Aus dem Institut für Allgemeinmedizin

der Heinrich-Heine-Universität Düsseldorf

Institutsleitung: Univ.-Prof. Dr. med. Stefan Wilm

Anxious-depressive symptoms in patients with clinically diagnosed chronic obstructive pulmonary disease in relation to their tobacco smoking status

Dissertation

zur Erlangung des Grades eines Doktors der Medizin der Medizinischen Fakultät der Heinrich-Heine-Universität Düsseldorf

vorgelegt von

Sarah Fullenkamp

2021

Als Inauguraldissertation gedruckt mit der Genehmigung der Medizinischen Fakultät der Heinrich-Heine-Universität Düsseldorf

gez.:

Dekan: Univ.-Prof. Dr. med. Nikolaj Klöcker

Erstgutachter: Univ.-Prof. Dr. Daniel Kotz

Zweitgutachter: Prof. Dr. med. Stefan Krüger

Meinen Eltern

Zusammenfassung

Hintergrund. Die chronisch obstruktive Lungenerkrankung (COPD) ist weltweit die vierthäufigste Todesursache. Für die meisten Personen liegt hier Tabakrauchen als wesentlicher Einflussfaktor zugrunde. Die Prävalenz von Depressionen und/oder Angst scheint bei COPD Patient/innen höher zu sein als in der restlichen Bevölkerung, vor allem in der Gruppe der aktuellen Raucher/innen. Ängstlich-depressive Symptome scheinen den Rauchstopp zu erschweren. Dennoch kann einzig der Rauchstopp das Fortschreiten der COPD verlangsamen. Derzeit ist der Zusammenhang zwischen Rauchen und dem Vorliegen ängstlich-depressiver Symptome bei COPD-Patient/innen noch nicht vollständig verstanden, es fehlen repräsentative Daten aus Deutschland.

Ziele. Ziel der Studie ist es, die Prävalenz der ängstlich-depressiven Symptome in Abhängigkeit vom Rauchstatus bei COPD-Patient/innen zu erfassen. Darüber hinaus soll der Zusammenhang zwischen dem Rauchstatus bzw. dem Grad der Tabakabhängigkeit und ängstlich-depressiven Symptomen untersucht werden.

Methode. Analysiert wurden Daten der Studie zur '"**R**eal-world" **E**ffectiveness of **S**moking cessation methods in **P**at**i**ents with ch**r**onic **o**bstructive pulmonary disease' (RESPIRO), einer Befragung im Querschnittsdesign in 21 Lungenfacharztpraxen aus Nordrhein Westphalen (10/2018 - 01/ 2020). Patient/innen mit klinisch diagnostizierter COPD (ICD-10 J44.x und FEV1/FVC ratio <0,7) wurden eingeschlossen, und befragt zu ihrem Rauchverhalten, gesundheitsbezogener Lebensqualität (COPD Assessment Test, CAT), soziodemographischen Daten, sowie zu ängstlich-depressiven Symptomatik (Patient Health Questionnaire, PHQ-T, 0-12 = keine bis schwere Symptome; Subskalen: 0-6). Analysiert wurden Zusammenhänge zwischen Rauchstatus und dem Vorliegen psychischer Belastung durch ängstlich-depressive Symptome (PHQ-T ≥ 6; Subskalen ≥ 3), sowie innerhalb der Untergruppe der aktuellen Raucher der Zusammenhang zwischen dem Grad der Tabakabhängigkeit (Heaviness of Smoking Index, HSI; 0-6 = geringe bis hohe Abhängigkeit) und dem Vorliegen ängstlich-depressiver Symptome mittels multivariabler logistischer Regressionsmodelle. Beide Modelle wurden für soziodemografische Faktoren, aktuelle Spirometrie sowie dem CAT Score adjustiert.

Ergebnisse. Insgesamt lieferten 1164 der Befragten Daten zum psychischen Zustand und wurden in die Analysen einbezogen (Durchschnittsalter 66,2±9,2 Jahre, 31,2% aktuelle Raucher/innen). Die Gesamtprävalenz psychischer Beschwerden betrug 20,7% (95%-Konfidenzintervall (KI): 18,4 – 23,2%), für depressive bzw. ängstliche Symptome 25,0% (95%-KI: 22,5 – 27,5%) bzw. 22,3% (95%-KI: 20,0 – 24,7%). Die höchsten Prävalenzraten wurden bei frischen Ex-Raucher/innen beobachtet, die niedrigsten bei den langjährigen Ex-Rauchern/innen. Das Vorhandensein dieser Symptome war im adjustierten Modell nicht signifikant mit dem Rauchstatus assoziiert (p>,05). Bei aktuellen Raucher/innen war jedoch ein höherer Abhängigkeitsgrad mit vermehrten psychischen Beschwerden verbunden (Psychische Belastung: Odds Ratio (OR)=1,38 (95%-KI: 1,09 – 1,75); Depressionen: OR=1,33 (95%-KI: 1,07 – 1,64); Angst: OR=1,29 (95%-KI: 1,03 – 1,62), pro Punkt Anstieg HSI; alle p<,05). In allen Analysen war ein höherer CAT score mit größerer psychischer Belastung assoziiert (p<,001).

Schlussfolgerung. Gut jede/r fünfte COPD-Patient/in in nordrhein-westfälischen Lungenfacharztpraxen berichtet über ängstlich-depressive Symptome. Bei rauchenden COPD Patient/innen sind diese Symptome stark mit dem Grad der Tabakabhängigkeit assoziiert. Es könnte nützlich sein, die psychologische Symptomatik im Zusammenhang mit der Raucherentwöhnung zu erfragen, um die Tabakentwöhnung bei Patient/innen mit COPD gezielt anpassen zu können.

Summary

Background. Chronic obstructive pulmonary disease (COPD) is ranked as the fourth leading cause of death worldwide. The main risk factor in the Western World for developing COPD is tobacco smoking. The prevalence of comorbid symptoms of depression and/or anxiety in COPD patients seems to be higher than among healthy subjects, particularly in current smokers. Anxious-depressive symptoms are reported to form a barrier preventing the patient from quitting smoking, even if this is the only way to slow down the progression of the disease. Yet, the link between smoking and anxious-depressive symptoms in COPD patients is not completely understood, and representative data from Germany are missing.
Aims. To assess the prevalence of anxious-depressive symptoms according to the tobacco smoking status in a pulmonary primary care sample of patients with COPD. To assess the association between tobacco smoking status/level of tobacco dependence and prevalent anxious-depressive symptoms, adjusted for confounders.
Methods. We analysed data from the '"**R**eal-world" **E**ffectiveness of **S**moking cessation methods in **P**at**i**ents with ch**r**onic **o**bstructive pulmonary disease' study; a cross-sectional survey (10/2018 - 01/2020) in COPD patients from 21 pulmonary practices in the German federal state of North Rhine-Westphalia (NRW). Patients with clinically diagnosed COPD (ICD-10 J44.x and FEV1/FVC ratio <0.7) were included and completed a questionnaire on their smoking status, health-related quality of life (COPD Assessment Test, CAT), sociodemographic data, and psychological distress (anxiety/depression, measured with the Patient Health Questionnaire, PHQ-T, range: 0-12 = none to severe symptoms, subscales anxiety/depression range: 0-6). Outcomes were analysed using multivariable logistic regression models, adjusted for potential confounding variables including socio-demographic data, lung function and CAT score. Outcome 1: associations between smoking status and prevalent anxious-depressive symptoms (PHQ-T ≥ 6, subscales ≥ 3); outcome 2 (subgroup of current smokers): associations between the level of tobacco dependence (measured with the Heaviness of Smoking Index, HSI; 0-6 = low to high dependency) and prevalent psychological distress.
Results. 1164 COPD patients were included (mean age 66.2 ± 9.2 years, 31.2% current smokers). The prevalence of psychological distress was 20.7% (95% confidence interval (CI): 18.4 – 23.2%), and 25.0% (95%-CI: 22.5 – 27.5%) and 22.3% (95%-CI: 20.0 – 24.7%) for depressive and anxious symptoms, respectively. The highest prevalence rates were observed in recent ex-smokers and the lowest were in long-term ex-smokers. The presence of symptoms was not significantly associated with smoking status in the fully adjusted model (p>.05). In current smokers, higher levels of dependence were associated with increased psychological burden (psychological distress: odds ratio (OR) = 1.38 (95%-CI: 1.09 – 1.75), depressive symptoms: OR = 1.33 (95%-CI: 1.07 – 1.64), and anxious symptoms: OR = 1.29 (95%-CI: 1.03 – 1.62), per point increase on the HSI; all p<.05). In all analyses, strongest associations with anxious-depressive symptoms were found for the CAT (p<.001). An increase in the CAT score was associated with more psychological distress and depressive and anxious symptoms.
Conclusion. The prevalence of psychological distress among COPD patients in NRW is high: at least one in five reports anxious-depressive symptoms. Within the group of current smokers, there is a strong association between tobacco dependence and anxious-depressive symptoms. It might be useful to assess psychological symptoms in the context of smoking cessation in order to adjust and individualize cessation treatment in patients with COPD.

Abbreviations

Abb	Abbreviation
BdP	Federal Association of pulmonologists/ Bund deutscher Pneumologen
CAT	COPD assessment test
CES-D	Center for Epidemiologic Studies Depression Scale
CI	Confidence Interval
COPD	Chronic obstructive pulmonary disease
DSM-IV	Diagnostic and Statistical Manual of Mental Health Disorders Version IV
GOLD	Global Initiative for Chronic Obstructive Lung Disease
FEV1	Forced expiratory volume in one second
Fig	Figure
FVC	Forced vital capacity
GAD-2	Generalized Anxiety Disorder 2
GAD-7	Generalized Anxiety Disorder 7
HADS	Hospital Anxiety and Depression Scale
HSI	Heaviness of Smoking Index
ICD-10	10th revision of the International Statistical Classification of Diseases and Related Health Problems
ifam	Institute of General Practice
PHQ-2	Patient Health Questionnaire-2
PHQ-4	Patient Health Questionnaire-4
PHQ-A	Patient Health Questionnaire symptoms of anxiety
PHQ-D	Patient Health Questionnaire symptoms of depression
PHQ-T	Patient Health Questionnaire total
SD	Standard deviation
STS	Smoking Toolkit Study
WHO	World Health Organisation

Table of Contents

1 Introduction

1.1 General information on tobacco smoking and COPD

Tobacco smoking is one of the main avoidable causes of death worldwide: One in 10 deaths around the world is due to tobacco smoking (1). In Germany, 28.3% of the population aged 14 years and older smoke tobacco regularly; 24.4% of females and 32.2% of males (2). Compared with other European high-income countries such as the Netherlands (19%), the United Kingdom (17%), or Sweden (7%), the smoking prevalence in Germany remains high (3).

Tobacco smoking leads to individual health problems and a decreased lifespan up to 10 years (4). Due to active tobacco smoking, more than seven million people worldwide die prematurely each year (1). Second-hand smoke exposure adds another 1.2 million deaths each year (1). Furthermore, it puts financial pressure on society. In Germany, in 2018, the annual direct and indirect costs of tobacco smoking were estimated at 30.32 billion and 66.92 billion euros, respectively (5). This is an increase of 19.3% for the direct costs and of 27% for the indirect costs compared to estimations from 2008 to 2014 (5, 6). The main part of the direct costs emerges through the cost of illnesses due to smoking (27.31 billion euros) and passive smoking (1.33 billion euros). For the indirect costs the biggest part arises out of resource loss through mortality (22.93 billion euros) and long-term unemployment (16.56 billion euros) (5).

The likelihood of consuming tobacco regularly depends on different factors. Several studies show that the smoking prevalence among people with a low socioeconomic status is strikingly high when compared to higher socioeconomic statuses, this enhances the already existing differences in health for people with different education and income levels (7, 8) Moreover, the school degree as well as the net household income, are associated with the tobacco smoking rate; the lower the school degree, and/or net household income the higher the likelihood to consume tobacco and the higher the consumption rate (2, 9). In Germany, more men smoke tobacco regularly than women (2). Lastly, age is another factor. According to the German Microcensus of 2017, the highest proportion of smokers can be found in the group of 30 – 35 year olds (10).

Tobacco smoking can cause addiction. The primary substance responsible for the development of addiction to tobacco smoking is nicotine (11). Dependence is a complex

neurophysiological process. Nicotine dependence emerges due to a reward-enhancing effect after consumption and a learning process, which either associates stimuli with the positive effects of nicotine or withdrawal leads to seeking and consuming nicotine (12, 13). Nicotine is a psychoactive substance, it influences serotonergic, noradrenergic, cholinergic and dopaminergic transmitter systems (12, 14). Regular nicotine consumption seems to lead to an increase in nicotinic acetylcholine receptor density (12, 15). After some time of regular nicotine consumption withdrawal leads to symptoms like anhedonia, restlessness, insomnia, hunger and inability to sleep. Symptoms can be divided into two main factors: negative affect and cravings (12, 14). Withdrawal can even lead to depressive symptoms (12, 16). According to the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) tobacco dependence is classified as 'Mental and behavioural disorders caused by tobacco' and is thus registered as a substance-related disorder (17). There are different criteria for diagnosing nicotine dependence (11, 17, 18). Main characteristics are tolerance to nicotine defined as a need for increased amounts or decreased effect with the same amount, withdrawal manifested by characteristic withdrawal symptoms (i.e., irritability, frustration, anxiety, depression, restlessness, and increased appetite) or using the substance to avoid or relieve symptoms (18). Other characteristics of addiction, which occur among smokers are consuming larger quantities than intended, continuous desire for or unsuccessful efforts to stop substance use, more time spent in activities to obtain or use a substance and a decrease in social, occupational or recreational activities due to substance use (18). Moreover, the German guideline for tobacco smoking cessation in chronic obstructive pulmonary disease (COPD) patients describes a pattern in consumption of tobacco smokers, which leads to a restriction of free will and continuous consumption despite the knowledge about health damage (13).

Current research shows that the harmful effect of smoking tobacco has a negative impact on almost every organ (19), but particularly the lungs. Tobacco smoking is the main cause of COPD in high- and middle-income countries (1, 20). The World Health Organisation (WHO) defines COPD as a "lung disease characterized by chronic obstruction of lung airflow that interferes with normal breathing and is not fully reversible"[1].

[1] World Health Organization. COPD: Definition, https://www.who.int/respiratory/copd/definition/en/

The estimated global prevalence of COPD among people aged >30 years was 11.7% in 2010 (21, 22). One study even stated that up to 40% of older smokers, who smoked most of their life develop COPD (23). The Burden of Obstructive Lung Disease (BOLD) study, a large multi-centered study to assess worldwide prevalence rates in 12 countries, found a significant variation in prevalence, ranging from 11.4% in Guangzhou, China to 26.1% in Salzburg, Austria. Overall prevalence rates were higher in men than in women (24). In Hannover, Germany, a COPD prevalence of 13.2% was reported among subjects aged >40 years which is low compared to other European countries like Poland (22.1%) or Norway (18.8%) (24). There is no representative and up-to-date data on COPD prevalence for Germany. A German study in 2007 in the area of Düsseldorf among smokers aged >40years found 6.9% had COPD as confirmed by lung function tests (spirometry) (25). In 2012, a study data of AOK *Nordost* (Northeast) health insurance revealed an unadjusted overall COPD prevalence of 8.3% (26). All of these studies in Germany are limited to one region and are thus not representative. A literature study on epidemiology and costs of COPD in Germany even found a prevalence of 1.3% (27). The most recent COPD prevalence data are from 2015; from a nation-wide study on the state of health of the German Robert-Koch-Institute collected data with a self-completed online or postal questionnaire, which assessed self-reported chronic bronchitis, chronic obstructive pulmonary disease or emphysema. The study revealed a 12-month prevalence of COPD of 5.8% for over 18 year olds and 7.5% for over 40 year olds (28). Previous studies showed that women are more susceptible for the hazardous effects of tobacco smoking than men, the same level of exposure more often leads to the development of COPD in women (29, 30). Nevertheless, one large, longitudinal, non-interventional German study in COPD patients found 60% of the patients to be male (31).

In 2015, 3.2 million people died from COPD worldwide, which is an increase of 11.6% compared to the number of deaths in 1990 (32). COPD was ranked the fourth leading cause of death worldwide in 2016 and the WHO predicts it to become the third leading cause by 2030 (33). For this reason, in 1998, in an effort to bring more attention to COPD, the US National Heart, Lung, and Blood Institute and the WHO formed the Global Initiative for Chronic Obstructive Lung Disease (GOLD). The aim is to improve the diagnosis and treatment of COPD worldwide (22). Furthermore, COPD is associated with an economic burden. As for tobacco smoking, COPD leads to direct and indirect costs (34). Direct costs are composed of primary and hospital care, drugs, and oxygen use and are estimated at 23.3 billion euros each year for countries in the European Union (EU). The annual indirect costs

for EU countries for COPD were 25.1 billion euros in 2011, those include lost production (e.g. work abstinence and early retirement) (34). A literature review on COPD costs in Europe included four German studies and estimated the mean direct costs per COPD patient per year with 7847€ (35). In a comparison to other EU countries, Germany has the third highest direct costs (35). Indirect costs, mainly comprised of the costs associated with early retirement in COPD patients <65 years, increase the costs by a factor of 2.4 to 4.4 depending on severity (36).

The population attributable fraction (PAF) in the Western World for COPD for inhaling tobacco is 80-90% (37-39). Nevertheless, never smokers can also develop COPD, but they seem to have fewer symptoms of airway obstruction and a milder disease (40). Moreover, a study implied that never smokers with chronic airway obstruction compared similarly to those without who do not have an increased risk to develop cardiovascular disease or lung cancer (40). In the Western World more than in low-income countries endogenous factors like genetics contribute to the development of COPD in never smokers, the best known is an alpha-1 antitrypsin deficiency which leads to the development of lung emphysema (22, 41). Exogenous factors other than tobacco smoking which contribute to the development of COPD are second-hand smoke, air and fine dust pollution, (occupational) exposure to organic and inorganic dust (coal mining), conditions that interfere with normal lung development in childhood (infections like tuberculosis, passive smoking during childhood), asthma and chronic bronchitis (22). Exposure to (indoor) air pollution, like biomass fuels used for cooking are the main risk factors in low-income countries for COPD (1). Nevertheless, the proportion of active smokers among COPD patients remains high with percentages between 30 – 40% (42) (43). Literature even showed more active smokers among COPD patients in a worse stage of the disease compared to a milder stage (20).

COPD is an inflammation of the lungs caused by the inhalation of noxious particles. The inflammatory process leads to tissue destruction and impairment of the defence mechanism like the disruption of the repair mechanism (41, 44). Next to inflammation, the noxious particles can lead to fibrosis and loss of parenchyma of the airways, especially squamous metaplasia of the epithelial cells (ciliary dysfunction), instability of the bronchial airways and mucus hypersecretion. Moreover, oxidative stress from tobacco smoke amplifies inflammation by enhancing transcription factor activation and inactivation of antiprotease (44). The inflammatory cells release proinflammatory cytokines, which

promote migration of destructive inflammatory cells into pulmonary tissue. The imbalance of protease and antiprotease facilitates the loss of parenchyma of the alveoli (44). All of these mechanisms result in detrimental pathological changes. Due to the airflow obstruction, air is trapped during expiration resulting in hyperinflation ("gas trapping"). The overinflation of the alveoli with loss of the lung exchange surface is called emphysema (44, 45). The result is breathlessness and activity intolerance due to a decreased tidal volume (due to an increased residual volume and an increased intrathoracic volume of gas). As a result of remodelling the small airways and loss of elastic recoil by emphysematous destruction a decline in the forced expiratory volume in one second (FEV1) can occur (41).

The main symptom of COPD is dyspnoea, initially only during exercise but later also during rest, and productive cough due to mucus hypersecretion. Depending on the severity of emphysema, gas exchange abnormalities occur, resulting in arterial hypoxemia (and hypercapnia), cyanosis and nail clubbing (44). At a later stage of COPD structural changes in the pulmonary arterioles can lead to pulmonary hypertension. This can progress to right ventricular hypertrophy with signs of right side decompensation cordis (oedema or congestion of the v. jugularis externa) due to progressive cor pulmonale (44). Thus the obstructive ventilation disorder and emphysema in progressive COPD are almost irreversible because they are caused by irreversible processes like fibrosis and destruction. The course of the disease is aggravated by exacerbations, which are periods where the typical symptom triad cough, dyspnoea and sputum production are enhanced (41).

The German Guidelines on the diagnosis and therapy of COPD patients give a detailed overview of these topics (46). In summary a detailed anamnesis with possible exposition factors and a physical examination should be conducted. If clinical symptoms like coughing, prolonged expiration with gills or whistles, cyanosis and/or over inflation of the thorax are present spirometry, a lung function test is used to manifest the diagnose COPD (46). Spirometry is performed before and after the inhalation of a bronchodilator, which is a requirement for diagnosing COPD. A more detailed description and interpretation of spirometry can be found in the Methods section of this paper. To measure the obstruction the guidelines follow the recommendation of the German *Atemwegsliga,* which uses the ratio of the volume of air exhaled during the first second (forced expiratory volume in one second, FEV1) and of the volume of air forcibly exhaled from the point of maximal inspiration (forced vital capacity, FVC) also known as the FEV1/FVC ratio (22, 47). It is important to

note that not every bronchial obstruction measured during spirometry means a clinical diagnosis of COPD. Nevertheless, it is a necessary criterion for the diagnosis of COPD (46). Another way to diagnose COPD is bodyplethysmography, it is indicated if patients do not cooperate during spirometry or if there is suspected emphysema (48). It will not be described any further as it has no added value for this paper. Nevertheless, it was mentioned to give a complete overview.

The GOLD system categorizes the level of obstruction into four stages (Table 1) (22). The classification can be found in table 1. For the diagnosis COPD a FEV1/FVC <0.7 is necessary, the further gradation is done by the FEV1% predicted, which is specified as a percentage of the predicted FEV1. The FEV1 is the best individual parameter for the prognosis of COPD (46). Studies concluded that a reduction in FEV1 means an impairment on quality of life (49, 50).

