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## ABSTRACT

**Introduction** Clinical onset of chronic obstructive pulmonary disease (COPD) is the point at which the disease is first identifiable by physicians. It is a poorly defined stage which seems to include both mild spirometric and non-spirometric disease, and could be described as early grade COPD, for practical purposes. While dyspnoea; chronic bronchitis and CT imaging evidence of emphysema and airway disease may be present very early, the lone significance of dyspnoea, the most relevant symptom in COPD in identifying these individuals, has been scarcely assessed. The Searching Clinical COPD Onset (SOON) Study was designed primarily to detect clinical, physiological and structural differences between dyspnoeic and non-dyspnoeic individuals with early grade COPD. It is hypothesised that presence of dyspnoea in early disease may identify a subtype of individuals with reduced exercise capacity, notwithstanding of their spirometry results. In addition, dyspnoeic individuals will share worse quality of life, lower physical activity, greater lung hyperinflation greater emphysema and airway thickness and reduced peripheral muscle mass than their non-dyspnoeic counterpart.

**Methods and analysis** SOON is a monocentric study, with a cross sectional design aimed at obtaining representative samples of current or ex-smoker-adults aged  $\geq 45$  and  $\leq 80$  years. Two hundred and forty participants will be enrolled into four strata, according to normal spirometry or mild spirometric obstruction and presence or not of dyspnoea modified Medical Research Council score  $\geq 1$ . The primary outcome will be the difference between dyspnoeic and non-dyspnoeic individuals on the 6-min walk test performance, regardless of their spirometry results. To account for the confounding effect of heart failure on dyspnoea, stress echocardiography will be also performed. Secondary outcomes will include clinical (quality of life, physical activity), physiological (exercise testing) and structural characteristics (emphysema, airway disease and peripheral muscle mass by CT imaging).

**Ethics and dissemination** The Institutional Ethics Committee from Pontificia Universidad Católica de Chile has approved the study protocol and signed informed consent will be obtained from all participants. The findings of the trial will be disseminated through relevant

## Strengths and limitations of this study

- One strength of this study is the inclusion of three subtypes of early grade chronic obstructive pulmonary disease (COPD), easily identifiable by presence of mild dyspnoea in current or ex-smokers, with or without spirometric bronchial obstruction. We have chosen dyspnoea as the clinical manifestation of symptomatic early grade disease, since dyspnoea is the most relevant symptom all over the range of the disease. Other studies used a composite of symptoms and/or CT imaging, with confounding results.
- The comparison of outcomes between symptomatic individuals with and without spirometric COPD is one of the relevant research questions presented in a recent American Thoracic Society/European Respiratory Society Statement.
- We will also measure heart function by stress echocardiography, to evaluate the possible role of undiagnosed heart failure on dyspnoea and exercise limitation in early grade COPD.
- Early grade COPD may include subtypes of disease with high-risk for greater and faster worsening over time in clinical, structural and/or physiological outcomes. After completion, another study will assess longitudinal changes in lung function in the same population.
- A potential limitation is selection bias, because the study is monocentric, non-population-based and restricted to patients able to perform exercise testing. Accordingly, the results of this study will be applicable to a relatively selected population of early grade COPD.



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peer-reviewed journals and international conference presentations.

