

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-025132
Article Type:	Research
Date Submitted by the Author:	07-Jul-2018
Complete List of Authors:	Nishimura, Koichi; National Center for Geriatrics and Gerontology, Department of Pulmonary Medicine Oga, Toru; Graduate School of Medicine, Kyoto University, Department of Respiratory Care and Sleep Control Medicine Nakayasu, Kazuhito; Kondo P.P. Inc., Data Research Section Ogasawara, Miyoko; Niigata Association of Occupational Health Incorporated Hasegawa, Yoshinori; Nagoya University Graduate School of Medicine, Division of Respiratory Medicine, Department of Medicine Mitsuma, Satoshi; Niigata Association of Occupational Health Incorporated
Keywords:	Chronic airways disease < THORACIC MEDICINE, EPIDEMIOLOGY, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

SCHOLARONE™
Manuscripts

1
2
3
4 **COPD-specific patient reported outcomes in a working**
5
6
7 **population: differences and similarities of health status,**
8
9
10 **dyspnoea and respiratory symptoms.**
11
12
13
14

15 Names of Authors:

16
17 Koichi Nishimura¹, koichi-nishimura@nifty.com

18
19 Toru Oga², ogato@kuhp.kyoto-u.ac.jp

20
21 Kazuhito Nakayasu³, nakayasu@mydo-kond.co.jp

22
23 Miyoko Ogasawara⁴, mi_ogasawara@niwell.or.jp

24
25 Yoshinori Hasegawa⁵, yhasega@med.nagoya-u.ac.jp

26
27 Satoshi Mitsuma⁴, s.mitsuma@mac.com
28
29
30
31
32
33

34 Author Affiliations:

- 35
36 1) Department of Respiratory Medicine, National Center for Geriatrics and Gerontology,
37 7-430, Morioka-cho, Obu 474-8511, Japan;
38
39
40 2) Department of Respiratory Care and Sleep Control Medicine, Graduate School of
41 Medicine, Kyoto University, 54 Kawaharacho, Syogoin, Sakyo-ku, Kyoto 606-8507,
42 Japan;
43
44
45 3) Data Research Section, Kondo Photo Process Co., LTD. 11-15, Shimizudani-cho,
46 Tenuujiku, Osaka 543-0011, Japan;
47
48
49 4) Niigata Association of Occupational Health Incorporated, 1-39-5, Kawagishi-cho,
50 Chuo-ku, Niigata 951-8133, Japan; and
51
52
53
54
55

1
2
3 5) Department of Respiratory Medicine, Nagoya University Graduate School of
4
5 Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8560, Japan
6
7
8

9
10 Corresponding Author:

11 Koichi Nishimura

12
13
14 National Center for Geriatrics and Gerontology,

15
16 Department of Respiratory Medicine,

17
18 7-430, Morioka-cho, Obu 474-8511, Japan
19

20
21 Tel: +81-562-46-2311; Fax: +81-562-44-8518
22

23 E-Mail: koichi-nishimura@nifty.com
24
25
26
27

28 Word count of text: 3,156 (except Abstract, References, Tables and Figures)
29
30
31

32 This study was partly supported by the Research Funding for Longevity Sciences (27-10)
33
34 from the National Center for Geriatrics and Gerontology (NCGG), Japan.
35
36
37
38

39 Running Title:

40
41 Health Status, Dyspnoea and Respiratory Symptoms in a Working Population
42
43
44
45

46 *Key words:*

47
48 *Chronic obstructive pulmonary disease (COPD);*

49
50
51 *Patient-reported outcome (PRO);*

52
53 *The COPD assessment test (CAT);*
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

*Dyspnoea-12 (D-12);
The Evaluating Respiratory Symptoms in COPD (E-RS).*

For peer review only

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

1
2 between smokers and subjects with COPD identified by spirometry. How to manage
3
4 these symptomatic non-COPD smokers should be investigated.
5
6
7
8

9 **Strengths and limitations of this study**

- 12 ➤ Chronic obstructive pulmonary disease (COPD)-specific health status may be
13 measured by the COPD assessment test (CAT), respiratory symptoms by the
14 Evaluating Respiratory Symptoms in COPD (E-RS) and dyspnoea by Dyspnoea-12
15 (D-12). They are independently based on specific conception and are not
16 interchangeable.
17
18
- 19 ➤ The cross-sectional data obtained from 1,566 healthy industrial workers showed
20 relationships between D-12, CAT and E-RS Total were statistically significant but
21 weak (Spearman's correlation coefficient, 0.274 to 0.446).
22
23
- 24 ➤ In 646 healthy non-smoking subjects, as the upper limit of normal, the Bootstrap
25 95th percentile values were 1.00 for D-12, 9.88 for CAT and 4.44 for E-RS.
26
27
- 28 ➤ The CAT and E-RS Total were significantly worse in non-COPD smokers and
29 subjects with COPD than non-COPD never smokers, although the D-12 was not as
30 sensitive.
31
32
- 33 ➤ These patient-reported measures were inadequate in differentiating between smokers
34 and subjects with COPD identified by spirometry.
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

1
2 similar. In subjects with COPD, it may be commonly accepted that breathlessness is
3 included in respiratory symptoms, and that this symptom is one of the essential
4 components of health status. Therefore, the D-12 would be reflected in the E-RS, and the
5 E-RS in the CAT.
6
7
8
9
10

11 We hypothesized that COPD-specific health status measured by the CAT, dyspnoea
12 by the D-12, and symptoms by the E-RS are independently based on specific conception
13 and are not interchangeable in a general population, and that comprehensive symptomatic
14 assessment of the CAT and E-RS would be preferable to dyspnoea by the D-12 in
15 identifying subjects who may have COPD among that population. Hence, the purpose of
16 the present study was to examine the discriminative properties of the CAT, D-12 and E-
17 RS in relation to smoking status and airflow limitation and to investigate whether health
18 status, dyspnoea and respiratory symptoms could be related to a diagnosis of COPD
19 based on the results of spirometry.
20
21
22
23
24
25
26
27
28
29
30
31

32 Additionally, we previously reported that the 95th percentile of the CAT scores was
33 13.6 in 512 healthy non-smoking subjects although the CAT score distribution
34 overlapped remarkably between both healthy non-smoking subjects and subjects with
35 COPD.¹⁷ As a secondary endpoint of the present study, it was our objective to determine
36 reference values of the scores obtained from the D-12 and E-RS for healthy non-smoking
37 subjects.
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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-470TM Spirometer (Fukuda Denshi Co., Ltd., Tokyo, Japan). All measurements were performed

1
2 by a laboratory technician in accordance with guidelines published by the American
3
4 Thoracic Society and European Respiratory Society.¹⁸ The spirometric forced vital
5
6 capacity (FVC) and forced expiratory volume in one second (FEV₁) values were the
7
8 largest FVC and largest FEV₁ selected from data obtained from at least three acceptable
9
10 forced expiratory curves, even if these values were not obtained from the same curve.¹⁹ In
11
12 this study, COPD was spirometrically defined as airflow limitation with a FEV₁/FVC less
13
14 than either a fixed ratio, 0.7, or lower limit of normal (LLN) without bronchodilator
15
16 administration.²⁰⁻²³ Healthy subjects were defined as those with a FEV₁ of >85%
17
18 predicted or a FEV₁/FVC of >0.7, forming two groups: subjects with a smoking history
19
20 of ≥10 pack-years, and non-smoking subjects with a smoking history of < 1 pack-year.
21
22 This definition was similar to that of the Evaluation of COPD Longitudinally to Identify
23
24 Predictive Surrogate End-points (ECLIPSE) study.^{24 25} The predicted values for
25
26 pulmonary function were calculated based on the proposal from the Japanese Respiratory
27
28 Society.²⁶ The LLN for the Japanese population was calculated in the present study
29
30 according to the method described by Osaka et al.²⁷

31
32 The Japanese versions of the EXACT, CAT and D-12 were self-administered under
33
34 supervision in a booklet form. The E-RS uses 11 respiratory symptom items from the 14-
35
36 item EXACT, where scores range from 0 to 40, with higher scores indicating more severe
37
38 symptoms.¹²⁻¹⁶ The RS-Total Score represents overall respiratory symptom severity.^{15 16}
39
40 Three subscales were not used in this analysis. The Japanese translation has been created
41
42 and provided by the original developers, and they recommend using an electronic version
43
44 to collect the answers. However, no electronic device with the Japanese version of the
45
46 EXACT or E-RS was available so all surveys were conducted using a paper-based
47
48
49
50
51
52
53
54

1
2 method. Health status was assessed with a previously validated Japanese version of the
3
4 CAT.²⁸ The CAT consists of eight items scored from 0 to 5 in relation to cough, sputum,
5
6 dyspnea, chest tightness, capacity for exercise and activities, sleep quality and energy
7
8 levels.^{7,8} The CAT Scores range from 0 to 40, with a score of zero indicating no
9
10 impairment. To assess the severity of dyspnoea, we used the Japanese version of the D-
11
12 12,²⁹ which consists of twelve items (seven physical items and five affective items), each
13
14 with a four point grading scale (0-3), producing a Total Score (range 0-36, with higher
15
16 scores representing more severe breathlessness).⁹⁻¹¹
17
18
19

20 21 **Patient and Public Involvement**

22
23 Patients were not involved in the study. The abstract of the paper published will appear
24
25 on the homepage of the institute.
26

27 28 **Ethics and Funding**

29
30 The present study was approved by the ethics committee of the Niigata Association of
31
32 Occupational Health Incorporated. Written informed consent was obtained from all
33
34 participants. This study was partly supported by the Research Funding for Longevity
35
36 Sciences (30-24) from the National Center for Geriatrics and Gerontology (NCGG),
37
38 Japan.
39
40

41 42 **Statistical Methods**

43
44 All results are expressed as means \pm standard deviation (SD). Relationships between two
45
46 sets of data were analysed by Spearman's rank correlation tests. In order to determine
47
48 reference values for each score, we calculated the 95th percentile of the scores in healthy,
49
50 non-smoking subjects using the Monte Carlo and bootstrap methods with 1,000 bootstrap
51
52 reps and used this as the upper limit of normal.³⁰ In comparing the groups of COPD, non-
53
54

1
2 COPD smokers and non-COPD never smokers, the significance of between-group
3
4 difference was determined by an analysis of variance (ANOVA) for FEV₁ or a Kruskal
5
6 Wallis test for PRO scores, and when a significant difference was observed, Tukey tests
7
8 or Steel-Dwass tests were used to analyze where the differences were significant,
9
10 respectively. Statistical analysis was performed using IBM SPSS Statistics 22.0
11
12 (International Business Machines Corp., Armonk, New York, USA) and BellCurve for
13
14 Excel (Social Survey Research Information Co., Ltd., Tokyo, Japan). A p value of less
15
16 than 0.05 was considered to be statistically significant.
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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 FEV₁ values were 99.6±13.1 %predicted. The FEV₁/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 FEV₁/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 FEV₁/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 FEV₁ (%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 FEV₁ (%predicted), D-12, CAT and E-RS Total (p<0.05). FEV₁ 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,

1
2 24 (2.9%) and 24 (2.8%) were >1 on the D-12, 79 (9.7%) and 80 (9.2%) were >10 on the
3
4 CAT, and 74 (9.1%) and 76 (8.8%) were >4 on the E-RS.
5
6

7 Regarding the group comparisons, significant differences were found between non-
8
9 COPD never smokers and non-COPD smokers on all of the measures; however,
10
11 significance was relatively weaker for the D-12 score ($p=0.025$ (Figure 1) and 0.029
12
13 (Figure 2)) as compared to the CAT and E-RS Total ($p<0.001$). On the CAT and E-RS
14
15 Total, significant differences were also found between non-COPD never smokers and
16
17 subjects with COPD ($p<0.05$); however, on the D-12, a significant difference was found
18
19 only by the LLN definition ($p=0.036$, Figure 1), but not by the fixed ratio definition
20
21 ($p=0.24$, Figure 1). Neither the D-12, CAT nor E-RS Total were significantly different
22
23 between COPD and non-COPD smokers).
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

1
2 based on spirometry,^{33 34} and that symptoms might be more sensitive than spirometry in
3
4 detecting smoking-related respiratory impairments. Actually, symptom-based
5
6 questionnaires to screen for COPD that do not include spirometry have been developed.³⁵
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

1
2 showing that the D-12 had the most marked floor effects even in subjects with COPD,
3
4 and that the CAT and E-RS seemed to be more sensitive in discriminating subjects based
5
6 on smoking and COPD than the D-12.
7
8

9 We reported in 2013 that the 95th percentile of the scores in 512 healthy, non-
10 smoking subjects were used as the upper limit of normal in exactly the same way as in
11
12 the present study.¹⁷ For the CAT, it was 13.6. In 2014 Pinto et al. published some of the
13
14 results of the Canadian Cohort Obstructive Lung Disease (CanCOLD) study and reported
15
16 that the normative value for the CAT score was determined to be 16 from a population-
17
18 based study where they used post-bronchodilator spirometric values.⁴⁰ Compared with
19
20 the above two reports, a score of 10 was the 95th percentile of the scores in healthy
21
22 industrial workers from Japan, and it is the lowest in the present study. The GOLD
23
24 currently states that the boundary between GOLD A and B and between GOLD C and D
25
26 is a CAT score of 10,^{37 41} which is consistent with the important result of the present
27
28 study although there might be some margin of error depending on the methodologies and
29
30 subjects of the studies.
31
32
33
34
35
36

37 This study has several limitations. Although we intended to determine the border of
38
39 the normal level of the D-12, CAT and E-RS Total scores, the study subjects were not
40
41 randomly sampled and there could be a risk of sample bias. The D-12, CAT and E-RS are
42
43 sufficiently validated for measuring PROs in subjects with COPD, but most participants
44
45 were not patients with COPD but rather healthy workers. As such, there is a possibility
46
47 that they are not appropriate tools for the study population. Although post-bronchodilator
48
49 spirometric values are recommended to be used to make a diagnosis of COPD,^{37 41} the
50
51
52
53
54
55
56
57
58
59
60

1
2 diagnosis was made only from pre-bronchodilator spirometric information in the present
3
4
5 study.

6
7 Three main conclusions may be drawn from our findings. First, associations among
8
9 dyspnoea measured by the D-12, health status by the CAT, and respiratory symptoms by
10
11 the E-RS, were statistically significant but weak, indicating that they cannot be used
12
13 interchangeably. Second, using the data obtained from 646 healthy non-smoking subjects,
14
15 the reference values of the D-12, CAT and E-RS were ≤ 1 , ≤ 10 and ≤ 4 , respectively.
16
17
18 Third, from a standpoint of the relationship with smoking status and airflow limitation,
19
20 health status and respiratory symptoms may be more closely related to non-COPD
21
22 smokers and subjects with COPD than dyspnoea as compared to non-COPD never
23
24 smokers; however, none of these PRO measures can differentiate between non-COPD
25
26 smokers and subjects with COPD. How to manage non-COPD symptomatic smokers
27
28 should be investigated in the future.
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Other information

Acknowledgements

The authors wish to thank Nancy Kline Leidy for permission to use the Japanese version of the E-RS.

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.

Funding

This study was partly supported by the Research Funding for Longevity Sciences (30-24) from the National Center for Geriatrics and Gerontology (NCGG), Japan.

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.

