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REVIEW

The Burden of COPD with Type 2 Inflammation in North-West Continental Europe

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Video abstract

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Abstract: Chronic obstructive pulmonary disease (COPD) is a complex and heterogeneous disease that places a huge burden on patients, health systems and societies. Yet despite this, COPD is often neglected: it is frequently underdiagnosed or misdiagnosed, and since tobacco exposure is a primary risk factor for its development, patients are often stigmatized and marginalized because they are perceived as having a "self-inflicted" disease. COPD is primarily understood to be a functional disorder with chronic airway obstruction, yet there are several underlying inflammatory pathways. For most patients with COPD, type 1 (neutrophilic) inflammation is the main such pathway; however, a considerable proportion has type 2 inflammation (associated with elevated eosinophil numbers). COPD with type 2 inflammation may represent a distinct COPD phenotype and a "treatable trait". In fact, the response to inhaled corticosteroids (ICS) is linked to blood eosinophil levels: treatment effects begin to increase in patients with blood eosinophil counts ≥100 cells/μL, and most treatment guidelines recommend considering ICS for patients with blood eosinophil counts ≥300 cells/μL. Data on the burden of COPD with type 2 inflammation are limited. COPD with type 2 inflammation may associate with poor outcomes, and higher blood eosinophil counts positively associate with an increased risk of moderate or severe exacerbations. Exacerbations are among the most dangerous aspects of COPD, accelerating disease progression and increasing morbidity and mortality. This review explores the burden of COPD – specifically eosinophilic COPD – across north-western Europe. It aims to provide information relevant to patients, clinicians and policymakers, educating them about type 2 inflammation and its contribution to the disease burden. It has been informed by multiple stakeholders, including patients, and offers practical and achievable recommendations for enhancing the care of all patients with COPD through a better understanding of COPD with type 2 inflammation.

Keywords: eosinophils, cost, mortality, morbidity, exacerbation

Introduction

Chronic obstructive pulmonary disease (COPD) places a huge burden on patients, clinicians and health systems. COPD severely limits patients' daily activity and impacts their quality of life, and associates with high levels of morbidity and mortality.[1,2] Additionally, COPD carries a substantial economic burden: on patients, carers, health systems and societies.[3,4]

COPD is a complex disease with marked heterogeneity in its clinical manifestations and natural history, arising from the interactions of numerous risk factors.[5] Despite this variability, COPD subtypes are poorly delineated, and their relevance to clinical practice is unclear. That said, a specific phenotype of COPD associated with type 2 inflammation –

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often indicated by elevated levels of blood eosinophils – is now recognized in a subgroup of patients, and although this subtype is poorly defined at present, this knowledge may offer both prognostic and predictive value for COPD management. This is especially relevant as new treatments targeted for this subtype reach approval. The exact burden of COPD with type 2 inflammation is, however, unclear. This is further complicated by the fact that COPD in general is underdiagnosed or misdiagnosed, mostly through ineffective differentiation from other common respiratory conditions such as asthma.

This review seeks to articulate what is known about the burden of COPD, and focuses on its type 2 inflammation subtype, specifically for countries in north-west continental Europe. It also attempts to clarify definitions of type 2 inflammation in COPD and explain why it is relevant to patient care. The review results from a series of interviews and round-table discussions with general practitioners, pulmonologists, health economists and a patient representative from Belgium, Denmark, Finland, the Netherlands, Norway and Sweden. It explores this burden in a way that is relevant to patients, primary care physicians, pulmonologists, and public health and policymakers.

Methodology

Each author was interviewed individually to gather their advice and perspective, as well as any known sources of data in each country. The interviews were done by an independent medical writer (Keena McKillen, CCN17, Cambridge, UK). These interviews revealed that the impact of Type 2 inflammation on the burden of COPD, most particularly in northern Europe, was a topic deserving of in-depth review.

Based on the outcomes of the interviews, English-language literature indexed in PubMed was non-systematically searched between 22–24 April 2024 using a variety of approaches, including combinations of key words "COPD, Type 2 inflammation" and "eosinophils", alongside search terms related to burden of disease and northern European countries. Additional references were identified using the "view similar citations" function, and by hand-searching for related papers. Primary research, meta-analyses, systematic and narrative reviews were considered as sources of original or amalgamated data. Titles were then reviewed for their relevance, with a particular focus on the region of northern continental Europe and their discussing the burden of disease.

The independent medical writer, working with another medical writer (Maria Dalby, Norse Horse, Ely, UK), then developed an outline based on the literature search and direction from the author interviews. This was shared with the authors on 10 May 2024 and discussed in detail at a virtual round table meeting on 17 May 2024. Follow-up meetings were held separately with authors who were unable to attend the round table meeting. The outputs of these meetings provided additional direction and suggested other sources of data. Each author read, revised and commented on the manuscript at each draft. The final draft was approved by all authors prior to submission.

COPD and Type 2 Inflammation

The term "COPD" is generally applied to the condition of patients who present with reduced lung function (post-bronchodilator forced expiratory volume in 1 second [FEV_1]/forced vital capacity [FVC] <0.7), symptoms such as dyspnea, wheeze, cough, sputum production and/or exacerbations, and genetic or environmental risk factors, such as exposure to tobacco smoke.[6] COPD exacerbations ("lung attacks" or "strokes of the lung") are acute episodes of worsening COPD symptoms and are particularly concerning because they associate with poor outcomes, including death, and can occur even in patients with disease considered low risk (ie Global Initiative for Chronic Obstructive Lung Disease [GOLD] groups A and B).[6,7]

COPD is a disease driven by the immune system. Studies of patients with exacerbations have shown that the underlying inflammatory pathways usually fall into one of two broad categories: Type 1 or Type 2 inflammation, and that each has its distinct biomarkers and biologic phenotypes, as identified in sputum studies of the last few decades.[8–11] The Type 1 inflammatory response associates primarily with neutrophils, cluster of differentiation (CD)4+ T-helper cell type (Th)1 and Th17 cells, which induce a pro-inflammatory cytokine response centred on IL-1α/β, IL-33, and IL-18, IL-17A/F, IFNγ.[11] This Type 1 response is the most common inflammatory phenotype in COPD; however, up to 40% of patients display type 2 inflammation, characterized by a predominance of eosinophils.[12] This has led to the theory that type 2 inflammation – indicated by elevated blood eosinophils – may characterize a distinct COPD phenotype, and that

this could be a "treatable trait".[5,13] Type 2 inflammation is associated with the presence of Th2 cells, type 2 innate lymphoid (ILC2) cells and eosinophils, as well as the secretion of the key cytokines interleukin (IL)-4, IL-13 and IL-5, as reviewed in detail by Rabe et al.[12]