Table 1: Classification of airflow limitation according to the Global Initiative for Chronic Obstructive Lung Disease

Classification	Severity	Description
In patients with FEV1/FVC < 0.70		
GOLD 1	Mild	FEV1≥ 80% predicted
GOLD 2	Moderate	50% ≤ FEV1 < 80% predicted
GOLD 3	Severe	30% ≤FEV1 <50% predicted
GOLD 4	Very severe	FEV1 <30% predicted

Abb. GOLD = Global Initiative for Chronic Obstructive Lung Disease; FEV1= Forced expiratory volume in one second; FVC= Forced vital capacity

Since 2011 the GOLD guideline recommends a sub-classification A – D, which is based on the classification of airflow limitation and additionally on the symptoms and risk of exacerbation (Figure 1) (51). For the new GOLD classification, the necessary symptom assessment according to the ABCD stadia is evaluated with the modified British Medical Research Council (mMRC) scale or COPD assessment test (CAT) (22). The therapy is based on the stadium of COPD, which next to the spirometry, is often accessed by the ABCD stadia (46).

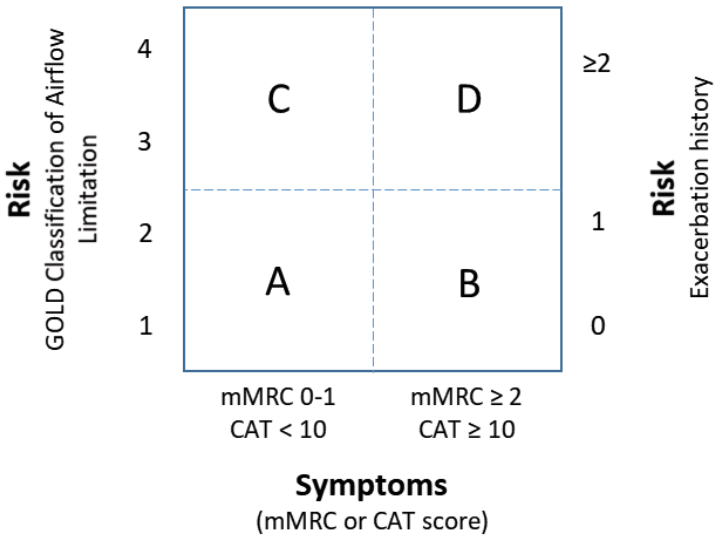

Figure 1: Combined COPD assessment. New GOLD classification taking symptom assessment and numbers of exacerbations into account. Classification used for treatment plan. Figure is based on Vogelmeier et. al., 2017 (52).
Abb. GOLD = Global Initiative for Chronic Obstructive Lung Disease, mMRC= modified British Medical Research Council, CAT= Chronic obstructive pulmonary disease assessment test

Pharmacotherapy is used to improve symptoms and decrease the frequency of exacerbations (46). The standard therapy is the inhalative use of bronchodilators (Anticholinergics/ Beta-2-sympathomimetics) and corticosteroids or a combination of both (46). Patients in symptom stadium A should receive a short or long-acting bronchodilator, or if patients have no symptoms watchful waiting can be performed (46). Stadium B includes patients with symptoms but no hospitalization due to an exacerbation treated with a long acting bronchodilator. If symptoms are severe, a combination of two bronchodilators of two separate classes can be administered (46). For patients in stadium C and D a long acting bronchodilator should be prescribed, preferably a long acting muscarine antagonist, if exacerbations remain a long acting beta agonist should be added. Then if symptoms still do not improve and exacerbations keep occurring, an inhalative corticosteroid should be administered in addition to the bronchodilators (46). So far, no study found medication, which was able to stop or at least slow down the decrease in lung function (53-55).

Tobacco abstinence is the only way to stop the decrease in lung function and it is the most efficient and cost-effective way to achieve a better prognosis (56). Continued smoking increases mortality due to COPD (22). Nevertheless, approximately 35-40% of the COPD patients keep on smoking tobacco (37). Those findings are supported by the 'Lung Health

Study' which analysed the disease progress of about 6 000 tobacco smokers for 11 years (57). The German guideline states that 25% of patients or more can achieve long term tobacco abstinence through a combination of behavioural therapy and pharmacotherapy (nicotine replacement therapy, vareniclin, or bupropion) (46). The earlier COPD patients quit smoking, the better the prognosis. Therefore, Germany has a special S3-guideline for smoking cessation in COPD patients. This guideline gives a detailed overview of methods to help patients quit smoking with a focus on motivational interviews by the health care professional (13). A special focus for smoking cessation in COPD patients is necessary as it seems as if COPD patients have a higher nicotine dependence than healthy tobacco smoking subjects (20). Next to a slowdown of decline in lung function, smoking cessation in COPD patients could lead to a fewer exacerbations, hospitalizations and lower mortality (57, 58).

1.2 Psychological comorbidities in COPD

COPD is associated with the presence of cardiovascular, metabolic and psychological comorbidities (59). A cross-sectional study in 3124 COPD patients aged >40 years showed that 90% of the patients with COPD have at least one other related disease, those comorbidities result in a negative impact in terms of quality of life, exacerbation and mortality (59, 60). The prevalence of psychological comorbidities seems to be higher in patients with a chronic disease like COPD (61). Depression and anxiety are the fifth most common chronic diseases occurring in patients with COPD and seem to be more common in women than in men (60). Psychological symptoms might be provoked by factors such as increased incidences of dyspnoea, physical inactivity, and social isolation (62, 63).

In international literature, the prevalence of depression in COPD patients varies by study and by the applied psychometric instrument used between 10 – 45% while that of anxiety ranges between 10 – 19% (60, 64-66). About one-fourth of COPD patients had persistent depressive symptoms over three years; the occurrence of depression seems to be almost doubled in COPD patients in comparison to patients with other chronic diseases like diabetes mellitus (67, 68). A recent German multicentered study included 2741 COPD patients and found the prevalence or rate of anxious-depressive symptoms increasing with the GOLD stadia; in GOLD I the prevalence of major depression measured with the PHQ-9 ≥ 10 was 16.3% and for GOLD IV 28.2% (69). This relationship between the severity of COPD and the prevalence of depression is supported by other studies (67, 70).

The association between the presence of COPD and the development of anxious-depressive symptoms has not yet been clarified. However, there are several explanatory theories. Studies suggest a pathophysiological relation between symptoms like dyspnoea or hyperventilation and emotional and mood components (71-73). One study descriebes a bidirectional relationship between anxiety and pulmonary-specific symptoms in COPD patients (74). This is in line with a meta-analysis from 2014 with a long-term follow-up which states that the relationship between depression and COPD is bidirectional, depression can be cause and/or consequence of COPD (75). Especially the feeling of respiratory discomfort is reported to be a source of anxiety or panic disorder in patients with COPD (76-78). Patients can experience a vicious cycle of dyspnoea and anxiety as the feeling of anxiety can lead to activation of sympathetic nervous system and trigger a ventilatory response (e.g. hyperventilation/dyspnoea) which in turn can result in more respiratory discomfort (79). Other theories include the hyperventilation model in which metabolic alkalosis caused by hyperventilation leads to vasoconstriction and panic symptoms (numbness, shortness of breath) or the implication that severe COPD causes hypercapnia which can activate noradrenergic neurons and lead to a panic response (78). Moreover, it seems as if COPD patients with more severe anxious-depressive symptoms have fewer coping strategies and a lower level of self-efficacy to manage symptoms (80). Social support seems to be a protective factor for anxious-depressive symptoms (80).

In his review, Norwood describes the etiology of depression in COPD patients (81): Genetic predisposition, environmental assaults, the respiratory illness itself with its "reaction" to the loss of function due to illness and last the direct neuropsychiatric effects of chronic respiratory disease as COPD leads to hypoxia which can cause cognitive impairment/depression. There seems to be increasing evidence for this theory as magnetic resonance imaging (MRI) and bio-chemical markers revealed that physiologic changes which are associated with COPD have direct effects on the vasculature of the brain; the same vascular effects have been associated with depression in the elderly (81).

An American study among retired persons found that within two years of diagnosis of a chronic lung disease the hazard ratio increased 2.2 times for the development of depressive symptoms (82). The study supports the idea that depression in COPD patients develops in response to the COPD diagnosis (82). This makes it difficult to diagnose anxious-depressive symptoms as it is difficult to decide if those symptoms are the expression

of the physical restriction or if it is an autonomous psychological disorder (76). This is in line with Doyle et al. who state an underdiagnosis of depression and anxiety in COPD patients due to an overlap of symptoms of depression and anxiety with those of COPD (e.g. higher levels of fatigue and shortness of breath), and variations in diagnostic assessment (74).

The long-term prognosis is worse in patients with psychological comorbidity (68, 75). Studies revealed an association between depression and impairment in physical performance (76, 83, 84). Furthermore, there is evidence that the prevalence of depressive- or anxiety-related disorders in COPD patients are associated with reduced functional ability, higher admission rates to the emergency room (52% vs. 19%) and rehospitalizations (84, 85). The effect of depression on mortality in elderly COPD patients is unclear. While some studies suggest depression and anxiety to be predictors for higher mortality in COPD (86-88); others did not support this association but instead suggested that FEV1 and long-term oxygenation are predictive of a higher mortality rate (89). Cognitive behavioural therapy in COPD patients with depression seems to improve the quality of life the effect is both physically and psychologically (70). The effect of pulmonary rehabilitation in COPD patients on depressive symptoms remains vague; with some studies reporting a positive effect and improvement in symptoms of depression while others do not (90, 91).

1.3 Tobacco smoking and depression/anxiety

Several current studies indicate an association between tobacco smoking and the presence of psychological comorbidities, especially depression and anxiety (92, 93). A report on smoking and mental health in England, which included three large United Kingdom (UK) population based studies, found a higher smoking prevalence among patients with depression (31.4 – 39.8%), anxiety (37.4%) or a mix of anxiety and depression (31.1%) than among the general population 19.7 – 22.2% (94). A large cross-sectional survey of the population in the UK found a decline in the prevalence of smoking in the last 12 years from 24.2% (2007) to 15.4% (2019) among the general population, unfortunately Royal College of Physicians and Royal College of Psychiatrists describe this decrease to be much less among psychologically ill people (94, 95). The sociodemographic effect on tobacco smoking as described above can also be noted in the occurrence of psychological/mental illness; the lower the school degree and/or net household income the higher the likelihood to develop a psychological illness (96).

This data indicate a (causal) association between tobacco smoking and anxious-depressive symptoms. Yet, the direction of the association remains unclear. There are four common models/theories used to discuss the association (92, 97, 98).

Within the **primary disorder model** the manifestation of a psychological disorder occurred before starting to smoke tobacco (99). Following the self-medication hypothesis tobacco smoking is used to relieve anxious-depressive symptoms. Tobacco abstinence leads to stress and then tobacco smoking which has a mood-lightening and stress-reducing effect in smokers due to the consumption of nicotine (97, 100). It is assumed that giving in to the addiction can give smokers a mood-lightening effect and creates the subjective impression of a positive effect on the mental state (98). Moreover, nicotine seems to directly act on the hippocampus and lead to an anxiolytic effect (101). This is supported by a study, which describes high levels of anxiety to be identified as a risk factor for the initiation of smoking in young adults (102).

The **primary smoking model** sees tobacco smoking and nicotine consumption as a risk factor for developing a psychological disorder. First, people consume tobacco regularly and then a psychological disorder was detected (97). A possible explanation is neuronal changes due to tobacco smoking and thus nicotine dependence (97, 103). It is known that nicotine has an effect on nicotinic acetylcholine receptors and leads to the release of different neurotransmitters like adrenaline, dopamine and serotonin. Especially the last two are associated with anxious-depressive disorders (101). A large systematic review in 2014 concluded a significant improvement in symptoms of both depression and anxiety in patients who successfully stopped smoking in comparison to those who continued smoking (104).

The foundation for the **bidirectional model** is the effect of a sustained interaction between tobacco smoking and psychological disorders and thus a mixture of the already mentioned models where it remains unclear if tobacco smoking or a psychological disorder came first (105). Patients enter a vicious circle: Smoking leads to temporary relaxation and satisfaction of the addiction which relieves anxious-depressive symptoms. However, as mentioned before, smoking leads to neuronal changes, which in turn influence psychological perception (105, 106).

Last, the **common factor model** is based on the theory of a common aetiology for tobacco dependence and psychological disorders (107). According to this model tobacco

smoking and psychological perception should be seen as independent constructs as all the known associations are due to shared risk factors such as sociodemographic and –economic status (108).

1.4 Association between smoking, anxious-depressive symptoms and COPD

There is a theory that the associations between depression/anxiety and COPD seem to be largely explained by confounding factors like history of tobacco smoking and nicotine dependence and the connection between mood disorders and COPD is only linked by nicotine dependence (109). Norwood describes psychological symptoms like depression, smoking and COPD to be interrelated in a sort of trinity (81). Depression seems to contribute to the initiation and continuation of smoking, as already described smoking leads to the onset of COPD and COPD plays a role in the development of depression (81). Literature supports the hypothesis that patients with COPD who also suffer from depression or anxiety are more likely to be smokers (110, 111). Tobacco smoking COPD patients describe an above-average motivation to stop-smoking (64, 97). Unfortunately, those quit-attempts seem to be less successful than in patients without COPD (64). In COPD patients, tobacco and nicotine withdrawal can lead to progressive exacerbations and depression or even suicidal thoughts (81, 112). Anxious-depressive symptoms (possibly or potentially) form a barrier for tobacco-consuming COPD patients attempting to quit smoking (81, 92).

A review supports this idea as it describes antidepressants to be helpful in increasing tobacco abstinence rates for up to three month (81). Additionally, a long history of tobacco consumption and stronger nicotine dependence of smoking COPD patients compered to smokers without COPD could play a role (113). Furthermore, literature stated that smokers in general with psychological comorbidities seem to smoke more and more often and heavily than smokers without such symptoms (20).

Figure 2 depicts a visual diagram explaining relationship between the trinity of psychological symptoms, smoking and COPD of Mühlig and Paulick (97). It summarises the hypothesis and facts mentioned before. First, it became clear that tobacco smoking causes and worsens COPD. Second, psychological comorbidities seem to lead to heavier smoking and less successful quit-attempts (20, 81, 92). And third, there seems to be a bidirectional association between COPD and the presence of psychological comorbidities, it is unclear if the COPD is also the cause of these (74, 75). Long-term smoking also causes neuronal

changes that contribute to the chronification of depression next to the already mentioned worsening of COPD symptoms (97, 103, 114). Moreover, in some patients with psychological comorbidities smoking is used as self-treatment of their symptoms (97, 100). Still, the interrelationship between depression/anxiety, smoking and COPD is not fully understood (115).

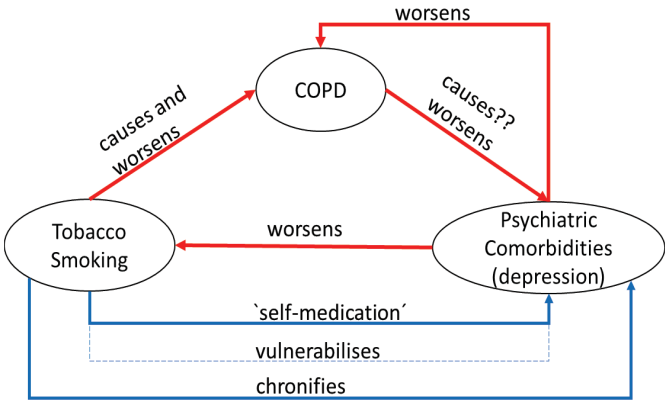

Figure 2: **Effect model: the vicious cycle of COPD – smoking – depression**.
Model is based on Mühlig and Paulick, 2016 (97).
Abb. COPD= Chronic Obstructive Pulmonary Disease

A recent study on smoking cessation in a primary care setting with data from the AOK in Sachsen and Thüringen is the only study which contains information on the prevalence of depressive symptoms among COPD patients. The study contained 209 smoking COPD patients and found that 44% of the participants had at least mild symptoms of depression (37).

1.5 Problem statement

Among patients with COPD the likelihood of developing a psychological comorbidity like depression or anxiety is higher in comparison to healthy subjects. Literature states that smoking increases the severity of COPD and increases the risk of developing a psychological disorder. Smoking cessation is the only way to slow down the progression of COPD. Yet, it is much more difficult for anxious-depressive as well as heavy smoking patients to quit smoking. Additionally, smoking cessation is linked to an improvement in depressive or anxious symptoms. There is also evidence that not even one-third of COPD patients with depressive and/or anxious symptoms receive appropriate treatment for those comorbidities (115).

To our knowledge there are no current data about the prevalence and the association of tobacco smoking and anxious-depressive symptoms in COPD patients in Germany. This information is necessary to offer more tailored support and treatment in smoking cessation to this specific patient group. Early detection of psychological comorbidities and adequate treatment are important to achieve tobacco abstinence and thus slow down the progression of COPD. Therefore, it is necessary to gain more insights on the association between smoking status and the presence of anxious-depressive symptoms in patients with clinically diagnosed COPD. Currently, no study describes the association between anxious-depressive symptoms according to their smoking status adjusted for socio-demographic parameters and factors like strength of tobacco dependence, and severity of COPD in a pulmonary primary care sample of patients with COPD in Germany.

1.6 Aims of the study

Primary aims: to assess, in a sample of clinically diagnosed COPD patients,

1. the overall prevalence of anxious-depressive symptoms measured with the Patient Health Questionnaire-4 (PHQ-T), and the prevalence of anxious-depressive symptoms measured with the PHQ-T depending on the tobacco smoking status (never smoker, long-term and recent ex-smoker, and current smoker)
2. the association between tobacco smoking status and anxious-depressive symptoms measured with the PHQ-T, adjusted for age, gender, level of education and burden of disease, displayed as the lung function parameter FEV1% predicted and the score of the COPD assessment test.

Secondary aim: to assess, in the subgroup of current tobacco-smoking COPD patients, the association between the level of tobacco dependence, measured with the Heaviness of Smoking Index and anxious-depressive symptoms measured with the PHQ-T, adjusted for age, gender and level of education and burden of disease displayed as the lung function parameter FEV1% predicted and the score of the COPD assessment test.

2 Methods

Data were taken from the '"**R**eal-world" **E**ffectiveness of **S**moking cessation methods in **P**at**i**ents with ch**r**onic **o**bstructive pulmonary disease' (**RESPIRO**) study, a cross-sectional survey coordinated by researchers from the Institute of General Practice (ifam) at the Heinrich-Heine-University Düsseldorf. The study was registered at the German Clinical Trials Register: DRKS00015450. The overall aim of the RESPIRO study was to provide detailed data on use and effectiveness of smoking cessation methods in COPD patients in the "real-world". The following sections contains an overview of the RESPIRO study. Relevant aspects for the present analysis are elaborated in more detail.

2.1 In- and exclusion criteria

2.1.1 Pulmonary practices

All pulmonary practices and pulmonologists could participate. They just needed to be informed about the study and sign the informed consent. There were no further in- and exclusion criteria for pulmonary practices.

2.1.2 COPD patients

Patients were eligible for the study if they visited the practice during the recruiting time, were ≥18 years old, agreed to participate by sending back the signed informed consent document along with the baseline questionnaire, and had clinically diagnosed COPD according to the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10), with one of the following codes (17):

a. J44.0 (Chronic obstructive pulmonary disease with acute lower respiratory infection),
b. J44.1 (Chronic obstructive pulmonary disease with acute exacerbation, unspecified),
c. J44.8 (Other specified chronic obstructive pulmonary disease, including chronic bronchitis: asthmatic (obstructive) – emphysematous – obstructive)
d. J44.9 (Chronic obstructive pulmonary disease, unspecified).

Exclusion criteria were all other severe or chronic pulmonary diagnoses (e.g. tuberculosis, lung cancer), a new COPD diagnosis made on the day of the visit, a language barrier, and moderate or severe cognitive impairment or low literacy (obtained from patient's record).

2.2 Setting and recruitment

Pulmonary practices were recruited between September 2018 and July 2019. Recruitment was done in two tiers. The first part consisted of the recruitment of the pulmonary practices and the second part was the recruitment of the COPD patients done by the practice. The first practice was included in September 2018 and the last one in July 2019. The first patient was included in September 2018 and recruitment of the patients took place until the end of December 2019. The minimum time for patient recruitment of the practices was five months and the mean recruitment time was eight months.

2.2.1 Recruitment pulmonary practices

Pulmonary practices in North Rhine-Westphalia were recruited through the "WINPNEU" network (http://winpneu.de), which is a scientific network, initiated by the Federal Association of pulmonologists. WINPNEU aims at improving the evaluation and development of pulmonary health care in pulmonary practices. Thus, participating practices are experienced in participating in scientific research projects. In the German federal state of North Rhine-Westphalia about 90 practices with 125 pulmonologists are members of WINPNEU. Those practices are spread throughout urban and rural areas of North Rhine-Westphalia with a broad socioeconomic variability.

Pulmonary practices were recruited by the WINPNEU Newsletter, which is usually send to the members once or twice a year. A „special edition" newsletter was prepared to recruit pulmonary practices for the RESPIRO study.. The newsletter contained a short presentation of the RESPIRO study: the aims and method of the study were discussed. Furthermore, the task of the pulmonary practices within the study was described. Last, all facts with the most important questions were summed up to give a thorough and brief overview. The original German version of the newsletter can be found in the appendix (see Appendix 6.1). A return form for participation was added to the newsletter and interested pulmonologists could send the form back to our research group at the ifam to receive more information. Interested pulmonologists needed to fill-in their name, telephone number and email address. Additionally, they needed to choose if they directly wanted to participate or first want to receive more information. Next to the newsletter, pulmonologists were informed about the study by a researcher of the ifam team during two separate training events by the *Ärztekammer Düsseldorf* in summer 2019. The WINPNEU newsletter was handed out

during both events. Again, interested pulmonologists could return the participation form by fax or post.

