular remodeling primarily affecting small size vessels, such as muscular walls of arteries and arterioles [55, 56]. The process of endothelial to mesenchymal transition might be central to this pathology [57]. Severe COPD can contribute to the development of PH due to several factors. These include chronic inflammation, loss of lung tissue elasticity, destruction of small blood vessels in the lungs, and hypoxemia [58]. Similarly, PH can also worsen COPD symptoms and prognosis. The increased pressure in the pulmonary arteries puts additional strain on the right side of the heart, leading to right heart failure [59]. This can further compromise lung function and exacerbate COPD symptoms.

Skeletal muscle wasting

Inactivity is common among COPD patients and significantly contributes to many systemic issues of COPD [60], especially during exacerbations [61]. Research indicate that inactivity independently increases the risk of

skeletal muscle wasting, osteoporosis [62], type 2 diabetes, cardiovascular disease and depression [63]. Among these, skeletal muscle wasting is a critical consequence of inactivity and around 20% of COPD patients suffer from severe skeletal muscle wasting, which leads to considerable morbidity and mortality [61]. Skeletal muscle wasting can initiate a "downward disease spiral", where muscle weakness and inefficient metabolism at low exercise intensity further decrease exercise capacity [64].

Osteoporosis

Osteoporosis is one of the most prevalent comorbidities in COPD, especially the severe airflow obstruction had the greatest risk of osteoporosis [65, 66]. Smoking is a common risk factor for both COPD and osteoporosis. Long-term smoking can result in reduction of bone density [67], degeneration of bone microstructure, and increased bone fragility [66]. Inactivity is another main risk factor osteoporosis in COPD. Due to respiratory failure and shortness of breath after activity in patients with COPD, reduced physical exercise ability becomes an important cause of bone mass loss [68]. Other factors, such as low body composition measures, pulmonary dysfunction, and inflammation, are associated with osteoporosis and COPD [69, 70]. Effective treatments with COPD-associated osteoporosis are unknown, and a specific treatment guideline is needed for better management of these patients [71].

Depression and anxiety

Patients with COPD are commonly experienced mental health conditions, such as depression and anxiety, more than the general population [72, 73]. Depression and anxiety have a significant negative impact on COPD prognosis by reducing physical activity, worsening dyspnea, increasing the frequency of exacerbations, and increase the burden of healthcare services [74]. Depression and anxiety also further interfere with other risk factors such as smoking and worsen patients' quality of life [75]. In particular, anxiety is linked to poor quality of life regarding mental and physical health outcomes in COPD patients [76]. Routine assessment for depression and anxiety are crucial and should become a standard practice in managing COPD [77]. Early detection and comprehensive treatment of depression and anxiety in COPD patients are essential for improving their overall quality of life and health outcomes.

Gastro-oesophageal reflux disease (GERD)

GERD is another commonly observed comorbidity in patients with COPD and can significantly impact the disease's progression and management [78]. Smoking is a known risk factor for GERD in general population [79] and COPD [80]. GERD is associated with an increase frequency of COPD exacerbations [81]. The reflux of stomach contents can irritate the airways and lungs, and further worsen respiratory symptoms such as coughing and shortness of breath and diminishing the quality of life for COPD patients [80]. Modification of lifestyle, including dietary changes [82], weight management, smoking cessation and appropriate medications to reduce stomach acid production can alleviate GERD symptoms [78, 83], improving quality of life in COPD patients.

Lung cancer

Individuals with COPD have a four-to-six-fold higher risk of developing lung cancer compared with the general population [84]. COPD and lung cancer share the same risk factors, such as exposure to tobacco smoke and indoor/outdoor air pollution [85, 86]. COPD and lung cancer often have overlapping symptoms, such as chronic cough, shortness of breath and chest discomfort. This can make it challenging to differentiate between the two conditions based on symptoms alone. Along with inflammation, epithelial to mesenchymal transition have been reported in people who smoke and patients with COPD, which may be one of the shared mechanisms leading to lung cancer in these patients [87–91]. High dose inhaled corticosteroids ameliorate epithelial to mesenchymal transition and improve vascular changes [92, 93]. Inhaled corticosteroids have been shown to reduce risk of lung cancer [94–96]. However, effects of inhaled corticosteroids against lung cancer in COPD remains controversial [97, 98].

Second-hand smoke and COPD

Exposure to second-hand smoke is a significant risk factor for the onset and progression of COPD. Exposure to second-hand smoke in both childhood and adulthood have been linked to an increased risk for COPD-related mortality [99]. Inhalation of second-hand smoke can adversely affect the respiratory system, particularly for individuals already affected by asthma, infections, or allergies. Prolonged exposure to second-hand smoke can cause airway inflammation, broncho-constriction, airway obstruction and lung tissue damage, increase the likelihood of developing COPD, worsen existing COPD symptoms and accelerate lung function decline [100, 101]. Second-hand smoke also increases the risk of developing lung cancer. Tobacco smoke exposure in utero may lead to preterm birth and increase the risk of respiratory diseases such as asthma and COPD in the offspring.

Smokeless tobacco and COPD

There is no direct evidence to date that smokeless tobacco (such as chewing tobacco or snuff) can lead to the development of COPD. Although smokeless tobacco does not involve inhaling smoke into the lungs, it still

exposes users to high level of nicotine and harmful chemicals and toxins that can cause oropharyngeal cancer, which could affect the lungs [102]. The use of smokeless tobacco can lead to chronic irritation and inflammation in the airways [103], contributing to the development of respiratory conditions such as large airway inflammation or bronchitis. We have defined different tobacco products in Table 1.