**Trial registration number** NCT03026439.

## BACKGROUND

Chronic obstructive pulmonary disease (COPD) has a protracted course before

clinical onset, following classical epidemiological principles of chronic disease and genetic predisposition. Clinical onset is the point at which the disease is first identifiable by physicians and could be defined either as a physiologic impairment expressed by a lone abnormal spirometric index and/or as a clinical manifestation of the disease, such as cough, phlegm, dyspnoea and exercise limitation. Consequently, clinical COPD onset may represent both mild spirometric disease, but also mild “non-spirometric COPD”, an entity mainly centred on symptoms and structural changes in lung and airway CT imaging.<sup>1,2</sup> In our view, the combination of both forms of disease characterise what we will describe as “early grade COPD”, in line with the definition of Decramer *et al.*<sup>3</sup> Please note that since many patients with non-spirometric COPD and asymptomatic mild disease will be detected in the present study by chance or because of spirometric screening indicated by their physicians, others groups should prefer to define these patients as “preclinical COPD”.<sup>4</sup> Early grade COPD should be distinguished from early COPD.<sup>5</sup> Early disease denotes a time-point during the natural history of COPD, either before the disease is present or a time-point when the disease has not yet fully evolved to their clinical expression.<sup>6</sup> Early grade COPD refers to the minimal loss of function, reflected in spirometry or symptoms, where COPD could be first diagnosed. Neither of these definitions take into account the activity of the disease, which is a concept related to the level of stimulation of the biological processes that drive disease progression.<sup>7</sup> Longitudinal measurements of lung function will be needed to establish disease activity. In summary, early disease refers to a point in a timescale before clinical disease onset, while early grade disease refers to a minimal disease severity able to be detected. A pragmatic view of early grade COPD is described on **Table 1**, including three subtypes of patients and a group of smokers with normal spirometry and absence of symptoms as a control group. These groups are roughly similar to Global initiative for Chronic Obstructive Lung Disease

(GOLD) grades 0 and 1,<sup>7</sup> although further characterised by the presence or absence of dyspnoea. Please note, however, that dyspnoea cut-off value chosen to separate symptomatic from asymptomatic subjects is a modified Medical Research Council (mMRC) score  $\geq 1$ , in line with several recent communications,<sup>8–10</sup> but differing from the cut-off recommended by GOLD (score  $\geq 2$ ).<sup>11</sup> Also note that GOLD 0 category,<sup>7</sup> included in the GOLD guidelines of 2001 and currently not in use, did not comprise a dyspnoeic subtype, which is now included in light of new evidence pointing out at their potential relevance.<sup>2,12</sup>

The first subtype of **table 1** (Group 2) has been reported by Woodruff *et al.*<sup>2</sup> on a large sample of smokers with normal spirometry who have chronic respiratory symptoms, exacerbations, lower than normal exercise tolerance and CT imaging evidence of bronchiolitis. These results complement previous findings of another large study from Regan *et al.*<sup>1</sup> showing that more than 50% of symptomatic smokers with normal spirometry have respiratory-related impairment and evidence of emphysema on CT imaging. Woodruff *et al.*<sup>2</sup> used the COPD Assessment Test (CAT) questionnaire to define symptoms<sup>13</sup> and found that both respiratory (cough and sputum) and less specific symptoms (dyspnoea, wheezing, activity limitation and energy level) were equally distributed among symptomatic smokers regardless of the presence of spirometric COPD. However, although CAT is intended to be specific for COPD,<sup>13</sup> most of its domains may reflect concomitant respiratory (asthma and bronchiectasis) and/or non-respiratory diseases (heart failure, ischaemic heart disease, obesity and depression).<sup>14</sup> In contrast, Regan *et al.*<sup>1</sup> measured seven ‘respiratory-related impairments’ and found one or more to be present in 54% of patients. Three of these impairments could be considered rather specific of COPD, like CT percentage of emphysema  $>5\%$  and gas trapping  $>20\%$  and SGRQ total score  $>25$ . Nevertheless, four impairments (chronic bronchitis, modified Medical Research Council (mMRC) dyspnoea score  $\geq 2$ , exacerbations and 6-min walk distance  $<350$  m) are non-specific as

**Table 1** Enrolment strata by dyspnoea and lung function

	Group 1	Group 2	Group 3	Group 4
	Asymptomatic smokers	Symptomatic smokers	Asymptomatic mild COPD	Symptomatic mild COPD
Smoking status	>10 pack-years	>10 pack-years	>10 pack-years	>10 pack-years
Dyspnoea mMRC score	0	$\geq 1$	0	$\geq 1$
Lung function assessment	Postbronchodilator	Postbronchodilator	Postbronchodilator	Postbronchodilator
FEV <sub>1</sub> /FVC ratio criteria	FEV <sub>1</sub> /FVC $\geq 0.7$	FEV <sub>1</sub> /FVC $\geq 0.7$	FEV <sub>1</sub> /FVC $<0.7$	FEV <sub>1</sub> /FVC $<0.7$
Other spirometric criteria	FVC $>80\%$ pred	FVC $>80\%$ pred	FEV <sub>1</sub> $>80\%$ pred	FEV <sub>1</sub> $>80\%$ pred
Sample size	n=120		n=120	
Sample size by groups (approximate)	$\approx 50\%$	$\approx 50\%$	$\approx 50\%$	$\approx 50\%$

For simplicity, we have excluded from this schema the Global Initiative for Chronic Obstructive Lung Disease unclassified group.