References

1. Kyte D, Duffy H, Fletcher B, et al. Systematic evaluation of the patient-reported outcome (PRO) content of clinical trial protocols. *PLoS One* 2014;9(10):e110229. doi: 10.1371/journal.pone.0110229
2. Jones PW. Health status measurement in chronic obstructive pulmonary disease. *Thorax* 2001;56(11):880-7.
3. DeMuro C, Clark M, Doward L, et al. Assessment of PRO label claims granted by the FDA as compared to the EMA (2006-2010). *Value Health* 2013;16(8):1150-5. doi: 10.1016/j.jval.2013.08.2293
4. Gnanasakthy A, Mordin M, Evans E, et al. A Review of Patient-Reported Outcome Labeling in the United States (2011-2015). *Value Health* 2017;20(3):420-29. doi: 10.1016/j.jval.2016.10.006
5. Jones PW, Quirk FH, Baveystock CM, et al. A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. *Am Rev Respir Dis* 1992;145(6):1321-7. [published Online First: 1992/06/01]
6. Gupta N, Pinto LM, Morogan A, et al. The COPD assessment test: a systematic review. *Eur Respir J* 2014;44(4):873-84. doi: 10.1183/09031936.00025214
7. Jones PW, Brusselle G, Dal Negro RW, et al. Properties of the COPD Assessment Test (CAT) in a cross-sectional European study. *Eur Respir J* 2011 doi: 09031936.00177210 [pii] 10.1183/09031936.00177210 [published Online First: 2011/05/14]
8. Jones PW, Harding G, Berry P, et al. Development and first validation of the COPD Assessment Test. *Eur Respir J* 2009;34(3):648-54. doi: 34/3/648 [pii] 10.1183/09031936.00102509 [published Online First: 2009/09/02]

- 1
2
3 9. Yorke J, Swigris J, Russell AM, et al. Dyspnea-12 is a valid and reliable measure of
4
5 breathlessness in patients with interstitial lung disease. *Chest* 2011;139(1):159-64. doi:
6 chest.10-0693 [pii] 10.1378/chest.10-0693 [published Online First: 2010/07/03]
7
8
9
- 10 10. Swigris JJ, Yorke J, Sprunger DB, et al. Assessing dyspnea and its impact on patients with
11
12 connective tissue disease-related interstitial lung disease. *Respir Med* 2010;104(9):1350-
13
14 5. doi: S0954-6111(10)00145-9 [pii] 10.1016/j.rmed.2010.03.027 [published Online
15
16 First: 2010/05/18]
17
18
- 19 11. Yorke J, Moosavi SH, Shuldham C, et al. Quantification of dyspnoea using descriptors:
20
21 development and initial testing of the Dyspnoea-12. *Thorax* 2010;65(1):21-6. doi:
22
23 10.1136/thx.2009.118521
24
25
- 26 12. Leidy NK, Wilcox TK, Jones PW, et al. Standardizing Measurement of Chronic Obstructive
27
28 Pulmonary Disease Exacerbations: Reliability and Validity of a Patient-reported Diary.
29
30 *Am J Respir Crit Care Med* 2011;183(3):323-29. doi: 201005-0762OC [pii]
31
32 10.1164/rccm.201005-0762OC [published Online First: 2010/09/04]
33
34
- 35 13. Jones PW, Chen WH, Wilcox TK, et al. Characterizing and Quantifying the Symptomatic
36
37 Features of COPD Exacerbations. *Chest* 2011;139(6):1388-94. doi: chest.10-1240 [pii]
38
39 10.1378/chest.10-1240 [published Online First: 2010/11/13]
40
41
- 42 14. Leidy NK, Wilcox TK, Jones PW, et al. Development of the EXacerbations of Chronic
43
44 Obstructive Pulmonary Disease Tool (EXACT): a patient-reported outcome (PRO)
45
46 measure. *Value Health* 2010;13(8):965-75. doi: 10.1111/j.1524-4733.2010.00772.x
47
48 VHE772 [pii] [published Online First: 2010/07/28]
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 15. Leidy NK, Murray LT, Monz BU, et al. Measuring respiratory symptoms of COPD:
4
5 performance of the EXACT- Respiratory Symptoms Tool (E-RS) in three clinical trials.
6
7 *Respir Res* 2014;15:124. doi: 10.1186/s12931-014-0124-z
8
9
- 10 16. Leidy NK, Sexton CC, Jones PW, et al. Measuring respiratory symptoms in clinical trials of
11
12 COPD: reliability and validity of a daily diary. *Thorax* 2014;69(5):443-9. doi:
13
14 10.1136/thoraxjnl-2013-204428
15
16
- 17 17. Nishimura K, Mitsuma S, Kobayashi A, et al. COPD and disease-specific health status in a
18
19 working population. *Respir Res* 2013;14:61. doi: 10.1186/1465-9921-14-61
20
21
- 22 18. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J*
23
24 2005;26(2):319-38. doi: 26/2/319 [pii] 10.1183/09031936.05.00034805 [published
25
26 Online First: 2005/08/02]
27
- 28 19. Koyama H, Nishimura K, Ikeda A, et al. A comparison of different methods of spirometric
29
30 measurement selection. *Respir Med* 1998;92(3):498-504. doi: S0954-6111(98)90298-0
31
32 [pii] [published Online First: 1998/08/06]
33
34
- 35 20. Garcia-Rio F, Soriano JB, Miravittles M, et al. Overdiagnosing subjects with COPD using
36
37 the 0.7 fixed ratio: correlation with a poor health-related quality of life. *Chest*
38
39 2011;139(5):1072-80. doi: 10.1378/chest.10-1721 [published Online First: 2010/12/25]
40
41
- 42 21. Swanney MP, Ruppel G, Enright PL, et al. Using the lower limit of normal for the
43
44 FEV1/FVC ratio reduces the misclassification of airway obstruction. *Thorax*
45
46 2008;63(12):1046-51. doi: thx.2008.098483 [pii] 10.1136/thx.2008.098483 [published
47
48 Online First: 2008/09/13]
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 22. van Dijk W, Tan W, Li P, et al. Clinical relevance of fixed ratio vs lower limit of normal of
4 FEV1/FVC in COPD: patient-reported outcomes from the CanCOLD cohort. *Ann Fam*
5 *Med* 2015;13(1):41-8. doi: 10.1370/afm.1714 [published Online First: 2015/01/15]
6
7
8
9
10 23. Vollmer WM, Gislason T, Burney P, et al. Comparison of spirometry criteria for the
11 diagnosis of COPD: results from the BOLD study. *Eur Respir J* 2009;34(3):588-97. doi:
12 09031936.00164608 [pii] 10.1183/09031936.00164608 [published Online First:
13 2009/05/23]
14
15
16
17
18
19 24. Vestbo J, Anderson W, Coxson HO, et al. Evaluation of COPD Longitudinally to Identify
20 Predictive Surrogate End-points (ECLIPSE). *Eur Respir J* 2008;31(4):869-73. doi:
21 09031936.00111707 [pii] 10.1183/09031936.00111707 [published Online First:
22 2008/01/25]
23
24
25
26
27
28 25. Agusti A, Calverley PM, Celli B, et al. Characterisation of COPD heterogeneity in the
29 ECLIPSE cohort. *Respir Res* 2010;11:122. doi: 1465-9921-11-122 [pii]
30 10.1186/1465-9921-11-122 [published Online First: 2010/09/14]
31
32
33
34
35 26. Society CPFCotJR. The predicted values of pulmonary function testing and arterial blood gas
36 in Japanese [in Japanese]. *Jpn J Thorac Dis* 2001;39(5):appendix.
37
38
39
40 27. Osaka D, Shibata Y, Abe S, et al. Relationship between habit of cigarette smoking and
41 airflow limitation in healthy Japanese individuals: the Takahata study. *Intern Med*
42 2010;49(15):1489-99. doi: JST.JSTAGE/internalmedicine/49.3364 [pii] [published
43 Online First: 2010/08/06]
44
45
46
47
48
49 28. Tsuda T, Suematsu R, Kamohara K, et al. Development of the Japanese version of the COPD
50 Assessment Test. *Respir Investig* 2012;50(2):34-9. doi: 10.1016/j.resinv.2012.05.003
51 [published Online First: 2012/07/04]
52
53
54
55

- 1
2
3 29. Kusunose M, Oga T, Nakamura S, et al. Frailty and patient-reported outcomes in subjects
4
5 with chronic obstructive pulmonary disease: are they independent entities? *BMJ Open*
6
7 *Respir Res* 2017;4(1):e000196. doi: 10.1136/bmjresp-2017-000196 [published Online
8
9 First: 2017/09/09]
- 10
11
12 30. Efron B, Tibshirani RJ. An Introduction to the Bootstrap (Chapman & Hall/CRC
13
14 Monographs on Statistics & Applied Probability). 1994
- 15
16
17 31. Elbehairy AF, Guenette JA, Faisal A, et al. Mechanisms of exertional dyspnoea in
18
19 symptomatic smokers without COPD. *Eur Respir J* 2016;48(3):694-705. doi:
20
21 10.1183/13993003.00077-2016 [published Online First: 2016/08/06]
- 22
23
24 32. Furlanetto KC, Mantoani LC, Bisca G, et al. Reduction of physical activity in daily life and
25
26 its determinants in smokers without airflow obstruction. *Respirology* 2014;19(3):369-75.
27
28 doi: 10.1111/resp.12236 [published Online First: 2014/02/04]
- 29
30
31 33. Regan EA, Lynch DA, Curran-Everett D, et al. Clinical and Radiologic Disease in Smokers
32
33 With Normal Spirometry. *JAMA Intern Med* 2015;175(9):1539-49. doi:
34
35 10.1001/jamainternmed.2015.2735 [published Online First: 2015/06/23]
- 36
37
38 34. Woodruff PG, Barr RG, Bleecker E, et al. Clinical Significance of Symptoms in Smokers
39
40 with Preserved Pulmonary Function. *N Engl J Med* 2016;374(19):1811-21. doi:
41
42 10.1056/NEJMoa1505971 [published Online First: 2016/05/12]
- 43
44
45 35. Martinez FJ, Raczek AE, Seifer FD, et al. Development and initial validation of a self-scored
46
47 COPD Population Screener Questionnaire (COPD-PS). *COPD* 2008;5(2):85-95. doi:
48
49 10.1080/15412550801940721 [published Online First: 2008/04/17]
- 50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 36. Price DB, Tinkelman DG, Halbert RJ, et al. Symptom-based questionnaire for identifying
4
5 COPD in smokers. *Respiration* 2006;73(3):285-95. doi: 10.1159/000090142 [published
6
7 Online First: 2005/12/07]
8
9
- 10 37. Vestbo J, Hurd SS, Agusti AG, et al. Global Strategy for the Diagnosis, Management, and
11
12 Prevention of Chronic Obstructive Pulmonary Disease: GOLD Executive Summary.
13
14 *American journal of respiratory and critical care medicine* 2013;187(4):347-65. doi:
15
16 10.1164/rccm.201204-0596PP rccm.201204-0596PP [pii] [published Online First:
17
18 2012/08/11]
19
20
- 21 38. Nishimura K, Izumi T, Tsukino M, et al. Dyspnea is a better predictor of 5-year survival than
22
23 airway obstruction in patients with COPD. *Chest* 2002;121(5):1434-40. [published
24
25 Online First: 2002/05/15]
26
27
- 28 39. Oga T, Nishimura K, Tsukino M, et al. Analysis of the factors related to mortality in chronic
29
30 obstructive pulmonary disease: role of exercise capacity and health status. *Am J Respir*
31
32 *Crit Care Med* 2003;167(4):544-9. doi: 10.1164/rccm.200206-583OC [published Online
33
34 First: 2002/11/26]
35
36
- 37 40. Pinto LM, Gupta N, Tan W, et al. Derivation of normative data for the COPD assessment test
38
39 (CAT). *Respir Res* 2014;15:68. doi: 10.1186/1465-9921-15-68
40
41
- 42 41. Vogelmeier CF, Criner GJ, Martinez FJ, et al. Global Strategy for the Diagnosis,
43
44 Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report. GOLD
45
46 Executive Summary. *Am J Respir Crit Care Med* 2017;195(5):557-82. doi:
47
48 10.1164/rccm.201701-0218PP
49
50
51
52
53
54
55
56
57
58
59
60

Figure Legends

Figure 1 Box plots representing the distributions of FEV₁ (%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 FEV₁/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 FEV₁ (%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 FEV₁/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

¶ FEV₁ of >85% predicted and FEV₁/FVC of >0.7, # a smoking history of <1 pack-year

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV₁, 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.

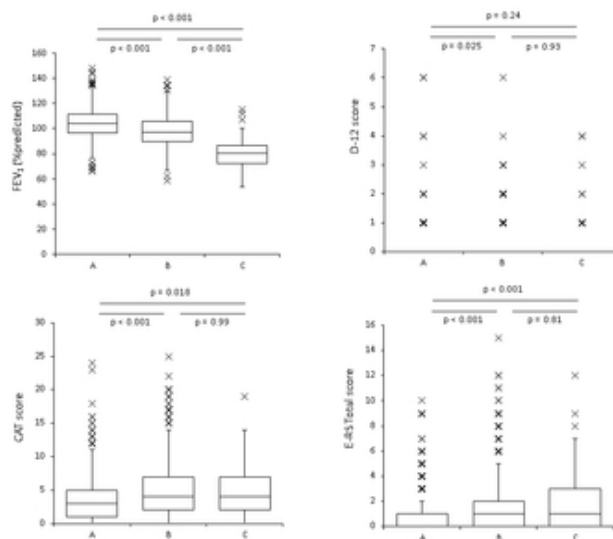
	D-12 score (0-36)					CAT score (0-40)					E-RS Total score (0-40)				
	mean	median	SD	max.	floor effect	mean	median	SD	max.	floor effect	mean	median	SD	max.	floor effect
All subjects	0.2	0.0	0.6	6.0	84.0%	4.3	3.0	3.9	25.0	14.6%	1.2	0.0	1.9	15.0	53.3%
Healthy non-smoking subjects¶#	0.2	0.0	0.5	6.0	86.5%	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%

¶ FEV₁ of >85% predicted and FEV₁/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; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; LLN, lower limit of normal.

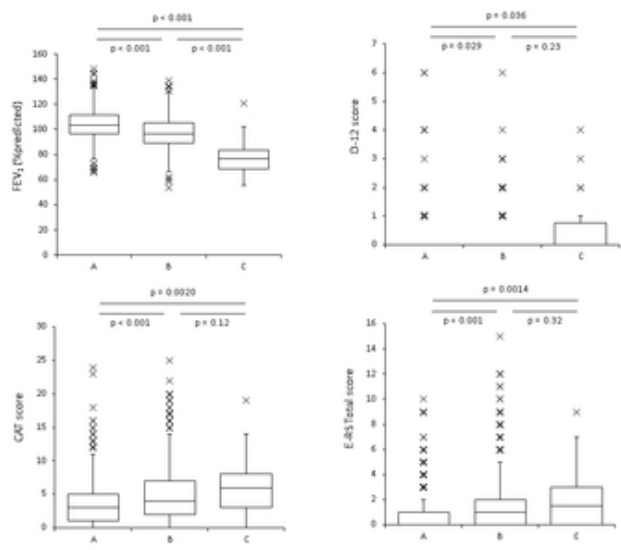
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only



45x25mm (300 x 300 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



45x25mm (300 x 300 DPI)

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 (b) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 4 Page 4 - 5	The cross-sectional data
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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants (b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	Page 8	
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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed	
		<i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	
		<i>Cross-sectional study</i> —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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —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

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-025132.R1
Article Type:	Research
Date Submitted by the Author:	09-Mar-2019
Complete List of Authors:	Nishimura, Koichi; National Center for Geriatrics and Gerontology, Department of Pulmonary Medicine Oga, Toru; Kawasaki Medical School, Department of Respiratory Medicine Nakayasu, Kazuhito; Kondo P.P. Inc., Data Research Section Ogasawara, Miyoko; Niigata Association of Occupational Health Incorporated Hasegawa, Yoshinori; Nagoya University Graduate School of Medicine, Division of Respiratory Medicine, Department of Medicine Mitsuma, Satoshi; Niigata Association of Occupational Health Incorporated
Primary Subject Heading:	Respiratory medicine
Secondary Subject Heading:	Diagnostics, Epidemiology
Keywords:	Chronic airways disease < THORACIC MEDICINE, EPIDEMIOLOGY, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Adult thoracic medicine < THORACIC MEDICINE, Epidemiology < THORACIC MEDICINE

SCHOLARONE™
Manuscripts

1
2
3
4 **COPD-specific patient reported outcomes in a working**
5
6
7 **population: how different are health status, dyspnoea**
8
9
10 **and respiratory symptoms?**
11
12
13
14

15 Names of Authors:

16 Koichi Nishimura¹, koichi-nishimura@nifty.com

17 Toru Oga², ogato@med.kawasaki-m.ac.jp

18 Kazuhito Nakayasu³, nakayasu@mydo-kond.co.jp

19 Miyoko Ogasawara⁴, mi_ogasawara@niwell.or.jp

20 Yoshinori Hasegawa⁵, yhasega@med.nagoya-u.ac.jp

21 Satoshi Mitsuma⁴, s.mitsuma@mac.com

22 Author Affiliations:

- 23
24
25
26
27
28
29
30
31
32
33
34
35
36 1) Department of Respiratory Medicine, National Center for Geriatrics and Gerontology,
37 7-430, Morioka-cho, Obu 474-8511, Japan;
38
39
40 2) Department of Respiratory Medicine, Kawasaki Medical School, 577 Matsushima,
41 Kurashiki, Okayama 701-0192, Japan
42
43
44 3) Data Research Section, Kondo Photo Process Co., LTD. 11-15, Shimizudani-cho,
45 Tennoujiku, Osaka 543-0011, Japan;
46
47
48 4) Niigata Association of Occupational Health Incorporated, 1-39-5, Kawagishi-cho,
49 Chuo-ku, Niigata 951-8133, Japan; and
50
51
52
53
54
55

1
2
3 5) Department of Respiratory Medicine, Nagoya University Graduate School of
4
5 Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8560, Japan
6
7
8

9
10 Corresponding Author:

11 Koichi Nishimura

12
13
14 National Center for Geriatrics and Gerontology,

15
16 Department of Respiratory Medicine,

17
18 7-430, Morioka-cho, Obu 474-8511, Japan
19

20
21 Tel: +81-562-46-2311; Fax: +81-562-44-8518
22

23 E-Mail: koichi-nishimura@nifty.com
24
25
26
27

28 Word count of text: 3,282 (except Abstract, References, Tables and Figures)
29
30
31

32 This study was partly supported by the Research Funding for Longevity Sciences (27-10)
33
34 from the National Center for Geriatrics and Gerontology (NCGG), Japan.
35
36
37
38

39 Running Title:

40
41 Health Status, Dyspnoea and Respiratory Symptoms in a Working Population
42
43
44
45

46 *Key words:*

47
48 *Chronic obstructive pulmonary disease (COPD);*

49
50
51 *Patient-reported outcome (PRO);*

52
53 *The COPD assessment test (CAT);*
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

*Dyspnoea-12 (D-12);
The Evaluating Respiratory Symptoms in COPD (E-RS).*

For peer review only

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.