After agreeing to participate one on-site initiation visit per practice was conducted by an ifam researcher. During this visit, the contact person for the practice received information on details and the procedure of the study and the tasks that needed to be fulfilled by the practice. Every pulmonology practice could decide if the contact person is the pulmonologist, a study nurse or a physician assistant (MFA). Further monitoring and support with baseline recruitment processes was performed via telephone with the contact person.

2.2.2 Recruitment COPD patients

Every practice obtained a prepared set of 100 – 300 large, yellow envelopes. The ifam's study team prepared the envelopes. Each envelope contained the same baseline material for the patients. The baseline material consists of a cover letter with information about the RESPIRO study, an informed consent form/data protection declaration with withdrawal information, the baseline questionnaire, a stamped return envelope and a non-financial incentive (Appendix 6.2). Pencils or candies were added to the envelopes as a non-financial incentive. The goal of incentives is to increase the response rate (116, 117). Baseline questionnaires had a specific identification number (ID, e.g. 00001, 00002…) allowing allocation to the practice and patient. The practice contact person (practice/study nurse/pulmonologist) approached all patients with a diagnosis of COPD (see also inclusion criteria) and verbally provided brief information on the content of the study. Smoking is a sensitive topic for many COPD patients. This might discourage them from participating or create feelings of guilt; thus, the focus during the explanation of the study was put on 'patient-physician communication'. Patients received the large, yellow envelope from the contact person. Before handing it out, the contact person was responsible for completing the first highlighted part of the baseline questionnaire. They documented the full ICD-10 diagnosis of the patient, the date of the most recent spirometry and the parameters of the spirometry relevant to this study for calculating the severity of the COPD diagnosis for study analyses. Patients were asked to take the envelope home, read the information carefully, and to decide if they would like to participate in the study, including one postal follow-up survey (which is not the object of the present analysis). If they decided to participate, the patient completed the baseline questionnaire and signed the informed consent. The return envelope was used to send the baseline questionnaire with informed consent back to our study team

at the ifam. During the practice visit, the contact person should emphasize that participation is voluntary. Patients only agreed to participate by signing the informed consent and sending the documents back to the study centre. Patients were able to withdrawal participation at any time until data analysis was finished and ready to be published.

Depending on the practice size and the number of patients per practice, practices received between 200 and 800 questionnaires for distribution. The effort of the practice was remunerated with 200€. A few outstanding practices with a large number of patients with COPD (around 400) per practice and thus a higher rate of recruitment, received an extra payment of 200€ at the end of the data collection period.

2.3 Sample Size

The sample size calculation is based on the main outcomes of the RESPIRO study. The present research is explorative and questions were developed in addition to the main outcomes. Thus, a separate power calculation for the research question of this study was not applicable.

The following describes the sample size calculation of the original RESPIRO protocol. The methodology of RESPIRO is based on studies on the real-world effectiveness of smoking cessation methods in the general English population (118-121). Assumptions about expected means and variances for the analyses are made on the basis of these results: data indicate that a baseline sample of 800 to 1,300 interviewed smokers with COPD is needed to yield adequate statistical power. The total required sample size was determined considering current prevalence rates of smoking in Germany (7), and data from the smoking toolkit study on rates of cessation attempts and physician visits within the past 12 months, "ever-use" of e-inhalation products and response rates at follow-up (118, 122-124).

From discussions with practicing pulmonologists we know that at least 400 patients with COPD will see their physician per quarter of whom approximately 70% (=~300) will be asked to participate. Approximately 35% of them are current or recent ex-smokers (20). We expected up to 90 current or recent ex-smokers with COPD per pulmonologist per quarter. According to estimations from previous studies, approximately 70% of these patients will participate in the study (n= 60).

2.4 Data collection

The baseline questionnaire contained questions on the patients' level of education as an indicator for the sociodemographic status, age, sex, current smoking status, and current use of electronic cigarettes (e-cigarettes). Furthermore, patients were asked about their mental health, to make an estimation on their current disease related health status, and about the number of COPD exacerbations within the last year. Current tobacco users and recent ex-users who quit tobacco smoking within the last 12 months were asked about their tobacco smoking behaviour, urges to smoke, and motivation and attempts to quit tobacco smoking. The completion of the questionnaire took between five and ten minutes

In the following sections the relevant items for the present analyses will be presented in more detail, the whole questionnaire can be found in section 6.3 of the appendix. Originally, the questionnaire was in German, for the appendix of this dissertation the questions were translated to English.

2.4.1 Sociodemographic data

In the baseline questionnaire, the following sociodemographic items were retrieved and used for further analyses. Patients stated their date of birth, thus age was listed in years. Gender was differentiated by female and male. Patients were asked to report their highest level of education using five categories: 1) no degree, 2) elementary/ lower secondary school leaving certificate (grade eight or nine), 3) intermediate secondary school leaving certificate (grade ten), 4) advanced technical college certificate, and 5) general higher education entrance qualification/ high school diploma.

For the statistical analyses, the answers to the level of education were summarized into three new categories: Low/no level of education (answers 1 and 2), moderate level of education (answer 3), and high level of education (answer 4 and 5).

2.4.2 Patient Health Questionnaire-4 (PHQ-T)

The Patient Health Questionnaire 4 (PHQ-4) is a well validated self-assessment questionnaire consisting of four items, which assess depressive and anxious symptoms (125-127). The first two measure symptoms of depression and the other two measure symptoms of anxiety. The questions have been developed from the PHQ-D, a screening instrument for mental disorders according to the Diagnostic and Statistical Manual of Mental Health Disorders Version IV (DSM-IV) (128). The PHQ-D contains, among other things, a 9-item

module on depression (PHQ-9). The first two items of the PHQ-9 were transferred to the PHQ-4 as the PHQ-D for the assessment of depressive symptoms.

Furthermore, the PHQ-D contains an anxiety module, the Generalized Anxiety Disorder 7 (GAD-7), which consists of seven items. Like those from the PHQ-9 the first two items of the GAD-7 were transferred to the PHQ-4 as GAD-2 to screen for anxiety symptoms. Together the PHQ-2 and the GAD-2 make up the PHQ-4. Overall, the PHQ-4 has an acceptable internal consistency (Cronbach's alpha=0.78), with an acceptable internal consistency of the PHQ-2 (Cronbach's alpha=0.75), and a good consistency for the GAD-2 (Cronbach's alpha=0.82) (126, 127).

Patients were asked "Over the last two weeks, how often have you been bothered by the following problems?", the answers and point allocation can be found in table 2.

Table 2. The Patient Health Questionnaire 4. The question and the four statements, which needed to be rated and their point allocation. The first two items belong to the symptoms of depression (PHQ-2/PHQ-D), the last two items assess anxiety symptoms (GAD-2/PHQ-A).

		Over the <u>last 2 weeks</u>, how often have you been bothered by the following problems? *(Use **"x"** to indicate your answer)*	Not at all	Several days	More than half the days	Nearly every day
PHQ-4/ PHQ-T	**GAD-2/ PHQ-A**	1. Feeling nervous, anxious or on edge	0	1	2	3
		2. Not being able to stop or control worrying	0	1	2	3
	PHQ-2/ PHQ-D	3. Little interest or pleasure in doing things	0	1	2	3
		4. Feeling down, depressed, or hopeless	0	1	2	3

Abb. PHQ= Patient Health Questionnaire, GAD= Generalized anxiety disorder

The answers were given on a 4-point Likert scale, where every answer was allocated to a score (0= not at all, 1= several days, 2= more than half of the days and 3= nearly every day). Thus, the total score is 0 – 12 or for each subscale (depression and anxiety) 0 – 6. The total PHQ-4 score is interpreted as normal (0-2), mild psychological symptoms (3-5), moderate psychological symptoms (6-8), and severe psychological symptoms (9-12). To

distinguish between the presence and absence of psychological distress a cut-off ≥6 was determined to classify as psychological stress through anxious-depressive symptoms. Moreover, a total score ≥3 for each subscale is considered positive for screening purposes of depressive or anxious symptoms (127).

For the analyses, the results of the PHQ-4, PHQ-2 and GAD-2 were translated to a binary variable: presence of psychological symptoms (yes=1 vs. no=0). As described above the threshold for the presence of psychological distress through anxious-depressive symptoms is considered met if the total score was ≥6, or ≥3 for each subscale (depressive or anxious symptoms). A total score <6 and subscale score <3 is regarded as absence of psychological symptoms.

For simplicity, in this following sections of this document the PHQ-4 is referred to as PHQ-T (total), the PHQ-2 is referred to as PHQ-D (symptoms of depression), and the GAD-2 is referred to as PHQ-A (symptoms of anxiety).

2.4.3 Tobacco smoking status

The tobacco smoking status was also recorded. The question was taken from the Smoking Toolkit Study (129). All the patients were asked "Which of the following best applies to you?". Participants were ask to provide one of the following answering options:

a. I smoke cigarettes (including hand-rolled) every day
b. I smoke cigarettes (including hand-rolled), but not every day
c. I do not smoke cigarettes at all, but I do smoke tobacco of some kind (e.g., pipe or cigar)
d. I have stopped smoking completely in the last year
e. I stopped smoking completely more than a year ago
f. I have never been a smoker

For statistical analysis, the answers were summarized and separated into four new categories: Current smoker (answers a, b and c), recent ex-smoker (less than 12 month; answer e), long-term ex-smoker (more than 12 month; answer e) and never-smoker (answer f).

2.4.4 Heaviness of Smoking Index (HSI)

The Heaviness of Smoking Index (HSI) is a tool to assess the patients' level of nicotine dependence (130, 131). It consists of two questions (table 3). In epidemiological studies the HSI often is preferred to the Fagerström Test for Cigarette Dependence (FTCD), which consists of six items making it longer and more prone to missing data (131, 132). Studies showed that two items from the FTCD provide a good and brief measure of high nicotine dependence (130, 131). Those items form the HSI. A high HSI has a relatively good sensitivity (94%) and specificity (88%) (130). Thus, the HSI consists of two self-reported items which seem to be valid predictors for physical tobacco dependence (131).

1. Cigarettes per day assessed by: "On average, how many cigarettes do you smoke each day, including both factory-made and roll-your-own cigarettes?"

2. Time to first cigarette assessed by: "How soon after waking-up do you usually have your first cigarette?"

The answers are summed up in four categories and allocated to values between zero and three (table 3). To receive a total score the value of both items are added up. The total scores of the HSI are then summarized into three categories which are designated as 0 – 2: low addiction, 3 – 4: moderate addiction, and 5 – 6: high addiction (131).

Table 3. Heaviness of Smoking Index (HSI). The two questions of the HSI and the answers with their point allocation. Scores need to be added to receive the total HSI score.

Score	***1.*** *On average, how many cigarettes do you smoke each day?*	***2.*** *How soon after waking-up do you usually have your first cigarette?*
0	≤10 cigarettes	> 60 min
1	11 – 20 cigarettes	31 – 60 min
2	21 – 30 cigarettes	6 – 30 min
3	≥ 31 cigarettes	≤ 5 min

2.4.5 Assessment of the severity of COPD

The severity of COPD can be determined by different measures. The most common way to diagnose and grade COPD is by the use of spirometry (22). In the following only measures, which are of importance for the present analyses, will be discussed. It should be noted that

all the important parameters to calculate the severity of the COPD were collected by the contact person of the pulmonary practice.

Spirometry is a non-invasive test to measure lung function. It is accessible in almost every pulmonology practice; there are healthcare workers who perform spirometry for each patient, as COPD patients undergo spirometry regularly. Spirometry is the most reproducible and objective measurement of airflow limitation (47). It has good sensitivity (22). Spirometry measures the volume of air forcibly exhaled from the point of maximal inspiration (forced vital capacity, FVC) and the volume of air exhaled during the first second (forced expiratory volume in one second, FEV1) (22). Those measures have to be completed after administration of an adequate dose of at least one short-acting inhaled bronchodilator for the diagnosis and assessment of COPD. As mentioned in the introduction the Global Initiative for Chronic Obstructive Lung Disease (GOLD) system categorizes airflow limitation into four stages (Table 1) (22). Therefore a FEV1/FVC ratio , the post-bronchodilator ratio of FEV1/FVC <0.7 is a requirement for the diagnosis of COPD (22). The classification of COPD then is based on the FEV1, which is specified as a percentage of the predicted (FEV1% predicted) (22).

For the statistical analyses it the FEV1% predicted was used as a parameter for lung function as a metric variable instead of the GOLD criteria. The FEV1% predicted is a valid parameter for the prognosis of COPD and the classification within the GOLD criteria is also made by the FEV1% predicted only after fulfilling the requirement of a FEV1/FVC ratio < 0.7 (22). As this requirement is already given in the pre analysis, using the FEV1% predicted, a metric variable is superior to a categorical variable (GOLD classification) as a categorical variable reduces statistical power.

For symptom assessment the COPD assessment test (CAT) was used in this questionnaire, it will now be described in more detail or it will be described in the following paragraph.

The CAT is a self-assessment measure for COPD patients, it assesses the severity of acute symptoms and their impact on the patient's life (22, 133). It contains eight items and the severity is rated on a Likert scale from zero (no symptoms) to five (most severe symptoms) (Appendix 6.3, Baseline Questionnaire) (134). The questionnaire begins with the request “For each item below, place a mark (x) in the box that best describes your current

situation. Please ensure that you only select one response for each question". Then the following symptoms are assessed: cough, phlegm, tight feeling in the chest, breathlessness while walking uphill/the stairs, limitations doing activities at home, confidence to leave home despite the lung condition, sleep and energy (135). The final score ranges between 0 – 40, it forms a reliable marker for the severity of disease (133, 135). The lower this score, the less effect COPD has on the patient's everyday life. In other publications a cut-off ≥10 can be found to describe at least moderate symptoms (135). Since there is no general classification of the CAT score and because of the better value in logistic regression analysis of metric variables, the CAT score will be used as a metric variable in the analysis.

2.5 Statistical Analysis

All analyses were carried out using IBM SPSS Statistics 25. First, within the whole sample the FEV1/FVC ratio was calculated to assess the severity of the COPD diagnosis according to the GOLD criteria. The sample was split in two groups: COPD patients fulfilling the requirement of the GOLD criteria with a FEV1/FVC ratio <0.7 and patients with a FEV1/FVC ratio ≥0.7. The socioeconomic and health status of the groups were compared using the Student's t-test for metric variables and the Chi^2-test for categorical variables. Data were presented as mean ± standard deviation (SD) and frequencies in percentages with their p-value, a p-value <0.05 was regarded as statistically significant.

Then, in the subgroup of patients with a FEV1/FVC ratio < 0.7 all patients, who did not complete all of the four questions of the PHQ-T were excluded from the further analysis and are referred to as the excluded sample. Thus, the following was only performed on the group with a FEV1/FVC ratio < 0.7 (included sample) and patients, who completed the PHQ-T. Sample characteristics were analysed using descriptive statistics. Frequencies were presented as percentages with a 95% confidence interval (95%CI), metric variables were displayed by mean ± SD.

For the missing values of the PHQ-T, PHQ-D and PHQ-A, a best and worst case analysis was performed to estimate the range of anxious-depressive symptoms in the sample. Therefore, all missing values of the three scales were substituted by either a score of zero (best case) or a score of six for the PHQ-T and a score of three for the subscales (worst case). Prevalence rates and standard error were calculated and presented as percentages of the sample.

Logistic regression analysis was used to assess the relationship between tobacco smoking and the presence of anxious-depressive symptoms in clinically diagnosed COPD patients. Associations between tobacco smoking status and three dependent variables, the PHQ-T (psychological distress yes/no), the PHQ-D (depressive symptoms yes/no) and the PHQ-A (anxious symptoms yes/no) were analysed using multivariable logistic regression models. For this purpose, the PHQ/GAD scores were dichotomised into the presence of psychological stress yes or no. Tobacco smoking status consists of four categories: current smoker, ex-smoker for less than 12 month, ex-smoker for more than 12 month and never smoker. The group of never smokers was used as a reference for all three models. The model was adjusted for potential relevant confounders: age, gender, level of education, the severity of COPD using the FEV1 and the self-assessment of the symptoms using the CAT. The same statistical model was applied to analyse the secondary aims. Within the sub-group of current smokers the association between the level of tobacco addiction and the presence of anxious-depressive symptoms in clinically diagnosed COPD patients was assessed. The logistic regression model used the same binary variables: PHQ-T, PHQ-D and PHQ-A. The heaviness of smoking index (HSI), a metric variable, was defined as the predictor (independent variable). As before, multivariable logistic regression was used and the model was adjusted for age, gender and level of education, FEV1 and CAT.

A complete case analysis was applied for each logistic regression model this means only patients without missing data necessary to calculate this model were included. As a consequence sample size will vary. It was chosen not to impute missing data.

2.6 Ethical Approval

The RESPIRO study received ethical permission by the Medical Ethics Committee of the Medical Faculty of the Heinrich-Heine-University Düsseldorf (5680R).

3 Results

In total, 21 pulmonary practices agreed to participate in the RESPIRO study, they were included between September 2018 and July 2019 and received the study material. By January 2020 three of those practices failed to hand out any baseline questionnaires and were excluded from the study. In total 21 pulmonary practices received 6100 baseline questionnaires and 18 practices distributed 4308 of those questionnaires among eligible patients. By mid-January 2020 we received a total of 1995 baseline questionnaires. This yields a response rate of 46.3%. 15 patients of the 1995 patients who sent back the baseline questionnaire were excluded from the study. Six withdrew their informed consent, two failed to meet the inclusion criteria because of a missing ICD-10 diagnosis and seven patients were missing FVC values or data (Figure 3). The used lung function parameter was taken of the most recent spirometry from the last year; only five patients' spirometry results were older than one year.

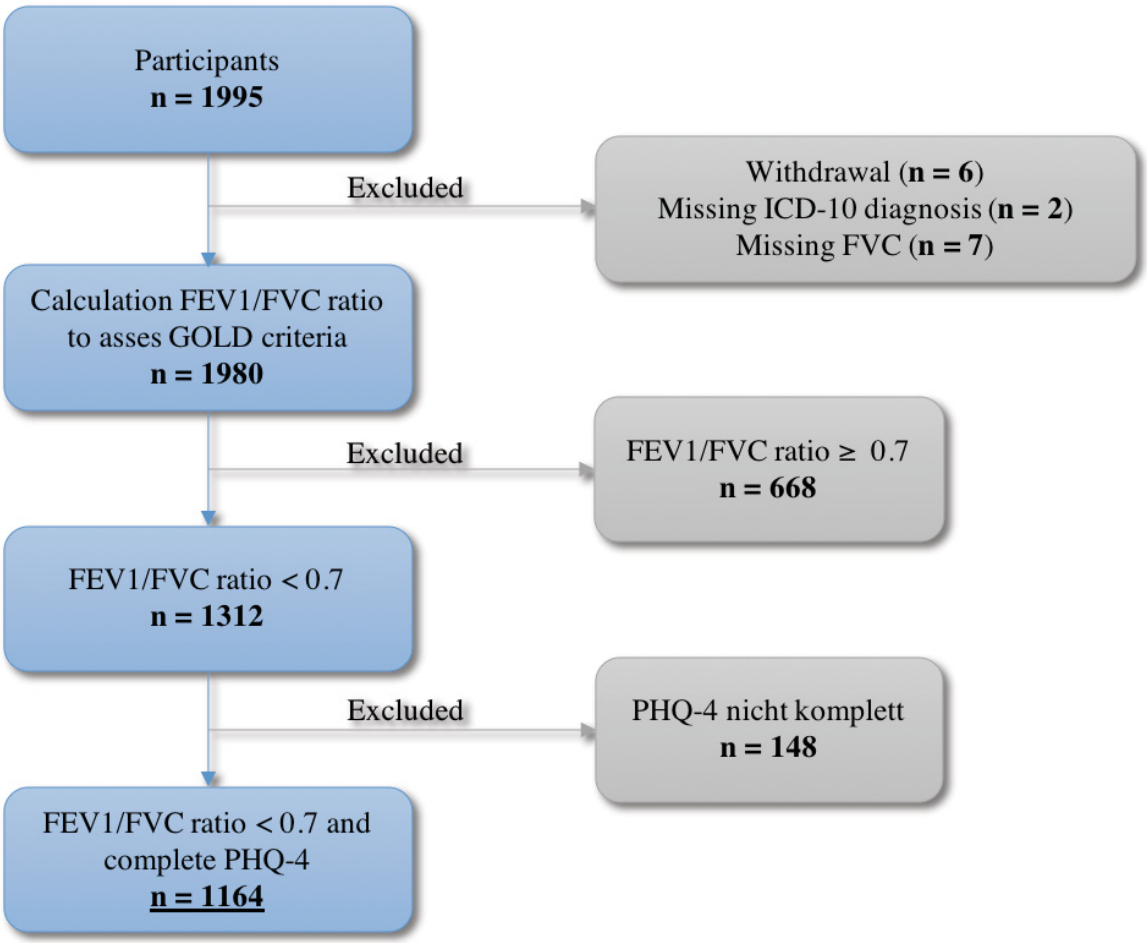

Figure 3. Flowchart of the patients included in the analysis.
Abb. GOLD= Global Initiative of Chronic Obstructive Lung Disease, PHQ= Patient Health Questionnaire

For 1980 patients the FEV1/FVC ratio was calculated to assess if the patients meet the GOLD criteria required for a COPD diagnosis. 1312 patients fulfilled the criteria of a FEV1/FVC ratio < 0.7 and thus 33.7% (N=668) were excluded for further analyses (Figure 3). 148 patients could not or did not complete all four questions of the PHQ-T and were excluded from the analyses (Figure 4). The total sample is referred to as the sample of the patients with a FEV1/FVC ratio < 0.7, who also completed the PHQ-T (n= 1164).