COPD, chronic obstructive pulmonary disease; FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity; LLN, lower limit of normal; mMRC, modified Medical Research Council dyspnoea score.

they may be partly or fully explained by comorbidities like gastro-oesophageal reflux disease, rhinosinusitis (upper airway cough syndrome/postnasal drip), obesity or heart failure, among others. In fact, retrospective data suggest that patients with COPD and comorbid conditions may have greater risk for having symptoms, rather than those without comorbidity.<sup>15 16</sup>

The second subtype (Group 3), that is, early grade smoking-induced lung disease with mildly abnormal spirometry but absence of symptoms (dyspnoea mMRC score equal to zero; absence of chronic cough and/or chronic expectoration) has been also described.<sup>17 18</sup> However, there is conflicting evidence about lung function and exercise performance in this group of patients. Two studies suggest that patients with mild non-dyspnoeic spirometric disease may include individuals with normal lung function and 6-min walk test performance<sup>18</sup> and subjects with resting lung hyperinflation, reduced diffusion capacity of the lung for carbon monoxide (DLCO) and slightly increased cycle-exercise-induced dyspnoea.<sup>17</sup>

The third subtype (Group 4) corresponds to symptomatic mild COPD. These patients have significant emphysema and airway thickness, lower DLCO, exercise-induced arterial desaturation and reduced 6-min walking distance.<sup>18 19</sup> In addition, during incremental cycle-exercise they exhibit increased ventilatory demand, lung hyperinflation and greater exertional dyspnoea than smoker controls.<sup>20</sup>

We consider that defining early grade COPD subtypes by clinical findings is the first step in pointing out a high-risk early grade disease group. If this high-risk group exists, it should exhibit in prospective studies greater and faster deterioration in symptoms, lung and/or peripheral muscle physiology and structure. Possible benefits in identifying such early grade COPD subtypes will depend on finding specific anomalies that could define the need of early interventions in terms, for instance, of smoking cessation, bronchodilation or pulmonary rehabilitation. And even though there are no established therapies to treat lung function decline, early identification of these subjects also allows prognostic information and perhaps targeting novel therapies.

## AIMS

This study intends to identify three early grade COPD subtypes defined by symptoms (dyspnoea) and spirometric airway obstruction (table 1) using differences in exercise capacity as the primary outcome. As secondary outcomes, we will intend to separate these groups by means of differences in clinical (quality of life, physical activity), physiological (exercise testing) and structural characteristics (emphysema, airway disease and peripheral muscle mass by CT imaging). Future analyses are planned to evaluate longitudinal deterioration in these clinical, physiological and structural characteristics. Potential influence of obesity and undiagnosed heart

failure on dyspnoea and thus, on exercise capacity, will be explored within the three subtypes.

## HYPOTHESES

For the present proposal, we will use dyspnoea to define a symptomatic subject. We hypothesise that dyspnoeic individuals notwithstanding of their spirometry results should share some clinical, structural and physiologic abnormalities. In particular, we expect that the two dyspnoeic groups with and without spirometric bronchial obstruction (Groups 2 and 4 in table 1) exhibit reduced exercise capacity, in addition to worse quality of life, lower physical activity, greater lung hyperinflation, greater emphysema and airway thickness and reduced peripheral muscle mass than their asymptomatic counterpart (Groups 1 and 3 in table 1).

## METHODS

Details on clinical definitions, inclusion/exclusion criteria and measurements are available in the online supplementary file 1.

### Study design

SOON has a cross-sectional design aimed at obtaining representative samples of adults between 45 and 80 years. Two hundred and forty participants will be enrolled into four strata as shown in table 1. Study subjects will be recruited from the outpatient clinics and the pulmonary function labs at the Pontifical Catholic University of Chile Health Network by means of physician referral, advertisement in clinical areas or self-referral at the study centre. The Institutional Ethics Committee approved the study protocol and signed informed consent will be obtained from all participants.