1
2
3 However, these patient-reported measures were inadequate in differentiating between
4
5 smokers and subjects with COPD identified by spirometry.
6
7

8 9 **Strengths and limitations of this study**

- 10
11
12 ➤ Chronic obstructive pulmonary disease (COPD)-specific health status may be
13
14 measured by the COPD assessment test (CAT), respiratory symptoms by the
15
16 Evaluating Respiratory Symptoms in COPD (E-RS) and dyspnoea by Dyspnoea-12
17
18 (D-12). They are independently based on specific conceptual frameworks and are not
19
20 interchangeable.
21
- 22
23 ➤ Health status, dyspnoea and respiratory symptoms may have been confused in the
24
25 literature since they have different but somewhat similar meanings.
26
27
- 28
29 ➤ The CAT, E-RS and D-12 are all simple and easy to administer since the
30
31 methodology used in their development is similar.
32
- 33
34 ➤ The reference values of the scores obtained from the D-12 and E-RS for healthy non-
35
36 smoking subjects have not been reported although a cutoff score of 10 on the CAT is
37
38 often used.
39
- 40
41 ➤ The main limitation of this study is that it was conducted with healthy industrial
42
43 workers, who were not randomly sampled, thereby potentially being biased due to
44
45 the “healthy worker effect”.
46
47
48
49
50
51
52
53
54

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

1
2 similar. In subjects with COPD, it may be commonly accepted that breathlessness is
3 included in respiratory symptoms, and that this symptom is one of the essential
4 components of health status. Therefore, the D-12 would be reflected in the E-RS, and the
5 E-RS in the CAT.
6
7
8
9
10

11 We hypothesized that COPD-specific health status measured by the CAT, dyspnoea
12 by the D-12, and symptoms by the E-RS are independently based on specific conceptual
13 frameworks and are not interchangeable in a general population, and that comprehensive
14 symptomatic assessment of the CAT and E-RS would be preferable to dyspnoea by the
15 D-12 in identifying subjects who may have COPD among that population. Hence, the
16 purpose of the present study was to examine the discriminative properties of the CAT, D-
17 12 and E-RS in relation to smoking status and airflow limitation and to investigate
18 whether health status, dyspnoea and respiratory symptoms could be related to a diagnosis
19 of COPD based on the results of spirometry.
20
21
22
23
24
25
26
27
28
29
30
31

32 Additionally, we previously reported that the 95th percentile of the CAT scores was
33 13.6 in 512 healthy non-smoking subjects although the CAT score distribution
34 overlapped remarkably between both healthy non-smoking subjects and subjects with
35 COPD.¹⁹ As a secondary endpoint of the present study, it was our objective to determine
36 reference values of the scores obtained from the D-12 and E-RS for healthy non-smoking
37 subjects.
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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-470TM Spirometer (Fukuda Denshi Co., Ltd., Tokyo, Japan). All measurements were performed

1
2
3 by a laboratory technician in accordance with guidelines published by the American
4
5 Thoracic Society and European Respiratory Society.²⁰ The spirometric forced vital
6
7 capacity (FVC) and forced expiratory volume in one second (FEV₁) values were the
8
9 largest FVC and largest FEV₁ selected from data obtained from at least three acceptable
10
11 forced expiratory curves, even if these values were not obtained from the same curve.²¹ In
12
13 this study, COPD was spirometrically defined as airflow limitation with a FEV₁/FVC less
14
15 than either a fixed ratio, 0.7, or lower limit of normal (LLN) without bronchodilator
16
17 administration.²²⁻²⁵ Healthy subjects were defined as those with a FEV₁ of >85%
18
19 predicted or a FEV₁/FVC of >0.7, forming two groups: subjects with a smoking history
20
21 of ≥10 pack-years, and non-smoking subjects with a smoking history of < 1 pack-year.
22
23 This definition is similar to that of the Evaluation of COPD Longitudinally to Identify
24
25 Predictive Surrogate End-points (ECLIPSE) study.^{26 27} The predicted values for
26
27 pulmonary function were calculated based on the proposal from the Japanese Respiratory
28
29 Society.²⁸ The LLN for the Japanese population was calculated in the present study
30
31 according to the method described by Osaka et al.²⁹

32
33
34
35
36
37 The Japanese versions of the EXACT, CAT and D-12 were self-administered under
38
39 supervision in a booklet form. The E-RS uses 11 respiratory symptom items from the 14-
40
41 item EXACT, where scores range from 0 to 40, with higher scores indicating more severe
42
43 symptoms.¹⁴⁻¹⁸ The RS-Total Score represents overall respiratory symptom severity.^{17 18}
44
45 Three subscales were not used in this analysis. The Japanese translation has been created
46
47 and provided by the original developers who recommend the use of an electronic version
48
49 to collect the answers. However, no electronic device with the Japanese version of the
50
51 EXACT or E-RS was available so all surveys were conducted using a paper-based
52
53
54
55

1
2 method. Health status was assessed with a previously validated Japanese version of the
3
4 CAT.³⁰ The CAT consists of eight items scored from 0 to 5 in relation to cough, sputum,
5
6
7 dyspnea, chest tightness, capacity for exercise and activities, sleep quality and energy
8
9 levels.^{9 10} The CAT Scores range from 0 to 40, with a score of zero indicating no
10
11 impairment. To assess the severity of dyspnoea, we used the Japanese version of the D-
12
13 12,³¹ which consists of twelve items (seven physical items and five affective items), each
14
15 with a four point grading scale (0-3), producing a Total Score (range 0-36, with higher
16
17 scores representing more severe breathlessness).¹¹⁻¹³
18
19

20 21 **Patient and Public Involvement**

22
23 Patients were neither involved in the development of the research question, the design of
24
25 this study, nor the recruitment to and conduct of the study. The abstract of the published
26
27 paper will appear on the homepage of the institute.
28
29

30 31 **Ethics and Funding**

32
33 The present study was approved by the ethics committee of the Niigata Association of
34
35 Occupational Health Incorporated. Written informed consent was obtained from all
36
37 participants. This study was partly supported by the Research Funding for Longevity
38
39 Sciences (30-24) from the National Center for Geriatrics and Gerontology (NCGG),
40
41 Japan.
42
43

44 45 **Statistical Methods**

46
47 All results are expressed as means \pm standard deviation (SD). Relationships between two
48
49 sets of data were analysed by Spearman's rank correlation tests. In order to determine
50
51 reference values for each score, we calculated the 95th percentile of the scores in healthy,
52
53 non-smoking subjects using the Monte Carlo and bootstrap methods with 1,000 bootstrap
54

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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 FEV₁ 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 FEV₁ value was 99.6±13.1 %predicted. The FEV₁/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.

1
2
3 In the same way, the reference value of the CAT was calculated to be 9.88, which rounds
4
5 up to 10, in the present study.
6
7
8

9 **Relationships of COPD-specific PROs with Smoking and Airflow Limitation**

10
11 We then divided the 1,566 subjects into three groups consisting of a COPD group based
12
13 on the FEV₁/FVC using a fixed ratio, 0.7, or LLN; non-COPD current or past smokers;
14
15 and non-COPD never smokers (Tables 1 and 2). Using the fixed ratio of the
16
17 FEV₁/FVC<0.7, 85 subjects (5.4%) were diagnosed with COPD, 817 (52.2%) were non-
18
19 COPD smokers, and 664 (42.4%) were non-COPD never smokers. Using the LLN
20
21 definition, 34 subjects (2.2%) were diagnosed with COPD, 867 (55.4%) were non-COPD
22
23 smokers, and 665 (42.5%) were non-COPD never smokers.
24
25
26

27
28 Relationships of the PROs between the three groups of subjects with COPD, non-
29
30 COPD smokers and non-COPD never smokers are shown in Table 2 and Figures 1
31
32 (COPD based on the fixed ratio) and 2 (COPD based on the LLN). The FEV₁
33
34 (%predicted), D-12, CAT and E-RS Total were significantly separated between the three
35
36 groups (p<0.05). There were significant differences between the three groups for FEV₁
37
38 (%predicted), D-12, CAT and E-RS Total (p<0.05). FEV₁ was significantly different
39
40 between any two of the three groups (p<0.001) (Figures 1 and 2). With regard to the
41
42 score distribution (Table 2), floor effect in subjects with COPD was most prominent for
43
44 the D-12 (81.2% by the fixed definition and 73.5% by the LLN), and their median scores
45
46 were 0.0 (Table 2). It was the least for the CAT (15.3% by the fixed definition and 14.7%
47
48 by the LLN).
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 In investigating how many were symptomatic among 817 (by the fixed definition)
4 and 867 (by the LLN definition) non-COPD smokers, using the above reference values,
5 24 (2.9%) and 24 (2.8%) were >1 on the D-12, 79 (9.7%) and 80 (9.2%) were >10 on the
6
7 CAT, and 74 (9.1%) and 76 (8.8%) were >4 on the E-RS.
8
9
10

11 Regarding the group comparisons, significant differences were found between non-
12 COPD never smokers and non-COPD smokers on all of the measures; however,
13
14 significance was relatively weaker for the D-12 score ($p=0.025$ (Figure 1) and 0.029
15
16 (Figure 2)) as compared to the CAT and E-RS Total ($p<0.001$). On the CAT and E-RS
17
18 Total, significant differences were also found between non-COPD never smokers and
19
20 subjects with COPD ($p<0.05$); however, on the D-12, a significant difference was found
21
22 only by the LLN definition ($p=0.036$, Figure 1), but not by the fixed ratio definition
23
24 ($p=0.24$, Figure 1). Neither the D-12, CAT nor E-RS Total were significantly different
25
26 between COPD and non-COPD smokers.
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

1
2 based on spirometry,^{35 36} and that symptoms might be more sensitive than spirometry in
3
4 detecting smoking-related respiratory impairments. Actually, symptom-based
5
6 questionnaires to screen for COPD that do not include spirometry have been developed.³⁷
7
8
9 38

10
11 Conversely, the present study adds that PROs in non-COPD smokers were not
12
13 significantly different from those in subjects with COPD. Actually, about 9% of smokers
14
15 with preserved pulmonary function were judged to be symptomatic according to the
16
17 reference values of CAT>10 or E-RS>4. Their symptoms may tend to exacerbate in the
18
19 future, advance to COPD, or be treated as if they were COPD. How to manage this group
20
21 of symptomatic smokers without airflow limitation is a key issue to be solved through
22
23 careful long-term follow-ups.
24
25
26
27

28
29 The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2011 consensus
30
31 report proposed a revised “combined COPD assessment” classification in which
32
33 symptoms should be assessed either as a dyspnoea measure using the modified Medical
34
35 Research Council (mMRC) dyspnoea scale, or as a health status measure using the
36
37 CAT.³⁹ We have contributed to the establishment of this concept by demonstrating the
38
39 significant predictive properties of dyspnoea and health status independently of airflow
40
41 limitation.^{40 41} There has hitherto been much debate over how to assess symptoms in this
42
43 new classification. Although dyspnoea was not measured by the mMRC dyspnoea scale
44
45 but by D-12, interrelationships between the D-12, CAT and E-RS were weak to
46
47 moderate. Therefore, it may be difficult to use dyspnoea, health status and respiratory
48
49 symptoms in a mutually complementary form. The GOLD recommends a comprehensive
50
51 assessment of symptoms rather than just a measure of dyspnoea. The present study
52
53
54
55

1
2 supports this by showing that the D-12 had the most marked floor effects even in subjects
3
4 with COPD, and that the CAT and E-RS seemed to be more sensitive in discriminating
5
6 subjects based on smoking and COPD than the D-12.
7
8

9
10 We reported in 2013 that the 95th percentile of the scores in 512 healthy, non-
11
12 smoking subjects were used as the upper limit of normal in exactly the same way as in
13
14 the present study.¹⁹ For the CAT, it was 13.6. In 2014 Pinto et al. published some of the
15
16 results of the Canadian Cohort Obstructive Lung Disease (CanCOLD) study and reported
17
18 that the normative value for the CAT score was determined to be 16 from a population-
19
20 based study where they used post-bronchodilator spirometric values.⁴² Compared with
21
22 the above two reports, a score of 10 was the 95th percentile of the scores in healthy
23
24 industrial workers from Japan, and it is the lowest in the present study. The GOLD
25
26 currently states that the boundary between GOLD A and B and between GOLD C and D
27
28 is a CAT score of 10,^{39 43} which is consistent with the important result of the present
29
30 study although there might be some margin of error depending on the methodologies and
31
32 subjects of the studies.
33
34
35
36

37
38 This study has several limitations. Although we intended to determine the border of
39
40 the normal level of the D-12, CAT and E-RS Total scores, the study subjects were not
41
42 randomly sampled and there could be a risk of sample bias. The D-12, CAT and E-RS are
43
44 sufficiently validated for measuring PROs in subjects with COPD, but most participants
45
46 were not patients with COPD but rather healthy workers. As such, there is a possibility
47
48 that they are not appropriate tools for the study population. However, since the successful
49
50 application of the CAT in a working population or a random sampling frame from the
51
52 populations has also been reported,^{19 42} there may be a reason to be hopeful for success
53
54
55
56
57
58
59
60

1
2
3 with the D-12 and E-RS. Although post-bronchodilator spirometric values are
4
5 recommended to be used to make a diagnosis of COPD,^{39 43} the diagnosis was made only
6
7 from pre-bronchodilator spirometric information in the present study. Furthermore, the
8
9 present study was conducted in Japanese so that each of the instruments would have been
10
11 translated from the original language of its development. Although the Japanese version
12
13 has been validated in each case, it may be a limit to the generalizability of the research
14
15 across the globe.
16
17

18
19 Three main conclusions may be drawn from our findings. First, associations among
20
21 dyspnoea measured by the D-12, health status by the CAT, and respiratory symptoms by
22
23 the E-RS, were statistically significant but weak, indicating that they cannot be used
24
25 interchangeably. Second, using the data obtained from 646 healthy non-smoking subjects,
26
27 the reference values of the D-12, CAT and E-RS were ≤ 1 , ≤ 10 and ≤ 4 , respectively.
28
29 Third, from a standpoint of the relationship with smoking status and airflow limitation,
30
31 health status and respiratory symptoms may be more closely related to non-COPD
32
33 smokers and subjects with COPD than dyspnoea as compared to non-COPD never
34
35 smokers; however, none of these PRO measures can differentiate between non-COPD
36
37 smokers and subjects with COPD. How to manage non-COPD symptomatic smokers
38
39 should be investigated in the future.
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Other information

Acknowledgements

The authors wish to thank Nancy Kline Leidy for permission to use the Japanese version of the E-RS.

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.

Funding

This study was partly supported by the Research Funding for Longevity Sciences (30-24) from the National Center for Geriatrics and Gerontology (NCGG), Japan.

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.