Although these inflammatory pathways are well known,[11] historically they have not featured prominently in diagnostic criteria: a fact that may have limited widespread awareness among clinicians of the role of type 2 inflammation in COPD. Indeed, such symptoms may be more commonly recognized as being associated with allergic asthma, and this may contribute to misdiagnosis and confusion between these two conditions.[14,15]

Treatment Guidelines and Type 2 Inflammation

Despite the emerging importance of type 2 inflammation in COPD and its value in guiding treatment decisions, general awareness of this treatable trait is limited and is inconsistently used to guide patient management in general practice across the Nordics, Belgium and the Netherlands. For example, a consensus project conducted across six European countries (Belgium, Finland, Greece, the Netherlands, Norway and Portugal) found that treatment selection prioritized the ability to inhale, breathlessness, exacerbation history and concomitant asthma over criteria such as blood eosinophils or comorbidities.[16]

The GOLD 2024 report on COPD states that blood eosinophil counts should guide the use of ICS as part of the pharmacological management of COPD, based on studies showing that blood eosinophil counts are repeatable and can predict the ability of ICS to prevent future exacerbations.[6,17] Further, while neutrophil-dominated Type 1 inflammation appears to associate with bacterial infection, raised sputum eosinophil counts as in Type 2 inflammation inversely correlate with bacterial infection.[18] These data provide further rationale for the recommendations to reserve ICS use only for patients with elevated eosinophils: patients with low eosinophils are likely to have a greater risk of pneumonia owing to bacterial colonisation, and ICS themselves have been shown in multiple trials to increase the risk of pneumonia.[19]

Indeed most of our included countries,[20–24] except Belgium, have adopted a form of these recommendations into their national guidelines. In general, blood eosinophil counts ≥150 cells/μL, and particularly ≥300 cells/μL are generally considered "elevated" and favour the use of ICS, although these cutoffs vary.

The GOLD guidelines recommend adding ICS to initial treatment for patients with blood eosinophils ≥300 cells/μL, and for treating exacerbations in these patients. However, they recognize that ICS could also be used to treat exacerbations in patients with a lower cut off – ≥100 cells/μL – if long-acting β-agonists (LABA) or long-acting muscarinic antagonists (LAMA) are insufficient.[6] As we will see, quantifying blood eosinophils can be difficult and the clinical relevance of the various cutoffs is disputed, so additional factors such as exacerbation frequency and severity, as well as asthma history, should also inform decision-making on ICS initiation. As new treatments targeting COPD with type 2 inflammation reach approval, this treatable trait may become increasingly important.

Assessing Type 2 Inflammation Using Blood Eosinophil Counts

There are many ways to measure type 2 inflammation in the lung. Eosinophils may be directly counted in blood, sputum, or bronchoalveolar lavage samples, or quantified histologically from proximal airway specimens.[10,25–28] Fractional exhaled nitric oxide (FeNO) may also be measured as a biomarker for eosinophilic airway inflammation.[29] However, apart from blood eosinophils—which can be quantified easily in primary care settings—the value of some of these techniques is limited by the difficulties in measuring them and achieving consistent results, as well as the availability of the necessary equipment in nonspecialist clinical settings.[12,30] For example, while directly counting eosinophils in bronchoalveolar lavage or tissue may most precisely measure eosinophilic inflammation in the lung,[26–28] the specialist knowledge and equipment needed to assess them are unavailable outside of specialist settings. This is especially true in primary care, where most COPD patients first present and are treated. Further, FeNO measurements are confounded by current smoking, and thus the utility of this measure may be limited only to never- or ex-smokers.[31]

Owing to these limitations and practical considerations, blood eosinophil count has become the preferred biomarker for type 2 inflammation given its availability, reliability, and prognostic and predictive value, and its correlation with sputum eosinophil counts.[10,12,26,30] Blood eosinophil counts, taken during stable COPD, are reasonably reproducible among patients treated in primary care.[32] Indeed, the longitudinal reliability of blood eosinophil count is fair/good,[32–35]

and similar to that for other common biomarkers such as blood pressure[36] or blood cholesterol.[37] However, as with many biomarkers, multiple factors, including disease state and treatment, impact the assessment of blood eosinophil counts. For example, both antibiotics and oral corticosteroids influence the reliability of blood eosinophil counts.[32]

To compound these intrinsic complications to achieving reliable counts, reporting of blood eosinophil counts in the literature is also heterogeneous: they may be expressed as absolute cell counts or as a percentage of white blood cell count. Further, there are different definitions of what constitutes "high" blood eosinophils. Frequently used cutoffs are ≥150 or ≥300 cells/μL, which are roughly equivalent to ~2% or ~3% of white blood cells.[30,38] Indeed, ≥300 cells/μL has been used in clinical trials of biologic therapy.[38] These different measures can lead to completely different estimates of the prevalence of COPD with type 2 inflammation, something that may be even more marked at a population level.[39] Adding further to this complexity, standard clinical laboratory reports often do not flag blood eosinophil counts as abnormal until they surpass 500 cells/μL. Therefore, noticing blood eosinophil counts ≥150 or ≥300 cells/μL requires especial vigilance, and in-depth knowledge of COPD among primary care physicians. Altogether, these ambiguities and challenges contribute to confusion among physicians on how to use blood eosinophil counts in their practice.

The General Burden of COPD and COPD with Type 2 Inflammation

In many ways, the course of COPD is a set of self-sustaining vicious circles that rapidly degrade health and quality of life. For example, poor lung function at diagnosis associates with more severe exacerbations,[40] yet each exacerbation accelerates the permanent decline in lung function.[41] Exacerbations can also increase the risk of cardiovascular disease,[42] which itself increases the risk of further COPD exacerbations.[43,44] Each cycle worsens quality of life and reduces physical activity;[45] itself increasing the likelihood of hospitalization and death.[46] And, as these inexorable cycles – and others like them – continue, healthcare costs rise.[47]

On top of this, most patients with COPD have comorbidities, which also increase their disease burden and risk of poor outcomes, as well as complicate their care and raise its costs.[48] Frailty is common even in younger patients with COPD and is another factor associated with disease severity, a high symptom burden and an increased risk of poor outcomes.[49]