New and emerging nicotine-delivery systems and other tobacco products and COPD

Electronic nicotine delivery systems (ENDS)

Serious health concerns regarding the use of electronic cigarettes (e-cigarettes) have been raised, particularly related to their use by adolescents and young adults [104, 105]. Early studies have shown a correlation between the use of e-cigarettes and lung injury [12, 106], with e-cigarette users showing increased respiratory symptoms, an elevated risk of developing airway disease and a decline in lung function [107]. However, to date, there is no direct evidence that use of electronic smoking devices leads to the development of COPD. However, based on the literature review, it is postulated that use of e-cigarettes could lead to lung health issues and be a risk factor for development of COPD among those who have never smoked. Osei et al. reported that current e-cigarette users have a 75% higher risk of developing COPD compared with those who have never used e-cigarettes [108]. Daily e-cigarette users and former tobacco cigarette users who currently use e-cigarettes are at a higher risk of developing COPD compared with individuals who have never smoked conventional cigarettes or never used e-cigarettes [109]. In addition, individuals who smoke conventional cigarettes and use e-cigarettes ("dual use") showed the highest likelihood of developing COPD compared with those who have never smoked conventional cigarettes or used e-cigarettes [108, 110–112]. These findings suggested that the use of e-cigarettes may potentially promote pathophysiological processes similar to those seen in COPD. Hence e-cigarettes should not be promoted as a tool for smoking cessation [110, 111]. Additional research is needed to examine the long-term risk of developing COPD among users of e-cigarette products, considering the heterogenous composition of e-cigarette products.

Heated tobacco products

Heated tobacco products (HTPs) emit toxic chemicals, including nicotine, when tobacco is heated or when a device containing tobacco is heated, and these are inhaled by the user. The tobacco industry markets these products as a "less harmful alternative" to conventional cigarettes [113, 114]. Currently, the existing evidence is insufficient to support the reduced exposure claims for HTPs, and existing evidence is also insufficient to support either the reduced risk or reduced harm claims for HTPs [115]. HTPs have recently gained popularity and are available in about 70 countries [114]. Research studies have shown that exposure to HTP emissions can be just as harmful to human lung cells as exposure to smoke from conventional cigarettes. It can cause a persistent allergic response, smoke- or environmental-triggered inflammation that leads to airway scarring, which are the principal causes of airflow limitation in COPD [116, 117]. There was a high prevalence of dual use of HTPs with conventional cigarettes among COPD patients (up to 33%), which did not reduce the harm for these patients [118] or the prevalence of smoking-related chronic diseases [119].

Impact of selected tobacco control interventions on COPD

There is no safe way to use tobacco. Tobacco control plays an important role in public health and chronic disease management. People should be supported to stop using tobacco in all forms, including e-cigarettes and HTPs. Smoking cessation has a great impact on reducing the health risks associated with smoking. It is a crucial intervention for all people who smoke and have COPD, as it can slow the decline in lung function and the progression of COPD [3], improve respiratory symptoms and reduce mortality in patients with COPD compared

Table 1 Tobacco definitions [131]

Smoked tobacco products	Any product made or derived from tobacco which generates smoke. Examples include manufactured cigarettes, roll-your-own tobacco, cigars, cigarillos, shisha (also known as waterpipe), kreteks and bidis.
Second-hand smoke (SHS)	The smoke emitted from the burning end of a cigarette or other tobacco products, usually in combination with the smoke exhaled by the people who smoke.
Smokeless tobacco	Any product that consists of cut, ground, powdered or other tobacco that is intended to be placed in the oral or nasal cavity. Examples include snuff, chewing tobacco, gutka, mishri and snus.
Heated tobacco product (HTP)	Tobacco products that produce aerosols containing nicotine and toxic chemicals when tobacco is heated or when a device containing tobacco is heat-activated. These aerosols are inhaled by users during a process of sucking or smoking involving a device. They contain the highly addictive substance nicotine, as well as non-tobacco additives, and are often flavored.
Electronic nicotine delivery system (ENDS) (also known as e-cigarette)	A device that heats a liquid to create an aerosol that is inhaled by the user, which typically contains nicotine and toxic substances that are harmful to both users and non-users who are exposed to the aerosols second-hand; the liquid is often flavored.

with those who continue to smoke [120]. Smoking cessation also benefits COPD patients who have nocturnal sleep disorders [121]. Health-care professionals should increase patients' awareness of the hazards of smoking and provide smoking cessation advice to enhance their self-efficacy in quitting [122, 123]. The WHO urges governments to include smoking cessation and treatment services as part of tobacco control programmes [124], also recommended in the United States Surgeon General's 2020 report on smoking cessation [125].

Population-level interventions to address tobacco use

Population-level interventions to combat tobacco-linked COPD morbidity and mortality are essential. WHO has well-established tools for implementing tobacco control measures. To support countries in implementing the WHO Framework Convention on Tobacco Control (FCTC), WHO introduced the MPOWER package in 2008 and reported on progress in a biennial report on the global tobacco epidemic [123]. MPOWER contained a set of six tobacco control demand reduction measures corresponding to one or more articles in the WHO FCTC. These are, (1) Monitoring tobacco use and prevention policies; (2) Protecting people from tobacco smoke; (3) Offering help to quit tobacco use; (4) Warning about the dangers of tobacco; (5) Enforcing bans on tobacco advertising, promotion, and sponsorship; (6) Raising taxes on tobacco (MPOWER). The WHO Package of Essential Noncommunicable (PEN) Disease Interventions for primary health care includes a module on the management of COPD. PEN emphasizes the need to inform people with COPD about the risks of smoking and indoor air pollution and the need to stop smoking [122]. The updated "best buys" and other recommended interventions for the prevention and control of noncommunicable diseases were adopted by the 76th World Health Assembly in 2023. These include six cost-effective interventions to reduce tobacco exposure and two on the management of COPD. The WHO recommends the following population-level and pharmacological interventions to ensure access to comprehensive cessation support (Table 2).

