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Quarterly Medical Review - Advances in understanding and managing COPD

Pre-COPD: Impact on prevention, detection, and treatment

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ABSTRACT

Background and Objectives: The ability to identify individuals at risk for progression to chronic obstructive pulmonary disease (COPD) remains challenging. The concept of pre-COPD has been proposed as a framework to identify patients without current airflow obstruction at greatest risk for progression to COPD using a constellation of symptoms, physiologic changes, and structural changes on chest imaging. While multiple biomarkers are linked to the subsequent development of COPD in at-risk individuals, no single biomarker has emerged as the best predictor. The goal of this review is to define the concept of pre-COPD, summarize known biomarkers associated with later development of COPD, and address the impact of pre-COPD on patient care.
Methods: Narrative Review
Conclusion: The concept of pre-COPD can help meet current gaps in screening and care for patients at risk of progression to COPD. A framework definition of pre-COPD allows for identification of individuals at risk for progression to COPD and indicates increased morbidity and mortality. While the ideal biomarker for pre-COPD has not been identified, multimodal risk prediction scores and practical clinical definitions are emerging for use in clinical practice. Additional research is needed to better understand optimal clinical screening and management of patients with pre-COPD.

1. Introduction

Although COPD as a disease entity has been extensively studied, the ability to identify at-risk patients, particularly in the clinical setting, has been limited. In 2001, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) proposed GOLD 0 as a category intended to identify patients at risk of developing COPD based on the presence of chronic respiratory symptoms [1]. Ultimately, however, GOLD 0 was discarded as the majority of at-risk individuals who progress to COPD do not have a high burden of respiratory symptoms [2–7]. Nonetheless, identifying patients at risk of developing COPD remains of clinical importance as it may lead to case finding, counselling, and earlier intervention [8]. Most recently, the term pre-COPD has been proposed to help identify individuals at risk for progression to COPD. In this chapter, we explore the concept of pre-COPD as a pre-disease state, identify known and emerging biomarkers, and summarize the utility of pre-COPD on detection, prevention, and treatment of COPD.

2. The concept of pre-COPD

2.1. Pre-disease states in medicine

The concept of a pre-disease state is commonly used in medicine to identify patients at increased risk for progression to a known disease. Conventionally, the presence of pre-disease state does not guarantee progression to the corresponding disease, and pre-disease states often carry independent morbidity and mortality, even in patients who do not progress to the disease. Pre-disease states have an observable objective clinical measurement, called a biomarker, which is used to identify patients at risk for progression to disease. A commonly used example of a pre-disease state is pre-diabetes. In pre-diabetes, patients demonstrate impaired glucose tolerance, measured by the HbA1c biomarker [9]. This biomarker provides risk information to clinicians regarding risk of progression to diabetes. For example, an HbA1c of 6.0 is associated with a hazard ratio of approximately 10 for progression to diabetes mellitus [9]. Pre-diabetes shares some pathophysiologic mechanisms with

Abbreviations: BEACON, British Early COPD Network Cohort Investigators; CT, Computed tomography; COPD, Chronic obstructive pulmonary disease; DPM, Disease probability measures; FEV1, Forced expiratory volume in the first second; FEV3, Forced expiratory volume in first three seconds; FEV6, Forced expiratory volume in first six seconds; FVC, Forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; mMRC, Modified Medical Research Council Dyspnea Scale; PRISm, Preserved ratio impaired spirometry; PRM, Parametric Response Mapping; RV, Residual Volume; SPIROMICS, Subpopulations and Intermediate Outcomes in COPD Study; SOURCE, SPIROMICS Study of Early COPD Progression; TLC, Total lung capacity

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diabetes mellitus, but the presence of pre-diabetes does not guarantee progression to diabetes mellitus [10,11]. Patients with pre-diabetes have an independent risk for morbidity and mortality even when not progressing to diabetes mellitus [12]. The usefulness of a pre-disease concept like the example above depends on the ability to identify patients at increased risk for progression to disease. It presents opportunities to prevent or delay development of the disease, with interventions ranging from lifestyle modification to pharmacologic therapies [11,13].

