

# Impact of gastro-oesophageal reflux disease symptoms on COPD exacerbation

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## ABSTRACT

**Background:** The association between gastro-oesophageal reflux disease (GORD) and chronic obstructive pulmonary disease (COPD) exacerbation has so far remained unclear.

**Objective:** To prospectively establish the clinical significance of GORD symptoms on exacerbation.

**Methods:** 82 patients with COPD and 40 age matched controls were enrolled in this study. Symptoms were evaluated by a questionnaire using the Frequency Scale for the Symptoms of GORD (FSSG). Patients with COPD were prospectively surveyed for 6 months, and episodes of exacerbation were identified using a diary based on modified Anthonisen's criteria. Exhaled breath condensate (EBC) pH was measured in both groups, and induced sputum was evaluated in patients with COPD.

**Results:** Positive GORD symptoms were reported in 22 (26.8%) patients with COPD and in five (12.5%) controls ( $p = 0.10$ ). The frequency of exacerbations was significantly associated with the FSSG score ( $p = 0.03$ ,  $r = 0.24$ , 95% CI 0.02 to 0.43). Multiple regression analysis revealed that GORD symptoms were significantly associated with the occurrence of exacerbations ( $p < 0.01$ ; relative risk 6.55, 95% CI 1.86 to 23.11). EBC pH was inversely correlated with FSSG score in both groups ( $p = 0.01$ ,  $r = -0.37$ , 95% CI  $-0.55$  to  $-0.14$  in patients with COPD, and  $p < 0.01$ ,  $r = -0.45$ , 95% CI  $-0.67$  to  $-0.16$  in control subjects).

**Conclusions:** GORD symptoms were identified as an important factor associated with COPD exacerbation.

Exacerbations of chronic obstructive pulmonary disease (COPD) are an important determinant of patient quality of life and can aggravate disease progression, which is associated with increased morbidity and use of healthcare resources.<sup>1</sup> Several clinical backgrounds are reportedly associated with exacerbation frequency, including age, low forced expiratory volume in 1 s (FEV<sub>1</sub>) and low body mass index (BMI).<sup>2–3</sup>

Gastro-oesophageal reflux disease (GORD) is a relatively common condition, affecting 10–29% of the Western population and 5–14% of Japanese adults, and is associated with a variety of respiratory disorders.<sup>4–7</sup> GOR has been shown to worsen asthma control through oesophagobronchial reflex, and to heighten bronchial reactivity and microaspiration.<sup>8–10</sup> GOR has also been reported to be accompanied by neutrophilic airway inflammation.<sup>11</sup> We therefore hypothesised that GOR could act as a confounding factor of exacerbations through similar mechanisms in asthma and/or by increasing airway inflammation.

To our knowledge, only one previous study has investigated the relationship between GORD symptoms and exacerbations. This research relied on a retrospective analysis of the number of exacerbations based on patient recall during the previous year, but the mechanism by which GORD symptoms affect COPD exacerbation remains to be elucidated.<sup>12</sup>

In the current study, we prospectively examined the association between exacerbations and GORD symptoms using the Frequency Scale for the Symptoms of GORD (FSSG) for qualitative and quantitative analysis of symptoms. We also investigated the usefulness of exhaled breath condensate (EBC) pH for reflecting airway inflammation and acid reflux, by analysing the association with GORD symptoms and inflammatory indices of induced sputum.<sup>13–14</sup>

## METHODS

### Subjects

Patients with moderate to severe COPD, as defined by the Global Initiative for Chronic Obstructive Lung Disease Guidelines (GOLD) 2003, were consecutively enrolled from the outpatient clinic of Kyoto University Hospital, Japan.<sup>1</sup> Exclusion criteria were as follows: smoking history  $< 20$  packs per year; comorbidities of respiratory disorders other than COPD; history of malignant disease within 5 years; active gastrointestinal diseases other than GORD; initiation and withdrawal of medications related to COPD and GORD during the follow-up period; daily use of systemic corticosteroids; and current use of long term oxygen therapy. In total, 40 controls from the Terada Clinic in Himeji, Japan, and the outpatient clinic at Kyoto University Hospital ( $n = 38$  and 2, respectively) were enrolled (age  $> 60$  years). Exclusion criteria were as follows: comorbidities of respiratory disorders, including COPD, confirmed by medical history, physical examination, chest radiography and spirometry; history of malignant diseases within 5 years; active gastrointestinal diseases other than GORD; and active infectious diseases. The research protocol was approved by the ethics committee of Kyoto University, and written informed consent was obtained from all subjects.