Emerging concerns and future directions

The primary strategy to reduce the burden of COPD is to address all risk factors, especially exposure to all forms of tobacco smoke throughout life, to promote respiratory health and overall well-being [126]. Lungs have not evolved to safely inhale tobacco smoke. Bold action is required by individuals, health practitioners and policymakers to create a tobacco-free world. In particular, the Tobacco Endgame targets to have a generation free of tobacco by 2030, banning sales in those born from 2012 and later [127]. Although smoking rates have fallen globally but still smoking is likely to remain a leading cause of preventable death throughout this century unless smoking cessation efforts can significantly and rapidly reduce the number of people who smoke, particularly in the developing countries [128]. The risk of developing COPD is present throughout life, and exposure to risk factors can be particularly harmful during lung growth and development (in utero, in childhood and in adolescence). Tobacco use among children, adolescents and young people is of particular concern. It is important to note in this context that worldwide, at least 37 million young people aged 13–15 years (9.7%) use some form of tobacco product [129]. In fact, it is now well known, that COPD may start in childhood, when genetic and environmental factors may lead to reduced lung growth; and repeated insults/exposures may add to the negative effects [130]. These vulnerable groups are being actively targeted by the tobacco industry with campaigns promoting nicotine and tobacco products, including e-cigarettes, HTPs and nicotine pouches. The emergence of a tobacco epidemic among populations already vulnerable to COPD through adverse early life events and exposure to indoor and outdoor air pollution is catastrophic for already overstretched health systems, which are ill-equipped to manage chronic conditions. Protecting these groups from the dangers of tobacco use through effective tobacco control legislation, including total product ban, it is not just a matter of public health, but also an ethical obligation. It is also crucial to expose the tobacco industry's tactics and equip the general public with knowledge and tools to combat the influence of the tobacco industry. Moreover,

Table 2 WHO recommended the following population-level and pharmacological interventions to ensure access to comprehensive cessation support [131, 132]

Brief advice: advice on how to stop using tobacco, usually taking only a few minutes, and given to all tobacco users during a routine consultation or interaction with a healthcare professional.

Toll-free quit lines: a telephone counselling service that provides proactive and reactive telephone counselling.

Pharmacological interventions: nicotine replacement therapy, bupropion, varenicline and cytisine should be considered for all tobacco users who want to quit.

mCessation and chatbots: a two-way messaging system based on the mCessation content library guides tobacco users through a six-month text-message quit support programme. The WHO has also developed chatbots in partnership with social media such as WhatsApp, WeChat, and Viber to give tobacco users the best advice on how to quit smoking.

WHO Quit Tobacco mobile application: The mobile phone app targets all forms of tobacco, including smokeless tobacco and other newer forms of tobacco products, and helps users identify triggers, set targets, manage cravings, and stay focused on quitting tobacco smoking.

Table 3 Five key messages from the WHO Tobacco Knowledge Summary (TKS) [131]

1. Smoking is the leading cause of COPD in high-income countries, contributing to approximately 70% of cases. Quitting tobacco is an essential step toward better lung health.
2. People with COPD face a significantly higher risk of developing lung cancer. Smoking cessation is a powerful measure to reduce cancer risk.
3. Cardiovascular disease, lung cancer and type-2 diabetes are common comorbidities in people with COPD. Quitting smoking not only improves COPD management, but also reduces the risk of developing these coexisting conditions.
4. Tobacco smoke also significantly impacts children's lung growth and development, increasing the risk of respiratory infections, asthma and up to ten other conditions, and COPD later in life. Governments should implement effective tobacco control measures to protect vulnerable populations.
5. The tobacco industry's aggressive strategies in the marketing of nicotine delivery systems and all tobacco products specifically target children, adolescents, and young adults. Protecting our youth from these harmful tactics is a top priority.

it is imperative that all tobacco users, particularly those living in low-to-middle income countries, have access to comprehensive cessation support aligned with WHO recommendations. This support should encompass brief advice from healthcare professionals, availability of toll-free quit lines, access to treatment for tobacco dependence, and digital cessation tools. Table 3 summarizes the five key messages from the WHO Tobacco Knowledge Summary [131] shared with the wider population.

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Author contributions
WL, RA, RS, SR, SSS conceived, designed the structure of the article, revised, and edited. WL wrote the first draft, made figures, and made revisions. KS, JH, EL, ET, NM, JBS, WB, DMGH, MPR, KMF, HK, AY, MG and DCLL reviewed and edited the manuscript. All authors read and approved the final manuscript.

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Data availability
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Declarations

Ethics approval and consent to participate
Not applicable.