The socioeconomic and clinical burden of even mild COPD is substantial[50] and increases with advancing disease severity. A snapshot of the overall clinical burden of COPD in north-west continental Europe is provided by comparative data from the Global Burden of Disease study. These show the age-standardized rates per 100,000 people for COPD prevalence, mortality and disability adjusted life years (DALYs) in 2019 (Table 1). It is worth noting that the point prevalences for COPD in Denmark and Belgium in 2019 were among the highest in the world.[1] However, it should be acknowledged that COPD is substantially under- or misdiagnosed; some reports estimate that the true prevalence of COPD is over twice that reported in north-western Europe.[51,52]

COPD with Type 2 Inflammation Associates with Poor Outcomes

Globally, type 2 inflammation, using its various definitions, has been reported in up to 40% of patients with COPD.[12,30] This proportion appears to hold true for both stable COPD and during exacerbations.[53] However, one meta-analysis reported that the proportion of patients with blood eosinophil counts ≥150 cells/μL ranged from 18.0% to 72.7%.[54] In north-west continental Europe, available population estimates of COPD with type 2 inflammation, defined as a blood eosinophil count ≥280 cells/μL, are in the range of 13.2–35.7% (Table 2).

Table 1 Global Burden of Disease Study: COPD in 2019 in the North-West Continental Europe[1]

	Global	Belgium	Denmark	Finland	The Netherlands	Norway	Sweden
COPD prevalence ASR per 100,000 (95% UI)	2638.2 (2492.2, 2796.1)	3927.7 (3803.7, 4052.9)	4299.5 (4174.3, 4411.8)	2199.6 (2060.4, 2341.8)	3863.8 (3695.2, 4023.1)	3705.2 (3434.5, 3982.7)	3216.7 (2956.6, 3508.4)
COPD mortality ASR per 100,000 (95% UI)	42.5 (37.6, 46.3)	24.8 (21.4, 27.5)	33.5 (26.4, 37.9)	11.4 (9.7, 13.2)	26.4 (21.7, 30.1)	23.0 (17.7, 25.2)	14.9 (11.6, 17.0)
DALYs due to COPD ASR per 100,000 (95% UI)	926.1 (848.8, 997.7)	621.9 (554.3, 680.4)	771.9 (648.1, 852.9)	311.0 (273.5, 348.9)	645.8 (557.6, 721.8)	548.6 (447.8, 605.3)	418.4 (359.1, 467.8)

Abbreviations: ASR, age-standardized rate; COPD, chronic obstructive pulmonary disease; DALY, disability-adjusted life year; UI, uncertainty interval.

Table 2 Prevalence of COPD with Type 2 Inflammation (High Blood Eosinophils) from Large Population Studies in North-West Continental Europe

	Year	Study	COPD Population	Measure/Cutoff	Proportion of Patients Achieving This Measure, %	Reference
Belgium	2011–2016	Belgium cohort of European Community Respiratory Health Survey (ECRHS3)	206	Proportion of patients with blood eosinophil count ≥310 cells/μL	14.7	[55]
Denmark	2003–2011	Copenhagen General Population Study	7225	Proportion of patients with blood eosinophil count ≥280 cells/μL	23.2	[56]
	2010–2011 with 3-year follow up	Bispebjerg Hospital retrospective study	811 patients hospitalized for an acute exacerbation COPD	Proportion of patients with an acute eosinophilic exacerbation of COPD (blood eosinophil count ≥300 cells/μL)	13.2	[39]
The Netherlands	2007–2017	Retrospective database study from an asthma/ COPD service	3532	Proportion of patients with blood eosinophil count ≥300 cells/μL	35.7	[57]
Finland	2004–2015	Non-interventional, retrospective registry study	2878	Proportion of patients with blood eosinophil count ≥300 cells/μL	31.3	[58]
Sweden	2014–2018	Tools Identifying Exacerbations	386	Proportion of patients with blood eosinophil count ≥300 cells/μL over 3 years	15.3	[33]

Abbreviations: COPD, chronic obstructive pulmonary disease.

These estimates are broad, perhaps given the heterogeneity in assessment and reporting methods for blood eosinophils, and perhaps also because there may be considerable overlap and misdiagnosis between asthma and COPD in these cohorts. Historically, many patients with an FEV_1/FVC ratio <0.7 have been diagnosed with COPD, even though more recent understanding suggests such patients may instead have untreated or poorly controlled asthma.[59] On the other hand, having high blood eosinophils may lead to an asthma diagnosis, especially if the diagnosis is otherwise unclear (eg due to non-conclusive spirometry).[14,15,60] Therefore, we thus need to acknowledge that the phenotyping of asthma and COPD is currently unclear and seems to partly overlap.

There is growing evidence suggesting that type 2 inflammation in COPD may associate with poor outcomes (see Figure 1). For example, eosinophilia and other markers of type 2 inflammation have been linked to airway remodelling and accelerated lung function decline.[38,61–63] A systematic review of studies published between January 2015 and July 2019 found a positive association between higher blood eosinophil counts and an increased risk of moderate or severe exacerbations, particularly in patients untreated with ICS.[44] Many studies also show that elevated blood eosinophil counts correlate with more severe exacerbations.[30,53,64,65] A large study in a UK primary care database studied patients with COPD with a frequent exacerbator profile, defined as a high risk of exacerbations (≥2 moderate/≥1 severe exacerbation[s] in the previous year and a prescription for triple therapy with ICS plus a LABA plus a LAMA) and a blood eosinophil count ≥150 cells/μL.[66] Compared with non-frequent exacerbators with normal blood eosinophil counts, the frequent exacerbator patients with type 2 inflammation had more frequent moderate or severe acute exacerbations and higher all-cause mortality.[66] In addition, COPD with type 2 inflammation may associate with an increased risk of first hospitalization for COPD, and of readmission.[66,67] Taken together, these findings show that even with triple therapy, patients with a frequent exacerbator profile and type 2 inflammation have a substantial disease burden.[66]

COPD Burden in North-Western Continental Europe

The remainder of this review will focus on what is known about the clinical and economic burden of COPD, and where data are available, specifically COPD with type 2 inflammation in Belgium, Denmark, Finland, the Netherlands, Norway and Sweden.

