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COPD-specific patient reported outcomes in a working population: differences and similarities of health status, dyspnoea and respiratory symptoms.

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Running Title:

Health Status, Dyspnoea and Respiratory Symptoms in a Working Population

Key words:

Chronic obstructive pulmonary disease (COPD);

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The COPD assessment test (CAT);

Dyspnoea-12 (D-12);

The Evaluating Respiratory Symptoms in COPD (E-RS).

Abstract

Introduction: We hypothesized that chronic obstructive pulmonary disease (COPD)-specific health status measured by the COPD assessment test (CAT), respiratory symptoms by the Evaluating Respiratory Symptoms in COPD (E-RS) and dyspnoea by Dyspnoea-12 (D-12) are independently based on specific conception and are not interchangeable. We aimed to investigate whether health status, dyspnoea or respiratory symptoms could be related to smoking status and airflow limitation in a working population.

Methods: The cross-sectional data, including spirometry, obtained from 1,566 healthy industrial workers were analyzed.

Results: Relationships between D-12, CAT and E-RS Total were statistically significant but weak (Spearman's correlation coefficient＝0.274 to 0.446). In 646 healthy non-smoking subjects, as the upper limit of normal, the Bootstrap 95th percentile values were 1.00 for D-12, 9.88 for CAT and 4.44 for E-RS. Of the 1,566 workers, 85 (5.4%) were diagnosed with COPD using the fixed ratio of the forced expiratory volume in one second/forced vital capacity<0.7, and 34 (2.2%) using the lower limit of normal. The CAT and E-RS Total were significantly worse in non-COPD smokers and subjects with COPD than non-COPD never smokers, although the D-12 was not as sensitive. None of these measures was significant between non-COPD smokers and subjects with COPD.

Discussion: Comprehensive assessment of health status and respiratory symptoms would be preferable to dyspnoea in view of smoking status and airflow limitation in a working population. However, these patient-reported measures were inadequate in differentiating

between smokers and subjects with COPD identified by spirometry. How to manage these symptomatic non-COPD smokers should be investigated.

Strengths and limitations of this study

- Chronic obstructive pulmonary disease (COPD)-specific health status may be measured by the COPD assessment test (CAT), respiratory symptoms by the Evaluating Respiratory Symptoms in COPD (E-RS) and dyspnoea by Dyspnoea-12 (D-12). They are independently based on specific conception and are not interchangeable.
- The cross-sectional data obtained from 1,566 healthy industrial workers showed relationships between D-12, CAT and E-RS Total were statistically significant but weak (Spearman's correlation coefficient, 0.274 to 0.446).
- In 646 healthy non-smoking subjects, as the upper limit of normal, the Bootstrap 95th percentile values were 1.00 for D-12, 9.88 for CAT and 4.44 for E-RS.
- The CAT and E-RS Total were significantly worse in non-COPD smokers and subjects with COPD than non-COPD never smokers, although the D-12 was not as sensitive.
- These patient-reported measures were inadequate in differentiating between smokers and subjects with COPD identified by spirometry.

Introduction

Over the last two decades, patient reported outcomes (PROs) have been considered to be important in the assessment of health care services.[1-4] The St. George's Respiratory Questionnaire (SGRQ) has been one of the most frequently used tools for health status measurements in subjects with chronic obstructive pulmonary disease (COPD).[5] Short and simple instruments have become commonplace since the reduction in the number of items has become possible by methodological innovations, including the use of Rasch analysis. First, Jones et al. developed the COPD assessment test (CAT), which has been considered to be almost equivalent to the SGRQ, making the tool easy to administer and easy for patients to complete.[6-8] Second, although dyspnoea is one of the most important perceptions experienced in subjects with respiratory or cardiac disorders, it has not been easy to measure this perception due to sensory quality and affective components of dyspnoea. Yorke et al. reported that Dyspnoea-12 (D-12) provides a global score of breathlessness severity and can measure dyspnoea in a variety of diseases.[9-11] Third, another tool designed specifically to quantify exacerbations in COPD is the Exacerbations of Chronic Pulmonary Disease Tool (EXACT) Patient-Reported Outcome (known as EXACT-PRO).[12-14] Leidy et al. reported that, using 11 respiratory symptom items from the 14-item EXACT, the Evaluating Respiratory Symptoms in COPD (E-RS) is a reliable and valid instrument for evaluating respiratory symptom severity in stable COPD.[15 16]

The developers of the CAT, D-12 and E-RS have stated that the three PROs derive from different conceptual frameworks, but the methodology used in the development is

similar. In subjects with COPD, it may be commonly accepted that breathlessness is included in respiratory symptoms, and that this symptom is one of the essential components of health status. Therefore, the D-12 would be reflected in the E-RS, and the E-RS in the CAT.

We hypothesized that COPD-specific health status measured by the CAT, dyspnoea by the D-12, and symptoms by the E-RS are independently based on specific conception and are not interchangeable in a general population, and that comprehensive symptomatic assessment of the CAT and E-RS would be preferable to dyspnoea by the D-12 in identifying subjects who may have COPD among that population. Hence, the purpose of the present study was to examine the discriminative properties of the CAT, D-12 and E-RS in relation to smoking status and airflow limitation and to investigate whether health status, dyspnoea and respiratory symptoms could be related to a diagnosis of COPD based on the results of spirometry.

Additionally, we previously reported that the 95th percentile of the CAT scores was 13.6 in 512 healthy non-smoking subjects although the CAT score distribution overlapped remarkably between both healthy non-smoking subjects and subjects with COPD.[17] As a secondary endpoint of the present study, it was our objective to determine reference values of the scores obtained from the D-12 and E-RS for healthy non-smoking subjects.

Methods

Study Design

This is a cross-sectional observational study.

Setting

The present study was conducted between March 2012 and April 2013 at the Niigata Association of Occupational Health Incorporated, Niigata, Japan.

Participants

The study subjects were healthy industrial workers over forty years old who underwent annual health checks at this Association. All underwent a comprehensive health screening, including conventional spirometry. The exclusion criteria included: 1) abnormal findings of the pulmonary parenchyma and chest wall revealed on chest radiographs; 2) receiving a thoracotomy in the past; 3) any admission to a hospital during the preceding three months (except hospitalization for routine tests); 4) any physician-diagnosed pulmonary diseases including lung cancer, pulmonary tuberculosis, bronchiectasis or non-tuberculous mycobacteriosis except COPD as well as asthma; and 5) unstable complications of cardiovascular, neuromuscular, renal, endocrinological, haematological, gastrointestinal, and hepatic co-morbidities. The information about their radiographic findings was obtained from annual health examinations. The participants also answered additional questions to investigate their smoking status and history.

Measurement

All eligible subjects completed the following examinations on the same day. Spirometry was performed with the use of nose clips in the sitting position with a Spiro Sift sp-470^{TM} Spirometer (Fukuda Denshi Co., Ltd., Tokyo, Japan). All measurements were performed

by a laboratory technician in accordance with guidelines published by the American Thoracic Society and European Respiratory Society.[18] The spirometric forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) values were the largest FVC and largest FEV_1 selected from data obtained from at least three acceptable forced expiratory curves, even if these values were not obtained from the same curve.[19] In this study, COPD was spirometrically defined as airflow limitation with a FEV_1/FVC less than either a fixed ratio, 0.7, or lower limit of normal (LLN) without bronchodilator administration.[20-23] Healthy subjects were defined as those with a FEV_1 of >85% predicted or a FEV_1/FVC of >0.7, forming two groups: subjects with a smoking history of ≥10 pack-years, and non-smoking subjects with a smoking history of < 1 pack-year. This definition was similar to that of the Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE) study.[24 25] The predicted values for pulmonary function were calculated based on the proposal from the Japanese Respiratory Society.[26] The LLN for the Japanese population was calculated in the present study according to the method described by Osaka et al.[27]

The Japanese versions of the EXACT, CAT and D-12 were self-administered under supervision in a booklet form. The E-RS uses 11 respiratory symptom items from the 14-item EXACT, where scores range from 0 to 40, with higher scores indicating more severe symptoms.[12-16] The RS-Total Score represents overall respiratory symptom severity.[15 16] Three subscales were not used in this analysis. The Japanese translation has been created and provided by the original developers, and they recommend using an electronic version to collect the answers. However, no electronic device with the Japanese version of the EXACT or E-RS was available so all surveys were conducted using a paper-based

method. Health status was assessed with a previously validated Japanese version of the CAT.[28] The CAT consists of eight items scored from 0 to 5 in relation to cough, sputum, dyspnea, chest tightness, capacity for exercise and activities, sleep quality and energy levels.[7 8] The CAT Scores range from 0 to 40, with a score of zero indicating no impairment. To assess the severity of dyspnoea, we used the Japanese version of the D-12,[29] which consists of twelve items (seven physical items and five affective items), each with a four point grading scale (0-3), producing a Total Score (range 0-36, with higher scores representing more severe breathlessness).[9-11]

Patient and Public Involvement

Patients were not involved in the study. The abstract of the paper published will appear on the homepage of the institute.

Ethics and Funding

The present study was approved by the ethics committee of the Niigata Association of Occupational Health Incorporated. Written informed consent was obtained from all participants. This study was partly supported by the Research Funding for Longevity Sciences (30-24) from the National Center for Geriatrics and Gerontology (NCGG), Japan.

Statistical Methods

All results are expressed as means ±standard deviation (SD). Relationships between two sets of data were analysed by Spearman's rank correlation tests. In order to determine reference values for each score, we calculated the 95th percentile of the scores in healthy, non-smoking subjects using the Monte Carlo and bootstrap methods with 1,000 bootstrap reps and used this as the upper limit of normal.[30] In comparing the groups of COPD, non-

COPD smokers and non-COPD never smokers, the significance of between-group difference was determined by an analysis of variance (ANOVA) for FEV_1 or a Kruskal Wallis test for PRO scores, and when a significant difference was observed, Tukey tests or Steel-Dwass tests were used to analyze where the differences were significant, respectively. Statistical analysis was performed using IBM SPSS Statistics 22.0 (International Business Machines Corp., Armonk, New York, USA) and BellCurve for Excel (Social Survey Research Information Co., Ltd., Tokyo, Japan). A p value of less than 0.05 was considered to be statistically significant.

Results

Subject Characteristics

A total of 1,634 subjects initially participated in the study but 68 were subsequently excluded from the data analysis because of uncertainty over their smoking or other history or having one of the exclusion criteria. Therefore, a total of 1,566 subjects (985 males) were analysed. Their demographic details and spirometric results are shown in Table 1. The mean age of the subjects was 53.0 years. The FEV_1 values were 99.6±13.1 %predicted. The FEV_1/FVC ratio used as an index of airflow limitation ranged from 52.5% to 97.4%, with a mean of 80.1%.

The scores for the D-12, CAT and E-RS are shown in Table 2. They were skewed to the milder ends, and a floor effect was seen in all of the scores. This effect was most pronounced for the D-12 (84.0%) and E-RS (53.3%), and least for the CAT (14.6%). Regarding the interrelationships between the D-12, CAT and E-RS, they were significantly but only weakly correlated with each other (D-12 versus CAT, Spearman's correlation coefficient (Rs) =0.398, $p<0.001$; D-12 versus E-RS, Rs=0.274, $p<0.001$; and CAT versus E-RS, Rs=0.446, $p<0.001$).

In order to determine the reference values, from the data obtained from 646 healthy non-smoking subjects (Tables 1 and 2), the Bootstrap 95th percentile values were subsequently calculated and used as the upper limit of normal. For the D-12, this was 1.00; for the E-RS, it was 4.44. Since these scores do not contain decimals, the reference values for the D-12 and E-RS Total Scores were considered to be ≤1 and ≤4, respectively. In the same way, the reference value of the CAT was calculated to be 9.88, which rounds up to 10, in the present study.

Relationships of COPD-specific PROs with Smoking and Airflow Limitation

We then divided the 1,566 subjects into three groups consisting of a COPD group based on the FEV_1/FVC using a fixed ratio, 0.7, or LLN; non-COPD current or past smokers; and non-COPD never smokers (Tables 1 and 2). Using the fixed ratio of the $FEV_1/FVC<0.7$, 85 subjects (5.4%) were diagnosed with COPD, 817 (52.2%) were non-COPD smokers, and 664 (42.4%) were non-COPD never smokers. Using the LLN definition, 34 subjects (2.2%) were diagnosed with COPD, 867 (55.4%) were non-COPD smokers, and 665 (42.5%) were non-COPD never smokers.

Relationships of the PROs between the three groups of subjects with COPD, non-COPD smokers and non-COPD never smokers are shown in Table 2 and Figures 1 (COPD based on the fixed ratio) and 2 (COPD based on the LLN). The FEV_1 (%predicted), D-12, CAT and E-RS Total were significantly separated between three groups ($p<0.05$). There were significant differences between the three groups for FEV_1 (%predicted), D-12, CAT and E-RS Total ($p<0.05$). FEV_1 was significantly different between any two of the three groups ($p<0.001$) (Figures 1 and 2). With regard to the score distribution (Table 2), floor effect in subjects with COPD was most prominent for the D-12 (81.2% by the fixed definition and 73.5% by the LLN), and their median scores were 0.0 (Table 2). It was the least for the CAT (15.3% by the fixed definition and 14.7% by the LLN).

In investigating how many were symptomatic among 817 (by the fixed definition) and 867 (by the LLN definition) non-COPD smokers, using the above reference values,

24 (2.9%) and 24 (2.8%) were >1 on the D-12, 79 (9.7%) and 80 (9.2%) were >10 on the CAT, and 74 (9.1%) and 76 (8.8%) were >4 on the E-RS.

Regarding the group comparisons, significant differences were found between non-COPD never smokers and non-COPD smokers on all of the measures; however, significance was relatively weaker for the D-12 score ($p=0.025$ (Figure 1) and 0.029 (Figure 2)) as compared to the CAT and E-RS Total ($p<0.001$). On the CAT and E-RS Total, significant differences were also found between non-COPD never smokers and subjects with COPD ($p<0.05$); however, on the D-12, a significant difference was found only by the LLN definition ($p=0.036$, Figure 1), but not by the fixed ratio definition ($p=0.24$, Figure 1). Neither the D-12, CAT nor E-RS Total were significantly different between COPD and non-COPD smokers).