2.2. Pre-COPD

The early framework definition of pre-COPD was proposed as a pre-disease state [8]. Pre-COPD describes a constellation of symptoms, objective physiologic data, and/or radiographic data indicating increased risk for progression to COPD in patients without current spirometric airflow obstruction, defined by FEV1/FVC $\geq$ 0.7 [8]. The framework of pre-COPD includes individuals previously identified by GOLD 0, but also encompasses additional phenotypes including abnormal physiologic and imaging findings in the absence of airflow obstruction on spirometry. Like other pre-disease states, pre-COPD shares pathophysiological pathways with COPD, including increased mucin production, small airway disease, and emphysematous changes [14−16]. Several biomarkers have been examined to help identify these abnormalities. In the case of both chronic bronchitis symptoms and significant tobacco exposure history, pre-COPD is independently associated with increased mortality risk, increased respiratory exacerbations, and lower quality of life even if disease does not progress to airflow obstruction [4,15,17−20]. Like pre-diabetes, pre-COPD describes only a risk of progression and not all patients who meet case definition will progress to COPD.

While pre-COPD was conceived as a pre-disease state, accumulating data suggests that some of these patients experience significant morbidity despite not meeting the spirometric criteria for COPD. The current GOLD document uses a post-bronchodilator FEV1/FVC ratio of <0.7 as a diagnostic criterion for COPD [6]. There has been debate surrounding the use of fixed cutoff ratio, and changes to the classification of COPD have been proposed [21−23]. Individuals with pre-COPD, including those with chronic bronchitis symptoms as well as significant tobacco exposure without chronic bronchitis, experience higher rates of respiratory exacerbations, dyspnea, and lower quality of life [15,20]. For instance, chronic tobacco users without airflow obstruction in the COPDGene study reported similar rates of dyspnea and respiratory exacerbations as individuals with GOLD 1 COPD [15]. Additionally, populations previously defined as GOLD 0 can have emphysema and other chronic airway changes present on imaging [24,25]. As a result of the clinical symptoms of individuals meeting criteria for pre-COPD, as well as the debate surrounding FEV1/FVC cutoffs, some have hypothesized that pre-COPD may in fact be a distinct phenotype of COPD not captured by the airflow criteria of FEV1/FVC < 0.70 [23].

2.3. Pre-COPD and early COPD overlap

This discussion is especially pertinent in younger individuals due to the current understanding of lung function trajectories with age. Various risk factors and exposures in childhood can affect normal lung growth and development, leading to heterogenous trajectories of both lung development and lung function loss [26−28]. The concept of early COPD has emerged in response. Martinez et al. have proposed a definition of early COPD as age < 50 years, a smoking history > 10 pack-years and any of the following: early airflow limitation below the lower limit of normal (but greater than 0.7), compatible CT abnormalities, or rapid decline in FEV1 [26]. Differing positions exist as to what extent airflow limitation should be considered in the diagnosis in early COPD [26,29]. Depending on the case definition used, this patient cohort can overlap with patients meeting proposed criteria for pre-COPD. The primary delineating feature between the current working concepts of pre-COPD and early COPD is age. Early COPD is currently being further explored through two longitudinal observational studies, the SPIROMICS Study of Early COPD Progression (SOURCE) and the British Early COPD Network Cohort Investigators (BEACON) [30−32]. GOLD currently uses the term early COPD to refer to the biological first steps of the disease in an experimental setting, focusing on the utility of the term to help understand disease pathogenesis. Proposed overlapping and distinguishing definitions are currently under consideration and will likely be further developed by the results of ongoing investigations.

3. Biomarkers

3.1. Role of biomarkers in pre-COPD

As noted previously, a unifying characteristic of pre-disease states is the presence of biomarkers that can be used to gauge risk. No biomarker has emerged as a single risk predictor for progression to airflow limitation. This may relate to the possible heterogenous underlying disease states that can precede COPD. Instead, a constellation of biomarkers and clinical parameters are being investigated in risk stratification tools. To better understand these tools, the individual biomarkers and their relative predictive values should be further explored. These biomarkers and the supporting data that have linked them to COPD progression are summarized below in the categories of symptoms, pulmonary function testing, airway mucin concentrations, and chest imaging findings.