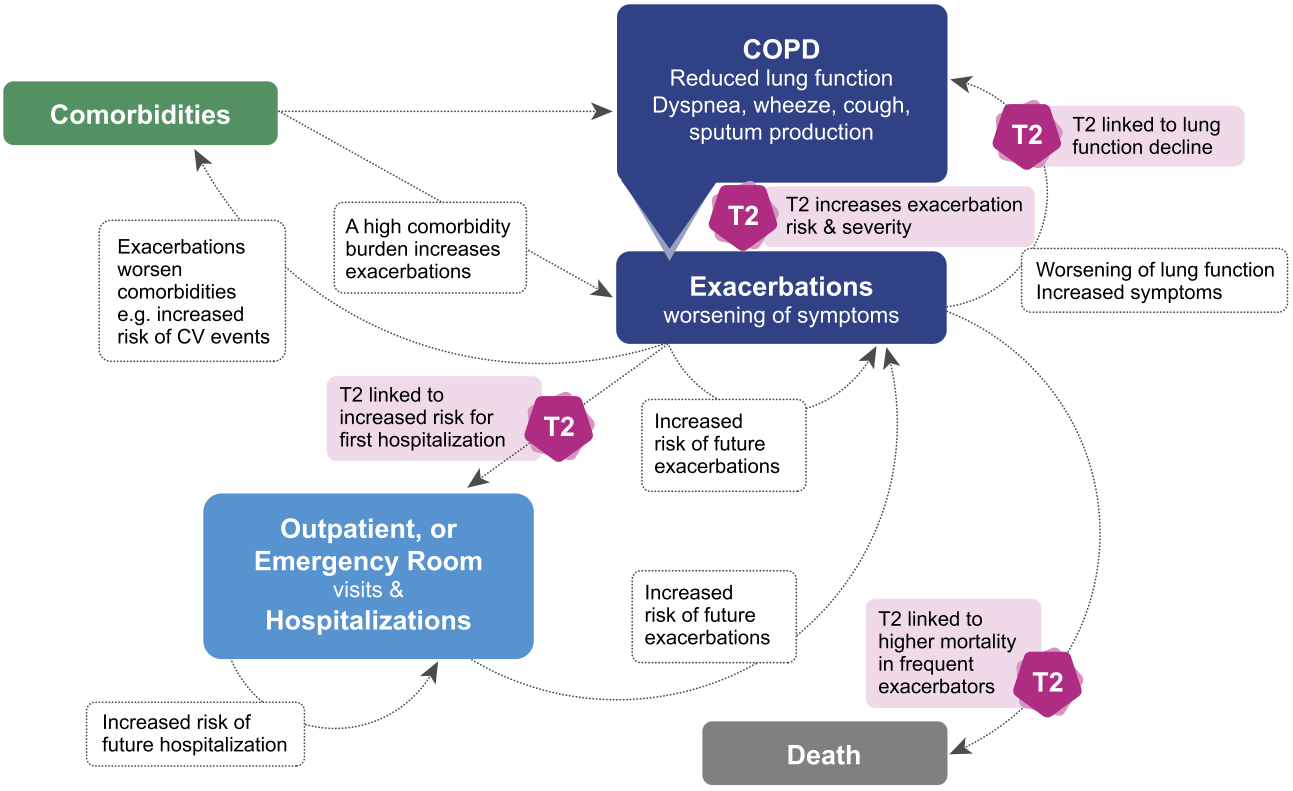

Figure 1 Outcomes in COPD and role of type 2 inflammation.
Abbreviation: T2, type 2 inflammation in COPD.

Exacerbations ("Lung Attacks" or "Strokes of the Lung")

An exacerbation is defined as an acute respiratory event characterized by increased respiratory symptoms.[6] This anodyne definition fails to convey just how exhausting and frightening these events are for patients,[68,69] or to capture their seriousness. Exacerbations are well recognized as hastening lung function decline, and for increasing the risk of future exacerbations, cardiovascular events, emergency room visits, hospitalizations and death. Exacerbations are not necessarily linked to disease severity, as even patients classified in GOLD groups A and B, mild or moderate COPD experience them.[6,70] Yet, despite this, many patients do not report exacerbations, and they therefore go unrecorded and untreated.[7]

Exacerbations range in severity: moderate exacerbations require treatment with antibiotics and/or oral corticosteroids, while severe or life-threatening exacerbations require hospitalization.[7] Exacerbation frequency also has clinical implications: patients experiencing two or more annually are said to have frequent exacerbations,[7] and exacerbation history is known to predict future exacerbations.[71–73] Their seriousness cannot be overstated: even a single moderate exacerbation increases the risk of future moderate or severe exacerbations and death.[70]

Exacerbations are common, and almost inevitable over the lifelong course of COPD. In a Swedish cohort study in which individuals with COPD were followed-up for 10 years after their diagnosis, three in four of them had an exacerbation at least once during those 10 years.[74] A study from a general practice population in the Netherlands reported that 28% of patients with COPD experienced at least one exacerbation annually and 7% experienced at least one severe exacerbation annually.[75] Another study in a Swedish primary care population reported that 22.4% of patients with COPD had frequent exacerbations, experiencing two or more annually.[76] The latter study also demonstrated that the higher the exacerbation frequency, the more rapidly lung function declined.[76]

The Role of Type 2 Inflammation in Exacerbations

Exacerbation-induced lung function decline has been linked to type 2 inflammation. A UK study of patients with mild-to-moderate COPD found that patients with blood eosinophil counts ≥350 cells/μL experienced a significant excess decline in lung function with every exacerbation, more so than in patients with lower blood eosinophil counts.[62]

As well as worsening exacerbations' outcomes, type 2 inflammation has also been linked to an increased risk of experiencing exacerbations at all. Among individuals with COPD in the general Danish population, blood eosinophil counts ≥340 cells/μL associated with a 1.76-fold increased risk of severe exacerbations.[56] Compellingly, an international study in patients with moderate-to-severe COPD demonstrated that exacerbation risk increases linearly with blood eosinophil count.[34] This increased exacerbation risk was more prominent in individuals with a history of frequent exacerbations.[34] Patients with ≥2 exacerbations in the prior year and high blood eosinophil counts had an annual exacerbation rate of 2.39, compared with 1.42 for patients without elevated blood eosinophils.[34] Indeed, high blood eosinophil counts may indicate a subset of patients at increased risk of more severe exacerbations, and who would benefit from ICS.[62] In contrast, one study in patients with mainly mild COPD in Denmark found no clear association between a high blood eosinophil count and future COPD exacerbations.[72] Exacerbation history (defined as a single exacerbation in the previous year), higher age and lower FEV_1 predicted the risk of future exacerbations, although there was no clear association with high blood eosinophil count.[72]

COPD exacerbations are overall more common in winter months than in summer, owing most likely to the effect of seasonal viral and bacterial infections.[77,78] Interestingly, a study of 127 patients from the UK found that although exacerbations were overall more common in winter than summer seasons, this seasonality was less pronounced in patients with persistent eosinophilic inflammation, who had similar exacerbation rates in both seasons. Further, the odds of an exacerbation associating with blood eosinophils ≥2% were 2.65 times higher in the summer than in the winter overall, increasing to 3.73 times higher among patients with persistently raised eosinophil counts.[26] This study also showed that eosinophilic inflammation associates with reduced odds of the presence of pathogenic bacteria, and other studies have shown that raised sputum eosinophil counts inversely correlate with bacterial infection.[18,26] These data suggest that factors other than infection underlie exacerbation biology in these patients: a topic that merits further study and raises questions for antibiotic stewardship and appropriate clinical management.

