**The German COPD cohort COSYCONET: Aims, methods and descriptive analysis of the study population at baseline**

Karch Aa#, Vogelmeier Cb#, Welte Tc, Bals Rd, Kauczor HUe, Biederer Je, Heinrich Jf, Schulz Hf, Gläser Sg, Holle Rh, Watz Hi, Korn Sj, Adaskina Na, Biertz Fa, Vogel Ca, Vestbo Jk, Wouters El, Rabe Ki, Söhler Sm, Koch Aa\*, Jörres RAn\* for the COSYCONET Study Group.

a Institute for Biostatistics, Hannover Medical School, Carl-Neuberg-Str. 1, 30625 Hannover, Germany

b Department of Respiratory Medicine, University of Marburg, Baldingerstraße, 35043 Marburg, University Giessen and Marburg Lung Center (UGMLC), Member of the German Center for Lung Research, Marburg, Germany

c Clinic for Pneumology, Hannover Medical School, Carl-Neuberg-Str. 1, 30625 Hannover, Member of the German Center for Lung Research, Hannover, Germany

d Department of Internal Medicine V – Pulmonology, Allergology, Respiratory Intensive Care Medicine, Saarland University Hospital, Kirrberger Straße 1, 66424 Homburg, Germany

e Department of Diagnostic and Interventional Radiology, University of Heidelberg, Im Neuenheimer Feld 110, 69120 Heidelberg, Translational Lung Research Center (TLRC), Member of the German Center for Lung Research, Heidelberg, Germany

f Institute of Epidemiology I, Helmholtz Zentrum München - German Research Center for Environmental Health, Member of the German Center for Lung Research, Comprehensive Pneumology Center Munich (CPC-M), Ingolstaedter Landstr. 1, 85764 Neuherberg, Germany

g Department of Internal Medicine B – Cardiology, Intensive Care, Pulmonary Medicine and Infectious Diseases, University Medicine Greifswald, Scientific Division of Pneumology and Pneumological Epidemiology, Ferdinand-Sauerbruch-Strasse, 17475 Greifswald, Germany

h Institute of Health Economics and Health Care Management, Helmholtz Zentrum München (GmbH) - German Research Center for Environmental Health, Member of the German Center for Lung Research, Comprehensive Pneumology Center Munich (CPC-M), Ingolstaedter Landstr. 1, 85764 Neuherberg, Germany

i Pulmonary Research Institute, LungClinic Grosshansdorf, Airway Research Center North, Member of the German Center for Lung Research, Woehrendamm 80, 22927 Grosshansdorf, Germany

j Pulmonary Department, Mainz University Hospital, Langenbeckstrasse 1, 55131 Mainz, Germany

k Respiratory Research Group, Wythenshawe Hospital, Southmoor Road, Manchester, M23 9LT, UK

l Department of Respiratory Medicine, NUTRIM School of Nutrition and Translational Research in Metabolism, University Hospital Maastricht, Universiteitssingel 40, 6229 ER Maastricht, The Netherlands

m ASCONET Study Coordination Office, University of Marburg, Baldingerstraße, 35043 Marburg, Germany

n Institute and Outpatient Clinic for Occupational, Social and Environmental Medicine, Ludwig-Maximilians-Universität München, Ziemssenstr. 1, 80336 Munich, Germany

# Karch A and Vogelmeier C contributed equally.

\* Corresponding authors:

Prof. Dr. Armin Koch, Institute for Biostatistics, Hannover Medical School, Carl-Neuberg-Str. 1, 30625 Hannover, Germany, Phone: +49-511-5324378, Fax: +49-511-5324295, E-mail: koch.armin@mh-hannover.de

PD Dr. Rudolf A. Jörres, Institute and Outpatient Clinic for Occupational, Social and Environmental Medicine, Ludwig-Maximilians-Universität München, Ziemssenstr. 1, 80336 München, Germany, Phone: +49-089-440052466, Fax: +49-089-440053957, E-mail: rudolf.joerres@med.uni-muenchen.de

***ABSTRACT***

*Background*

The German COPD cohort study COSYCONET (COPD SYstemic consequences-COmorbidities NETwork) investigates the interaction of lung disease, comorbidities and systemic inflammation. Recruitment took place between 2010 and 2013 in 31 study centers. In addition to the baseline visit, 4 follow-up visits were/are scheduled at 6, 18, 36 and 54 months after baseline. The study also comprises a biobank, image bank and the collection of data for health economic analyses. Results are compared with those of two large population-based German cohorts (KORA, SHIP). Here we describe the study design of COSYCONET and present data on the baseline characteristics of our COPD cohort.

*Methods*

Inclusion criteria were very broad in order to cover a wide range of patterns of the disease. In each visit, patients undergo a panel of assessments including clinical history, spirometry, body plethysmography and diffusing capacity for carbon monoxide, blood samples, 6-minute walk distance, electrocardiogram, echocardiography, as well as questionnaires covering generic and disease-specific quality of life, depression/anxiety, cognitive impairment, physical activity, risk for osteoporosis and health care utilization. Chest CTs are collected if available and CTs and MRIs are prospectively performed in a subcohort. Data are entered into eCRFs and subjected to several stages of quality control. The study is registered in ClinicalTrials.gov with number NCT01245933.

*Results*

Overall, 2741 subjects with a clinical diagnosis of COPD were included (59% male; mean (±SD) age 65 ± 8.6 years (range 40-90)). Of these, 8/35/32/9% presented with GOLD stages I-IV, respectively; 16% were uncategorized, including the former GOLD 0 category. More than 24% were active smokers, 68% ex-smokers and 8% never-smokers. Data completeness was 96% for the items of the baseline visit.

*Conclusion*

In addition to patients with advanced disease the German COPD cohort comprises a high percentage of less advanced COPD. This seems particularly useful for studying the time course of lung disease and comorbidities in relation to each other. COSYCONET offers the opportunity to investigate these research questions in a large-scale, high-quality dataset.

Supported by BMBF Competence Network Asthma and COPD (ASCONET) and performed in collaboration with the German Center for Lung Research (DZL).

Funding sources: funded by the Federal Ministry of Education and Research (BMBF) with grant number 01 GI 0881; funded by unrestricted grants from GlaxoSmithKline, Novartis Deutschland GmbH, Boehringer Ingelheim/Pfizer, Bayer Schering Pharma AG, Astra Zeneca GmbH, MSD Sharp & Dohme GmbH, Nycomed Deutschland GmbH, Talecris Biotherapeutics, Mundipharma GmbH

**Keywords:** COPD, comorbidity, systemic inflammation, cohort, study design

**Introduction**

With regard to prevalence, mortality and costs, chronic obstructive pulmonary disease (COPD) is one of the most important diseases worldwide [1,2]. Although usually progressive, its clinical course varies considerably between individuals [3,4] and appears to depend on extrapulmonary comorbidities [5–8], such as cardiovascular diseases [9,10], muscle weakness and wasting [11], depression or anxiety [12], osteoporosis [13] and metabolic disorders [14]. The majority of deceased COPD patients did not die directly from their pulmonary disease, but from other conditions [15]. It is not sufficiently known, whether these conditions are independent disorders induced by the same risk factors (e.g. smoking), or whether they are induced and promoted by the lung disease. Systemic inflammation has been suggested to mediate between the lung disorder and other organ manifestations [16] but it is not clarified whether this provides a causative link or predominantly is an epiphenomenon [6,17,18].

