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Clinical Review

Revealing Methodological Challenges in Chronic Obstructive Pulmonary Disease Studies Assessing Comorbidities: A Narrative Review

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Abstract

Beyond respiratory impairment, patients with chronic obstructive pulmonary disease (COPD) often suffer from comorbidities which are associated with worse health status, higher health care costs and worse prognosis. Reported prevalences of comorbidities largely differ between studies which might be explained by different assessment methods (objective assessment, self-reported assessment, or assessment by medical records), heterogeneous study populations, inappropriate control groups, incomparable methodologies, etc. This narrative review demonstrates and further evaluates the variability in prevalence of several comorbidities in patients with COPD and control individuals and discusses several shortcomings and pitfalls which need to be considered when interpreting comorbidity data. Like in other chronic organ diseases, the accurate diagnosis and integrated management of comorbidities is a key for outcome in COPD. This review highlights that there is a need to move from the starting point of an established index disease towards the concept of the development of multimorbidity in the elderly including COPD as an important and highly prevalent pulmonary component.

Abbreviations: chronic obstructive pulmonary disease, **COPD**; Global initiative for chronic Obstructive Lung Disease, **GOLD**; atrial fibrillation, **AF**; electrocardiography, **ECG**; Hospital Anxiety and Depression Scale, **HADS**; cardiovascular disease, **CVD**

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Introduction

Multimorbidity is a major challenge for health care systems in the next decades.[1] Beyond respiratory impairment, patients with chronic obstructive pulmonary disease (COPD) often suffer from comorbidities which are associated with worse health status,[2] higher health care costs[3] and worse prognosis.[4]

The Global initiative for chronic Obstructive Lung

Disease (GOLD) Global Strategy for the Diagnosis, Management, and Prevention of Obstructive Lung Disease 2017 report suggests that disease management in COPD must include identification and treatment of comorbidities.[5] According to GOLD, most common comorbidities are cardiovascular disease (heart failure, ischemic heart disease, arrhythmias), peripheral vascular disease, hypertension, osteoporosis, anxiety and depression, lung cancer, metabolic syndrome and diabetes, gastroesophageal reflux, bronchiectasis and obstructive sleep apnea[5] which might further be extended with skeletal muscle dysfunction and loss of muscle mass, cognitive impairment, anemia, renal insufficiency and infections.[6]

During the last 2 decades, publications regarding COPD and its associated comorbidities exponentially increased supporting the concept of COPD as "COmorbidity with Pulmonary Disease."[7] But does this explosion of epidemiological studies and clinical trials help us to understand the association between COPD and comorbidities or does it rather cause confusion?

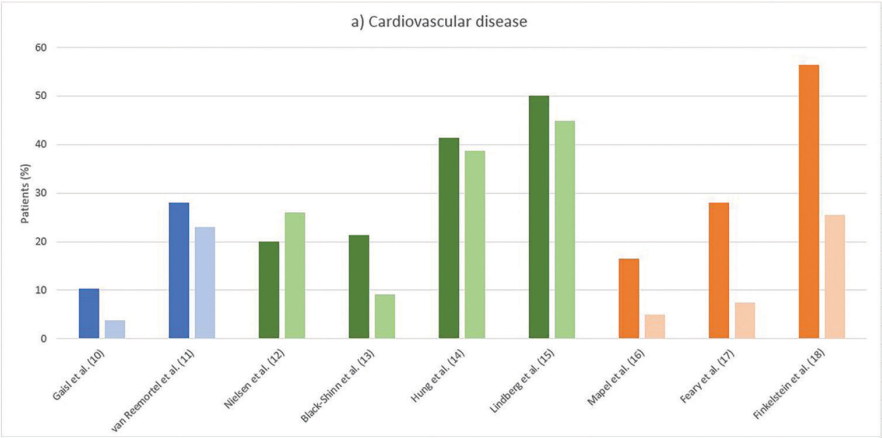
Reported prevalences of comorbidities largely differ between studies. For instance, the prevalence of cardiovascular diseases in patients with COPD ranges from 13% to 68% and the prevalence of mental disorders ranges from 8% to 45%.[8] These discrepancies might be explained by heterogeneous study populations, incomparable methodologies, different assessment methods and diverse definitions of the respective comorbidity. Besides an appropriate study design, an adequate control group is necessary to understand and correctly interpret the prevalence at hand. Confounding variables, such as the definition of the study population, are a major potential cause of bias.[9] To demonstrate and further evaluate the variability in prevalences of several comorbidities in patients with COPD and control individuals, we conducted a broad literature search (using search terms 'COPD' and 'comorbidities' in PubMed and consulting relevant references) to narratively review existing findings.