Consent to publish
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Disclaimer
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References

1. Chronic obstructive pulmonary disease (COPD). Key facts.: World Health Organization. 2023 [updated 16 March 2023. https://www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-(copd).
2. Fabbri LM, Celli BR, Agusti A, Criner GJ, Dransfield MT, Divo M, et al. COPD and multimorbidity: recognising and addressing a syndemic occurrence. Lancet Respir Med. 2023;11(11):1020–34.
3. Global Strategy for Prevention. Diagnosis and management of COPD: 2023 report. Fontana: Global Initiative for Chronic Obstructive Lung Disease; 2023.
4. McDonough JE, Yuan R, Suzuki M, Seyednejad N, Elliott WM, Sanchez PG, et al. Small-airway obstruction and Emphysema in Chronic Obstructive Pulmonary Disease. N Engl J Med. 2011;365(17):1567–75.
5. Hogg JC, Timens W. The pathology of chronic obstructive pulmonary disease. Annu Rev Pathol. 2009;4:435–59.
6. Eapen MS, Hansbro PM, Larsson-Callerfelt AK, Jolly MK, Myers S, Sharma P, et al. Chronic obstructive Pulmonary Disease and Lung Cancer: underlying pathophysiology and New Therapeutic modalities. Drugs. 2018;78(16):1717–40.
7. Atto B, Eapen MS, Sharma P, Frey U, Ammit AJ, Markos J, et al. New therapeutic targets for the prevention of infectious acute exacerbations of COPD: role of epithelial adhesion molecules and inflammatory pathways. Clin Sci (Lond). 2019;133(14):1663–703.