The German COPD and systemic consequences-comorbidities network (COSYCONET) started in 2009 as part of the German Asthma and COPD Network (ASCONET). COSYCONET specifically addresses COPD manifestations beyond the lung, aiming to clarify whether extrapulmonary organ involvement depends on COPD severity and conversely, as well as to elucidate the relationship between systemic inflammation and pathologic changes.

This article describes the goals and design of the COSYCONET cohort study and presents a first descriptive analysis of the enrolled study population. The cohort study is registered on ClinicalTrials.gov with identifier NCT01245933 and on GermanCTR.de with identifier DRKS00000284. Further information can be obtained on the website [www.asconet.net](http://www.asconet.net).

Network structure

COSYCONET comprises seven subprojects. The cohort study (subproject 1) is the core of the network, involving the recruitment and long-term follow-up of a National COPD cohort. Within subproject 1, a subcohort is studied regarding sleep disturbances by polysomnography. Subprojects 2 and 3 focus on the comparison of COSYCONET patients with reference populations derived from the two population-based cohorts KORA [19,20] and SHIP [21,22]. These cohorts also allow a comparison of risk factor profiles and of patients with subclinical (GOLD 0) or mild COPD in terms of representativeness in the general population. COSYCONET is supplemented by a biobank (subproject 4), an imaging bank (subproject 5), and health economic analyses (subproject 6). In subproject 7, a subcohort of 600 patients from subproject 1 is prospectively studied with proton magnetic resonance imaging (MRI) for functional and morphological imaging, in comparison to computed tomography (CT) upon inspiration and expiration.

The network is guided by a steering committee and administered in a central coordination office located at the University of Marburg. Data management and statistics are performed at Hannover Medical School. The biobank is located at the University of Saarland in Homburg and the imaging bank at the University of Heidelberg. Further support is provided by a scientific advisory board and a data safety monitoring board, both with annual meetings.

**Materials and Methods**

Study objectives

The primary aim of COSYCONET is to assess the impact of extrapulmonary disorders on the risk for progression of COPD and vice versa. As primary endpoint to define COPD progression, the BODE index [23] was chosen as a validated measure to categorize and predict outcome in COPD. It captures the dimensions Body-mass index, (airflow) Obstruction, Dyspnoea and Exercise capacity. A change in BODE index of one point is considered to be of clinical relevance [24,25].

Secondary aims are

1. to determine the patterns of extrapulmonary disorders in COPD of different severity,

2. to assess the joint impact of extrapulmonary disorders, gender and lifestyle factors on morbidity, risk for progression and mortality in COPD,

3. to investigate whether extrapulmonary disorders are prognostic for the development of COPD by comparison with controls matched from population-based cohorts (KORA and SHIP),

4. to evaluate the relationship between COPD and the development or time course of extrapulmonary disorders and to determine whether there is a typical sequence,

5. to collect data on morphological alterations of the lung by available CT scans of the lung,

6. to evaluate the role of age with respect to the function of the lung and other organs,

7. to assess markers in the blood to evaluate systemic inflammation and organ involvement,

8. to investigate whether the pattern of functional and morphological indices, systemic markers and clinical diagnoses allows to define novel disease phenotypes,

9. to quantify health care utilization and costs induced by comorbidities vs. the lung disorder,

10. to determine sensitivity and specificity of MRI for the assessment of COPD-phenotypes with CT serving as the gold standard.

Study design

COSYCONET is a prospective, observational, multicenter cohort study [26]. After the baseline visit, subjects are evaluated in follow-up visits at 6, 18, 36 and 54 months. The study is currently conducted in 31 study centers all over Germany (Figure 1). Two population-based German cohorts (KORA, SHIP) are used as reference populations providing matched controls. Consistency in questionnaire items and assessments between these cohorts and COSYCONET has been established as far as feasible. COSYCONET complies with the Declaration of Helsinki and Good Clinical Practice Guidelines and has been approved by the ethics committees of the participating centers and by the concerned data security authority. All participants provided written informed consent.

Figure 1: Location of all participating study centers in COSYCONET



Study population

It was planned to include 3.500 patients with a recruitment strategy primarily based on the cooperation with pneumologists and general practitioners who were asked to send patients to the nearby study site. Inclusion criteria were as broad as possible in order to cover a wide spectrum of presentations of COPD. For example, it was allowed to recruit subject without a smoking history and subjects with co-existing asthma.

Patients were enrolled, if the following inclusion criteria were fulfilled:

(i) aged 40 years and older,

(ii) diagnosis of COPD (according to GOLD criteria) or chronic bronchitis,

(iii) availability for repeated study visits over at least 18 months;

and if none of the following exclusion criteria were fulfilled:

(iv) having undergone major lung surgery (e.g. lung volume reduction, lung transplant),

(v) moderate or severe exacerbation within the last 4 weeks,

(vi) having a lung tumor,

(vii) physical or cognitive impairment resulting in an inability to walk or to understand the intention of the project.

Measurements

Patients were/are investigated using a broad panel of assessments (table 1). It was designed to characterize their clinical and functional state in as much detail as possible within a study protocol that was still feasible to be performed within one visit. High priority was given to the assessment of pulmonary function and cardiovascular comorbidities. Moreover, a huge number of comorbidities (>50) were systematically recorded by a structured interview (“Has a medical doctor ever diagnosed the following comorbidity with you?”).

A standard operating procedure (SOP) was issued with a recommended order of the scheduled assessments and tests. Table 1 represents this temporal order. Due to logistic reasons echocardiography and CIMT were/are generally performed as the last assessments and bronchodilator administration directly after blood sampling. Most questionnaires and items for health economics are sent to the patients at home prior to the visits, except for the SGRQ-C (to be completed after bioimpedance analysis) and DemTect (following 6-minute walk test).

All procedures are guided by detailed SOPs that are available through the central office and follow common recommendations, as far as available (see table 1). Patients are instructed to bring their medication to the study site at each visit; additionally medication is evaluated via interview.