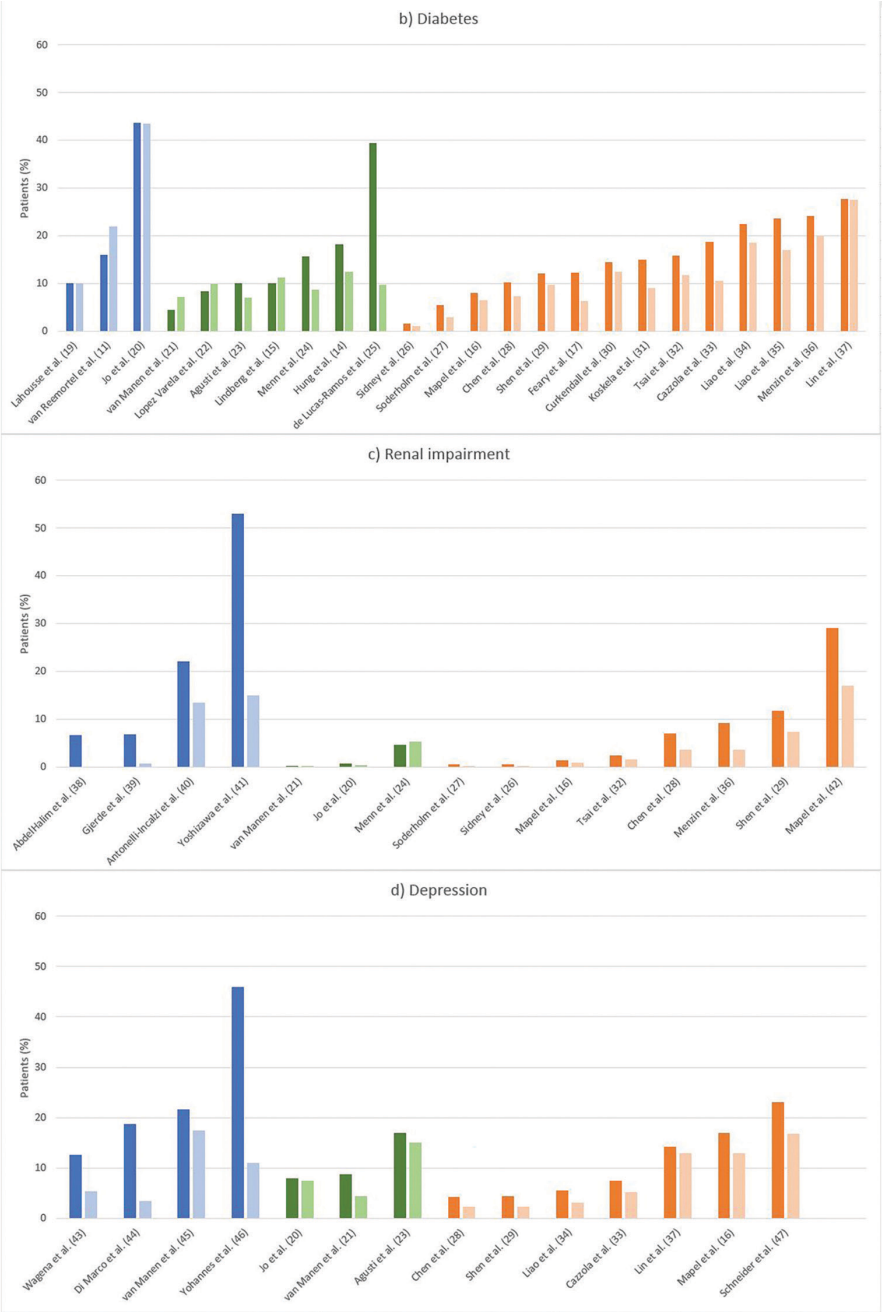
We aim to discuss several shortcomings and pitfalls which need to be considered when interpreting these data and possibly explaining part of the variance in prevalences found. Furthermore, we aim to open a discussion on future research directions related to comorbidity in COPD and on the concept of multimorbidity in the elderly with COPD as a pulmonary component.

