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# COPD: Long Term Lung Function Decline, Utilization of Care and Quality of Life in Modified GOLD stage 1

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## ABSTRACT

**Background:** Little is known on the long term outcomes of individuals with mild COPD, as defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD).
**Methods:** A population cohort of 6671 randomly selected adults without asthma was stratified into categories of modified GOLD-defined COPD (pre-bronchodilator spirometry). Further stratification was based on the presence or absence of respiratory symptoms. After 11 years, associations between baseline categories of COPD and $FEV_1$ decline, respiratory care utilization, and quality of life as measured by the SF-36 questionnaire, were examined after controlling for age, sex, smoking and educational status.
**Results:** At baseline, modified GOLD criteria were met by 610 (9.1%) participants from whom 519 (85.1%) had stage 1 COPD. At follow-up, individuals with symptomatic stage 1 COPD (n=224) had faster $FEV_1$ decline (-9 ml/yr [CI95% -13; -5]), increased respiratory care utilization (OR 1.6 [CI95% 1.0 ; 2.6]) and lower quality of life compared to asymptomatic subjects with normal lung function (n=3627, reference group). By contrast, asymptomatic stage 1 COPD subjects (n=295) had no significant differences in $FEV_1$ decline (-3 ml/yr [CI95% -7; +1]), respiratory care utilization (OR 1.05 [CI95% 0.63 ;1.73]) or quality of life scores when compared to the reference group.
**Conclusions:** In population-based studies, respiratory symptoms are of major importance for predicting long-term clinical outcomes in COPD subjects with mild obstruction. Population studies that are based on spirometry only may misestimate the prevalence of clinically relevant COPD.

## INTRODUCTION

The Global Initiative for Chronic Obstructive Lung Disease (GOLD), updated in 2006, distinguishes four categories of chronic obstructive lung disease (COPD) severity based on a fixed ratio of forced expiratory volume in one second ($FEV_1$) / forced vital capacity (FVC) and the percent predicted $FEV_1$ value.[1] This classification has been issued to help clinicians detect COPD and offer up-to-date therapy to patients; it has been proposed as a research tool for international comparisons of COPD prevalence, as well as a common definition in clinical trials. Finally, the GOLD classification has been promoted to estimate future health care resources as a result of the growing prevalence of the disease.

Many population studies on the prevalence of COPD rely on airflow obstruction as measured by spirometry, without requirement for reporting symptom, exposure to noxious particles or fumes. [2-9] During the period 1990-2004, Halbert et al found a pooled prevalence of spirometry-defined COPD of 9.2% whereas the prevalence of physician-diagnosed or self-reported COPD were lower.[10] More recently the Burden Of Obstructive Lung Disease (BOLD) Initiative reported a prevalence of GOLD 1 COPD varying between 1.4% (Philippines) and 15.5% (Austria).[8] Also, in population studies, GOLD 1 COPD is frequently the most prevalent stage of the disease. For example, in 5 Latin American cities, the prevalence of GOLD 1 COPD ranged from 5.2% to 12.5% whereas stage 2 or higher was uniformly lower (2.6% to 7.1%).[9]

The impact on mortality, health care utilization and quality of life of GOLD stage 2-4 COPD which include subjects with abnormal $FEV_1$/FVC ratio and $FEV_1$ below 80%, 50% and 30% respectively, is well recognized.[11, 12] In contrast, the clinical significance of GOLD 1 COPD, that encompasses subjects with $FEV_1$/FVC <70% and $FEV_1$ ≥80% predicted is much less clear.

Two population-based studies have specifically addressed the question of mortality in COPD according to the GOLD classification.[13, 14] Both showed that GOLD 1 COPD was associated with a slightly increased mortality, but only when these subjects had symptoms of chronic bronchitis. Data on the association between GOLD 1 COPD and health care utilization are scarce. The net risk for COPD-related hospitalization was increased in subjects with GOLD 1 COPD in one report. However, these data suggested that this risk was not higher than in chronic bronchitis without obstruction.[15]

Since subjects with mild GOLD 1 COPD generally constitute more than half of the individuals with COPD in population studies, it is crucial to have more information about them on clinically relevant outcomes. This could help provide accurate estimates of health care need and risk prediction for individuals with mild, GOLD-defined abnormal lung function.

Therefore, the aim of this study was to compare the long-term $FEV_1$ decline, respiratory care utilization and quality of life (QoL) between individuals with symptomatic or asymptomatic stage 1 COPD.

## METHODS

### Study population:

The SAPALDIA cohort (Swiss Study on Air Pollution and Lung Diseases in Adults) (n=9651), a random sample of the Swiss population, was initially assembled in 1991 to address the effect of air pollution on respiratory health. Detailed descriptions of the SAPALDIA study are published elsewhere.[16, 17] Briefly, individuals, aged 18-60 years, were randomly drawn from local registries of 8 areas chosen to represent cultural and geographical diversity of Switzerland (Geneva, Basel, Lugano, Aarau, Wald, Payerne, Davos and Montana). Of those, 8876 had interpretable spirometry and provided information about respiratory symptoms in 1991. For this study, subjects who reported physician-diagnosed asthma at SAPALDIA 1 (1991) were excluded (n=594). **(Figure 1)**. Out of 8282 eligible subjects from the 1991 sample, the follow up study in 2002 included 6671 subjects (participation rate 80.5%). In the present analysis, 5498 (66.4%) underwent pulmonary function tests, 6670 (80.5%) reported health care utilization, and 5000 (60.4%) filled in the Short-Form 36 questionnaire (SF-36). Ethics committee approvals were obtained from the participating centers and from the Swiss Academy of Medical Science.

### Pulmonary function tests and symptoms assessment

Pulmonary function tests were performed according to the American Thoracic Society Standards, in 1991 and 2002, using the same spirometers (SensorMedics 2200 SP Yorba Linda, CA, USA). The longitudinal validity of the spirometers was also verified.[18] Forced expiratory maneuver was obtained without bronchodilators. We calculated the predicted values for $FEV_1$ and FVC using the 1993 European Respiratory Society equation.[19] The modified-GOLD classification was adapted to group subjects with $FEV_1/FVC < 0.7$ and pre-bronchodilator $FEV_1 \geq 80\%$ into the stage 1 COPD category and those with $FEV_1 < 80\%$ into a single stage 2-4 category. Respiratory symptoms were considered present if subjects reported at baseline examination (1991) chronic cough, phlegm or shortness of breath while walking. Respiratory questionnaires are detailed in the online supplement (http://thorax.bmj.com/supplemental). Finally, the cohort (n=6671) was stratified on the basis of the GOLD classification and the presence/absence of respiratory symptoms at the first examination (SAPALDIA 1 [1991]).