Discussion

This is the first study to directly compare differences among three COPD-specific outcomes, including dyspnoea, respiratory symptoms or health status in a general working population. First, the associations between dyspnoea measured by the D-12, health status by the CAT, and respiratory symptoms by the E-RS were significant but weak, indicating that they were far below the level of conceptual similarity. This relationship may be expected since the three PRO measurement tools were created by each developer from independent conceptual frameworks. Second, from the data obtained from 646 healthy non-smoking subjects, the Bootstrap 95th percentile values were an E-RS Total score of 4.44 indicating that the reference value is ≤4. The reference values for the D-12 and CAT score are also ≤1 and ≤10, respectively. Third, from a standpoint of the relationship with smoking status and airflow limitation, in comparison to non-COPD never smokers, health status by the CAT and respiratory symptoms by the E-RS were worse in non-COPD smokers and subjects with COPD, although dyspnoea by the D-12 was not as sensitive. None of these PRO measures were adequate in differentiating between non-COPD smokers and subjects with COPD.

In the present study, there were considerable numbers of smokers with preserved pulmonary function, or without airflow limitation, 52.2% by the fixed ratio and 55.4% by the LLN, respectively, who may be diagnosed as COPD- free by spirometric criteria. Their dyspnoea, health status and respiratory symptoms were significantly worse than those in never smokers, which is compatible with recent population studies.[31-34] They also indicated that pulmonary disease and impairments were common in smokers with preserved pulmonary function although they did not meet the current criteria of COPD

based on spirometry,[33 34] and that symptoms might be more sensitive than spirometry in detecting smoking-related respiratory impairments. Actually, symptom-based questionnaires to screen for COPD that do not include spirometry have been developed.[35 36]

Conversely, the present study adds that PROs in non-COPD smokers were not significantly different from those in subjects with COPD. Actually, about 9% of smokers with preserved pulmonary function were judged to be symptomatic according to the reference values of CAT>10 or E-RS>4. Their symptoms may tend to exacerbate in the future, advance to COPD, or be treated as if they were COPD. How to manage this group of symptomatic smokers without airflow limitation is a key issue to be solved through careful long-term follow-ups.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2011 consensus report proposed a revised "combined COPD assessment" classification in which symptoms should be assessed either as a dyspnoea measure using the modified Medical Research Council (mMRC) dyspnoea scale, or as a health status measure using the CAT.[37] We have contributed to the establishment of this concept by demonstrating the significant predictive properties of dyspnoea and health status independently of airflow limitation.[38 39] There has hitherto been much debate over how to assess symptoms in this new classification. Although dyspnoea was not measured by mMRC dyspnoea scale but by D-12, interrelationships between the D-12, CAT and E-RS were weak to moderate. Therefore, it may be difficult to use dyspnoea, health status and respiratory symptoms in a mutually complementary form. The GOLD recommends a comprehensive assessment of symptoms rather than just a measure of dyspnoea. The present study supports this by

showing that the D-12 had the most marked floor effects even in subjects with COPD, and that the CAT and E-RS seemed to be more sensitive in discriminating subjects based on smoking and COPD than the D-12.

We reported in 2013 that the 95th percentile of the scores in 512 healthy, non-smoking subjects were used as the upper limit of normal in exactly the same way as in the present study.[17] For the CAT, it was 13.6. In 2014 Pinto et al. published some of the results of the Canadian Cohort Obstructive Lung Disease (CanCOLD) study and reported that the normative value for the CAT score was determined to be 16 from a population-based study where they used post-bronchodilator spirometric values.[40] Compared with the above two reports, a score of 10 was the 95th percentile of the scores in healthy industrial workers from Japan, and it is the lowest in the present study. The GOLD currently states that the boundary between GOLD A and B and between GOLD C and D is a CAT score of 10,[37 41] which is consistent with the important result of the present study although there might be some margin of error depending on the methodologies and subjects of the studies.

This study has several limitations. Although we intended to determine the border of the normal level of the D-12, CAT and E-RS Total scores, the study subjects were not randomly sampled and there could be a risk of sample bias. The D-12, CAT and E-RS are sufficiently validated for measuring PROs in subjects with COPD, but most participants were not patients with COPD but rather healthy workers. As such, there is a possibility that they are not appropriate tools for the study population. Although post-bronchodilator spirometric values are recommended to be used to make a diagnosis of COPD,[37 41] the

diagnosis was made only from pre-bronchodilator spirometric information in the present study.

Three main conclusions may be drawn from our findings. First, associations among dyspnoea measured by the D-12, health status by the CAT, and respiratory symptoms by the E-RS, were statistically significant but weak, indicating that they cannot be used interchangeably. Second, using the data obtained from 646 healthy non-smoking subjects, the reference values of the D-12, CAT and E-RS were ≤1, ≤10 and ≤4, respectively. Third, from a standpoint of the relationship with smoking status and airflow limitation, health status and respiratory symptoms may be more closely related to non-COPD smokers and subjects with COPD than dyspnoea as compared to non-COPD never smokers; however, none of these PRO measures can differentiate between non-COPD smokers and subjects with COPD. How to manage non-COPD symptomatic smokers should be investigated in the future.

Other information

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Contributors

KN contributed, as the principal investigator, to the study concept and design, analysis of the results, and writing of the manuscript.

TO contributed to statistical analysis, the interpretation and editing of the manuscript.

KN contributed to statistical analysis.

MO contributed to acquisition of data.

YH contributed to the interpretation and editing of the manuscript.

SM contributed to performance of the study and acquisition of data.

All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

Ethics Approval

The present study was approved by the ethics committee of the Niigata Association of Occupational Health Incorporated (No. 6, lastly dated January 8, 2013).

Data Sharing Statement

No additional data are available.

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Figure Legends

Figure 1 Box plots representing the distributions of FEV_1 (%predicted), D-12 (Dyspnoea-12) score, CAT (COPD assessment test) score and E-RS (Evaluating Respiratory Symptoms in COPD) Total score in non-COPD never smokers (Group A, n=664), non-COPD current or past smokers (Group B, n=817) and COPD based on FEV_1/FVC using a fixed ratio, 0.7 (Group C, n=85). The horizontal lines in the boxes represent the median, and the top and bottom of the boxes represent the 75th and 25th percentiles, respectively. Bars represent the upper adjacent value (75th percentile plus 1.5 times the interquartile range) and the lower adjacent value (25th percentile minus 1.5 times the interquartile range), and the crosses represent outliers.

Figure 2 Box plots representing the distributions of FEV_1 (%predicted), D-12 (Dyspnoea-12) score, CAT (COPD assessment test) score and E-RS (Evaluating Respiratory Symptoms in COPD) Total score in non-COPD never smokers (Group A, n=665), non-COPD current or past smokers (Group B, n=867) and COPD based on FEV_1/FVC using the LLN (Group C, n=34). The horizontal lines in the boxes represent the median, and the top and bottom of the boxes represent the 75th and 25th percentiles, respectively. Bars represent the upper adjacent value (75th percentile plus 1.5 times the interquartile range) and the lower adjacent value (25th percentile minus 1.5 times the interquartile range), and the crosses represent outliers.

Table 1. Demographic details and spirometric results.

	Total subjects	Age	Male	Cumulative smoking	Prior diagnosis of asthma	Prior diagnosis of COPD	FEV_1	FEV_1/FVC
	Number	Years	Number (%)	Pack-years	Number (%)	Number (%)	%predicted	%
All subjects	1566	53.0 ± 8.7	985 (62.9%)	14.1 ± 18.6	46 (2.9%)	10 (0.6%)	99.6 ± 13.1	80.1 ± 5.8
Healthy non-smoking subjects¶#	646	53.3 ± 8.8	189 (29.3%)	0.0 ± 0.1	17 (2.6%)	2 (0.3%)	105.5 ± 10.7	82.3 ± 4.4
COPD defined by fixed ratio	85	60.4 ± 9.4	83 (97.6%)	36.9 ± 28.1	5 (5.9%)	4 (4.7%)	80.2 ± 11.6	66.0 ± 4.1
Non-COPD smokers	817	51.9 ± 8.0	704 (86.2%)	23.1 ± 16.9	23 (2.8%)	4 (0.5%)	97.9 ± 11.8	80.1 ± 4.7
Non-COPD never smokers	664	53.4 ± 8.9	198 (29.8%)	0.0 ± 0.0	18 (2.7%)	2 (0.3%)	104.2 ± 12.0	82.0 ± 4.5
COPD defined by LLN	34	57.7 ± 10.4	29 (85.3%)	31.9 ± 25.8	2 (5.9%)	2 (5.9%)	77.3 ± 13.1	63.0 ± 4.9
Non-COPD smokers	867	52.4 ± 8.3	755 (87.1%)	24.2 ± 18.3	26 (3.0%)	6 (0.7%)	97.1 ± 12.3	79.4 5.3
Non-COPD never smokers	665	53.5 ± 8.9	201 (30.2%)	0.0 ± 0.0	18 (2.7%)	2 (0.3%)	104.1 ± 12.1	82.0 ± 4.5

¶ FEV_1 of >85% predicted and FEV_1/FVC of >0.7, # a smoking history of <1 pack-year

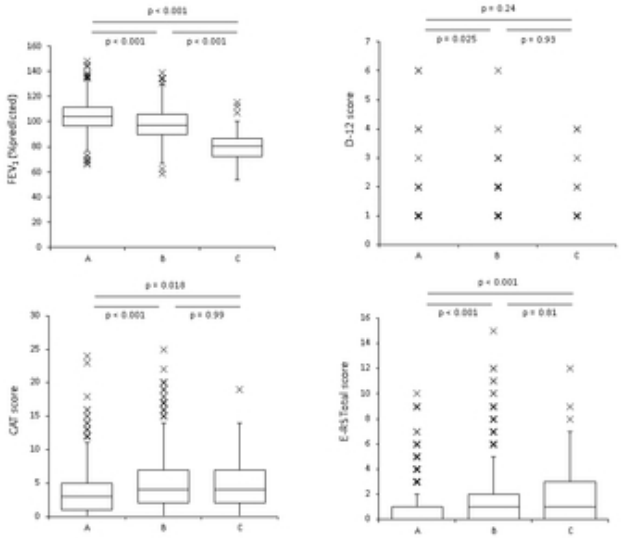
Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; LLN, lower limit of normal.

Table 2. Distributions of the D-12, CAT and E-RS Total scores.

	D-12 score (0-36)					CAT score (0-40)					E-RS Total score (0-40)				
	mean	median	SD	max.	floor effect	mean	median	SD	max.	floor effect	mean	median	SD	max.	floor effect
All subjects	0.2	0.0	0.6	6.0	84.0%	4.3	3.0	3.9	25.0	14.6%	1.2	0.0	1.9	15.0	53.3%
Healthy non-smoking subjects¶#	0.2	0.0	0.5	6.0	86.5%	3.6	3.0	3.3	24.0	15.9%	0.9	0.0	1.6	10.0	62.5%
COPD defined by fixed ratio	0.3	0.0	0.8	4.0	81.2%	4.8	4.0	4.1	19.0	15.3%	1.6	1.0	2.2	12.0	44.7%
Non-COPD smokers	0.2	0.0	0.5	6.0	82.0%	4.8	4.0	4.1	25.0	13.1%	1.5	1.0	2.1	15.0	46.5%
Non-COPD never smokers	0.2	0.0	0.5	6.0	86.7%	3.6	3.0	3.4	24.0	16.3%	0.9	0.0	1.6	12.0	62.7%
COPD defined by LLN	0.5	0.0	1.0	4.0	73.5%	6.2	6.0	4.8	19.0	14.7%	1.8	1.5	2.1	9.0	38.2%
Non-COPD smokers	0.2	0.0	0.5	6.0	82.2%	4.8	4.0	4.1	25.0	13.0%	1.5	1.0	2.1	15.0	46.6%
Non-COPD never smokers	0.2	0.0	0.6	6.0	86.8%	3.6	3.0	3.4	24.0	16.5%	0.9	0.0	1.6	10.0	62.7%

¶ FEV_1 of >85% predicted and FEV_1/FVC of >0.7, # a smoking history of <1 pack-year. Numbers in parentheses indicate the theoretical score range, and higher scores indicate worse status.

Abbreviations: CAT, COPD assessment test; COPD, chronic obstructive pulmonary disease; D-12, Dyspnoea-12; E-RS, Evaluating Respiratory Symptoms in COPD; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; LLN, lower limit of normal.



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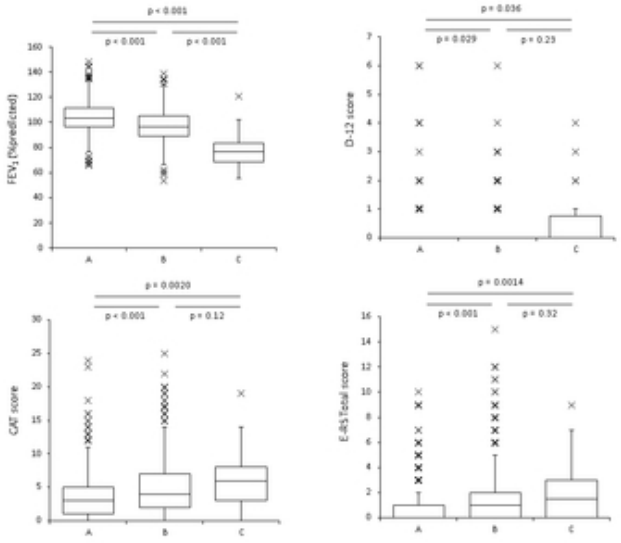

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 4	The cross-sectional data
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 4 - 5	
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 6 - 7	
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 7	
Methods				
Study design	4	Present key elements of study design early in the paper	Page 8	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 8	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	Page 8	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 8 - 10	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 8 - 10	
Bias	9	Describe any efforts to address potential sources of bias		
Study size	10	Explain how the study size was arrived at		

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 10 - 11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 10 - 11
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 12
		(b) Give reasons for non-participation at each stage	Page 12
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page 12
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Page 13 - 14
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 15, 18
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 17-18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 15 - 18
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 15 - 18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 10, 19

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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COPD-specific patient reported outcomes in a working population: how different are health status, dyspnoea and respiratory symptoms?

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COPD-specific patient reported outcomes in a working population: how different are health status, dyspnoea and respiratory symptoms?

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Running Title:

Health Status, Dyspnoea and Respiratory Symptoms in a Working Population

Key words:

Chronic obstructive pulmonary disease (COPD);

Patient-reported outcome (PRO);

The COPD assessment test (CAT);

Dyspnoea-12 (D-12);

The Evaluating Respiratory Symptoms in COPD (E-RS).