3.2. Symptoms as biomarkers for pre-COPD

After the introduction of the concept of GOLD 0, several large studies have explored the relationship between respiratory symptoms, including cough, mucus production, dyspnea, and wheezing, with future development of COPD [8]. Many of these studies noted associations between symptoms and subsequent increased incidence of airflow obstruction [2,3,18,33,34,35]. These studies primarily examined chronic cough and mucus production, which are hallmark symptoms of non-obstructive chronic bronchitis [8], but also included ancillary findings related to dyspnea, wheezing, and gender-stratified results [3]. The data, however, are not completely harmonious. For instance, in the Copenhagen City Heart study, the relationship between chronic mucus hypersecretion and excess FEV1 decline was significant among men but not women [36]. Yet, in the overall analysis, the majority of individuals who ultimately developed obstruction did not have preceding symptoms, challenging the utility of GOLD Stage 0 as a predictor for developing COPD [5]. Additionally, a recent analysis from the Subpopulations and Intermediate Outcomes in COPD study (SPIROMICS), also demonstrated no significant excess risk in individuals with symptoms over asymptomatic individuals in developing subsequent COPD, although the overall follow-up time was shorter than some of the studies demonstrating a relationship between chronic bronchitis and subsequent development of COPD [19]. Hypotheses have been made as to the discordant results related to symptoms and COPD risk between studies, and the investigators of these important studies note that instability of symptoms over time, gender differences in participants, and multiple underlying phenotypes leading to symptoms may have contributed to differing results [5,8]. Hence, while there is evidence linking symptoms of chronic productive cough and phlegm production in unobstructed individuals with subsequent development of COPD, it does not identify most patients who progress to COPD. Despite these limitations, due to the significant supporting evidence, the presence of chronic bronchitis is one of the most compelling individual biomarkers with respect to later development of COPD.

3.3. Lung function biomarkers of pre-COPD

In addition to respiratory symptoms, spirometric measurements have also been proposed as potential biomarkers to identify pre-COPD. In the

Lovelace cohort of participants exposed to tobacco without airflow obstruction at enrollment, the participants with the lowest FEV1 quartile with loss >40 ml/yr over an 18-month observation period had a 36-fold risk of developing GOLD stage 2 COPD over the 42-month period of observation. These participants also demonstrated higher mMRC dyspnea scale scores and worse health status scores than others in the cohort [37]. Despite this significant finding, FEV1 decline has limitations, specifically in terms of FEV1 variability over short time-periods as well as the requirement that historical measurements be available [38]. In addition to FEV1, FEV1/FVC ratio has been examined with respect to COPD risk. An analysis from the SPIROMICS cohort demonstrated that participants with reversible obstruction defined as pre-bronchodilator FEV1/FVC < 0.7, but post-bronchodilator FEV1/FVC >0.7, had a hazard ratio of 6.2 for the development of COPD compared to reference participants [39]. DLCO has also been considered as another important physiologic biomarker as it related to pre-COPD. A small cohort in NY demonstrated that low DLCO correlated with significantly increased comparative incidence of COPD [40]. One additional spirometry finding of particular interest is preserved ratio impaired spirometry (PRISm). Significant data from multiple cohorts has supported the relationship of PRISm with the development of future airflow limitation, as well as lung function decline and increased mortality [41−44]. Data from the COPDGene cohort demonstrated transition to flow limitation in 25 % of subjects with PRISM at 5-year follow-up, increased mortality rates compared to tobacco exposed subjects without PRISM or obstructive disease, and increased proportion of cardiovascular mortality [42,45].