Yearly $FEV_1$ decline was calculated by subtracting the first to the second $FEV_1$ absolute value, divided by the time between the two measurements.

### Respiratory care utilization

Any report to the interviewer of inhaler use, emergency room visit or hospitalization due to respiratory problems, ambulatory visit to a chest physician, to an asthma specialist or to a primary care provider for respiratory problems during the year preceding the follow up survey (SAPALDIA 2 [2002]) was considered as “respiratory care utilization”.

### Quality of Life

The Medical Outcomes Study 36-item Short-Form General Health Survey (SF-36) was filled in at the follow up examination (2002). As Switzerland is a multilingual country, German, French or Italian versions were administered.[20-22] The Physical Component Summary (PCS) and the Mental Component Summary (MCS) were derived from the questionnaires.[23]

### Covariates

Nationality, education level, smoking status (never, former, current), and lifetime smoking (pack/yr) were derived from the main health inventory questionnaires. Height, weight and body-mass index (BMI) were recorded immediately before the pulmonary function testing.[17]

**Statistical analysis**

Outcomes of interest were mean $FEV_1$ decline per year, respiratory care utilization and SF-36 summary scores. Main predictors of interest were the modified GOLD categories stratified by presence or absence of respiratory symptoms. We developed mixed linear and logistic regression models with adjustment for age, sex, baseline $FEV_1$, smoking status, lifetime smoking, baseline BMI ($kg/m^2$), weight change, education level, nationality and study area (random effect).

To address the issue of missing responses, we fitted a logistic regression model to predict probability of non-participation using baseline variables. As a sensitivity analysis, regression models were rerun while weighting each observation by the inverse of the respective subject's propensity of participation.. We performed additional analyses without excluding those with physician-diagnosed asthma in 1991. The association between the specific outcome "emergency room visits or hospitalization due to respiratory problems" and modified GOLD and symptom categories was also examined. Finally, the effect of smoking persistence or cessation between the 2 surveys was assessed.

All analyses were conducted with Stata 10.0 version (StataCorp, 4905 Lakeway Drive, College Station, Texas 77845 USA).

**RESULTS**

**Characteristics of the SAPALDIA cohort and of participants**

**Table A** (http://thorax.bmj.com/supplemental) displays the characteristics of the cohort at SAPALDIA 1 [1991]. Overall, 610 (9.1%) subjects had a $FEV_1/FVC$ ratio <0.7 and were classified as COPD according to the pre-bronchodilator GOLD-defined fixed ratio. Among those, 519 (85.1%) had a $FEV_1$ ≥80% of the predicted value and were classified as stage 1 COPD. More than half of subjects classified as stage 1 COPD were free of respiratory symptoms (n=295; 56.8%). Overall, individuals with modified GOLD-defined obstruction were older, more frequently male and ever-smoker.

Compared with participants, non-participants at SAPALDIA 2 were more likely to be younger, non-Swiss citizens, current smokers, obese and to have respiratory symptoms at SAPALDIA 1. More information on non-participants is given in the online supplement. (Table B & C http://thorax.bmj.com/supplemental).

**$FEV_1$ decline**

Net annual $FEV_1$ decline over 11 years was 35 ml/yr (SD 29) for subjects with normal lung function (n=4997), 40 ml/yr (SD 37) for stage 1 COPD (n=430) and 28 ml/yr (SD 40) for stage 2-4 COPD (n=71) ($p<0.01$). **Table 1** summarizes unadjusted $FEV_1$ decline by modified GOLD and by symptom categories. Compared to asymptomatic subjects with normal lung function (reference group), the unadjusted $FEV_1$ decline was faster only for symptomatic subjects with normal lung function ($p=0.001$) and for symptomatic stage 1 COPD ($p<0.001$) categories. Within stage 1 COPD, a trend toward faster $FEV_1$ decline was measured before adjustment for symptomatic [- 44 ml (SD 38)] versus asymptomatic subjects [- 38 ml (SD 36)] ($p=0.11$).

**Table 1: Unadjusted $FEV_1$ decline over 11 years, respiratory care utilization and SF-36 summary score at follow up (SAPALDIA 2 [2002]), stratified by modified GOLD† and symptom categories at SAPALDIA 1 (1991)**

| | | $FEV_1$ decline (ml/year) mean, (SD) n= 5498 | *P*§ | Respiratory care utilization, % [n] n=6670 | *P* ‡ | PCS mean, (SD) n= 5000 | *P*§ | MCS mean, (SD) n=5000 | *P*§ |
|---|---|---|---|---|---|---|---|---|---|
| **Normal lung function†** | **No symptom,** | -34 (29) | | 7.3 [265/3626] | | 53.1 (6.7) | | 51.5 (7.7) | |
| | **with symptom*** | -37 (30) | <0.01 | 14.7 [358/2434] | <0.01 | 50.6 (9.1) | <0.01 | 48.7 (9.4) | <0.01 |
| **Stage 1 COPD†** | **No symptom** | -38 (36) | 0.08 | 8.1 [24/295] | 0.60 | 51.2 (8.2) | <0.01 | 52.5 (7.6) | 0.05 |
| | **with symptom*** | -44 (38) | <0.01 | 12.5 [28/224] | <0.01 | 48.7 (10.8) | <0.01 | 48.9 (10.1) | <0.01 |
| **Stage 2-4 COPD†** | **No symptom** | -25 (43) | 0.33 | 23.4 [7/30] | <0.01 | 51.4 (4.4) | 0.09 | 53.9 (6.3) | 0.08 |
| | **with symptom*** | -29 (39) | 0.38 | 34.4 [21/61] | <0.01 | 44.2 (12.1) | <0.01 | 50.5 (9.8) | 0.54 |

†: pre-bronchodilator spirometry. § t-test for unequal variances for comparison to the reference category: "Normal lung function, no symptom"
*: report of chronic cough or phlegm or shortness of breath while walking. see online supplement for detailed questions.
‡ $\chi^2$ test for comparison to the reference category: "Normal lung function, no symptom"
PCS = Physical Component Summary of SF-36
MCS = Mental Component Summary of SF-36

**Figure 2** depicts the results of the multivariate analysis of mean annual $FEV_1$ decline over 11 years by categories of modified GOLD and stratified by the presence of symptoms at SAPALDIA 1 (1991). Presence of symptoms in subjects with normal lung function at baseline was associated with significant difference in $FEV_1$ decline compared to the reference group [-4 ml/yr (CI95% -5 ; -2)]. Likewise, symptomatic stage 1 COPD subjects exhibited an additional $FEV_1$ loss of -9 ml/yr (CI95% -13 ; -5) compared to the reference group. In contrast, asymptomatic subjects with stage 1 COPD and the reference group had similar $FEV_1$ decline [-3 ml/yr (CI95% -7 ; +1)]. Moreover, a significant difference in $FEV_1$ decline was observed when comparing asymptomatic and symptomatic subjects within the stage 1 COPD category [- 6 ml/yr (CI 95% -11; -1)]. stage 2-4 COPD subjects showed consistently greater $FEV_1$ losses compared to the reference group.