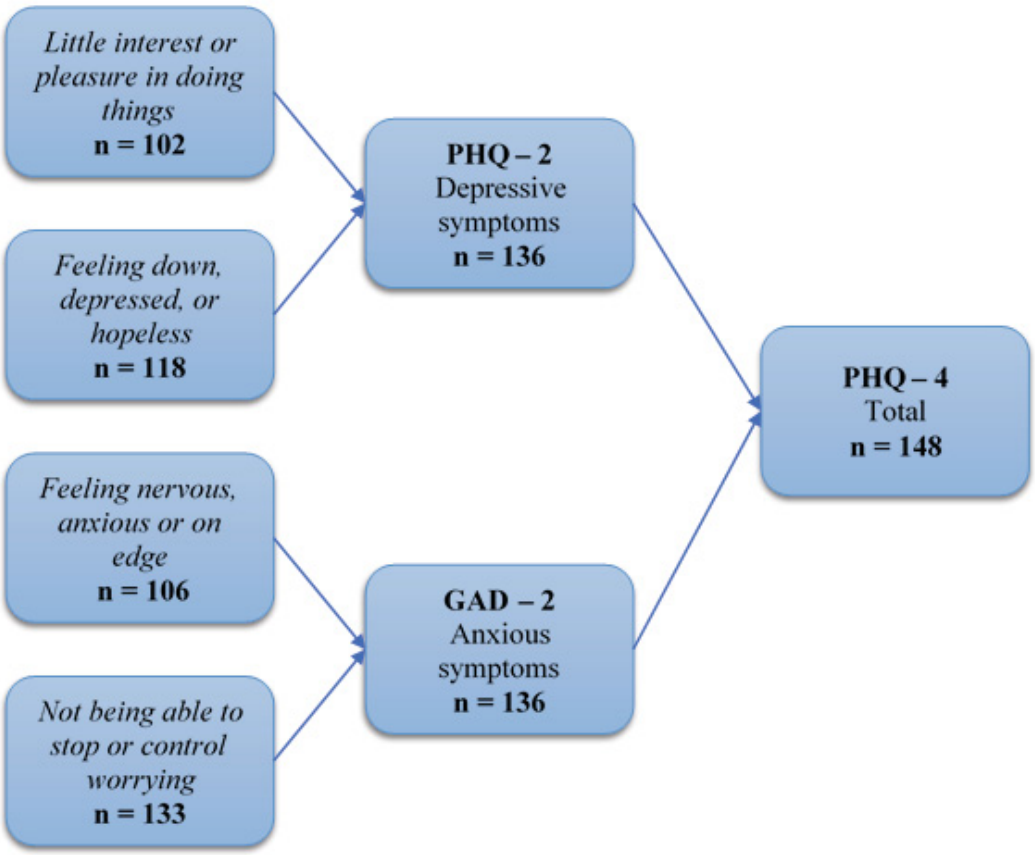

Figure 4. Overview of the missing values for the Patient Health Questionnaire-4 (n= 1312). Given are all four initial questions and the number of missings per question. Moreover, missings for the subscales of the PHQ-T and the PHQ-T total are presented. Numbers cannot be added up to the PHQ-T total, since all four questions had to be answered

Abb. PHQ= Patient Health questionnaire, GAD= Generalized Anxiety Disorder

3.1 Comparison between the included and excluded sample

The characteristics of both groups with an ICD-10 diagnosis of COPD are shown in table 4. The two groups FEV1/FVC ratio < 0.7 (included sample) and ≥ 0.7 (excluded sample) do not differ significantly in their level of education, their age and the presence of depressive or anxious symptoms measured with the PHQ-D or PHQ-A, respectively.

There is a statistically significant difference in the gender distribution, with a lower prevalence of females (41.1%) in the included sample compared to the excluded sample (52.2%; $Chi^2 = 23.94$, df = 1, $p < .001$). Furthermore, the smoking status ($Chi^2 = 37.21$, df = 3, p-value < .001) and the occurrence of psychological distress measured with the PHQ-T ($Chi^2 = 4.41$, df = 1, p-value = 0.036) were significantly different between the groups. The included sample only had 5.6% never smokers compared to 12.1% in the other group. In the included sample, more than half of the COPD patients were long-term ex-smokers (51.7%) compared to only 40.9% in the excluded sample. The prevalence of psychological distress, depressive and anxious symptoms was higher among the included sample. As expected – because the group classification was done by the ratio of the FEV1 and the FVC – the groups differ in the severity of the COPD. The mean ± SD FEV1% predicted for the group with a FEV1/FVC ratio < 0.7 is 48.13 ± 16.13 versus 67.88 ± 17.93 for the other group ($F = 1.897$, df = 1978, p-value < .001). Lastly, the symptom assessment measured as the score of the CAT is statistically different with a mean ± SD score of 19.74 ± 8.29 compared to 17.44 ± 8.35 for the included and excluded sample, respectively ($F = 5.32$, df = 1644, p-value < 0.001).

Table 4. Overview of the comparison of the included and excluded sample among all patients with an ICD-10 diagnosis of COPD

	FEV1/FVC ratio[a] < 0.7	FEV1/FVC ratio[a] ≥ 0.7	p-value[b]
	N= 1312	N= 668	
Age, years (mean ± SD)	66.64 ± 9.33	67.13 ± 10.04	> 0.05[b]
Gender			**<0.001**[c]
Female	41.1 (539)	52.2	
Male	58.9 (773)	47.3	
Smoking status			**< 0.001**[c]
Current smoker	31.2 (409)	35.6 (238)	
Recent ex-smoker	7.0 (92)	7.2 (48)	
Long-term ex-smoker	51.7 (678)	40.9 (273)	
Never smoker	5.6 (74)	12.1 (81)	
Psychological distress[d]			**0.036**[c]
PHQ-T ≥ 6	18.4 (241)	14.7 (98)	
PHQ-T < 6	70.4 (923)	74.1 (495)	
Symptoms of depression[e]			> 0.05[c]
PHQ-D ≥ 3	22.3 (293)	19.5 (130)	
PHQ-D < 3	67.3 (883)	70.4 (470)	
Symptoms of anxiety[e]			> 0.05[c]
PHQ-A ≥ 3	20.0 (262)	17.8 (119)	
PHQ-A < 3	69.7 (914)	72.5 (484)	
School degree			> 0.05[c]
None/Low	61.2 (803)	59.9 (400)	
Medium	18.9 (248)	19.6 (131)	
High	11.0 (144)	10.6 (71)	
FEV1% predicted, % (mean ± SD)	48.13 ± 16.13	67.88 ± 17.93	**< 0.001**[b]
CAT score, score (mean ± SD)	20.66 ± 31.54	17.44 ± 8.35	**0.017**[b]

Note. First part of the table: All answers in % and absolute numbers (). Per variable category adds up to ~100.00%, missing values not shown.

Abb. PHQ= Patient Health Questionnaire, GAD= Generalized anxiety disorder, FEV1= forced expiratory volume in one second, CAT= COPD Assessment Test, SD = standard deviation

[a] FEV1/FVC ratio: Ratio of forced expiratory one-second capacity to vital capacity (spirometry)
[b] Based on students t-test
[c] Based on Chi^2 test
[d] Cut-off psychological distress ≥ 6
[e] Cut-off anxious/depressive symptoms ≥ 3

3.1 Descriptive statistics

3.1.1 Sample characteristics

As already described all patients with a FEV1/FVC ratio < 0.7 who completed the PHQ-T were included in the analysis (n= 1164). The sociodemographic characteristics of the included sample are described in Table 5. The sample included 41.8% (n= 486) female patients and 58.2% (n= 678) male. The mean age was 66.2 years (SD= 9.2, range= 31 – 94 years). Almost two-thirds did not have any or had a low level of education (62.4%, n= 726); 20.6% (n= 240) had a medium level of education (secondary school leaving certificate (grade ten)) and just 11.9% (n= 139) achieved a high level of education (general higher education entrance qualification/ high school diploma).

The tobacco smoking status was not specified by 3.1% (n= 36), the rest gave the following answers: 31.2% (n= 363) indicated that they currently smoke tobacco, 7.7% (n= 90) described themselves as recent ex-smokers, 52.6% (n= 612) characterized themselves as long-term ex-smokers and 5.4% (n= 63) answered that they have never smoked tobacco. Within the subgroup of current smokers (n= 363) the level of tobacco dependence was evaluated using the HSI (table 5). For 8.3% (n= 30) of the smokers it was not possible to calculate the HSI because of missing items (figure 5). Almost half (46.6%; n= 170) of the patients showed a low, 36.1% (n= 131) a moderate and 8.8% (n= 32) a high level of addiction.

According to their lung function, most of the participants were in either GOLD II and III (44.1%, n= 513 and 40.8%, n= 475, respectively), only 2.1% (n= 24) had a FEV ≥ 80% predicted which would classify them in GOLD I and 13.1% (n= 152) had a FEV1 <30% predicted which allocates them to GOLD IV. The mean FEV1% predicted is 47.9 ± 15.9 (mean ± SD). The mean CAT score was 19.7 ± 8.2 on a scale from zero to 40, few to many symptoms.

Table 5. Sociodemographic characteristics of the sample and in dependence of the presence of anxious-depressive symptoms

	Total	PHQ-T[a]	PHQ-D[b] (Depressive)	PHQ-A[b] (Anxious)
	N= 1164	20.7% (241)	25.0% (291)	22.3% (260)
Age (years)				
<65	48.6 (566)	24.0 (136)	29.2 (165)	26.5 (150)
65+	51.3(597)	17.6 (105)	21.1 (126)	18.4 (110)
N/A	0.1 (1)			
Sex				
Female	41.8 (486)	21.4 (104)	25.1 (122)	24.3 (118)
Male	58.2 (678)	20.2 (137)	24.9 (171)	20.9 (142)
Smoking status				
Current smoker	31.2 (363)	23.7 (86)	29.8 (108)	25.1 (91)
Recent ex-smoker	7.7 (90)	27.8 (25)	31.1 (28)	31.1 (28)
Long-term ex-smoker	52.6 (612)	17.6 (108)	20.6 (126)	19.0 (116)
Never smoker	5.4 (63)	20.6 (13)	30.2 (19)	22.2 (14)
N/A	3.1 (36)			
School degree				
None/Low	62.4 (726)	20.0 (145)	25.3 (184)	20.8 (151)
Medium	20.6 (240)	23.3 (56)	26.3 (63)	25.8 (62)
High	11.9 (139)	18.0 (25)	20.1 (28)	21.6 (30)
N/A	5.1 (59)			
GOLD Stadia				
GOLD I	2.1 (24)	16.7 (4)	25.0 (6)	8.3 (2)
GOLD II	44.1 (513)	16.6 (85)	19.7 (101)	17.7 (91)
GOLD III	40.8 (475)	24.0 (114)	28.2 (134)	25.7 (122)
GOLD IV	13.1 (152)	25.0 (38)	32.9 (50)	39.6 (45)

Note. All answers in %, absolute numbers in (). Column proportions of total per variable category are added up to ~100.00%

Abbreviations. PHQ= Patient Health Questionnaire, GAD= Generalized anxiety disorder, GOLD= Global Initiative for Obstructive Lung Disease, HSI= Heaviness of smoking index, N/A= No answer

[a] Cut-off psychological distress ≥ 6

[b] Cut-off anxious/depressive symptoms ≥ 3

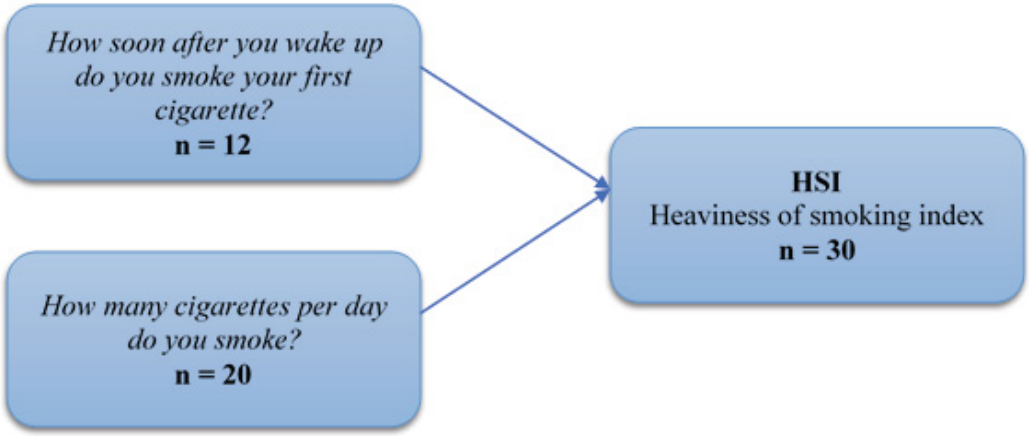

Figure 5. Overview of the missing values for the Heaviness of Smoking Index (n= 363). Given are both questions of the HSI and their number of missings. Moreover, missings for the HSI total are presented. Numbers cannot be added up, as both questions needed to be answered to receive a HSI score in the end

Abb. HSI= Heaviness of smoking index

3.1.2 Anxious-depressive symptoms according to tobacco smoking and level of tobacco dependence

Table 5 shows that 20.7% (n= 241; 95%-CI: 18.4 – 23.2%) of the patients had a PHQ-T score ≥ 6, which indicates psychological distress due to anxious-depressive symptoms. For the subscales (cut-off ≥ 3) the prevalence of depressive symptoms (PHQ-D) was 25.0% (n= 291; 95%-CI: 22.5 – 27.5%) and for anxious symptoms (PHQ-A) 22.3% (n= 260; 95%-CI: 20.0 – 24.7%), respectively (table 5).

For the 148 non-responders of the PHQ-T with a FEV1/FVC ratio < 0.7 a best and worst case analysis was performed, as described in the methods section. Based on a sample size of n= 1312 the prevalence for psychological distress (PHQ-T score ≥ 6) could range from 18.4% (n= 241; 95%-CI: 16.3 – 20.5%) to 29.6% (n= 389; 95%-CI: 27.1% – 32.1%), for depressive symptoms (PHQ-D score ≥ 3) is from 22.3% (n= 293; 95%-CI: 20.0% – 24.6%) to 32.7% (n= 429; 95%-CI: 30.2% – 35.2%) and for anxious symptoms (PHQ-A score ≥ 3) is from 20.0 (n= 262; 95%-CI: 17.8% – 22.2%) to 30.2% (n= 398; 95%-CI: 27.7% – 32.7%) (Figure 6). The total numbers for the best case and the general prevalence for PHQ-D and PHQ-A vary because in the best case analysis all cases were included. Additionally, four cases (two for each subscale) are missing in the sample description as they did not complete the all questions of the PHQ-T but did however complete two questions from one of the subscales two questions of one of the subscales (Figure 4).

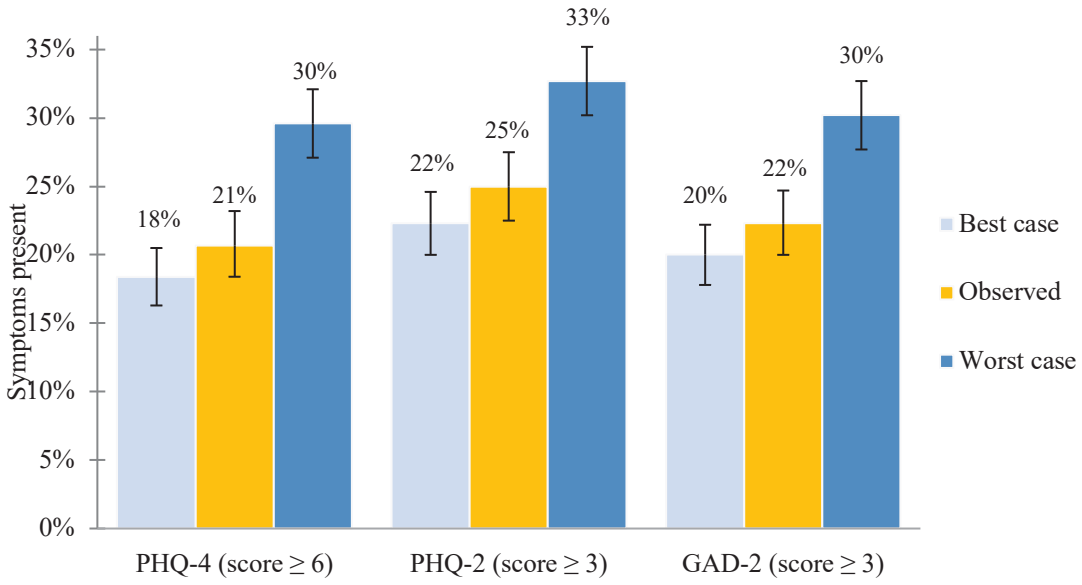

Figure 6. Overview of the prevalence of psychological distress including a best and worst case analysis. Displayed are the observed prevalence (complete cases) of anxious/-depressive symptoms for the sample and the prevalence for the estimated best and worst case (imputed data of the PHQ-T). Data are expressed as rounded mean and error bars show the 95%-confidence interval of the mean.

Abb. PHQ= Patient Health Questionnaire, GAD= Generalized anxiety disorder.

The PHQ-T indicates psychological distress due to the presence of anxious-depressive symptoms for 23.7% (95%-CI: 21.2 – 26.2%; n= 86) of the current smokers, for recent ex-smokers the prevalence was 27.8% (95%-CI: 25.2 – 30.4%; n= 25) and for long-term ex-smokers 17.6% (95%-CI: 15.4 – 19.8%; n= 108). The prevalence for never smokers was 20.6% (95%-CI: 18.2 – 22.9%; n= 13) (Figure 7). Comparable trends can be observed for the two subscales. 29.8% (95%-CI: 27.1 – 32.4%; n= 108) of the current smokers showed depressive symptoms (PHQ-D score ≥ 3). The prevalence of depressive symptoms for recent ex-smokers was 31.1% (95%-CI: 28.4 – 33.8%; n= 28), for the long-term ex-smokers 20.6% (95%-CI: 18.2 – 23.0%; n= 126), and 30.2% (95%-CI: 27.9 – 33.8%; n= 19) for the never smokers (Figure 7). The prevalence of anxious symptoms (PHQ-A score ≥ 3) for the current smokers was 25.1% (95%-CI: 22.6 – 27.6%; n= 91), for recent ex-smokers was 31.1% (95%-CI: 28.4 – 33.8%; n= 28), for the long-term ex-smokers 19.0% (95%-CI: 16-7 – 21.3%; n= 116) and 22.2% (95%-CI: 19.8 – 24.6%; n= 14) for the never smokers (Figure 7).

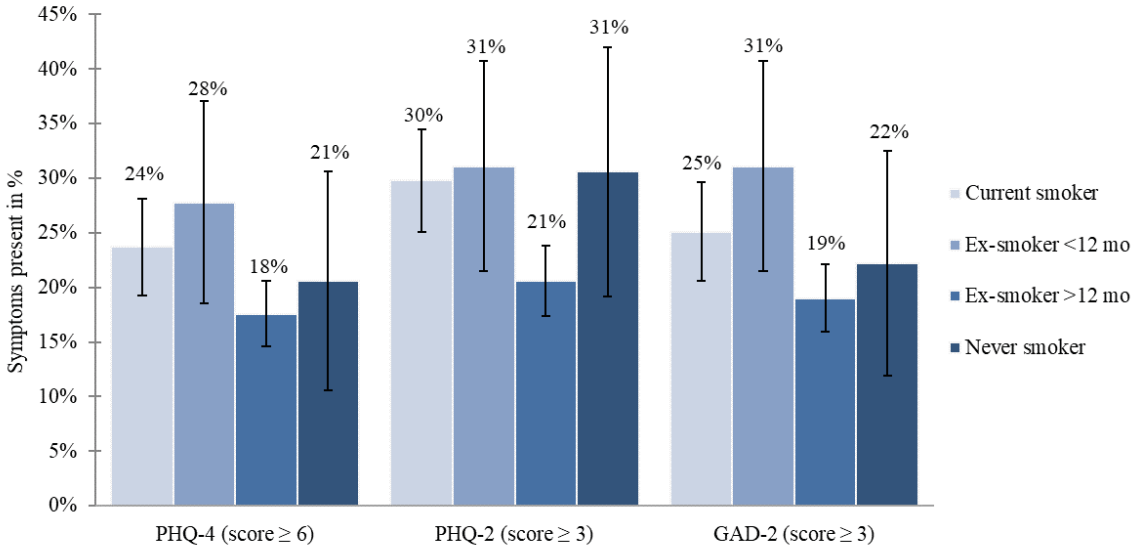

Figure 7. Prevalence of psychological distress according to their smoking status.
All data are based on n= 1128 and are expressed as rounded mean and error bars are the 95%-confidence interval of the mean.
Abb. PHQ= Patient Health Questionnaire, GAD= Generalized anxiety disorder

Table 6 shows the level of tobacco dependence among the subgroup of current smokers and the level of tobacco dependence according to the presence of anxious-depressive symptoms. In the subgroup of current smokers the prevalence of psychological symptoms due to anxious-depressive symptoms was higher among smokers with high tobacco dependence measured with the HSI (table 6). In the group of patients with a low level of dependence (n= 170), 17.1% (n= 29) reported psychological distress, 24.1% (n= 41) showed depressive symptoms and 19.4% (n= 33) showed anxious symptoms. The prevalence for psychological distress, depressive and anxious symptoms among smokers with moderate addiction were 27.5% (n=36), 33.6% (n= 44) and 27.5% (n= 36), respectively. The smokers with the highest level of tobacco dependence also had the highest prevalence of anxious-depressive symptoms on all three scales: 43.8% (n= 14) scored a PHQ-T ≥ 6, 46.9% (n= 15) reached a PHQ-D score ≥ 3 and 40.6% (n= 13) obtained a PHQ-A score ≥ 3.