Abstract

Introduction: We hypothesized that chronic obstructive pulmonary disease (COPD)-specific health status measured by the COPD assessment test (CAT), respiratory symptoms by the Evaluating Respiratory Symptoms in COPD (E-RS) and dyspnoea by Dyspnoea-12 (D-12) are independently based on specific conceptual frameworks and are not interchangeable. We aimed to discover whether health status, dyspnoea or respiratory symptoms could be related to smoking status and airflow limitation in a working population.

Methods: The cross-sectional data, including spirometry, obtained from 1,566 healthy industrial workers were analyzed.

Results: Relationships between D-12, CAT and E-RS Total were statistically significant but weak (Spearman's correlation coefficient＝0.274 to 0.446). In 646 healthy non-smoking subjects, as the reference scores for healthy non-smoking subjects, that is, upper threshold, the Bootstrap 95th percentile values were 1.00 for D-12, 9.88 for CAT and 4.44 for E-RS. Of the 1,566 workers, 85 (5.4%) were diagnosed with COPD using the fixed ratio of the forced expiratory volume in one second/forced vital capacity<0.7, and 34 (2.2%) using the lower limit of normal. The CAT and E-RS Total were significantly worse in non-COPD smokers and subjects with COPD than non-COPD never smokers, although the D-12 was not as sensitive. There were no significant differences between non-COPD smokers and subjects with COPD on any of the measures.

Discussion: Assessment of health status and respiratory symptoms would be preferable to dyspnoea in view of smoking status and airflow limitation in a working population.

However, these patient-reported measures were inadequate in differentiating between smokers and subjects with COPD identified by spirometry.

Strengths and limitations of this study

- Chronic obstructive pulmonary disease (COPD)-specific health status may be measured by the COPD assessment test (CAT), respiratory symptoms by the Evaluating Respiratory Symptoms in COPD (E-RS) and dyspnoea by Dyspnoea-12 (D-12). They are independently based on specific conceptual frameworks and are not interchangeable.
- Health status, dyspnoea and respiratory symptoms may have been confused in the literature since they have different but somewhat similar meanings.
- The CAT, E-RS and D-12 are all simple and easy to administer since the methodology used in their development is similar.
- The reference values of the scores obtained from the D-12 and E-RS for healthy non-smoking subjects have not been reported although a cutoff score of 10 on the CAT is often used.
- The main limitation of this study is that it was conducted with healthy industrial workers, who were not randomly sampled, thereby potentially being biased due to the "healthy worker effect".

Introduction

Over the last two decades, patient reported outcomes (PROs) have been considered to be important in the assessment of health care services.[1-4] The St. George's Respiratory Questionnaire (SGRQ) has been one of the most frequently used tools for health status measurements in subjects with chronic obstructive pulmonary disease (COPD).[5] Short and simple instruments have become commonplace since the reduction in the number of items has become possible by methodological innovations, including the use of Rasch analysis.[6 7] First, Jones et al. developed the COPD assessment test (CAT), which has been considered to be almost equivalent to the SGRQ, making the tool easy both to administer and for patients to complete.[8-10] Second, although dyspnoea is one of the most important perceptions experienced in subjects with respiratory or cardiac disorders, it has not been easy to measure this perception due to sensory quality and affective components of dyspnoea. Yorke et al. reported that Dyspnoea-12 (D-12) provides a global score of breathlessness severity and can measure dyspnoea in a variety of diseases.[11-13] Third, another tool designed specifically to quantify exacerbations in COPD is the Exacerbations of Chronic Pulmonary Disease Tool (EXACT) Patient-Reported Outcome (known as EXACT-PRO).[14-16] Leidy et al. reported that, using 11 respiratory symptom items from the 14-item EXACT, the Evaluating Respiratory Symptoms in COPD (E-RS) is a reliable and valid instrument for evaluating respiratory symptom severity in stable COPD.[17 18]

The developers of the CAT, D-12 and E-RS have stated that the three PROs derive from different conceptual frameworks, but the methodology used in the development is

similar. In subjects with COPD, it may be commonly accepted that breathlessness is included in respiratory symptoms, and that this symptom is one of the essential components of health status. Therefore, the D-12 would be reflected in the E-RS, and the E-RS in the CAT.

We hypothesized that COPD-specific health status measured by the CAT, dyspnoea by the D-12, and symptoms by the E-RS are independently based on specific conceptual frameworks and are not interchangeable in a general population, and that comprehensive symptomatic assessment of the CAT and E-RS would be preferable to dyspnoea by the D-12 in identifying subjects who may have COPD among that population. Hence, the purpose of the present study was to examine the discriminative properties of the CAT, D-12 and E-RS in relation to smoking status and airflow limitation and to investigate whether health status, dyspnoea and respiratory symptoms could be related to a diagnosis of COPD based on the results of spirometry.

Additionally, we previously reported that the 95th percentile of the CAT scores was 13.6 in 512 healthy non-smoking subjects although the CAT score distribution overlapped remarkably between both healthy non-smoking subjects and subjects with COPD.[19] As a secondary endpoint of the present study, it was our objective to determine reference values of the scores obtained from the D-12 and E-RS for healthy non-smoking subjects.

Methods

Study Design

This is a cross-sectional observational study.

Setting

The present study was conducted between March 2012 and April 2013 at the Niigata Association of Occupational Health Incorporated, Niigata, Japan.

Participants

The study subjects were healthy industrial workers over forty years old who underwent annual health checks at this Association. All underwent a comprehensive health screening, including conventional spirometry. The exclusion criteria included: 1) abnormal findings of the pulmonary parenchyma and chest wall revealed on chest radiographs; 2) undergoing a thoracotomy in the past; 3) any admission to a hospital during the preceding three months (except hospitalization for routine tests); 4) any physician-diagnosed pulmonary diseases including lung cancer, pulmonary tuberculosis, bronchiectasis or non-tuberculous mycobacteriosis except COPD as well as asthma; and 5) unstable complications of cardiovascular, neuromuscular, renal, endocrinological, haematological, gastrointestinal, and hepatic co-morbidities. The information about their radiographic findings was obtained from annual health examinations. The participants also answered additional questions to investigate their smoking status and history.

Measurement

All eligible subjects completed the following examinations on the same day. Spirometry was performed with the use of nose clips in the sitting position with a Spiro Sift sp-470^{TM} Spirometer (Fukuda Denshi Co., Ltd., Tokyo, Japan). All measurements were performed

by a laboratory technician in accordance with guidelines published by the American Thoracic Society and European Respiratory Society.[20] The spirometric forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) values were the largest FVC and largest FEV_1 selected from data obtained from at least three acceptable forced expiratory curves, even if these values were not obtained from the same curve.[21] In this study, COPD was spirometrically defined as airflow limitation with a FEV_1/FVC less than either a fixed ratio, 0.7, or lower limit of normal (LLN) without bronchodilator administration.[22-25] Healthy subjects were defined as those with a FEV_1 of >85% predicted or a FEV_1/FVC of >0.7, forming two groups: subjects with a smoking history of ≥10 pack-years, and non-smoking subjects with a smoking history of < 1 pack-year. This definition is similar to that of the Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE) study.[26 27] The predicted values for pulmonary function were calculated based on the proposal from the Japanese Respiratory Society.[28] The LLN for the Japanese population was calculated in the present study according to the method described by Osaka et al.[29]

The Japanese versions of the EXACT, CAT and D-12 were self-administered under supervision in a booklet form. The E-RS uses 11 respiratory symptom items from the 14-item EXACT, where scores range from 0 to 40, with higher scores indicating more severe symptoms.[14-18] The RS-Total Score represents overall respiratory symptom severity.[17 18] Three subscales were not used in this analysis. The Japanese translation has been created and provided by the original developers who recommend the use of an electronic version to collect the answers. However, no electronic device with the Japanese version of the EXACT or E-RS was available so all surveys were conducted using a paper-based

method. Health status was assessed with a previously validated Japanese version of the CAT.[30] The CAT consists of eight items scored from 0 to 5 in relation to cough, sputum, dyspnea, chest tightness, capacity for exercise and activities, sleep quality and energy levels.[9 10] The CAT Scores range from 0 to 40, with a score of zero indicating no impairment. To assess the severity of dyspnoea, we used the Japanese version of the D-12,[31] which consists of twelve items (seven physical items and five affective items), each with a four point grading scale (0-3), producing a Total Score (range 0-36, with higher scores representing more severe breathlessness).[11-13]

Patient and Public Involvement

Patients were neither involved in the development of the research question, the design of this study, nor the recruitment to and conduct of the study. The abstract of the published paper will appear on the homepage of the institute.

Ethics and Funding

The present study was approved by the ethics committee of the Niigata Association of Occupational Health Incorporated. Written informed consent was obtained from all participants. This study was partly supported by the Research Funding for Longevity Sciences (30-24) from the National Center for Geriatrics and Gerontology (NCGG), Japan.

Statistical Methods

All results are expressed as means ±standard deviation (SD). Relationships between two sets of data were analysed by Spearman's rank correlation tests. In order to determine reference values for each score, we calculated the 95th percentile of the scores in healthy, non-smoking subjects using the Monte Carlo and bootstrap methods with 1,000 bootstrap

reps and used this as the upper limit of normal.[32] In comparing the groups of COPD, non-COPD smokers and non-COPD never smokers, the significance of between-group difference was determined by an analysis of variance (ANOVA) for FEV_1 or a Kruskal Wallis test for PRO scores, and when a significant difference was observed, Tukey tests or Steel-Dwass tests were used to analyze where the differences were significant, respectively. Statistical analysis was performed using IBM SPSS Statistics 22.0 (International Business Machines Corp., Armonk, New York, USA) and BellCurve for Excel (Social Survey Research Information Co., Ltd., Tokyo, Japan). A p value of less than 0.05 was considered to be statistically significant.

Results

Subject Characteristics

A total of 1,634 subjects initially participated in the study but 68 were subsequently excluded from the data analysis because of uncertainty over their smoking or other history or having one of the exclusion criteria. Therefore, a total of 1,566 subjects (985 males) were analysed. Their demographic details and spirometric results are shown in Table 1. The mean age of the subjects was 53.0 years. The mean FEV_1 value was 99.6±13.1 %predicted. The FEV_1/FVC ratio used as an index of airflow limitation ranged from 52.5% to 97.4%, with a mean of 80.1%. There was no difference between groups in the frequency of self-reported history of asthma.

The scores for the D-12, CAT and E-RS are shown in Table 2. They were skewed to the milder ends, and a floor effect was seen in all of the scores. This effect was most pronounced for the D-12 (84.0%) and E-RS (53.3%), and least for the CAT (14.6%). Regarding the interrelationships between the D-12, CAT and E-RS, they were significantly but only weakly correlated with each other (D-12 versus CAT, Spearman's correlation coefficient (Rs) =0.398, $p<0.001$; D-12 versus E-RS, Rs=0.274, $p<0.001$; and CAT versus E-RS, Rs=0.446, $p<0.001$).

In order to determine the reference values, from the data obtained from 646 healthy non-smoking subjects (Tables 1 and 2), the Bootstrap 95th percentile values were subsequently calculated and used as the upper limit of normal. For the D-12, this was 1.00; for the E-RS, it was 4.44. Since these scores do not contain decimals, the reference values for the D-12 and E-RS Total Scores were considered to be ≤1 and ≤4, respectively.

In the same way, the reference value of the CAT was calculated to be 9.88, which rounds up to 10, in the present study.

Relationships of COPD-specific PROs with Smoking and Airflow Limitation

We then divided the 1,566 subjects into three groups consisting of a COPD group based on the FEV_1/FVC using a fixed ratio, 0.7, or LLN; non-COPD current or past smokers; and non-COPD never smokers (Tables 1 and 2). Using the fixed ratio of the $FEV_1/FVC<0.7$, 85 subjects (5.4%) were diagnosed with COPD, 817 (52.2%) were non-COPD smokers, and 664 (42.4%) were non-COPD never smokers. Using the LLN definition, 34 subjects (2.2%) were diagnosed with COPD, 867 (55.4%) were non-COPD smokers, and 665 (42.5%) were non-COPD never smokers.

Relationships of the PROs between the three groups of subjects with COPD, non-COPD smokers and non-COPD never smokers are shown in Table 2 and Figures 1 (COPD based on the fixed ratio) and 2 (COPD based on the LLN). The FEV_1 (%predicted), D-12, CAT and E-RS Total were significantly separated between the three groups ($p<0.05$). There were significant differences between the three groups for FEV_1 (%predicted), D-12, CAT and E-RS Total ($p<0.05$). FEV_1 was significantly different between any two of the three groups ($p<0.001$) (Figures 1 and 2). With regard to the score distribution (Table 2), floor effect in subjects with COPD was most prominent for the D-12 (81.2% by the fixed definition and 73.5% by the LLN), and their median scores were 0.0 (Table 2). It was the least for the CAT (15.3% by the fixed definition and 14.7% by the LLN).

In investigating how many were symptomatic among 817 (by the fixed definition) and 867 (by the LLN definition) non-COPD smokers, using the above reference values, 24 (2.9%) and 24 (2.8%) were >1 on the D-12, 79 (9.7%) and 80 (9.2%) were >10 on the CAT, and 74 (9.1%) and 76 (8.8%) were >4 on the E-RS.

Regarding the group comparisons, significant differences were found between non-COPD never smokers and non-COPD smokers on all of the measures; however, significance was relatively weaker for the D-12 score ($p=0.025$ (Figure 1) and 0.029 (Figure 2)) as compared to the CAT and E-RS Total ($p<0.001$). On the CAT and E-RS Total, significant differences were also found between non-COPD never smokers and subjects with COPD ($p<0.05$); however, on the D-12, a significant difference was found only by the LLN definition ($p=0.036$, Figure 1), but not by the fixed ratio definition ($p=0.24$, Figure 1). Neither the D-12, CAT nor E-RS Total were significantly different between COPD and non-COPD smokers.

Discussion

This is the first study to directly compare differences among three COPD-specific outcomes, including dyspnoea, respiratory symptoms or health status in a general working population. First, the associations between dyspnoea measured by the D-12, health status by the CAT, and respiratory symptoms by the E-RS were significant but weak, indicating that they were far below the level of conceptual similarity. This relationship may be expected since the three PRO measurement tools were created by each developer from independent conceptual frameworks. Second, from the data obtained from 646 healthy non-smoking subjects, the Bootstrap 95th percentile values were an E-RS Total score of 4.44 indicating that the reference value is ≤4. The reference values for the D-12 and CAT score are also ≤1 and ≤10, respectively. Third, from a standpoint of the relationship with smoking status and airflow limitation, in comparison to non-COPD never smokers, health status by the CAT and respiratory symptoms by the E-RS were worse in non-COPD smokers and subjects with COPD, although dyspnoea by the D-12 was not as sensitive. None of these PRO measures were adequate in differentiating between non-COPD smokers and subjects with COPD.