### Definition of exacerbation and stable condition

Exacerbations were defined according to the modified Anthonisen's criteria as the occurrence of two or more of three major symptoms (ie, increase in dyspnoea, sputum purulence and

increased sputum volume), or any one major symptom with any one minor symptom (ie, increase in nasal discharge, wheezing, sore throat, cough or fever) for at least 2 consecutive days.<sup>15–17</sup> Patients were issued with diaries in which each symptom was quantified on a graded scale from 1 to 5 (where 1 = much better than usual, 2 = better than usual, 3 = the same as usual, 4 = worse than usual and 5 = much worse than usual) based on previous recommendations.<sup>17</sup>

Exacerbations were identified using diaries at each visit to our clinic, and were confirmed by at least two respiratory physicians who were unaware of the EBC pH and FSSG score. The end of an exacerbation was defined as the time point when the rolling 3 day mean symptom score returned to the pre-exacerbation level.<sup>18</sup> Stable conditions were defined as exacerbation free intervals that lasted for more than 4 weeks, as confirmed in a diary, and episodes of worsening symptoms within 2 weeks that met the criteria of exacerbation were considered as one episode.<sup>19</sup>

### Study protocol

Patients with COPD and control subjects were compared using a cross sectional survey. The association between GORD symptoms and exacerbations was investigated using a cohort survey. GORD symptom evaluation, EBC and sputum sampling, and lung function tests were performed on the same day under stable conditions. Subsequently, the numbers of exacerbations recorded in the diaries were calculated over a period of more than 6 months between 1 June 2006 and 31 December 2006.

### GORD evaluation

GORD symptoms were evaluated with a self-reported FSSG questionnaire consisting of 12 items. The frequency of each item was quantified on a scale ranging from 0 to 4 points as follows: 0 = none (not in the past year); 1 = rarely (a few times in the past year); 2 = sometimes (a few times in the past month); 3 = often (a few times in the past week); 4 = always (everyday). The cut-off score for GORD symptoms was set at 8 points.<sup>13</sup> The questionnaire included items related to two symptom subtypes: those associated with GOR (eg, “Do you get heartburn?”) and those associated with gastric dysmotility

(eg, “Does your stomach get bloated?” and “Does your stomach ever feel heavy?”).<sup>14</sup> We also validated the FSSG results by evaluating GORD symptoms with the Questionnaire for the Diagnosis of Reflux Disease (QUEST) using a cut-off score for GORD symptoms of 4 points.<sup>19</sup>

### Lung function tests

FEV<sub>1</sub>, forced vital capacity, vital capacity, diffusing capacity of the lung for carbon monoxide (DLCO), residual volume (RV), total lung capacity (TLC) and arterial blood gas were measured. The predicted values for FEV<sub>1</sub> were calculated according to the method of the Japan Society of Chest Diseases.<sup>20</sup>

### EBC sample collection and analysis of pH

EBC samples were collected in a liquid state during tidal breathing for 8 min, using a disposable portable collector (Rtube; Respiratory Research, Charlottesville, Virginia, USA) under supervised conditions.<sup>21</sup> Each sample was bubbled through argon gas (350 ml/min) for 8 min. The EBC pH was measured with a 9669-10D glass micro-pH electrode attached to an F 52 pH meter (Horiba Corporation, Kyoto, Japan) immediately after argon flushing. The F 52 pH meter was calibrated at pH 4, pH 7 and pH 9 against standards, prior to each series of assays.

### Sputum induction and processing

Sputum induction and processing were performed on subjects with an FEV<sub>1</sub> >1 l according to the European Respiratory Society recommendations, with slight modifications, following evaluation of GORD symptoms and sampling of EBC.<sup>22–24</sup> Briefly, subjects were assessed using spirometric tests (Chest MI Corp, Tokyo, Japan) 10 min after premedication with 200 µg of inhaled salbutamol, and then inhaled 3% saline for 20 min using an ultrasonic nebuliser (MU-32; Azwell Inc, Osaka, Japan). Each collected sample was immediately separated from contaminating saliva by visual examination, then mixed with 0.1% dithiothreitol (Suptasol; Oxoid, Hampshire, UK) and diluted with Dulbecco's phosphate buffered saline according to the recommended methodology.<sup>24</sup> After centrifugation, cell differentiation was determined by counting at least 400 non-squamous cells stained using the Diffquik method. The supernatants were stored at –80°C. Levels of interleukin 8 and tumour necrosis factor α in the supernatants were measured using quantitative sandwich immunoassay techniques (R&D Systems, Minneapolis, Minnesota, USA).