References

1. Kyte D, Duffy H, Fletcher B, et al. Systematic evaluation of the patient-reported outcome (PRO) content of clinical trial protocols. *PLoS One* 2014;9(10):e110229. doi: 10.1371/journal.pone.0110229
2. Jones PW. Health status measurement in chronic obstructive pulmonary disease. *Thorax* 2001;56(11):880-7.
3. DeMuro C, Clark M, Doward L, et al. Assessment of PRO label claims granted by the FDA as compared to the EMA (2006-2010). *Value Health* 2013;16(8):1150-5. doi: 10.1016/j.jval.2013.08.2293
4. Gnanasakthy A, Mordin M, Evans E, et al. A Review of Patient-Reported Outcome Labeling in the United States (2011-2015). *Value Health* 2017;20(3):420-29. doi: 10.1016/j.jval.2016.10.006
5. Jones PW, Quirk FH, Baveystock CM, et al. A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. *Am Rev Respir Dis* 1992;145(6):1321-7. [published Online First: 1992/06/01]
6. Andrich D. Rasch models for measurement. Newbury Park, CA: Sage Publications 1998.
7. Rasch G. Probabilistic models for some intelligence and attainment tests. Chicago, IL: University of Chicago Press 1960.
8. Gupta N, Pinto LM, Morogan A, et al. The COPD assessment test: a systematic review. *Eur Respir J* 2014;44(4):873-84. doi: 10.1183/09031936.00025214
9. Jones PW, Brusselle G, Dal Negro RW, et al. Properties of the COPD Assessment Test (CAT) in a cross-sectional European study. *Eur Respir J* 2011 doi: 09031936.00177210 [pii] 10.1183/09031936.00177210 [published Online First: 2011/05/14]

- 1
2
3 10. Jones PW, Harding G, Berry P, et al. Development and first validation of the COPD
4
5 Assessment Test. *Eur Respir J* 2009;34(3):648-54. doi: 34/3/648 [pii]
6
7 10.1183/09031936.00102509 [published Online First: 2009/09/02]
8
9
10 11. Yorke J, Swigris J, Russell AM, et al. Dyspnea-12 is a valid and reliable measure of
11
12 breathlessness in patients with interstitial lung disease. *Chest* 2011;139(1):159-64. doi:
13
14 chest.10-0693 [pii]
15
16 10.1378/chest.10-0693 [published Online First: 2010/07/03]
17
18
19 12. Swigris JJ, Yorke J, Sprunger DB, et al. Assessing dyspnea and its impact on patients with
20
21 connective tissue disease-related interstitial lung disease. *Respir Med* 2010;104(9):1350-
22
23 5. doi: S0954-6111(10)00145-9 [pii]
24
25 10.1016/j.rmed.2010.03.027 [published Online First: 2010/05/18]
26
27
28 13. Yorke J, Moosavi SH, Shuldham C, et al. Quantification of dyspnoea using descriptors:
29
30 development and initial testing of the Dyspnoea-12. *Thorax* 2010;65(1):21-6. doi:
31
32 10.1136/thx.2009.118521
33
34
35 14. Leidy NK, Wilcox TK, Jones PW, et al. Standardizing Measurement of Chronic Obstructive
36
37 Pulmonary Disease Exacerbations: Reliability and Validity of a Patient-reported Diary.
38
39 *Am J Respir Crit Care Med* 2011;183(3):323-29. doi: 201005-0762OC [pii]
40
41 10.1164/rccm.201005-0762OC [published Online First: 2010/09/04]
42
43
44 15. Jones PW, Chen WH, Wilcox TK, et al. Characterizing and Quantifying the Symptomatic
45
46 Features of COPD Exacerbations. *Chest* 2011;139(6):1388-94. doi: chest.10-1240 [pii]
47
48 10.1378/chest.10-1240 [published Online First: 2010/11/13]
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 16. Leidy NK, Wilcox TK, Jones PW, et al. Development of the EXAcerbations of Chronic
4
5 Obstructive Pulmonary Disease Tool (EXACT): a patient-reported outcome (PRO)
6
7 measure. *Value Health* 2010;13(8):965-75. doi: 10.1111/j.1524-4733.2010.00772.x
8
9 VHE772 [pii] [published Online First: 2010/07/28]
- 10
11
12 17. Leidy NK, Murray LT, Monz BU, et al. Measuring respiratory symptoms of COPD:
13
14 performance of the EXACT- Respiratory Symptoms Tool (E-RS) in three clinical trials.
15
16 *Respir Res* 2014;15:124. doi: 10.1186/s12931-014-0124-z
17
18
- 19 18. Leidy NK, Sexton CC, Jones PW, et al. Measuring respiratory symptoms in clinical trials of
20
21 COPD: reliability and validity of a daily diary. *Thorax* 2014;69(5):443-9. doi:
22
23 10.1136/thoraxjnl-2013-204428
24
25
- 26 19. Nishimura K, Mitsuma S, Kobayashi A, et al. COPD and disease-specific health status in a
27
28 working population. *Respir Res* 2013;14:61. doi: 10.1186/1465-9921-14-61
29
30
- 31 20. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J*
32
33 2005;26(2):319-38. doi: 26/2/319 [pii]
34
35 10.1183/09031936.05.00034805 [published Online First: 2005/08/02]
36
37
- 38 21. Koyama H, Nishimura K, Ikeda A, et al. A comparison of different methods of spirometric
39
40 measurement selection. *Respir Med* 1998;92(3):498-504. doi: S0954-6111(98)90298-0
41
42 [pii] [published Online First: 1998/08/06]
43
44
- 45 22. Garcia-Rio F, Soriano JB, Miravittles M, et al. Overdiagnosing subjects with COPD using
46
47 the 0.7 fixed ratio: correlation with a poor health-related quality of life. *Chest*
48
49 2011;139(5):1072-80. doi: 10.1378/chest.10-1721 [published Online First: 2010/12/25]
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 23. Swanney MP, Ruppel G, Enright PL, et al. Using the lower limit of normal for the
4
5 FEV1/FVC ratio reduces the misclassification of airway obstruction. *Thorax*
6
7 2008;63(12):1046-51. doi: thx.2008.098483 [pii]
8
9 10.1136/thx.2008.098483 [published Online First: 2008/09/13]
10
11
12 24. van Dijk W, Tan W, Li P, et al. Clinical relevance of fixed ratio vs lower limit of normal of
13
14 FEV1/FVC in COPD: patient-reported outcomes from the CanCOLD cohort. *Ann Fam*
15
16 *Med* 2015;13(1):41-8. doi: 10.1370/afm.1714 [published Online First: 2015/01/15]
17
18
19 25. Vollmer WM, Gislason T, Burney P, et al. Comparison of spirometry criteria for the
20
21 diagnosis of COPD: results from the BOLD study. *Eur Respir J* 2009;34(3):588-97. doi:
22
23 09031936.00164608 [pii]
24
25 10.1183/09031936.00164608 [published Online First: 2009/05/23]
26
27
28 26. Vestbo J, Anderson W, Coxson HO, et al. Evaluation of COPD Longitudinally to Identify
29
30 Predictive Surrogate End-points (ECLIPSE). *Eur Respir J* 2008;31(4):869-73. doi:
31
32 09031936.00111707 [pii]
33
34 10.1183/09031936.00111707 [published Online First: 2008/01/25]
35
36
37 27. Agusti A, Calverley PM, Celli B, et al. Characterisation of COPD heterogeneity in the
38
39 ECLIPSE cohort. *Respir Res* 2010;11:122. doi: 1465-9921-11-122 [pii]
40
41 10.1186/1465-9921-11-122 [published Online First: 2010/09/14]
42
43
44 28. Society CPFCotJR. The predicted values of pulmonary function testing and arterial blood gas
45
46 in Japanese [in Japanese]. *Jpn J Thorac Dis* 2001;39(5):appendix.
47
48
49 29. Osaka D, Shibata Y, Abe S, et al. Relationship between habit of cigarette smoking and
50
51 airflow limitation in healthy Japanese individuals: the Takahata study. *Intern Med*
52
53
54
55
56
57
58
59
60

- 2010;49(15):1489-99. doi: JST.JSTAGE/internalmedicine/49.3364 [pii] [published Online First: 2010/08/06]
30. Tsuda T, Suematsu R, Kamohara K, et al. Development of the Japanese version of the COPD Assessment Test. *Respir Investig* 2012;50(2):34-9. doi: 10.1016/j.resinv.2012.05.003 [published Online First: 2012/07/04]
31. Kusunose M, Oga T, Nakamura S, et al. Frailty and patient-reported outcomes in subjects with chronic obstructive pulmonary disease: are they independent entities? *BMJ Open Respir Res* 2017;4(1):e000196. doi: 10.1136/bmjresp-2017-000196 [published Online First: 2017/09/09]
32. Efron B, Tibshirani RJ. An Introduction to the Bootstrap (Chapman & Hall/CRC Monographs on Statistics & Applied Probability). 1994
33. Elbehairy AF, Guenette JA, Faisal A, et al. Mechanisms of exertional dyspnoea in symptomatic smokers without COPD. *Eur Respir J* 2016;48(3):694-705. doi: 10.1183/13993003.00077-2016 [published Online First: 2016/08/06]
34. Furlanetto KC, Mantoani LC, Bisca G, et al. Reduction of physical activity in daily life and its determinants in smokers without airflow obstruction. *Respirology* 2014;19(3):369-75. doi: 10.1111/resp.12236 [published Online First: 2014/02/04]
35. Regan EA, Lynch DA, Curran-Everett D, et al. Clinical and Radiologic Disease in Smokers With Normal Spirometry. *JAMA Intern Med* 2015;175(9):1539-49. doi: 10.1001/jamainternmed.2015.2735 [published Online First: 2015/06/23]
36. Woodruff PG, Barr RG, Bleecker E, et al. Clinical Significance of Symptoms in Smokers with Preserved Pulmonary Function. *N Engl J Med* 2016;374(19):1811-21. doi: 10.1056/NEJMoa1505971 [published Online First: 2016/05/12]

- 1
2
3 37. Martinez FJ, Raczek AE, Seifer FD, et al. Development and initial validation of a self-scored
4
5 COPD Population Screener Questionnaire (COPD-PS). *COPD* 2008;5(2):85-95. doi:
6
7 10.1080/15412550801940721 [published Online First: 2008/04/17]
8
9
10 38. Price DB, Tinkelman DG, Halbert RJ, et al. Symptom-based questionnaire for identifying
11
12 COPD in smokers. *Respiration* 2006;73(3):285-95. doi: 10.1159/000090142 [published
13
14 Online First: 2005/12/07]
15
16
17 39. Vestbo J, Hurd SS, Agusti AG, et al. Global Strategy for the Diagnosis, Management, and
18
19 Prevention of Chronic Obstructive Pulmonary Disease: GOLD Executive Summary.
20
21 *American journal of respiratory and critical care medicine* 2013;187(4):347-65. doi:
22
23 10.1164/rccm.201204-0596PP
24
25
26 rccm.201204-0596PP [pii] [published Online First: 2012/08/11]
27
28
29 40. Nishimura K, Izumi T, Tsukino M, et al. Dyspnea is a better predictor of 5-year survival than
30
31 airway obstruction in patients with COPD. *Chest* 2002;121(5):1434-40. [published
32
33 Online First: 2002/05/15]
34
35
36 41. Oga T, Nishimura K, Tsukino M, et al. Analysis of the factors related to mortality in chronic
37
38 obstructive pulmonary disease: role of exercise capacity and health status. *Am J Respir*
39
40 *Crit Care Med* 2003;167(4):544-9. doi: 10.1164/rccm.200206-583OC [published Online
41
42 First: 2002/11/26]
43
44
45 42. Pinto LM, Gupta N, Tan W, et al. Derivation of normative data for the COPD assessment test
46
47 (CAT). *Respir Res* 2014;15:68. doi: 10.1186/1465-9921-15-68
48
49
50 43. Vogelmeier CF, Criner GJ, Martinez FJ, et al. Global Strategy for the Diagnosis,
51
52 Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report. GOLD
53
54
55
56
57
58
59
60

1
2
3 Executive Summary. *Am J Respir Crit Care Med* 2017;195(5):557-82. doi:
4

5 10.1164/rccm.201701-0218PP
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

Figure Legends

Figure 1 Box plots representing the distributions of FEV₁ (%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 FEV₁/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 FEV₁ (%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 FEV₁/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

[¶] FEV₁ of >85% predicted and FEV₁/FVC of >0.7, # a smoking history of <1 pack-year

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV₁, 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%

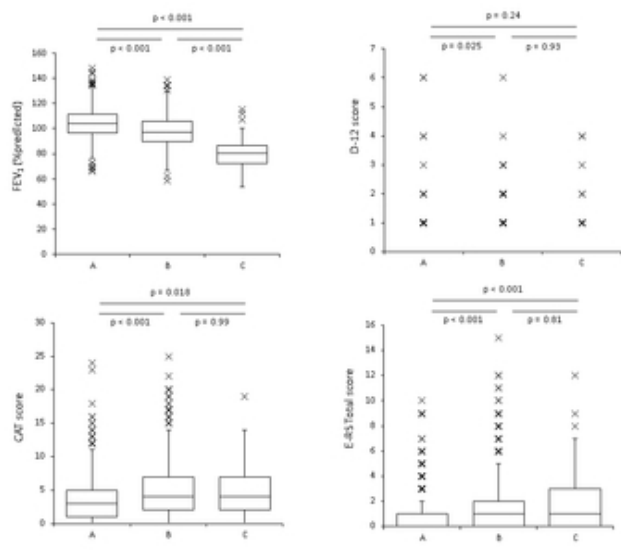
¶ FEV₁ of >85% predicted and FEV₁/FVC of >0.7, # a smoking history of <1 pack-year. Numbers in parentheses indicate the theoretical score range, and higher scores indicate worse status.

Abbreviations: CAT, COPD assessment test; COPD, chronic obstructive pulmonary disease; D-12, Dyspnoea-12; E-RS, Evaluating Respiratory Symptoms in COPD; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; LLN, lower limit of normal.

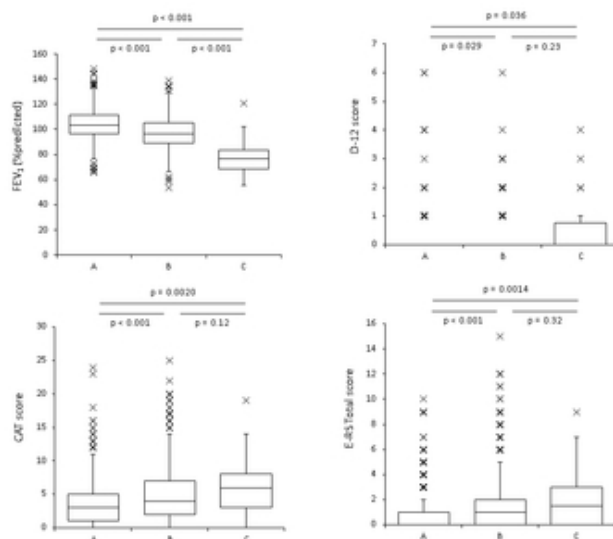
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



45x25mm (300 x 300 DPI)



45x25mm (300 x 300 DPI)

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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	Page 8	
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed	
		<i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	
		<i>Cross-sectional study</i> —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	
		(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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

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.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-025132.R2
Article Type:	Research
Date Submitted by the Author:	17-Jun-2019
Complete List of Authors:	Nishimura, Koichi; National Center for Geriatrics and Gerontology, Department of Respiratory Medicine Oga, Toru; Kawasaki Medical School, Department of Respiratory Medicine Nakayasu, Kazuhito; Kondo P.P. Inc., Data Research Section Ogasawara, Miyoko; Niigata Association of Occupational Health Incorporated Hasegawa, Yoshinori; Nagoya University Graduate School of Medicine, Division of Respiratory Medicine, Department of Medicine Mitsuma, Satoshi; Niigata Association of Occupational Health Incorporated
Primary Subject Heading:	Respiratory medicine
Secondary Subject Heading:	Diagnostics, Epidemiology
Keywords:	Chronic airways disease < THORACIC MEDICINE, EPIDEMIOLOGY, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Adult thoracic medicine < THORACIC MEDICINE, Epidemiology < THORACIC MEDICINE

SCHOLARONE™
Manuscripts

1
2
3
4 **How different are COPD-specific patient reported**
5
6
7 **outcomes, health status, dyspnoea and respiratory**
8
9
10 **symptoms? An observational study in a working**
11
12
13 **population.**
14

15
16 Names of Authors:

17
18 Koichi Nishimura¹, koichi-nishimura@nifty.com

19
20 Toru Oga², ogato@med.kawasaki-m.ac.jp

21
22 Kazuhito Nakayasu³, nakayasu@mydo-kond.co.jp

23
24 Miyoko Ogasawara⁴, mi_ogasawara@niwell.or.jp

25
26 Yoshinori Hasegawa⁵, yhasega@med.nagoya-u.ac.jp

27
28 Satoshi Mitsuma⁴, s.mitsuma@mac.com
29
30
31
32
33

34 Author Affiliations:

- 35
36
37 1) Department of Respiratory Medicine, National Center for Geriatrics and Gerontology,
38 7-430, Morioka-cho, Obu 474-8511, Japan;
39
40
41 2) Department of Respiratory Medicine, Kawasaki Medical School, 577 Matsushima,
42 Kurashiki, Okayama 701-0192, Japan;
43
44
45 3) Data Research Section, Kondo Photo Process Co., LTD. 11-15, Shimizudani-cho,
46 Tennoujiku, Osaka 543-0011, Japan;
47
48
49 4) Niigata Association of Occupational Health Incorporated, 1-39-5, Kawagishi-cho,
50 Chuo-ku, Niigata 951-8133, Japan; and
51
52
53
54

1
2
3 5) Department of Respiratory Medicine, Nagoya University Graduate School of
4
5 Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8560, Japan
6
7

8
9 Corresponding Author:

10
11 Koichi Nishimura

12
13 National Center for Geriatrics and Gerontology,
14

15
16 Department of Respiratory Medicine,
17

18
19 7-430, Morioka-cho, Obu 474-8511, Japan
20

21
22 Tel: +81-562-46-2311; Fax: +81-562-44-8518
23

24
25 E-Mail: koichi-nishimura@nifty.com
26
27

28 Word count of text: 3,353 (except Abstract, References, Tables and Figures)
29
30

31
32 This study was partly supported by the Research Funding for Longevity Sciences (27-10)
33
34 from the National Center for Geriatrics and Gerontology (NCGG), Japan.
35
36

37
38
39 Running Title:

40
41 Health Status, Dyspnoea and Respiratory Symptoms in a Working Population
42
43
44
45

46
47 *Key words:*

48
49 *Chronic obstructive pulmonary disease (COPD);*

50
51 *Patient-reported outcome (PRO);*

52
53 *The COPD assessment test (CAT);*
54
55

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

*Dyspnoea-12 (D-12);
The Evaluating Respiratory Symptoms in COPD (E-RS).*

For peer review only

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.