**Respiratory care utilization**

Unadjusted differences in the report of respiratory care utilization at SAPALDIA 2 (2002) between the subjects' categories are summarized in **Table 1**. Overall, 10.3% of individuals with normal lung function at SAPALDIA 1 (1991) reported utilization of respiratory care during the year preceding the SAPALDIA 2 survey, compared to 10.0% (p=0.85) and 30.8% (p<0.01) of individuals with stage 1 and stage 2-4 COPD respectively.

**Figure 3** shows the results of the multivariate analysis stratified by GOLD categories and presence of symptoms. Symptomatic subjects with normal lung function were more likely to report respiratory care utilization (OR 1.9 [CI95% 1.6; 2.3]). Asymptomatic subjects with stage 1 COPD reported similar rates of respiratory care utilization as the reference category (OR 1.05 [CI95% 0.63; 1.73]), whereas symptomatic stage 1 COPD subjects had increased rates (OR 1.62 [CI95% 1.10; 2.61]). Finally, the strongest predictors for reporting respiratory care utilization were having stage 2-4 COPD without or with symptoms (OR 4.05 [CI95% 1.59 ; 10.30] and 5.67 [CI95% 2.86; 11.22] respectively). Detailed results are accessible in the online supplement (Table D http://thorax.bmj.com/supplemental).

**Quality of life scores**

The unadjusted SF-36 summary scores are displayed in **Table 1**. GOLD defined COPD was associated with lower physical QoL. In subjects with normal lung function, stage 1 and stage 2-4 COPD, PCS scores were 52 (SD 8), 50 (SD 9) and 47 (SD 11), respectively (p<0.01). MCS scores were not different between the three above-mentioned categories [mean 50 (SD 9)] (p= 0.17).

After controlling for covariates, only those with symptoms at baseline had significantly lower PCS scores compared to asymptomatic subjects with normal lung function irrespective of the modified GOLD classification status (**Figure 4**). Compared to reference category, the PCS were lower for symptomatic subjects with stage 2-4 COPD (-5.2 points), for symptomatic stage 1 COPD (-1.6 points) and symptomatic individuals with normal lung function (-1.6 points). In contrast, those who were free of symptoms at baseline reported QoL scores close to the reference category. In parallel with lung function decline and respiratory care utilization, differences were present in PCS or MCS scores between asymptomatic and symptomatic stage 1 COPD subjects (PCS difference -1.4 [CI95% -3.0 ; +0.2]; MCS difference -3.2 [CI95% -4.9 ; -1.4]).

**Sensitivity analyses**

In the weighted data analysis, the associations between $FEV_1$ decline, respiratory care utilization, SF-36 summary scores and GOLD and symptom categories were robust and unchanged.

When including subjects with physician-diagnosed asthma in the analysis, we found that estimates of $FEV_1$ decline for GOLD and symptom categories were close to those using the original cohort. Moreover in this analysis, the difference in $FEV_1$ decline between asymptomatic and symptomatic stage 1 COPD subjects was larger (-8 ml/yr [CI95% -13 ; -3]) than in the analysis excluding asthmatics. (table E, (http://thorax.bmj.com/supplemental).The analysis centered on emergency room visit / hospitalisations for respiratory problems, as a specific respiratory care utilization outcome, showed that asymptomatic stage 1 COPD subjects had a similar rate of event than asymptomatic subjects with normal lung function (OR 0.83 [CI95% 0.19 – 3.71]). (Table F, http://thorax.bmj.com/supplemental). As expected, smoking persistence was associated with faster $FEV_1$ decline in stage 1 COPD compared to persistent smokers with normal lung function. However, within persistent smokers with stage 1 COPD, $FEV_1$ decline was not significantly faster for symptomatic subjects when compared with asymptomatic subjects (data not shown). Stage 1 COPD quitters had similar long-term outcomes compared to quitters with normal lung function. Finally, the interaction between amount of smoking (pack years between SAPALDIA 1 and 2) and GOLD-symptom categories, added to the multivariate models for asymptomatic and symptomatic mild COPD subjects, was not significant for $FEV_1$ decline (p=0.52), QoL (PCS, p=0.23; MCS, p=0.68) and respiratory care use (p=0.19).

## DISCUSSION

In this population-based cohort, we found that the presence or absence of respiratory symptoms at baseline in adults with stage 1 COPD significantly modified long-term $FEV_1$ decline, respiratory care utilization patterns and HRQoL scores. Symptomatic stage 1 COPD had long-term faster functional decline, increased respiratory care utilization and lower health-related quality of life compared to asymptomatic subjects with normal lung function, whereas asymptomatic stage 1 subjects were similar to the reference group regarding these outcomes.

In contrast, subjects with stage 2-4 COPD had worse long term outcomes, independently of the presence or absence of symptoms at baseline.

### Lung function decline

Historically, accelerated lung function decline has been recognized as a hallmark of COPD.[24] In the present study, net $FEV_1$ decline in subjects with stage 1 COPD, taken together, was faster compared to subjects with normal lung function. However, we found that $FEV_1$ decline within stage 1 COPD subjects was statistically different in relation to absence or presence of respiratory symptoms. Those with stage 1 COPD and symptoms had a significantly faster $FEV_1$ decline compared to the asymptomatic subjects with normal spirometry. On the other hand, asymptomatic subjects labelled as stage 1 COPD had trend toward faster $FEV_1$ decline, which was not statistically significant. Symptoms might be linked to a remodelling process of higher intensity in the airways and can represent as a consequence, a prognostic marker of functional impairment.[25] This hypothesis is consistent with the observation that chronic bronchitis, without obstruction, is a risk factor for developing COPD[26, 27]. For example, Lindberg et al reported a 2 to 3-fold increase in the cumulative 10-year incidence of COPD in the presence of respiratory symptoms.[26] This was also noticed by de Marco et al in a longitudinal population study: the risk of COPD was higher for those with persistent bronchitis symptoms compared to asymptomatic subjects (relative risk 2.9 [CI95% 1.4 ; 5.8]).[27] However, to our knowledge, this is the first report to show that respiratory symptoms, as defined by chronic cough, phlegm or shortness of breath

by walking predict accelerated lung function decline and other clinically relevant outcomes in stage 1 COPD subjects.