8. Park SC, Kim DW, Park EC, Shin CS, Rhee CK, Kang YA, et al. Mortality of patients with chronic obstructive pulmonary disease: a nationwide populationbased cohort study. Korean J Intern Med. 2019;34(6):1272–8.
9. Sin DD, Anthonisen NR, Soriano JB, Agusti AG. Mortality in COPD: role of comorbidities. Eur Respir J. 2006;28(6):1245.
10. Adeloye D, Song P, Zhu Y, Campbell H, Sheikh A, Rudan I, et al. Global, regional, and national prevalence of, and risk factors for, chronic obstructive pulmonary disease (COPD) in 2019: a systematic review and modelling analysis. Lancet Respir Med. 2022;10(5):447–58.
11. Safiri S, Carson-Chahhoud K, Noori M, Nejadghaderi SA, Sullman MJM, Ahmadian Heris J, et al. Burden of chronic obstructive pulmonary disease and its attributable risk factors in 204 countries and territories, 1990–2019: results from the global burden of Disease Study 2019. BMJ. 2022;378:e069679.
12. Christenson SA, Smith BM, Bafadhel M, Putcha N. Chronic obstructive pulmonary disease. Lancet. 2022;399(10342):2227–42.
13. Borgerding M, Klus H. Analysis of complex mixtures–cigarette smoke. Exp Toxicol Pathol. 2005;57(Suppl 1):43–73.
14. What is in a cigarette? American Lung Association. 2023. https://www.lung.org/quit-smoking/smoking-facts/whats-in-a-cigarette
15. Lugg ST, Scott A, Parekh D, Naidu B, Thickett DR. Cigarette smoke exposure and alveolar macrophages: mechanisms for lung disease. Thorax. 2022;77(1):94–101.
16. Maung TZ, Bishop JE, Holt E, Turner AM, Pfrang C. Indoor air Pollution and the health of vulnerable groups: a systematic review focused on Particulate Matter (PM), volatile Organic compounds (VOCs) and their effects on children and people with Pre-existing Lung Disease. Int J Environ Res Public Health. 2022;19(14).
17. Pathak U, Gupta NC, Suri JC. Risk of COPD due to indoor air pollution from biomass cooking fuel: a systematic review and meta-analysis. Int J Environ Health Res. 2020;30(1):75–88.
18. Mannino DM, Buist AS. Global burden of COPD: risk factors, prevalence, and future trends. Lancet. 2007;370(9589):765–73.
19. Khalequzzaman M, Kamijima M, Sakai K, Hoque BA, Nakajima T. Indoor air pollution and the health of children in biomass- and fossil-fuel users of Bangladesh: situation in two different seasons. Environ Health Prev Med. 2010;15(4):236–43.
20. Gordon SB, Bruce NG, Grigg J, Hibberd PL, Kurmi OP, Lam KB, et al. Respiratory risks from household air pollution in low and middle income countries. Lancet Respir Med. 2014;2(10):823–60.
21. Anderson DO, Ferris BG Jr. Role of tobacco smoking in the causation of chronic respiratory disease. N Engl J Med. 1962;267:787–94.
22. Nicolaou L, Checkley W. Differences between cigarette smoking and biomass smoke exposure: an in silico comparative assessment of particulate deposition in the lungs. Environ Res. 2021;197:111116.
23. Martinez FJ, Curtis JL, Sciurba F, Mumford J, Giardino ND, Weinmann G, et al. Sex differences in severe pulmonary emphysema. Am J Respir Crit Care Med. 2007;176(3):243–52.
24. Downs SH, Brandli O, Zellweger JP, Schindler C, Kunzli N, Gerbase MW, et al. Accelerated decline in lung function in smoking women with airway obstruction: SAPALDIA 2 cohort study. Respir Res. 2005;6(1):45.
25. Silverman EK, Weiss ST, Drazen JM, Chapman HA, Carey V, Campbell EJ, et al. Gender-related differences in severe, early-onset chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2000;162(6):2152–8.
26. Camp PG, Coxson HO, Levy RD, Pillai SG, Anderson W, Vestbo J, et al. Sex differences in emphysema and airway disease in smokers. Chest. 2009;136(6):1480–8.
27. Dransfield MT, Davis JJ, Gerald LB, Bailey WC. Racial and gender differences in susceptibility to tobacco smoke among patients with chronic obstructive pulmonary disease. Respir Med. 2006;100(6):1110–6.
28. Harmful. and potentially harmful constituents in tobacco products and tobacco smoke; established list. US Food and Drug Administration Fed Regist. 2012;77(64):20034–7.
29. Pappas RS. Toxic elements in tobacco and in cigarette smoke: inflammation and sensitization. Metallomics. 2011;3(11):1181–98.
30. Huang MF, Lin WL, Ma YC. A study of reactive oxygen species in mainstream of cigarette. Indoor Air. 2005;15(2):135–40.
31. Djordjevic MV, Doran KA. Nicotine content and delivery across tobacco products. Handb Exp Pharmacol. 2009;192:61–82.
32. Addictiveness and Attractiveness of Tobacco Additives Brussels. 2010 [updated 12 November. https://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_031.pdf
33. Rabinoff M, Caskey N, Rissling A, Park C. Pharmacological and chemical effects of cigarette additives. Am J Public Health. 2007;97(11):1981–91.
34. Salvi S. Tobacco smoking and environmental risk factors for chronic obstructive pulmonary disease. Clin Chest Med. 2014;35(1):17–27.
35. Wiegman CH, Li F, Ryffel B, Togbe D, Chung KF. Oxidative stress in ozone-Induced chronic lung inflammation and Emphysema: a facet of Chronic Obstructive Pulmonary Disease. Front Immunol. 2020;11:1957.
36. Gunen H, Tarraf H, Nemati A, Al Ghobain M, Al Mutairi S, Aoun Bacha Z. Water-pipe tobacco smoking. Tuberk Toraks. 2016;64(1):94–6.
37. She J, Yang P, Wang Y, Qin X, Fan J, Wang Y, et al. Chinese water-pipe smoking and the risk of COPD. Chest. 2014;146(4):924–31.
38. Smoking and Tobacco Use. Fast facts and fact sheets 2021. Atlanta (GE)2023 https://www.cdc.gov/tobacco/data_statistics/fact_sheets/fast_facts/index.htm
39. Santoro A, Tomino C, Prinzi G, Lamonaca P, Cardaci V, Fini M, et al. Tobacco Smoking: risk to develop addiction, Chronic Obstructive Pulmonary Disease, and Lung Cancer. Recent Pat Anticancer Drug Discov. 2019;14(1):39–52.
40. Papke RL. The many enigmas of nicotine. Adv Pharmacol. 2024;99:327–54.
41. Agustí A, Hogg JC. Update on the Pathogenesis of Chronic Obstructive Pulmonary Disease. N Engl J Med. 2019;381(13):1248–56.
42. Brightling C, Greening N. Airway inflammation in COPD: progress to precision medicine. Eur Respir J. 2019;54(2).
43. Eapen MS, McAlinden K, Tan D, Weston S, Ward C, Muller HK, et al. Profiling cellular and inflammatory changes in the airway wall of mild to moderate COPD. Respirology. 2017;22(6):1125–32.
44. Eapen MS, Hansbro PM, McAlinden K, Kim RY, Ward C, Hackett TL, et al. Abnormal M1/M2 macrophage phenotype profiles in the small airway wall and lumen in smokers and chronic obstructive pulmonary disease (COPD). Sci Rep. 2017;7(1):13392.
45. Liu G, Haw TJ, Starkey MR, Philp AM, Pavlidis S, Nalkurthi C, et al. TLR7 promotes smoke-induced experimental lung damage through the activity of mast cell tryptase. Nat Commun. 2023;14(1):7349.
46. O'Beirne SL, Kikkers SA, Oromendia C, Salit J, Rostmai MR, Ballman KV, et al. Alveolar macrophage immunometabolism and lung function impairment in Smoking and Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med. 2020;201(6):735–9.
47. Stoller JK, Aboussouan LS. α1-antitrypsin deficiency. Lancet. 2005;365(9478):2225–36.
48. Shrine N, Guyatt AL, Erzurumluoglu AM, Jackson VE, Hobbs BD, Melbourne CA, et al. New genetic signals for lung function highlight pathways and chronic obstructive pulmonary disease associations across multiple ancestries. Nat Genet. 2019;51(3):481–93.
49. Obeidat Me, Hao K, Bossé Y, Nickle DC, Nie Y, Postma DS, et al. Molecular mechanisms underlying variations in lung function: a systems genetics analysis. Lancet Respiratory Med. 2015;3(10):782–95.
50. Zhou JJ, Cho MH, Castaldi PJ, Hersh CP, Silverman EK, Laird NM. Heritability of chronic obstructive pulmonary disease and related phenotypes in smokers. Am J Respir Crit Care Med. 2013;188(8):941–7.
51. Barnes PJ, Celli BR. Systemic manifestations and comorbidities of COPD. Eur Respir J. 2009;33(5):1165.
52. André S, Conde B, Fragoso E, Boléo-Tomé JP, Areias V, Cardoso J. COPD and Cardiovascular Disease. Pulmonology. 2019;25(3):168–76.
53. Bhattarai P, Lu W, Gaikwad AV, Dey S, Chia C, Larby J et al. Arterial remodelling in smokers and in patients with small airway disease and COPD: implications for lung physiology and early origins of pulmonary hypertension. ERJ Open Res. 2022;8(4).
54. Padeletti M, Jelic S, LeJemtel TH. Coexistent chronic obstructive pulmonary disease and heart failure in the elderly. Int J Cardiol. 2008;125(2):209–15.
55. Barberà JA. Mechanisms of development of chronic obstructive pulmonary disease-associated pulmonary hypertension. Pulm Circ. 2013;3(1):160–4.
56. Santos S, Peinado VI, Ramirez J, Melgosa T, Roca J, Rodriguez-Roisin R, et al. Characterization of pulmonary vascular remodelling in smokers and patients with mild COPD. Eur Respir J. 2002;19(4):632–8.
57. Bhattarai P, Lu W, Hardikar A, Dey S, Gaikwad AV, Shahzad AM et al. Endothelial to mesenchymal transition is an active process in smokers and patients with early COPD contributing to pulmonary arterial pathology. ERJ Open Res. 2024;10(1).
58. Chaouat A, Naeije R, Weitzenblum E. Pulmonary hypertension in COPD. Eur Respir J. 2008;32(5):1371.
59. Nathan SD, Barbera JA, Gaine SP, Harari S, Martinez FJ, Olschewski H et al. Pulmonary hypertension in chronic lung disease and hypoxia. Eur Respir J. 2019;53(1).