1
2
3 However, these patient-reported measures were inadequate in differentiating between
4
5 smokers and subjects with COPD identified by spirometry.
6
7
8

9 10 **Strengths and limitations of this study**

- 11
12 ➤ The COPD assessment test (CAT), the Evaluating Respiratory Symptoms in COPD
13
14 (E-RS) and Dyspnoea-12 (D-12) are all easy to administer since the methodology
15
16 used in their development is similar.
17
- 18
19 ➤ The associations between dyspnoea measured by the D-12, health status by the CAT,
20
21 and respiratory symptoms by the E-RS were significant but weak, indicating that
22
23 they were far below the level of conceptual similarity.
24
- 25
26 ➤ As the reference scores for healthy non-smoking subjects, that is, upper threshold,
27
28 the Bootstrap 95th percentile values were 1.00 for D-12, 9.88 for CAT and 4.44 for
29
30 E-RS.
31
- 32
33 ➤ The main limitation of this study is that it was conducted with healthy industrial
34
35 workers who were not randomly sampled, thereby potentially being biased due to the
36
37 “healthy worker effect”.
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

1
2 similar. In subjects with COPD, it may be commonly accepted that breathlessness is
3 included in respiratory symptoms, and that this symptom is one of the essential
4 components of health status. Therefore, the D-12 would be reflected in the E-RS, and the
5 E-RS in the CAT.
6
7
8
9
10

11 We hypothesized that COPD-specific health status measured by the CAT, dyspnoea
12 by the D-12, and symptoms by the E-RS are independently based on specific conceptual
13 frameworks and are not interchangeable in a general population, and that comprehensive
14 symptomatic assessment of the CAT and E-RS would be preferable to dyspnoea by the
15 D-12 in identifying subjects who may have COPD among that population. Hence, the
16 purpose of the present study was to examine the discriminative properties of the CAT, D-
17 12 and E-RS in relation to smoking status and airflow limitation and to investigate
18 whether health status, dyspnoea and respiratory symptoms could be related to a diagnosis
19 of COPD based on the results of spirometry.
20
21
22
23
24
25
26
27
28
29
30
31

32 Additionally, we previously reported that the 95th percentile of the CAT scores was
33 13.6 in 512 healthy non-smoking subjects although the CAT score distribution
34 overlapped remarkably between both healthy non-smoking subjects and subjects with
35 COPD.¹⁹ As a secondary endpoint of the present study, it was our objective to determine
36 reference values of the scores obtained from the D-12 and E-RS for healthy non-smoking
37 subjects.
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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-470TM Spirometer (Fukuda Denshi Co., Ltd., Tokyo, Japan). All measurements were performed

1
2
3 by a laboratory technician in accordance with guidelines published by the American
4
5 Thoracic Society and European Respiratory Society.²⁰ The spirometric forced vital
6
7 capacity (FVC) and forced expiratory volume in one second (FEV₁) values were the
8
9 largest FVC and largest FEV₁ selected from data obtained from at least three acceptable
10
11 forced expiratory curves, even if these values were not obtained from the same curve.²¹ In
12
13 this study, COPD was spirometrically defined as airflow limitation with a FEV₁/FVC less
14
15 than either a fixed ratio, 0.7, or lower limit of normal (LLN) without bronchodilator
16
17 administration.²²⁻²⁵ Healthy subjects were defined as those with a FEV₁ of >85%
18
19 predicted or a FEV₁/FVC of >0.7, forming two groups: subjects with a smoking history
20
21 of ≥10 pack-years, and non-smoking subjects with a smoking history of < 1 pack-year.
22
23 This definition is similar to that of the Evaluation of COPD Longitudinally to Identify
24
25 Predictive Surrogate End-points (ECLIPSE) study.^{26 27} The predicted values for
26
27 pulmonary function were calculated based on the proposal from the Japanese Respiratory
28
29 Society.²⁸ The LLN for the Japanese population was calculated in the present study
30
31 according to the method described by Osaka et al.²⁹

32
33
34
35
36
37 The Japanese versions of the EXACT, CAT and D-12 were self-administered in the
38
39 same order under supervision in a booklet form prior to the pulmonary function tests. The
40
41 E-RS uses 11 respiratory symptom items from the 14-item EXACT, where scores range
42
43 from 0 to 40, with higher scores indicating more severe symptoms.¹⁴⁻¹⁸ The RS-Total
44
45 Score represents overall respiratory symptom severity.^{17 18} Three subscales were not used
46
47 in this analysis. The Japanese translation has been created and provided by the original
48
49 developers who recommend the use of an electronic version to collect the answers.
50
51 However, no electronic device with the Japanese version of the EXACT or E-RS was
52
53
54

1
2 available so all surveys were conducted using a paper-based method. Health status was
3
4 assessed with a previously validated Japanese version of the CAT.³⁰ The CAT consists of
5
6 eight items scored from 0 to 5 in relation to cough, sputum, dyspnea, chest tightness,
7
8 capacity for exercise and activities, sleep quality and energy levels.^{9 10} The CAT Scores
9
10 range from 0 to 40, with a score of zero indicating no impairment. To assess the severity
11
12 of dyspnoea, we used the Japanese version of the D-12,³¹ which consists of twelve items
13
14 (seven physical items and five affective items), each with a four point grading scale (0-3),
15
16 producing a Total Score (range 0-36, with higher scores representing more severe
17
18 breathlessness).¹¹⁻¹³
19
20
21
22

23 **Patient and Public Involvement**

24
25 Patients were neither involved in the development of the research question, the design of
26
27 this study, nor the recruitment to and conduct of the study. The abstract of the published
28
29 paper will appear on the homepage of the institute.
30
31

32 **Ethics and Funding**

33
34 The present study was approved by the ethics committee of the Niigata Association of
35
36 Occupational Health Incorporated. Written informed consent was obtained from all
37
38 participants. This study was partly supported by the Research Funding for Longevity
39
40 Sciences (30-24) from the National Center for Geriatrics and Gerontology (NCGG),
41
42 Japan.
43
44
45

46 **Statistical Methods**

47
48 All results are expressed as means \pm standard deviation (SD). Relationships between two
49
50 sets of data were analysed by Spearman's rank correlation tests. In order to determine
51
52 reference values for each score, we calculated the 95th percentile of the scores in healthy,
53
54
55

1
2 non-smoking subjects using the Monte Carlo and bootstrap methods with 1,000 bootstrap
3
4
5 reps and used this as the upper limit of normal.³² In comparing the groups of COPD, non-
6
7 COPD smokers and non-COPD never smokers, the significance of between-group
8
9 difference was determined by an analysis of variance (ANOVA) for FEV₁ or a Kruskal-
10
11 Wallis test for PRO scores, and when a significant difference was observed, Tukey tests
12
13 or Steel-Dwass tests were used to analyse where the differences were significant,
14
15 respectively. Statistical analysis was performed using IBM SPSS Statistics 22.0
16
17 (International Business Machines Corp., Armonk, New York, USA) and BellCurve for
18
19 Excel (Social Survey Research Information Co., Ltd., Tokyo, Japan). A p value of less
20
21 than 0.05 was considered to be statistically significant.
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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 FEV₁ value was 99.6±13.1 %predicted. The FEV₁/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.

1
2 In the same way, the reference value of the CAT was calculated to be 9.88, which rounds
3 up to 10, in the present study.
4
5

6
7 Concordant and discordant results between tools were set to be examined using the
8 above cut-off values (Table 3). However, since there were only a small number of
9 subjects with higher scores on each instrument due to skewed score distribution, those
10 with higher scores on one instrument and lower scores on another were less than one-
11 tenth of all of the subjects involved.
12
13
14
15
16
17

18 19 20 21 **Relationships of COPD-specific PROs with Smoking and Airflow Limitation**

22
23 We then divided the 1,566 subjects into three groups consisting of a COPD group based
24 on the FEV₁/FVC using a fixed ratio, 0.7, or LLN; non-COPD current or past smokers;
25 and non-COPD never smokers (Tables 1 and 2). Using the fixed ratio of the
26 FEV₁/FVC<0.7, 85 subjects (5.4%) were diagnosed with COPD, 817 (52.2%) were non-
27 COPD smokers, and 664 (42.4%) were non-COPD never smokers. Using the LLN
28 definition, 34 subjects (2.2%) were diagnosed with COPD, 867 (55.4%) were non-COPD
29 smokers, and 665 (42.5%) were non-COPD never smokers.
30
31
32
33
34
35
36
37
38

39 Relationships of the PROs between the three groups of subjects with COPD, non-
40 COPD smokers and non-COPD never smokers are shown in Table 2 and Figures 1
41 (COPD based on the fixed ratio) and 2 (COPD based on the LLN). The FEV₁
42 (%predicted), D-12, CAT and E-RS Total were significantly separated between the three
43 groups (p<0.05). There were significant differences between the three groups for FEV₁
44 (%predicted), D-12, CAT and E-RS Total (p<0.05). FEV₁ was significantly different
45 between any two of the three groups (p<0.001) (Figures 1 and 2). With regard to the
46
47
48
49
50
51
52
53
54
55

1
2
3 score distribution (Table 2), floor effect in subjects with COPD was most prominent for
4
5 the D-12 (81.2% by the fixed definition and 73.5% by the LLN), and their median scores
6
7 were 0.0 (Table 2). It was the least for the CAT (15.3% by the fixed definition and 14.7%
8
9 by the LLN).
10

11
12 In investigating how many were symptomatic among 817 (by the fixed definition)
13
14 and 867 (by the LLN definition) non-COPD smokers, using the above reference values,
15
16 24 (2.9%) and 24 (2.8%) were >1 on the D-12, 79 (9.7%) and 80 (9.2%) were >10 on the
17
18 CAT, and 74 (9.1%) and 76 (8.8%) were >4 on the E-RS.
19

20
21 Regarding the group comparisons, significant differences were found between non-
22
23 COPD never smokers and non-COPD smokers on all of the measures; however,
24
25 significance was relatively weaker for the D-12 score ($p=0.025$ (Figure 1) and 0.029
26
27 (Figure 2)) as compared to the CAT and E-RS Total ($p<0.001$). On the CAT and E-RS
28
29 Total, significant differences were also found between non-COPD never smokers and
30
31 subjects with COPD ($p<0.05$); however, on the D-12, a significant difference was found
32
33 only by the LLN definition ($p=0.036$, Figure 1), but not by the fixed ratio definition
34
35 ($p=0.24$, Figure 1). Neither the D-12, CAT nor E-RS Total were significantly different
36
37 between COPD and non-COPD smokers.
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

1
2 based on spirometry,^{35 36} and that symptoms might be more sensitive than spirometry in
3
4 detecting smoking-related respiratory impairments. Actually, symptom-based
5
6 questionnaires to screen for COPD that do not include spirometry have been developed.³⁷
7
8
9 38

10
11 Conversely, the present study adds that PROs in non-COPD smokers were not
12
13 significantly different from those in subjects with COPD. Actually, about 9% of smokers
14
15 with preserved pulmonary function were judged to be symptomatic according to the
16
17 reference values of CAT>10 or E-RS>4. Their symptoms may tend to exacerbate in the
18
19 future, advance to COPD, or be treated as if they were COPD. How to manage this group
20
21 of symptomatic smokers without airflow limitation is a key issue to be solved through
22
23 careful long-term follow-ups.
24
25
26
27

28
29 The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2011 consensus
30
31 report proposed a revised “combined COPD assessment” classification in which
32
33 symptoms should be assessed either as a dyspnoea measure using the modified Medical
34
35 Research Council (mMRC) dyspnoea scale, or as a health status measure using the
36
37 CAT.³⁹ We have contributed to the establishment of this concept by demonstrating the
38
39 significant predictive properties of dyspnoea and health status independently of airflow
40
41 limitation.^{40 41} There has hitherto been much debate over how to assess symptoms in this
42
43 new classification. Although dyspnoea was not measured by the mMRC dyspnoea scale
44
45 but by D-12, interrelationships between the D-12, CAT and E-RS were weak to
46
47 moderate. Therefore, it may be difficult to use dyspnoea, health status and respiratory
48
49 symptoms in a mutually complementary form. The GOLD recommends a comprehensive
50
51 assessment of symptoms rather than just a measure of dyspnoea. The present study
52
53
54
55

1
2 supports this by showing that the D-12 had the most marked floor effects even in subjects
3
4 with COPD, and that the CAT and E-RS seemed to be more sensitive in discriminating
5
6 subjects based on smoking and COPD than the D-12.
7
8

9
10 We reported in 2013 that the 95th percentile of the scores in 512 healthy, non-
11
12 smoking subjects were used as the upper limit of normal in exactly the same way as in
13
14 the present study.¹⁹ For the CAT, it was 13.6. In 2014 Pinto et al. published some of the
15
16 results of the Canadian Cohort Obstructive Lung Disease (CanCOLD) study and reported
17
18 that the normative value for the CAT score was determined to be 16 from a population-
19
20 based study where they used post-bronchodilator spirometric values.⁴² Compared with
21
22 the above two reports, a score of 10 was the 95th percentile of the scores in healthy
23
24 industrial workers from Japan, and it is the lowest in the present study. The GOLD
25
26 currently states that the boundary between GOLD A and B and between GOLD C and D
27
28 is a CAT score of 10,^{39 43} which is consistent with the important result of the present
29
30 study although there might be some margin of error depending on the methodologies and
31
32 subjects of the studies.
33
34
35
36

37
38 This study has several limitations. Although we intended to determine the border of
39
40 the normal level of the D-12, CAT and E-RS Total scores, the study subjects were not
41
42 randomly sampled and there could be a risk of sample bias. The D-12, CAT and E-RS are
43
44 sufficiently validated for measuring PROs in subjects with COPD, but most participants
45
46 were not patients with COPD but rather healthy workers. As such, there is a possibility
47
48 that they are not appropriate tools for the study population. However, since the successful
49
50 application of the CAT in a working population or a random sampling frame from the
51
52 populations has also been reported,^{19 42} there may be a reason to be hopeful for success
53
54
55
56
57
58
59
60

1
2
3 with the D-12 and E-RS. Although post-bronchodilator spirometric values are
4
5 recommended to be used to make a diagnosis of COPD,^{39 43} the diagnosis was made only
6
7 from pre-bronchodilator spirometric information in the present study. Furthermore, the
8
9 present study was conducted in Japanese so that each of the instruments would have been
10
11 translated from the original language of its development. Although the Japanese version
12
13 has been validated in each case, it may be a limit to the generalizability of the research
14
15 across the globe.
16
17

18
19 Three main conclusions may be drawn from our findings. First, associations among
20
21 dyspnoea measured by the D-12, health status by the CAT, and respiratory symptoms by
22
23 the E-RS, were statistically significant but weak, indicating that they cannot be used
24
25 interchangeably. Second, using the data obtained from 646 healthy non-smoking subjects,
26
27 the reference values of the D-12, CAT and E-RS were ≤ 1 , ≤ 10 and ≤ 4 , respectively.
28
29 Third, from a standpoint of the relationship with smoking status and airflow limitation,
30
31 health status and respiratory symptoms may be more closely related to non-COPD
32
33 smokers and subjects with COPD than dyspnoea as compared to non-COPD never
34
35 smokers; however, none of these PRO measures can differentiate between non-COPD
36
37 smokers and subjects with COPD. How to manage non-COPD symptomatic smokers
38
39 should be investigated in the future.
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Other information

Acknowledgements

The authors wish to thank Nancy Kline Leidy for permission to use the Japanese version of the E-RS.

