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

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ABSTRACT

Background: The German COPD cohort study COSYCONET ("**CO**PD and **SY**stemic consequences-**CO**morbidities **NET**work") investigates the interaction of lung disease, comorbidities and systemic inflammation. Recruitment took place from 2010 to 2013 in 31 study centers. In addition to the baseline visit, follow-up visits are scheduled at 6, 18, 36 and 54 months after baseline. The study also comprises a biobank, image bank, and includes health economic data. Here we describe the study design of COSYCONET and present baseline data of our COPD cohort.

Methods: Inclusion criteria were broad in order to cover a wide range of patterns of the disease. In each visit, patients undergo a large panel of assessments including e.g. clinical history, spirometry, body plethysmography, diffusing capacity, blood samples, 6-min walk-distance, electrocardiogram and

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Cohort
Study design

echocardiography. Chest CTs are collected if available and CTs and MRIs are performed in a subcohort. Data are entered into eCRFs and subjected to several stages of quality control.
Results: Overall, 2741 subjects with a clinical diagnosis of COPD were included (59% male; mean age 65 ± 8.6 years (range 40–90)). Of these, 8/35/32/9% presented with GOLD stages I–IV; 16% were uncategorized, including the former GOLD-0 category. 24% were active smokers, 68% ex-smokers and 8% never-smokers. Data completeness was 96% for the baseline items.
Conclusion: The German COPD cohort comprises patients with advanced and less advanced COPD. This is particularly useful for studying the time course of COPD in relation to comorbidities. Baseline data indicate that COSYCONET offers the opportunity to investigate our research questions in a large-scale, high-quality dataset.

1. 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.

1.1. 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 two population-based cohorts: KORA (“**CO**operative Health Research in the **R**egion of **A**ugsburg”) [19,20] and SHIP (“**S**tudy of **H**ealth **I**n **P**omerania”) [21,22]. These cohorts do not only provide matched non-COPD controls, particularly for the analysis of comorbidities, but are also suitable to compare risk factor profiles and characteristics of patients with subclinical (GOLD 0) or mild to moderate COPD in terms of representativeness of the COSYCONET cohort when compared to 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) in 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.

2. Materials and methods

2.1. 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 the imaging phenotypes of COPD with CT serving as the gold standard [26,27].

2.2. Study design

COSYCONET is a prospective, observational, multicenter cohort study [28]. 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 (Fig. 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.

2.3. 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.

2.4. Measurements

Patients were/are investigated using a broad panel of

Fig. 1. Location of all participating study centers in COSYCONET.

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-min 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 = 28) 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 subpopulations of the cohort and will be described separately.

COPD severity was determined according to GOLD criteria [29],

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 baseline: 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	pO_2, pCO_2, pH, BE; samples from hyperaemic earlobe
Pulmonary function	
Bronchodilator administration	Prior to measurements 400 μg salb. + 80 μg ipratropium bromide
Spirometry	Standard procedures [33,34]
Body plethysmography	Standard procedures [35,36]
Lung transfer factor for CO (TLCO)	Single breath-maneuver [37]
Bioimpedance analysis (BIA)	Resistance & reactance, Fat-free mass index [38]
Cardiology	
ECG at rest	Supine position, electronic recording and storage
Ankle-brachial index (ABI)	Ratio of systolic pressures [39]
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 [40]
6-min walk distance (6-MWD)	Standard protocol, Borg scale at beginning and end [41]
COPD-related questionnaires	
Dyspnoea (mMRC)	Modified MRC dyspnoea scale
Health-specific QoL (SGRQ-C)	COPD-specific version of St. George Respiratory Questionnaire [42]
COPD Assessment Test (CAT)[a)]	[43]
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 [44]
Cognitive impairment (DemTect)	Sensitive to beginning cognitive impairments [45]
Osteoporosis (FRAX)	WHO questionnaire, anthropometric OST-score
Daily physical activity (IPAQ)	International Physical Activity Questionnaire [46]
Health economics	Medical consultations, hospitalization, rehabilitation, physiotherapy, absent days from work, medical aids
Supply of chest CT	If available (up to 5 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

[a] COPD Assessment Test is a trade mark of the GlaxoSmithKline group of companies. ©2009 GlaxoSmithKline group of companies. All rights reserved.
[b] EQ-5D™ is a trade mark of the EuroQol Group. ©EuroQol Group.

requiring a post-bronchodilator Tiffeneau-index (FEV_1/FVC) below a fixed value of 70% and being categorized according to the predicted FEV_1 value. Reference values for FEV_1 und FVC were derived using the recent prediction equations from the Global Lung Function Initiative (GLI) [30], those of ITGV from Koch et al. [31], and those for TLCO from Cotes et al. [32] with adjustment for hemoglobin. GOLD severity stages ABCD were determined based on CAT (and mMRC if CAT not available).