Table 6. Tobacco dependence characteristics of the subgroup of current smokers and in dependence of the presence of anxious-depressive symptoms

	Total	PHQ-T[a]	PHQ-D[b] (depressive)	PHQ-A[b] (anxious)
HSI[c]	N= 363			
Low	46.6 (170)	17.1 (29)	24.1 (41)	19.4 (33)
Moderate	36.1 (131)	27.5 (36)	33.6 (44)	27.5 (36)
High	8.8 (32)	43.8 (14)	46.9 (15)	40.6 (13)
N/A	8.3 (30)			

Note. All answers in %, absolute numbers in (). Column proportions of total per variable category are added up to ~100.00%

Abbreviations. PHQ= Patient Health Questionnaire, GAD= Generalized anxiety disorder, GOLD= Global Initiative for Obstructive Lung Disease, HSI= Heaviness of smoking index, N/A= No answer

[a] Cut-off psychological distress ≥ 6

[b] Cut-off anxious/depressive symptoms ≥ 3

[c] Heaviness of smoking index (131): Only subgroup of current smokers, addiction score: 0 – 2: low, 3 – 4: moderate, and 5 – 6: high

3.2 Multivariable logistic regression analyses

3.2.1 Association between smoking status and psychological distress

Table 7 shows the association between tobacco smoking status and the presence of psychological distress, depressive and anxious symptoms. This model includes 945 patients and 18.9% had missing data. Adjusted multivariable logistic regression analysis revealed no statistically significant higher risk for current smokers with COPD compared with never smokers in this group of reporting psychological distress (adjusted Odds ratio (aOR) = 1.43, 95%-CI = 0.58 – 3.55). No significant difference in the risk to show depressive (PHQ-D; aOR = 0.96, 95%-CI = 0.43 – 2.16) or anxious (PHQ-A; aOR = 1.07, 95%-CI = 0.46 – 2.46) symptoms could be observed for current smokers when compared with never smokers. The group of recent ex-smokers compared to the never smokers showed the highest odds ratio and thus these patients had a higher risk of reporting psychological symptoms on all three subscales (PHQ-T: aOR= 1.85, 95%-CI 0.67 – 5.11; PHQ-D: aOR = 1.20, 95%-CI = 0.47 – 3.04; PHQ-A: aOR= 1.44, 95%-CI = 0.56 – 3.71).

Table 7. Multivariable logistic regression analysis: Associations between smoking status of patients with CPD and the presence of anxious-depressive, depressive and anxious symptoms

	Model 1[a]		
	PHQ-T[1] (psychological distress) aOR (95%-CI)	**PHQ-D**[2] (depressive) aOR (95%-CI)	**PHQ-A**[3] (anxious) aOR (95%-CI)
Age	0.98 (0.96 – 1.00)	**0.98 (0.96 – 0.99)***	0.98 (0.96 – 1.00)
Sex			
Female	1	1	1
Male	1.17 (0.80 – 1.71)	1.31 (0.92 – 1.86)	0.98 (0.68 – 1.40)
Smoking status			
Never smoker (reference)	1	1	1
Current smoker	1.43 (0.58 – 3.55)	0.96 (0.43- 2.16)	1.07 (0.46 – 2.46)
Recent ex-smoker	1.85 (0.67 – 5.11)	1.20 (0.47 – 3.04)	1.44 (0.56 – 3.71)
Long-term ex-smoker	1.22 (0.51 – 2.93)	0.76 (0.35 – 1.66)	0.92 (0.41 – 2.04)
CAT score	**1.20 (1.16 - 1.24)****	**1.18 (1.15 – 1.22)****	**1.16 (1.13 – 1.19)****
FEV1% predicted	1.01 (0.99 – 1.02)	1.01 (0.99 – 1.02)	1.00 (0.99 – 1.01)
Education			
High (reference)	1	1	1
Moderate	1.00 (0.20 – 1.93)	1.21 (0.65 – 2.56)	0.87 (0.47 – 1.59)
None/Low	0.84 (0.47 – 1.50)	1.19 (0.69 – 2.07)	0.68 (0.40 – 1.15)

Abb. aOR= adjusted Odds Ratio, CAT= COPD assessment test (score 0 – 40, low to high impact due to symptoms), FEV1= Forced expiratory volume in one second, GAD= Generalized anxiety disorder, PHQ= Patient Health Questionnaire, 95%-CI= 95% confidence interval

*p-value <.05, ** p-value < .001

[1]Cox&Snell R^2= 0.21; Nagelkerkes R^2= 0.33; [2]Cox&Snell R^2= 0.22; Nagelkerkes R^2= 0.33;

[3]Cox&Snell R^2= 0.17; Nagelkerkes R^2= 0.27;

[a] adjusted for sex, age, level of education, lung function as the FEV1% predicted and CAT score

The CAT score is significantly associated with all three subscales (Table 7). A one unit increase of the CAT score increases the odds of reporting symptoms of psychological distress by 20% (aOR = 1.20, 95%-CI = 1.16 – 1.24, p-value < .001), the odds of reporting depressive symptoms by 18% (aOR = 1.18, 95%-CI = 1.15 – 1.24, p-value < .001), and the odds of anxious symptoms by 16% (aOR = 1.16, 95%-CI = 1.13 – 1.19, p-value < .001).

3.2.2 Association between level of tobacco dependence and psychological distress

Table 8 shows the association between tobacco dependence and the presence of anxious-depressive, depressive and anxious symptoms in the subgroup of current smokers. This model excluded 24.5% (n= 89) of currently smoking patients. The adjusted multivariable logistic regression analysis revealed that in all three scales (PHQ-T, PHQ-D and PHQ-A) the probability of the presence of corresponding symptoms is associated with the degree of tobacco dependence (table 8).

The results show that a one unit increase of the HSI score increases the odds of anxious-depressive symptoms by 38% (aOR = 1.38, 95%-CI = 1.09 – 1.75, p-value = .007), the odds of depressive symptoms by 33% (aOR = 1.33, 95%-CI = 1.07 – 1.64, p-value = .009), and the odds of anxious symptoms by 29% (aOR = 1.29, 95%-CI = 1.03 – 1.62, p-value = .030).

The influence of the CAT score is stronger than in the first model. A one point increase of the CAT score increases the odds of anxious-depressive symptoms by 23% (aOR = 1.23, 95%-CI = 1.16 – 1.31, p-value < .001), the odds of depressive symptoms by 21% (aOR = 1.21, 95%-CI = 1.14 – 1.27, p-value < .001), and the odds of anxious symptoms by 21% (aOR = 1.21, 95%-CI = 1.15 – 1.29, , p-value < .001).

Table 8. Multivariable logistic regression analysis: Association between tobacco dependence and the presence of anxious-depressive, depressive and anxious symptoms **in the subgroup of current smokers**

	Model 2[a]		
	PHQ-T[1] (psychological distress) aOR (95%-CI)	**PHQ-D**[2] (depression) aOR (95%-CI)	**PHQ-A**[3] (anxiety) aOR (95%-CI)
Age	0.99 (0.96 – 1.04)	1.02 (0.98 – 1.06)	0.99 (0.95 – 1.03)
Sex			
Female	1	1	1
Male	0.83 (0.41 – 1.68)	1.42 (0.74 – 2.72)	0.71 (0.36 – 1.43)
HSI score[b]	**1.38 (1.09 – 1.75)****	**1.33 (1.07 – 1.64)****	**1.29 (1.03 – 1.62)***
CAT score	**1.23 (1.16 – 1.31)*****	**1.21 (1.14 – 1.27)*****	**1.21 (1.15 – 1.29)*****
FEV1% predicted	1.00 (0.98 – 1.03)	0.99 (0.98 – 1.02)	1.00 (0.98 – 1.02)
Education			
High (reference)	1	1	1
Moderate	1.07 (0.33 – 3.44)	1.44 (0.47 – 4.37)	0.79 (0.26 – 2.42)
None/Low	0.66 (0.23 – 1.93)	1.05 (0.39 – 2.85)	0.52 (0.19 – 1.44)

Abb. aOR= adjusted Odds Ratio, CAT= COPD assessment test test (score 0 – 40, low to high impact due to symptoms), FEV1= Forced expiratory volume in one second GAD= Generalized anxiety disorder, PHQ= Patient Health Questionnaire, 95%-CI= 95% confidence interval
*p-value <.05, ** p-value <.01, *** p-value < .001
[1]Cox&Snell R^2 = 0.27, Nagelkerkes R^2= 0.406; [2]Cox&Snell R^2 = 0.27, Nagelkerkes R^2 = 0.384;
[3] Cox&Snell R^2 = 0.26, Nagelkerkes R^2= 0.384

[a] adjusted for sex, age, level of education, lung function as the FEV1% predicted and CAT score
[b] measured by the Heaviness of Smoking Index (131): Only subgroup of current smokers, addiction score: 0 – 2: low, 3 – 4: moderate, and 5 – 6: high

4 Discussion

4.1 Main results

One primary aim of this study was to collect data on the prevalence of psychological distress due to anxious-depressive symptoms in COPD patients and those symptoms according to the tobacco smoking status. At least one in five patients reported experiencing symptoms of psychological distress. Prevalence rates for psychological distress varied from 17.6% (long-term ex-smokers) to 27.8% (recent ex-smokers), for depressive symptoms from 20.6% (long-term ex-smokers) to 31.1% (recent ex-smokers), and for anxious symptoms from 19.0% (long-term ex-smokers) to 31.1% (recent ex-smokers).

The second primary aim was to investigate the association between the presence of psychological distress and the tobacco smoking status adjusted for sociodemographic characteristics, lung function parameter and CAT score. It revealed that neither smokers nor recent or long-term ex-smokers had a higher risk of presenting psychological distress, depressive or anxious symptoms compared to never smokers. However, all three scales the CAT score, representing the severity of symptoms and their impact on the patient's life had the strongest association with psychological distress. Per point increase on the CAT (score 0 – 40), the risk of presenting psychological distress increased by 23%, for depressive or anxious symptoms the increase was 21% per point increase on the CAT. Lastly, younger COPD patients reported more depressive symptoms.

The third aim was to evaluate the association between anxious-depressive symptoms and the level of tobacco dependence among current smokers. Analysis showed that with increasing tobacco dependency the risk for the presence of self-reported symptoms of psychological distress, depression and anxiety increased. Per point increase on the HSI (score 0 – 6) the risk to suffer from psychological distress increased by 38% which means COPD patients with the highest HSI score have an 228% increased risk to report psychological distress compared to COPD patients with a HSI score of zero. For depressive and anxious symptoms the risk increased by 33% and 29% respectively per point increase on the HSI. Again, an increase in the CAT score was strongly associated with a higher risk for the presence of psychological distress, depressive and anxious symptoms.

4.2 Comparison with the literature

In this study, the mean age of the COPD patients was 66.2 years, 58.2% were male and 31.2% were current smokers, the FEV1 47.9% predicted and most patients belonged to GOLD II (44.1%). Those characteristics match with the description of the 'real-life COPD patient' in Germany of a previous longitudinal, prospective non-interventional study within the German COPD National Prospective Registry (31). Of 5924 patients in this study, 60% were male, the mean age of the patients was 65.7 years and 48.6% of them were in GOLD II. However, the percentage of current smokers (38.3%) and patient with a higher FEV1% predicted (61.6%) was slightly higher than in the present sample (31).

4.2.1 Prevalence of smoking and psychological distress among COPD patients

Our finding of 31.2% of the COPD patients to be current smokers is in line with a United Kingdom based patient record study, which found that 31.8% of COPD patients currently smoke (65). The Rotterdam Study, a Dutch prospective population-based cohort study published in 2016 with 1993 participants with COPD diagnosed by spirometry (FEV1/FVC ratio < 0.7), found 41% to be current smokers this number slightly differs from our findings (136). Thus, European studies have varying prevalence rates of current smokers among COPD patients (20, 31, 136). A possible reason is that data collection for the Rotterdam study took place in three waves between 1989 and 2009. Over the last decades, the smoking prevalence in the Dutch general population decreased from 35.7% in 1990 to 27.8% in 2009 and to 22.9% in 2017 (137). It might be assumed that there was also a decrease in smoking prevalence among COPD patients during this time and thus the higher numbers are not currently representative. The prevalence of current smokers among COPD patients is slightly higher than in the general German population (31.2% vs 28.3%) (2). This is in line with findings of the Health Survey of England where they found a prevalence of 34.9% of current smokers among COPD patients, which is high compared to the general population of the United Kingdom which has a 17% prevalence rate of current smokers (3, 20).

The Burden of Burden of Obstructive Lung Disease (BOLD) study, a population-based prevalence study among COPD patients stated the prevalence of never smokers to be 4.3% in men and 2.9% in women in Germany this is comparable to our 5.4% but they only had 683 participants from around Hannover. In their analysis for every participating country

the range of never smokers varies between 2.9% and 11.2% in women and 3.1% and 9.4% in men (24). Overall, countries that are socioeconomically and environmentally comparable to Germany like Norway and Austria had a smaller range (3.8 – 8.6%) and come close to our prevalence of never smokers among COPD patients (24). The Rotterdam study found 16.3% of the COPD patients to be never smokers (136). Variation between the countries could be explained by potential risk factors for COPD, like occupational exposures to (fine) dust (coal mine working) or exposure to biomass fuels (indoor heating and cooking). They were not taken into consideration and might play a bigger role in some of the countries than in others.

In the literature, the prevalence of psychological symptoms among COPD patients varies per study and diagnostic measures used (60, 64-66, 77). We found psychological distress among 20.7% of the patients, divided in depressive and anxious symptoms the prevalence was 25.0% and 22.3% respectively.

The findings for depression are in line with the study by Schneider et al., a United Kingdom based study for the General Practice Research Database, they included 35 722 patients with COPD between 1995 and 2005 (65). Of all the included patients, 23.1% had a medical record of depression in their record (65). This finding is supported by the study by Yohannes et al. They analysed data of a non-interventional, observational, multicentre, 3-year study in patients with COPD, where COPD patients from clinics in 12 countries were evaluated (68). In this study, COPD was confirmed by spirometry and for the assessment of depression, participants completed the Centre for Epidemiologic Studies Depression (CES-D) Scale with 20 items, each with answers on a 4-point Likert scale and a cut-off of ≥16 for diagnosis depression (68). Within this setting, they found a depression prevalence of 24% among COPD patients (68), which is comparable to our finding. Garcia-Olmos et al. found a similar prevalence of depression in their observational cross-sectional study in 2013 in the area of Madrid (60). Participants were recruited by Family Practitioners, data were taken from clinical records, but COPD was not confirmed by spirometry (n=3183). Anxiety/depression was recorded in 20.2% of the clinical records of COPD patients, which is also in line with our findings for these symptoms (60).

A significantly higher prevalence of depression was found in the studies by Ng et al. and Schane et al. The study of Ng et al. conducted a prospective cohort study in 376 hospitalized COPD patients (because of exacerbation) in Singapore (64). COPD diagnosis

was confirmed by spirometry (FEV1/FVC ratio < 0.7), and depression was assessed with the Hospital Anxiety and Depression Scale (HADS) score. The assessment took place during the hospital stay or within two to four weeks after hospital discharge. They found a 44.4% prevalence rate of depression among COPD patients (64). This is in line with Schane et al., they evaluated data of a nationally representative population-based study of subjects age 50 and older and interviews (in person or via telecommunication) were conducted (138). COPD diagnosis was assessed if the patient answered with "yes" to the question: "Has a doctor ever told you that you have a lung disease, such as chronic bronchitis or emphysema?". Depressive symptoms were measured with the CES-D8 scale, a short version of the CES-D (138). 40.4 % of the COPD patients showed depressive symptoms according to CES-D8 (138). Those high numbers should be seen in perspective, as the study of Ng et al. had a relatively small sample size and depressive symptoms were assessed during or right after hospitalization due to an exacerbation of the COPD. This might lead to overestimation of the depression as the overall condition of those patients is worse than in 'normal', non-exacerbated COPD patients and this reflects in the mood (64). Literature shows that increasing the severity of COPD, which is particularly the case during exacerbations, is associated with a higher rate of depressive symptoms (65). There also might be an overestimation of the prevalence in the study of Schane et al. as they used a relatively low cut-off ≥3 for the CES-D8 on the scale ranging from 0 – 24. However, literature already doubts that the cut-off ≥16 is acceptable for screening for depression (139). For the CES-D8 the sensitivity and specificity were 98 and 83%, respectively for a score of 9/24 which is three times higher than the cut-off ≥3 chosen in the study (140). Moreover, they only used self-reported COPD diagnosis and did not verify it by a clinical diagnosis.

The already described DACCORD study asked patients about their comorbidities, which also included a category containing psychiatric disorders. They found a self-reported prevalence of 11% in this category (31). This comparably low prevalence might be due to the fact that self-reported psychiatric disorder requires a diagnosis by a doctor or psychiatrist and that participants are willing to share this obvious fact. Moreover, psychiatric diagnoses usually also include more serious illnesses such as schizophrenia or post-traumatic stress disorder where the prevalence is also much lower. Other studies, like ours, only screen for depressive and anxious symptoms with implying questions, which possible make the topic a little less sensitive as patients are not directly classified as mentally ill.

In academic literature, the presence of psychological distress according to smoking status is not often documented as usually only overall prevalence is given. The few studies providing information on this subject often only compare current smokers with non-smokers, in this second group, never smokers, as well as ex-smokers, were combined. For example, in the Wagena study, they used cross-sectional data from the Maastricht Cohort study, a population-based cohort study among employees in the Netherlands (111). COPD and asthma patients were summarized in one group based on a self-reported diagnosis. The General Health Questionnaire 12 was used to assess psychological distress and one extra question to assess depressed mood (111). They found a prevalence of psychological distress of 28.3% for current smokers among the COPD or asthma patients and 29.3% smokers with a depressed mood (111). Prevalence of psychological distress and depressive mood was much lower among non-smoking COPD patients with 16.8% and 10.4% respectively (111). Those numbers are difficult to compare to our data due to many differences in the study design.

Other literature found higher prevalence of depressive symptoms among smoking COPD patients in comparison to non-smoking COPD patients. For example, Schane et al. stated a prevalence of 48.2%, the possible overestimation was previously explained (138). In their recently published prospective cohort study on smoking COPD patients (n=209) in Saxony and Thuringia Loth et al. noted that 25% of participants had a psychiatric disorder according to their patient record (37). Beyond this, the current psychological status was measured in the context of this study with the initial PHQ-D. Loth et al. found clinically significant depression in 14% of the smoking COPD patients and a mild to severe depression in 44% (37). The difference in prevalence rates of current smokers with depressive symptoms might be explained by differences in the methods of the study. In our study we did not measure did not measure different levels of severity of depression and used an ultra-short form of the PHQ, which misses patients with only mild symptoms of psychological distress. This was supported by a PHQ validation study among COPD patients, where they found that the PHQ-9 classified more patients as depressed as the initial PHQ-D did (141).

Interestingly, we observed that the prevalence of psychological symptoms was higher in recent ex-smokers and never smokers compared to the other categories. One reason might be the relatively small number of patients in these groups, which is represented by the larger confidence intervals (Figure 7). This could have led to a measurement error. Thus, one

unique patient may influence the prevalence more than, for example in the group of current smokers. Another theory explaining the higher prevalence among recent ex-smokers might be that smoking cessation and tobacco withdrawal leads to anhedonia, a worsening of depressive symptoms and even suicidal thoughts in the short-term (112, 142, 143). An explanation might be the finding that withdrawal leads to an increase in the mood-related protein monoamine oxidase-A (142). In contrast, recent ex-smokers stopped smoking due to a more severe stadium of the disease or due to a subjective higher burden of COPD, which is associated with an increased risk for depression (64). Patients in this stage possibly saw smoking cessation as their last resort and thus in this group, the prevalence is higher.

4.2.2 Association between smoking status and psychological distress

In our analysis, we did not find any statistically significant association between smoking status and the presence of psychological distress from anxious-depressive symptoms in the fully adjusted model but a strong association between the COPD symptom assessment and the presence of psychological distress symptoms. This is in line with data from a cross-sectional population-based postal survey study of primary care COPD patients in Scotland in 2004. 110 patients with a COPD diagnosis confirmed by spirometry were included and anxious and depressive symptoms were assessed with the HADS (144). In an adjusted model the study found an association between self-perceived COPD symptoms assessed with the COPD symptom control questionnaire (CCQ) and the presence of depression or anxiety. Patients who reported more severe COPD symptoms had an almost nine times higher risk for depression and an almost nineteen times higher risk for anxiety (144). The primary care setting is similar to our research environment. Anxious and depressive symptoms were assessed with a validated tool like in our study. Moreover, like our study, they did find a significant association between depression or anxiety and smoking status in the adjusted model.

In line with our findings, a Dutch cross-sectional study of 2005 who investigated the association between demographic data, smoking status and depression, measured with the Beck Depression Inventory (cut-off for depression >10) among 147 COPD diagnosed patients (145). Current smoking was associated with depression in the univariate model but in the fully adjusted model (amongst other sociodemographic factors adjusted for gender,

age, lung function, dyspnoea) it did not remain significantly associated with depression (145). The adjustment and results are comparable to our outcomes for the association between smoking status and depression. Furthermore, in this study a significant association was found between an increase in dyspnoea measured with the MRC Dyspnea Index and the presence of depression (OR= 1.8; 95%-CI 1.1 – 2.9) which is conform our results of an association between COPD symptom assessment and the presence of psychological distress, depression, and anxiety (145).

The cross-sectional study in 2008 in the US population of Schane et al., has been previously described (138). In their sample of 1736 patients with a self-reported COPD diagnosis or self-reported COPD they found in contrast to our results a higher risk for current smokers to have depressive symptoms when compared to participants currently not smoking (OR= 1.46; 95%-CI 1.29 – 1.66) (138). In line with our findings, Schane et al., stated the strongest association in the adjusted model between the severity of COPD-related symptoms (dyspnoea and walking distance) and the presence of depression, and an decrease in the presence of depression with an increase in age (138). The statistic model used in their analysis was adjusted for sex, age, education, smoking status, respiratory symptoms and other comorbidities among other variables (138). Limitations of the study by Schane et al., compared to our analysis are that the diagnosis of COPD was self-reported, and the group of non-smokers consisted of both, never and ex-smokers. Moreover, it should be mentioned that their overall prevalence of depression in the study population was high and the scale and cut-off to measure depression is debatable (see before).