In the present study, there were considerable numbers of smokers with preserved pulmonary function, or without airflow limitation, 52.2% by the fixed ratio and 55.4% by the LLN, respectively, who may be diagnosed as COPD-free by spirometric criteria. Their dyspnoea, health status and respiratory symptoms were significantly worse than those in never smokers, which is compatible with recent population studies.[33-36] They also indicated that pulmonary disease and impairments were common in smokers with preserved pulmonary function although they did not meet the current criteria of COPD

based on spirometry,[35 36] and that symptoms might be more sensitive than spirometry in detecting smoking-related respiratory impairments. Actually, symptom-based questionnaires to screen for COPD that do not include spirometry have been developed.[37 38]

Conversely, the present study adds that PROs in non-COPD smokers were not significantly different from those in subjects with COPD. Actually, about 9% of smokers with preserved pulmonary function were judged to be symptomatic according to the reference values of CAT>10 or E-RS>4. Their symptoms may tend to exacerbate in the future, advance to COPD, or be treated as if they were COPD. How to manage this group of symptomatic smokers without airflow limitation is a key issue to be solved through careful long-term follow-ups.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2011 consensus report proposed a revised "combined COPD assessment" classification in which symptoms should be assessed either as a dyspnoea measure using the modified Medical Research Council (mMRC) dyspnoea scale, or as a health status measure using the CAT.[39] We have contributed to the establishment of this concept by demonstrating the significant predictive properties of dyspnoea and health status independently of airflow limitation.[40 41] There has hitherto been much debate over how to assess symptoms in this new classification. Although dyspnoea was not measured by the mMRC dyspnoea scale but by D-12, interrelationships between the D-12, CAT and E-RS were weak to moderate. Therefore, it may be difficult to use dyspnoea, health status and respiratory symptoms in a mutually complementary form. The GOLD recommends a comprehensive assessment of symptoms rather than just a measure of dyspnoea. The present study

supports this by showing that the D-12 had the most marked floor effects even in subjects with COPD, and that the CAT and E-RS seemed to be more sensitive in discriminating subjects based on smoking and COPD than the D-12.

We reported in 2013 that the 95th percentile of the scores in 512 healthy, non-smoking subjects were used as the upper limit of normal in exactly the same way as in the present study.[19] For the CAT, it was 13.6. In 2014 Pinto et al. published some of the results of the Canadian Cohort Obstructive Lung Disease (CanCOLD) study and reported that the normative value for the CAT score was determined to be 16 from a population-based study where they used post-bronchodilator spirometric values.[42] Compared with the above two reports, a score of 10 was the 95th percentile of the scores in healthy industrial workers from Japan, and it is the lowest in the present study. The GOLD currently states that the boundary between GOLD A and B and between GOLD C and D is a CAT score of 10,[39 43] which is consistent with the important result of the present study although there might be some margin of error depending on the methodologies and subjects of the studies.

This study has several limitations. Although we intended to determine the border of the normal level of the D-12, CAT and E-RS Total scores, the study subjects were not randomly sampled and there could be a risk of sample bias. The D-12, CAT and E-RS are sufficiently validated for measuring PROs in subjects with COPD, but most participants were not patients with COPD but rather healthy workers. As such, there is a possibility that they are not appropriate tools for the study population. However, since the successful application of the CAT in a working population or a random sampling frame from the populations has also been reported,[19 42] there may be a reason to be hopeful for success

with the D-12 and E-RS. Although post-bronchodilator spirometric values are recommended to be used to make a diagnosis of COPD,[39 43] the diagnosis was made only from pre-bronchodilator spirometric information in the present study. Furthermore, the present study was conducted in Japanese so that each of the instruments would have been translated from the original language of its development. Although the Japanese version has been validated in each case, it may be a limit to the generalizability of the research across the globe.

Three main conclusions may be drawn from our findings. First, associations among dyspnoea measured by the D-12, health status by the CAT, and respiratory symptoms by the E-RS, were statistically significant but weak, indicating that they cannot be used interchangeably. Second, using the data obtained from 646 healthy non-smoking subjects, the reference values of the D-12, CAT and E-RS were ≤1, ≤10 and ≤4, respectively. Third, from a standpoint of the relationship with smoking status and airflow limitation, health status and respiratory symptoms may be more closely related to non-COPD smokers and subjects with COPD than dyspnoea as compared to non-COPD never smokers; however, none of these PRO measures can differentiate between non-COPD smokers and subjects with COPD. How to manage non-COPD symptomatic smokers should be investigated in the future.

Other information

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Contributors

KN contributed, as the principal investigator, to the study concept and design, analysis of the results, and writing of the manuscript.

TO contributed to statistical analysis, the interpretation and editing of the manuscript.

KN contributed to statistical analysis.

MO contributed to acquisition of data.

YH contributed to the interpretation and editing of the manuscript.

SM contributed to performance of the study and acquisition of data.

All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

Ethics Approval

The present study was approved by the ethics committee of the Niigata Association of Occupational Health Incorporated (No. 6, lastly dated January 8, 2013).

Data Sharing Statement

No additional data are available.

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Figure Legends

Figure 1 Box plots representing the distributions of FEV_1 (%predicted), D-12 (Dyspnoea-12) score, CAT (COPD assessment test) score and E-RS (Evaluating Respiratory Symptoms in COPD) Total score in non-COPD never smokers (Group A, n=664), non-COPD current or past smokers (Group B, n=817) and COPD based on FEV_1/FVC using a fixed ratio, 0.7 (Group C, n=85). The horizontal lines in the boxes represent the median, and the top and bottom of the boxes represent the 75th and 25th percentiles, respectively. Bars represent the upper adjacent value (75th percentile plus 1.5 times the interquartile range) and the lower adjacent value (25th percentile minus 1.5 times the interquartile range), and the crosses represent outliers.

Figure 2 Box plots representing the distributions of FEV_1 (%predicted), D-12 (Dyspnoea-12) score, CAT (COPD assessment test) score and E-RS (Evaluating Respiratory Symptoms in COPD) Total score in non-COPD never smokers (Group A, n=665), non-COPD current or past smokers (Group B, n=867) and COPD based on FEV_1/FVC using the LLN (Group C, n=34). The horizontal lines in the boxes represent the median, and the top and bottom of the boxes represent the 75th and 25th percentiles, respectively. Bars represent the upper adjacent value (75th percentile plus 1.5 times the interquartile range) and the lower adjacent value (25th percentile minus 1.5 times the interquartile range), and the crosses represent outliers.

Table 1. Demographic details and spirometric results.

	Total subjects	Age	Male	Cumulative smoking	Prior diagnosis of asthma	Prior diagnosis of COPD	FEV_1	FEV_1/FVC
	Number	Years	Number (%)	Pack-years	Number (%)	Number (%)	%predicted	%
All subjects	1566	53.0 ± 8.7	985 (62.9%)	14.1 ± 18.6	46 (2.9%)	10 (0.6%)	99.6 ± 13.1	80.1 ± 5.8
Healthy non-smoking subjects¶#	646	53.3 ± 8.8	189 (29.3%)	0.0 ± 0.1	17 (2.6%)	2 (0.3%)	105.5 ± 10.7	82.3 ± 4.4
COPD defined by fixed ratio	85	60.4 ± 9.4	83 (97.6%)	36.9 ± 28.1	5 (5.9%)	4 (4.7%)	80.2 ± 11.6	66.0 ± 4.1
Non-COPD smokers	817	51.9 ± 8.0	704 (86.2%)	23.1 ± 16.9	23 (2.8%)	4 (0.5%)	97.9 ± 11.8	80.1 ± 4.7
Non-COPD never smokers	664	53.4 ± 8.9	198 (29.8%)	0.0 ± 0.0	18 (2.7%)	2 (0.3%)	104.2 ± 12.0	82.0 ± 4.5
COPD defined by LLN	34	57.7 ± 10.4	29 (85.3%)	31.9 ± 25.8	2 (5.9%)	2 (5.9%)	77.3 ± 13.1	63.0 ± 4.9
Non-COPD smokers	867	52.4 ± 8.3	755 (87.1%)	24.2 ± 18.3	26 (3.0%)	6 (0.7%)	97.1 ± 12.3	79.4 5.3
Non-COPD never smokers	665	53.5 ± 8.9	201 (30.2%)	0.0 ± 0.0	18 (2.7%)	2 (0.3%)	104.1 ± 12.1	82.0 ± 4.5

¶ FEV_1 of >85% predicted and FEV_1/FVC of >0.7, # a smoking history of <1 pack-year

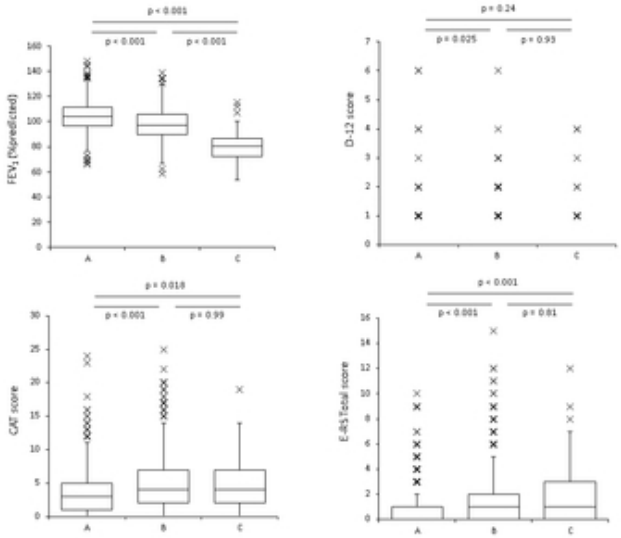
Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; LLN, lower limit of normal.

Table 2. Distributions of the D-12, CAT and E-RS Total scores.

	D-12 score (0-36)					CAT score (0-40)					E-RS Total score (0-40)				
	mean	median	SD	max.	floor effect	mean	median	SD	max.	floor effect	mean	median	SD	max.	floor effect
All subjects	0.2	0.0	0.6	6.0	84.0%	4.3	3.0	3.9	25.0	14.6%	1.2	0.0	1.9	15.0	53.3%
Healthy non-smoking subjects¶#	0.2	0.0	0.5	6.0	86.5%	3.6	3.0	3.3	24.0	15.9%	0.9	0.0	1.6	10.0	62.5%
COPD defined by fixed ratio	0.3	0.0	0.8	4.0	81.2%	4.8	4.0	4.1	19.0	15.3%	1.6	1.0	2.2	12.0	44.7%
Non-COPD smokers	0.2	0.0	0.5	6.0	82.0%	4.8	4.0	4.1	25.0	13.1%	1.5	1.0	2.1	15.0	46.5%
Non-COPD never smokers	0.2	0.0	0.5	6.0	86.7%	3.6	3.0	3.4	24.0	16.3%	0.9	0.0	1.6	12.0	62.7%
COPD defined by LLN	0.5	0.0	1.0	4.0	73.5%	6.2	6.0	4.8	19.0	14.7%	1.8	1.5	2.1	9.0	38.2%
Non-COPD smokers	0.2	0.0	0.5	6.0	82.2%	4.8	4.0	4.1	25.0	13.0%	1.5	1.0	2.1	15.0	46.6%
Non-COPD never smokers	0.2	0.0	0.6	6.0	86.8%	3.6	3.0	3.4	24.0	16.5%	0.9	0.0	1.6	10.0	62.7%

¶ FEV_1 of >85% predicted and FEV_1/FVC of >0.7, # a smoking history of <1 pack-year. Numbers in parentheses indicate the theoretical score range, and higher scores indicate worse status.

Abbreviations: CAT, COPD assessment test; COPD, chronic obstructive pulmonary disease; D-12, Dyspnoea-12; E-RS, Evaluating Respiratory Symptoms in COPD; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; LLN, lower limit of normal.



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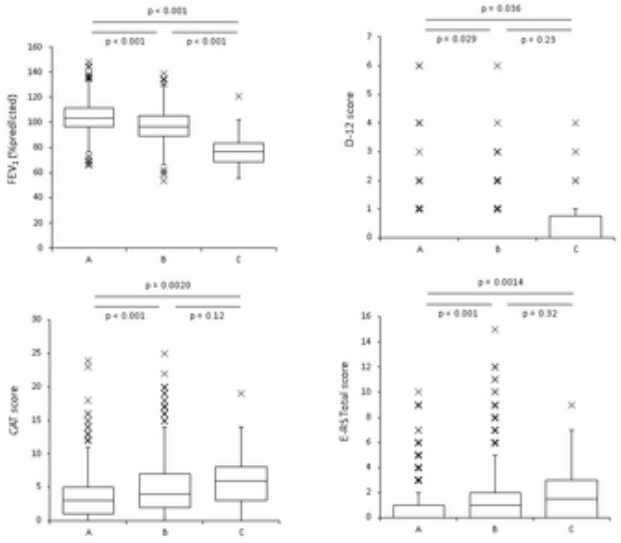

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 4	The cross-sectional data
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 4 - 5	
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 6 - 7	
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 7	
Methods				
Study design	4	Present key elements of study design early in the paper	Page 8	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 8	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	Page 8	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 8 - 10	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 8 - 10	
Bias	9	Describe any efforts to address potential sources of bias		
Study size	10	Explain how the study size was arrived at		

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 10 - 11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 10 - 11
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 12
		(b) Give reasons for non-participation at each stage	Page 12
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page 12
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Page 13 - 14
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 15, 18
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 17-18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 15 - 18
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 15 - 18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 10, 19

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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How different are COPD-specific patient reported outcomes, health status, dyspnoea and respiratory symptoms? An observational study in a working population.

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How different are COPD-specific patient reported outcomes, health status, dyspnoea and respiratory symptoms? An observational study in a working population.

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Running Title:

Health Status, Dyspnoea and Respiratory Symptoms in a Working Population

Key words:

Chronic obstructive pulmonary disease (COPD);

Patient-reported outcome (PRO);

The COPD assessment test (CAT);

Dyspnoea-12 (D-12);

The Evaluating Respiratory Symptoms in COPD (E-RS).

Abstract

Introduction: We hypothesized that chronic obstructive pulmonary disease (COPD)-specific health status measured by the COPD assessment test (CAT), respiratory symptoms by the Evaluating Respiratory Symptoms in COPD (E-RS) and dyspnoea by Dyspnoea-12 (D-12) are independently based on specific conceptual frameworks and are not interchangeable. We aimed to discover whether health status, dyspnoea or respiratory symptoms could be related to smoking status and airflow limitation in a working population.