Methodologies Used to Assess Comorbidity

Figure 1 demonstrates differences in prevalences of selected comorbidities within as well as between 3 different assessment methods: objective assessment, self-reported assessment, or assessment by medical records. Table 1 as well as e-Figures 1-3 in the online data supplement demonstrate prevalences of all comorbidities found.

Figure 1. Prevalences of Cardiovascular Disease, Diabetes, Renal Impairment and Depression Stratified by Assessment Method





blue: objectively assessed; green: self-reported; orange: assessed by medical records; light-colored bars represent prevalences of control individuals

Objective Assessment

Objective assessment is considered an independent assessment by validated measures (without the interpretation of the individual studied). Although the objective assessment of comorbidities is generally reported as strength of a study, there are also some concerns which need to be taken into account when comparing and interpreting study findings.

First, studies might use the same assessment measure but apply a different study protocol. For instance, Konecny and colleagues and Lahousse and colleagues detected a prevalence of atrial fibrillation (AF) of 23.3% and 11%, respectively, using electrocardiography (ECG)[19,48]; however, Konecny used a 24-hour monitoring[48] probably increasing the chance of detecting an AF event while a single resting ECG had been performed in the Rotterdam study.[49]

Second, studies objectively assessing certain

Table 1. Prevalences Expressed as Median and Interquartile Range (If Applicable) for Each Comorbidity Stratified by Assessment Group