2.5. 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 [47] 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.

2.6. 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 at visit 3 with $n = 3000$ patients.

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. Refs. [48–51]). A direct, detailed comparison with COSYCONET data is to be presented in separate papers.

3. Results

3.1. 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 (Fig. 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 (12 centers) even more than 100 patients, and only one study site recruited less than 10 patients. The most active study center enrolled 259 patients.

3.2. GOLD stages

Classification into severity stages according to GOLD [29] resulted in 206/962/874/249 patients of stages I–IV, corresponding to 8%/35%/32%/9% of the total study population (Fig. 3). Expressed in GOLD stages ABCD, which are additionally based on symptoms and risk for exacerbations [29], the distribution is 184 (7%)/672 (25%)/104 (4%)/1322 (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 (FEV_1/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 analyze 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 [52,53].

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” ($n = 76$, 3%). For additional 20 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

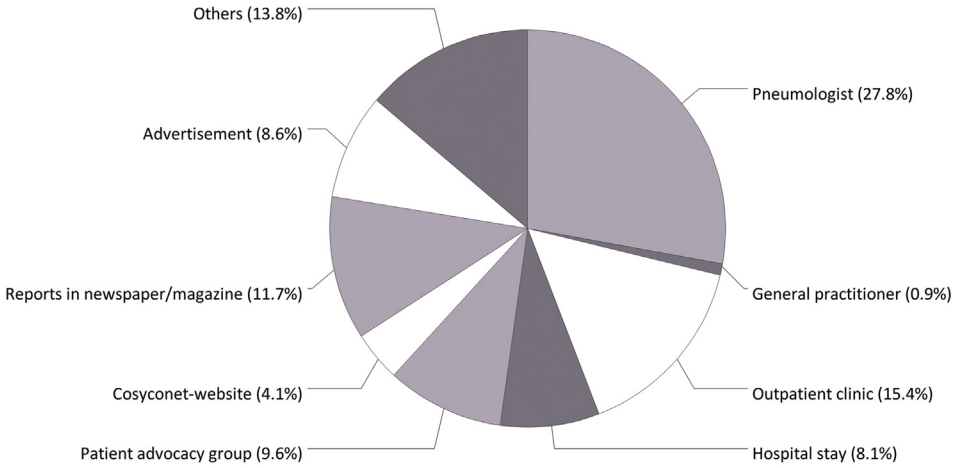

Fig. 2. Sources of recruitment.