Multimorbidity

Most patients with COPD have chronic comorbidities;[6] even those who are newly diagnosed have a substantial comorbidity burden.[79] A retrospective study in the Netherlands reported that two-thirds of patients with COPD in primary care had between one and four comorbidities, with a fifth having five or more.[80] However, it is not only the number of comorbidities that impacts COPD disease burden, but also their severity. Indeed, because of this, the Charlson Comorbidity Index (CCI; a summary measure of the number of comorbidities divided by their severity) is often discussed in COPD studies. A modelling study in a Swedish COPD population highlighted the value of using the CCI in predicting hospitalization for exacerbations.[71] In this study, ischaemic heart disease and respiratory diseases other than COPD strongly predicted hospitalization due to acute exacerbations.[71] Similarly, another retrospective study in a Swedish COPD primary care population found that CCI score associated with both exacerbations and an increased risk of death.[81]

Overall, the presence of several chronic comorbidities associates with more frequent exacerbations and an increased exacerbation risk compared with no comorbidities.[80,81] Indeed, a retrospective study of patients with COPD in primary care in the Netherlands showed that having several comorbidities significantly associated with frequent exacerbations (≥2 exacerbations annually).[80] These comorbidities included heart failure, blindness and impaired vision, lung cancer, depression, prostate disorders, asthma, osteoporosis, diabetes, dyspepsia and peripheral vascular disease.[80] The comorbidity associated with the highest risk of future COPD exacerbations was having another chronic respiratory disease.[80]

An analysis of comorbidities in patients with COPD participating in the Norwegian Trøndelag Health Study (HUNT) examined how clusters of comorbidities informed patient outcomes during a 25-year follow-up period.[82] From the five clusters described in the study, two – the "psychological" and a "cachectic" clusters – associated with higher all-cause

mortality and an increased risk of exacerbations than a control "low comorbidity" cluster.[82] Patients with the "psychological" cluster had a high prevalence of depression and anxiety as well as obesity, hypertension, dyslipidaemia and osteoporosis.[82] Patients with the "cachectic" cluster had a high prevalence of underweight and osteoporosis, as well as high levels of anxiety, depression and hypertension.[82]

Some studies show that comorbidity patterns may differ between men and women. A population study in Sweden reported more asthma, fractures, osteoporosis, rheumatoid arthritis, rhinitis, depression, and anxiety in women than in men with COPD.[83] Conversely, type I and II diabetes, kidney disease and cardiovascular diseases were more common in men than in women.[83]

When considering patients with severe COPD (as defined by GOLD criteria), impaired kidney function was independently associated with increased all-cause and respiratory mortality in a Swedish secondary care population.[84] Further, increased age, decreased lung function and low body mass index predicted an increased mortality risk.[84]

Cardiovascular Comorbidities

Cardiovascular disease and COPD are strongly associated: patients with COPD are at high cardiopulmonary risk, from serious respiratory events such as exacerbations, and/or cardiovascular events such as myocardial infarction, stroke, heart failure decompensation and arrhythmia.[85] A systematic review of studies published between January 2015 and July 2019 found that of all comorbidities, cardiovascular comorbidity showed the strongest association with COPD readmissions to emergency departments.[44]

The association between cardiovascular comorbidity and poor outcomes is also apparent in studies in COPD populations in north-west continental Europe. A study of Danish patients with COPD and concomitant cardiovascular disease showed that stable COPD associates with an elevated cardiopulmonary risk.[43] A large, retrospective, observational study of a Swedish real-world primary care COPD population found that comorbid heart failure, stroke and myocardial infarction were the comorbidities that most strongly predicted death.[81] A Finnish national health survey found that having a diagnosis of COPD at baseline predicted higher total mortality and premature death from cardiovascular disease during an 18-year follow-up than patients without such a diagnosis.[86] Importantly, this study found that the hazard ratio for death among patients with COPD is comparable with that for patients who have cardiovascular disease or diabetes (hazard ratio: 1.50 vs 1.51 and 1.43, respectively, relative to individuals without these conditions).[86] This reinforces the fact that COPD is as serious a health condition as many diseases attracting greater focus.

A link between COPD exacerbations and cardiovascular events is also well established. A recent systematic review and meta-analysis of studies published between 2000 and 2021 identified a significant and marked increase in the risk of stroke or acute myocardial infarction within 1 to 3 months of an exacerbation.[87] A study in a large Dutch primary care population found that a moderate or severe COPD exacerbation was related to a substantial increase in the risk of severe cardiovascular events or all-cause death, with the risk being highest in the period immediately after an exacerbation.[75] In a Danish study of patients with COPD and concomitant cardiovascular disease, severe exacerbations associated with an increased risk of major cardiovascular events.[43] In most patients, the cardiovascular event occurred within 30 days of the exacerbation.[43]

Hospitalizations and Readmissions

As we have seen, exacerbations are a major cause of emergency room visits, hospitalizations and death across north-west continental Europe.[70,72,73,75] A recent systematic review and meta-analysis of individual COPD patient cases examined the global in-hospital mortality, post-discharge mortality and readmission rates after a hospitalization for an acute COPD exacerbation.[2] Despite the heterogeneity in studies and countries, overall global outcomes were poor, with a pooled in-hospital mortality of 6.2% (Table 3).[2] In general, about half of the deaths occurred within the first week of hospitalization, while over 70% occurred within the following year.[2] To put these figures into perspective, and to underscore just how serious COPD exacerbations are, in comparison, mortality rates in the 30 days following an acute myocardial infarction are 3.5% or less in most European countries (Denmark and Finland have higher rates: 4.5% and 6.8%, respectively),[88] and 5.4% or less in the 30 days following a stroke (8.4% in Finland).[89]

Table 3 Global Post-Discharge Mortality and Readmission Rates Following COPD Exacerbation-Related Hospitalization[2]

		30 Days Post-Discharge	90 Days Post-Discharge	365 Days Post-Discharge	
Pooled and stratified post-discharge mortality rate, %	**Global**	**1.8**	**5.5**	**10.9**	
	Countries			Belgium: Denmark: Finland: The Netherlands: Norway: Sweden:	4.7 30.4 1.7 14.3 1.0 21.8
Pooled and stratified hospital re-admission rate, %	**Global**	**7.1**	**12.6**	**32.1**	
	Countries			Belgium: Denmark: Finland: The Netherlands: Norway: Sweden:	38.2 59.1 51.7 33.4 64.6 44.8

Abbreviation: COPD, chronic obstructive pulmonary disease.