Methods: This is an observational study. The cross-sectional data, including spirometry, obtained from 1,566 healthy industrial workers were analyzed.

Results: Relationships between D-12, CAT and E-RS Total were statistically significant but weak (Spearman's correlation coefficient＝0.274 to 0.446). In 646 healthy non-smoking subjects, as the reference scores for healthy non-smoking subjects, that is, upper threshold, the Bootstrap 95th percentile values were 1.00 for D-12, 9.88 for CAT and 4.44 for E-RS. Of the 1,566 workers, 85 (5.4%) were diagnosed with COPD using the fixed ratio of the forced expiratory volume in one second/forced vital capacity<0.7, and 34 (2.2%) using the lower limit of normal. The CAT and E-RS Total were significantly worse in non-COPD smokers and subjects with COPD than non-COPD never smokers, although the D-12 was not as sensitive. There were no significant differences between non-COPD smokers and subjects with COPD on any of the measures.

Conclusions: Assessment of health status and respiratory symptoms would be preferable to dyspnoea in view of smoking status and airflow limitation in a working population.

However, these patient-reported measures were inadequate in differentiating between smokers and subjects with COPD identified by spirometry.

Strengths and limitations of this study

- The COPD assessment test (CAT), the Evaluating Respiratory Symptoms in COPD (E-RS) and Dyspnoea-12 (D-12) are all easy to administer since the methodology used in their development is similar.
- The associations between dyspnoea measured by the D-12, health status by the CAT, and respiratory symptoms by the E-RS were significant but weak, indicating that they were far below the level of conceptual similarity.
- As the reference scores for healthy non-smoking subjects, that is, upper threshold, the Bootstrap 95th percentile values were 1.00 for D-12, 9.88 for CAT and 4.44 for E-RS.
- The main limitation of this study is that it was conducted with healthy industrial workers who were not randomly sampled, thereby potentially being biased due to the "healthy worker effect".

Introduction

Over the last two decades, patient reported outcomes (PROs) have been considered to be important in the assessment of health care services.[1-4] The St. George's Respiratory Questionnaire (SGRQ) has been one of the most frequently used tools for health status measurements in subjects with chronic obstructive pulmonary disease (COPD).[5] Short and simple instruments have become commonplace since the reduction in the number of items has become possible by methodological innovations, including the use of Rasch analysis.[6 7] First, Jones et al. developed the COPD assessment test (CAT), which has been considered to be almost equivalent to the SGRQ, making the tool easy both to administer and for patients to complete.[8-10] Second, although dyspnoea is one of the most important perceptions experienced in subjects with respiratory or cardiac disorders, it has not been easy to measure this perception due to sensory quality and affective components of dyspnoea. Yorke et al. reported that Dyspnoea-12 (D-12) provides a global score of breathlessness severity and can measure dyspnoea in a variety of diseases.[11-13] Third, another tool designed specifically to quantify exacerbations in COPD is the Exacerbations of Chronic Pulmonary Disease Tool (EXACT) Patient-Reported Outcome (known as EXACT-PRO).[14-16] Leidy et al. reported that, using 11 respiratory symptom items from the 14-item EXACT, the Evaluating Respiratory Symptoms in COPD (E-RS) is a reliable and valid instrument for evaluating respiratory symptom severity in stable COPD.[17 18]

The developers of the CAT, D-12 and E-RS have stated that the three PROs derive from different conceptual frameworks, but the methodology used in the development is

similar. In subjects with COPD, it may be commonly accepted that breathlessness is included in respiratory symptoms, and that this symptom is one of the essential components of health status. Therefore, the D-12 would be reflected in the E-RS, and the E-RS in the CAT.

We hypothesized that COPD-specific health status measured by the CAT, dyspnoea by the D-12, and symptoms by the E-RS are independently based on specific conceptual frameworks and are not interchangeable in a general population, and that comprehensive symptomatic assessment of the CAT and E-RS would be preferable to dyspnoea by the D-12 in identifying subjects who may have COPD among that population. Hence, the purpose of the present study was to examine the discriminative properties of the CAT, D-12 and E-RS in relation to smoking status and airflow limitation and to investigate whether health status, dyspnoea and respiratory symptoms could be related to a diagnosis of COPD based on the results of spirometry.

Additionally, we previously reported that the 95th percentile of the CAT scores was 13.6 in 512 healthy non-smoking subjects although the CAT score distribution overlapped remarkably between both healthy non-smoking subjects and subjects with COPD.[19] As a secondary endpoint of the present study, it was our objective to determine reference values of the scores obtained from the D-12 and E-RS for healthy non-smoking subjects.

Methods

Study Design

This is a cross-sectional observational study.

Setting

The present study was conducted between March 2012 and April 2013 at the Niigata Association of Occupational Health Incorporated, Niigata, Japan.

Participants

The study subjects were healthy industrial workers over forty years old who underwent annual health checks at this Association. All underwent a comprehensive health screening, including conventional spirometry. The exclusion criteria included: 1) abnormal findings of the pulmonary parenchyma and chest wall revealed on chest radiographs; 2) undergoing a thoracotomy in the past; 3) any admission to a hospital during the preceding three months (except hospitalization for routine tests); 4) any physician-diagnosed pulmonary diseases including lung cancer, pulmonary tuberculosis, bronchiectasis or non-tuberculous mycobacteriosis except COPD as well as asthma; and 5) unstable complications of cardiovascular, neuromuscular, renal, endocrinological, haematological, gastrointestinal, and hepatic co-morbidities. The information about their radiographic findings was obtained from annual health examinations. The participants also answered additional questions to investigate their smoking status and history.

Measurement

All eligible subjects completed the following examinations on the same day. Spirometry was performed with the use of nose clips in the sitting position with a Spiro Sift sp-470^{TM} Spirometer (Fukuda Denshi Co., Ltd., Tokyo, Japan). All measurements were performed

by a laboratory technician in accordance with guidelines published by the American Thoracic Society and European Respiratory Society.[20] The spirometric forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) values were the largest FVC and largest FEV_1 selected from data obtained from at least three acceptable forced expiratory curves, even if these values were not obtained from the same curve.[21] In this study, COPD was spirometrically defined as airflow limitation with a FEV_1/FVC less than either a fixed ratio, 0.7, or lower limit of normal (LLN) without bronchodilator administration.[22-25] Healthy subjects were defined as those with a FEV_1 of >85% predicted or a FEV_1/FVC of >0.7, forming two groups: subjects with a smoking history of ≥10 pack-years, and non-smoking subjects with a smoking history of < 1 pack-year. This definition is similar to that of the Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE) study.[26 27] The predicted values for pulmonary function were calculated based on the proposal from the Japanese Respiratory Society.[28] The LLN for the Japanese population was calculated in the present study according to the method described by Osaka et al.[29]

The Japanese versions of the EXACT, CAT and D-12 were self-administered in the same order under supervision in a booklet form prior to the pulmonary function tests. The E-RS uses 11 respiratory symptom items from the 14-item EXACT, where scores range from 0 to 40, with higher scores indicating more severe symptoms.[14-18] The RS-Total Score represents overall respiratory symptom severity.[17 18] Three subscales were not used in this analysis. The Japanese translation has been created and provided by the original developers who recommend the use of an electronic version to collect the answers. However, no electronic device with the Japanese version of the EXACT or E-RS was

available so all surveys were conducted using a paper-based method. Health status was assessed with a previously validated Japanese version of the CAT.[30] The CAT consists of eight items scored from 0 to 5 in relation to cough, sputum, dyspnea, chest tightness, capacity for exercise and activities, sleep quality and energy levels.[9 10] The CAT Scores range from 0 to 40, with a score of zero indicating no impairment. To assess the severity of dyspnoea, we used the Japanese version of the D-12,[31] which consists of twelve items (seven physical items and five affective items), each with a four point grading scale (0-3), producing a Total Score (range 0-36, with higher scores representing more severe breathlessness).[11-13]

Patient and Public Involvement

Patients were neither involved in the development of the research question, the design of this study, nor the recruitment to and conduct of the study. The abstract of the published paper will appear on the homepage of the institute.

Ethics and Funding

The present study was approved by the ethics committee of the Niigata Association of Occupational Health Incorporated. Written informed consent was obtained from all participants. This study was partly supported by the Research Funding for Longevity Sciences (30-24) from the National Center for Geriatrics and Gerontology (NCGG), Japan.

Statistical Methods

All results are expressed as means ±standard deviation (SD). Relationships between two sets of data were analysed by Spearman's rank correlation tests. In order to determine reference values for each score, we calculated the 95th percentile of the scores in healthy,

non-smoking subjects using the Monte Carlo and bootstrap methods with 1,000 bootstrap reps and used this as the upper limit of normal.[32] In comparing the groups of COPD, non-COPD smokers and non-COPD never smokers, the significance of between-group difference was determined by an analysis of variance (ANOVA) for FEV_1 or a Kruskal-Wallis test for PRO scores, and when a significant difference was observed, Tukey tests or Steel-Dwass tests were used to analyse where the differences were significant, respectively. Statistical analysis was performed using IBM SPSS Statistics 22.0 (International Business Machines Corp., Armonk, New York, USA) and BellCurve for Excel (Social Survey Research Information Co., Ltd., Tokyo, Japan). A p value of less than 0.05 was considered to be statistically significant.

Results

Subject Characteristics

A total of 1,634 subjects initially participated in the study but 68 were subsequently excluded from the data analysis because of uncertainty over their smoking or other history or having one of the exclusion criteria. Therefore, a total of 1,566 subjects (985 males) were analysed. Their demographic details and spirometric results are shown in Table 1. The mean age of the subjects was 53.0 years. The mean FEV_1 value was 99.6±13.1 %predicted. The FEV_1/FVC ratio used as an index of airflow limitation ranged from 52.5% to 97.4%, with a mean of 80.1%. There was no difference between groups in the frequency of self-reported history of asthma.

The scores for the D-12, CAT and E-RS are shown in Table 2. They were skewed to the milder ends, and a floor effect was seen in all of the scores. This effect was most pronounced for the D-12 (84.0%) and E-RS (53.3%), and least for the CAT (14.6%). Regarding the interrelationships between the D-12, CAT and E-RS, they were significantly but only weakly correlated with each other (D-12 versus CAT, Spearman's correlation coefficient (Rs) =0.398, $p<0.001$; D-12 versus E-RS, Rs=0.274, $p<0.001$; and CAT versus E-RS, Rs=0.446, $p<0.001$).

In order to determine the reference values, from the data obtained from 646 healthy non-smoking subjects (Tables 1 and 2), the Bootstrap 95th percentile values were subsequently calculated and used as the upper limit of normal. For the D-12, this was 1.00; for the E-RS, it was 4.44. Since these scores do not contain decimals, the reference values for the D-12 and E-RS Total Scores were considered to be ≤1 and ≤4, respectively.

In the same way, the reference value of the CAT was calculated to be 9.88, which rounds up to 10, in the present study.

Concordant and discordant results between tools were set to be examined using the above cut-off values (Table 3). However, since there were only a small number of subjects with higher scores on each instrument due to skewed score distribution, those with higher scores on one instrument and lower scores on another were less than one-tenth of all of the subjects involved.

Relationships of COPD-specific PROs with Smoking and Airflow Limitation

We then divided the 1,566 subjects into three groups consisting of a COPD group based on the FEV_1/FVC using a fixed ratio, 0.7, or LLN; non-COPD current or past smokers; and non-COPD never smokers (Tables 1 and 2). Using the fixed ratio of the $FEV_1/FVC<0.7$, 85 subjects (5.4%) were diagnosed with COPD, 817 (52.2%) were non-COPD smokers, and 664 (42.4%) were non-COPD never smokers. Using the LLN definition, 34 subjects (2.2%) were diagnosed with COPD, 867 (55.4%) were non-COPD smokers, and 665 (42.5%) were non-COPD never smokers.

Relationships of the PROs between the three groups of subjects with COPD, non-COPD smokers and non-COPD never smokers are shown in Table 2 and Figures 1 (COPD based on the fixed ratio) and 2 (COPD based on the LLN). The FEV_1 (%predicted), D-12, CAT and E-RS Total were significantly separated between the three groups ($p<0.05$). There were significant differences between the three groups for FEV_1 (%predicted), D-12, CAT and E-RS Total ($p<0.05$). FEV_1 was significantly different between any two of the three groups ($p<0.001$) (Figures 1 and 2). With regard to the

score distribution (Table 2), floor effect in subjects with COPD was most prominent for the D-12 (81.2% by the fixed definition and 73.5% by the LLN), and their median scores were 0.0 (Table 2). It was the least for the CAT (15.3% by the fixed definition and 14.7% by the LLN).

In investigating how many were symptomatic among 817 (by the fixed definition) and 867 (by the LLN definition) non-COPD smokers, using the above reference values, 24 (2.9%) and 24 (2.8%) were >1 on the D-12, 79 (9.7%) and 80 (9.2%) were >10 on the CAT, and 74 (9.1%) and 76 (8.8%) were >4 on the E-RS.

Regarding the group comparisons, significant differences were found between non-COPD never smokers and non-COPD smokers on all of the measures; however, significance was relatively weaker for the D-12 score ($p=0.025$ (Figure 1) and 0.029 (Figure 2)) as compared to the CAT and E-RS Total ($p<0.001$). On the CAT and E-RS Total, significant differences were also found between non-COPD never smokers and subjects with COPD ($p<0.05$); however, on the D-12, a significant difference was found only by the LLN definition ($p=0.036$, Figure 1), but not by the fixed ratio definition ($p=0.24$, Figure 1). Neither the D-12, CAT nor E-RS Total were significantly different between COPD and non-COPD smokers.

Discussion

This is the first study to directly compare differences among three COPD-specific outcomes, including dyspnoea, respiratory symptoms or health status in a general working population. First, the associations between dyspnoea measured by the D-12, health status by the CAT, and respiratory symptoms by the E-RS were significant but weak, indicating that they were far below the level of conceptual similarity. This relationship may be expected since the three PRO measurement tools were created by each developer from independent conceptual frameworks. Second, from the data obtained from 646 healthy non-smoking subjects, the Bootstrap 95th percentile values were an E-RS Total score of 4.44 indicating that the reference value is ≤4. The reference values for the D-12 and CAT score are also ≤1 and ≤10, respectively. Third, from a standpoint of the relationship with smoking status and airflow limitation, in comparison to non-COPD never smokers, health status by the CAT and respiratory symptoms by the E-RS were worse in non-COPD smokers and subjects with COPD, although dyspnoea by the D-12 was not as sensitive. None of these PRO measures were adequate in differentiating between non-COPD smokers and subjects with COPD.