### Definitions

Mild COPD will be defined according to a fixed forced expiratory volume in 1 s (FEV<sub>1</sub>)/forced vital capacity (FVC) ratio <0.70 and a FEV<sub>1</sub> ≥80% of predicted value. We are aware that such definition will result in more frequent diagnosis of COPD in the elderly<sup>21</sup> compared to a cut-off using the lower limit of normal (LLN) values for FEV<sub>1</sub>/FVC.<sup>22</sup> However, LLN values are highly dependent on the choice of valid reference equations using post-bronchodilator FEV<sub>1</sub>, and neither longitudinal studies validating the use of the LLN, nor studies using reference equations in populations where smoking is not the major cause of COPD are available. Under diagnosis will be unlikely because individuals younger than 45 years will be excluded.<sup>23</sup> For the purposes of the present study, we have defined “early grade disease” when former or ex-smoker-adults: a) complain of dyspnoea but have normal spirometry; b) complain of dyspnoea and have mild bronchial obstruction; and, c) have mild bronchial obstruction without dyspnoea.

## Inclusion and exclusion criteria

Patients must be 45–80 years of age, have a smoking history of >10 pack-years and meet lung function criteria as shown in [table 1](#). Patients will be excluded if they have a significant disease other than COPD, cognitive disorders, conditions precluding them from exercise, recent diagnosis of cancer, history of diseases or treatments likely to interfere with interpretation of study tests, body mass index >40 kg/m<sup>2</sup> and diagnosis of unstable cardiovascular disease. Lung surgery and metal in the chest that may affect the chest CT interpretation are also exclusionary. Online supplementary table contains the complete list of exclusion criteria. The presence of usual comorbidities, such as essential hypertension, diabetes, osteoporosis,

hypothyroidism, under proper medical control and obesity, excluding extreme obesity, will not be considered an exclusion criterion.

## Measurements

Assessment will include anthropometry, clinical history, health-related quality of life, conventional haematology and blood chemistry analysis, physical activity, lung physiology, lung and mid-tight CT imaging, stress echocardiography and exercise testing ([table 2](#)). For lung physiology, subjects will undergo spirometry, static lung volumes and DLCO. For lung, airway and peripheral muscle structure CT imaging will be assessed with volumetric chest CT scan at full inspiration and right

**Table 2** Outcome measurements

Measurement	Description
Health measurements	
Depression questionnaire	Centre for Epidemiologic Studies of Depression scale
Anxiety questionnaire	Anxiety subscale of the Hospital Anxiety and Depression Scale
Health status	Saint George Respiratory Questionnaire, COPD Assessment Test
Dyspnoea	Modified Medial Research Council dyspnoea scale
Haematology and blood chemistry analyses	
Complete blood count	Red and white blood cells, platelets
Comprehensive metabolic panel	Glucose, calcium, albumin and total blood protein, blood urea nitrogen, creatinine, alkaline phosphatase, alanine amino transferase, aspartate amino transferase and bilirubin
Lipid panel	Total cholesterol, high-density lipoproteins cholesterol, low-density lipoproteins cholesterol and triglycerides
Lung function	
Spirometry pre-postbronchodilator FEV <sub>1</sub> , FVC, FEV <sub>1</sub> /FVC, IC, reversibility	
Pulmonary plethysmography RV, TLC, FRC	
Diffusion capacity of the lung for carbon monoxide	
Heart function	
Resting echocardiography	Measurement of diastolic and systolic function
Stress echocardiography	Measurement of systolic function and potential myocardial ischemia
Chest CT	
	Measurement of airway characteristics
	Quantification of emphysema
Mid-tight CT	Measurements of right mid-tight area
Exercise capacity	Supervised, encouraged 6-min walk test
Cardiopulmonary exercise test on a cycle ergometer	
Peak VO <sub>2</sub> , VCO <sub>2</sub> , VE	Symptom-limited incremental cycle exercise test
Iso-time and iso-work measurements	Constant work rate cycle endurance test
Physical activity	
Triaxial accelerometer measurement	Step count
	Spent physical activity time per day
	Physical activity level

COPD, chronic obstructive pulmonary disease; IC, inspiratory capacity; FEV<sub>1</sub>, forced expiratory volume in 1 s; FRC, functional residual capacity; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity; VCO<sub>2</sub>, carbon dioxide production; VE, minute ventilation; VO<sub>2</sub>, oxygen consumption.

mid-tight CT. At rest and end-exercise, heart function will be assessed by stress echocardiography. Exercise performance will be evaluated with the 6-min walk test and with symptom-limited incremental and constant workload cycle exercise testing. A summary of full protocol measures is shown in **table 2** and operative definition is reported in online supplementary appendix 1.