The study centers were equipped with identical instruments to assess bioimpedance (Nutribox, Data Input)**,** ECG (ELI 10 electrocardiograph, Mortara Instrument GmbH) and ankle-brachial index (ABI, VascAssist, Isymed). Instruments for lung function testing were not supplied via COSYCONET, but devices were rather homogeneous across study sites, a majority of sites using CareFusion (n=30) and only 3 sites using Ganshorn or ZAN devices (exclusively or additional to CareFusion). Equipment for echocardiography was more heterogeneous: most centers used devices of GE Healthcare, Philips or Siemens (see appendix).

All scheduled assessments were/are performed at all visits except for visit 2 (at 6 months) which was shortened by omitting echocardiography, SGRQ-C, DEMTECT, IPAQ and health economic questions. Some assessments (see lower part of table 1) are only included in the follow-up visits at 36 and/or 54 months. Polysomnography and prospective MRI/CT are performed in sub-populations of the cohort and will be described separately.

COPD severity was determined according to GOLD criteria [27], requiring a post-bronchodilator Tiffeneau-index (FEV1/FVC) below a fixed value of 70% and being categorized according to the predicted FEV1 value. Reference values for FEV1 und FVC were derived using the recent prediction equations from the Global Lung Function Initiative (GLI) [28], those of ITGV from Koch et al. [29], and those for TLCO from Cotes et al. [30] with adjustment for hemoglobin.

Table 1: Scheduled assessments and tests in the COSYCONET cohort study

|  |  |
| --- | --- |
| **Assessment / Test** | **Details** |
| **Demography and exposure** | Basic data, education, profession, previous exposures (smoking, harmful substances/dusts/radiation) |
| **Blood and urine samples** | Panel of samples (systemic inflammation, organ-specific markers, telomeres, genome): 2x whole blood for serum, 2x citrate for plasma, urine; at visit 1: 2x EDTA (DNA analysis), BD P100 for proteomics, PAXgene for gene expression |
| **Clinical history** | Structured interview: comorbidities, familial history, medical support, exacerbations in the last 12 months |
| **Medication** | Drugs currently used, interview for past medication  |
| **Anthropometric data** | Weight, height, waist/hip ratio, upper thighs circumference |
| **Blood gas analysis** | pO2, pCO2, pH, BE; samples from hyperaemic earlobe |
| **Pulmonary function** |  |
|  | Bronchodilator administration | Prior to measurements 400 µg salb. + 80 µg ipratropium bromide brom |
|  | Spirometry | Standard procedures [31,32] |
|  | Body plethysmography | Standard procedures [33,34] |
|  | Lung transfer factor for CO (TLCO) | Single breath-maneuver[35] |
| **Bioimpedance analysis (BIA)** | Resistance & reactance, Fat-free mass index [36] |
| **Cardiology** |  |
|  | ECG at rest  | Supine position, electronic recording and storage  |  |
|  | Ankle-brachial index (ABI) | Ratio of systolic pressures [37] |  |
|  | Echocardiography | Adapted from the German Society for Cardiology  |
|  | Carotid intima-media thickness (CIMT) | Optional; standard procedure |
| **Exercise capacity and functioning** |  |  |
|  | Timed up&go test  | Functionality test for daily life [38] |
|  | 6-minute walk distance (6-MWD) | Standard protocol, Borg scale at beginning and end [39] |
| **COPD-related questionnaires** |  |
|  | Dyspnoea (mMRC) | Modified MRC dyspnoea scale |
|  | Health-specific QoL (SGRQ-C) | COPD-specific version of St. George Respiratory Questionnaire [40] |
|  | COPD Assessment Test (CAT) a) | [41] |
| **Health-related questionnaires** |  |
|  | Generic QoL (EQ-5D) b) | Quality of life measure (5 Items and Visual Analogue Scale) |
|  | Anxiety/depression (PHQ-D) | Patient Health Questionnaire – Depression [42] |
|  | Cognitive impairment (DemTect) | Sensitive to beginning cognitive impairments [43]  |
|  | Osteoporosis (FRAX) | WHO questionnaire, anthropometric OST-score |
|  | Daily physical activity (IPAQ) | International Physical Activity Questionnaire [44] |
| **Health economics** | Medical consultations, hospitalization, rehabilitation, physiotherapy, absent days from work, medical aids |
| **Supply of chest CT** | If available (up to 4 years old). Semi-quantitative, standardized evaluation 🡪 imaging bank |
| Assessments added with the second funding period (performed only at 36 and/or 54 months): |
| **Polyneuropathy** | Rydel-Seiffer tuning fork, monofilament test, symptom score |
| **Sputum and pharyngeal lavage** | Spontaneous sputum if possible, standard microbial analysis |
| **Health economics II** | Disease management |
| **Functional & morphological imaging** | In 14 study centers 🡪 imaging bank |
|  | CT | Inspiration/expiration |
|  | MRI | Dedicated lung protocol |
| **Polysomnography at home** | In 10 study centers |

1. COPD Assessment Test is a trade mark of the GlaxoSmithKline group of companies.©2009 GlaxoSmithKline group of companies. All rights reserved.
2. EQ-5DTM is a trade mark of the EuroQol Group. ©EuroQol Group.

Quality control and assurance

To reduce errors during data capture and ensure standardized data collection across study sites, the following measures were taken:

Extensive plausibility checks and explanatory comments were implemented to the eCRFs. A detailed user manual for data entry and monitoring and SOPs for each medical assessment and questionnaire were provided, combined with regular (at least annual) training of the clinical investigators and data entry users. Calibrations were/are scheduled on a daily basis for spirometric measures and at least every week for body plethysmography and diffusing capacity.

Incoming data was intensively monitored by permanent data quality checks [45] followed by online queries. Periodic monitoring reports were/are issued and sent to the study centers and the coordination office via email: (1) Site-specific reports are prepared on a monthly basis providing support for the organization of study visits (due and overdue patients) as well as for timely eCRF entry and signature. Site-specific problems and open queries are issued in tables. (2) Additionally, site-specific query listings resulting from advanced quality analyses of the data set are sent to the study sites. (3) Quarterly overall quality reports are issued with the number of patients per visit, number and reasons for drop-out, information on completeness and results of benchmark quality analyses where mean values and frequencies of relevant variables are compared across centers. Special emphasis is placed on extensive quality control of lung function and ECG, including for instance visual inspection of spirometric curves performed centrally by a lung function expert, if necessary.

Statistical methods

Sample size estimation was performed prior to the study and targeted at 90% power for detecting associations between a specific risk factor (especially comorbidities) and a one-point increase in BODE scores with an Odds Ratio greater than 1.5. Calculations were done under various assumptions (homogeneity or heterogeneity across GOLD I/II and III/IV strata, different prevalence rates for comorbidities) and resulted for most scenarios in an adequate power (around 80%) for detecting Odds Ratios greater 1.25.