**Respiratory care utilization**

Symptomatic individuals with stage 1 COPD at SAPALDIA 1 were 1.6-times more likely to report respiratory care utilization, whereas those free of respiratory symptoms had similar rates compared to asymptomatic subjects with normal lung function. In the sensitivity analysis, results were unchanged when respiratory care utilization was strictly defined by emergency room visit or hospitalization for respiratory problems. The odds ratio of respiratory care utilization was also increased for symptomatic subjects with normal lung function. To date, no other population study specifically reported long-term utilization of respiratory care in subjects with stage 1 COPD. The similar rate of respiratory care utilization for subjects with asymptomatic stage 1 COPD and those with normal lung function could be interpreted in several ways: individuals labelled as stage 1 COPD may represent a normal variant of lung function, with little potential for developing clinical disease. Another interpretation could be that a larger cohort or a follow-up longer than 11 year may have more power to observe differences in terms of respiratory care utilization.

Individuals with stage 2-4 COPD at baseline had up to a 6-fold higher risk of respiratory care utilization later. This last result is in line with published literature. A case-control study showed that utilization of respiratory care was 12-times higher for those with physician-diagnosed COPD compared to controls.[28] Similarly, a population study reported a 5 to 15-fold higher risk of hospitalization for stage 2-4 COPD.[29] In another cohort of patients with severe to very severe COPD, lower lung function and QoL were independent predictors of hospitalizations or emergency department visits.[30]

**Quality of Life**

In parallel with respiratory care utilization, asymptomatic subjects with stage 1 COPD and those with normal lung function are similar in terms of QoL scores. These results are in line with a previous study: Antonelli-Incalzi found that stage 1 COPD did not correspond to meaningful alteration in QoL.[31] This same study suggested that the deterioration of the health status was possibly due to respiratory symptoms, which is also indicated by our results. Overall, symptomatic subjects with normal lung function, stage 1 or stage 2-4 COPD had significantly lower physical and mental health scores in the present cohort.

Quality of life in COPD has been mainly assessed in patients recruited from primary care clinics. [12, 32] Compared to these studies, the physical and mental health scores of our subjects were higher, even for stage 2/4 COPD. This is not unexpected as our subjects were sampled from the general population, and were not primarily identified as patients.

**Strengths and limitations**

Strengths of our study are the size of the cohort, which is a representative sample of the Swiss population. For example, in terms of BMI or smoking behaviour, the SAPALDIA sample compares with other population studies in Europe and with the Swiss population, thus supporting external validity [33]. Participation rate at follow up was high. We were able to use detailed information on confounding factors such as lifetime smoking, nationality or

education. Nevertheless some residual confounding related to socio-demographic variables may still be present. Another strength is the rigorous quality control of spirometric records.[16-18]

Limitations are related to the absence of post bronchodilator spirometry and repeated lung function measures, which may result in overdiagnosis of mild COPD. The potential of misclassification was recently evaluated at 27% by Johannessen et al in a population study in Norway using bronchodilation and was higher for younger subjects and never-smokers.[34] Another Korean study reported a higher misclassification risk of 52%. [6] However, the effect of this potential misclassification is in part reduced in our study since we excluded asthmatics unlike the studies in Norway or Korea. In addition, our subjects with modified stage 1 COPD were on average older than the reference group and less likely to be never smokers.. Another limitation may be due to the differential loss to follow-up. Like in other cohort studies, subjects with lower education level and worse lung function were more likely to be non-participant at follow-up. [35] Such a bias would actually decrease the differences between the GOLD and symptom categories compared to the reference group. It should also be noticed that in our cohort, loss to follow-up in the stage 1 COPD category was close to loss to follow-up in the reference group. In addition, the weighted sensitivity analyses showed that our results were only marginally affected by missing data.

Finally, we noted that the subgroup of subjects with stage 1 COPD who were persistent smokers between both surveys had accelerated $FEV_1$ decline without significant difference between symptomatic and asymptomatic individuals. Therefore the presence or absence of symptoms might not be such a strong determinant of $FEV_1$ decline in persistent smokers as it is in other subjects. However, lack of power in these subgroups analysis requires caution. As a whole, our results indicate that different biological mechanisms may interact in symptomatic and asymptomatic subjects with mild COPD.

## Conclusions

In summary, we show that in a population-based study, symptomatic and asymptomatic adults with stage 1 COPD have contrasted long term $FEV_1$ decline, respiratory care utilization and QoL scores. In addition, respiratory symptoms at baseline in subjects without GOLD-defined COPD come out as predictors of these outcomes. This suggests that population cross-sectional studies that are based only on spirometry may misestimate the prevalence of clinically relevant COPD. The risk of COPD misclassification is likely increased by the absence of bronchodilation to define airways obstruction . The heterogeneity of subjects with spirometry-defined stage 1 COPD should be addressed in future population studies in order to predict their long term clinical outcomes and to estimate the public health needs related to COPD.