Hanania et al. described similar findings as Schane et al. in their observational prospective multicentre study in 2011 (146). Hanania et al. found a higher risk for depressive symptoms measured with the CES-D in current smokers compared to former smokers (146). They only included patients with at least 10 pack-years of smoking, thus light and never smokers were not taken into consideration. In contrast to our analysis, Hanania et al., did not distinguish between recent, long-term ex-smokers or never smokers. Also, the study compared former smokers with current smokers, and thus it is not comparable to our design where we compared the current smokers with never smokers. The study used a large sample and the fully adjusted model contained sex, age, smoking status, quality of life, and chronic cough as confounders. As in the previous studies younger age was significantly associated with depression (OR= 0.81 per one year increase; 95%-CI 0.68 – 0.96), and a strong

association between quality of life assessed with the St. George's Respiratory for COPD patients and depression was revealed (OR 1.30; 95%-CI 1.26 – 1.34) (146).

To our knowledge, the most recent data on the association between smoking status and psychological distress in COPD patients are from a Chinese prospective cohort study among 53 spirometry-confirmed COPD patients (147). Xu et al. collected data in 2015 and 2016. Depression was measured with the Hamilton Depression Rating Scale. In line with our findings they did not find an association between smoking and depression in the multivariate model (147). The study did not assess COPD symptoms but adjusted for the FEV1 in the statistical model. The authors found an association between a lower FEV1 and higher levels of depression (147). Even though the findings are in line with the results of our study, it should be taken into consideration that the study of Xu et al. did not describe smoking status any further, the sample is small and it remains questionable if it is comparable to our population. Additionally, they did not mention the cut-off for depression on the scale they used.

It became clear that research in this field is not broad and most of the studies report data collected more than 10 years ago. Moreover, most of those studies only assess data on depression and even less was found about anxiety. First, our study is in line with the literature, which stated a strong association between COPD symptom assessment and the presence of depression, anxiety and psychological distress. One study indicated that with a CAT score >20, patients do have an increased risk to report depressive and anxious symptoms (148). On the one hand, a possible explanation can be the fact that COPD symptoms like dyspnoea, coughing and lower physical capabilities lead to limitations in general participation in daily life. This promotes depressive and anxious symptoms. Moreover, problems with breathing can trigger feeling of anxiety. On the other hand, it might be possible that depressive patients have an increased symptom perception (149). Second, in our study as well as in other studies a younger age was associated with the presence of depressive symptoms. A possible explanation is that younger patients have a lower threshold for depression as they have not had as much time as older patients to adjust for living with COPD. Receiving a COPD diagnosis could potentially be seen as some kind of shocking/traumatising event which influences mental health. However, this can also be observed in the general population, the lifetime prevalence of depression is highest among 60-69 year olds, and 50-59 year olds have the highest 12-month prevalence of depression

(150). Researchers are still debating the association between smoking status and psychological distress among COPD patients. However, some of the studies in contrast to ours only analysed the univariate relation and neglected potential relevant confounders. Moreover, none of the studies distinguished between recent and long-term ex-smokers, but there seems to be a difference between these groups. As mentioned before, psychological distress seems to be higher in recent ex-smokers compared to long-term ex-smokers (149). Moreover, depressive symptoms seem to improve after at least one year of tobacco abstinence (151). In addition, in some studies, never smokers were analysed together with ex-smokers. In our analysis, we compared current, recent, and long-term ex-smokers with never smokers, thus no assumptions about the comparison between current and ex-smokers can be made. Our finding of no association between psychological distress due to depressive or anxious symptoms and tobacco smoking status may possibly be explained by some kind of selection bias. Smoking is associated with psychological comorbidities in the general population, and smoking is associated with COPD (37-39, 92, 93). Moreover, prevalence of psychological comorbidities is higher among COPD patients (61, 152). COPD itself seems to be a risk factor for lower mood, possibly due to brain changes like white matter microstructural abnormalities (153). Probably due to the high prevalence of psychological distress in this chronically sick patient group the role of smoking is not that important as the presence of psychological distress due to depressive or anxious symptoms.

4.2.3 Association between level of tobacco dependence and psychological distress

Our search for literature about the association between the degree of tobacco dependence and psychological distress in COPD patients revealed that almost no studies are investigating this relation. There is one recent German prospective cohort study which originally investigates smoking cessation in COPD patients which took a subsample of the study to examine smoking behaviour among COPD patients with depressive comorbidity (37). The study assessed tobacco dependence with the Fagerström Test for Cigarette Dependence (FTCD), depressive symptoms with the PHQ-D, Beck Depression Inventory and medical register, and COPD diagnosis according to the GOLD criteria. The study reported a positive significant correlation between the score on the FTCD and depression. Our findings support those results as higher levels of dependence were significantly associated with higher odds of symptoms of psychological distress, depression, and anxiety. In contrast to our study Loth

et al. neither adjusted their analyses for sociodemographic factors nor for symptoms of COPD or lung function (37). Another Romanian study among 60 hospitalized COPD patients assessed depression and anxiety with the HADS and tobacco dependence with the FTCD (154). Their prevalence of depressive (76.7%) and anxious (83.3%) symptoms are rather high. In their bivariate correlation analysis, they did not find an association between heavy smoking and depression or anxiety (154). This study is difficult to compare to ours and has some limitations as the study population is small, includes 86.6% males and only hospitalized patients, and associations were analysed unadjusted for potential relevant confounders.

Since data on degree of tobacco dependence in combination with psychological distress is sparse, we examined academic literature on the association between the degree of tobacco dependence and psychological distress amongst the general population. Even there not much could be found but studies investigating this topic were in line with our findings. One study published in January 2020 of 1086 smoking patients in the area of Wisconsin, US assessed nicotine dependence with the FTCD, anxiety sensitivity with the 18-item Anxiety Sensitivity Index-3, and distress tolerance and nicotine dependence with the Distress Tolerance Scale (155). Schlam et al., found a strong positive correlation between the FTCD and nicotine dependence as well as a strong negative correlation between distress tolerance and nicotine dependence (155). Another study among 2397 US college students (aged 18-25) examined the role of multiple drugs in relation to externalizing versus internalizing (anxiety) factors. Anxiety was measured with the Zung Self-Rating Anxiety Scale scores. Analyses revealed that nicotine dependence was correlated with greater anxiety symptoms ($p = .026$) (156). The German Study on Tobacco Use (DEBRA), a cross-sectional representative household survey assessed psychological distress with the PHQ-T and tobacco dependence with the HSI score in 7291 participants. A multivariable logistic regression model adjusted for age, gender, education, and net household income among all smoking participants found an association between a higher degree of tobacco dependence and the presence of anxious as well as depressive symptoms (157).

Thus, among the general population, literature revealed an association between the degree of tobacco dependence and psychological distress, this is in line with our findings among COPD patients. Thus, even in this special patient cohort where no association between smoking status and psychological distress was found, the degree of tobacco

dependence seems to influence the prevalence of psychological distress, anxious or depressive symptoms. One reason might be the assumption that depressive COPD patients seem to be extremely heavy smokers, who inhale deeper and smoking possibly plays a role in their coping with psychological distress (37). Another explanatory approach is that long-term and heavy smoking leads to a more severe COPD classification with more limitations in daily life due to increased symptoms and this might make the patient more susceptible for psychological distress by depressive or anxious symptoms as their quality of life is impaired. This is supported by our results as in the fully adjusted model COPD symptom assessment remained strongly associated with psychological distress next to the HSI score.

4.3 Strength and limitations

The RESPIRO study delivers current data on prevalence of anxious-depressive symptoms according to the smoking status among COPD patients in North Rhine Westphalia, Germany through self-completed questionnaires. As every study the RESPIRO study has strength and limitations.

As data collection was performed in a pulmonary specialised primary care setting we have a broad patient-collective. In this setting both 'emergency' patients with current symptoms of (respiratory) infection and/or exacerbation as well as routine control patients of the disease management programme of COPD had appointments and were asked to participate. This possibly represents the patient variety of COPD better than only in a hospital and thus emergency setting. In general, our study sample seems to be roughly representative for the German COPD patient. As described before in the discussion the mean age, smoking status and the distribution over the GOLD stadia in our study are comparable with the results of a study on 'real-life' German COPD patients (31).

It is a strength that data collection of the medical data (spirometry results) took place by the study nurse/physician assistant of the pulmonary practices. This is less prone to errors and thus more reliable than patient reported data. Moreover, data of almost every patient are complete and could be traced back in case of mistakes in the data/filling the data in and other questions of the study team like missing values.

A study nurse/physician assistant or the pulmonologist handed out questionnaires in the pulmonary practice. Practice employees have a bond and trustful relation with their patients. This trust might have led to a higher motivation to participate in the study compared

to be asked by an anonymous research assistant. Especially sceptical and anxious patients might be more eager to participate. This might be a reason for the response rate, which was higher than expected. The study design, which enabled patients to take the study material home and then decide about the participation has a positive and a negative site. On the one hand it might lower the threshold of patients to answer more private/personal questions like the PHQ-T honestly as there is no feeling of being judged by someone. Possibly, this reduced the intention to answer as it is seen socially desirable. On the other hand, it remains a self-completed questionnaire which leads to more missing data than for example in a face-to-face interview and it is not clear if patients left the questions blank on purpose or by mistake. Differences between responders and non-responders cannot be identified as no sensitivity analysis could be performed. Such an analysis would provide information on whether the groups differ in terms of socio-demographic factors, smoking status and self-reported COPD symptoms. The group of non-responders may exhibit higher values of tobacco smoking, COPD symptom burden and psychological distress and thus tend to omit the questions belonging to the PHQ-T. Furthermore, multiple imputation was not conducted to deal with missing data of non-responders. We are aware of the disadvantages like falsification of the remaining sample and loss of information through non-responses.

A limitation of the present study is that the PHQ-T is an extremely short screening instrument, which only records symptoms and no clinical diagnoses. PHQ-T distinguishes between conspicuous and inconspicuous symptoms and is not suitable for diagnosing the clinical disorders of depression or anxiety disorders. Following the German guidelines, diagnosis of a depressive disorder and determination of its severity is only possible according to ICD-10 (158). PHQ-T data could be influenced by not asking whether psychoactive substances (psychotropic drugs or illegal substances) were taken that could potentially influence the psychological sensation. Especially as a study stated that in subjects with COPD antidepressants were prescribed more often than to healthy smoking and non-smoking controls (146). Next to medication, we did not collect information on the work environment and other comorbidities of the patients. Information on the work environment could reveal causes or influences on the development of COPD and possibly self-management with the disease and should be taken into consideration in further studies. Also, other comorbidities of the patients could influence the self-management and thus mood and behaviour of the patient.

Additionally, the choice of the reference group 'never smokers' in the logistic regression analysis can be discussed as it is a very small group (5.4%) compared to the rest. This could lead to an information bias as one person with a positive screening for psychological symptoms has a bigger influence on the prevalence in this group than in the other groups (smoker, ex-smoker).

Moreover, we had a high drop-out rate (33.7%) of patients due to the choice of using the FEV1/FVC ratio <0.7 as a criteria to be included in the analyses. However, this enabled us to only include patients who had a reliable COPD diagnosis according to the GOLD guidelines of 2010. Other studies often rely on the diagnosis in the patient record or self-reported data of the patients. The process of patient inclusion for this study is described clearly and the choice to stick to the criteria for diagnosis recommended in the GOLD guidelines makes the patients more comparable in a research setting. We found a statistically significant difference between the two groups with a FEV1/FVC ratio < 0.7 and ≥0.7. The comparison showed significantly more current smokers and fewer long-term ex-smokers in the group with a FEV1/FVC ratio ≥ 0.7, a reason might be the significantly lower CAT score and thus fewer symptoms attributable to COPD thus patients do not experience as many problems and do not see a reason to quit smoking. Last, the prevalence of psychological distress was significantly higher in the group of patients with a FEV1/FVC ratio <0.7 this might also be related to the higher burden of symptoms due to COPD in this group. However, it has to be noted that those were the absolute numbers, not adjusted for potential confounders.

All of the participants received the ICD-10 diagnosis of COPD in their pulmonary practices, although the diagnosis does not does not always correspond to their lung values according to GOLD criteria. Therefore, they had to be excluded from the study retrospectively. This 'misclassification' can have several reasons. First, in practice the classification and diagnosis of COPD is based on symptoms and patient risk profiles and thus patients can receive a diagnosis of COPD without spirometry. There is a relation with the many different COPD phenotypes (159). Second, it is possible that during a first spirometry measurement patients have a relevant obstruction and symptoms and thus are diagnosed with COPD but in a future spirometry, they have an improvement of their pulmonary obstruction as, for example, during their first measurement other factors played a role like an allergy. This might be the case in patients with Asthma-COPD-Overlap

Syndrome (160). Third, the remuneration system of the German health insurance possibly plays a role; pulmonologists only receive appropriate compensation for treating the COPD patients if those patients have an ICD-10 COPD diagnosis. Thus, if patients do have symptoms and need medication but this is not seen in the spirometry results, adequate treatment would not be paid by the health insurance.

Last, it is important to note that due to the study design no etiologic or causal conclusions between COPD, depression and smoking status can be drawn from the available findings.

4.4 Conclusion

The prevalence of psychological distress caused by anxious-depressive symptoms among COPD patients in pulmonary practices in North Rhine-Westphalia, Germany is high: at least one in five patient report symptoms of psychological distress and one in four reports symptoms of depression. These high prevalence rates confirm the importance to screen for and treat, comorbid depression and anxiety in COPD patients. Self-perceived and self-reported health-related quality of life seems to have a stronger association with the presence of psychological distress than the smoking status alone. However, within the subgroup of current smokers, there is a strong association between tobacco dependence and anxious-depressive symptoms. This should be kept in mind by physicians while helping COPD patients to quit tobacco smoking, which is much more difficult in smokers with symptoms of psychological distress.

4.5 Future perspectives

The present results indicate the development and implication of measures that address the problem of tobacco dependence and mental illness in COPD patients. The current German guidelines on smoking cessation in COPD patients recommend regular documentation of the smoking status and motivation of smoking patients to stop smoking (13). The guidelines want the patients to receive medical and psychosocial support. However, the importance of assessing psychological symptoms is not addressed any further.

Lasting smoking cessation is already a great challenge for healthy smokers and many do not succeed without medical support, the success rate of achieving smoking cessation without evidence-based help is only 3 - 5 % (161). Literature showed that smoking cessation is even harder for COPD patients and patients with psychological distress (20, 81, 92, 113). In COPD patients, the relation between depressive symptoms, smoking as self-medication to relieve mental problems and the resulting higher relapse rates possibly makes smoking cessation much more difficult (97). With this in mind, it is questionable why this subject is not addressed in the guidelines any further because literature showed only smoking cessation can slow down the progression of COPD. Our data indicate the importance of addressing psychological symptoms as part of the smoking cessation plan in current smokers, as we found an association between the level of tobacco dependence and the presence of psychological distress. This proves the relevance for more tailored tobacco smoking cessation programmes in smoking COPD patients with mental health problems.

Further research should investigate effective measures to assist smoking COPD with psychological distress in quitting tobacco consumption. It is of high interest to examine the causal relationship of tobacco smoking or tobacco dependence and psychological distress in COPD patients. Additionally, the different success rates of smoking cessation with the current guidelines between smoking COPD patients with and without psychological distress could be assessed. Moreover, special psychological interventions to treat anxious/-depressive symptoms in combination with evidence-based smoking cessation treatment in smoking COPD patients with mental health problems could be investigated.

5 References

1. World Health Organization. WHO report on the global tobacco epidemic, 2017: monitoring tobacco use and prevention policies. Geneva; 2017.
2. Kotz D, Bockmann M, Kastaun S. The Use of Tobacco, E-Cigarettes, and Methods to Quit Smoking in Germany. Dtsch Arztebl Int. 2018;115(14):235-42.
3. Commission E. Special Eurobarometer 458 "Attitudes of Europeans towards tobacco and electronic cigarettes". 2017.
4. Kastaun S, Leve V, Böckmann M, Reddemann O, Kotz D. Brief Advice in Primary Care According to the S3-Clinical Practice Guideline "Screening, Diagnosis and Treatment of Harmful and Addictive Tobacco Use". German Journal of Family Medicine. 2017;93(5):210 - 5.
5. Effertz T. Die Kosten des Rauchens in Deutschland im Jahr 2018 – aktuelle Situation und langfristige Perspektive. Atemwegs- und Lungenkrankheiten. 2019;45(7):307-14.
6. Schaller K, Poetschke-Langer M, Kahnert S, Viarisio V, Heidt C, Schunk S, et al. Tabakatlas Deutschland. Heidelberg: Pabst Science Publishers; 2015.
7. Lampert T, von der Lippe E, Muters S. [Prevalence of smoking in the adult population of Germany: results of the German Health Interview and Examination Survey for Adults (DEGS1)]. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 2013;56(5-6):802-8.
8. Lampert T. [Social determinants of tobacco consumption among adults in Germany]. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 2010;53(2):108-16.
9. DKFZ. Rauchen und soziale Ungleichheit – Konsequenzen für die Tabakkontrollpolitik. Heidelberg; 2004.
10. Statistisches, Bundesamt. Rauchgewohntheiten nach Altersgruppe und Geschlecht. 2019 [12.08.2019]. Available from: https://www.destatis.de/DE/Themen/Gesellschaft-Umwelt/Gesundheit/Gesundheitszustand-Relevantes-Verhalten/Tabellen/liste-rauchverhalten.html.
11. World Health Organization. Addiction to Nicotine. IN: Gender, women, and the tobacco epidemic: WHO Press; 2010. p. 137 - 49.
12. Markou A. Review. Neurobiology of nicotine dependence. Philosophical transactions of the Royal Society of London Series B, Biological sciences. 2008;363(1507):3159-68.
13. Andreas S, Batra A, Behr J, Chenot J-F, Gillissen A, Hering T, et al. Tabakentwöhnung bei COPD: Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF); 2013 [Available from: https://www.awmf.org/uploads/tx_szleitlinien/020-005l_S3_Tabakentwöhnung_bei_COPD_2014-03-abgelaufen.pdf.
14. Balfour DJK. The effects of nicotine on brain neurotransmitter systems. Pharmacology & Therapeutics. 1982;16(2):269-82.
15. Locker AR, Marks MJ, Kamens HM, Klein LC. Exposure to nicotine increases nicotinic acetylcholine receptor density in the reward pathway and binge ethanol consumption in C57BL/6J adolescent female mice. Brain Res Bull. 2016;123:13-22.
16. Piper ME, Schlam TR, Cook JW, Sheffer MA, Smith SS, Loh WY, et al. Tobacco withdrawal components and their relations with cessation success. Psychopharmacology (Berl). 2011;216(4):569-78.

17. Dilling H, Mombour W, Schmidt MH. ICD-10-GM Version 2019, Systematisches Verzeichnis, Internationale statistische Klassifikation der Krankheiten und verwandter Gesundheitsprobleme, 10. Revision. Hogrefe Verlag. 2015.
18. Diagnostic and statistical manual of mental disorders. 4th ed. Washington DC: American Psychiatric Association; 2000.
19. National Center for Chronic Disease P, Health Promotion Office on S, Health. Reports of the Surgeon General. The Health Consequences of Smoking-50 Years of Progress: A Report of the Surgeon General. Atlanta (GA): Centers for Disease Control and Prevention (US); 2014.
20. Shahab L, Jarvis MJ, Britton J, West R. Prevalence, diagnosis and relation to tobacco dependence of chronic obstructive pulmonary disease in a nationally representative population sample. Thorax. 2006;61(12):1043-7.
21. Adeloye D, Chua S, Lee C, Basquill C, Papana A, Theodoratou E, et al. Global and regional estimates of COPD prevalence: Systematic review and meta-analysis. J Glob Health. 2015;5(2):020415.
22. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Global Initiative for Chronic Obstructive Lung Disease 2018 [Available from: https://goldcopd.org/wp-content/uploads/2017/11/GOLD-2018-v6.0-FINAL-revised-20-Nov_WMS.pdf.
23. Lokke A, Lange P, Scharling H, Fabricius P, Vestbo J. Developing COPD: a 25 year follow up study of the general population. Thorax. 2006;61(11):935-9.
24. Buist AS, McBurnie MA, Vollmer WM, Gillespie S, Burney P, Mannino DM, et al. International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. Lancet. 2007;370(9589):741-50.
25. Gingter C, Wilm S, Abholz HH. Is COPD a rare disease? Prevalence and identification rates in smokers aged 40 years and over within general practice in Germany. Fam Pract. 2009;26(1):3-9.
26. Kauhl B, Maier W, Schweikart J, Keste A, Moskwyn M. Who is where at risk for Chronic Obstructive Pulmonary Disease? A spatial epidemiological analysis of health insurance claims for COPD in Northeastern Germany. PloS one. 2018;13(2):e0190865.
27. Aumann I, Prenzler A. Epidemiologie und Kosten der COPD in Deutschland - Eine Literaturrecherche zu Prävalenz, Inzidenz und Krankheitskosten. Der Klinikarzt. 2013;42:168-72.
28. Steppuhn H, Kuhnert R, Scheidt-Nave C. 12-Monats-Prävalenz der bekannten chronisch obstruktiven Lungenerkrankung (COPD) in Deutschland. Journal of Health Monitoring. 2017;2(3):46-54.
29. Prescott E, Bjerg AM, Andersen PK, Lange P, Vestbo J. Gender difference in smoking effects on lung function and risk of hospitalization for COPD: results from a Danish longitudinal population study. European Respiratory Journal. 1997;10(4):822.
30. Chapman KR. Chronic obstructive pulmonary disease: are women more susceptible than men? Clinics in chest medicine. 2004;25(2):331-41.
31. Worth H, Buhl R, Criee CP, Kardos P, Mailander C, Vogelmeier C. The 'real-life' COPD patient in Germany: The DACCORD study. Respir Med. 2016;111:64-71.
32. Soriano JB, Abajobir AA, Abate KH, Abera SF, Agrawal A, Ahmed MB, et al. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. The Lancet Respiratory Medicine. 2017;5(9):691-706.
33. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med. 2006;3(11):e442.