### Statistical analysis

Statistical analyses were performed using JMP 6.0 (SAS Campus Drive, Cary, North Carolina, USA). Data are presented as mean (SD) or as the median (interquartile range). Statistical analyses were performed using parametric (Student's *t* test and analysis

**Table 1** Patient characteristics

Characteristic	COPD patients (n = 2)	Healthy controls (n = 40)	p Value
Age (y)	73.0 (8.0)	70.9 (9.3)	0.32
Sex (male:female)	77:5	19:21	<0.01
Smoking status (current:former:never)	10:72:0	1:17:22	<0.01
No of cigarette packs*year	65.3 (37.8)	11.2 (15.9)	<0.01
BMI (kg/m <sup>2</sup> )	21.5 (3.0)	24.1 (3.5)	<0.01
FEV <sub>1</sub> (l)	1.5 (0.6)	2.2 (0.7)	<0.01
%FEV <sub>1</sub> (% pred)	56.9 (20.4)	101.3 (15.9)	<0.01
RV/TLC (%)	43.6 (7.7)	ND	
DLCO/VA (ml/min/mmHg/l)	2.7 (1.0)	ND	
PaO <sub>2</sub> (kPa)	8.3 (0.9)	ND	
PacO <sub>2</sub> (kPa)	4.6 (0.5)	ND	

Gender and smoking status were evaluated by the  $\chi^2$  test. The number of cigarette packs\*year was evaluated by the Mann–Whitney U test. All other indices were evaluated by the unpaired *t* test. BMI, body mass index; COPD, chronic obstructive pulmonary disease; DLCO, diffusing capacity of the lung for carbon monoxide; FEV<sub>1</sub>, forced expiratory volume in 1 s; ND, not done; PacO<sub>2</sub>, partial pressure of arterial carbon dioxide; PaO<sub>2</sub>, partial pressure of oxygen in arterial blood; RV, residual volume; TLC, total lung capacity; VA, alveolar volume.

**Table 2** GORD symptoms in patients with COPD and in healthy subjects

Subjects	Evaluation by FSSG		Prevalence (%)	p Value
	Positive	Negative		
Healthy	5	35	12.5	0.10
COPD	22	60	26.8	

Data were evaluated by the  $\chi^2$  test. The relative risk for GORD symptoms in patients with COPD compared with controls was 2.15 (95% CI 0.88 to 5.25; *p* = 0.10). COPD, chronic obstructive pulmonary disease; FSSG, Frequency Scale for the Symptoms of GORD; GORD, gastro-oesophageal reflux disease.

**Table 3** Associations between exacerbations and GORD symptoms in patients with COPD

GORD symptoms	COPD exacerbation		Exacerbation frequency over 6 months
	Did not occur	Did occur	
Negative	36	24	0.70 (1.20)
Positive	5	17	1.73 (1.58)
p Value	<0.01		<0.01

Data were evaluated by the  $\chi^2$  test and the unpaired t test. The relative risk for the occurrence of exacerbation in patients with GORD symptoms compared with patients without such symptoms was 1.93 (95% CI 1.32 to 2.84;  $p < 0.01$ ).

COPD, chronic obstructive pulmonary disease; GORD, gastro-oesophageal reflux disease.