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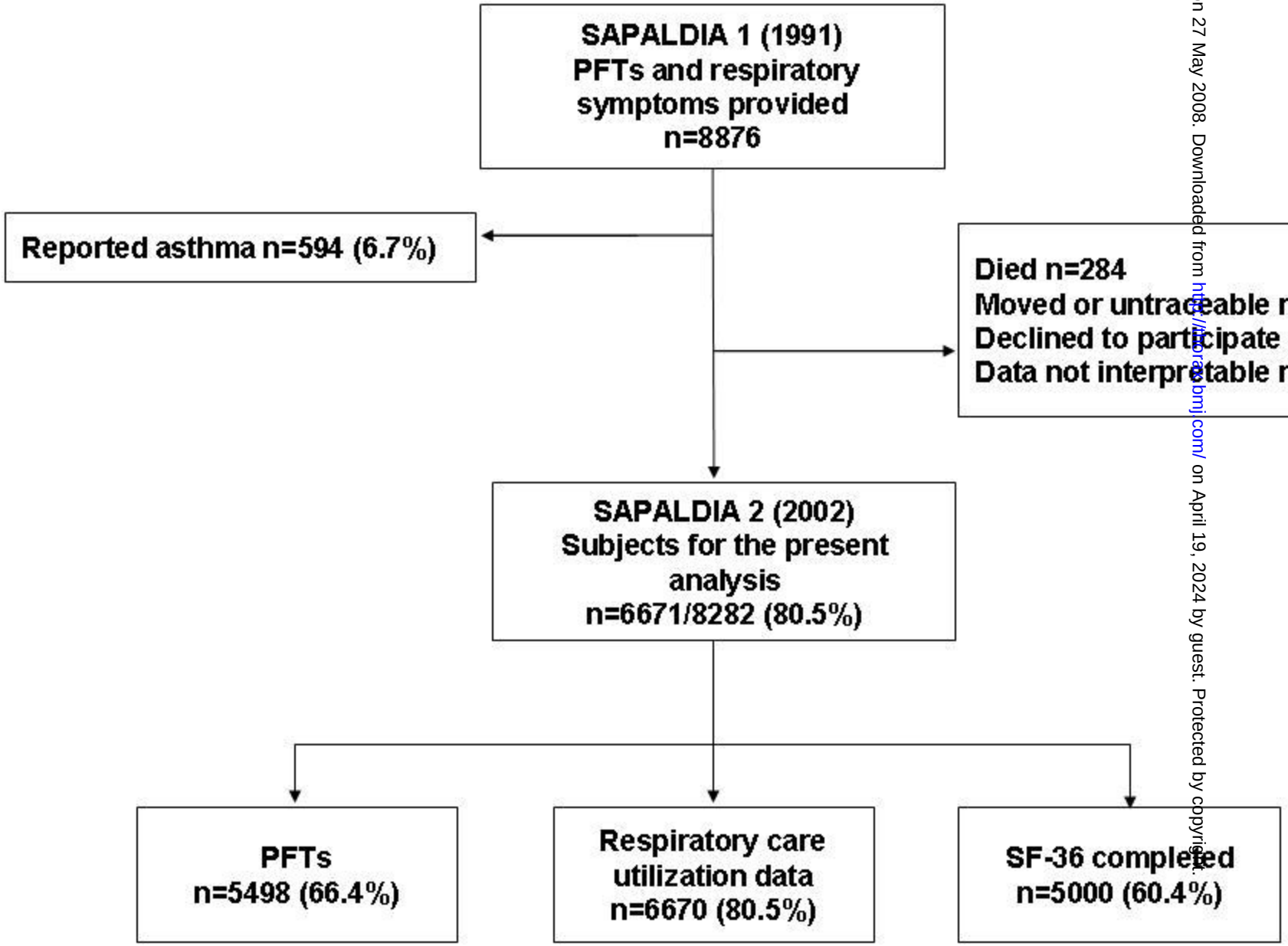
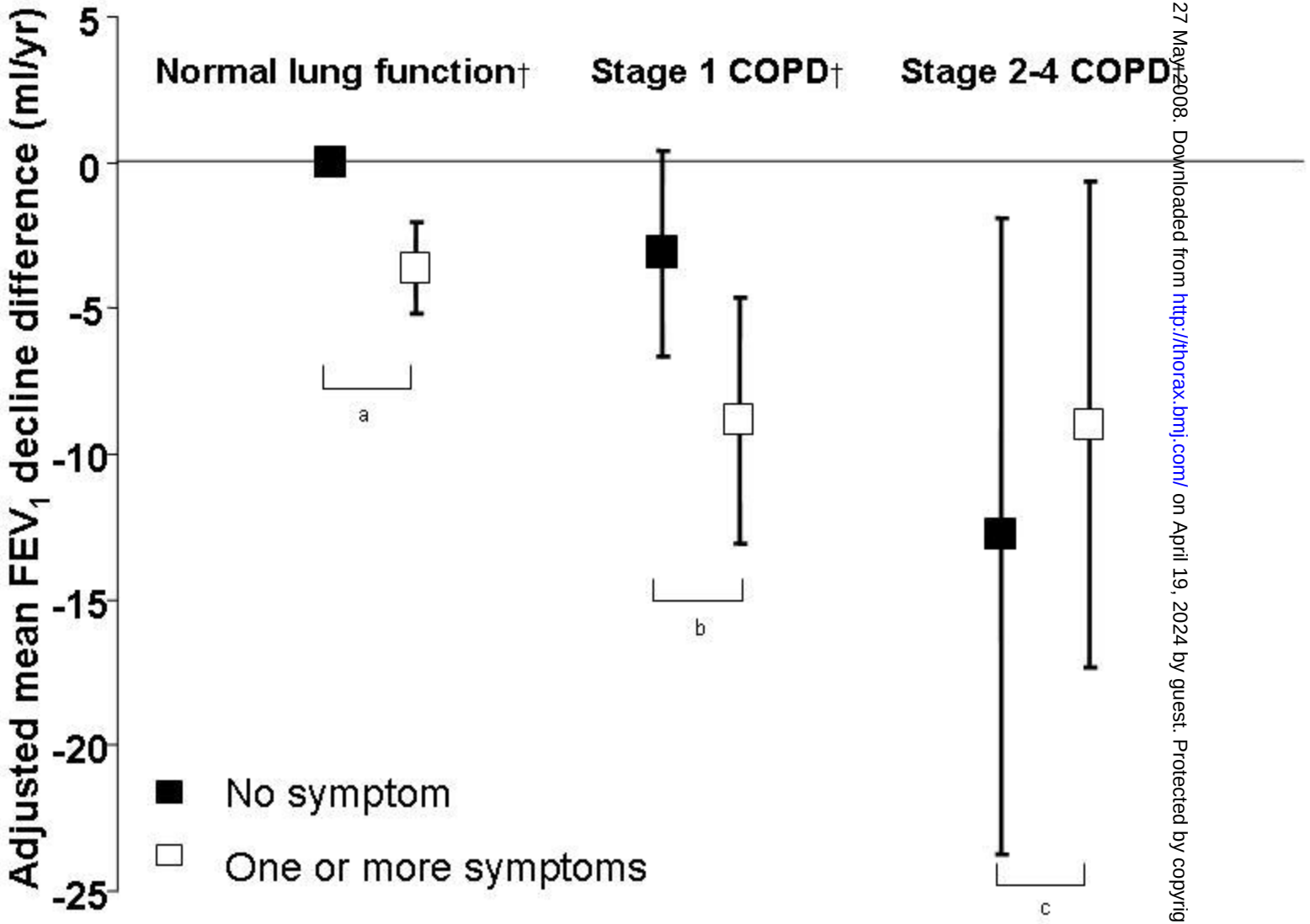
**Figure 1: Flow chart of participants included in the present study (SAPALDIA, 1991-2002)**