	Objectively Assessed		Self-reported		Medical Records	
	COPD	*Control*	*COPD*	*Control*	*COPD*	*Control*
CVD	10[a]	4[a]	31 (20-48)	32 (13-43)	28 (-)[b]	7 (-)[b]
Heart disease	-	-	16 (13-24)	12 (11-15)	-	-
HF	3[a]	2[a]	16 (-)[b]	1 (-)[b]	11 (7-17)	3 (2-6)
MI	-	-	9[a]	3[a]	7 (2-13)	3 (1-4)
IHD	14 (-)[b]	13 (-)[b]	13 (-)[b]	4 (-)[b]	22 (16-31)	15 (8-17)
AF/ arrythmias	14 (-)[b]	8 (-)[b]	14 (-)[b]	5 (-)[b]	9 (4-17)	5 (1-10)
PAD	9[a]	2[a]	12 (-)[b]	4 (-)[b]	5 (2-8)	2 (1-4)
Hypertension	56 (-)[b]	48 (-)[b]	40 (30-56)	36 (28-39)	45 (32-58)	37 (22-46)
Anemia	5[a]	3[a]	14[a]	1[a]	9[a]	6[a]
Diabetes	16 (-)[b]	22 (-)[b]	10 (8-18)	10 (7-11)	15 (10-23)	10 (6-17)
Hypercholesterolemia/ Dyslipidemia	76[a]	79[a]	32 (-)[b]	23 (-)[b]	14 (9-25)	12 (10-18)
Metabolic Syndrome	23 (-)[b]	21 (-)[b]	-	-	1[a]	0[a]
Obesity	31[a]	42[a]	35[a]	34[a]	5 (-)[b]	2 (-)[b]
Osteoporosis	24 (-)[b]	10 (-)[b]	15 (-)[b]	4 (-)[b]	15[a]	11[a]
Insomnia / Sleeping Problems	41 (-)[b]	20 (-)[b]	17[a]	11[a]	-	-
GERD	37 (-)[b]	18 (-)[b]	22 (-)[b]	21 (-)[b]	-	-
Renal Impairment	15 (7-45)	7 (0-15)	1 (-)[b]	0 (-)[b]	5 (1-11)	3 (0-6)
Brain Pathology/ Cognitive Impairment	36 (-)[b]	13 (-)[b]	-	-	-	-
Depression	20 (14-40)	8 (4-16)	9 (-)[b]	7 (-)[b]	7 (4-17)	5 (2-13)
Anxiety	23 (-)[b]	6 (-)[b]	-	-	6[a]	3[a]
Psychatric/ Mental Disorders	-	-	46[a]	11[a]	39 (-)[b]	20 (-)[b]
Restless Legs	37[a]	11[a]	-	-	14[a]	2[a]
Asthma	-	-	23[a]	11[a]	27 (-)[b]	2 (-)[b]
Stroke/ Cerebrovascular Disease	-	-	6 (-)[b]	3 (-)[b]	10 (6-19)	5 (3-9)
Cancer	-	-	10 (-)[b]	8 (-)[b]	7 (4-20)	7 (3-11)
Lung Cancer	-	-	0 (-)[b]	0 (-)[b]	2[a]	0[a]
Ulcers/ Gastritis	-	-	11 (-)[b]	7 (-)[b]	3 (-)[b]	2 (-)[b]
Liver Disease	-	-	2 (-)[b]	1 (-)[b]	3 (1-21)	2 (1-14)
Arthritis/ Rheumatologic	-	-	13 (-)[b]	9 (-)[b]	4 (3-24)	4 (2-18)
Locomotive Disease	-	-	36[a]	29[a]	-	-
Dementia	-	-	-	-	2 (-)[b]	1 (-)[b]
Interstinal Disease	-	-	6 (-)[b]	4 (-)[b]	-	-
Skin Disease	-	-	4 (-)[b]	3 (-)[b]	-	-

Abbreviations: CVD=cardiovascular disease; HF=heart failure; MI=myocardial infarction; IHD= ischemic heart disease; AF=atrial fibrillation; PAD=peripheral artery disease; GERD=gastro-esophageal reflux

[a]n=1 study
[b]median without interquartile range (n<4 studies)

comorbidities often focus on a certain research question, i.e., the comorbidity of interest, potentially ignoring other relevant findings. Ideally, investigators should be blinded to specific research questions and/or medical histories. Otherwise, consulting the medical history and medication used is necessary to accurately interpret and classify findings. For instance, assessment of hypertension by a sphygmomanometer might show unremarkable results when properly treated with antihypertensive medications. The same is true for diabetes, dyslipidemia and adequately treated depressive disorder with use of maintenance medication. Thus, objective assessment might often be a (biased) snap-shot of a current situation. In this

context, it is a matter of debate whether or not an adequately treated or "cured" comorbidity is still a comorbidity.

Third, due to limited facilities and/or personal preferences, only a limited number of comorbidities can be assessed at a time, consequently limiting results or findings for several comorbidities in the clinic as well as literature. Indeed, as demonstrated in Figure 1, the number of comorbidities as well as studies objectively assessing comorbidities are limited compared to the rest.

Fourth, we often do not detect or assess a comorbidity at hand but we often consider several risk factors or biomarkers leading to a disease; for instance, a low bone mineral density (defined as a low t-score) is associated with a higher risk of fractures but not a disease per se. This also applies to conditions like dyslipidemia, obesity and metabolic syndrome.

Fifth, validated questionnaires might be used as *objective* measures although outcomes are patient-reported. Furthermore, the cut-point used can differ between studies explaining part of the variance in prevalences.[50,51]

Sixth, for assessing psychological comorbidities, such as depression or anxiety, the generic Hospital Anxiety and Depression Scale (HADS)[52] might be used. The HADS is often used as a screening instrument indicating symptoms of depression or anxiety rather than diagnosing a psychiatric disorder. Furthermore, somatic items can overlap with symptoms of COPD and side effects of medications underlining the need for a disease-specific instrument to screen and measure anxiety in patients with COPD.[53]

Self-reported Assessment

Compared to objective measures, subjective measures and patient recall have been demonstrated to be more variable.[54] Indeed, there are several limitations which are summarized below.