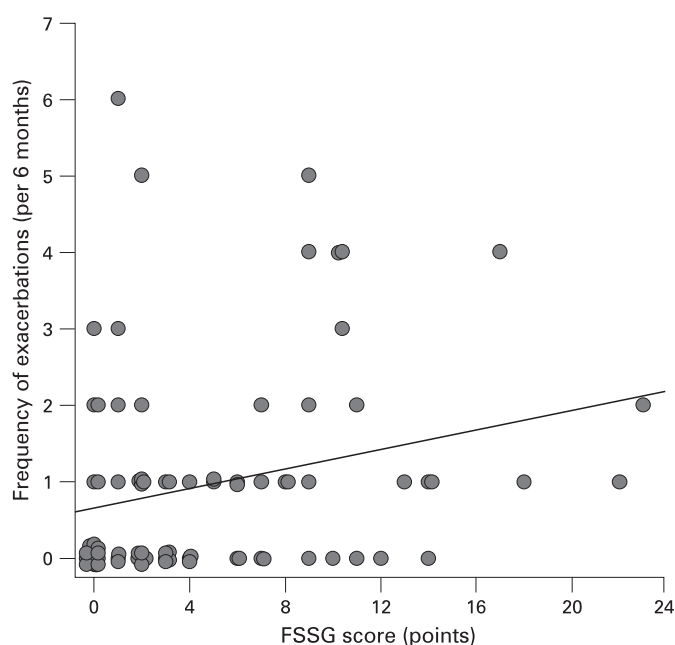
of variance (ANOVA) or non-parametric (Mann–Whitney two sample test and Spearman's rank correlation test) methods as appropriate. The relationship between the two groups was evaluated with a  $\chi^2$  test. Logistic regression was used to test whether individual factors were associated with exacerbations. A p value  $< 0.05$  was considered statistically significant.

## RESULTS

The clinical characteristics of the subjects are shown in table 1. In total, 82 patients with COPD and 40 controls met the entry criteria. There was no significant difference in age between the two groups.

Positive GORD symptoms were reported in 22 (26.8%) patients with COPD and in five (12.5%) controls (table 2). The total FSSG score was similar in both groups (4.9 (5.3) in patients with COPD vs 3.0 (3.2) in controls,  $p = 0.10$ ).

The association between clinical indices and GORD symptoms in patients with COPD is shown in table 1S (available online). There was no significant difference between subjects with and without GORD symptoms in terms of age, gender, smoking status, BMI, lung function or medications.



**Figure 1** Correlation between exacerbation frequency and the Frequency Scale for the Symptoms of GORD (FSSG) score. The FSSG score ( $p = 0.03$ ,  $r = 0.24$ , 95% CI 0.02 to 0.43) was correlated with the frequency of exacerbations. GORD, gastro-oesophageal reflux disease.

The incidence of exacerbation was significantly higher in patients with GORD symptoms than in patients without such symptoms (relative risk (RR) 1.93, 95% confidence interval (CI) 1.32 to 2.84;  $p < 0.01$ ) (table 3). The average number of exacerbations over 6 months was 0.98 (1.38) in all patients, and those with GORD symptoms experienced significantly more episodes than those without (1.73 (1.58) vs 0.70 (1.20);  $p < 0.01$ ).

Figure 1 shows the relationship between the FSSG score and exacerbation frequency. The FSSG score was significantly correlated with the number of exacerbations ( $r = 0.24$ , 95% CI 0.02 to 0.43;  $p = 0.03$ ).

The known confounding factors for exacerbations are shown in table 2S (available online). Demographic and other clinical characteristics were similar between the two groups.

GORD symptoms were also identified by multiple regression analysis as a significant factor associated with the occurrence of exacerbation (RR 6.55 (95% CI 1.86 to 23.11);  $p < 0.01$ ) (see table 3S online).

To exclude the effects of both daily treatment with proton pump inhibitors or  $H_2$  receptor antagonists and seasonal variability of exacerbations (eg, the frequency of exacerbations might increase in winter in association with the occurrence of influenza epidemics), 52 patients who were not receiving antacid therapy among the sample population were surveyed for an additional 6 months (12 months in total). In those patients, GORD symptoms was also significantly associated with annual frequency; the frequency was 2.6 (2.0) in subjects with GORD symptoms and 1.5 (1.7) in subjects without such symptoms ( $p = 0.048$ ). GORD symptoms were significantly related to frequent (three or more episodes per year) exacerbations (RR 2.18, 95% CI 1.10 to 5.70;  $p = 0.046$  for frequent exacerbations in patients with compared with those without GORD symptoms).

The EBC pH was similar between patients with COPD and controls. However, the EBC pH was significantly lower in subjects with GORD symptoms than in subjects without GORD symptoms (6.47 (1.22) vs 7.17 (1.05),  $p = 0.02$  in patients with COPD, and 6.34 (1.22) vs 7.22 (0.53),  $p = 0.03$  in controls) (see table 4S online). The EBC pH was inversely correlated with the FSSG score in both groups ( $r = -0.37$ , 95% CI  $-0.55$  to  $0.34$ ,  $p = 0.01$  in patients with COPD, and  $r = -0.45$ , 95% CI  $-0.67$  to  $0.16$ ,  $p < 0.01$  in controls). However, no significant correlation was found between the EBC pH and exacerbation frequency ( $r = 0.13$ , 95% CI  $-0.11$  to  $0.35$ ;  $p = 0.29$ ).