The primary analysis strategy to be applied after the third visit at 18 months is the following: Univariate Odds Ratios will be used to assess the impact of a certain systemic manifestation or risk factor on the risk for progression in an individual patient (defined as an increase of 1 point in the BODE index). Variables identified as prognostic will be included in a logistic regression model that also includes established risk factors (such as age) for the joint assessment of their impact on disease progression. Backward selection will be used to identify a parsimonious model, and sensitivity analyses to further explore the impact of competing variables for the description of a certain systemic manifestation. Besides this, further modelling strategies will be applied (fixed effects modelling with a priori set basic variables). The same approach will be used for mortality and hospitalization data. Cox regression will be used to investigate the joint impact of potential risk factors on time-to-event data.

Results presented in this article provide the cross-sectional, descriptive analysis of the COSYCONET data obtained at baseline. Means and standard deviations are given for numeric variables. For categorical variables, absolute and relative frequencies are presented. Analysis was performed in SAS 9.3. The article does not include results of the population-based cohorts KORA and SHIP. Basic results of these cohorts have been provided in previous publications (e.g. [46–48]) A direct, detailed comparison with COSYCONET data is to be presented in separate papers.

Results

*Recruitment*

A total of 2741 patients were recruited from September 2010 to December 2013 in 31 study centers throughout Germany. After study initiation, a pilot phase of three months duration was conducted in selected study sites, and the study was continued up from January 2011.

Since the original recruitment strategy was not as successful as expected, the mode of recruitment was extended to outpatient clinics, patient groups and organizations and to advertising in local media (figure 2). Considering the study period from July 2011 to recruitment termination, the mean recruitment rate was 85 patients per month. Most of the centers contributed very well to patient recruitment: 25 centers included more than 50 patients, many of them (13 centers) even more than 100 patients, and only one study site recruited less than 10 patients. The most active study center enrolled 259 patients.

Figure 2: Sources of recruitment



*GOLD stages*

Classification into severity stages according to GOLD [27] resulted in 206 / 962 / 874 / 249 patients of stages I-IV, corresponding to 8% / 35% / 32% / 9% of the total study population (figure 3). Expressed in GOLD stages ABCD, which are additionally based on symptoms and risk for exacerbations [27], the distribution is 184 (7%) / 674 (25%) / 104 (4%) / 1320 (48%) for A/B/C/D, respectively. Patients not categorized into GOLD I-IV were not classified into GOLD A-D.

During the early recruitment period, data quality checks revealed a proportion of patients (10-15%) exhibiting a Tiffeneau-index (FEV1 / FVC) above 70% at the baseline visit and thus not fulfilling the inclusion criteria of at least GOLD stage I. Intense discussions of this issue led to the decision to further analyse and follow these patients and to relax the respective inclusion criterion. A major argument was, that the high-dose bronchodilator administration – used to standardize the patients’ condition prior to functional assessments – could have induced an improvement in spirometric lung function that raised these patients above the thresholds used to define COPD stage I. Hence we also recruited patients of the former GOLD category 0 [49,50].

GOLD 0 was defined as having a Tiffeneau-index > 70% and either (i) having a doctor diagnosis of chronic bronchitis and/or (ii) indicating a severity of cough of at least 3 in the respective CAT item and/or (iii) indicating a severity of phlegm of at least 3 in the respective CAT item. A total of 354 patients (13%) were classified as GOLD 0 according to these criteria. Some patients with a Tiffeneau > 70% did not fulfil the conditions for GOLD 0 upon re-examination and formed the group of “GOLD unclassified” (n=77, 3%). For 19 patients, GOLD stages were not assessable due to missing variables for classification. For a comprehensive presentation of results, patients not fulfilling GOLD 0-IV and patients with missing GOLD stage are combined to GOLD “Unclassified” throughout the results section.

Figure 3: Flow-chart of patient inclusion

\*Unclassified means that patients had the diagnosis of COPD but at the time of study inclusion normal lung function and no chronic symptoms of bronchitis.

*Baseline characteristics*

The descriptive results for selected baseline characteristics are shown in table 2. Patients were aged 40-90 years, with a mean age of 65 years. There were more males (59.1%) than females (40.9%). Patients had a mean duration of diagnosed COPD of 7.7 years, with an interquartile range from 3 to 10 years. 24% of individuals enrolled were currently smoking, 68% ex-smokers and 8% never-smokers. Smokers and ex-smokers reported on average 45-50 pack-years. The percentages of
(ex-)smokers as well as the amount of pack-years were lower in the GOLD-0 group and unclassified patients. In general, BMI was high with a mean value of 27 kg/m². BMI and FFMI were reduced in GOLD-IV patients and showed higher values in GOLD-0 and unclassified patients.

*Functional characteristics, comorbidities and medication*

Lung function and further characteristics in the GOLD subgroups are presented in table 3. The spirometric data demonstrated the impairment to be expected owing to the COPD classification. In addition, the rise of ITGV (%predicted: 108/118/139/158) and decline of TLCO (%predicted: 70/58/45/33) over GOLD stages I-IV are visible.

Exercise capacity showed a strong difference between GOLD stages, with 6-minute walk distance decreasing from nearly 500m in GOLD-I to 330m in GOLD-IV. Likewise, the time for the Timed up&go test (overall mean 7 seconds) increased across GOLD stages. GOLD-0 and unclassified patients showed an exercise capacity comparable to GOLD-II/III patients. The same was true for all COPD-related questionnaires: a trend was observable across severity stages and GOLD-0 was basically on the level of GOLD-II. For health-related questionnaires, quality of life decreased (mean EQ-5D from 0.85 falling to 0.74) and depression and anxiety as measured by the PHQ-D increased (from 5.6 to 7.0) with increasing GOLD stages. There were only small differences in mental impairment, the mean value of the DemTect being 15.3. The primary endpoint of this study, the BODE index – having a possible range from 1 to 10 – was on average 2.3, with strong differences between GOLD stages.

Frequencies of selected comorbidities are shown in table 4. Obviously, a number of comorbidities also reflected the advanced age of the study population. Comorbidities were fairly homogeneously distributed over COPD stages; this and their relationship to function will be analyzed in detail in forthcoming papers.

*Data quality*

The overall data quality in terms of completeness and plausibility was/is very high. Overall completeness across all CRFs of the baseline visit was 96%. Most of the missing values were attributable to echocardiography, either because of limitations in single study centers (e.g. in echocardiographic devices) or because of poor sonographic conditions in patients. Leaving echocardiography CRFs out of overall calculation, completeness increases to 98.5%. A large number of plausibility analyses were established during the recruitment phase and were intensified in the data cleaning phase. All queries related to the baseline visit were answered, and procedures were set to handle further implausible patterns becoming apparent in the advanced statistical analysis.