First, recall periods might not be specified, specifically mentioned or properly recorded by the researcher and/or health care professional which is important, however, to understand variation which may affect the results.[55] Additionally, patients might incorrectly recall or remember several events, dates and/or certain comorbidities: repeatability of self-reported clinical features, e.g., exacerbation history or childhood diagnosis of asthma, has been shown to be weak to moderate.[54] Additionally, previous studies demonstrated significant knowledge gaps of patients regarding COPD and general health[56] as well as prevalent cognitive impairment[57] and poor health literacy[58,59] possibly partly explaining the variability in patient recall.

Second, there are several relevant response bias which need to be considered. Patients might tend to give socially desirable answers or have a tendency to agree with the questions asked. In addition, ordering of questions can further influence the results or the interviewer can be biased by a specific research question, have prejudices or ask leading questions. Finally, the situation itself (e.g., being in a health care setting) might further impact the patient's response.

Third, patients might report less often diseases they do not know or understand. For instance, diabetes might be more common or understood than, for instance, renal impairment (especially in patients with impaired cognitive impairment or poor health literacy, as mentioned earlier). Patients may also recall more comorbidities which are or were meaningful for them, their autonomy and/or social environment and might less often recall comorbidities they are embarrassed about (e.g., depression) or which are not disabling.

Fourth, "self-reported" can mean as assessed by a questionnaire or by a (semi)structured interview while questionnaires are often regarded as cheap instruments with a low response rate but large sample size compared to interviews which are generally more expensive, have a high response rate, but a smaller sample size.[9] Thus, to reveal further differences, the way of self-reporting can influence the results.

Assessment by Medical Records

Another possibility of studying the prevalence of comorbidities is the assessment by medical records or medical history. Using medical records can prevent or overcome recall bias by "using data recorded, for other purposes, before the outcome had occurred and therefore before the study had started. The success of this strategy is limited by the availability and reliability of the data collected."[9] However, there are also some concerns which need to be taken into account.

First, although it might overcome recall bias, the question arises when the individual "medical history" starts; what is the definition (starting from birth or adulthood or date of COPD diagnosis)? This is of relevance for understanding possible causal relationships. Also, patients might be treated in

different hospitals for different conditions and medical history may be stored in different forms (electronic/paper), contributing to inconsistency in information.

Second, Figure 1 demonstrates that the widest range of comorbidities was recognized in comorbidities as assessed by medical records. The medical history records all relevant conditions that have ever been diagnosed in an individual. While this gives a holistic view of the patient, the number of comorbidities can be over- or underestimated as conditions may have been temporary or clinically unrecognized.

Third, an enormous range of prevalences within medical records can be observed. It is not clear (1) if the respective comorbidities are currently treated or might even be cured in the meantime and (2) which assessment has been used. Specified comorbidities in administrative data can be both, objectively assessed or self-reported, or by considering medication lists for instance. Most studies reviewed national health databases without any further specification.

Fourth, studies assessing comorbidities using medical history are often characterized by an exceptionally large population size (>20,000 patients and controls[29,34]) potentially leading to significant results for all comparisons which needs to be taken into account when interpreting the results.

Fifth, there are also differences within the assessment of medical records. A recent study determined the accuracy of comorbidity information derived from electronic health records by comparing electronic health records' problem list-based comorbidity assessment with a manual review of electronic health records free-text notes in men with prostate cancer. The authors showed that problem list-based comorbidity assessment had poor sensitivity for detecting major comorbidities while free-text-based scores were predictive for mortality.[60] Another study aimed to compare the number and types of comorbidities determined from medical records with 10 discharge codes obtained from the hospital administrative records and concluded that "administrative data based on hospital discharge codes consistently underestimate the presence of comorbid conditions. [...] Researchers also need to be aware when using administrative data based on hospital discharge codes to assess [patient's] comorbidities that they may be widely underreported."[61]