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.

Funding

This study was partly supported by the Research Funding for Longevity Sciences (30-24) from the National Center for Geriatrics and Gerontology (NCGG), Japan.

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.

References

1. Kyte D, Duffy H, Fletcher B, et al. Systematic evaluation of the patient-reported outcome (PRO) content of clinical trial protocols. *PLoS One* 2014;9(10):e110229. doi: 10.1371/journal.pone.0110229
2. Jones PW. Health status measurement in chronic obstructive pulmonary disease. *Thorax* 2001;56(11):880-7.
3. DeMuro C, Clark M, Doward L, et al. Assessment of PRO label claims granted by the FDA as compared to the EMA (2006-2010). *Value Health* 2013;16(8):1150-5. doi: 10.1016/j.jval.2013.08.2293
4. Gnanasakthy A, Mordin M, Evans E, et al. A Review of Patient-Reported Outcome Labeling in the United States (2011-2015). *Value Health* 2017;20(3):420-29. doi: 10.1016/j.jval.2016.10.006
5. Jones PW, Quirk FH, Baveystock CM, et al. A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. *Am Rev Respir Dis* 1992;145(6):1321-7. [published Online First: 1992/06/01]
6. Andrich D. Rasch models for measurement. Newbury Park, CA: Sage Publications 1998.
7. Rasch G. Probabilistic models for some intelligence and attainment tests. Chicago, IL: University of Chicago Press 1960.
8. Gupta N, Pinto LM, Morogan A, et al. The COPD assessment test: a systematic review. *Eur Respir J* 2014;44(4):873-84. doi: 10.1183/09031936.00025214
9. Jones PW, Brusselle G, Dal Negro RW, et al. Properties of the COPD Assessment Test (CAT) in a cross-sectional European study. *Eur Respir J* 2011 doi: 09031936.00177210 [pii] 10.1183/09031936.00177210 [published Online First: 2011/05/14]

- 1
2
3 10. Jones PW, Harding G, Berry P, et al. Development and first validation of the COPD
4
5 Assessment Test. *Eur Respir J* 2009;34(3):648-54. doi: 34/3/648 [pii]
6
7 10.1183/09031936.00102509 [published Online First: 2009/09/02]
8
9
10 11. Yorke J, Swigris J, Russell AM, et al. Dyspnea-12 is a valid and reliable measure of
11
12 breathlessness in patients with interstitial lung disease. *Chest* 2011;139(1):159-64. doi:
13
14 chest.10-0693 [pii]
15
16 10.1378/chest.10-0693 [published Online First: 2010/07/03]
17
18
19 12. Swigris JJ, Yorke J, Sprunger DB, et al. Assessing dyspnea and its impact on patients with
20
21 connective tissue disease-related interstitial lung disease. *Respir Med* 2010;104(9):1350-
22
23 5. doi: S0954-6111(10)00145-9 [pii]
24
25 10.1016/j.rmed.2010.03.027 [published Online First: 2010/05/18]
26
27
28 13. Yorke J, Moosavi SH, Shuldham C, et al. Quantification of dyspnoea using descriptors:
29
30 development and initial testing of the Dyspnoea-12. *Thorax* 2010;65(1):21-6. doi:
31
32 10.1136/thx.2009.118521
33
34
35 14. Leidy NK, Wilcox TK, Jones PW, et al. Standardizing Measurement of Chronic Obstructive
36
37 Pulmonary Disease Exacerbations: Reliability and Validity of a Patient-reported Diary.
38
39 *Am J Respir Crit Care Med* 2011;183(3):323-29. doi: 201005-0762OC [pii]
40
41 10.1164/rccm.201005-0762OC [published Online First: 2010/09/04]
42
43
44 15. Jones PW, Chen WH, Wilcox TK, et al. Characterizing and Quantifying the Symptomatic
45
46 Features of COPD Exacerbations. *Chest* 2011;139(6):1388-94. doi: chest.10-1240 [pii]
47
48 10.1378/chest.10-1240 [published Online First: 2010/11/13]
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 16. Leidy NK, Wilcox TK, Jones PW, et al. Development of the EXAcerbations of Chronic
4
5 Obstructive Pulmonary Disease Tool (EXACT): a patient-reported outcome (PRO)
6
7 measure. *Value Health* 2010;13(8):965-75. doi: 10.1111/j.1524-4733.2010.00772.x
8
9 VHE772 [pii] [published Online First: 2010/07/28]
- 10
11
12 17. Leidy NK, Murray LT, Monz BU, et al. Measuring respiratory symptoms of COPD:
13
14 performance of the EXACT- Respiratory Symptoms Tool (E-RS) in three clinical trials.
15
16 *Respir Res* 2014;15:124. doi: 10.1186/s12931-014-0124-z
17
18
- 19 18. Leidy NK, Sexton CC, Jones PW, et al. Measuring respiratory symptoms in clinical trials of
20
21 COPD: reliability and validity of a daily diary. *Thorax* 2014;69(5):443-9. doi:
22
23 10.1136/thoraxjnl-2013-204428
24
25
- 26 19. Nishimura K, Mitsuma S, Kobayashi A, et al. COPD and disease-specific health status in a
27
28 working population. *Respir Res* 2013;14:61. doi: 10.1186/1465-9921-14-61
29
30
- 31 20. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J*
32
33 2005;26(2):319-38. doi: 26/2/319 [pii]
34
35 10.1183/09031936.05.00034805 [published Online First: 2005/08/02]
36
37
- 38 21. Koyama H, Nishimura K, Ikeda A, et al. A comparison of different methods of spirometric
39
40 measurement selection. *Respir Med* 1998;92(3):498-504. doi: S0954-6111(98)90298-0
41
42 [pii] [published Online First: 1998/08/06]
43
44
- 45 22. Garcia-Rio F, Soriano JB, Miravittles M, et al. Overdiagnosing subjects with COPD using
46
47 the 0.7 fixed ratio: correlation with a poor health-related quality of life. *Chest*
48
49 2011;139(5):1072-80. doi: 10.1378/chest.10-1721 [published Online First: 2010/12/25]
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 23. Swanney MP, Ruppel G, Enright PL, et al. Using the lower limit of normal for the
4
5 FEV1/FVC ratio reduces the misclassification of airway obstruction. *Thorax*
6
7 2008;63(12):1046-51. doi: thx.2008.098483 [pii]
8
9 10.1136/thx.2008.098483 [published Online First: 2008/09/13]
10
11
12 24. van Dijk W, Tan W, Li P, et al. Clinical relevance of fixed ratio vs lower limit of normal of
13
14 FEV1/FVC in COPD: patient-reported outcomes from the CanCOLD cohort. *Ann Fam*
15
16 *Med* 2015;13(1):41-8. doi: 10.1370/afm.1714 [published Online First: 2015/01/15]
17
18
19 25. Vollmer WM, Gislason T, Burney P, et al. Comparison of spirometry criteria for the
20
21 diagnosis of COPD: results from the BOLD study. *Eur Respir J* 2009;34(3):588-97. doi:
22
23 09031936.00164608 [pii]
24
25 10.1183/09031936.00164608 [published Online First: 2009/05/23]
26
27
28 26. Vestbo J, Anderson W, Coxson HO, et al. Evaluation of COPD Longitudinally to Identify
29
30 Predictive Surrogate End-points (ECLIPSE). *Eur Respir J* 2008;31(4):869-73. doi:
31
32 09031936.00111707 [pii]
33
34 10.1183/09031936.00111707 [published Online First: 2008/01/25]
35
36
37 27. Agusti A, Calverley PM, Celli B, et al. Characterisation of COPD heterogeneity in the
38
39 ECLIPSE cohort. *Respir Res* 2010;11:122. doi: 1465-9921-11-122 [pii]
40
41 10.1186/1465-9921-11-122 [published Online First: 2010/09/14]
42
43
44 28. Society CPFCotJR. The predicted values of pulmonary function testing and arterial blood gas
45
46 in Japanese [in Japanese]. *Jpn J Thorac Dis* 2001;39(5):appendix.
47
48
49 29. Osaka D, Shibata Y, Abe S, et al. Relationship between habit of cigarette smoking and
50
51 airflow limitation in healthy Japanese individuals: the Takahata study. *Intern Med*
52
53
54
55
56
57
58
59
60

- 2010;49(15):1489-99. doi: JST.JSTAGE/internalmedicine/49.3364 [pii] [published Online First: 2010/08/06]
30. Tsuda T, Suematsu R, Kamohara K, et al. Development of the Japanese version of the COPD Assessment Test. *Respir Investig* 2012;50(2):34-9. doi: 10.1016/j.resinv.2012.05.003 [published Online First: 2012/07/04]
31. Kusunose M, Oga T, Nakamura S, et al. Frailty and patient-reported outcomes in subjects with chronic obstructive pulmonary disease: are they independent entities? *BMJ Open Respir Res* 2017;4(1):e000196. doi: 10.1136/bmjresp-2017-000196 [published Online First: 2017/09/09]
32. Efron B, Tibshirani RJ. An Introduction to the Bootstrap (Chapman & Hall/CRC Monographs on Statistics & Applied Probability). 1994
33. Elbehairy AF, Guenette JA, Faisal A, et al. Mechanisms of exertional dyspnoea in symptomatic smokers without COPD. *Eur Respir J* 2016;48(3):694-705. doi: 10.1183/13993003.00077-2016 [published Online First: 2016/08/06]
34. Furlanetto KC, Mantoani LC, Bisca G, et al. Reduction of physical activity in daily life and its determinants in smokers without airflow obstruction. *Respirology* 2014;19(3):369-75. doi: 10.1111/resp.12236 [published Online First: 2014/02/04]
35. Regan EA, Lynch DA, Curran-Everett D, et al. Clinical and Radiologic Disease in Smokers With Normal Spirometry. *JAMA Intern Med* 2015;175(9):1539-49. doi: 10.1001/jamainternmed.2015.2735 [published Online First: 2015/06/23]
36. Woodruff PG, Barr RG, Bleecker E, et al. Clinical Significance of Symptoms in Smokers with Preserved Pulmonary Function. *N Engl J Med* 2016;374(19):1811-21. doi: 10.1056/NEJMoa1505971 [published Online First: 2016/05/12]

- 1
2
3 37. Martinez FJ, Raczek AE, Seifer FD, et al. Development and initial validation of a self-scored
4
5 COPD Population Screener Questionnaire (COPD-PS). *COPD* 2008;5(2):85-95. doi:
6
7 10.1080/15412550801940721 [published Online First: 2008/04/17]
8
9
10 38. Price DB, Tinkelman DG, Halbert RJ, et al. Symptom-based questionnaire for identifying
11
12 COPD in smokers. *Respiration* 2006;73(3):285-95. doi: 10.1159/000090142 [published
13
14 Online First: 2005/12/07]
15
16
17 39. Vestbo J, Hurd SS, Agusti AG, et al. Global Strategy for the Diagnosis, Management, and
18
19 Prevention of Chronic Obstructive Pulmonary Disease: GOLD Executive Summary.
20
21 *American journal of respiratory and critical care medicine* 2013;187(4):347-65. doi:
22
23 10.1164/rccm.201204-0596PP
24
25
26 rccm.201204-0596PP [pii] [published Online First: 2012/08/11]
27
28
29 40. Nishimura K, Izumi T, Tsukino M, et al. Dyspnea is a better predictor of 5-year survival than
30
31 airway obstruction in patients with COPD. *Chest* 2002;121(5):1434-40. [published
32
33 Online First: 2002/05/15]
34
35
36 41. Oga T, Nishimura K, Tsukino M, et al. Analysis of the factors related to mortality in chronic
37
38 obstructive pulmonary disease: role of exercise capacity and health status. *Am J Respir*
39
40 *Crit Care Med* 2003;167(4):544-9. doi: 10.1164/rccm.200206-583OC [published Online
41
42 First: 2002/11/26]
43
44
45 42. Pinto LM, Gupta N, Tan W, et al. Derivation of normative data for the COPD assessment test
46
47 (CAT). *Respir Res* 2014;15:68. doi: 10.1186/1465-9921-15-68
48
49
50 43. Vogelmeier CF, Criner GJ, Martinez FJ, et al. Global Strategy for the Diagnosis,
51
52 Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report. GOLD
53
54
55
56
57
58
59
60

1
2
3 Executive Summary. *Am J Respir Crit Care Med* 2017;195(5):557-82. doi:

4
5 10.1164/rccm.201701-0218PP
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

Figure Legends

Figure 1 Box plots representing the distributions of FEV₁ (%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 FEV₁/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 FEV₁ (%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 FEV₁/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	

[¶] FEV₁ of >85% predicted and FEV₁/FVC of >0.7, # a smoking history of <1 pack-year

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV₁, 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%

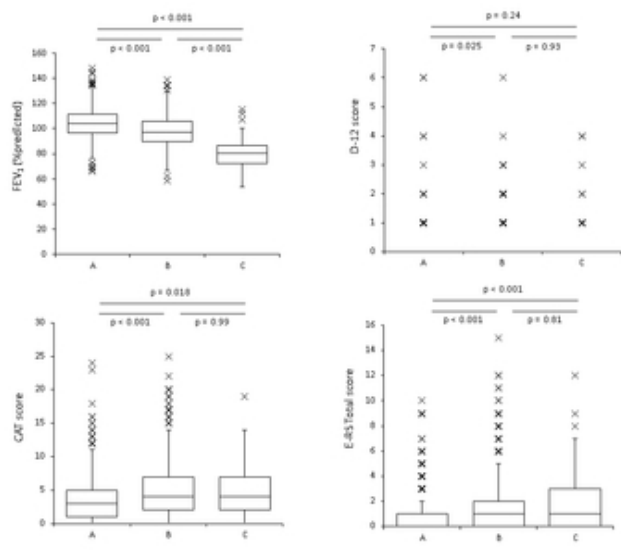
¶ FEV₁ of >85% predicted and FEV₁/FVC of >0.7, # a smoking history of <1 pack-year. Numbers in parentheses indicate the theoretical score range, and higher scores indicate worse status.

Abbreviations: CAT, COPD assessment test; COPD, chronic obstructive pulmonary disease; D-12, Dyspnoea-12; E-RS, Evaluating Respiratory Symptoms in COPD; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; LLN, lower limit of normal.

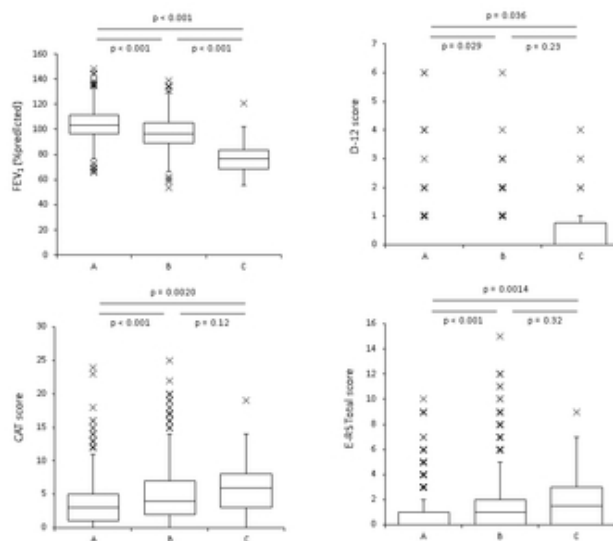
Table 3. Concordant and discordant results between tools using the cut-off values.