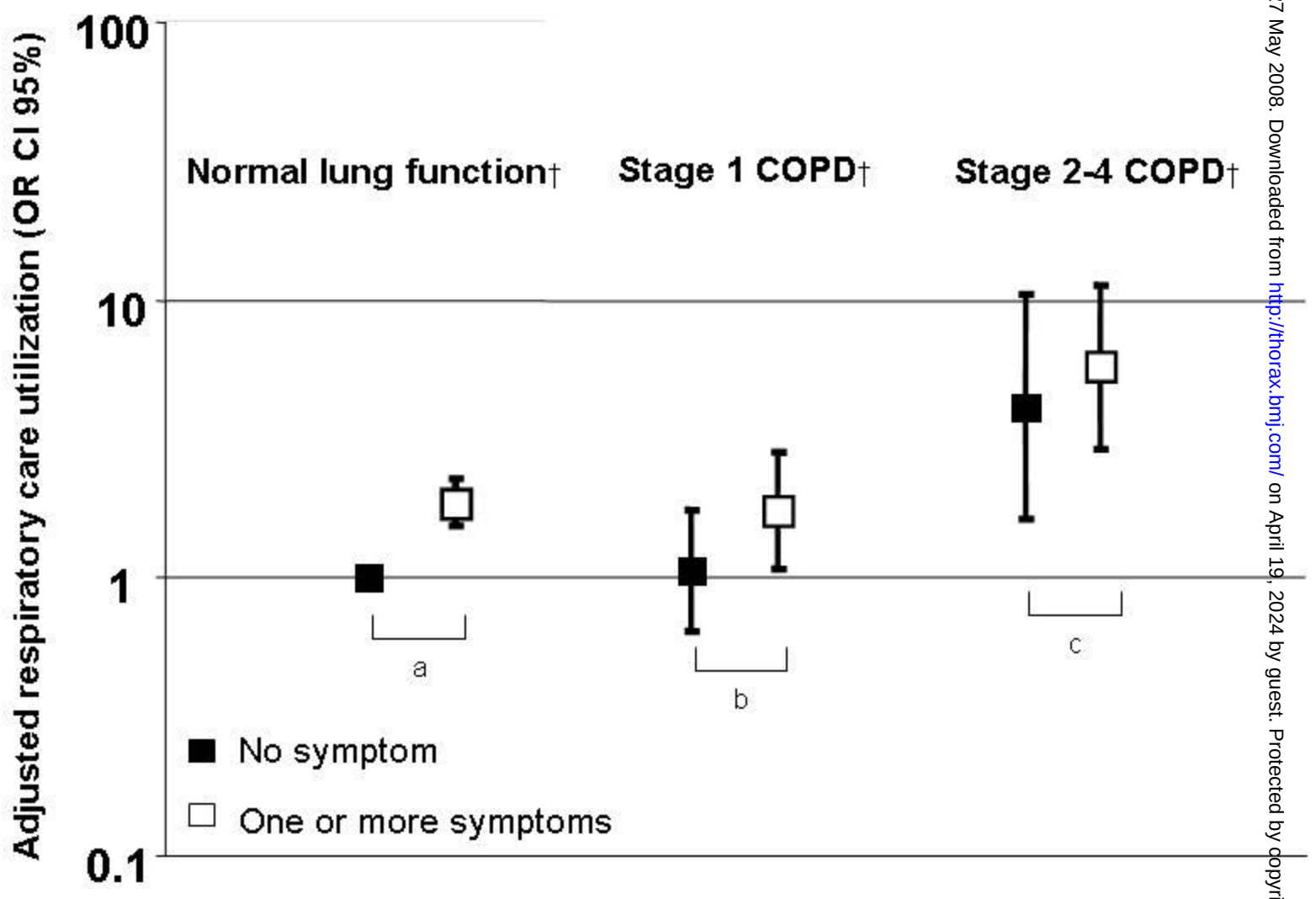

PFTs : Pulmonary functions tests, SF-36 : Medical Outcomes Study 36-item Short-Form General Health Survey

**Figure 2: Adjusted $FEV_1$ decline difference* (ml/yr with 95% confidence interval) over 11 years, stratified by modified GOLD† and symptom‡ categories at SAPALDIA 1 (1991)**