To examine whether the EBC pH reflected tracheobronchial inflammation, sputum induction was performed in 42 patients, 35 of whom met the inclusion criterion for evaluating sputum as a lower respiratory tract sample (squamous cell contamination  $< 20\%$ ). There was no significant correlation between the EBC pH and sputum inflammatory indices, such as differential cell counts and interleukin 8 and tumour necrosis factor  $\alpha$  concentrations (see table 5S online).

According to QUEST, the prevalence of positive GORD symptoms was 24.4% in patients with COPD and 10.0% in controls, the RR of the exacerbation in patients with GORD symptoms compared with patients without such symptoms was 1.61 (95% CI 1.07 to 2.41,  $p = 0.07$ ), the EBC pH values of subjects with and without GORD symptoms were 6.56 (1.19) and 7.12 (1.09), respectively ( $p = 0.07$ ) and the GORD symptoms were marginally associated with exacerbation occurrence (RR 3.21, 95% CI 1.11 to 13.27;  $p = 0.05$ ).



## DISCUSSION

This prospective cohort study demonstrated, for the first time, that COPD exacerbations are associated with GORD symptoms, the frequency of which is inversely correlated with the EBC pH.

A recent retrospective study suggested that GORD symptoms were associated with exacerbations; however, the subjects were asked to report the number of exacerbations that had occurred during the previous year, which was an approach that did not meet the criteria used in previous studies and resulted in recall bias.<sup>12</sup> To resolve this problem, we conducted a prospective questionnaire based study that allowed us to identify exacerbations according to the modified Anthonisen's criteria.<sup>15–17</sup> In order to determine the associations among GORD symptoms, airway inflammation and exacerbation frequency, we also evaluated the EBC pH and induced sputum under stable conditions.

We found the EBC pH to be correlated inversely with the FSSG score in both groups. Recently, Hunt *et al* reported that transient EBC acidification occurred during acid reflux cough, and that the EBC pH profile collected immediately subsequent to a coughing episode was a strong predictor of GOR in the diagnosis of chronic cough.<sup>5</sup> In our current study, we were unable to determine the time lag between the actual acid reflux and the sampling of EBC pH. However, we speculated that asymptomatic acid reflux occurred more frequently in accordance with increased GORD symptoms. This might have resulted in the sampling point of EBC being contiguous to the acid reflux as the GORD symptoms worsened, lowering the EBC pH. In several previous studies, EBC pH has been reported to reflect the lining fluid of the inflamed lower respiratory tract, and considerable variability has been seen among patients with COPD. Kostikas *et al* demonstrated an inverse correlation between EBC pH and the percentage of neutrophils in induced sputum in 20 patients with COPD.<sup>25</sup> However, we found that none of the sputum inflammatory indices correlated with the EBC pH (see table 5S online).<sup>22–24 26</sup> Moreover, the EBC pH was not correlated with the frequency of exacerbations, and was similar between patients with COPD and controls. These findings suggest that the EBC pH might have reflected acid reflux rather than tracheobronchial inflammation under stable conditions in our sample population. Further examination is necessary to determine whether EBC pH is a marker of acid reflux.

From the several different questionnaires developed for the symptom based diagnosis of GORD, we chose the FSSG for the current study for the following reasons.<sup>12 13 19 27 28</sup> Firstly, GORD symptoms can be quantified with the FSSG, but not with QUEST. Secondly, symptoms related not only to acid reflux but also to gastric dysmotility can be evaluated with the FSSG; this is of particular importance, and a descriptive questionnaire that covers symptoms associated with both acid reflux and gastric dysmotility is useful for recognising these conditions.<sup>29 30</sup> We found that both the FSSG and QUEST identified GORD symptoms to a similar level. However, although QUEST showed a similar tendency for associations with exacerbations, it failed to reach statistical significance. This discrepancy between the FSSG and QUEST might be because of differences in the characteristics of the questionnaires: the latter focuses on ulcer-like and reflux-like symptoms and lacks items concerning dysmotility-like symptoms, whereas the former covers all symptom subtypes.<sup>13 19</sup>