60. Fiorentino G, Esquinas AM, Annunziata A. Exercise and Chronic Obstructive Pulmonary Disease (COPD). Adv Exp Med Biol. 2020;1228:355–68.
61. Henrot P, Dupin I, Schilfarth P, Esteves P, Blervaque L, Zysman M et al. Main pathogenic mechanisms and recent advances in COPD Peripheral skeletal muscle wasting. Int J Mol Sci. 2023;24(7).
62. Osteoporosis prevention. Diagnosis, and therapy. JAMA. 2001;285(6):785–95.
63. Cully JA, Graham DP, Stanley MA, Ferguson CJ, Sharafkhaneh A, Souchek J, et al. Quality of life in patients with chronic obstructive pulmonary disease and comorbid anxiety or depression. Psychosomatics. 2006;47(4):312–9.
64. Polkey MI, Moxham J. Attacking the disease spiral in chronic obstructive pulmonary disease. Clin Med. 2006;6(2):190–6.
65. Sin DD, Man JP, Man SFP. The risk of osteoporosis in caucasian men and women with obstructive airways disease. Am J Med. 2003;114(1):10–4.
66. Li Y, Gao H, Zhao L, Wang J. Osteoporosis in COPD patients: risk factors and pulmonary rehabilitation. Clin Respir J. 2022;16(7):487–96.
67. Pompe E, Bartstra J, Verhaar HJ, de Koning HJ, van der Aalst CM, Oudkerk M, et al. Bone density loss on computed tomography at 3-year follow-up in current compared to former male smokers. Eur J Radiol. 2017;89:177–81.
68. Lau RY, Guo X. A review on current osteoporosis research: with special focus on disuse bone loss. J Osteoporos. 2011;2011:293808.
69. Graat-Verboom L, Wouters EF, Smeenk FW, van den Borne BE, Lunde R, Spruit MA. Current status of research on osteoporosis in COPD: a systematic review. Eur Respir J. 2009;34(1):209–18.
70. Okazaki R, Watanabe R, Inoue D. Osteoporosis Associated with Chronic Obstructive Pulmonary Disease. J Bone Metab. 2016;23(3):111–20.
71. Inoue D, Watanabe R, Okazaki R. COPD and osteoporosis: links, risks, and treatment challenges. Int J Chron Obstruct Pulmon Dis. 2016;11:637–48.
72. Homętowska H, Klekowski J, Świątoniowska-Lonc N, Jankowska-Polańska B, Chabowski M. Fatigue, Depression, and anxiety in patients with COPD, asthma and Asthma-COPD overlap. J Clin Med. 2022;11(24).
73. Kunik ME, Roundy K, Veazey C, Souchek J, Richardson P, Wray NP, et al. Surprisingly high prevalence of anxiety and Depression in Chronic Breathing disorders. Chest. 2005;127(4):1205–11.
74. García-Sanz MT, González-Barcala FJ. COPD is more than just lung function: Let's not forget depression. Arch Bronconeumol. 2021;57(8):519–20.
75. Martínez-Gestoso S, García-Sanz MT, Carreira JM, Salgado FJ, Calvo-Álvarez U, Doval-Oubiña L, et al. Impact of anxiety and depression on the prognosis of copd exacerbations. BMC Pulm Med. 2022;22(1):169.
76. Willgoss TG, Yohannes AM. Anxiety disorders in patients with COPD: a systematic review. Respir Care. 2013;58(5):858–66.
77. Yohannes AM, Alexopoulos GS. Depression and anxiety in patients with COPD. Eur Respir Rev. 2014;23(133):345–9.
78. Benson VS, Müllerová H, Vestbo J, Wedzicha JA, Patel A, Hurst JR. Associations between gastro-oesophageal reflux, its management and exacerbations of chronic obstructive pulmonary disease. Respir Med. 2015;109(9):1147–54.
79. Pandolfino JE, Kahrilas PJ. Smoking and gastro-oesophageal reflux disease. Eur J Gastroenterol Hepatol. 2000;12(8):837–42.
80. Lee AL, Goldstein RS. Gastroesophageal reflux disease in COPD: links and risks. Int J Chron Obstruct Pulmon Dis. 2015;10:1935–49.
81. Ingebrigtsen TS, Marott JL, Vestbo J, Nordestgaard BG, Hallas J, Lange P. Gastro-esophageal reflux disease and exacerbations in chronic obstructive pulmonary disease. Respirology. 2015;20(1):101–7.
82. Dore MP, Maragkoudakis E, Fraley K, Pedroni A, Tadeu V, Realdi G, et al. Diet, lifestyle and gender in gastro-esophageal reflux disease. Dig Dis Sci. 2008;53(8):2027–32.
83. Sasaki T, Nakayama K, Yasuda H, Yoshida M, Asamura T, Ohrui T, et al. A Randomized, single-blind study of Lansoprazole for the Prevention of exacerbations of Chronic Obstructive Pulmonary Disease in older patients. J Am Geriatr Soc. 2009;57(8):1453–7.
84. Barnes PJ, Burney PG, Silverman EK, Celli BR, Vestbo J, Wedzicha JA, et al. Chronic obstructive pulmonary disease. Nat Rev Dis Primers. 2015;1:15076.
85. de Torres JP, Marin JM, Casanova C, Cote C, Carrizo S, Cordoba-Lanus E, et al. Lung cancer in patients with chronic obstructive pulmonary disease– incidence and predicting factors. Am J Respir Crit Care Med. 2011;184(8):913–9.
86. Tahery N, Zarea K, Cheraghi M, Hatamzadeh N, Farhadi M, Dobaradarn S, et al. Chronic obstructive Pulmonary Disease (COPD) and Air Pollution: a review. Jundishapur J Chronic Dis Care. 2021;10(1):e110273.
87. Lu W, Eapen MS, Hardikar A, Chia C, Robertson I, Singhera GK et al. Epithelial-mesenchymal transition changes in nonsmall cell lung cancer patients with early COPD. ERJ Open Res. 2023;9(6).