In the present study, there were considerable numbers of smokers with preserved pulmonary function, or without airflow limitation, 52.2% by the fixed ratio and 55.4% by the LLN, respectively, who may be diagnosed as COPD-free by spirometric criteria. Their dyspnoea, health status and respiratory symptoms were significantly worse than those in never smokers, which is compatible with recent population studies.[33-36] They also indicated that pulmonary disease and impairments were common in smokers with preserved pulmonary function although they did not meet the current criteria of COPD

based on spirometry,[35 36] and that symptoms might be more sensitive than spirometry in detecting smoking-related respiratory impairments. Actually, symptom-based questionnaires to screen for COPD that do not include spirometry have been developed.[37 38]

Conversely, the present study adds that PROs in non-COPD smokers were not significantly different from those in subjects with COPD. Actually, about 9% of smokers with preserved pulmonary function were judged to be symptomatic according to the reference values of CAT>10 or E-RS>4. Their symptoms may tend to exacerbate in the future, advance to COPD, or be treated as if they were COPD. How to manage this group of symptomatic smokers without airflow limitation is a key issue to be solved through careful long-term follow-ups.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2011 consensus report proposed a revised "combined COPD assessment" classification in which symptoms should be assessed either as a dyspnoea measure using the modified Medical Research Council (mMRC) dyspnoea scale, or as a health status measure using the CAT.[39] We have contributed to the establishment of this concept by demonstrating the significant predictive properties of dyspnoea and health status independently of airflow limitation.[40 41] There has hitherto been much debate over how to assess symptoms in this new classification. Although dyspnoea was not measured by the mMRC dyspnoea scale but by D-12, interrelationships between the D-12, CAT and E-RS were weak to moderate. Therefore, it may be difficult to use dyspnoea, health status and respiratory symptoms in a mutually complementary form. The GOLD recommends a comprehensive assessment of symptoms rather than just a measure of dyspnoea. The present study

supports this by showing that the D-12 had the most marked floor effects even in subjects with COPD, and that the CAT and E-RS seemed to be more sensitive in discriminating subjects based on smoking and COPD than the D-12.

We reported in 2013 that the 95th percentile of the scores in 512 healthy, non-smoking subjects were used as the upper limit of normal in exactly the same way as in the present study.[19] For the CAT, it was 13.6. In 2014 Pinto et al. published some of the results of the Canadian Cohort Obstructive Lung Disease (CanCOLD) study and reported that the normative value for the CAT score was determined to be 16 from a population-based study where they used post-bronchodilator spirometric values.[42] Compared with the above two reports, a score of 10 was the 95th percentile of the scores in healthy industrial workers from Japan, and it is the lowest in the present study. The GOLD currently states that the boundary between GOLD A and B and between GOLD C and D is a CAT score of 10,[39 43] which is consistent with the important result of the present study although there might be some margin of error depending on the methodologies and subjects of the studies.

This study has several limitations. Although we intended to determine the border of the normal level of the D-12, CAT and E-RS Total scores, the study subjects were not randomly sampled and there could be a risk of sample bias. The D-12, CAT and E-RS are sufficiently validated for measuring PROs in subjects with COPD, but most participants were not patients with COPD but rather healthy workers. As such, there is a possibility that they are not appropriate tools for the study population. However, since the successful application of the CAT in a working population or a random sampling frame from the populations has also been reported,[19 42] there may be a reason to be hopeful for success

with the D-12 and E-RS. Although post-bronchodilator spirometric values are recommended to be used to make a diagnosis of COPD,[39 43] the diagnosis was made only from pre-bronchodilator spirometric information in the present study. Furthermore, the present study was conducted in Japanese so that each of the instruments would have been translated from the original language of its development. Although the Japanese version has been validated in each case, it may be a limit to the generalizability of the research across the globe.

Three main conclusions may be drawn from our findings. First, associations among dyspnoea measured by the D-12, health status by the CAT, and respiratory symptoms by the E-RS, were statistically significant but weak, indicating that they cannot be used interchangeably. Second, using the data obtained from 646 healthy non-smoking subjects, the reference values of the D-12, CAT and E-RS were ≤1, ≤10 and ≤4, respectively. Third, from a standpoint of the relationship with smoking status and airflow limitation, health status and respiratory symptoms may be more closely related to non-COPD smokers and subjects with COPD than dyspnoea as compared to non-COPD never smokers; however, none of these PRO measures can differentiate between non-COPD smokers and subjects with COPD. How to manage non-COPD symptomatic smokers should be investigated in the future.

Other information

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Contributors

KN contributed, as the principal investigator, to the study concept and design, analysis of the results, and writing of the manuscript.

TO contributed to statistical analysis, the interpretation and editing of the manuscript.

KN contributed to statistical analysis.

MO contributed to acquisition of data.

YH contributed to the interpretation and editing of the manuscript.

SM contributed to performance of the study and acquisition of data.

All authors have read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

Ethics Approval

The present study was approved by the ethics committee of the Niigata Association of Occupational Health Incorporated (No. 6, lastly dated January 8, 2013).

Data Sharing Statement

No additional data are available.

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Figure Legends

Figure 1 Box plots representing the distributions of FEV_1 (%predicted), D-12 (Dyspnoea-12) score, CAT (COPD assessment test) score and E-RS (Evaluating Respiratory Symptoms in COPD) Total score in non-COPD never smokers (Group A, n=664), non-COPD current or past smokers (Group B, n=817) and COPD based on FEV_1/FVC using a fixed ratio, 0.7 (Group C, n=85). The horizontal lines in the boxes represent the median, and the top and bottom of the boxes represent the 75th and 25th percentiles, respectively. Bars represent the upper adjacent value (75th percentile plus 1.5 times the interquartile range) and the lower adjacent value (25th percentile minus 1.5 times the interquartile range), and the crosses represent outliers.

Figure 2 Box plots representing the distributions of FEV_1 (%predicted), D-12 (Dyspnoea-12) score, CAT (COPD assessment test) score and E-RS (Evaluating Respiratory Symptoms in COPD) Total score in non-COPD never smokers (Group A, n=665), non-COPD current or past smokers (Group B, n=867) and COPD based on FEV_1/FVC using the LLN (Group C, n=34). The horizontal lines in the boxes represent the median, and the top and bottom of the boxes represent the 75th and 25th percentiles, respectively. Bars represent the upper adjacent value (75th percentile plus 1.5 times the interquartile range) and the lower adjacent value (25th percentile minus 1.5 times the interquartile range), and the crosses represent outliers.

Table 1. Demographic details and spirometric results.

	Total subjects	Age	Male	Cumulative smoking	Prior diagnosis of asthma	Prior diagnosis of COPD	FEV_1	FEV_1/FVC
	Number	Years	Number (%)	Pack-years	Number (%)	Number (%)	%predicted	%
All subjects	1,566	53.0 ± 8.7	985 (62.9%)	14.1 ± 18.6	46 (2.9%)	10 (0.6%)	99.6 ± 13.1	80.1 ± 5.8
Healthy non-smoking subjects¶#	646	53.3 ± 8.8	189 (29.3%)	0.0 ± 0.1	17 (2.6%)	2 (0.3%)	105.5 ± 10.7	82.3 ± 4.4
COPD defined by fixed ratio	85	60.4 ± 9.4	83 (97.6%)	36.9 ± 28.1	5 (5.9%)	4 (4.7%)	80.2 ± 11.6	66.0 ± 4.1
Non-COPD smokers	817	51.9 ± 8.0	704 (86.2%)	23.1 ± 16.9	23 (2.8%)	4 (0.5%)	97.9 ± 11.8	80.1 ± 4.7
Non-COPD never smokers	664	53.4 ± 8.9	198 (29.8%)	0.0 ± 0.0	18 (2.7%)	2 (0.3%)	104.2 ± 12.0	82.0 ± 4.5
COPD defined by LLN	34	57.7 ± 10.4	29 (85.3%)	31.9 ± 25.8	2 (5.9%)	2 (5.9%)	77.3 ± 13.1	63.0 ± 4.9
Non-COPD smokers	867	52.4 ± 8.3	755 (87.1%)	24.2 ± 18.3	26 (3.0%)	6 (0.7%)	97.1 ± 12.3	79.4 5.3
Non-COPD never smokers	665	53.5 ± 8.9	201 (30.2%)	0.0 ± 0.0	18 (2.7%)	2 (0.3%)	104.1 ± 12.1	82.0 ± 4.5

¶ FEV_1 of >85% predicted and FEV_1/FVC of >0.7, # a smoking history of <1 pack-year

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; LLN, lower limit of normal.

Table 2. Distributions of the D-12, CAT and E-RS Total scores.

	D-12 score (0-36)					CAT score (0-40)					E-RS Total score (0-40)				
	mean	median	SD	max.	floor effect	mean	median	SD	max.	floor effect	mean	median	SD	max.	floor effect
All subjects	0.2	0.0	0.6	6.0	84.0%	4.3	3.0	3.9	25.0	14.6%	1.2	0.0	1.9	15.0	53.3%
Healthy non-smoking subjects¶#	0.2	0.0	0.5	6.0	86.5%	3.6	3.0	3.3	24.0	15.9%	0.9	0.0	1.6	10.0	62.5%
COPD defined by fixed ratio	0.3	0.0	0.8	4.0	81.2%	4.8	4.0	4.1	19.0	15.3%	1.6	1.0	2.2	12.0	44.7%
Non-COPD smokers	0.2	0.0	0.5	6.0	82.0%	4.8	4.0	4.1	25.0	13.1%	1.5	1.0	2.1	15.0	46.5%
Non-COPD never smokers	0.2	0.0	0.5	6.0	86.7%	3.6	3.0	3.4	24.0	16.3%	0.9	0.0	1.6	12.0	62.7%
COPD defined by LLN	0.5	0.0	1.0	4.0	73.5%	6.2	6.0	4.8	19.0	14.7%	1.8	1.5	2.1	9.0	38.2%
Non-COPD smokers	0.2	0.0	0.5	6.0	82.2%	4.8	4.0	4.1	25.0	13.0%	1.5	1.0	2.1	15.0	46.6%
Non-COPD never smokers	0.2	0.0	0.6	6.0	86.8%	3.6	3.0	3.4	24.0	16.5%	0.9	0.0	1.6	10.0	62.7%

¶ FEV_1 of >85% predicted and FEV_1/FVC of >0.7, # a smoking history of <1 pack-year. Numbers in parentheses indicate the theoretical score range, and higher scores indicate worse status.

Abbreviations: CAT, COPD assessment test; COPD, chronic obstructive pulmonary disease; D-12, Dyspnoea-12; E-RS, Evaluating Respiratory Symptoms in COPD; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; LLN, lower limit of normal.

Table 3. Concordant and discordant results between tools using the cut-off values.

COPD assessment test (CAT) and Evaluating Respiratory Symptoms in COPD (E-RS)

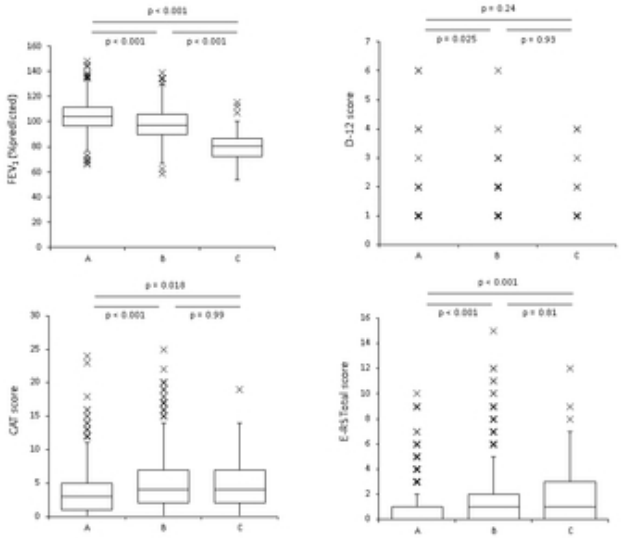
		E-RS Total Score	
		0-4	5 or more
CAT Score	0-9	1,343 (86%)	63 (4%)
	10 or more	113 (7%)	47 (3%)

COPD assessment test (CAT) and Dyspnoea-12 (D-12)

		D-12 Score	
		0-1	2 or more
CAT Score	0-9	1,386 (89%)	20 (1%)
	10 or more	141 (9%)	19 (1%)

Evaluating Respiratory Symptoms in COPD (E-RS) and Dyspnoea-12 (D-12)

		D-12 Score	
		0-1	2 or more
E-RS Total Score	0-4	1,428 (91%)	28 (2%)
	5 or more	99 (6%)	11 (1%)



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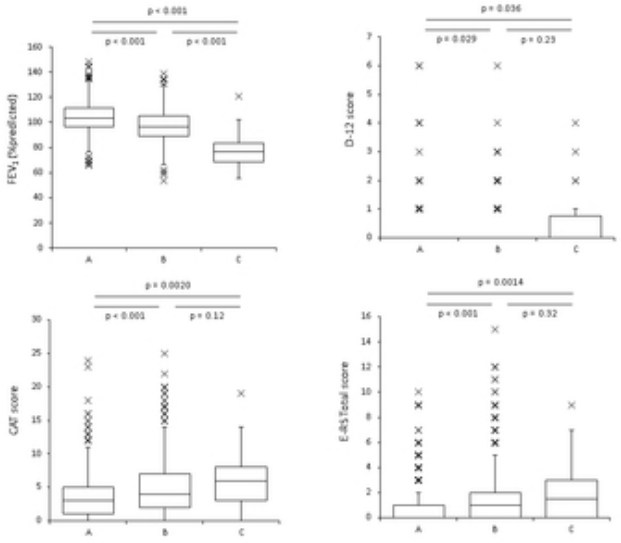

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 4	The cross-sectional data
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 4 - 5	
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 6 - 7	
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 7	
Methods				
Study design	4	Present key elements of study design early in the paper	Page 8	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 8	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	Page 8	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 8 - 10	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 8 - 10	
Bias	9	Describe any efforts to address potential sources of bias		
Study size	10	Explain how the study size was arrived at		

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 10 - 11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 10 - 11
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 12
		(b) Give reasons for non-participation at each stage	Page 12
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page 12
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Page 13 - 14
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 15, 18
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 17-18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 15 - 18
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 15 - 18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 10, 19

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

How different are COPD-specific patient reported outcomes, health status, dyspnoea and respiratory symptoms? An observational study in a working population.

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How different are COPD-specific patient reported outcomes, health status, dyspnoea and respiratory symptoms? An observational study in a working population.