Table 2: Baseline characteristics of the COSYCONET cohort

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Missings**(in total) | **Total**(n=2741) | **GOLD-I**(n=206) | **GOLD-II**(n=962) | **GOLD-III**(n=874) | **GOLD-IV**(n=249) | **GOLD-0**(n=354) | **Unclassified**(n=96) |
| **Demography and exposure** |
| Age (years) | 0 | 65.1 ± 8.6 | 66.2 ± 8.7 | 65.7 ± 8.5 | 65.0± 8.2 | 62.1 ± 7.9 | 64.6 ± 9.7 | 66.7± 9.2 |
| Male sex | 0 | 1619 (59%) | 124 (60%) | 579 (60%) | 533 (61%) | 160 (64%) | 176 (50%) | 47 (49%) |
| Education\* | 18 |  |  |  |  |  |  |  |
|  | High |  | 547 (20%) |  61 (30%) | 206 (22%) | 150 (17%) |  37 (15%) | 70 (20%) |  23 (24%) |
|  | Intermediate |  | 1062 (39%) |  77 (38%) | 384 (40%) | 325 (37%) |  105 (42%) | 141 (41%) |  30 (32%) |
|  | Low |  | 1114 (41%) | 66 (32%) | 366 (38%) | 397 (46%) | 106 (43%) | 137 (39%) |  42 (44%) |
| Full- and part-time employers | 13 | 590 (22%) | 50 (24%) | 228 (24%) | 157 (18%) | 35 (14%) | 93 (26%) | 27 (28%) |
| Smoking | 4 |  |  |  |  |  |  |  |
|  | Current smoker |  | 666 (24%) |  62 (30%) | 277 (29%) | 190 (22%) |  36 (15%) | 86 (24%) | 15 (16%) |
|  | Ex-smoker |  | 1852 (68%) | 129 (63%) | 610 (64%) | 634 (73%) | 199 (80%) | 213 (60%) | 67 (70%) |
|  | Never smoker |  | 219 (8%) |  15 (7%) |  73 (8%) |  49 (6%) |  13 (5%) | 55 (16%) | 14 (15%) |
| Pack-years\*\* | 234\*\* | 47.9 ± 35.7 | 45.1± 31.2 | 51.0± 37.7 | 48.4± 34.9 | 48.1± 33.4 | 40.4 ± 36.2 | 43.2± 32.9 |
| **Clinical history** |
| Years of COPD | 25 | 7.7 ± 7.0 | 7.2 ± 7.1 | 7.5 ± 7.0 | 8.4 ± 7.1 | 8.6 ± 5.7 | 6.7 ± 6.9 | 6.2 ± 7.7 |
| Exacerbations in last 12 months | 1 | 1.3 ± 2.6 | 0.6 ± 1.2 | 1.1 ± 2.5 | 1.6 ± 3.0 | 1.9 ± 2.8 | 1.2 ± 2.7 | 0.5 ± 1.0 |
| **Anthropometric data** |
| Weight | 2 | 79.1 ± 18.1 | 79.0 ± 15.5 | 80.7 ± 17.4 | 77.2 ± 18.4 | 71.3 ± 17.3 | 83.6 ± 18.4 | 84.2 ± 19.5 |
| Height | 0 | 170.7 ± 9.1 | 172.0 ± 8.4 | 171.2 ± 9.1 | 170.5 ± 9.3 | 170.4 ± 8.6 | 169.5 ± 9.3 | 170.3 ± 9.6 |
| BMI (kg/m²) | 2 | 27.0 ± 5.4 | 26.6 ± 4.6 | 27.4 ± 5.1 | 26.4 ± 5.4 | 24.4 ± 5.0 | 29.0 ± 5.8 | 28.8 ± 5.2 |
| **Bioimpedance analysis** |
| FFMI (kg/m²) | 125 | 18.4 ± 2.7  | 18.3 ± 2.2 | 18.6 ± 2.6 | 18.0 ± 2.7 | 16.9 ± 2.6 | 19.5 ± 2.9 | 19.6 ± 2.7 |

\* Education is categorized as follows. Low: ≤8 years of school education, High: at least (vocational) diploma of secondary school or university degree, Intermediate: inbetween low and high;

\*\* Pack-years were computed excluding never smokers

Table 3: Lung function, exercise function and self-rating scales of the COSYCONET cohort at baseline

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Missings**(in total) | **Total**(n=2741) | **GOLD-I**(n=206) | **GOLD-II**(n=962) | **GOLD-III**(n=874) | **GOLD-IV**(n=249) | **GOLD-0**(n=354) | **Unclassified**(n=96) |
| **Pulmonary function** |
| FEV1 (l) | 16 | 1.7 ± 0.7 | 2.6 ± 0.6 | 1.8 ± 0.5 | 1.2 ± 0.3 | 0.7 ± 0.2 | 2.3 ± 0.8 | 2.2 ± 0.7 |
| FEV1 (%predicted) | 16 | 56.9 ± 21.2 | 88.6 ± 8.1 | 62.7 ± 8.3 | 40.7 ± 5.6 | 24.8 ± 3.9 | 80.6 ± 18.8 | 78.1 ± 19.6 |
| FVC (l) | 20 | 3.0 ± 1.0 | 4.1 ± 0.9 | 3.3 ± 0.9 | 2.7 ± 0.8 | 2.1 ± 0.6 | 3.0 ± 1.0 | 2.9 ± 0.9 |
| FVC (%predicted) | 20 | 78.6 ± 19.0 | 106.8 ± 10.8 | 86.3 ± 12.9 | 69.8 ± 13.4 | 52.4 ± 13.0 | 81.0 ± 18.3 | 79.8 ± 17.1 |
| ITGV (%predicted) | 80 | 124.7 ± 33.0 | 108.5 ± 19.6 | 118.5 ± 26.3 | 139.4 ± 32.0 | 157.6 ± 33.7 | 99.6 ± 22.9 | 96.6 ± 26.7 |
| TLCO (%predicted) | 181 | 54.4 ± 21.4 | 70.1 ± 21.2 | 57.7 ± 18.3 | 44.7 ± 17.1 | 32.1 ± 14.3 | 69.6 ± 19.4 | 67.8 ± 23.0 |
| **Exercise capacity and functioning** |
| 6-minute walk distance (metres) | 77 | 419 ± 109 | 487 ± 87 | 443 ± 94 | 391 ± 103 | 329 ± 110 | 441 ± 113 | 421 ± 115 |
| Timed up&go test (seconds) | 72 | 7.0 ± 2.4 | 6.2 ± 2.1 | 6.8 ± 2.3 | 7.1 ± 2.2 | 7.7 ± 2.8 | 7.2 ± 2.6 | 7.4 ± 2.5 |
| **COPD-related questionnaires** |
| mMRC | 23 | 1.6 ± 0.9 | 1.0 ± 0.7 | 1.3 ± 0.8 | 1.9 ± 0.9 | 2.3 ± 0.9 | 1.3 ± 0.9 | 1.2 ± 0.8 |
| SGRQ-c total score | 27 | 42.7 ± 20.0 | 28.0± 15.8 | 38.7 ± 19.1 | 48.6 ± 17.9 | 58.4 ± 18.0 | 39.3 ± 19.7 | 32.1 ± 17.5 |
| CAT | 17 | 18.0 ± 7.3 | 14.2 ± 6.8 | 16.9 ± 7.1 | 19.4 ± 7.2 | 22.1 ± 6.8 | 18.1 ± 7.1 | 13.7 ± 5.9 |
| **Health-related questionnaires** |
| EQ-5D utility score | 16 | 0.82 ± 0.21 | 0.85 ± 0.18 | 0.84 ± 0.19 | 0.81 ± 0.21 | 0.74 ± 0.24 | 0.80 ± 0.23 | 0.84 ± 0.21 |
| PHQ-D score | 34 | 6.3 ± 4.7 | 5.6 ± 4.2 | 6.0 ± 4.5 | 6.5 ± 4.9 | 7.0 ± 5.1 | 7.1 ± 5.0 | 5.3 ± 3.9 |
| DemTect | 44 | 15.3 ± 2.8 | 15.6 ± 2.6 | 15.4 ± 2.6 | 15.2 ± 2.8 | 14.9 ± 3.1 | 15.1 ± 2.8 | 15.4 ± 2.8 |
| **Primary endpoint of COPD impairment** |
| BODE index | 207 | 2.3 ± 2.0 | 0.4 ± 0.7 | 1.3 ± 1.2 | 3.7 ± 1.5 | 5.3 ± 1.6 | 1.0 ± 1.4 | 0.9 ± 1.4 |