The occurrence of GORD symptoms in our sample population was similar to those reported in previous studies. Although

the prevalence of GORD symptoms was reportedly higher in patients with COPD than in controls, this trend did not achieve statistical significance for the following reasons.<sup>4 27 28</sup> Firstly, the sample size was small. Secondly, the confounding factors of the prevalence of GORD, such as gender, smoking status and BMI, were not matched between the patients with COPD and controls.<sup>31 32</sup>

The symptom based diagnosis of GORD could be affected by symptoms related to comorbidities such as COPD. In COPD, overinflation of the lung could cause dysmotility-like dyspepsia, giving a sensation of gastric fullness without GORD. However, we did not find any significant associations between GORD symptoms and physiological indices, such as BMI, %FEV<sub>1</sub> (an index of COPD severity), RV, TLC, RV/TLC (a physiological parameter related to overinflation) and DLCO/VA (reflecting parenchymal destruction and V/Q mismatch). Therefore, we believe that the GORD symptoms were not dependent on COPD severity.

It is difficult to determine whether GORD itself directly affects exacerbation or merely coexists in patients who experience frequent exacerbations. In patients with asthma, coexistence of GORD was shown to be associated with deteriorating symptoms through several mechanisms, including oesophageal-bronchial reflex, heightened bronchial reactivity and microaspiration.<sup>8–10 33</sup> Carpagnano *et al* reported that GOR is characterised by neutrophilic airway inflammation, although it does not aggravate pre-existing airway inflammation in asthma.<sup>11</sup> However, it remains unclear whether GOR itself alters lung function or the clinical course in COPD. Previous reports have shown that patients with COPD lack a broncho-constrictive reflex to distal oesophageal acidification.<sup>34</sup> Ravelli *et al* used gastro-oesophageal <sup>99</sup>Tc scintigraphy with lung scanning to show that microaspiration of gastric contents occurred even if pathological GOR was not detected with 24 h intraoesophageal pH monitoring.<sup>35</sup> Moreover, to determine whether the EBC pH reflected GOR, and whether GOR or gastric dysmotility was more strongly associated with the frequency of exacerbations, we investigated the associations among the frequency of exacerbations, EBC pH and the symptom subtypes of the FSSG associated with GOR and gastric dysmotility. The number of exacerbations was significantly correlated with those associated with gastric dysmotility but not with GOR (see fig 1S online), whereas the EBC pH was inversely correlated with those associated with GOR but not with gastric dysmotility (see fig 2S online). We also demonstrated that the sputum inflammatory indices under stable conditions were similar between patients with GORD symptoms and those without (see table 6S online). Considering these findings, we speculated that GOR might occur frequently even under stable conditions that cause the EBC pH to fall without aggravating airway inflammation, whereas gastric dysmotility might predispose an individual to episodic aspiration of low acidic gastric contents and induce exacerbations. Moreover, impaired gastric motility might disturb the clearance of swallowed contents from the pharynx to the oesophagus, leading to their aspiration into the tracheobronchial tree and thereby causing exacerbations. Further objective examinations are necessary to confirm the associations between GOR, impaired gastric motility and exacerbations.

There was a limitation to our study. We did not confirm GOR objectively using 24 h intraoesophageal pH monitoring. The sensitivity and specificity of questionnaire based diagnosis is not satisfactory compared with 24 h intraoesophageal pH monitoring for the diagnosis of GORD; however, 24 h

intraoesophageal pH probes are of limited relevance to acid reflux respiratory diseases, are uncomfortable for subjects and are generally reserved for research purposes.<sup>5</sup> We found an inverse correlation between the FSSG score and the EBC pH. Further investigations are thus necessary to determine whether the EBC pH reflects GOR or some aspects of airway pathophysiology that relate to exacerbation.

In conclusion, we found that patients with COPD with GORD symptoms were more likely to experience exacerbations than those lacking these symptoms. GORD might increase the tracheobronchial aspiration of gastric juice directly and/or disturb the clearance of swallowed contents from the pharynx to the oesophagus indirectly, leading to frequent exacerbations. Further examinations are needed to clarify whether treatment for GORD symptoms ameliorates COPD exacerbations.

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**Competing interests:** None.

**Ethics approval:** The research protocol was approved by the ethics committee of Kyoto University.

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