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Dyspnoea-12 (D-12);

The Evaluating Respiratory Symptoms in COPD (E-RS).

Abstract

Objectives: We hypothesized that chronic obstructive pulmonary disease (COPD)-specific health status measured by the COPD assessment test (CAT), respiratory symptoms by the Evaluating Respiratory Symptoms in COPD (E-RS) and dyspnoea by Dyspnoea-12 (D-12) are independently based on specific conceptual frameworks and are not interchangeable. We aimed to discover whether health status, dyspnoea or respiratory symptoms could be related to smoking status and airflow limitation in a working population.

Design: This is an observational, cross-sectional study.

Participants: 1,566 healthy industrial workers were analyzed.

Results: Relationships between D-12, CAT and E-RS Total were statistically significant but weak (Spearman's correlation coefficient＝0.274 to 0.446). In 646 healthy non-smoking subjects, as the reference scores for healthy non-smoking subjects, that is, upper threshold, the Bootstrap 95th percentile values were 1.00 for D-12, 9.88 for CAT and 4.44 for E-RS. Of the 1,566 workers, 85 (5.4%) were diagnosed with COPD using the fixed ratio of the forced expiratory volume in one second/forced vital capacity<0.7, and 34 (2.2%) using the lower limit of normal. The CAT and E-RS Total were significantly worse in non-COPD smokers and subjects with COPD than non-COPD never smokers, although the D-12 was not as sensitive. There were no significant differences between non-COPD smokers and subjects with COPD on any of the measures.

Conclusions: Assessment of health status and respiratory symptoms would be preferable to dyspnoea in view of smoking status and airflow limitation in a working population.

However, these patient-reported measures were inadequate in differentiating between smokers and subjects with COPD identified by spirometry.

Strengths and limitations of this study

- The COPD assessment test (CAT), the Evaluating Respiratory Symptoms in COPD (E-RS) and Dyspnoea-12 (D-12) are all easy to administer since the methodology used in their development is similar.
- The authors sought the reference values of the scores obtained from the D-12 and E-RS for healthy non-smoking subjects that has not been reported although it has been considered that a CAT score of 10 is a cutoff value.
- The main limitation of this study is that it was conducted with healthy industrial workers who were not randomly sampled, thereby potentially being biased due to the "healthy worker effect".

Introduction

Over the last two decades, patient reported outcomes (PROs) have been considered to be important in the assessment of health care services.[1-4] The St. George's Respiratory Questionnaire (SGRQ) has been one of the most frequently used tools for health status measurements in subjects with chronic obstructive pulmonary disease (COPD).[5] Short and simple instruments have become commonplace since the reduction in the number of items has become possible by methodological innovations, including the use of Rasch analysis.[6 7] First, Jones et al. developed the COPD assessment test (CAT), which has been considered to be almost equivalent to the SGRQ, making the tool easy both to administer and for patients to complete.[8-10] Second, although dyspnoea is one of the most important perceptions experienced in subjects with respiratory or cardiac disorders, it has not been easy to measure this perception due to sensory quality and affective components of dyspnoea. Yorke et al. reported that Dyspnoea-12 (D-12) provides a global score of breathlessness severity and can measure dyspnoea in a variety of diseases.[11-13] Third, another tool designed specifically to quantify exacerbations in COPD is the Exacerbations of Chronic Pulmonary Disease Tool (EXACT) Patient-Reported Outcome (known as EXACT-PRO).[14-16] Leidy et al. reported that, using 11 respiratory symptom items from the 14-item EXACT, the Evaluating Respiratory Symptoms in COPD (E-RS) is a reliable and valid instrument for evaluating respiratory symptom severity in stable COPD.[17 18]

The developers of the CAT, D-12 and E-RS have stated that the three PROs derive from different conceptual frameworks, but the methodology used in the development is

similar. In subjects with COPD, it may be commonly accepted that breathlessness is included in respiratory symptoms, and that this symptom is one of the essential components of health status. Therefore, the D-12 would be reflected in the E-RS, and the E-RS in the CAT.

We hypothesized that COPD-specific health status measured by the CAT, dyspnoea by the D-12, and symptoms by the E-RS are independently based on specific conceptual frameworks and are not interchangeable in a general population, and that comprehensive symptomatic assessment of the CAT and E-RS would be preferable to dyspnoea by the D-12 in identifying subjects who may have COPD among that population. Hence, the purpose of the present study was to examine the discriminative properties of the CAT, D-12 and E-RS in relation to smoking status and airflow limitation and to investigate whether health status, dyspnoea and respiratory symptoms could be related to a diagnosis of COPD based on the results of spirometry.

Additionally, we previously reported that the 95th percentile of the CAT scores was 13.6 in 512 healthy non-smoking subjects although the CAT score distribution overlapped remarkably between both healthy non-smoking subjects and subjects with COPD.[19] As a secondary endpoint of the present study, it was our objective to determine reference values of the scores obtained from the D-12 and E-RS for healthy non-smoking subjects.

Methods

Study Design

This is a cross-sectional observational study.

Setting

The present study was conducted between March 2012 and April 2013 at the Niigata Association of Occupational Health Incorporated, Niigata, Japan.

Participants

The study subjects were healthy industrial workers over forty years old who underwent annual health checks at this Association. All underwent a comprehensive health screening, including conventional spirometry. The exclusion criteria included: 1) abnormal findings of the pulmonary parenchyma and chest wall revealed on chest radiographs; 2) undergoing a thoracotomy in the past; 3) any admission to a hospital during the preceding three months (except hospitalization for routine tests); 4) any physician-diagnosed pulmonary diseases including lung cancer, pulmonary tuberculosis, bronchiectasis or non-tuberculous mycobacteriosis except COPD as well as asthma; and 5) unstable complications of cardiovascular, neuromuscular, renal, endocrinological, haematological, gastrointestinal, and hepatic co-morbidities. The information about their radiographic findings was obtained from annual health examinations. The participants also answered additional questions to investigate their smoking status and history.

Measurement

All eligible subjects completed the following examinations on the same day. Spirometry was performed with the use of nose clips in the sitting position with a Spiro Sift sp-470^{TM} Spirometer (Fukuda Denshi Co., Ltd., Tokyo, Japan). All measurements were performed

by a laboratory technician in accordance with guidelines published by the American Thoracic Society and European Respiratory Society.[20] The spirometric forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) values were the largest FVC and largest FEV_1 selected from data obtained from at least three acceptable forced expiratory curves, even if these values were not obtained from the same curve.[21] In this study, COPD was spirometrically defined as airflow limitation with a FEV_1/FVC less than either a fixed ratio, 0.7, or lower limit of normal (LLN) without bronchodilator administration.[22-25] Healthy subjects were defined as those with a FEV_1 of >85% predicted or a FEV_1/FVC of >0.7, forming two groups: subjects with a smoking history of ≥10 pack-years, and non-smoking subjects with a smoking history of < 1 pack-year. This definition is similar to that of the Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE) study.[26 27] The predicted values for pulmonary function were calculated based on the proposal from the Japanese Respiratory Society.[28] The LLN for the Japanese population was calculated in the present study according to the method described by Osaka et al.[29]

The Japanese versions of the EXACT, CAT and D-12 were self-administered in the same order under supervision in a booklet form prior to the pulmonary function tests. The E-RS uses 11 respiratory symptom items from the 14-item EXACT, where scores range from 0 to 40, with higher scores indicating more severe symptoms.[14-18] The RS-Total Score represents overall respiratory symptom severity.[17 18] Three subscales were not used in this analysis. The Japanese translation has been created and provided by the original developers who recommend the use of an electronic version to collect the answers. However, no electronic device with the Japanese version of the EXACT or E-RS was

available so all surveys were conducted using a paper-based method. Health status was assessed with a previously validated Japanese version of the CAT.[30] The CAT consists of eight items scored from 0 to 5 in relation to cough, sputum, dyspnea, chest tightness, capacity for exercise and activities, sleep quality and energy levels.[9 10] The CAT Scores range from 0 to 40, with a score of zero indicating no impairment. To assess the severity of dyspnoea, we used the Japanese version of the D-12,[31] which consists of twelve items (seven physical items and five affective items), each with a four point grading scale (0-3), producing a Total Score (range 0-36, with higher scores representing more severe breathlessness).[11-13]

Patient and Public Involvement

Patients were neither involved in the development of the research question, the design of this study, nor the recruitment to and conduct of the study. The abstract of the published paper will appear on the homepage of the institute.

Ethics

The present study was approved by the ethics committee of the Niigata Association of Occupational Health Incorporated. Written informed consent was obtained from all participants.

Statistical Methods

All results are expressed as means ±standard deviation (SD). Relationships between two sets of data were analysed by Spearman's rank correlation tests. In order to determine reference values for each score, we calculated the 95th percentile of the scores in healthy, non-smoking subjects using the Monte Carlo and bootstrap methods with 1,000 bootstrap reps and used this as the upper limit of normal.[32] In comparing the groups of COPD, non-

COPD smokers and non-COPD never smokers, the significance of between-group difference was determined by an analysis of variance (ANOVA) for FEV_1 or a Kruskal-Wallis test for PRO scores, and when a significant difference was observed, Tukey tests or Steel-Dwass tests were used to analyse where the differences were significant, respectively. Statistical analysis was performed using IBM SPSS Statistics 22.0 (International Business Machines Corp., Armonk, New York, USA) and BellCurve for Excel (Social Survey Research Information Co., Ltd., Tokyo, Japan). A p value of less than 0.05 was considered to be statistically significant.

Results

Subject Characteristics

A total of 1,634 subjects initially participated in the study but 68 were subsequently excluded from the data analysis because of uncertainty over their smoking or other history or having one of the exclusion criteria. Therefore, a total of 1,566 subjects (985 males) were analysed. Their demographic details and spirometric results are shown in Table 1. The mean age of the subjects was 53.0 years. The mean FEV_1 value was 99.6±13.1 %predicted. The FEV_1/FVC ratio used as an index of airflow limitation ranged from 52.5% to 97.4%, with a mean of 80.1%. There was no difference between groups in the frequency of self-reported history of asthma.

The scores for the D-12, CAT and E-RS are shown in Table 2. They were skewed to the milder ends, and a floor effect was seen in all of the scores. This effect was most pronounced for the D-12 (84.0%) and E-RS (53.3%), and least for the CAT (14.6%). Regarding the interrelationships between the D-12, CAT and E-RS, they were significantly but only weakly correlated with each other (D-12 versus CAT, Spearman's correlation coefficient (Rs) =0.398, $p<0.001$; D-12 versus E-RS, Rs=0.274, $p<0.001$; and CAT versus E-RS, Rs=0.446, $p<0.001$).

In order to determine the reference values, from the data obtained from 646 healthy non-smoking subjects (Tables 1 and 2), the Bootstrap 95th percentile values were subsequently calculated and used as the upper limit of normal. For the D-12, this was 1.00; for the E-RS, it was 4.44. Since these scores do not contain decimals, the reference values for the D-12 and E-RS Total Scores were considered to be ≤1 and ≤4, respectively.

In the same way, the reference value of the CAT was calculated to be 9.88, which rounds up to 10, in the present study.

Concordant and discordant results between tools were set to be examined using the above cut-off values (Table 3). However, since there were only a small number of subjects with higher scores on each instrument due to skewed score distribution, those with higher scores on one instrument and lower scores on another were less than one-tenth of all of the subjects involved.

Relationships of COPD-specific PROs with Smoking and Airflow Limitation

We then divided the 1,566 subjects into three groups consisting of a COPD group based on the FEV_1/FVC using a fixed ratio, 0.7, or LLN; non-COPD current or past smokers; and non-COPD never smokers (Tables 1 and 2). Using the fixed ratio of the $FEV_1/FVC<0.7$, 85 subjects (5.4%) were diagnosed with COPD, 817 (52.2%) were non-COPD smokers, and 664 (42.4%) were non-COPD never smokers. Using the LLN definition, 34 subjects (2.2%) were diagnosed with COPD, 867 (55.4%) were non-COPD smokers, and 665 (42.5%) were non-COPD never smokers.

Relationships of the PROs between the three groups of subjects with COPD, non-COPD smokers and non-COPD never smokers are shown in Table 2 and Figures 1 (COPD based on the fixed ratio) and 2 (COPD based on the LLN). The FEV_1 (%predicted), D-12, CAT and E-RS Total were significantly separated between the three groups ($p<0.05$). There were significant differences between the three groups for FEV_1 (%predicted), D-12, CAT and E-RS Total ($p<0.05$). FEV_1 was significantly different between any two of the three groups ($p<0.001$) (Figures 1 and 2). With regard to the

score distribution (Table 2), floor effect in subjects with COPD was most prominent for the D-12 (81.2% by the fixed definition and 73.5% by the LLN), and their median scores were 0.0 (Table 2). It was the least for the CAT (15.3% by the fixed definition and 14.7% by the LLN).

In investigating how many were symptomatic among 817 (by the fixed definition) and 867 (by the LLN definition) non-COPD smokers, using the above reference values, 24 (2.9%) and 24 (2.8%) were >1 on the D-12, 79 (9.7%) and 80 (9.2%) were >10 on the CAT, and 74 (9.1%) and 76 (8.8%) were >4 on the E-RS.

Regarding the group comparisons, significant differences were found between non-COPD never smokers and non-COPD smokers on all of the measures; however, significance was relatively weaker for the D-12 score ($p=0.025$ (Figure 1) and 0.029 (Figure 2)) as compared to the CAT and E-RS Total ($p<0.001$). On the CAT and E-RS Total, significant differences were also found between non-COPD never smokers and subjects with COPD ($p<0.05$); however, on the D-12, a significant difference was found only by the LLN definition ($p=0.036$, Figure 1), but not by the fixed ratio definition ($p=0.24$, Figure 1). Neither the D-12, CAT nor E-RS Total were significantly different between COPD and non-COPD smokers.

Discussion

This is the first study to directly compare differences among three COPD-specific outcomes, including dyspnoea, respiratory symptoms or health status in a general working population. First, the associations between dyspnoea measured by the D-12, health status by the CAT, and respiratory symptoms by the E-RS were significant but weak, indicating that they were far below the level of conceptual similarity. This relationship may be expected since the three PRO measurement tools were created by each developer from independent conceptual frameworks. Second, from the data obtained from 646 healthy non-smoking subjects, the Bootstrap 95th percentile values were an E-RS Total score of 4.44 indicating that the reference value is ≤4. The reference values for the D-12 and CAT score are also ≤1 and ≤10, respectively. Third, from a standpoint of the relationship with smoking status and airflow limitation, in comparison to non-COPD never smokers, health status by the CAT and respiratory symptoms by the E-RS were worse in non-COPD smokers and subjects with COPD, although dyspnoea by the D-12 was not as sensitive. None of these PRO measures were adequate in differentiating between non-COPD smokers and subjects with COPD.