## STATISTICAL ANALYSIS

### Outcomes

The primary outcome will be the difference between dyspnoeic and non-dyspnoeic individuals on the 6-min walk test performance, regardless of their spirometry results.

Secondary outcomes will include differences on anthropometry, clinical history, health-related quality of life, conventional haematology and blood chemistry analysis, lung physiology, lung and mid-tight CT imaging, stress echocardiography and exercise testing.

### Analysis

Between-group comparisons will be analysed using  $\chi^2$ , Fisher's test and one-way analysis of variance for categorical and continuous variables, respectively.

Main differences between dyspnoeic groups 2 and 3 (**table 1**) will be assessed first using a univariate model and later on a multivariate model taking into account potential confounders. In order to understand the influence of obesity and systolic or diastolic heart failure on dyspnoea, a stratified analysis will be performed testing for potential confounding or interaction effects. Data will be reported with OR with a 95% CI. All data will be processed using SPSS software version 15.0 (Chicago, Illinois, USA).

### Sample size

A sample size of at least 52 subjects per group provide enough power (80%) to detect a significant difference (95% CI or alpha 0.05) in the 6-min walk test among symptomatic and asymptomatic participants, based on a conservative relevant difference in walking distance of 50 m with a common SD of 110 m. Such difference was found when comparing symptomatic and asymptomatic subjects with normal spirometry,<sup>2</sup> but may be an underestimation in patients with mild spirometric COPD,<sup>18</sup> where the difference between symptomatic and asymptomatic patients was 100 m. Forestalling a participant loss rate of 20%, 60 patients will be included in each group.

## DISCUSSION

In this study, we will attempt to identify early grade COPD subtypes, according to the presence of dyspnoea among smokers with and without spirometric bronchial obstruction.

The first subset of patients (Group 2 in **table 1**) is grossly similar to the 'Stage 0', labelled so by the 2001 GOLD Report.<sup>7</sup> However, GOLD 0 was defined by the sole

presence of chronic cough and phlegm, usually referred to as chronic bronchitis, with normal spirometry. We are widening the definition to include subjects with dyspnoea independently of the presence of chronic bronchitis. Previous studies have shown that broadening the GOLD stage 0 definition to chronic bronchitis and/or dyspnoea increased the risk of death for this grade.<sup>24–26</sup> Other studies have suggested that the presence of chronic cough<sup>27–29</sup> but not dyspnoea<sup>28</sup> identified individuals with high risk of future occurrence of COPD. Nevertheless, chronic bronchitis is not necessarily a chronic condition and can vary over time,<sup>28 30</sup> the main determinant of this variation being smoking status.<sup>30</sup> Development or resolution of chronic bronchitis does not seem to relate directly with worsening lung function, such that lung function decline has been similar in patients with and without chronic bronchitis.<sup>30 31</sup> Thus, while it appears that chronic bronchitis may be a marker of future COPD development and probably modulate early phases of COPD development, dyspnoea is more likely a manifestation of disease already present. It remains to be proven, however, if this form of early grade disease corresponds to COPD or to other smoking-related lung disease.

The second subtype (Group 3 in **table 1**) includes patients with abnormal spirometry but absence of dyspnoea. As already mentioned, two studies have found conflicting results regarding lung function, CT imaging emphysema, CT airways structure, and exercise performance in this group of patients. Soumagne *et al*,<sup>17</sup> using FEV<sub>1</sub>/FVC below the lower limit of normal (LLN) to define mild COPD, found resting hyperinflation, lower DLCO, reduced peak oxygen consumption (VO<sub>2</sub>) and increased cycle exercise-induced dyspnoea compared with smoker controls. On the contrary, using FEV<sub>1</sub>/FVC <0.70, Díaz *et al*<sup>18</sup> did not find differences in lung function, quality of life, emphysema, bronchial wall thickness or exercise capacity between asymptomatic mild COPD and smoker controls. Smoker controls in both studies are well described by asymptomatic smokers (Group 1) of **table 1**. Although asymptomatic mild COPD patients from the study of Diaz *et al*<sup>18</sup> had greater mean FEV<sub>1</sub>/FVC (68% vs 61%) and may thus represent normal people misclassified by using fixed spirometric indexes, a posthoc analysis of their data have shown that 72% of these patients also had a FEV<sub>1</sub>/FVC below the LLN. Hence, these two studies suggest that patients with mild asymptomatic spirometric disease may represent a continuous spectrum from complete absence to slightly increased cycle-exercise-induced dyspnoea. Such variability has been also shown by Gagnon *et al*.<sup>32</sup> In the present study, we will evaluate a larger sample to disentangle these inconsistencies.