88. Gohy ST, Hupin C, Fregimilicka C, Detry BR, Bouzin C, Gaide Chevronay H, et al. Imprinting of the COPD airway epithelium for dedifferentiation and mesenchymal transition. Eur Respir J. 2015;45(5):1258–72.
89. Milara J, Peiró T, Serrano A, Cortijo J. Epithelial to mesenchymal transition is increased in patients with COPD and induced by cigarette smoke. Thorax. 2013;68(5):410–20.
90. Karacosta LG, Anchang B, Ignatiadis N, Kimmey SC, Benson JA, Shrager JB, et al. Mapping lung cancer epithelial-mesenchymal transition states and trajectories with single-cell resolution. Nat Commun. 2019;10(1):5587.
91. Karacosta LG, Pancirer D, Preiss JS, Benson JA, Trope W, Shrager JB, et al. Phenotyping EMT and MET cellular states in lung cancer patient liquid biopsies at a personalized level using mass cytometry. Sci Rep. 2023;13(1):21781.
92. Sohal SS, Soltani A, Reid D, Ward C, Wills KE, Muller HK, et al. A randomized controlled trial of inhaled corticosteroids (ICS) on markers of epithelial-mesenchymal transition (EMT) in large airway samples in COPD: an exploratory proof of concept study. Int J Chron Obstruct Pulmon Dis. 2014;9:533–42.
93. Soltani A, Walters EH, Reid DW, Shukla SD, Nowrin K, Ward C, et al. Inhaled corticosteroid normalizes some but not all airway vascular remodeling in COPD. Int J Chron Obstruct Pulmon Dis. 2016;11:2359–67.
94. Parimon T, Chien JW, Bryson CL, McDonell MB, Udris EM, Au DH. Inhaled corticosteroids and Risk of Lung Cancer among patients with chronic obstructive Pulmonary Disease. Am J Respir Crit Care Med. 2007;175(7):712–9.
95. Ge F, Feng Y, Huo Z, Li C, Wang R, Wen Y, et al. Inhaled corticosteroids and risk of lung cancer among chronic obstructive pulmonary disease patients: a comprehensive analysis of nine prospective cohorts. Transl Lung Cancer Res. 2021;10(3):1266–76.
96. Tareke AA, Debebe W, Alem A, Bayileyegn NS, Zerfu TA, Ayana AM. Inhaled corticosteroids and the risk of Lung Cancer in Chronic Obstructive Pulmonary Disease patients: a systematic review and Meta-analysis. Pulm Med. 2022;2022:9799858.
97. Pitre T, Kiflen M, Ho T, Seijo LM, Zeraatkar D, de Torres JP. Inhaled corticosteroids, COPD, and the incidence of lung cancer: a systematic review and dose response meta-analysis. BMC Pulm Med. 2022;22(1):275.
98. Park JE, Lee E, Singh D, Kim EK, Park B, Park JH. The effect of inhaler prescription on the development of lung cancer in COPD: a nationwide population-based study. Respir Res. 2024;25(1):229.
99. Diver WR, Jacobs EJ, Gapstur SM. Secondhand smoke exposure in Childhood and Adulthood in Relation to Adult Mortality among Never smokers. Am J Prev Med. 2018;55(3):345–52.
100. Putcha N, Barr RG, Han MK, Woodruff PG, Bleecker ER, Kanner RE, et al. Understanding the impact of second-hand smoke exposure on clinical outcomes in participants with COPD in the SPIROMICS cohort. Thorax. 2016;71(5):411.
101. Yin P, Jiang CQ, Cheng KK, Lam TH, Lam KH, Miller MR, et al. Passive smoking exposure and risk of COPD among adults in China: the Guangzhou Biobank Cohort Study. Lancet. 2007;370(9589):751–7.
102. Hecht SS, Hatsukami DK. Smokeless tobacco and cigarette smoking: chemical mechanisms and cancer prevention. Nat Rev Cancer. 2022;22(3):143–55.
103. Hatsukami D, Zeller M, Gupta P, Parascandola M, Asma S. Smokeless tobacco and public health: a global perspective. 2014.
104. Kass AP, Overbeek DL, Chiel LE, Boyer EW, Casey AMH. Case series: adolescent victims of the vaping public health crisis with pulmonary complications. Pediatr Pulmonol. 2020;55(5):1224–36.
105. McAlinden KD, Eapen MS, Lu W, Sharma P, Sohal SS. The rise of electronic nicotine delivery systems and the emergence of electronic-cigarette-driven disease. Am J Physiol Lung Cell Mol Physiol. 2020;319(4):L585–95.
106. Park JA, Crotty Alexander LE, Christiani DC. Vaping and lung inflammation and Injury. Annu Rev Physiol. 2022;84:611–29.
107. Bowler RP, Hansel NN, Jacobson S, Graham Barr R, Make BJ, Han MK, et al. Electronic cigarette use in US adults at risk for or with COPD: analysis from two observational cohorts. J Gen Intern Med. 2017;32(12):1315–22.
108. Osei AD, Mirbolouk M, Orimoloye OA, Dzaye O, Uddin SMI, Benjamin EJ, et al. Association between E-Cigarette Use and Chronic Obstructive Pulmonary Disease by Smoking Status: behavioral risk factor Surveillance System 2016 and 2017. Am J Prev Med. 2020;58(3):336–42.
109. Perez MF, Atuegwu NC, Mead EL, Oncken C, Mortensen EM. Adult E-Cigarettes use Associated with a self-reported diagnosis of COPD. Int J Environ Res Public Health. 2019; 16(20).
110. Wang JB, Olgin JE, Nah G, Vittinghoff E, Cataldo JK, Pletcher MJ, et al. Cigarette and e-cigarette dual use and risk of cardiopulmonary symptoms in the Health eHeart Study. PLoS ONE. 2018;13(7):e0198681.