Other spirometric measures such as FEV3/FEV6, volume-time curve shapes, and FEF25 %−75 % have also been explored [46−48]. In addition to the above findings, there is a rising interest in forced oscillation technique in detecting early changes to airways which is also being further investigated [49,50]. The link between physiologic measures of hyperinflation (e.g., total lung capacity on plethysmography) and exercise capacity (e.g., 6-minute walk test, cardiopulmonary exercise test) with progression to COPD may be important areas of future research, as current data on these markers in Pre-COPD are limited [51,52]. While the objective measures listed above show promise as biomarkers, many of these measurements are not obtained routinely in the population of interest, in part due to current screening guidelines [53]. As with symptoms, there is initial compelling data but not yet a clear single objective biomarker that can reliably identify all patients with pre-COPD.

3.4. Mucin concentration as a biomarker of pre-COPD

Another area of ongoing investigation is the relationship between airway surface mucin concentration and COPD pathogenesis. In the SPIROMICS cohort, mucin concentration was measured through samples collected by induced sputum among participants [14]. Individuals meeting criteria for non-obstructive chronic bronchitis demonstrated higher mucin concentration than individuals not meeting criteria. Furthermore, individuals with chronic bronchitis and emphysematous changes on imaging demonstrated elevated mucin concentrations over individuals with chronic bronchitis alone [14]. Mucous protein was also investigated in this same cohort, revealing that a protein named MUC5AC was most reliably associated with manifestations of COPD [16]. This data taken together may suggest that mucin concentrations, specifically MUC5AC, may serve as a potential biomarker for pre-COPD.

3.5. Imaging changes as biomarkers of pre-COPD

Imaging findings represent a final category of potential biomarker as they can display evidence of structural changes to the large airways, small airways and lung parenchyma that are shared with COPD. Examples of imaging findings that have been explored include extent of emphysematous tissue, airway diameter, surrogates of small airway disease, dysanapsis, and multimodal measures of parenchymal changes. To evaluate emphysema, a measure known as Perc15 has been utilized. Perc15 is a measure of computed tomography lung attenuation under which 15 % of lung tissue falls and can be used to quantify the degree of emphysematous tissue. The Nelson study examined multiple CT measures and noted significantly lower mean Perc 15 in participants that subsequently developed airflow obstruction compared to participants who did not develop airflow obstruction in 3-year follow-up [54−56]. The finding of this larger study contrasts with that of two smaller studies that did not find a relationship between Perc15 or emphysematous lung tissue and subsequent airflow obstruction [57,58]. In terms of airway morphology, the MESA lung study demonstrated greater Pi10, a normalized measure of airway wall thickness, is associated with FEV1 decline, incident 5-year COPD, and higher risk of hospitalization [59]. The Nelson trial also examined Pi10, and noted that a 1-mm increase in Pi10 corresponded to an OR of 2.45 for subsequent airflow limitation [54−56]. Parametric response mapping (PRM) is a novel imaging analytic technique that co-registers inspiratory and expiratory CT images to distinguish between emphysema and non-emphysematous air trapping referred to as functional small airway disease [60]. Two studies using data from COPDGene demonstrated that functional small airway disease as measured by PRM was associated with higher FEV1 decline [24] and emphysema progression over 5 years of follow-up in participants without airflow obstruction [25]. Dysanapsis, a measure of mismatched development of airway size when compared to total lung volume, was examined from pooled data from three cohorts (MESA, canCOLD, and SPIROMICS) and was associated with incident COPD [61]. In an analysis of the SPIROMICS cohort, a higher residual volume to-total lung capacity ratio on chest CT was also associated with the development of future airflow obstruction [51]. Finally, the BEACON cohort in the UK demonstrated six quantitative CT measures associated with FEV1 decline in FEV1 in individuals with a smoking history under the age of 45 years, including disease probability measures (DPM), increased Pi10, increased volume of small pulmonary blood vessels, increased extent of ground glass opacities, and more prominent bronchovascular bundles [32]. In summary, multiple advanced imaging biomarkers may be associated with a higher risk of COPD by identifying various lung structural changes that precede airflow limitation in COPD. It remains to be determined which combination of imaging findings have the highest predictive value for development of COPD, and emerging technologies including applications of artificial intelligence are currently being investigated.