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%)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



45x25mm (300 x 300 DPI)



45x25mm (300 x 300 DPI)

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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Page 8	
		<i>Case-control study</i> —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		
		<i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants		
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed		
		<i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed		
		<i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed		
		<i>Cross-sectional study</i> —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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)		
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time		
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure		
		<i>Cross-sectional study</i> —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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

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.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-025132.R3
Article Type:	Research
Date Submitted by the Author:	23-Jun-2019
Complete List of Authors:	Nishimura, Koichi; National Center for Geriatrics and Gerontology, Department of Respiratory Medicine Oga, Toru; Kawasaki Medical School, Department of Respiratory Medicine Nakayasu, Kazuhito; Kondo P.P. Inc., Data Research Section Ogasawara, Miyoko; Niigata Association of Occupational Health Incorporated Hasegawa, Yoshinori; Nagoya University Graduate School of Medicine, Division of Respiratory Medicine, Department of Medicine Mitsuma, Satoshi; Niigata Association of Occupational Health Incorporated
Primary Subject Heading:	Respiratory medicine
Secondary Subject Heading:	Diagnostics, Epidemiology
Keywords:	Chronic airways disease < THORACIC MEDICINE, EPIDEMIOLOGY, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Adult thoracic medicine < THORACIC MEDICINE, Epidemiology < THORACIC MEDICINE

SCHOLARONE™
Manuscripts

1
2
3
4 **How different are COPD-specific patient reported**
5
6
7 **outcomes, health status, dyspnoea and respiratory**
8
9
10 **symptoms? An observational study in a working**
11
12 **population.**
13
14

15
16 Names of Authors:

17
18 Koichi Nishimura¹, koichi-nishimura@nifty.com

19
20 Toru Oga², ogato@med.kawasaki-m.ac.jp

21
22 Kazuhito Nakayasu³, nakayasu@mydo-kond.co.jp

23
24 Miyoko Ogasawara⁴, mi_ogasawara@niwell.or.jp

25
26 Yoshinori Hasegawa⁵, yhasega@med.nagoya-u.ac.jp

27
28 Satoshi Mitsuma⁴, s.mitsuma@mac.com
29
30
31
32
33

34 Author Affiliations:

- 35
36
37 1) Department of Respiratory Medicine, National Center for Geriatrics and Gerontology,
38 7-430, Morioka-cho, Obu 474-8511, Japan;
39
40
41 2) Department of Respiratory Medicine, Kawasaki Medical School, 577 Matsushima,
42 Kurashiki, Okayama 701-0192, Japan;
43
44
45 3) Data Research Section, Kondo Photo Process Co., LTD. 11-15, Shimizudani-cho,
46 Tennoujiku, Osaka 543-0011, Japan;
47
48
49 4) Niigata Association of Occupational Health Incorporated, 1-39-5, Kawagishi-cho,
50 Chuo-ku, Niigata 951-8133, Japan; and
51
52
53
54

1
2
3 5) Department of Respiratory Medicine, Nagoya University Graduate School of
4
5 Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8560, Japan
6
7
8

9
10 Corresponding Author:

11 Koichi Nishimura

12
13
14 National Center for Geriatrics and Gerontology,

15
16 Department of Respiratory Medicine,

17
18 7-430, Morioka-cho, Obu 474-8511, Japan
19

20
21 Tel: +81-562-46-2311; Fax: +81-562-44-8518
22

23 E-Mail: koichi-nishimura@nifty.com
24
25
26
27

28 Word count of text: 3,353 (except Abstract, References, Tables and Figures)
29
30
31

32 This study was partly supported by the Research Funding for Longevity Sciences (27-10)
33
34 from the National Center for Geriatrics and Gerontology (NCGG), Japan.
35
36
37
38

39 Running Title:

40
41 Health Status, Dyspnoea and Respiratory Symptoms in a Working Population
42
43
44
45

46 *Key words:*

47
48 *Chronic obstructive pulmonary disease (COPD);*

49
50
51 *Patient-reported outcome (PRO);*

52
53 *The COPD assessment test (CAT);*
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Dyspnoea-12 (D-12);

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

For peer review only

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.

1
2
3 However, these patient-reported measures were inadequate in differentiating between
4
5 smokers and subjects with COPD identified by spirometry.
6
7

8 9 **Strengths and limitations of this study**

- 10
11
- 12 ➤ The COPD assessment test (CAT), the Evaluating Respiratory Symptoms in COPD
13 (E-RS) and Dyspnoea-12 (D-12) are all easy to administer since the methodology
14 used in their development is similar.
15
16
 - 17 ➤ The authors sought the reference values of the scores obtained from the D-12 and E-
18 RS for healthy non-smoking subjects that has not been reported although it has been
19 considered that a CAT score of 10 is a cutoff value.
20
21
 - 22 ➤ The main limitation of this study is that it was conducted with healthy industrial
23 workers who were not randomly sampled, thereby potentially being biased due to the
24 “healthy worker effect”.
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

1
2 similar. In subjects with COPD, it may be commonly accepted that breathlessness is
3 included in respiratory symptoms, and that this symptom is one of the essential
4 components of health status. Therefore, the D-12 would be reflected in the E-RS, and the
5 E-RS in the CAT.
6
7
8
9
10

11 We hypothesized that COPD-specific health status measured by the CAT, dyspnoea
12 by the D-12, and symptoms by the E-RS are independently based on specific conceptual
13 frameworks and are not interchangeable in a general population, and that comprehensive
14 symptomatic assessment of the CAT and E-RS would be preferable to dyspnoea by the
15 D-12 in identifying subjects who may have COPD among that population. Hence, the
16 purpose of the present study was to examine the discriminative properties of the CAT, D-
17 12 and E-RS in relation to smoking status and airflow limitation and to investigate
18 whether health status, dyspnoea and respiratory symptoms could be related to a diagnosis
19 of COPD based on the results of spirometry.
20
21
22
23
24
25
26
27
28
29
30
31

32 Additionally, we previously reported that the 95th percentile of the CAT scores was
33 13.6 in 512 healthy non-smoking subjects although the CAT score distribution
34 overlapped remarkably between both healthy non-smoking subjects and subjects with
35 COPD.¹⁹ As a secondary endpoint of the present study, it was our objective to determine
36 reference values of the scores obtained from the D-12 and E-RS for healthy non-smoking
37 subjects.
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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-470TM Spirometer (Fukuda Denshi Co., Ltd., Tokyo, Japan). All measurements were performed

1
2
3 by a laboratory technician in accordance with guidelines published by the American
4 Thoracic Society and European Respiratory Society.²⁰ The spirometric forced vital
5 capacity (FVC) and forced expiratory volume in one second (FEV₁) values were the
6
7 largest FVC and largest FEV₁ selected from data obtained from at least three acceptable
8
9 forced expiratory curves, even if these values were not obtained from the same curve.²¹ In
10
11 this study, COPD was spirometrically defined as airflow limitation with a FEV₁/FVC less
12
13 than either a fixed ratio, 0.7, or lower limit of normal (LLN) without bronchodilator
14
15 administration.²²⁻²⁵ Healthy subjects were defined as those with a FEV₁ of >85%
16
17 predicted or a FEV₁/FVC of >0.7, forming two groups: subjects with a smoking history
18
19 of ≥10 pack-years, and non-smoking subjects with a smoking history of < 1 pack-year.
20
21 This definition is similar to that of the Evaluation of COPD Longitudinally to Identify
22
23 Predictive Surrogate End-points (ECLIPSE) study.^{26 27} The predicted values for
24
25 pulmonary function were calculated based on the proposal from the Japanese Respiratory
26
27 Society.²⁸ The LLN for the Japanese population was calculated in the present study
28
29 according to the method described by Osaka et al.²⁹

30
31
32 The Japanese versions of the EXACT, CAT and D-12 were self-administered in the
33
34 same order under supervision in a booklet form prior to the pulmonary function tests. The
35
36 E-RS uses 11 respiratory symptom items from the 14-item EXACT, where scores range
37
38 from 0 to 40, with higher scores indicating more severe symptoms.¹⁴⁻¹⁸ The RS-Total
39
40 Score represents overall respiratory symptom severity.^{17 18} Three subscales were not used
41
42 in this analysis. The Japanese translation has been created and provided by the original
43
44 developers who recommend the use of an electronic version to collect the answers.
45
46 However, no electronic device with the Japanese version of the EXACT or E-RS was
47
48
49
50
51
52
53
54

1
2 available so all surveys were conducted using a paper-based method. Health status was
3
4 assessed with a previously validated Japanese version of the CAT.³⁰ The CAT consists of
5
6 eight items scored from 0 to 5 in relation to cough, sputum, dyspnea, chest tightness,
7
8 capacity for exercise and activities, sleep quality and energy levels.^{9 10} The CAT Scores
9
10 range from 0 to 40, with a score of zero indicating no impairment. To assess the severity
11
12 of dyspnoea, we used the Japanese version of the D-12,³¹ which consists of twelve items
13
14 (seven physical items and five affective items), each with a four point grading scale (0-3),
15
16 producing a Total Score (range 0-36, with higher scores representing more severe
17
18 breathlessness).¹¹⁻¹³
19
20
21
22

23 **Patient and Public Involvement**

24
25 Patients were neither involved in the development of the research question, the design of
26
27 this study, nor the recruitment to and conduct of the study. The abstract of the published
28
29 paper will appear on the homepage of the institute.
30
31

32 **Ethics**

33
34 The present study was approved by the ethics committee of the Niigata Association of
35
36 Occupational Health Incorporated. Written informed consent was obtained from all
37
38 participants.
39
40

41 **Statistical Methods**

42
43 All results are expressed as means \pm standard deviation (SD). Relationships between two
44
45 sets of data were analysed by Spearman's rank correlation tests. In order to determine
46
47 reference values for each score, we calculated the 95th percentile of the scores in healthy,
48
49 non-smoking subjects using the Monte Carlo and bootstrap methods with 1,000 bootstrap
50
51 reps and used this as the upper limit of normal.³² In comparing the groups of COPD, non-
52
53
54

1
2 COPD smokers and non-COPD never smokers, the significance of between-group
3
4 difference was determined by an analysis of variance (ANOVA) for FEV₁ or a Kruskal-
5
6 Wallis test for PRO scores, and when a significant difference was observed, Tukey tests
7
8 or Steel-Dwass tests were used to analyse where the differences were significant,
9
10 respectively. Statistical analysis was performed using IBM SPSS Statistics 22.0
11
12 (International Business Machines Corp., Armonk, New York, USA) and BellCurve for
13
14 Excel (Social Survey Research Information Co., Ltd., Tokyo, Japan). A p value of less
15
16 than 0.05 was considered to be statistically significant.
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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 FEV₁ value was 99.6±13.1 %predicted. The FEV₁/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.

1
2
3 In the same way, the reference value of the CAT was calculated to be 9.88, which rounds
4
5 up to 10, in the present study.

6
7 Concordant and discordant results between tools were set to be examined using the
8
9 above cut-off values (Table 3). However, since there were only a small number of
10
11 subjects with higher scores on each instrument due to skewed score distribution, those
12
13 with higher scores on one instrument and lower scores on another were less than one-
14
15 tenth of all of the subjects involved.

20 21 **Relationships of COPD-specific PROs with Smoking and Airflow Limitation**

22
23 We then divided the 1,566 subjects into three groups consisting of a COPD group based
24
25 on the FEV₁/FVC using a fixed ratio, 0.7, or LLN; non-COPD current or past smokers;
26
27 and non-COPD never smokers (Tables 1 and 2). Using the fixed ratio of the
28
29 FEV₁/FVC<0.7, 85 subjects (5.4%) were diagnosed with COPD, 817 (52.2%) were non-
30
31 COPD smokers, and 664 (42.4%) were non-COPD never smokers. Using the LLN
32
33 definition, 34 subjects (2.2%) were diagnosed with COPD, 867 (55.4%) were non-COPD
34
35 smokers, and 665 (42.5%) were non-COPD never smokers.

36
37
38
39 Relationships of the PROs between the three groups of subjects with COPD, non-
40
41 COPD smokers and non-COPD never smokers are shown in Table 2 and Figures 1
42
43 (COPD based on the fixed ratio) and 2 (COPD based on the LLN). The FEV₁
44
45 (%predicted), D-12, CAT and E-RS Total were significantly separated between the three
46
47 groups (p<0.05). There were significant differences between the three groups for FEV₁
48
49 (%predicted), D-12, CAT and E-RS Total (p<0.05). FEV₁ was significantly different
50
51 between any two of the three groups (p<0.001) (Figures 1 and 2). With regard to the
52
53
54

1
2
3 score distribution (Table 2), floor effect in subjects with COPD was most prominent for
4
5 the D-12 (81.2% by the fixed definition and 73.5% by the LLN), and their median scores
6
7 were 0.0 (Table 2). It was the least for the CAT (15.3% by the fixed definition and 14.7%
8
9 by the LLN).
10

11
12 In investigating how many were symptomatic among 817 (by the fixed definition)
13
14 and 867 (by the LLN definition) non-COPD smokers, using the above reference values,
15
16 24 (2.9%) and 24 (2.8%) were >1 on the D-12, 79 (9.7%) and 80 (9.2%) were >10 on the
17
18 CAT, and 74 (9.1%) and 76 (8.8%) were >4 on the E-RS.
19

20
21 Regarding the group comparisons, significant differences were found between non-
22
23 COPD never smokers and non-COPD smokers on all of the measures; however,
24
25 significance was relatively weaker for the D-12 score ($p=0.025$ (Figure 1) and 0.029
26
27 (Figure 2)) as compared to the CAT and E-RS Total ($p<0.001$). On the CAT and E-RS
28
29 Total, significant differences were also found between non-COPD never smokers and
30
31 subjects with COPD ($p<0.05$); however, on the D-12, a significant difference was found
32
33 only by the LLN definition ($p=0.036$, Figure 1), but not by the fixed ratio definition
34
35 ($p=0.24$, Figure 1). Neither the D-12, CAT nor E-RS Total were significantly different
36
37 between COPD and non-COPD smokers.
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

1
2 based on spirometry,^{35 36} and that symptoms might be more sensitive than spirometry in
3
4 detecting smoking-related respiratory impairments. Actually, symptom-based
5
6 questionnaires to screen for COPD that do not include spirometry have been developed.³⁷
7
8
9 38

10
11 Conversely, the present study adds that PROs in non-COPD smokers were not
12
13 significantly different from those in subjects with COPD. Actually, about 9% of smokers
14
15 with preserved pulmonary function were judged to be symptomatic according to the
16
17 reference values of CAT>10 or E-RS>4. Their symptoms may tend to exacerbate in the
18
19 future, advance to COPD, or be treated as if they were COPD. How to manage this group
20
21 of symptomatic smokers without airflow limitation is a key issue to be solved through
22
23 careful long-term follow-ups.
24
25
26
27

28
29 The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2011 consensus
30
31 report proposed a revised “combined COPD assessment” classification in which
32
33 symptoms should be assessed either as a dyspnoea measure using the modified Medical
34
35 Research Council (mMRC) dyspnoea scale, or as a health status measure using the
36
37 CAT.³⁹ We have contributed to the establishment of this concept by demonstrating the
38
39 significant predictive properties of dyspnoea and health status independently of airflow
40
41 limitation.^{40 41} There has hitherto been much debate over how to assess symptoms in this
42
43 new classification. Although dyspnoea was not measured by the mMRC dyspnoea scale
44
45 but by D-12, interrelationships between the D-12, CAT and E-RS were weak to
46
47 moderate. Therefore, it may be difficult to use dyspnoea, health status and respiratory
48
49 symptoms in a mutually complementary form. The GOLD recommends a comprehensive
50
51 assessment of symptoms rather than just a measure of dyspnoea. The present study
52
53
54
55

1
2 supports this by showing that the D-12 had the most marked floor effects even in subjects
3 with COPD, and that the CAT and E-RS seemed to be more sensitive in discriminating
4 subjects based on smoking and COPD than the D-12.
5
6
7
8

9 We reported in 2013 that the 95th percentile of the scores in 512 healthy, non-
10 smoking subjects were used as the upper limit of normal in exactly the same way as in
11 the present study.¹⁹ For the CAT, it was 13.6. In 2014 Pinto et al. published some of the
12 results of the Canadian Cohort Obstructive Lung Disease (CanCOLD) study and reported
13 that the normative value for the CAT score was determined to be 16 from a population-
14 based study where they used post-bronchodilator spirometric values.⁴² Compared with
15 the above two reports, a score of 10 was the 95th percentile of the scores in healthy
16 industrial workers from Japan, and it is the lowest in the present study. The GOLD
17 currently states that the boundary between GOLD A and B and between GOLD C and D
18 is a CAT score of 10,^{39 43} which is consistent with the important result of the present
19 study although there might be some margin of error depending on the methodologies and
20 subjects of the studies.
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36

37 This study has several limitations. Although we intended to determine the border of
38 the normal level of the D-12, CAT and E-RS Total scores, the study subjects were not
39 randomly sampled and there could be a risk of sample bias. The D-12, CAT and E-RS are
40 sufficiently validated for measuring PROs in subjects with COPD, but most participants
41 were not patients with COPD but rather healthy workers. As such, there is a possibility
42 that they are not appropriate tools for the study population. However, since the successful
43 application of the CAT in a working population or a random sampling frame from the
44 populations has also been reported,^{19 42} there may be a reason to be hopeful for success
45
46
47
48
49
50
51
52
53
54
55

1
2 with the D-12 and E-RS. Although post-bronchodilator spirometric values are
3
4 recommended to be used to make a diagnosis of COPD,^{39 43} the diagnosis was made only
5
6 from pre-bronchodilator spirometric information in the present study. Furthermore, the
7
8 present study was conducted in Japanese so that each of the instruments would have been
9
10 translated from the original language of its development. Although the Japanese version
11
12 has been validated in each case, it may be a limit to the generalizability of the research
13
14 across the globe.
15
16
17

18
19 Three main conclusions may be drawn from our findings. First, associations among
20
21 dyspnoea measured by the D-12, health status by the CAT, and respiratory symptoms by
22
23 the E-RS, were statistically significant but weak, indicating that they cannot be used
24
25 interchangeably. Second, using the data obtained from 646 healthy non-smoking subjects,
26
27 the reference values of the D-12, CAT and E-RS were ≤ 1 , ≤ 10 and ≤ 4 , respectively.
28
29 Third, from a standpoint of the relationship with smoking status and airflow limitation,
30
31 health status and respiratory symptoms may be more closely related to non-COPD
32
33 smokers and subjects with COPD than dyspnoea as compared to non-COPD never
34
35 smokers; however, none of these PRO measures can differentiate between non-COPD
36
37 smokers and subjects with COPD. How to manage non-COPD symptomatic smokers
38
39 should be investigated in the future.
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Other information

Acknowledgements

The authors wish to thank Nancy Kline Leidy for permission to use the Japanese version of the E-RS.