111. Xie Z, Ossip DJ, Rahman I, Li D. Use of Electronic cigarettes and Self-reported chronic obstructive Pulmonary Disease diagnosis in adults. Nicotine Tob Res. 2020;22(7):1155–61.
112. Chen DT, Grigg J, Filippidis FT. European Respiratory Society statement on novel nicotine and tobacco products, their role in tobacco control and harm reduction. Eur Respir J. 2024;63(2).
113. Glantz SA. The cigarette papers. Univ of California; 1996.
114. Glantz SA. Heated tobacco products: the example of IQOS. Tob Control. 2018;27(Suppl 1):s1.
115. Bravo-Gutierrez OA, Falfan-Valencia R, Ramirez-Venegas A, Sansores RH, Ponciano-Rodriguez G, Perez-Rubio G. Lung damage caused by Heated Tobacco Products and Electronic Nicotine Delivery systems: a systematic review. Int J Environ Res Public Health. 2021;18(8).
116. Leigh NJ, Tran PL, O'Connor RJ, Goniewicz ML. Cytotoxic effects of heated tobacco products (HTP) on human bronchial epithelial cells. Tob Control. 2018;27(Suppl 1):s26–9.
117. Sohal SS, Eapen MS, Naidu GMV, Sharma P. IQOS exposure impairs human airway cell homeostasis: direct comparison with traditional cigarette and e-cigarette. ERJ Open Res. 2019;5(1):00159–2018.
118. Nakama C, Tabuchi T. Use of heated tobacco products by people with chronic diseases: the 2019 JASTIS study. PLoS ONE. 2021;16(11):e0260154.
119. Glantz SA. PMI's own in vivo clinical data on biomarkers of potential harm in americans show that IQOS is not detectably different from conventional cigarettes. Tob Control. 2018;27(Suppl 1):s9.
120. Tashkin DP. Smoking Cessation in Chronic Obstructive Pulmonary Disease. Semin Respir Crit Care Med. 2015;36(4):491–507.
121. Pezzuto A, Carico E. Effectiveness of smoking cessation in smokers with COPD and nocturnal oxygen desaturation: functional analysis. Clin Respir J. 2020;14(1):29–34.
122. WHO Package of Essential Noncomunicable (PEN). Disease Interventions for Primary Health Care. World Health Organization; 2020.
123. WHO Report on the Global Tobacco Epidemic. 2023: protect people from tobacco smoke. Geneva: World Health Organization; 2023.
124. WHO calls on governments to include smoking cessation in tobacco control strategies. Geneva: World Health Organizition. 2023. https://www.who.int/news/item/06-08-2003-who-calls-on-governments-to-includesmoking-cessation-in-tobacco-control-strategies
125. United States Public Health Service Office of the Surgeon G, National Center for Chronic Disease P. Health Promotion Office on S, Health. Publications and reports of the Surgeon General. Smoking Cessation: a report of the Surgeon General. Washington (DC): US Department of Health and Human Services; 2020.
126. Soriano JB, Jenkins C. How should good lung health be defined at the population and individual levels? Eur Respir J. 2023;62(3):2301166.
127. Malone RE. Imagining things otherwise: new endgame ideas for tobacco control. Tob Control. 2010;19(5):349–50.
128. Dai X, Gakidou E, Lopez AD. Evolution of the global smoking epidemic over the past half century: strengthening the evidence base for policy action. Tob Control. 2022;31(2):129.
129. WHO global report on trends in prevalence of tobacco use. 2000–2030: World Health Organization; 2024 [updated 16 January 2024. https://www.who.int/publications/i/item/9789240088283
130. Melén E, Faner R, Allinson JP, Bui D, Bush A, Custovic A et al. Lung-function trajectories: relevance and implementation in clinical practice. Lancet. 2024.
131. Lu W, Aarsand R, Rylance S, Schotte K, Han J, Lebedeva E et al. Tobacco and chronic obstructive pulmonary disease (COPD). WHO; 2023 14 November.
132. WHO clinical. Treatment guideline for tobacco cessation in adults. Geneva: World Health Organization; 2024.

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