34. Gibson G, Loddenkemper R, Sibille Y, Lundbäck B. The economic burden of lung disease In: Society ER, editor. THE EUROPEAN LUNG white book2013.
35. Rehman AU, Hassali MAA, Muhammad SA, Harun SN, Shah S, Abbas S. The economic burden of chronic obstructive pulmonary disease (COPD) in Europe: results from a systematic review of the literature. Eur J Health Econ. 2019.
36. Wacker ME, Jörres RA, Schulz H, Heinrich J, Karrasch S, Karch A, et al. Direct and indirect costs of COPD and its comorbidities: Results from the German COSYCONET study. Respiratory Medicine. 2016;111:39-46.
37. Loth FG, Zeschke M, Bickhardt J, Heindl T, Mühlig S. Tabakabhängigkeit, Rauchverhalten und Depressivität bei COPD- Patienten: Teilergebnisse einer naturalistischen Studie zur krankheitsspezifischen Tabak- entwöhnung in pneumologischen Facharztpraxen (ATEMM-Studie). SUCHT 2019;65(1):23-33
38. Andreas S, Hering T, Mühlig S, Nowak D, Raupach T, Worth H. Smoking cessation in chronic obstructive pulmonary disease: an effective medical intervention. Deutsches Arzteblatt international. 2009;106(16):276-82.
39. Kamal R, Srivastava AK, Kesavachandran CN. Meta-analysis approach to study the prevalence of chronic obstructive pulmonary disease among current, former and non-smokers. Toxicol Rep. 2015;2:1064-74.
40. Thomsen M, Nordestgaard BG, Vestbo J, Lange P. Characteristics and outcomes of chronic obstructive pulmonary disease in never smokers in Denmark: a prospective population study. The Lancet Respiratory medicine. 2013;1(7):543-50.
41. Decramer M, Janssens W, Miravitlles M. Chronic obstructive pulmonary disease. Lancet. 2012;379(9823):1341-51.
42. Tashkin DP, Celli B, Senn S, Burkhart D, Kesten S, Menjoge S, et al. A 4-Year Trial of Tiotropium in Chronic Obstructive Pulmonary Disease. New England Journal of Medicine. 2008;359(15):1543-54.
43. Fabbri LM, Calverley PMA, Izquierdo-Alonso JL, Bundschuh DS, Brose M, Martinez FJ, et al. Roflumilast in moderate-to-severe chronic obstructive pulmonary disease treated with longacting bronchodilators: two randomised clinical trials. The Lancet. 2009;374(9691):695-703.
44. Macnee W. Pathogenesis of chronic obstructive pulmonary disease. Clinics in chest medicine. 2007;28(3):479-513, v.
45. Hogg JC, McDonough JE, Gosselink JV, Hayashi S. What drives the peripheral lung-remodeling process in chronic obstructive pulmonary disease? Proceedings of the American Thoracic Society. 2009;6(8):668-72.
46. Vogelmeier C, Buhl R, Burghuber O, Criée C-P, Ewig S, Godnic-Cvar J, et al. S2k-Leitlinie zur Diagnostik und Therapie von Patienten mit chronisch obstruktiver Bronchitis und Lungenemphysem (COPD) [Leitlinie]. Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF); 2018 [Available from: https://www.awmf.org/uploads/tx_szleitlinien/020-006l_S2k_COPD_chronisch-obstruktive-Lungenerkrankung_2018-01.pdf.
47. Criée CP, Baur X, Berdel D, Bösch D, Gappa M, Haidl P, et al. Leitlinie zur Spirometrie. Pneumologie. 2015;69(03):147-64.
48. Criée CP, Sorichter S, Smith HJ, Kardos P, Merget R, Heise D, et al. Body plethysmography – Its principles and clinical use. Respiratory Medicine. 2011;105(7):959-71.
49. Peruzza S, Sergi G, Vianello A, Pisent C, Tiozzo F, Manzan A, et al. Chronic obstructive pulmonary disease (COPD) in elderly subjects: impact on functional status and quality of life. Respiratory Medicine. 2003;97(6):612-7.

50. Jones PW. Issues concerning health-related quality of life in COPD. Chest. 1995;107(5 Suppl):187S-93S.
51. Vestbo J, Hurd SS, Agusti AG, Jones PW, Vogelmeier C, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. American journal of respiratory and critical care medicine. 2013;187(4):347-65.
52. Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report. GOLD Executive Summary. American journal of respiratory and critical care medicine. 2017;195(5):557-82.
53. Burge PS, Calverley PMA, Jones PW, Spencer S, Anderson JA, Maslen TK. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. BMJ. 2000;320(7245):1297.
54. Pauwels RA, Löfdahl C-G, Laitinen LA, Schouten JP, Postma DS, Pride NB, et al. Long-Term Treatment with Inhaled Budesonide in Persons with Mild Chronic Obstructive Pulmonary Disease Who Continue Smoking. New England Journal of Medicine. 1999;340(25):1948-53.
55. Calverley PM, Page C, Dal Negro RW, Fontana G, Cazzola M, Cicero AF, et al. Effect of Erdosteine on COPD Exacerbations in COPD Patients with Moderate Airflow Limitation. Int J Chron Obstruct Pulmon Dis. 2019;14:2733-44.
56. Andreas S, Batra A, Behr J, Berck H, Chenot JF, Gillissen A, et al. Guidelines for smoking cessation in patients with COPD issued by the Deutsche Gesellschaft fur Pneumologie und Beatmungsmedizin. Pneumologie. 2008;62(5):255-72.
57. Anthonisen NR. Lessons from the Lung Health Study. Proceedings of the American Thoracic Society. 2004;1(2):143-5.
58. Polednak AP. Trends in Mortality from COPD in Selected U.S. States Differing in Tobacco Control Efforts. COPD: Journal of Chronic Obstructive Pulmonary Disease. 2011;7(1):63-9.
59. Cavailles A, Brinchault-Rabin G, Dixmier A, Goupil F, Gut-Gobert C, Marchand-Adam S, et al. Comorbidities of COPD. Eur Respir Rev. 2013;22(130):454-75.
60. García-Olmos L, Alberquilla Á, Ayala V, García-Sagredo P, Morales L, Carmona M, et al. Comorbidity in patients with chronic obstructive pulmonary disease in family practice: a cross sectional study. BMC Family Practice. 2013;14(1):11.
61. Wagena EJ, Arrindell WA, Wouters EF, van Schayck CP. Are patients with COPD psychologically distressed? The European respiratory journal. 2005;26(2):242-8.
62. van Eerd EA, van Rossem CR, Spigt MG, Wesseling G, van Schayck OC, Kotz D. Do we need tailored smoking cessation interventions for smokers with COPD? A comparative study of smokers with and without COPD regarding factors associated with tobacco smoking. Respiration; international review of thoracic diseases. 2015;90(3):211-9.
63. Hill K, Geist R, Goldstein RS, Lacasse Y. Anxiety and depression in end-stage COPD. The European respiratory journal. 2008;31(3):667-77.
64. Ng TP, Niti M, Tan WC, Cao Z, Ong KC, Eng P. Depressive symptoms and chronic obstructive pulmonary disease: effect on mortality, hospital readmission, symptom burden, functional status, and quality of life. Arch Intern Med. 2007;167(1):60-7.
65. Schneider C, Jick SS, Bothner U, Meier CR. COPD and the risk of depression. Chest. 2010;137(2):341-7.
66. Maurer J, Rebbapragada V, Borson S, Goldstein R, Kunik ME, Yohannes AM, et al. Anxiety and depression in COPD: current understanding, unanswered questions, and research needs. Chest. 2008;134(4 Suppl):43S-56S.

67. Matte DL, Pizzichini MM, Hoepers AT, Diaz AP, Karloh M, Dias M, et al. Prevalence of depression in COPD: A systematic review and meta-analysis of controlled studies. Respir Med. 2016;117:154-61.
68. Yohannes AM, Mullerova H, Hanania NA, Lavoie K, Tal-Singer R, Vestbo J, et al. Long-term Course of Depression Trajectories in Patients With COPD: A 3-Year Follow-up Analysis of the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints Cohort. Chest. 2016;149(4):916-26.
69. von Siemens SM, Jörres RA, Behr J, Alter P, Lutter J, Lucke T, et al. Effect of COPD severity and comorbidities on the result of the PHQ-9 tool for the diagnosis of depression: results from the COSYCONET cohort study. Respiratory research. 2019;20(1):30.
70. Wilson I. Depression in the patient with COPD. International journal of chronic obstructive pulmonary disease. 2006;1(1):61-4.
71. Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. Thorax. 1999;54(7):581.
72. Hajiro T, Nishimura K, Tsukino M, Ikeda A, Oga T. Stages of disease severity and factors that affect the health status of patients with chronic obstructive pulmonary disease. Respiratory Medicine. 2000;94(9):841-6.
73. Smoller JW, Pollack MH, Otto MW, Rosenbaum JF, Kradin RL. Panic anxiety, dyspnea, and respiratory disease. Theoretical and clinical considerations. American journal of respiratory and critical care medicine. 1996;154(1):6-17.
74. Doyle T, Palmer S, Johnson J, Babyak MA, Smith P, Mabe S, et al. Association of anxiety and depression with pulmonary-specific symptoms in chronic obstructive pulmonary disease. Int J Psychiatry Med. 2013;45(2):189-202.
75. Atlantis E, Fahey P, Cochrane B, Smith S. Bidirectional Associations Between Clinically Relevant Depression or Anxiety and COPD: A Systematic Review and Meta-analysis. Chest. 2013;144(3):766-77.
76. Zöckler N, Rief W, Kühl K, Kenn K. COPD-Specific Anxiety and Depressive Symptoms in COPD Patients. Pneumologie. 2012;66:290-6.
77. Hynninen KM, Breitve MH, Wiborg AB, Pallesen S, Nordhus IH. Psychological characteristics of patients with chronic obstructive pulmonary disease: a review. J Psychosom Res. 2005;59(6):429-43.
78. Tselebis A, Pachi A, Ilias I, Kosmas E, Bratis D, Moussas G, et al. Strategies to improve anxiety and depression in patients with COPD: a mental health perspective. Neuropsychiatr Dis Treat. 2016;12:297-328.
79. Bailey PH. The dyspnea-anxiety-dyspnea cycle--COPD patients' stories of breathlessness: "It's scary /when you can't breathe". Qual Health Res. 2004;14(6):760-78.
80. McCathie HCF, Spence SH, Tate RL. Adjustment to chronic obstructive pulmonary disease: the importance of psychological factors. European Respiratory Journal. 2002;19(1):47.
81. Norwood RJ. A review of etiologies of depression in COPD. International journal of chronic obstructive pulmonary disease. 2007;2(4):485-91.
82. Polsky D, Doshi JA, Marcus S, Oslin D, Rothbard A, Thomas N, et al. Long-term Risk for Depressive Symptoms After a Medical Diagnosis. JAMA Internal Medicine. 2005;165(11):1260-6.
83. Felker B, Katon W, Hedrick SC, Rasmussen J, McKnight K, McDonnell MB, et al. The association between depressive symptoms and health status in patients with chronic pulmonary disease. Gen Hosp Psychiatry. 2001;23(2):56-61.

84. Kim HFS, Kunik ME, Molinari VA, Hillman SL, Lalani S, Orengo CA, et al. Functional Impairment in COPD Patients: The Impact of Anxiety and Depression. Psychosomatics. 2000;41(6):465-71.
85. Dahlén I, Janson C. Anxiety and Depression are Related to the Outcome of Emergency Treatment in Patients with Obstructive Pulmonary Disease. Chest. 2002;122(5):1633-7.
86. Almagro P, Calbo E, Ochoa de Echaguïen A, Barreiro B, Quintana S, Heredia JL, et al. Mortality After Hospitalization for COPD. Chest. 2002;121(5):1441-8.
87. Ashutosh K, Haldipur C, Boucher ML. Clinical and Personality Profiles and Survival in Patients With COPD. Chest. 1997;111(1):95-8.
88. Lou P, Chen P, Zhang P, Yu J, Wang Y, Chen N, et al. Effects of smoking, depression, and anxiety on mortality in COPD patients: a prospective study. Respir Care. 2014;59(1):54-61.
89. Yohannes AM, Baldwin RC, Connolly M. Mortality predictors in disabling chronic obstructive pulmonary disease in old age. Age and Ageing. 2002;31(2):137-40.
90. Goldberg RT, Hillberg R, Reinecker L, Goldstein R. Evaluation of patients with severe pulmonary disease before and after pulmonary rehabilitation. Disability and Rehabilitation. 2004;26(11):641-8.
91. de Godoy DV, de Godoy RF. A randomized controlled trial of the effect of psychotherapy on anxiety and depression in chronic obstructive pulmonary disease. Archives of Physical Medicine and Rehabilitation. 2003;84(8):1154-7.
92. Fluharty M, Taylor AE, Grabski M, Munafo MR. The Association of Cigarette Smoking With Depression and Anxiety: A Systematic Review. Nicotine Tob Res. 2017;19(1):3-13.
93. Schmitz N, Kruse J, Kugler J. Disabilities, Quality of Life, and Mental Disorders Associated With Smoking and Nicotine Dependence. American Journal of Psychiatry. 2003;160(9):1670-6.
94. Royal College of Physicians and Royal College of Psychiatrists. Smoking and mental health. Royal College of Psychiatrists Council Report CR178. London:2013.
95. West R, Mohr G, Proudfoot H, Brown J. Top-line findings on smoking in England from the Smoking Toolkit Study: Smoking Toolkit Study; 2019 [updated 09.12.2019. Available from: http://www.smokinginengland.info/sts-documents/.
96. Robert-Koch-Institut. Welche Auswirkungen hat der demografische Wandel auf Gesundheit und Gesundheitsversorgung? : Robert Koch-Institut, Epidemiologie und Gesundheitsberichterstattung; 2015.
97. Mühlig S, Paulick J. Psychische Rauchstoppbarrieren. Der Pneumologe. 2016;13(3):174-80.
98. Munafò MR, Araya R. Cigarette smoking and depression: a question of causation. British Journal of Psychiatry. 2010;196(6):425-6.
99. Practice guideline for the treatment of patients with nicotine dependence. American Psychiatric Association. Am J Psychiatry. 1996;153(10 Suppl):1-31.
100. Markou A, Kosten TR, Koob GF. Neurobiological Similarities in Depression and Drug Dependence: A Self-Medication Hypothesis. Neuropsychopharmacology. 1998;18(3):135-74.
101. Picciotto MR, Caldarone BJ, King SL, Zachariou V. Nicotinic receptors in the brain. Links between molecular biology and behavior. Neuropsychopharmacology. 2000;22(5):451-65.
102. Patton GC, Hibbert M, Rosier MJ, Carlin JB, Caust J, Bowes G. Is smoking associated with depression and anxiety in teenagers? Am J Public Health. 1996;86(2):225-30.

103. Boden JM, Fergusson DM, Horwood LJ. Cigarette smoking and depression: tests of causal linkages using a longitudinal birth cohort. British Journal of Psychiatry. 2010;196(6):440-6.
104. Taylor G, McNeill A, Girling A, Farley A, Lindson-Hawley N, Aveyard P. Change in mental health after smoking cessation: systematic review and meta-analysis. BMJ : British Medical Journal. 2014;348:g1151.
105. Paperwalla KN, Levin TT, Weiner J, Saravay SM. Smoking and depression. Medical Clinics of North America. 2004;88(6):1483-94.
106. Chaiton MO, Cohen JE, O'Loughlin J, Rehm J. A systematic review of longitudinal studies on the association between depression and smoking in adolescents. BMC Public Health. 2009;9:356.
107. Breslau N, Peterson EL, Schultz LR, Chilcoat HD, Andreski P. Major depression and stages of smoking. A longitudinal investigation. Arch Gen Psychiatry. 1998;55(2):161-6.
108. Kendler KS, Neale MC, MacLean CJ, Heath AC, Eaves LJ, Kessler RC. Smoking and Major Depression: A Causal Analysis. Archives of General Psychiatry. 1993;50(1):36-43.
109. Goodwin RD, Lavoie KL, Lemeshow AR, Jenkins E, Brown ES, Fedoronko DA. Depression, anxiety, and COPD: the unexamined role of nicotine dependence. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco. 2012;14(2):176-83.
110. van Manen JG, Bindels PJE, Dekker FW, Ijzermans CJ, van der Zee JS, Schadé E. Risk of depression in patients with chronic obstructive pulmonary disease and its determinants. Thorax. 2002;57(5):412.
111. Wagena EJ, Kant I, Huibers MJ, van Amelsvoort LG, Swaen GM, Wouters EF, et al. Psychological distress and depressed mood in employees with asthma, chronic bronchitis or emphysema: a population-based observational study on prevalence and the relationship with smoking cigarettes. Eur J Epidemiol. 2004;19(2):147-53.
112. Glassman AH, Covey LS, Stetner F, Rivelli S. Smoking cessation and the course of major depression: a follow-up study. The Lancet. 2001;357(9272):1929-32.
113. Jiménez-Ruiz CA, Masa F, Miravitlles M, Gabriel R, Viejo JL, Villasante C, et al. Smoking Characteristics: Differences in Attitudes and Dependence Between Healthy Smokers and Smokers With COPD. Chest. 2001;119(5):1365-70.
114. Wagena EJ, Knipschild PG, Huibers MJ, Wouters EF, van Schayck CP. Efficacy of bupropion and nortriptyline for smoking cessation among people at risk for or with chronic obstructive pulmonary disease. Arch Intern Med. 2005;165(19):2286-92.
115. Yohannes AM, Alexopoulos GS. Depression and anxiety in patients with COPD. European Respiratory Review. 2014;23(133):345.
116. Edwards P, Roberts I, Clarke M, DiGuiseppi C, Pratap S, Wentz R, et al. Increasing response rates to postal questionnaires: systematic review. Bmj. 2002;324(7347):1183.
117. CHURCH AH. ESTIMATING THE EFFECT OF INCENTIVES ON MAIL SURVEY RESPONSE RATES: A META-ANALYSIS. Public Opinion Quarterly. 1993;57(1):62-79.
118. Kotz D, Brown J, West R. 'Real-world' effectiveness of smoking cessation treatments: a population study. Addiction. 2014;109(3):491-9.
119. Kotz D, Brown J, West R. Prospective cohort study of the effectiveness of smoking cessation treatments used in the "real world". Mayo Clinic Proceedings. 2014;89(10):1360-7.

120. Kotz D, Brown J, West R. Prospective cohort study of the effectiveness of varenicline versus nicotine replacement therapy for smoking cessation in the "real world". BMC Public Health. 2014;14(1):1163.
121. Brown J, Beard E, Kotz D, Michie S, West R. Real-world effectiveness of e-cigarettes when used to aid smoking cessation: a cross-sectional population study. Addiction. 2014;109(9):1531-40.
122. Kotz D, Fidler J, West R. Factors associated with the use of aids to cessation in English smokers. Addiction. 2009;104(8):1403-10.
123. Kotz D, Fidler J, West R. Very low rate and light smokers: smoking patterns and cessation-related behaviour in England, 2006–11. Addiction. 2012;107(5):995-1002.
124. Fidler JA, Shahab L, West O, Jarvis MJ, McEwen A, Stapleton JA, et al. 'The smoking toolkit study': a national study of smoking and smoking cessation in England. BMC Public Health. 2011;11:479.
125. Cano-Vindel A, Munoz-Navarro R, Medrano LA, Ruiz-Rodriguez P, Gonzalez-Blanch C, Gomez-Castillo MD, et al. A computerized version of the Patient Health Questionnaire-4 as an ultra-brief screening tool to detect emotional disorders in primary care. J Affect Disord. 2018;234:247-55.
126. Lowe B, Wahl I, Rose M, Spitzer C, Glaesmer H, Wingenfeld K, et al. A 4-item measure of depression and anxiety: validation and standardization of the Patient Health Questionnaire-4 (PHQ-T) in the general population. J Affect Disord. 2010;122(1-2):86-95.
127. Kroenke K, Spitzer RL, Williams JB, Lowe B. An ultra-brief screening scale for anxiety and depression: the PHQ-T. Psychosomatics. 2009;50(6):613-21.
128. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. JAMA. 1999;282(18):1737-44.
129. West R. Feasibility of a national longitudinal study ('The Smoking Toolkit Study') to monitor smoking cessation and attempts at harm reduction in the UK.: Smoking Toolkit Study; 2006 [Available from: www.smokinginengland.info/Ref/stp001.pdf.
130. de Leon J, Diaz FJ, Becona E, Gurpegui M, Jurado D, Gonzalez-Pinto A. Exploring brief measures of nicotine dependence for epidemiological surveys. Addict Behav. 2003;28(8):1481-6.
131. Heatherton TF, Kozlowski LT, Frecker RC, Rickert W, Robinson J. Measuring the heaviness of smoking: using self-reported time to the first cigarette of the day and number of cigarettes smoked per day. Br J Addict. 1989;84(7):791-9.
132. Fagerström K. Determinants of Tobacco Use and Renaming the FTND to the Fagerström Test for Cigarette Dependence. Nicotine & Tobacco Research. 2011;14(1):75-8.
133. Mackay AJ, Donaldson GC, Patel AR, Jones PW, Hurst JR, Wedzicha JA. Usefulness of the Chronic Obstructive Pulmonary Disease Assessment Test to evaluate severity of COPD exacerbations. American journal of respiratory and critical care medicine. 2012;185(11):1218-24.
134. Pinto LM, Gupta N, Tan W, Li PZ, Benedetti A, Jones PW, et al. Derivation of normative data for the COPD assessment test (CAT). Respiratory research. 2014;15:68.
135. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD Assessment Test. European Respiratory Journal. 2009;34(3):648.
136. Terzikhan N, Verhamme KMC, Hofman A, Stricker BH, Brusselle GG, Lahousse L. Prevalence and incidence of COPD in smokers and non-smokers: the Rotterdam Study. European journal of epidemiology. 2016;31(8):785-92.