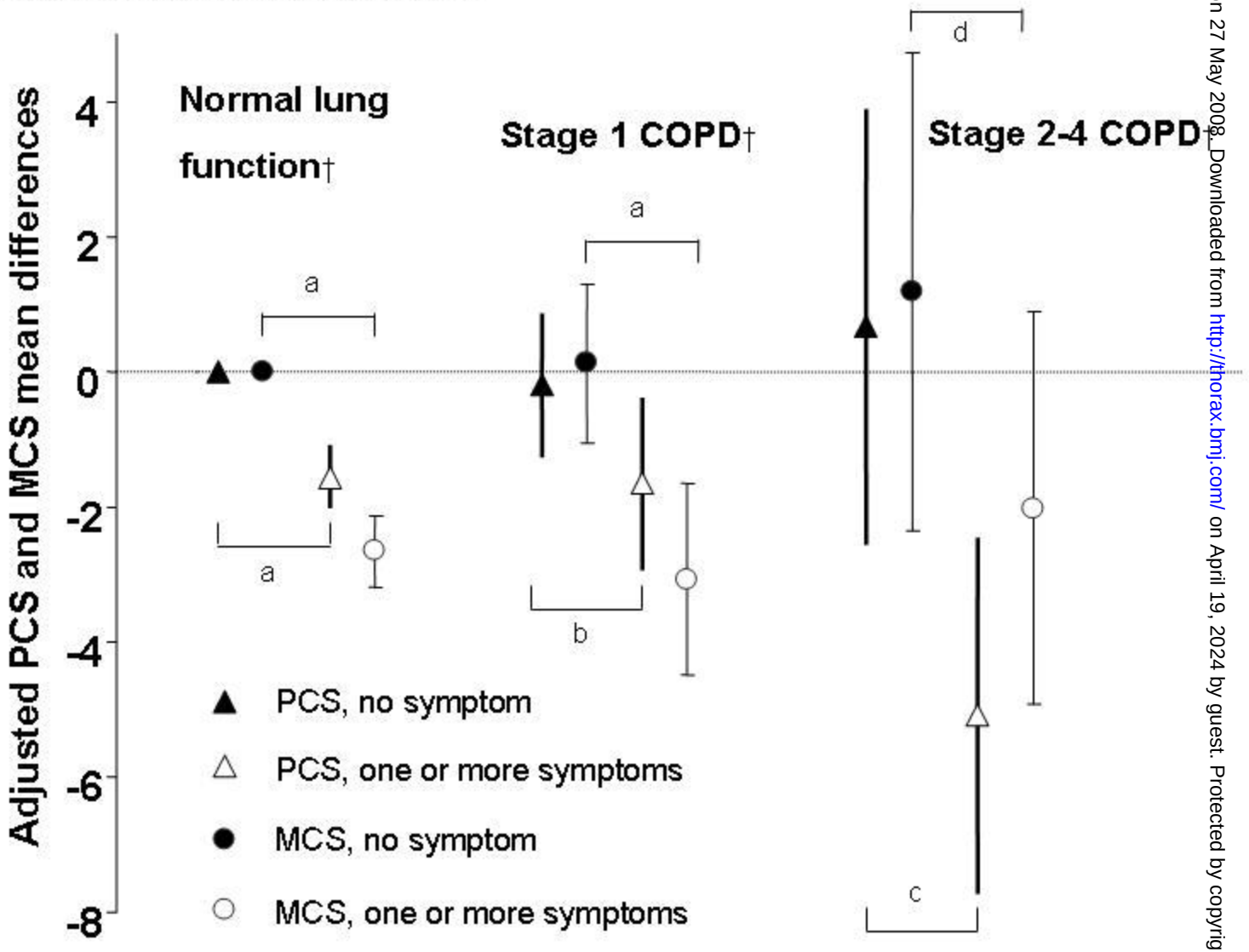

*adjusted for age, age squared, gender, baseline $FEV_1$, smoking status, lifetime smoking (pack/yr), baseline BMI, weight change, education level, nationality and study area (random effect). †: pre-bronchodilator spirometry. ‡: one or more symptoms = report of chronic cough or phlegm or shortness of breath while walking. Normal lung function: $FEV_1$/FVC ratio ≥0.7, $FEV_1$ value ≥80% predicted (Normal lung function, no symptom = full black square =reference category). stage 1: $FEV_1$/FVC ratio <0.7, $FEV_1$ value ≥80% predicted. stage 2-4: $FEV_1$/FVC ratio <0.7, $FEV_1$ value <80% predicted. a: P<0.001, b:P=0.031, c:P=0.576

**Figure 3: Adjusted* odds ratio of respiratory care utilization (with 95% confidence interval) at SAPALDIA 2 (2002), stratified by GOLD† and symptom‡ categories at SAPALDIA 1 (1991)**




*adjusted for age, age squared, gender, baseline $FEV_1$, smoking status, lifetime smoking (pack/yr), baseline BMI, weight change, education level, nationality and study area (random effect). †: pre-bronchodilator spirometry. ‡: one or more symptoms = report of chronic cough or phlegm or shortness of breath while walking. Normal lung function: $FEV_1$/FVC ratio ≥0.7, $FEV_1$ value ≥80% predicted (Normal lung function, No symptom = full black square =reference category). stage 1: $FEV_1$/FVC ratio <0.7, $FEV_1$ value ≥80% predicted. Stage 2-4: $FEV_1$/FVC ratio <0.7, $FEV_1$ value <80% predicted. a: P<0.001, b:P=0.179, c:P=0.543

**Figure 4: SF-36 summary scores adjusted differences (with 95% confidence interval) at SAPALDIA 2 (2002), stratified by GOLD† and symptom‡ categories at SAPALDIA 1(1991)**




*adjusted for age, age squared, gender, baseline $FEV_1$, smoking status, lifetime smoking (pack/yr), baseline BMI, weight change, education level, nationality and study area (random effect). PCS (SF-36 Physical Component Summary), MCS (SF-36 Mental Component Summary). †: pre-bronchodilator spirometry. ‡: one or more symptoms = report of chronic cough or phlegm or shortness of breath while walking. Normal lung function: $FEV_1$/FVC ratio ≥0.7, $FEV_1$ value ≥80% predicted (Normal lung function, No symptom = full black triangle or circle =reference category). stage 1: $FEV_1$/FVC ratio <0.7, $FEV_1$ value ≥80% predicted. stage 2-4: $FEV_1$/FVC ratio <0.7, $FEV_1$ value <80% predicted. a: P<0.001, b:P=0.083, c:P=0.005, d:P=0.159

# *Online Repository Supplement*

## COPD: Long Term Lung Function Decline, Utilization of Care and Quality of Life in Modified GOLD stage 1

Pierre-Olivier Bridevaux, Margaret W Gerbase, Nicole M. Probst-Hensch, Christian Schindler, Jean-Michel Gaspoz, Thierry Rochat

**Respiratory questionnaires at SAPALDIA 1**

Subjects were considered symptomatic if they answered yes to one of the following questions:

*Chronic cough:*

"Do you usually cough first thing in the morning?" or

"Do you usually cough during the day, or at night?" or

"Do you cough like this on most days for as much as 3 months each year?"

*Chronic phlegm:*

"Do you usually bring up phlegm from your chest first thing in the morning?" or

"Do you bring up phlegm like this on most days for as much as 3 months each year?" or

"Do you usually bring up any phlegm from your chest during the day, or at night?"

*Chronic dyspnea*:

"Are you troubled by shortness of breath when hurrying on level ground or walking up a slight hill?" or

"Do you get short of breath walking with other people of your own age on level ground?" or

"Do you have to stop for breath when walking at your own pace on level ground?

**Table A (online supplement): Demographic characteristics of subjects, stratified by modified GOLD† and symptom categories at baseline (SAPALDIA 1 [1991])**