Sixth, differences in prevalences can also depend on differences in the definition of the comorbidity. For instance, 1 study defined cardiovascular disease (CVD) as having at least 1 of the following: heart failure, poor circulation in legs, stroke, coronary heart disease, angina (angina pectoris), irregular heartbeats, or heart attack (myocardial infarction)[18] whereas another defined CVD as having angina, myocardial infarction, heart failure, peripheral vascular disease and aortic aneurysm, and having undergone a previous angioplasty procedure (while cardiac arrhythmias and valvular heart disease were excluded).[17]

Samples Studied

As demonstrated above, even with comparable or even identical assessment methods, prevalences of particular comorbidities can still vary. Another explanation for this variance is the population studied. For example, the Rotterdam study included a population-based cohort[49] while the ECLIPSE cohort specifically studied patients with COPD included in a clinical setting.[62] Patients included from in- or outpatient settings are a selected population, as these patients reach out for a health care provider because of health problems. This explains smaller prevalences in population-based cohorts. Furthermore, some comorbidities might be more prevalent in more severe disease[13] and patients with exacerbations may report more comorbidities or have a higher risk of developing comorbidities.[63] However, there is a relevant bias: hospitalized patients or patients with more severe disease and higher health care utilization undergo more examinations consequently leading to more findings. Moreover, this selected group of patients (i.e., patients with an exacerbation) might suffer from "temporal complications" rather than "chronic comorbidities" (e.g., symptoms of anxiety and depression, hyperglycemia related to the use of systemic glucocorticosteroids).

Moreover, elderly patients with comorbid conditions are frequently excluded from clinical trials,[64] also described as "comorbidity gap" between clinical studies and the elderly patient population. This limits the generalizability and external validity of scientific results to the real-world setting.[65]

Finally, how COPD is defined or diagnosed is relevant for the interpretation of the results. Not all studies assessed lung function to confirm the diagnosis of COPD: the diagnosis can rely on self-report[14,43] or can be defined by a series of International Classification of

Disease codes (J40: bronchitis, not specified as acute or chronic; J41: simple and mucopurulent chronic bronchitis; J42: unspecified chronic bronchitis; J43: emphysema and J44: other chronic obstructive pulmonary disease).[66] Certainly, an appropriate description of the population studied is crucial to interpret and evaluate study findings.

Control Group

A control group can be defined as "a group of people without the condition of interest, or unexposed to or not treated with the agent of interest."[9] A control group (i.e., non-COPD controls) is ideally similar to the experimental group (i.e., patients with COPD) in terms of relevant characteristics (e.g., risk factors) but where the factor thought to be causing an effect (i.e., COPD) is removed. For instance, compared with control individuals, patients with COPD studied by Black-Shinn and colleagues[13] were older, more often former smokers and had more pack years, demonstrating some selection bias. Control groups can be selected by using 1 of the following 4 techniques: (1) convenience sample, (2) matching, (3) using 2 or more control groups or (4) population-based sample for both cases and controls.[9] However, with regards to convenience sample and matching, there are also some concerns which need to be taken into account.

A convenience sample for instance can reduce the external validity, while "overmatching" (too closely matched) can underestimate the true difference.[9] Exclusion criteria can be too narrowed, possibly excluding relevant individuals; for instance, comorbidities are often excluded, especially in control groups referred to as "healthy participants." Indeed, Abdelhalim and colleagues excluded patients with COPD who had "chronic comorbid disease" while the only exclusion criterion for the control group were any respiratory and nonrespiratory disease.[38] Furthermore, smoking is a relevant confounder which needs attention during participant selection since it influences the prevalences studied.[67] Age is a crucial determinant since comorbidities evolve with ageing. Matching for gender might be relevant since several risk factors/comorbidities are more present in males/females. Finally, control groups might be recruited or extracted from other cohorts limiting the reproducibility/comparability of the results. Other potential confounders might be physical activity and/or nutrition which are rarely reported or considered.