Table 4: Prevalences of selected comorbidities and classes of medication at baseline

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Comorbidities** | **Total**(n=2741) |  | **Medication** | **Total**(n=2741) |
| Asthma | 509 | (18.6%) | Rapid-acting Beta-2-agonists | 1076  | (39.3%) |
| Chronic bronchitis | 1710 | (62.4%) | Long-acting Beta-2-agonists | 965  | (35.2%) |
| Sleep apnea | 308 | (11.2%) | Rapid-acting anticholinergics | 125  | ( 4.6%) |
| Hypertension | 1545 | (56.4%) | Long-acting anticholinergics | 1893  | (69.1%) |
| Coronary artery disease | 436 | (15.9%) | Theophylline | 491  | (17.9%) |
| Cardiac infarction | 225 | ( 8.2%) | Inhalative steroids | 479  | (17.5%) |
| Cardiac dysrhythmia | 247 | (16.9%) | Oral steroids | 325  | (11.9%) |
| Heart failure | 148 | (10.1%) | Anticholinergic + Beta-2-agonist | 545  | (19.9%) |
| Stroke | 120 | ( 4.4%) | Bronchodilator + inhalative C.steroids | 1267  | (46.2%) |
| Venous thrombosis | 197 | ( 7.2%) | Cardiovascular medication | 1806  | (65.9%) |
| Gastritis | 692 | (25.3%) |  |  |  |
| GE reflux disease | 414 | (28.3%) | Sum of any taken medication | 17,897 |
| Peptic ulcer | 325 | (11.9%) | Medication per patient (mean ± sd)  | 6.7 (± 3.7) |
| Diabetes with insulin | 143 | ( 5.2%) |  |  |  |
| Diabetes without insulin | 247 | ( 9.0%) |  |  |  |
| Elevated cholesterol level | 1072 | (39.1%) |  |  |  |
| Gout | 465 | (17.0%) |  |  |  |
| Tumor general | 315 | (11.5%) |  |  |  |
| Arthrosis | 1099 | (40.1%) |  |  |  |
| Arthritis | 248 | ( 9.1%) |  |  |  |
| Osteoporosis | 409 | (14.9%) |  |  |  |
| Psychiatric disorders | 583 | (21.3%) |  |  |  |
| Cognitive impairment | 153 | ( 5.6%) |  |  |  |
| Peripheral neuropathy | 178 | ( 6.5%) |  |  |  |
| Allergy overall | 919 | (33.5%) |  |  |  |

Discussion

The COSYCONET cohort is a large national multicenter COPD cohort studied by a comprehensive set of assessments and follow-up visits. It focusses on the time course and relationship between lung disease and comorbidities. The cohort comprises the full spectrum of COPD severities, starting with the former disease category GOLD 0. The assessments include functional tests and questionnaires and have been designed to cover important aspects of COPD and establish comparability with known data. In the majority of patients echocardiographic data are available allowing an in-depth evaluation of cardiac comorbidities in a large, well characterized COPD cohort.

COSYCONET was originally powered with 90% to detect risk factors – especially comorbidities – that lead to an increase in the Odds Ratio greater than 1.5 for relevant BODE worsening. The final sample size (n=2741 at visit 1, n=2000-2200 expected at visit 3) was lower than the initially planned sample size (n=3000 at visit 3) but still provides a power of 70-80% for detecting Odds Ratios greater than 1.5.

Most of the patients were male as expected from the course of smoking habits over time and the duration of smoking needed to develop COPD. Despite this, women already accounted for more than one third of patients. For data analysis this is encouraging because it suggests that we have the statistical power to investigate sex differences in the risk profile of the disease.

The patients’ baseline characteristics regarding functional and questionnaire results were those typically seen in COPD cohorts, suggesting that the cohort is not selected to a degree to be fundamentally different from other cohorts. This is not a trivial issue since the very broad inclusion criteria could have resulted in the inclusion of many “untypical” patients who would have been excluded in other studies. This comparability also offers possibilities for pooling COSYCONET data with those from other large cohorts for the purpose of clustering of phenotypes or checking the robustness of relationships between disease characteristics. The patterns of comorbidities as well as their relationship to functional measures, questionnaire data and medication will be analyzed in detail in forthcoming papers.

Only a minority of patients had stage IV disease. The most likely explanation is that many of these patients are handicapped to a degree that they were not capable of performing the assessments. It is clear that the study protocol is demanding, although – given enough time – in the experience of most investigators it was manageable even for patients of GOLD stage IV. Despite this, at the end of the recruitment period these patients were underrepresented. With regard to the aim of the study, we do not consider this as a major disadvantage. These patients have reached the final stage of the disease which suggests that the chance to gain additional insights regarding the development of comorbidities is limited. Probably clinical questions regarding stage IV patients are better answered in specific studies. Nonetheless, patients of this stage are important in the cohort in order to complete the spectrum of the disease. In addition, some patients of lower stages are expected to progress into stage IV; therefore, this group will not necessarily become much smaller over time despite its excess mortality.