Specific data from this meta-analysis were available for some countries in north-west continental Europe and, although they are presented as pooled and stratified rates, they indicate the relative outcomes. Interestingly, these countries are generally among those with the highest 1-year readmission rates:[2] the pooled and stratified in-hospital mortality was 2.7% for Belgium, 5.4% for Denmark, and 7.1% for the Netherlands (other relevant countries were not included).[2] Information on the pooled and stratified 1-year readmission and post-discharge mortality for Belgium, Denmark, Finland, the Netherlands, Norway and Sweden are listed in Table 3.

Absolute reported outcome measures for outpatient visits, hospitalizations, length of hospital stay and readmissions for COPD are highly heterogenous across north-west continental Europe (see Tables S1–S6 for some individual country data). However, some results from individual studies are worth noting. For example, in a general COPD population in Norway, increased use of outpatient services was strongly associated with future hospitalizations.[90] In another study from Sweden, patients with COPD experienced significantly more days each year in hospital for both respiratory and non-respiratory causes than did patients without COPD.[91] The recent COPD Index, a global tool that evaluates the way countries prevent and manage COPD, has collated key outcomes across 34 countries and provides useful comparative information, including on hospitalizations and readmissions.[92]

It is worth noting the trajectory of hospital care provision for COPD, which may vary from country to country. A study in Finland showed that the number of emergency department visits increased by almost two-thirds between 1996 and 2018, even though COPD prevalence has remained relatively constant.[93] In contrast, in Sweden, hospitalizations for exacerbations have been stable despite decreasing prevalence of COPD.[94,95]

Given that hospitalizations are linked to exacerbations and that patients with COPD and type 2 inflammation are known to experience many exacerbations, it seems probable that eosinophilic COPD should associate with high hospital admissions and greater healthcare resource use. Despite this, data from north-west continental Europe are limited and contradictory. On one hand, a retrospective registry study in a Finnish hospital population reported that patients with COPD and type 2 inflammation (blood eosinophil counts ≥300 cells/μL) had more outpatient visits and inpatient days than patients with blood eosinophil counts <300 cells/μL.[58] This makes sense since those with high blood eosinophil counts have exacerbations more often than those with normal blood eosinophil counts. Yet conversely, a Danish study of patients with COPD in secondary care reported that patients with blood eosinophil counts ≥300 cells/μL had shorter inpatient stays than those with blood eosinophil counts below this cutoff, although readmission rates were similar for both groups.[39]

Mortality

According to the Global Burden of Disease study, the global standardized mortality rate for COPD in 2019 was 41.7%,[1] yet for our countries this ranged from 11.4% in Finland to 33.0% in Denmark (Table 2). When considering potential years of life lost (PYLL), a study in Finland showed that for patients with COPD aged ≥60 years, PYLL was 6400 in 2018, an increase of almost a third since 1996, possibly owing to increased life expectancy over that time, but also to the increased prevalence of multimorbidities and sedentary lifestyles that can exacerbate COPD mortality.[93] In this same study, total mortality for COPD increased by 23% over the same period, partially due to the same factors, but also perhaps due to improvements in diagnosis and awareness of COPD as a cause of death.[93]

Older age and lower FEV_1 were predictors for all-cause, respiratory and cardiac mortality in one national registry study of patients with COPD in Sweden.[96] In addition, worse dyspnea and a higher exacerbation frequency both associated with respiratory mortality.[96]

Trends in mortality for patients with COPD and type 2 inflammation in north-west continental Europe appear to show a lower risk of mortality in patients with high blood eosinophil counts than in patients with lower counts. This is supported by reports from individual studies in secondary care settings in Finland and Denmark, which suggest that mortality risk is lower for patients with blood eosinophil counts ≥300 cells/μL than in patients who have blood eosinophil counts <300 cells/μL.[39,58,97] The reasons for this trend are unclear. In one of the Danish studies, patients with lower blood eosinophils counts had high levels of pneumonia, which could explain the higher mortality.[39] Alternatively, patients with a predominantly type 1 inflammatory profile may have limited responses to bronchodilators and corticosteroids, resulting in a relatively high short-term mortality.[97]

A potential consequence of the lower mortality in patients with COPD and type 2 inflammation is that these patients survive while carrying a high morbidity burden resulting from the increased risk of frequent and severe exacerbations associated with type 2 inflammation.

Quality of Life

The health-related quality of life (HRQoL) of patients with COPD deteriorates as airflow limitation worsens and as exacerbation frequency increases: in turn, frequent and recurrent hospitalizations further reduce HRQoL.[45] COPD limits daily life, reduces physical activity and sleep quality, increases depression and anxiety, and worsens disease-associated pain.[45] In a Danish study, significantly higher anxiety, depression and stress symptoms were reported in patients with COPD than in those without.[98]

Stigma

A major cause of COPD is tobacco smoking, and smoking cessation is a key intervention to reduce its burden at both population and individual level.[6] Indeed, patients with COPD are more likely to try quitting smoking than patients who do not have COPD.[99] In Sweden, the prevalence of COPD declined significantly between 1994 and 2009 following a substantial reduction in tobacco smoking.[100] Furthermore, in Norway, the impact of smoking cessation is one reason why experts believe that COPD morbidity decreased between 2001 and 2017.[101]

This link with smoking has led to a considerable stigma being associated with a COPD diagnosis. Patients feel guilty that their tobacco smoking has caused COPD, and they are blamed by others, including healthcare professionals, for the self-inflicted nature of their condition.[102–105] Such stigma impairs patients' ability to manage their condition and to engage with healthcare professionals.[106] Furthermore, it reduces patients' ability to quit smoking.[107] This stigmatization appears to be a particularly acute issue with smoking-related diseases such as lung cancer and COPD: other chronic diseases such cardiovascular disease and most other cancers are less burdened with such stigma.[106,108,109]