4. Multimodal risk prediction scores

Although many biomarkers can be related to the clinical state of pre-COPD, no single biomarker has ideal sensitivity and specificity. As a result, two recent multimodal risk prediction scores have been proposed. The first of these risk prediction scores, known as the SLIM criteria, was derived from the Lovelace cohort and included all patients with tobacco exposure and at least three PFT's spaced 1 year apart with a spirometry within normal limits at baseline [62]. The model utilized chronic airflow limitation as surrogate for a COPD diagnosis. Multiple predictors of interest were identified but four dichotomized variables were included in the final risk prediction model. These predictors of developing chronic airflow limitation included chronic bronchitis, ≥30 pack-year tobacco history, BMI ≤ 25, and FEV1/FVC < 75 %. When all four of these predictors were present, the model predicted an 85 % probability of developing chronic airflow limitation over a 6-year period as opposed to 2 % probability when all four predictors were absent, with a sensitivity of 0.72 and specificity of 0.85 in the initial cohort. This model was externally validated using the COPDGene cohort. A second risk score was created from cumulative data from the Copenhagen General Population and Copenhagen City Heart study, in which a risk score was created using five factors: chronic bronchitis, preserved ratio impaired spirometry (PRISm), early airflow limitation defined as FEV1/FVC >0.7 but below LLN, active smoking history and history of asthma. This score was stratified into low risk, intermediate risk, high risk, and very high risk

based on the number of risk factors and demonstrated a stepwise increase in OR to approximately 16 in the very high risk group with relation to COPD development at both 10 and 25 year follow-up [44]. The predictions of this risk score performed better than tobacco exposure alone.

Common features among these two scoring methods include chronic bronchitis, initial spirometric signs of possible obstructive ventilatory defect not captured by FEV1/FVC < 0.7, and tobacco history. Notably, many of the participants from both groups meet the criteria for early COPD as described in Section 2.3. The relevance of this distinction will now be explored in discussing COPD detection, impact on prevention, and interventions to prevent the progression of pre-COPD to COPD.

5. Pre-COPD case definition

5.1. Conceptualized definition for pre-COPD

Given the discussion of biomarkers and multimodal risk prediction models above, a conceptualized definition can be further delineated. For the clinician, pre-COPD can be suspected in patients with risk factors for COPD, including genetic, environmental, and developmental who also have symptoms or objective physiologic or imaging findings suggestive of early lung disease (Fig. 1) [8,29,44,62]. These individuals may be brought to the clinician's attention due to chronic symptoms, abnormal pulmonary function testing, or evidence of early airway or lung parenchymal abnormalities present on imaging, including low-dose CT scans ordered for lung cancer screening. Multimodal risk score prediction can act in conjunction with clinical history to raise or lower the estimated probability of progression to COPD [44,62]. In patients under the age of 50, care should be taken by the clinician to distinguish between pre-COPD and possible early COPD, especially as case definitions and management are further defined [26,38].

5.2. Pragmatic definitions of pre-COPD

We have previously utilized a framework definition of pre-COPD as a pre-disease condition present in the absence of spirometric airflow limitation with a constellation of symptoms, functional changes, and structural changes observable through objective clinical data indicating both increased risk for progression to COPD and independent risk for morbidity and mortality (FEV1/FVC < 0.7). This framework appropriately acknowledges the ongoing exploration of biomarkers but has limitations in clinical use. A pragmatic definition has been proposed, which includes the following required criteria: FEV1/FVC ≥ 0.7, and symptoms of cough and phlegm daily for 3 months over a period of three years. In addition to the required criteria, patients must demonstrate either a reduction in function measured by DLCO <80 % predicted, FEV1 decline >40 ml/yr, or the presence of PRISm, as well as the presence of imaging findings such as emphysema or vascular remodeling [29]. While the clear criteria in this definition can be used in the clinical setting, it notably excludes individuals who are at risk for progression to COPD and do not demonstrate symptoms of chronic bronchitis, which was one of the major criticisms of the prior GOLD 0 framework [7].