In contrast, there could be reason to be concerned in view of the small proportion of patients of stage I, as these patients seem to be the primary candidates for a long-term follow-up aiming to assess the course of COPD and comorbidities. First, it is known that many early stage patients cope with their functional limitations without consulting a physician. A second factor appears to be that the high-dose bronchodilator administration that we used to standardize the patients’ condition prior to functional assessments, may have raised these patients above the thresholds used to define COPD stage I. Prior to this medication patients might have been of stage I, despite having taken their regular medication, but afterwards no more. Since most of the patients also reported respiratory symptoms such as cough and phlegm, they were classified into the former category of COPD stage 0, which was defined by chronic symptoms without significant airflow limitation, or a previous doctor diagnosis of COPD.

These circumstances have enabled us to recruit about 350 patients of stage GOLD 0. Discussions about the usefulness of defining a GOLD 0 “at risk” stage were held in the past [51–53] and stage 0 has been excluded from GOLD strategy reports in 2006 [54]. Conversely, studies suggested that subjects of the stage 0 are at risk for developing COPD and comorbidities and for experiencing increased mortality [55]. We thus included these subjects in a controlled manner, requiring chronic symptoms of cough and phlegm as required by the former GOLD criteria. In concordance with the former GOLD definition we did not demand a smoking history.

Conclusions

To our knowledge this is the first large COPD cohort that has a focus on lung and comorbidities with a long-term follow-up concept. Recruitment resulted in 2741 patients of all COPD severity stages, for whom data of a large panel of assessments was collected in very high data quality. The follow-up is ongoing. We expect first results on the relationship between disease characteristics after the 18-month follow-up visit and additional insight from the further visits extending up to (at least) 54 months after inclusion.

References

[1] GBD 2013 Mortality and Causes of Death Collaborators. Global , regional and national levels of age-specific mortality and 240 causes of death , 1990-2013 : A systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015. doi:10.1016/S0140-6736(14)61682-2.

[2] Mannino DM, Higuchi K, Yu T-C, Zhou H, Li Y, Tian H, et al. Economic Burden of Chronic Obstructive Pulmonary Disease by Presence of Comorbidities. Chest 2015. doi:10.1007/s00246-002-9361-x.

[3] Vestbo J, Edwards LD, Scanlon PD, Yates JC, Agusti A, Bakke P, et al. Changes in Forced Expiratory Volume in 1 Second over Time in COPD. N Engl J Med 2011;365:1184–92. doi:10.1056/NEJMoa1105482.

[4] Agusti A, Calverley PM a, Celli B, Coxson HO, Edwards LD, Lomas D a, et al. Characterisation of COPD heterogeneity in the ECLIPSE cohort. Respir Res 2010;11:122. doi:10.1186/1465-9921-11-122.

[5] Gershon A, Mecredy G. Quantifying comorbidity in individuals with chronic obstructive pulmonary disease: a population study. Eur … 2014:1–9. doi:10.1183/09031936.00061414.

[6] Vanfleteren LEGW, Spruit M a., Groenen M, Gaffron S, Van Empel VPM, Bruijnzeel PLB, et al. Clusters of comorbidities based on validated objective measurements and systemic inflammation in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2013;187:728–35. doi:10.1164/rccm.201209-1665OC.

[7] Smith MC, Wrobel JP. Epidemiology and clinical impact of major comorbidities in patients with COPD. Int J COPD 2014;9:871–88.

[8] Cavaillès A, Brinchault-Rabin G, Dixmier A, Goupil F, Gut-Gobert C, Marchand-Adam S, et al. Comorbidities of COPD. Eur Respir Rev 2013;22:454–75. doi:10.1183/09059180.00008612.

[9] Anthonisen NR, Skeans MA, Wise RA, Manfreda J, Kanner RE, Connett JE, et al. The effects of a smoking cessation intervention on 14.5-year mortality. Ann Intern Med 2005;142:234–9.

[10] Calverley PMA, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med 2007;356:775–89. doi:10.1056/NEJMoa063070.

[11] Vestbo J, Prescott E, Almdal T, Dahl M, Nordestgaard BG, Andersen T, et al. Body Mass, Fat Free Body Mass and Prognosis in COPD Patients from a Random Population Sample. Am J Respir Crit Care Med 2005;173:79–83. doi:10.1164/rccm.200506-969OC.

[12] Ng T, Mathew N, Tan W, Cao Z, Ong K, Eng P. Depressive Symptoms and Chronic Obstructive Pulmonary Disease. Arch Intern Med 2007;167:60–7. doi:10.1001/archinte.167.1.60.

[13] Sarkar M, Bhardwaj R, Madabhavi I, Khatana J. Osteoporosis in chronic obstructive pulmonary disease. Clin Med Insights Circ Respir Pulm Med 2015;9:5–21. doi:10.1183/09031936.03.00004609.

[14] Mirrakhimov AE. Chronic obstructive pulmonary disease and glucose metabolism: a bitter sweet symphony. Cardiovasc Diabetol 2012;11:132. doi:10.1186/1475-2840-11-132.

[15] Rabe KF, Wedzicha J a. Controversies in treatment of chronic obstructive pulmonary disease. Lancet 2011;378:1038–47. doi:10.1016/S0140-6736(11)61295-6.

[16] Barnes PJ, Celli BR. Systemic manifestations and comorbidities of COPD. Eur Respir J 2009;33:1165–85. doi:10.1183/09031936.00128008.

[17] Magnussen H, Watz H. Systemic inflammation in chronic obstructive pulmonary disease and asthma: relation with comorbidities. Proc Am Thorac Soc 2009;6:648–51. doi:10.1513/pats.200906-053DP.

[18] Vogelmeier CF, Wouters EFM. Treating the systemic effects of chronic obstructive pulmonary disease. Proc Am Thorac Soc 2011;8:376–9. doi:10.1513/pats.201102-020RM.

[19] Holle R, Happich M, Löwel H, Wichmann H. KORA - A Research Platform for Population Based Health Research. Das Gesundheitswes 2005;67:19–25. doi:10.1055/s-2005-858235.

[20] Peters A, Döring A, Ladwig K-H, Meisinger C, Linkohr B, Autenrieth C, et al. Multimorbidity and successful aging. Z Gerontol Geriatr 2011;44:41–54. doi:10.1007/s00391-011-0245-7.

[21] John U, Greiner B, Hensel E, Lüdemann J, Piek M, Sauer S, et al. Study of Health in Pomerania(SHIP): a health examination survey in an east German region: Objectives and design. Soz Praventivmed 2001;46:186–94.