In the present study, there were considerable numbers of smokers with preserved pulmonary function, or without airflow limitation, 52.2% by the fixed ratio and 55.4% by the LLN, respectively, who may be diagnosed as COPD-free by spirometric criteria. Their dyspnoea, health status and respiratory symptoms were significantly worse than those in never smokers, which is compatible with recent population studies.[33-36] They also indicated that pulmonary disease and impairments were common in smokers with preserved pulmonary function although they did not meet the current criteria of COPD

based on spirometry,[35 36] and that symptoms might be more sensitive than spirometry in detecting smoking-related respiratory impairments. Actually, symptom-based questionnaires to screen for COPD that do not include spirometry have been developed.[37 38]

Conversely, the present study adds that PROs in non-COPD smokers were not significantly different from those in subjects with COPD. Actually, about 9% of smokers with preserved pulmonary function were judged to be symptomatic according to the reference values of CAT>10 or E-RS>4. Their symptoms may tend to exacerbate in the future, advance to COPD, or be treated as if they were COPD. How to manage this group of symptomatic smokers without airflow limitation is a key issue to be solved through careful long-term follow-ups.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2011 consensus report proposed a revised "combined COPD assessment" classification in which symptoms should be assessed either as a dyspnoea measure using the modified Medical Research Council (mMRC) dyspnoea scale, or as a health status measure using the CAT.[39] We have contributed to the establishment of this concept by demonstrating the significant predictive properties of dyspnoea and health status independently of airflow limitation.[40 41] There has hitherto been much debate over how to assess symptoms in this new classification. Although dyspnoea was not measured by the mMRC dyspnoea scale but by D-12, interrelationships between the D-12, CAT and E-RS were weak to moderate. Therefore, it may be difficult to use dyspnoea, health status and respiratory symptoms in a mutually complementary form. The GOLD recommends a comprehensive assessment of symptoms rather than just a measure of dyspnoea. The present study

supports this by showing that the D-12 had the most marked floor effects even in subjects with COPD, and that the CAT and E-RS seemed to be more sensitive in discriminating subjects based on smoking and COPD than the D-12.

We reported in 2013 that the 95th percentile of the scores in 512 healthy, non-smoking subjects were used as the upper limit of normal in exactly the same way as in the present study.[19] For the CAT, it was 13.6. In 2014 Pinto et al. published some of the results of the Canadian Cohort Obstructive Lung Disease (CanCOLD) study and reported that the normative value for the CAT score was determined to be 16 from a population-based study where they used post-bronchodilator spirometric values.[42] Compared with the above two reports, a score of 10 was the 95th percentile of the scores in healthy industrial workers from Japan, and it is the lowest in the present study. The GOLD currently states that the boundary between GOLD A and B and between GOLD C and D is a CAT score of 10,[39 43] which is consistent with the important result of the present study although there might be some margin of error depending on the methodologies and subjects of the studies.

This study has several limitations. Although we intended to determine the border of the normal level of the D-12, CAT and E-RS Total scores, the study subjects were not randomly sampled and there could be a risk of sample bias. The D-12, CAT and E-RS are sufficiently validated for measuring PROs in subjects with COPD, but most participants were not patients with COPD but rather healthy workers. As such, there is a possibility that they are not appropriate tools for the study population. However, since the successful application of the CAT in a working population or a random sampling frame from the populations has also been reported,[19 42] there may be a reason to be hopeful for success

with the D-12 and E-RS. Although post-bronchodilator spirometric values are recommended to be used to make a diagnosis of COPD,[39 43] the diagnosis was made only from pre-bronchodilator spirometric information in the present study. Furthermore, the present study was conducted in Japanese so that each of the instruments would have been translated from the original language of its development. Although the Japanese version has been validated in each case, it may be a limit to the generalizability of the research across the globe.

Three main conclusions may be drawn from our findings. First, associations among dyspnoea measured by the D-12, health status by the CAT, and respiratory symptoms by the E-RS, were statistically significant but weak, indicating that they cannot be used interchangeably. Second, using the data obtained from 646 healthy non-smoking subjects, the reference values of the D-12, CAT and E-RS were ≤1, ≤10 and ≤4, respectively. Third, from a standpoint of the relationship with smoking status and airflow limitation, health status and respiratory symptoms may be more closely related to non-COPD smokers and subjects with COPD than dyspnoea as compared to non-COPD never smokers; however, none of these PRO measures can differentiate between non-COPD smokers and subjects with COPD. How to manage non-COPD symptomatic smokers should be investigated in the future.

Other information

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Contributors

KN contributed, as the principal investigator, to the study concept and design, analysis of the results, and writing of the manuscript.

TO contributed to statistical analysis, the interpretation and editing of the manuscript.

KN contributed to statistical analysis.

MO contributed to acquisition of data.

YH contributed to the interpretation and editing of the manuscript.

SM contributed to performance of the study and acquisition of data.

All authors have read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

Ethics Approval

The present study was approved by the ethics committee of the Niigata Association of Occupational Health Incorporated (No. 6, lastly dated January 8, 2013).

Data Sharing Statement

No additional data are available.

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Figure Legends

Figure 1 Box plots representing the distributions of FEV_1 (%predicted), D-12 (Dyspnoea-12) score, CAT (COPD assessment test) score and E-RS (Evaluating Respiratory Symptoms in COPD) Total score in non-COPD never smokers (Group A, n=664), non-COPD current or past smokers (Group B, n=817) and COPD based on FEV_1/FVC using a fixed ratio, 0.7 (Group C, n=85). The horizontal lines in the boxes represent the median, and the top and bottom of the boxes represent the 75th and 25th percentiles, respectively. Bars represent the upper adjacent value (75th percentile plus 1.5 times the interquartile range) and the lower adjacent value (25th percentile minus 1.5 times the interquartile range), and the crosses represent outliers.

Figure 2 Box plots representing the distributions of FEV_1 (%predicted), D-12 (Dyspnoea-12) score, CAT (COPD assessment test) score and E-RS (Evaluating Respiratory Symptoms in COPD) Total score in non-COPD never smokers (Group A, n=665), non-COPD current or past smokers (Group B, n=867) and COPD based on FEV_1/FVC using the LLN (Group C, n=34). The horizontal lines in the boxes represent the median, and the top and bottom of the boxes represent the 75th and 25th percentiles, respectively. Bars represent the upper adjacent value (75th percentile plus 1.5 times the interquartile range) and the lower adjacent value (25th percentile minus 1.5 times the interquartile range), and the crosses represent outliers.

Table 1. Demographic details and spirometric results.

	Total subjects	Age	Male	Cumulative smoking	Prior diagnosis of asthma	Prior diagnosis of COPD	FEV_1	FEV_1/FVC
	Number	Years	Number (%)	Pack-years	Number (%)	Number (%)	%predicted	%
All subjects	1,566	53.0 ± 8.7	985 (62.9%)	14.1 ± 18.6	46 (2.9%)	10 (0.6%)	99.6 ± 13.1	80.1 ± 5.8
Healthy non-smoking subjects¶#	646	53.3 ± 8.8	189 (29.3%)	0.0 ± 0.1	17 (2.6%)	2 (0.3%)	105.5 ± 10.7	82.3 ± 4.4
COPD defined by fixed ratio	85	60.4 ± 9.4	83 (97.6%)	36.9 ± 28.1	5 (5.9%)	4 (4.7%)	80.2 ± 11.6	66.0 ± 4.1
Non-COPD smokers	817	51.9 ± 8.0	704 (86.2%)	23.1 ± 16.9	23 (2.8%)	4 (0.5%)	97.9 ± 11.8	80.1 ± 4.7
Non-COPD never smokers	664	53.4 ± 8.9	198 (29.8%)	0.0 ± 0.0	18 (2.7%)	2 (0.3%)	104.2 ± 12.0	82.0 ± 4.5
COPD defined by LLN	34	57.7 ± 10.4	29 (85.3%)	31.9 ± 25.8	2 (5.9%)	2 (5.9%)	77.3 ± 13.1	63.0 ± 4.9
Non-COPD smokers	867	52.4 ± 8.3	755 (87.1%)	24.2 ± 18.3	26 (3.0%)	6 (0.7%)	97.1 ± 12.3	79.4 5.3
Non-COPD never smokers	665	53.5 ± 8.9	201 (30.2%)	0.0 ± 0.0	18 (2.7%)	2 (0.3%)	104.1 ± 12.1	82.0 ± 4.5

¶ FEV_1 of >85% predicted and FEV_1/FVC of >0.7, # a smoking history of <1 pack-year

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; LLN, lower limit of normal.

Table 2. Distributions of the D-12, CAT and E-RS Total scores.

	D-12 score (0-36)					CAT score (0-40)					E-RS Total score (0-40)				
	mean	median	SD	max.	floor effect	mean	median	SD	max.	floor effect	mean	median	SD	max.	floor effect
All subjects	0.2	0.0	0.6	6.0	84.0%	4.3	3.0	3.9	25.0	14.6%	1.2	0.0	1.9	15.0	53.3%
Healthy non-smoking subjects¶#	0.2	0.0	0.5	6.0	86.5%	3.6	3.0	3.3	24.0	15.9%	0.9	0.0	1.6	10.0	62.5%
COPD defined by fixed ratio	0.3	0.0	0.8	4.0	81.2%	4.8	4.0	4.1	19.0	15.3%	1.6	1.0	2.2	12.0	44.7%
Non-COPD smokers	0.2	0.0	0.5	6.0	82.0%	4.8	4.0	4.1	25.0	13.1%	1.5	1.0	2.1	15.0	46.5%
Non-COPD never smokers	0.2	0.0	0.5	6.0	86.7%	3.6	3.0	3.4	24.0	16.3%	0.9	0.0	1.6	12.0	62.7%
COPD defined by LLN	0.5	0.0	1.0	4.0	73.5%	6.2	6.0	4.8	19.0	14.7%	1.8	1.5	2.1	9.0	38.2%
Non-COPD smokers	0.2	0.0	0.5	6.0	82.2%	4.8	4.0	4.1	25.0	13.0%	1.5	1.0	2.1	15.0	46.6%
Non-COPD never smokers	0.2	0.0	0.6	6.0	86.8%	3.6	3.0	3.4	24.0	16.5%	0.9	0.0	1.6	10.0	62.7%

¶ FEV_1 of >85% predicted and FEV_1/FVC of >0.7, # a smoking history of <1 pack-year. Numbers in parentheses indicate the theoretical score range, and higher scores indicate worse status.

Abbreviations: CAT, COPD assessment test; COPD, chronic obstructive pulmonary disease; D-12, Dyspnoea-12; E-RS, Evaluating Respiratory Symptoms in COPD; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; LLN, lower limit of normal.

Table 3. Concordant and discordant results between tools using the cut-off values.

COPD assessment test (CAT) and Evaluating Respiratory Symptoms in COPD (E-RS)

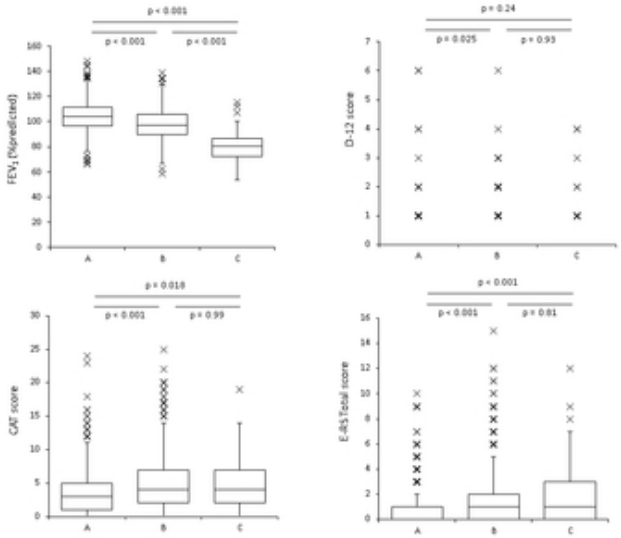
		E-RS Total Score	
		0-4	5 or more
CAT Score	0-9	1,343 (86%)	63 (4%)
	10 or more	113 (7%)	47 (3%)

COPD assessment test (CAT) and Dyspnoea-12 (D-12)

		D-12 Score	
		0-1	2 or more
CAT Score	0-9	1,386 (89%)	20 (1%)
	10 or more	141 (9%)	19 (1%)

Evaluating Respiratory Symptoms in COPD (E-RS) and Dyspnoea-12 (D-12)

		D-12 Score	
		0-1	2 or more
E-RS Total Score	0-4	1,428 (91%)	28 (2%)
	5 or more	99 (6%)	11 (1%)



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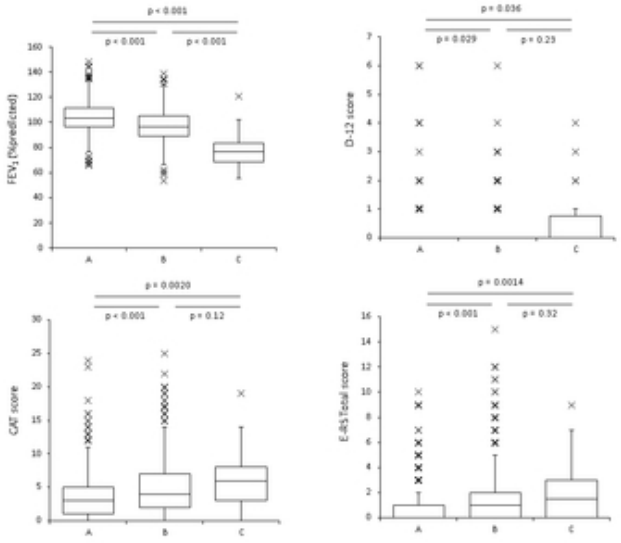

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 4	The cross-sectional data
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 4 - 5	
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 6 - 7	
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 7	
Methods				
Study design	4	Present key elements of study design early in the paper	Page 8	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 8	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	Page 8	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 8 - 10	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 8 - 10	
Bias	9	Describe any efforts to address potential sources of bias		
Study size	10	Explain how the study size was arrived at		

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 10 - 11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 10 - 11
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 12
		(b) Give reasons for non-participation at each stage	Page 12
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page 12
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Page 13 - 14
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 15, 18
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 17-18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 15 - 18
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 15 - 18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 10, 19

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.