The Cost of COPD Care

Despite the variability of health systems and general costs, some conclusions can be made about COPD care costs in general. Firstly, healthcare costs are higher for people with than without COPD, with real-world studies in Sweden and Denmark estimating that such costs are two to five times higher.[47,110,111] Secondly, most patients are treated in primary care, yet most costs are incurred in secondary care.[112,113] For example, a Danish population study found that 60% of

Table 4 Mean per Patient Costs (€) of COPD Care Normalized to 2019 Prices for Key Countries[4]

Cost (€)	Belgium[116]	Denmark[117,118]	Norway[113]	Sweden[111,119]
Direct costs	1963	9580	10,701	7045
Hospitalization	840	6162	6291	5094
Prescription costs	903	1973	2765	722
Outpatient consultation	222	874	1601	869
Work productivity loss	–	2033	–	–
Early retirement cost	–	15,722	–	–

Notes: Original published costs were converted to Euros (if required) and adjusted to Euro 2019 rates.
Abbreviation: COPD, chronic obstructive pulmonary disease.

patients with COPD were treated in primary care, yet these accounted for only 40% of the total cost of COPD care.[112] Thirdly, increasing COPD severity, and more frequent or severe exacerbations associate with higher direct costs.[48,76,111,114] Treatment costs are three times higher for a patient who experiences two or more annual exacerbations than for a patient who has no annual exacerbations.[76] Fourthly, the main care costs arise from hospitalization (mainly due to exacerbations), medication use, outpatient visits and diagnostic procedures:[4] studies show that managing acute exacerbations contributes 45–70% of the total costs of COPD care, and that the estimated direct cost of COPD in Europe is reported to range from €1963 to €10,701 per patient per year.[115] Finally, the indirect costs arising from inactivity, sick leave and social care place a substantial and poorly understood burden on patients and societies.

Direct Care Costs

The profound effect of COPD in terms of DALYs for the global population and our countries is shown in Table 2. Direct costs typically include those for hospital admission, medications, outpatient consultations and diagnosis. As expected, direct costs vary across north-west continental Europe. Standardized costs derived from a systematic review are available for Belgium, Denmark, Norway and Sweden for 2019[4] (Table 4).

As well as being major drivers of morbidity, as we have seen, exacerbations are also major drivers of COPD costs, and these vary by exacerbation severity. A Danish study estimated that mean costs per moderate and severe exacerbation were €888 and €7091, respectively, but found that these costs barely differed with COPD severity.[47]

The presence of comorbid conditions also increases care costs,[113] with one Swedish study finding that conditions other than COPD may account for a large proportion of hospitalization costs.[111] This is unsurprising given the link between COPD exacerbations and cardiovascular and respiratory events.

Direct Care Costs for Patients with COPD and Type 2 Inflammation

Type 2 inflammation associates with higher hospitalization costs. A study in a Canadian COPD population with blood eosinophil counts ≥200 cells/μL had significantly increased total 1-year COPD-related costs than did those with lower blood eosinophil counts.[120] A Finnish study found that total costs per patient-year were higher for patients with blood eosinophil counts ≥300 cells/μL than for those with counts below this level.[58]

Indirect and Societal Costs

A 2023 analysis estimated that between 2020 and 2050, COPD will cost the world economy INT$4.3 trillion, or the equivalent of a global per-capita burden of INT$490.[3] This is massive, and makes plain the vast worldwide economic burden of this disease. The per-capita burden for our countries is even higher than this global average, ranging from INT $557 in Finland to INT$1877 in the Netherlands (Table 5).

Much of these indirect costs relate to the morbidity that COPD causes. Even before diagnosis, patients with COPD are at a financial disadvantage, earning around half the income of patients with non-COPD conditions.[110] Compared with

Table 5 Predicted Economic Impact of COPD on National Incomes[3]

Cost	Belgium	Denmark	Finland	Luxembourg	The Netherlands	Norway	Sweden
Economic loss, millions of 2017 INT$	12,509 (10,127–15,222)	10,024 (8000–12,376)	3092 (2483–3820)	757 (599–958)	32,605 (26,048–39,900)	8629 (7393–9649)	11,949 (10,396–13,617)
Proportion of total GDP 2020–2050 accounted for by COPD, % x103	91 (72–110)	115 (92–142)	48 (39–59)	37 (29–47)	131 (105–161)	99 (85–110)	82 (71–93)
Per capita loss due to COPD, 2017 INT$	1044 (845–1270)	1655 (1321–2043)	557 (447–690)	1058 (837–1340)	1877 (1500–2297)	1425 (1221–1593)	1107 (963–1261)

Notes: All estimations are shown in 2017 INT$. Uncertainty intervals (shown in brackets) were calculated in the sensitivity analysis based on the lower and upper bounds of 95% uncertainty intervals for Global Burden of Disease Study 2019 mortality and morbidity data.
Abbreviation: COPD, chronic obstructive pulmonary disease.

the non-COPD population, employment and income rates are lower for patients with COPD and also for their spouses, showing the wide-reaching impact of COPD.[110,117] Furthermore, the spouses of patients with COPD also had significantly higher rates of health-related contacts and medication use compared with non-COPD reference populations.[117]

Loss of income was shown to be the largest single financial burden experienced by working age patients with COPD in Sweden in 2013.[111] Overall, early retirement has been estimated to contribute up to 85% of the indirect cost of COPD and 65% of the total COPD care costs.[4] For Denmark, average per-patient early retirement costs were estimated at €15,722 for 2019.[4]

Improving COPD Care and Reducing Its Clinical and Economic Burden

We suggest that there are several ways in which COPD care can be enhanced and the burden on patients, healthcare systems and society can be alleviated. None is a quick fix, and all will require concerted efforts by multiple stakeholders if they are to pay dividends for the future. The importance of such a "whole system" approach to COPD management is also advocated in the COPD Index, a global tool that evaluates the way different countries prevent and manage COPD.[92] The COPD Index also highlights the work our countries need to do to enhance COPD care; only Finland and Sweden rank among the top ten best-performing countries, with Norway ranked 16, the Netherlands ranked 18, Denmark ranked 22 and Belgium ranked 31 out of 34.[92]

Primary Care is Key

While policy and wider health systems are important, general practitioners (GPs) are especially critical in providing optimal COPD care, as most patients are diagnosed and managed in primary care. No other clinicians are as well placed to take a holistic, evidence-based view of the patient, and GPs should be encouraged and supported in this, through receiving disease-awareness training, easy-to-use digital tools and distilled guidelines to aid their decision-making.