[22] Völzke H, Alte D, Schmidt CO, Radke D, Lorbeer R, Friedrich N, et al. Cohort profile: The study of health in Pomerania. Int J Epidemiol 2011;40:294–307. doi:10.1093/ije/dyp394.

[23] Celli BR, Celli BR, Cote CG, Cote CG, Marin JM, Marin JM, et al. The Body-Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity Index in Chronic Obstructive Pulmonary Disease. Society 2004:1005–12.

[24] Cote CG, Celli BR. Pulmonary rehabilitation and the BODE index in COPD. Eur Respir J 2005;26:630–6. doi:10.1183/09031936.05.00045505.

[25] Ko FWS, Tam W, Tung AHM, Ngai J, Ng SSS, Lai K, et al. A longitudinal study of serial BODE indices in predicting mortality and readmissions for COPD. Respir Med 2011;105:266–73. doi:10.1016/j.rmed.2010.06.022.

[26] Jörres RA, Welte T, Bals R, Koch A, Schnoor M, Vogelmeier C. Einfluss systemischer Manifestationen und Komorbiditäten auf den klinischen Zustand und den Verlauf bei COPD: Eine Übersicht über die Kohortenstudie COSYCONET. Dtsch Medizinische Wochenschrift 2010;135:446–9. doi:10.1055/s-0030-1249185.

[27] From the Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2015. http://www.goldcopd.org/.

[28] Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: The global lung function 2012 equations. Eur Respir J 2012;40:1324–43. doi:10.1183/09031936.00080312.

[29] Koch B, Friedrich N, Völzke H, Jörres R a., Felix SB, Ewert R, et al. Static lung volumes and airway resistance reference values in healthy adults. Respirology 2013;18:170–8. doi:10.1111/j.1440-1843.2012.02268.x.

[30] Cotes JE, Chinn DJ, Quanjer PH, Roca J YJ. Standardization of the measurement of transfer factor (diffusing capacity). Eur Respir J 1993;6:41–52.

[31] Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J 2005;26:319–38.

[32] Criée C, Berdel D, Heise D, Kardos P, Köhler D, Leupold W, et al. Empfehlungen der Deutschen Atemwegsliga zur Spirometrie. Pneumologie 2006;60:576–84.

[33] Wanger J, Clausen JL, Coates A, Pedersen OF, Brusasco V, Burgos F, et al. Standardisation of the measurement of lung volumes. Eur Respir J 2005;26:511–22.

[34] Criée CP, Sorichter S, Smith HJ, Kardos P, Merget R, Heise D, et al. Body plethysmography--its principles and clinical use. Respir Med 2011;105:959–71. doi:10.1016/j.rmed.2011.02.006.

[35] MacIntyre N, Crapo RO, Viegi G, Johnson DC, van der Grinten CPM, Brusasco V, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. Eur Respir J 2005;26:720–35.

[36] Kyle UG, Bosaeus I, De Lorenzo AD, Deurenberg P, Elia M, Manuel Gómez J, et al. Bioelectrical impedance analysis-part II: utilization in clinical practice. Clin Nutr 2004;23:1430–53. doi:10.1016/j.clnu.2004.09.012.

[37] Diehm C, Darius H, Pittrow D, Allenberg JR. Knöchel-Arm-Index. Dtsch Arztebl 2005;102:2310–4.

[38] Podsiadlo D, Richardson S. The Timed “Up & Go”: A Test of Basic Functional Mobility for Frail Elderly Persons. J Am Geriatr Soc 1991;39:142–8.

[39] Crapo RO, Casaburi R, Coates AL, Enright PL, MacIntyre NR, McKay RT, et al. ATS statement: Guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166:111–7.

[40] Meguro M, Barley E a., Spencer S, Jones PW. Development and validation of an improved, COPD-specific version of the St. George respiratory questionnaire. Chest 2007;132:456–63. doi:10.1378/chest.06-0702.

[41] Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD Assessment Test. Eur Respir J 2009;34:648–54.

[42] Kroenke K, Spitzer RL, Williams JBW. The PHQ-9: Validity of a brief depression severity measure. J Gen Intern Med 2001;16:606–13.

[43] Kalbe E, Kessler J, Calabrese P, Smith R, Passmore a. P, Brand M, et al. DemTect: A new, sensitive cognitive screening test to support the diagnosis of mild cognitive impairment and early dementia. Int J Geriatr Psychiatry 2004;19:136–43. doi:10.1002/gps.1042.

[44] Craig CL, Marshall AL, Sjöström M, Bauman AE, Booth ML, Ainsworth BE, et al. International physical activity questionnaire: 12-Country reliability and validity. Med Sci Sports Exerc 2003;35:1381–95.

[45] Nonnemacher M, Weiland D, Stausberg J. Datenqualität in der medizinischen Forschung - Leitlinie zum adaptiven Management von Datenqualität in Kohortenstudien und Registern. MWV Medizinisch Wissenschaftliche Verlagsgesellschaft; 2007.

[46] Karrasch S, Flexeder C, Behr J, Holle R, Huber RM, Jörres RA, et al. Spirometric reference values for advanced age from a South German population. Respiration 2013;85:210–9.

[47] Albrecht E, Sillanpää E, Karrasch S, Alves AC, Codd V, Hovatta I, et al. Telomere length in circulating leukocytes is associated with lung function and disease. Eur Respir J 2014;43:983–92.

[48] Glaser S, Ittermann T, Koch B, Volzke H, Wallaschofski H, Nauck M, et al. Airflow limitation, lung volumes and systemic inflammation in a general population. Eur Respir J 2012;39:29–37. doi:10.1183/09031936.00009811.

[49] From the Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2001. http://www.goldcopd.org/.

[50] Pauwels RA, Buist AS, Calverley PM, Jenkins CR, Hurd SS. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. Am J Respir Crit Care Med 2001;163:1256–76. doi:10.1164/ajrccm.163.5.2101039.

[51] Vestbo J, Lange P. Can GOLD stage 0 provide information of prognostic value in chronic obstructive pulmonary disease? Am J Respir Crit Care Med 2002;166:329–32. doi:10.1164/rccm.2112048.

[52] Calverley PMA. The GOLD Classification Has Advanced Understanding of COPD. Am J Respir Crit Care Med 2004;170:211–2. doi:10.1164/rccm.2405008.

[53] Kerstjens HHM. The GOLD Classification Has Not Advanced Understanding of COPD. Am J Respir Crit Care Med 2004;170:212–3. doi:10.1164/rccm.2405008.

[54] From the Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2006. http://www.goldcopd.org/.

[55] Maleki-Yazdi MR, Lewczuk CK, Haddon JM, Choudry N, Ryan N. Early detection and impaired quality of life in COPD GOLD stage 0: a pilot study. COPD 2007;4:313–20. doi:10.1080/15412550701595740.