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.

Funding

This study was partly supported by the Research Funding for Longevity Sciences (30-24) from the National Center for Geriatrics and Gerontology (NCGG), Japan.

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.

References

1. Kyte D, Duffy H, Fletcher B, et al. Systematic evaluation of the patient-reported outcome (PRO) content of clinical trial protocols. *PLoS One* 2014;9(10):e110229. doi: 10.1371/journal.pone.0110229
2. Jones PW. Health status measurement in chronic obstructive pulmonary disease. *Thorax* 2001;56(11):880-7.
3. DeMuro C, Clark M, Doward L, et al. Assessment of PRO label claims granted by the FDA as compared to the EMA (2006-2010). *Value Health* 2013;16(8):1150-5. doi: 10.1016/j.jval.2013.08.2293
4. Gnanasakthy A, Mordin M, Evans E, et al. A Review of Patient-Reported Outcome Labeling in the United States (2011-2015). *Value Health* 2017;20(3):420-29. doi: 10.1016/j.jval.2016.10.006
5. Jones PW, Quirk FH, Baveystock CM, et al. A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. *Am Rev Respir Dis* 1992;145(6):1321-7. [published Online First: 1992/06/01]
6. Andrich D. Rasch models for measurement. Newbury Park, CA: Sage Publications 1998.
7. Rasch G. Probabilistic models for some intelligence and attainment tests. Chicago, IL: University of Chicago Press 1960.
8. Gupta N, Pinto LM, Morogan A, et al. The COPD assessment test: a systematic review. *Eur Respir J* 2014;44(4):873-84. doi: 10.1183/09031936.00025214
9. Jones PW, Brusselle G, Dal Negro RW, et al. Properties of the COPD Assessment Test (CAT) in a cross-sectional European study. *Eur Respir J* 2011 doi: 09031936.00177210 [pii] 10.1183/09031936.00177210 [published Online First: 2011/05/14]

- 1
2
3 10. Jones PW, Harding G, Berry P, et al. Development and first validation of the COPD
4
5 Assessment Test. *Eur Respir J* 2009;34(3):648-54. doi: 34/3/648 [pii]
6
7 10.1183/09031936.00102509 [published Online First: 2009/09/02]
8
9
10 11. Yorke J, Swigris J, Russell AM, et al. Dyspnea-12 is a valid and reliable measure of
11
12 breathlessness in patients with interstitial lung disease. *Chest* 2011;139(1):159-64. doi:
13
14 chest.10-0693 [pii]
15
16 10.1378/chest.10-0693 [published Online First: 2010/07/03]
17
18
19 12. Swigris JJ, Yorke J, Sprunger DB, et al. Assessing dyspnea and its impact on patients with
20
21 connective tissue disease-related interstitial lung disease. *Respir Med* 2010;104(9):1350-
22
23 5. doi: S0954-6111(10)00145-9 [pii]
24
25 10.1016/j.rmed.2010.03.027 [published Online First: 2010/05/18]
26
27
28 13. Yorke J, Moosavi SH, Shuldham C, et al. Quantification of dyspnoea using descriptors:
29
30 development and initial testing of the Dyspnoea-12. *Thorax* 2010;65(1):21-6. doi:
31
32 10.1136/thx.2009.118521
33
34
35 14. Leidy NK, Wilcox TK, Jones PW, et al. Standardizing Measurement of Chronic Obstructive
36
37 Pulmonary Disease Exacerbations: Reliability and Validity of a Patient-reported Diary.
38
39 *Am J Respir Crit Care Med* 2011;183(3):323-29. doi: 201005-0762OC [pii]
40
41 10.1164/rccm.201005-0762OC [published Online First: 2010/09/04]
42
43
44 15. Jones PW, Chen WH, Wilcox TK, et al. Characterizing and Quantifying the Symptomatic
45
46 Features of COPD Exacerbations. *Chest* 2011;139(6):1388-94. doi: chest.10-1240 [pii]
47
48 10.1378/chest.10-1240 [published Online First: 2010/11/13]
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 16. Leidy NK, Wilcox TK, Jones PW, et al. Development of the EXAcerbations of Chronic
4
5 Obstructive Pulmonary Disease Tool (EXACT): a patient-reported outcome (PRO)
6
7 measure. *Value Health* 2010;13(8):965-75. doi: 10.1111/j.1524-4733.2010.00772.x
8
9 VHE772 [pii] [published Online First: 2010/07/28]
- 10
11
12 17. Leidy NK, Murray LT, Monz BU, et al. Measuring respiratory symptoms of COPD:
13
14 performance of the EXACT- Respiratory Symptoms Tool (E-RS) in three clinical trials.
15
16 *Respir Res* 2014;15:124. doi: 10.1186/s12931-014-0124-z
17
18
- 19 18. Leidy NK, Sexton CC, Jones PW, et al. Measuring respiratory symptoms in clinical trials of
20
21 COPD: reliability and validity of a daily diary. *Thorax* 2014;69(5):443-9. doi:
22
23 10.1136/thoraxjnl-2013-204428
24
25
- 26 19. Nishimura K, Mitsuma S, Kobayashi A, et al. COPD and disease-specific health status in a
27
28 working population. *Respir Res* 2013;14:61. doi: 10.1186/1465-9921-14-61
29
30
- 31 20. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J*
32
33 2005;26(2):319-38. doi: 26/2/319 [pii]
34
35 10.1183/09031936.05.00034805 [published Online First: 2005/08/02]
36
37
- 38 21. Koyama H, Nishimura K, Ikeda A, et al. A comparison of different methods of spirometric
39
40 measurement selection. *Respir Med* 1998;92(3):498-504. doi: S0954-6111(98)90298-0
41
42 [pii] [published Online First: 1998/08/06]
43
44
- 45 22. Garcia-Rio F, Soriano JB, Miravittles M, et al. Overdiagnosing subjects with COPD using
46
47 the 0.7 fixed ratio: correlation with a poor health-related quality of life. *Chest*
48
49 2011;139(5):1072-80. doi: 10.1378/chest.10-1721 [published Online First: 2010/12/25]
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 23. Swanney MP, Ruppel G, Enright PL, et al. Using the lower limit of normal for the
4
5 FEV1/FVC ratio reduces the misclassification of airway obstruction. *Thorax*
6
7 2008;63(12):1046-51. doi: thx.2008.098483 [pii]
8
9 10.1136/thx.2008.098483 [published Online First: 2008/09/13]
10
11
12 24. van Dijk W, Tan W, Li P, et al. Clinical relevance of fixed ratio vs lower limit of normal of
13
14 FEV1/FVC in COPD: patient-reported outcomes from the CanCOLD cohort. *Ann Fam*
15
16 *Med* 2015;13(1):41-8. doi: 10.1370/afm.1714 [published Online First: 2015/01/15]
17
18
19 25. Vollmer WM, Gislason T, Burney P, et al. Comparison of spirometry criteria for the
20
21 diagnosis of COPD: results from the BOLD study. *Eur Respir J* 2009;34(3):588-97. doi:
22
23 09031936.00164608 [pii]
24
25 10.1183/09031936.00164608 [published Online First: 2009/05/23]
26
27
28 26. Vestbo J, Anderson W, Coxson HO, et al. Evaluation of COPD Longitudinally to Identify
29
30 Predictive Surrogate End-points (ECLIPSE). *Eur Respir J* 2008;31(4):869-73. doi:
31
32 09031936.00111707 [pii]
33
34 10.1183/09031936.00111707 [published Online First: 2008/01/25]
35
36
37 27. Agusti A, Calverley PM, Celli B, et al. Characterisation of COPD heterogeneity in the
38
39 ECLIPSE cohort. *Respir Res* 2010;11:122. doi: 1465-9921-11-122 [pii]
40
41 10.1186/1465-9921-11-122 [published Online First: 2010/09/14]
42
43
44 28. Society CPFCotJR. The predicted values of pulmonary function testing and arterial blood gas
45
46 in Japanese [in Japanese]. *Jpn J Thorac Dis* 2001;39(5):appendix.
47
48
49 29. Osaka D, Shibata Y, Abe S, et al. Relationship between habit of cigarette smoking and
50
51 airflow limitation in healthy Japanese individuals: the Takahata study. *Intern Med*
52
53
54
55
56
57
58
59
60

- 2010;49(15):1489-99. doi: JST.JSTAGE/internalmedicine/49.3364 [pii] [published Online First: 2010/08/06]
30. Tsuda T, Suematsu R, Kamohara K, et al. Development of the Japanese version of the COPD Assessment Test. *Respir Investig* 2012;50(2):34-9. doi: 10.1016/j.resinv.2012.05.003 [published Online First: 2012/07/04]
31. Kusunose M, Oga T, Nakamura S, et al. Frailty and patient-reported outcomes in subjects with chronic obstructive pulmonary disease: are they independent entities? *BMJ Open Respir Res* 2017;4(1):e000196. doi: 10.1136/bmjresp-2017-000196 [published Online First: 2017/09/09]
32. Efron B, Tibshirani RJ. An Introduction to the Bootstrap (Chapman & Hall/CRC Monographs on Statistics & Applied Probability). 1994
33. Elbehairy AF, Guenette JA, Faisal A, et al. Mechanisms of exertional dyspnoea in symptomatic smokers without COPD. *Eur Respir J* 2016;48(3):694-705. doi: 10.1183/13993003.00077-2016 [published Online First: 2016/08/06]
34. Furlanetto KC, Mantoani LC, Bisca G, et al. Reduction of physical activity in daily life and its determinants in smokers without airflow obstruction. *Respirology* 2014;19(3):369-75. doi: 10.1111/resp.12236 [published Online First: 2014/02/04]
35. Regan EA, Lynch DA, Curran-Everett D, et al. Clinical and Radiologic Disease in Smokers With Normal Spirometry. *JAMA Intern Med* 2015;175(9):1539-49. doi: 10.1001/jamainternmed.2015.2735 [published Online First: 2015/06/23]
36. Woodruff PG, Barr RG, Bleecker E, et al. Clinical Significance of Symptoms in Smokers with Preserved Pulmonary Function. *N Engl J Med* 2016;374(19):1811-21. doi: 10.1056/NEJMoa1505971 [published Online First: 2016/05/12]

- 1
2
3 37. Martinez FJ, Raczek AE, Seifer FD, et al. Development and initial validation of a self-scored
4
5 COPD Population Screener Questionnaire (COPD-PS). *COPD* 2008;5(2):85-95. doi:
6
7 10.1080/15412550801940721 [published Online First: 2008/04/17]
8
9
10 38. Price DB, Tinkelman DG, Halbert RJ, et al. Symptom-based questionnaire for identifying
11
12 COPD in smokers. *Respiration* 2006;73(3):285-95. doi: 10.1159/000090142 [published
13
14 Online First: 2005/12/07]
15
16
17 39. Vestbo J, Hurd SS, Agusti AG, et al. Global Strategy for the Diagnosis, Management, and
18
19 Prevention of Chronic Obstructive Pulmonary Disease: GOLD Executive Summary.
20
21 *American journal of respiratory and critical care medicine* 2013;187(4):347-65. doi:
22
23 10.1164/rccm.201204-0596PP
24
25
26 rccm.201204-0596PP [pii] [published Online First: 2012/08/11]
27
28
29 40. Nishimura K, Izumi T, Tsukino M, et al. Dyspnea is a better predictor of 5-year survival than
30
31 airway obstruction in patients with COPD. *Chest* 2002;121(5):1434-40. [published
32
33 Online First: 2002/05/15]
34
35
36 41. Oga T, Nishimura K, Tsukino M, et al. Analysis of the factors related to mortality in chronic
37
38 obstructive pulmonary disease: role of exercise capacity and health status. *Am J Respir*
39
40 *Crit Care Med* 2003;167(4):544-9. doi: 10.1164/rccm.200206-583OC [published Online
41
42 First: 2002/11/26]
43
44
45 42. Pinto LM, Gupta N, Tan W, et al. Derivation of normative data for the COPD assessment test
46
47 (CAT). *Respir Res* 2014;15:68. doi: 10.1186/1465-9921-15-68
48
49
50 43. Vogelmeier CF, Criner GJ, Martinez FJ, et al. Global Strategy for the Diagnosis,
51
52 Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report. GOLD
53
54
55
56
57
58
59
60

1
2
3 Executive Summary. *Am J Respir Crit Care Med* 2017;195(5):557-82. doi:
4

5 10.1164/rccm.201701-0218PP
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

Figure Legends

Figure 1 Box plots representing the distributions of FEV₁ (%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 FEV₁/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 FEV₁ (%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 FEV₁/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

[¶] FEV₁ of >85% predicted and FEV₁/FVC of >0.7, # a smoking history of <1 pack-year

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV₁, 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%

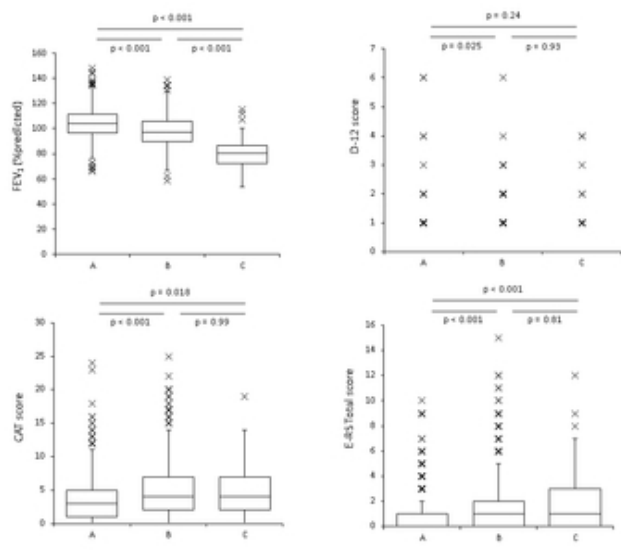
¶ FEV₁ of >85% predicted and FEV₁/FVC of >0.7, # a smoking history of <1 pack-year. Numbers in parentheses indicate the theoretical score range, and higher scores indicate worse status.

Abbreviations: CAT, COPD assessment test; COPD, chronic obstructive pulmonary disease; D-12, Dyspnoea-12; E-RS, Evaluating Respiratory Symptoms in COPD; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; LLN, lower limit of normal.

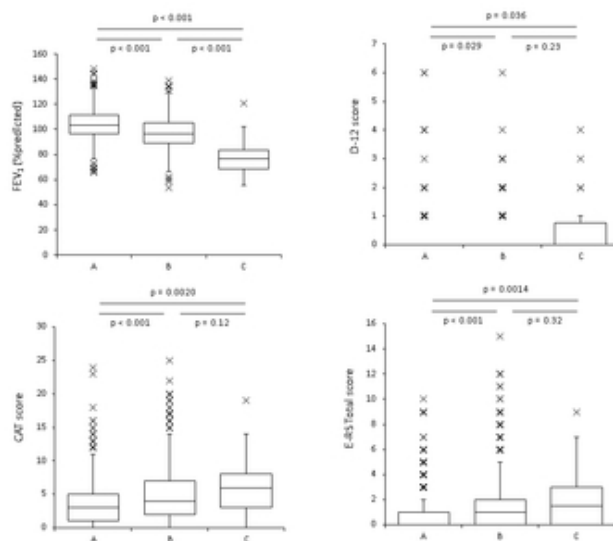
Table 3. Concordant and discordant results between tools using the cut-off values.

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%)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



45x25mm (300 x 300 DPI)



45x25mm (300 x 300 DPI)

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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Page 8	
		<i>Case-control study</i> —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		
		<i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants		
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed		
		<i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed		
		<i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed		
		<i>Cross-sectional study</i> —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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)		
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time		
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure		
		<i>Cross-sectional study</i> —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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

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.