The third subset of patients (Group 4 in **table 1**) is more easily identifiable, since it belongs to GOLD group B-spirometric grade 1.<sup>11</sup> The only difference is that we will use a dyspnoea mMRC cut-off score  $\geq 1$ , at variance of the GOLD recommendation (mMRC score  $\geq 2$ ).<sup>11</sup> We have already pointed out that in our opinion the dyspnoea cut-off which best separates symptomatic from

asymptomatic subjects is a mMRC score  $\geq 1$ , because several communications indicate that cut off of mMRC score  $\geq 1$  and CAT score  $\geq 10$  are equivalent in separating low from high-symptom patients<sup>8 9 33</sup> and that this cut-off correlates best with CAT  $\geq 10$ <sup>8-10</sup> than the criteria recommended by GOLD (score  $\geq 2$ ).<sup>11</sup> Moreover, at least two studies have found reduced physical activity from dyspnoea mMRC score 1 or greater, independently of disease severity.<sup>34 35</sup> The importance of mMRC dyspnoea  $\geq 1$  as an inflection point to differentiate patients from smoker subjects without COPD in terms of reduced physical activity has also been highlighted in another study where only dyspnoeic COPD patient's exhibited reduced physical activity, while non-dyspnoeic individuals had similar physical activity levels than controls.<sup>36</sup> We are confident, however, that future studies will properly define which thresholds are the best to make CAT and mMRC equivalent, refining current recommendations.

The true prevalence of Groups 2 and 4 is poorly known. Concerning Group 4, at least three studies have found dyspnoea mMRC score  $\geq 1$  in approximately 45%–50% of patients with mild COPD.<sup>18 37 38</sup> A similar proportion (43%) reported dyspnoea mMRC  $\geq 1$  in mild-to-moderate COPD patients from the Lung Health Study.<sup>39</sup> The prevalence of higher dyspnoea scores (mMRC  $\geq 2$ ) in mild COPD is apparently broader, ranging from 9% to 22%.<sup>1 40 41</sup> The distribution of dyspnoea scores among Group 2 is even less well known. In the COPDGene Study, prevalence of mMRC  $\geq 2$  was 24%,<sup>1</sup> but we have found no data regarding prevalence of milder dyspnoea, that is, mMRC=1. Therefore, a potential risk of the SOON study is under-representation of Group 2 (dyspnoeic GOLD 0).

Groups 2 and 4 probably represent high-risk individuals with active disease, but at different grades of disease severity, which in future follow-up could exhibit faster deterioration of clinical, structural and physiological characteristics than low-risk individuals. In the SAPALDIA cohort, for instance, subjects with symptomatic mild COPD had a faster rate of decline in lung function, greater respiratory resource utilisation and worse quality of life than asymptomatic mild COPD patients and asymptomatic subjects with normal lung function.<sup>42</sup> Similar information from Group 2 (dyspnoeic GOLD 0) is lacking. As pointed out by Rodriguez-Roisin *et al.*<sup>43</sup> “the dilemma remains as to whether we are confronted with an *early phase* of what will become COPD in the traditional sense or a separate smoking-related condition without progression to spirometric COPD”.<sup>43</sup>

## Perpectives

The present study was designed primarily to detect clinical, physiological and structural differences between dyspnoeic and non-dyspnoeic individuals with early grade COPD. Disease progression at early grade COPD is currently unpredictable, but we suspect that individuals at greater risk of accelerated lung function decline may be singled out. It is hypothesized that dyspnoea may identify those individuals. Consequently, after completion,

another study has been planned to evaluate longitudinal changes in lung function in the same population.

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