Remission of COPD is, at least currently, an unrealistic goal. But a stable disease, meaning no exacerbations, no worsening of respiratory symptoms and no further lung function decline in terms of FEV_1 in percent predicted (other than usual age-expected decline), should be a feasible goal. Communicating this clearly to patients might help improve their medication compliance and adherence to lifestyle changes like smoking cessation and daily physical exercise, which in itself might improve patient quality of life.

One promising tool that may help GPs is a COPD version of the Asthma Optimiser.[121] This is an e-health decision-support tool that helps clinicians ask the right questions to support their decisions, with a view to better align these to guidelines. The Asthma Optimser has been shown to improve patients' outcomes; the COPD Optimizer is available and registered as a class IIa medical device in Europe and COPD studies are recruiting.[122]

Optimize Early Diagnosis

Early diagnosis of COPD is important: the earlier interventions are started, the earlier prevention strategies can begin and the higher the impact of these. Such strategies include smoking cessation, promoting physical activity and a healthy lifestyle, and prescribing inhaled medications.

Early COPD diagnosis, as well as reducing exacerbations and comorbidities, can lower healthcare use.[123] Yet as we have seen, clinicians' adherence to diagnostic and treatment guidelines is variable,[74] especially regarding the assessment of blood eosinophils. We suggest that improving this would allow a better assessment of the patient's risk profile and guide more appropriate use of ICS and help prevent the all-too-frequent misdiagnoses between asthma and COPD. Further, education is needed for both clinicians and patients on the heterogeneity, complexity and consequences of COPD multimorbidity, and the need to proactively diagnose and address not just COPD, but also its comorbid conditions.[43] Of particular relevance is the need to reframe COPD as a cardiopulmonary disease, rather than just a respiratory disease. This would highlight and address the cyclical risks of cardiovascular events in patients with COPD and of COPD exacerbations in patients with cardiovascular disease.

Establishing suitable fast-track referral pathways may enhance early diagnosis and treatment for patients with COPD. These could include, for example, specialized spirometry clinics, or support for patients with complex disease such as unstable COPD and multimorbidity.

Prevent Exacerbations

Preventing exacerbations and limiting disease progression may reduce the overall costs of COPD management.[4] In Sweden, estimates suggest that even a one percentage reduction in exacerbation numbers could save 84 million kronor (~ €74 million) per year.[124] We stress the need to prioritize exacerbation prevention, as exacerbations are among the most dangerous aspects of COPD. Using more relatable terms, such as "flare-up" or "lung attacks" when talking about exacerbations with patients[69] may improve disease awareness and enhance self-management. Sadly, it is impossible to obviate or predict all exacerbations, but more effective follow-up of patients post-hospitalization – currently poor in a number of countries[74] – may go some way to reducing future exacerbations and the likelihood of readmission.[90,124] This may require better collaboration between primary and secondary care settings.

As we better understand the phenotypes and endotypes of COPD, we are becoming better equipped to individualize patients' care by more effectively stratifying them for risk and designing and using targeted treatments.[5,13] New medications targeting type 2 cytokines may offer promise in patients with COPD and high blood eosinophil counts.[12,65,125,126] To date, the results with anti–IL-5, and anti–IL-13 biologics in patients with COPD have been disappointing.[127,128] For example, in the METREX and METREO trials of anti–IL-5 monoclonal antibody (mAb) mepolizumab in patients with a history of exacerbations despite triple therapy, the annualized exacerbation rate was lower among mepolizumab-treated than placebo-treated patients, but this was significant only in METREX.[129] Similar non-significant results were seen in the GALATHEA and TERRANOVA trials of anti–IL-5Rα mAb benralizumab.[130] In METREX, a greater effect was observed in some – but not all – patients with baseline eosinophil counts ≥300 cells/mm^3 (rate ratio: 0.82, 95% confidence interval [CI]: 0.68–0.98, adjusted $p = 0.004$), suggesting that eosinophils play at least some role in exacerbations but that other factors may contribute.[129] Perhaps, eosinophils are not effectors of disease exacerbations, but rather surrogate markers of the specific pathways that are driving these events. On the other hand, promising evidence is emerging that targeting both IL-13 and IL-4 may be effective for COPD, with such targeted therapies now being approved in both the USA and European Union.[125–127] In the BOREAS trial, dupilumab, an anti–IL-4/IL-13 mAb, significantly reduced the annualized rate of moderate-to-severe exacerbations among patients with blood eosinophil counts ≥300 cells/μL despite triple therapy (rate ratio: 0.70, 95% CI 0.58–0.86; $p < 0.001$), and improved measures of lung function and quality of life.[125]

Promote Healthy Living Without Stigmatization

Compared with the general population, patients with COPD are at a greater risk of health complications arising from serious infections.[131] Therefore, the GOLD 2024 report on COPD recommends that people with COPD should receive all

recommended vaccinations in line with relevant local guidelines. Studies have shown that the influenza vaccine significantly reduces COPD exacerbations; this, as well as pneumococcal, respiratory syncytial virus and other vaccines are all recommended in patients with COPD and other chronic lung diseases.[6]

The most important advice of all, however, is to continue to advocate smoking cessation with all patients with COPD in whom it is appropriate,[6] in a way that seeks to reduce their stigmatization and guilt. Additional policy tools that continue to support smoking cessation are to be encouraged. As COPD is a frequent disease with several comorbidities, these patients are seen by doctors and nurses of a variety of specialities. Hence, there is a need for an information strategy towards the whole healthcare community to combat the COPD stigma.

Conclusions

COPD is a neglected disease, with patients stigmatized for their illness; yet COPD is a major health issue that is costly to societies. We need to shift the perception of COPD to start seeing its exacerbations as equal in seriousness to heart attacks and cancer. We all need to play a role in tackling COPD, starting with disease prevention through smoking cessation and lifestyle counselling: this is of course relevant to policymakers and clinicians alike. Primary care providers especially need to improve COPD detection and ensure the accurate diagnosis of its underlying drivers, such as type 2 inflammation, which shape both its treatment strategies and patient outcomes. Care at all levels needs to be better integrated to optimize follow-up care, and prevent patients falling through the cracks of disjointed healthcare systems.

Abbreviations

CCI, Charlson Comorbidity Index; CD, cluster of differentiation; COPD, chronic obstructive pulmonary disease; DALYs, disability adjusted life years; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; GP, general practitioner; HRQoL, health-related quality of life; HUNT, Norwegian Trøndelag Health Study; ICS, inhaled corticosteroids; IL, interleukin; ILC2, type 2 innate lymphoid; LABA, long-acting β-agonists; LAMA, long-acting muscarinic antagonists; PYLL, potential years of life lost; Th2, T-helper cell type 2.

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