6. Pre-COPD impact on care

6.1. Impact of pre-COPD on patient counselling

One of the considerations for utilizing pre-COPD as a pre-disease state is the impact on early detection of COPD. COPD is significantly underdiagnosed or misdiagnosed in actual practice [63,64]. Data from the National Health and Nutrition Examination Surveys suggests that greater than 70 % of patients with spirometry-defined airflow limitation did not have a diagnosis of COPD [65]. Despite these findings, the United States Preventative Task Force currently recommends no screening for COPD, specifically in asymptomatic persons [53]. Additionally, there are currently competing approaches proposed in utilizing forced spirometry in case finding for COPD [6]. These guidelines are currently not risk-stratified for high and low risk populations and the ideal timing, follow-up, and screening for patients with pre-COPD has not yet been clearly established. As biomarkers and risk scores are further explored, providers may consider different frequency of follow-up and spirometry screening for populations at elevated risk [66]. Additionally, incidental findings of airway wall thickening or emphysema present on chest

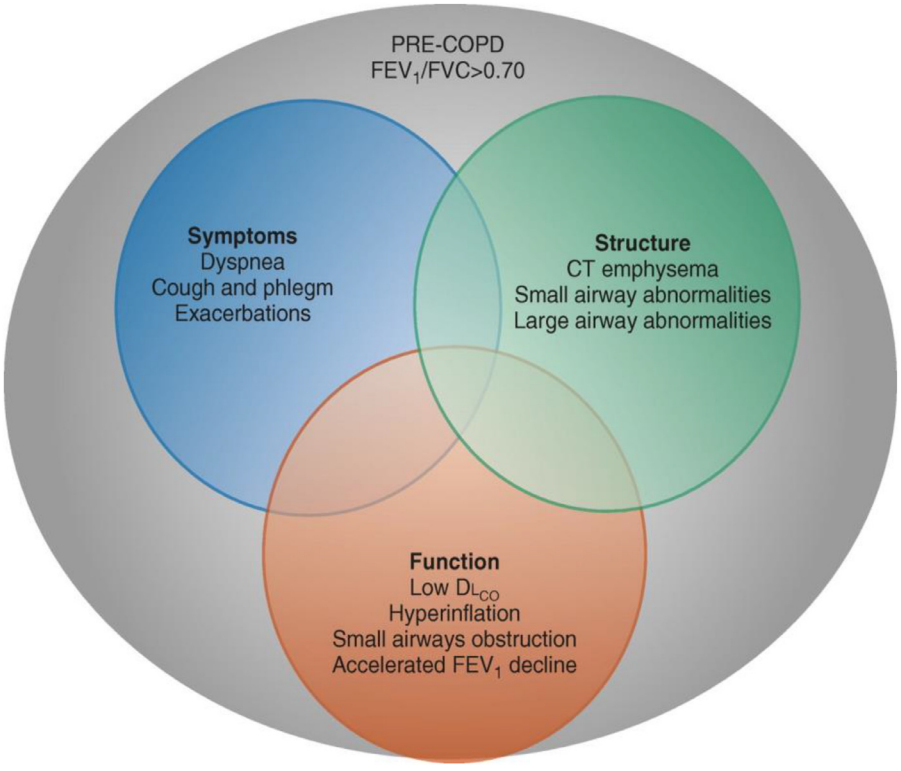

Fig. 1. Conceptualized definition of pre-COPD. Reproduced from Figure 1 from "From GOLD 0 to COPD" [8]. Conceptualized understanding of the relationships among symptoms, structure, and function with respect to pre-COPD. Reprinted with permission of the American Thoracic Society. Copyright © 2024 American Thoracic Society. All rights reserved. Cite: MeiLan K. Han; Alvar Agusti; Bartolome R. Celli; Gerard J. Criner; David M. G. Halpin; Nicolas Roche; Alberto Papi; Robert A. Stockley; Jadwiga Wedzicha; Claus F. Vogelmeier; Am J Respir Crit Care Med 203,414−423. The American Journal of Respiratory and Critical Care Medicine is an official journal of the American Thoracic Society.

imaging for lung cancer screening should be considered by the clinician to assess symptom burden and order spirometry if not already done [67]. Pre-COPD can also be a useful tool for the provider to utilize for patient counselling. When approaching motivational interviewing for tobacco cessation and lifestyle changes, the concept of pre-COPD may be introduced to the patient to further emphasize the importance of these changes and appropriately frame patient risk for progression to COPD [68,69]. The changes in preventative counselling and care in the context of pre-COPD should be explored in further research once case definitions have been fully established.