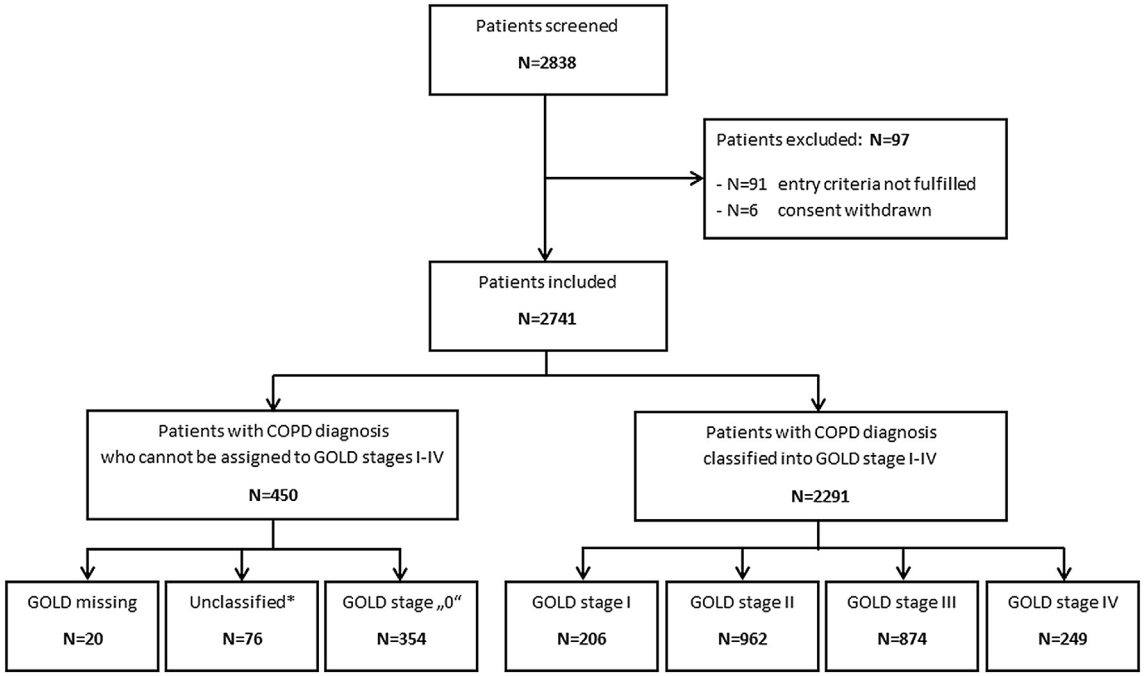

Fig. 3. Flow-chart of patient inclusion (*Unclassified means that patients had the diagnosis of COPD but at the time of study inclusion normal lung function and no chronic symptoms of bronchitis.).

missing GOLD stage are combined to GOLD “Unclassified” throughout the results section.

3.3. Baseline characteristics

The descriptive results for selected baseline characteristics are presented 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/m^2. BMI was reduced in GOLD-IV patients and showed higher values in GOLD-0 and unclassified patients.

The spirometric data demonstrated the impairment to be expected owing to the COPD classification. A strong difference between GOLD stages could be observed for exercise capacity, with 6-min walk distance decreasing from nearly 500 m in GOLD-I to 330 m in GOLD-IV. Likewise, the time for the Timed up&go Test (overall mean 7 s) increased across GOLD stages. GOLD-0 and unclassified patients showed an exercise capacity comparable to GOLD-II/III patients. The primary endpoint of this study, the BODE index (having a possible range from 0 to 10) was on average 2.2, with strong differences between GOLD stages.

Obviously, the number of comorbidities and a high average of medications per patient (6.7) reflect the advanced age of the study population (Table 3). Comorbidities were fairly homogeneously

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[a]	19							
High		480 (18%)	54 (26%)	185 (19%)	130 (15%)	32 (13%)	63 (18%)	21 (22%)
Intermediate		740 (27%)	52 (25%)	275 (29%)	220 (25%)	73 (29%)	97 (28%)	26 (27%)
Low		1482 (55%)	98 (48%)	495 (52%)	522 (60%)	143 (58%)	188 (54%)	48 (51%)
Full- and part-time employees	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[b]	234[b]	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/m^2)	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
Pulmonary function								
FEV_1 (%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 (%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
Exercise capacity and functioning								
6-min 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
Primary endpoint of COPD impairment								
BODE index	117	2.2 ± 2.0	0.4 ± 0.7	1.3 ± 1.2	3.6 ± 1.5	5.3 ± 1.6	1.0 ± 1.4	0.9 ± 1.4

[a] Education is categorized according to years of school education: Low: ≤9 years, Intermediate: = 10 years, High: ≥ 11 years or university degree.
[b] Pack-years were computed excluding never smokers.

Table 3
Prevalences of selected self-reported comorbidities and classes of medication at baseline.

Comorbidities	Total (n = 2741)	Medication	Total (n = 2741)
Asthma	509 (18.6%)	Respiratory-related medication	
Chronic bronchitis	1710 (62.4%)	Rapid-acting Beta-2-agonists	1076 (39.3%)
Sleep apnea	308 (11.2%)	Long-acting Beta-2-agonists	965 (35.2%)
Hypertension	1545 (56.4%)	Rapid-acting anticholinergics	125 (4.6%)
Coronary artery disease	436 (15.9%)	Long-acting anticholinergics	1893 (69.1%)
Cardiac infarction	225 (8.2%)	Theophylline	491 (17.9%)
Cardiac dysrhythmia	247 (16.9%)	Inhalative steroids	479 (17.5%)
Heart failure	148 (10.1%)	Oral steroids	325 (11.9%)
Stroke	120 (4.4%)	Anticholinergic + Beta-2-agonist	545 (19.9%)
Venous thrombosis	197 (7.2%)	Bronchodilator + inhalative C.steroids	1267 (46.2%)
Gastritis	692 (25.3%)		
GE reflux disease	414 (28.3%)	Cardiovascular medication	1806 (65.9%)
Peptic ulcer	325 (11.9%)		
Diabetes with insulin	143 (5.2%)	Sum of any taken medication	17,897
Diabetes without insulin	247 (9.0%)	Medication per patient (mean ± sd)	6.7 ± 3.7
Elevated cholesterol level	1072 (39.1%)		
Gout	465 (17.0%)		
Alpha-1-antitrypsin deficiency	168 (6.1%)		
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%)		