Lessons Learned for Future Research

Several assessment methods, differences in study populations, (in)appropriate control groups and other sources of bias make it challenging to identify a particular pattern and/or to compare study findings. This also underlines the need to pay attention to the individual patient; one might benefit from useful case studies demonstrating the complexity of an individual and treatment possibilities. Researchers are encouraged to critically evaluate methodologies used and review study findings before drawing conclusions. They should discuss their study limitations or challenges in their reports creating a learning environment for future research and/or others. To extend the generalizability and to be able to discover new relationships, exclusion criteria should not be too strict. Researchers need to be aware of recent developments in their field of interest to evaluate and/or apply innovative knowledge to their activities. For instance, ≥10 pack years is often used as inclusion criterion for COPD studies. However, recent data from the COPD Genetic Epidemiology--COPDGene®-cohort demonstrated that smoking duration alone provides a stronger risk estimate of COPD than pack years[68] challenging this traditional approach and encouraging researchers to critically review their methodology.

Beyond the methodological differences or shortcomings, there are other, increasingly important elements which need to be taken into account when interpreting the prevalence as well as occurrence of comorbidities: scientific studies often neglect real-world situations including environmental influences (i.e., exposures) as well as the impact of time, consequently disregarding the individual complexity.

Individuals can already be exposed to environmental risk factors in utero, during perinatal life and in early childhood as well as in adulthood.[69] For instance, a recent study assessed childhood predictors of lung function trajectories and future COPD risk and showed that allergic diseases, lung infections, parental asthma, and maternal smoking in early life predicted 3 unfavorable lung function trajectories.[70] An impaired lung function in early adulthood has further been shown to be associated with a higher risk for early comorbidities and premature death.[71] Another study presented temporal disease progression patterns using

15 years of registry data. The authors identified COPD as a central diagnosis and demonstrated the relevance of adding the temporal dimension to understand the development of future diseases of individual patients.[72] As stated before, the authors concluded that "we need [...] to identify the interactions between, on the one hand, intrinsic biological processes that drive the many chronic diseases and disabilities for which age is by far the largest risk factor and, on the other hand, the social and lifestyle factors that influence our individual trajectories of health in old age."[73] Indeed, Hu and colleagues depicted the development of diseases using a "multimorbidity space" where patients' disease trajectories can be described as transitions between points in this space, affected by genetic and environmental parameters.[74] This underlines the importance of time, ageing and the environment in the development of diseases and underlines the need for holistic approaches considering the coexistence of morbidities. To reveal the complex concept of (the development of) comorbidities including the dynamic role of time and the environment, we need to release the idea of COPD as an index disease and move from comorbidity in COPD to multimorbidity in the ageing population.

Lessons Learned for Daily Practice

Management of patients with COPD needs a holistic approach,[8] considering the coexistence of morbidities with their treatments and impact on patients.[75] Unraveling the underlying relationships for each patient is the determining factor for an appropriate therapeutic approach.[76]

In daily practice, a combination of the above described methodologies is used. A detailed and rigorous registration of self-reported and physician-diagnosed comorbidities and verified current pharmacological therapy is an important starting point for the further objective assessment of the most relevant comorbidities in patients with COPD. Established diagnoses need to be reviewed and re-evaluated whether or not follow-up is performed or indicated. In addition, the use of different pharmacological therapies needs to be evaluated on necessity, adequate dosages, and interactions with other pharmacotherapies.[77]

Fabbri and colleagues[78] concluded that "we need to integrate our skills and treatment options between disciplines for optimal management in order to look for the synergistic effect of our efforts in contrast with the potential harmful effect of pharmacological interactions, polypharmacy and certain disease-specific interventions. The single disease-centered clinical guidelines do not consider the reality of care for a patient with multiple chronic conditions."

Although this manuscript highlights important limitations concerning the assessment of comorbidities in COPD, there is no doubt that COPD is associated with (an increased risk of) comorbidities. However, COPD studies reporting prevalences of comorbidities should be interpreted with caution: all that glitters is not gold.

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