6.2. *Pre-COPD pharmacologic interventions*

Patients with pre-COPD, especially with non-obstructive chronic bronchitis phenotype, may require symptomatic treatment. The effectiveness of current treatments for these patients is under investigation. One of the major motivations behind the concept of pre-COPD is to prevent tissue destruction and slow or stop the progression of disease [38]. Some therapies have been studied in the context of early COPD and have not yet been investigated in the context of pre-COPD. For instance, one randomized controlled trial, the Tie-COPD trial, demonstrated that early treatment with tiotropium may decrease subsequent lung function decline in patients with mild and moderate COPD as well as increase quality of life [70]. The recent RETHINC trial, however, demonstrated that dual bronchodilators did not decrease respiratory symptoms in symptomatic tobacco exposed participants without airflow obstruction [71]. This 12-week trial did not establish if dual bronchodilator therapy would affect other important clinical outcomes in these participants such as the frequency of respiratory exacerbations or lung function decline. Many other important therapeutic questions have not yet been investigated, including the effects of common pulmonary interventions like inhaled corticosteroids and the risk-reduction potential of lifestyle modification once a pre-COPD case definition is met. These therapies and interventions should be further investigated in relationship to risk reduction and symptom control. Finally, as the role of biologics have been established in asthma [72] and are being investigated in COPD [73–76], novel treatments may be investigated in the future.

7. Future directions

A persistent challenge to our current definition for pre-COPD is that it may not be easily implementable in clinical practice. Symptoms can certainly be easily assessed but less routine physiologic and imaging metrics may be more challenging. The biomarkers in use are currently being further refined, although two risk scores have been described. We also have much less data among patients with non-tobacco exposures. Given the rising attention globally to air pollution as an independent risk factor for COPD, as well as the associated decline in lung function [77], literature is needed to distinguish COPD pathways in non-tobacco users. Furthermore, biomass fuel exposure, poorly controlled asthma, prior history of tuberculosis infection and other exposures have been associated with COPD and represent global health challenges that have been poorly characterized in the current literature related to pre-COPD [29]. The lack of evidence in the current literature regarding these exposures may inappropriately skew case definitions in a manner not representative of non-tobacco users. Significant further research is needed in the following domains: revision of pre-COPD case definition and risk prediction scores as well as validation of existing scores, differentiation between pre-COPD and early COPD, inclusion of non-tobacco exposed populations, the use of lung cancer screening in the identification of individuals with pre-COPD, consideration of spirometry screening in pre-COPD populations as well as frequency of follow-up, and treatment for pre-COPD both for symptom management and to lower risk of progression to COPD.

8. Conclusion

The concept of pre-COPD can help meet current gaps in screening and care for patients at risk of progression to COPD. As a framework, pre-COPD is defined as a pre-disease condition present in the absence of spirometric airflow limitation with a constellation of symptoms, functional changes, and structural changes demonstrating early lung disease. The ideal biomarkers for pre-COPD are currently being investigated and multiple biomarkers and risk factors are being included in multimodal risk prediction scores. For the clinician, pre-COPD can be suspected in patients with known risk exposure for COPD, with associated symptoms of chronic bronchitis, physiologic changes associated with pre-COPD on spirometry, or incidental imaging findings. Additional research is needed to better understand best screening, counselling, and therapeutics once pre-COPD is identified.

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declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Christopher B. Bosma: Conceptualization, Writing – review & editing, Writing – original draft. **Wassim W. Labaki:** Writing – original draft, Supervision, Writing – review & editing, Conceptualization. **Mei-Lan K. Han:** Conceptualization, Writing – review & editing, Supervision, Writing – original draft.

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