distributed over COPD stages; this and their relationship to function will be analyzed in detail in forthcoming papers.

3.4. 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.

4. 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. A direct comparison of the COSYCONET cohort with other COPD cohorts (Table 4) shows that the baseline characteristics are completely within the range observed in the other cohorts. In this respect, COSYCONET is comparable and does not suffer from specific biases resulting e.g. from the recruitment procedures. Some of the other cohorts include control groups. In COSYCONET, the external population-based cohorts KORA and SHIP have this purpose. Moreover, patients of the GOLD category 0, who have been recruited exactly the same way as those of categories 1–4, allow for the comparison with the large number of patients with normal lung function in KORA and SHIP regarding the pattern and distribution of comorbidities which might have favored inclusion in COSYCONET.

This comparability to other COPD cohorts 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 COSYCONET 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 and it has to be assumed that participating GOLD stage IV patients are “healthier” than common stage IV patients. With regard to the aim of the study, we do not consider the

Table 4
Basic characteristics of longitudinal COPD cohorts.

Cohort	Recruitment	N	N COPD[a]	Age COPD[a]	Male COPD[a]	GOLD stages				Other participants, N	
						I	II	III	IV		
COSYCONET	2009–2012 Germany	2741	2291	65.1	59%	206 (9%)	962 (42%)	874 (38%)	249 (11%)	• GOLD “0” • Unclassified	354 96
Bergen cohort [54–56]	2006–2007 Norway	758	433	63.6	60%	0 (0%)	204 (47%)	180 (42%)	49 (11%)	• Healthy	325
INITIATIVES BPCO[b] [57]	2002-ongoing France	1194	1194	64.0	75%	110 (9%)	538 (45%)	349 (29%)	197 (17%)	–	–
CanCOLD [58,59]	2005–2009 Canada	4893	557	61.9	43%	242 (43%)		315 (57%)		• Smoking • Non-Smoking	2202 2134
COPDGene [60]	2008–2011 USA	10,300	4484	63.3	56%	794 (18%)	1922 (43%)	1162 (26%)	606 (13%)	• Unclassified • Smoking GOLD “0” • Non-Smoking	1320 4388 108
ECLIPSE [4]	2005–2007 multinational	2746	2163	61.6	65%	2 (0.1%)	954 (44%)	911 (42%)	296 (14%)	• Unclassified • Smoking • Non-Smoking	1 337 245
Hokkaido cohort [61,62]	2003–2005 Japan	300	279	70.0	94%	72 (26%)	126 (45%)	68 (24%)	13 (5%)	• GOLD “0”	21
London cohort[b] [63,64]	1995–2009 UK	386	386	68.4	58%	0(0%)	158(41%)	148(39%)	78(20%)	–	–
Swiss cohort [65]	2007–2010 Switzerland	454	354	68.1	66%	43 (12%)	164 (46%)	119 (34%)	28 (8%)	• GOLD “0”	100

Data that were not directly given in the cited publication(s) were computed from available data in the respective publication (e.g. we calculated overall age in some cases as the weighted mean of age from different subgroups).

[a] COPD as defined by GOLD [29] with FEV1/FVC ≤ 0.70.

[b] Recent data was obtained from personal communication in February 2016.

underrepresentation 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 [66–68] and stage 0 has been excluded from GOLD strategy reports in 2006 [69]. Conversely, studies suggested that subjects of the stage 0 are at risk for developing COPD and comorbidities and for experiencing increased mortality [70]. 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.

5. 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.

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Appendix

Table A.1Devices used for echocardiography in COSYCONET

Device from …	Study centers using the device	% of study centers
General Electric LOGIQ	3	10%
General Electric VIVID	18	58%
Hitachi	1	3%
Philips	18	58%
Siemens	5	16%
Toshiba	2	6%

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