137. Zantinge E, Plasmans M, van der Wilk E. Trend roken volwassenen Volksgezondheidenzorg.info2019 [Available from: https://www.volksgezondheidenzorg.info/onderwerp/roken/cijfers-context/trends#bron--node-aanvragen-data-voor-wetenschappelijk-onderzoek.
138. Schane RE, Woodruff PG, Dinno A, Covinsky KE, Walter LC. Prevalence and Risk Factors for Depressive Symptoms in Persons with Chronic Obstructive Pulmonary Disease. Journal of General Internal Medicine. 2008;23(11):1757-62.
139. Vilagut G, Forero CG, Barbaglia G, Alonso J. Screening for Depression in the General Population with the Center for Epidemiologic Studies Depression (CES-D): A Systematic Review with Meta-Analysis. PloS one. 2016;11(5):e0155431.
140. Briggs R, Carey D, O'Halloran A, Kenny R, Kennelly DS. Validation of the 8-item Centre for Epidemiological Studies Depression Scale in a cohort of community-dwelling older people: data from The Irish Longitudinal Study on Ageing (TILDA). European Geriatric Medicine. 2018;9.
141. Schuler M, Strohmayer M, Muhlig S, Schwaighofer B, Wittmann M, Faller H, et al. Assessment of depression before and after inpatient rehabilitation in COPD patients: Psychometric properties of the German version of the Patient Health Questionnaire (PHQ-9/PHQ-D). J Affect Disord. 2018;232:268-75.
142. Bacher I, Houle S, Xu X, Zawertailo L, Soliman A, Wilson AA, et al. Monoamine Oxidase A Binding in the Prefrontal and Anterior Cingulate Cortices During Acute Withdrawal From Heavy Cigarette Smoking. Archives of General Psychiatry. 2011;68(8):817-26.
143. Hughes JR, Klemperer EM, Peasley-Miklus C. Possible New Symptoms of Tobacco Withdrawal II: Anhedonia—A Systematic Review. Nicotine & Tobacco Research. 2018;22(1):11-7.
144. Cleland JA, Lee AJ, Hall S. Associations of depression and anxiety with gender, age, health-related quality of life and symptoms in primary care COPD patients. Family Practice. 2007;24(3):217-23.
145. Chavannes NH, Huibers MJH, Schermer TRJ, Hendriks A, van Weel C, Wouters EFM, et al. Associations of depressive symptoms with gender, body mass index and dyspnea in primary care COPD patients. Family Practice. 2005;22(6):604-7.
146. Hanania NA, Mullerova H, Locantore NW, Vestbo J, Watkins ML, Wouters EF, et al. Determinants of depression in the ECLIPSE chronic obstructive pulmonary disease cohort. American journal of respiratory and critical care medicine. 2011;183(5):604-11.
147. Xu K, Li X. Risk Factors for Depression in Patients with Chronic Obstructive Pulmonary Disease. Med Sci Monit. 2018;24:1417-23.
148. Jones PW, Tabberer M, Chen W-H. Creating scenarios of the impact of copd and their relationship to copd assessment test (CAT™) scores. BMC Pulmonary Medicine. 2011;11(1):42.
149. Vögele C, von Leupoldt A. Mental disorders in chronic obstructive pulmonary disease (COPD). Respiratory Medicine. 2008;102(5):764-73.
150. Busch M, Maske U, Ryl L, Schlack R, Hapke U. Prävalenz von depressiver Symptomatik und diagnostizierter Depression bei Erwachsenen in Deutschland. Robert Koch-Institut, Epidemiologie und Gesundheitsberichterstattung; 2013.
151. Stepankova L, Kralikova E, Zvolska K, Pankova A, Ovesna P, Blaha M, et al. Depression and Smoking Cessation: Evidence from a Smoking Cessation Clinic with 1-Year Follow-Up. Ann Behav Med. 2017;51(3):454-63.
152. Härter M, Baumeister H, Reuter K, Wunsch A, Bengel J. Epidemiologie komorbider psychischer Störungen bei Rehabilitanden mit muskuloskelettalen und kardiovaskulären Erkrankungen. Rehabilitation. 2002;41(06):367-74.

153. Spilling CA, Bajaj MK, Burrage DR, Ruickbie S, Thai NJ, Baker EH, et al. Contributions of cardiovascular risk and smoking to chronic obstructive pulmonary disease (COPD)-related changes in brain structure and function. Int J Chron Obstruct Pulmon Dis. 2019;14:1855-66.
154. Pascal OI, Trofor AC, Lotrean LM, Filipeanu D, Trofor L. Depression, anxiety and panic disorders in chronic obstructive pulmonary disease patients: correlations with tobacco use, disease severity and quality of life. Tob Induc Dis. 2017;15:23-.
155. Schlam TR, Baker TB, Smith SS, Cook JW, Piper ME. Anxiety Sensitivity and Distress Tolerance in Smokers: Relations With Tobacco Dependence, Withdrawal, and Quitting Successdagger. Nicotine Tob Res. 2020;22(1):58-65.
156. Bierhoff J, Haardörfer R, Windle M, Berg CJ. Psychological Risk Factors for Alcohol, Cannabis, and Various Tobacco Use among Young Adults: A Longitudinal Analysis. Substance Use & Misuse. 2019;54(8):1365-75.
157. Kastaun S, Scholz EF, Kotz D. Hängt Tabakrauchen mit ängstlich-depressiver Symptomatik zusammen? Ergebnisse einer repräsentativen Befragung der Bevölkerung Deutschlands (DEBRA Studie). Gesundheitswesen. 2019;81(08/09):7D-5.
158. DGPPN., BÄK., KBV., AWMF. S3-Leitlinie/Nationale VersorgungsLeitlinie Unipolare Depression – Kurzfassung. 2017;2(1).
159. Corlateanu A, Mendez Y, Wang Y, Garnica RdJA, Botnaru V, Siafakas N. "Chronic obstructive pulmonary disease and phenotypes: a state-of-the-art.". Pulmonology. 2019.
160. Postma DS, Rabe KF. The Asthma–COPD Overlap Syndrome. New England Journal of Medicine. 2015;373(13):1241-9.
161. Hughes JR, Keely J, Naud S. Shape of the relapse curve and long-term abstinence among untreated smokers. Addiction. 2004;99(1):29-38.

6 Appendix

6.1 WINPNEU newsletter (German)

Figure 8. German WINPNEU Newsletter. A) First page of the newsletter (right) with a general introduction and the return form (left); B) Second and third page of the newsletter with more detailed information about the study (left) and a fact sheet (right)

6.2 Content of the patient envelope

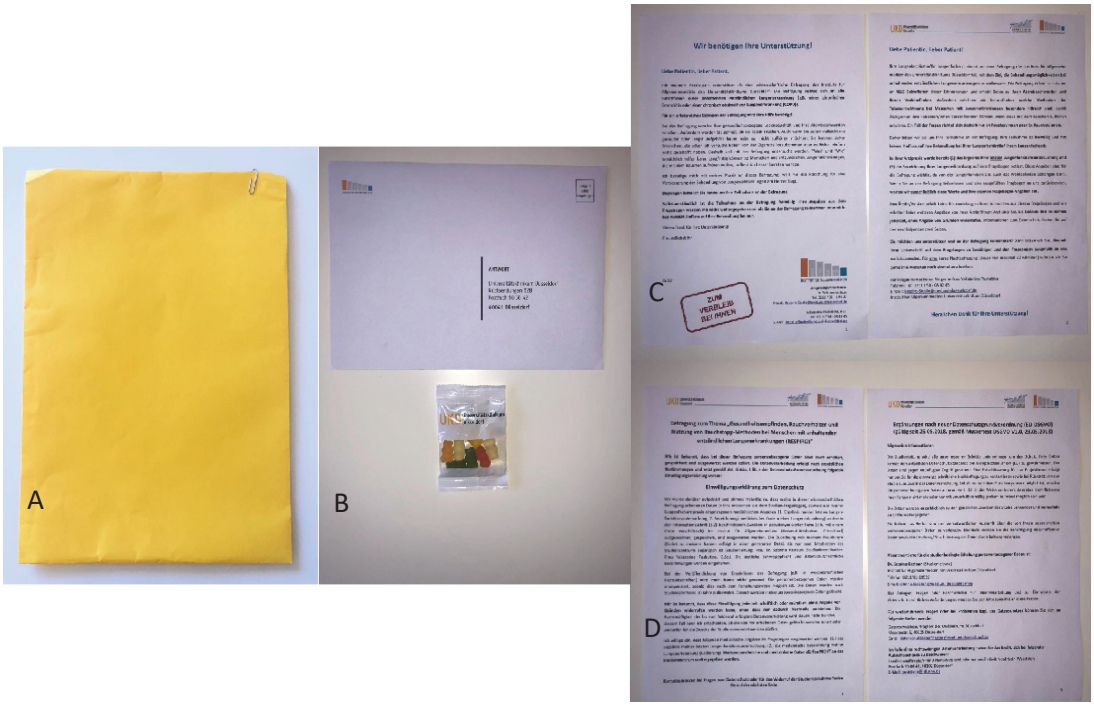

Figure 9. Content of the DIN-A4 envelops handed out by the practice. A) Front of the yellow envelop; B) stamped return envelope and incentive; C) cover letter with information about the RESPIRO study; D) informed consent form/data protection declaration with withdrawal information

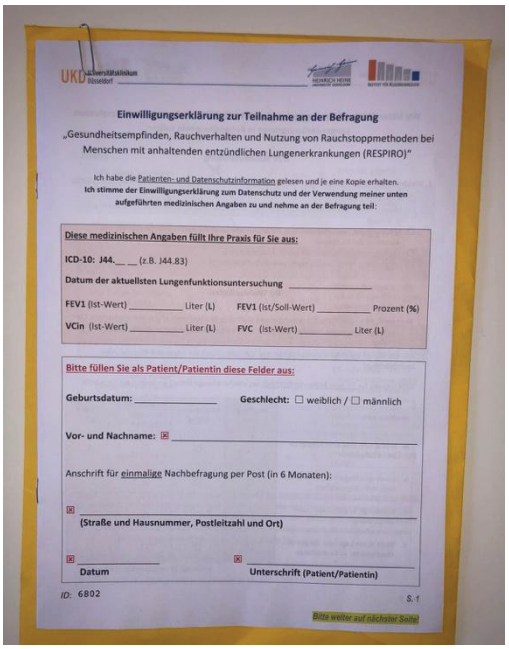

Figure 10. Back of the yellow envelope with baseline questionnaire attached. The baseline questionnaire was attached to the outside of the envelope so medical data could be filled in easier by the contact person of the pulmonary practice

6.3 Baseline questionnaire (translated)

17. Have you ever used an electric cigarette (E-cigarette) or similar product (such as E-shisha, E-cigar or E-pipe)? Please, make only one statement.

- ☐ Yes, and I still use them
- ☐ Yes, I used it regularly but I do not use them anymore
- ☐ Yeah, I tried those once, but I do not use them anymore
- ☐ No, I have never used these ☐ **for you the questionnaire ends here**

18. If you currently smoke tobacco or used to smoke tobacco regularly: Have you noticed any physical changes as a result of switching (fully or partially) from tobacco to e-cigarette? Please indicate the appropriate box for each answer option.

Symptoms	has improved (= fewer complaints)	No changes	has declined (= more complaints)
Cough	☐	☐	☐
Phlegm (mucus)	☐	☐	☐
Chest tightness	☐	☐	☐
Shortness of breath during activity (e. g. stairs)	☐	☐	☐
Difficulties with domestic activities (e.g. vacuum cleaning)	☐	☐	☐
Courage/self-confidence to leave home despite lung problems	☐	☐	☐
Quality of sleep	☐	☐	☐
Energy (efficiency)	☐	☐	☐

Would you like to be informed about the results at the end of the study, in about 1 year?

- ☐ **Yes,**
  - ☐ **per email. My email address is: _____**
  - ☐ **per post**
- ☐ **No**

Declaration of consent to participate in the survey

"**R**eal-world" **E**ffectiveness of **S**moking cessation methods in **P**atients with chronic **o**bstructive pulmonary disease (RESPIRO)'

I have read the patient and data protection information and received a copy each.
I agree to the privacy statement and the use of my medical information listed below and participate in the survey:

Your pulmonary practice will fill in these medical details for you:

ICD-10: J44.__ __ (e.g. J44.83)

Most recent spirometry _____

FEV1 (Ist-Wert) _____ Liters (L) **FEV1** (Ist/Soll-Wert) _____ Percent (%)

VCin (Ist-Wert) _____ Liters (L) **FVC** (Ist-Wert) _____ Liters (L)

Please fill in these fields as a patient:

Date of birth: _____ **Gender:** ☐ female / ☐ male

First and last name: ☒ _____

Address for one-time follow-up survey by mail (in 6 months):

☒ _____
(Address)

☒ _____ **Date** ☒ _____ **Signature (Patient)**

Please continue on next page!

We ask you to fill in the questionnaire only once, even if more than one lung specialist is treating you.

Education

1. What is your highest general school leaving certificate/diploma? Please make only one statement.

- ☐ No diploma
- ☐ Secondary school/elementary school diploma (also polytechnic secondary school with completion of the 8th or 9th grade)
- ☐ Secondary school leaving certificate, technical school leaving certificate (also polytechnic secondary school with completion of 10th grade)
- ☐ Advanced technical college entrance qualification, completion of a technical secondary school
- ☐ High school diploma (general or subject-related higher education entrance qualification)

Health/Well-being

We know that physical illness and mental well-being are closely related. The following questions therefore relate to your general mental well-being

2. Over the last two weeks, how often have you been bothered by the following problems?

For each answer option, please tick which statement currently best applies to you.

Symptoms	Not at all	Several days	More than half of the days	Nearly every day
a. Little interest or pleasure in doing things	☐	☐	☐	☐
b. Feeling down, depressed or hopeless	☐	☐	☐	☐
c. Feeling nervous, anxious or on edge	☐	☐	☐	☐
d. Not being able to stop or control worrying	☐	☐	☐	☐

14. Please, remember your last attempt to quit smoking. Did you first smoke less before you stopped smoking completely?
Please, make only one statement.

- ☐ Smoked less at first
- ☐ Stop smoking immediately and completely, without having to smoke less.

15. Please, remember your last attempt to quit smoking. Which of the following ways did you apply?
Please, make only one statement.

- ☐ I have planned the attempt for a later time of the same day or for a future day
- ☐ I made the attempt the moment I decided to stop smoking.

16. Which of the following methods did you use to support your last attempt of smoking cessation?
Several answers possible.

- ☐ Brief advice from a doctor
- ☐ Brief advice from a pharmacist
- ☐ Behavioural therapy for smoking cessation (for example individual or group therapy)
- ☐ Telephone advice on smoking cessation
- ☐ Nicotine replacement therapy (e.g. nicotine patches) with prescription from a doctor
- ☐ Nicotine replacement therapy (e.g. nicotine patches) without prescription from a doctor
- ☐ Zyban (Bupropion)
- ☐ Champix (Vareniclin)
- ☐ E-cigarette with nicotine
- ☐ E-cigarette without nicotine
- ☐ Tobacco heating system (for example IQOS or heatsticks)
- ☐ App for quitting smoking on a smartphone or tablet PC
- ☐ Smoking cessation website
- ☐ 'Easy way to stop smoking' by Allen Carr (book)
- ☐ Other books about smoking cessation
- ☐ Hypnotherapy
- ☐ Acupuncture
- ☐ Alternative practitioners
- ☐ Own willpower
- ☐ Social environment (family, friends, colleagues)
- ☐ Other, specifically _____

Please continue on next page!

11. How many serious attempts have you made to quit smoking in the last 12 months?

By serious attempt, we mean that you intended to never smoke again. If you have quit successfully in the last year or are currently trying to quit, count this as an attempt.

Number: _____ **quit attempts in the last 12 months**

If you have seriously tried to stop smoking **at least once** in the last 12 months (= if you entered a **number greater than 0 [zero] in question 11**), then please **continue with question no. 12 (below)**

If you have **not tried to quit smoking once** in the last 12 months, please continue **with question no. 17 (page 8)**

12. How long has it been since your last attempt to quit smoking?

Please make only one statement.

- ☐ Last week
- ☐ More than one week
- ☐ More than one month
- ☐ More than two month
- ☐ More than three month
- ☐ More than six month
- ☐ More than twelve month **with question no. 17 (page 8)**

13. How long lasted your last attempt to quit smoking before you started again?

Please, make only one statement.

- ☐ I still do not smoke
- ☐ Less than a day
- ☐ Less than one week
- ☐ Less than one month
- ☐ Less than two month
- ☐ Less than three month
- ☐ Less than six month
- ☐ Less than one year

How do you feel today?

3. For each answer option, please indicate which statement currently best applies to you.

Example I have **no** pain	0	X	2	3	4	5	I have pain **permanently**
I **never** cough	0	1	2	3	4	5	I cough **all the time**
I have **no phlegm** (mucus) on my chest at all	0	1	2	3	4	5	My chest is **full of phlegm** (mucus)
My chest **does not feel tight** at all	0	1	2	3	4	5	My chest feels **very** tight
When I walk up a hill or a flight of stairs I am **not** out of breath	0	1	2	3	4	5	When I walk up a hill or a flight of stairs I am **completely** out of breath
I am **not** limited to doing any activities at home	0	1	2	3	4	5	I am **completely** limited to doing all activities at home
I am **confident** leaving my home despite my lung condition	0	1	2	3	4	5	I am **not confident** leaving my home at all because of my lung condition
I **sleep soundly**	0	1	2	3	4	5	I **do not sleep soundly** because of my lung condition
I have **lots of** energy	0	1	2	3	4	5	I have **no** energy at all

4. Please, think back to the last12 months. How often did you experience **significant worsening of your lung disease within the last 12 months**? By significant worsening, we mean whether you had to be hospitalised or have had an emergency consultation with a doctor because of severe shortness of breath, coughing, sputum or fever, for example, or whether you needed additional medication because of your lung disease (e.g. an antibiotic or cortisone).
   - ☐ None (0) within the last12 month
   - ☐ One (1) within the last12 month
   - ☐ Twice (2) or more (>2) within the last12 months

Please continue on next page!

5. Which of the following conditions applies best to you? Please note that smoking tobacco is meant and not electric cigarettes or tobacco heating systems (IQOS).
Please, make only one statement.

- ☐ I smoke cigarettes daily
- ☐ I smoke cigarettes but not daily
- ☐ I do not smoke cigarettes at all, but tobacco in another form (e.g. pipe or cigar)
- ☐ I have completely stopped smoking within the past 12 months → **continue with question no. 8 (page 5)**
- ☐ I quit smoking completely more than a year ago → **continue with question no. 17 (page 8)**
- ☐ I have never smoked (or at least never for more than a year) → **continue with question no. 17 (page 8)**

Short survey on smoking behaviour

6. On the days that you smoke, how soon after you wake up do you have your first cigarette)?
Please, make only one statement.

- ☐ Within 5 minutes
- ☐ 6-30 minutes
- ☐ 31-60 minutes
- ☐ After 60 minutes

7. Which of the following statements applies to you? Please, make only one statement.

- ☐ I do not want to quit smoking.
- ☐ I should quit smoking, but I do not really want to.
- ☐ I want to quit smoking, but I have not thought about when.
- ☐ I **really want to** quit smoking, but I have not decided when.
- ☐ I want to quit smoking and hope to do so in the near future.
- ☐ I **really want to** quit smoking and intend to do so over the next three months.
- ☐ I **really want to** quit smoking and plan to do so next month.

8. How many filter cigarettes or self-rolled or self-stuffed cigarettes or cigars/pipes do you usually smoke or did you smoke before you stopped smoking?

Indicate the amount per day or, if you are or have been an occasional smoker, per week or month.
Multiple answers possible.

Filter cigarettes:	_____ per day or	_____ per week or	_____ per month
Self-rolled cigarettes:	_____ per day or	_____ per week or	_____ per month
Self-stuffed cigarettes:	_____ per day or	_____ per week or	_____ per month
Cigars:	_____ per day or	_____ per week or	_____ per month
Cigarillos:	_____ per day or	_____ per week or	_____ per month
Pipes:	_____ per day or	_____ per week or	_____ per month

9. How often have you felt the urge to smoke in the past 24 hours?
Please, make only one statement.

- ☐ Not at all → **weiter bei Frage Nr. 11 (Seite 6)**
- ☐ Rarely
- ☐ Sometimes
- ☐ Often
- ☐ Almost all the time
- ☐ All the time

10. How strong was this desire? Please, make only one statement.

- ☐ Low
- ☐ Medium
- ☐ Strong
- ☐ Very strong
- ☐ Extremely strong

Please continue on next page!

7. Danksagung

Ein besonderer Dank gilt meinem Doktorvater Professor Dr. Daniel Kotz. Danke, dass du mir die Möglichkeit gegeben hast mich zu entfalten, mir zugehört und zugesprochen und mich stets motiviert hast. Auch meiner Betreuerin und Projektleiterin Frau Dr. Sabrina Kastaun gebührt ein großer Dank für ihre unermüdliche Unterstützung bei sämtlichen Fragestellungen, ein offenes Ohr und zuletzt auch für ihre Geduld. Ohne eure großartige Betreuung, tatkräftige Unterstützung und konstruktive Kritik hätte ich das so nicht geschafft.

Danken möchte ich auch Herrn Professor Dr. Stefan Wilm, an dessen Institut diese Arbeit angefertigt wurde.

Frau Yekatarina Pashutina danke ich für ihre Unterstützung und ständige Hilfsbereitschaft bei der Datenerhebung und -verarbeitung. Ebenso danke ich meinen ifam-Kolleg*innen für gute, konstruktive Gespräche und die notwendige Aufmunterung im Büro.
Des Weiteren danke ich Herrn Sebastian Böing und allen weiteren kooperierenden Pneumologen, die diese Studie ermöglicht haben.

Für stundenlanges Korrekturlesen meiner Doktorarbeit bedanke ich mich herzlichst bei Julia Mann.

Meinen Eltern danke ich von ganzem Herzen mir all das überhaupt ermöglicht zu haben. Mama, Papa, Peer und Henni, danke für all eure uneingeschränkte Unterstützung, die Aufmunterungen und die Nachsicht, wenn es darum ging, meine Launen zu ertragen. Abschließend Niclas, danke, dass du da bist.