| SAPALDIA 1 Characteristics n=6671 | Normal lung function† n=6061 | | Stage 1 COPD† n=519 | | Stage 2-4 COPD† n=91 | |
|---|---|---|---|---|---|---|
| | No symptom n=3627 | With symptom* n=2434 | No symptom n=295 | With symptom* n=224 | No symptom n=30 | With symptom* n=61 |
| Age, mean (SD) | 39.4 (11.4) | 41.8 (11.4) | 48.2 (11.4) | 48.7 (9.7) | 45.9 (10.2) | 49.8 (10.2) |
| Male, % | 51.6 | 36.5 | 67.5 | 54.0 | 73.3 | 62.3 |
| BMI, kg/m$^2$ (SD) | 23.4 (3.4) | 24.1 (4.1) | 24.8 (3.1) | 25.1 (3.6) | 24.9 (3.3) | 25.2 (4.4) |
| Obesity (BMI ≥30 kg/m$^2$ ), % [n] | 4.1 [147] | 7.9 [192] | 7.1 [21] | 8.5 [19] | 10.0 [3] | 11.5 [7] |
| Swiss citizenship, % [n] | 88.0 [3193] | 83.6 [2034] | 88.1 [258] | 86.2 [193] | 87.0 [26] | 88.5 [54] |
| Low education, % [n] | 5.6 [202] | 10.7 [261] | 6.4 [19] | 15.2 [34] | 10.0 [3] | 14.8 [5] |
| **Smoking status** | | | | | | |
| Current smoker, % [n] | 26.0 [943] | 37.5 [913] | 37.5 [110] | 49.1 [110] | 36.7 [11] | 52.5 [32] |
| Former smoker, % [n] | 23.1 [839] | 20.7 [504] | 27.3 [80] | 23.2 [52] | 36.7 [11] | 26.2 [16] |
| Never smoker, % [n] | 50.8 [1843] | 41.8 [1017] | 35.2 [103] | 27.7 [62] | 26.7 [8] | 21.3 [13] |
| Lifetime smoking (pack-year), mean (SD) in ever smoker | 15.0 (15) | 18 (19) | 24 (20) | 32 (25) | 21 (13) | 41 (29) |
| **Pulmonary function tests** | | | | | | |
| $FEV_1$, (% predicted), mean (SD) | 109 (13) | 108 (14) | 101 (12) | 99 (12) | 71 (7) | 68 (9) |
| $FEV_1$/FVC ratio, mean (SD) | 81 (6) | 81 (6) | 67 (3) | 66 (4) | 59 (8) | 58 (9) |
| Restrictive pattern‡, % [n] | 0.7 [25] | 1.6 [38] | - | - | - | - |
| **Respiratory symptoms** | | | | | | |
| Chronic cough, % | - | 8.8 | - | 15.2 | - | 23.0 |
| Chronic phlegm, % | - | 13.4 | - | 17.9 | - | 23.0 |
| Chronic shortness of breath, % | - | 91.5 | - | 88.0 | - | 88.5 |
| Chronic bronchitis§, % | - | 19.0 | - | 29.5 | - | 34.4 |

BMI: Body-mass Index; $FEV_1$: Forced Expiratory Volume in 1 sec; FVC: Forced Vital Capacity. †: pre-bronchodilator spirometry

*: report of chronic cough or phlegm or shortness of breath while walking, see online supplement for detailed questions. ‡: $FEV_1/FVC \geq 0.7$ & FVC<80% predicted. §: chronic cough or phlegm

**Table B (online supplement): Odds ratio* of non participation to the pulmonary function test (PFTs), the respiratory care collection forms and the SF-36 questionnaires.**

| | OR* of no PFTs at follow up (CI 95%) | OR* of no response to respiratory care questions at follow up (CI 95%) | OR* of no response to SF-36 questionnaire at follow up (CI 95%) |
|---|---|---|---|
| | Non-participants n=2784/8282 | Non-participants n=1612/8282 | Non-participants n=3282/8282 |
| **Age categories** | | | |
| 55+ | 1 | 1 | 1 |
| 45 - 55 | 0.8 (0.6 – 1.0) | 0.8 (0.7 – 1.1) | 0.9 (0.7 – 1.2) |
| 35 - 45 | 0.8 (0.6 – 1.1) | 0.9 (0.7 – 1.1) | 1.0 (0.8 – 1.4) |
| 25 -35 | 1.0 (0.7 – 1.3) | 1.0 (0.8 – 1.2) | 1.1 (0.8 –1.4) |
| <25 | 1.2 (0.8 -1.6) | 1.4 (1.1 -1.8) | 1.4 (1.0 – 2.0) |
| **Gender** | | | |
| Male | 1 | 1 | 1 |
| Female | 1.0 (0.9 – 1.2) | 0.9 (0.7 – 1.1) | 1.1 (0.9 – 1.3) |
| **Nationality** | | | |
| Swiss | 1 | 1 | 1 |
| Non-Swiss | 2.4 (2.0 – 3.0) | 2.9 (2.5 – 3.4) | 2.7 (2.2 – 3.3) |
| **Smoking status** | | | |
| Never smoker | 1 | 1 | 1 |
| Former smoker | 1.2 (0.9 – 1.5) | 1.3 (1.1 – 1.5) | 1.2 (1.0 – 1.4) |
| Current smoker | 1.5 (1.3 – 1.8) | 1.5 (1.3 – 1.8) | 1.5 (1.3 – 1.8) |
| **Body mass index** | | | |
| Normal (<24.9 kg/m$^2$) | 1 | 1 | 1 |
| Overweight (25 to 29.9 kg/m$^2$) | 1.2 (1.0 – 1.5) | 1.1 (0.8 – 1.4) | 1.1 (0.9 – 1.4) |
| Obese (>30 kg/m$^2$) | 1.8 (1.3 – 2.5) | 1.6 (1.0 – 2.6) | 1.8 (1.3 – 2.5) |
| **GOLD and symptom categories** | | | |
| Normal lung function† | 1 | 1 | 1 |
| Stage 1† | 0.9 (0.6 – 1.2) | 1.1 (0.8 – 1.4) | 1.0 (0.7 – 1.3) |
| Stage 2-4 † | 1.3 (0.7 – 2.4) | 1.6 (1.0 – 2.6) | 2.0 (0.7 – 1.3) |
| | | | |
| No respiratory symptoms‡ | 1 | 1 | 1 |
| Respiratory symptoms‡ | 1.2 (1.0 – 1.4) | 1.2 (1.1 – 1.4) | 1.1 (0.9 – 1.4) |

*Multivariate logistic regression model controlling for the above-mentioned variable and the study area (random effect); †: pre-bronchodilator spirometry

‡: one or more symptoms = report of chronic cough or phlegm or shortness of breath while walking

**Table C (online supplement): Participation rate by modified GOLD† and symptom categories at SAPALDIA 1 (1991)**

| n=6671 | | Potential participants | Pulmonary function tests, n, (%) | Respiratory care utilization data, n, (%) | SF-36 questionnaire, n, (%) |
|---|---|---|---|---|---|
| **All, n, (%)** | | 8282 | 5498 (66.4) | 6670 (80.5) | 5000 (60.4) |
| **Normal lung function†** | **No symptom,** | 4377 | 3034 (69.3) | 3626 (82.8) | 2779 (63.5) |
| | **with symptom‡** | 3089 | 1963 (63.6) | 2434 (78.8) | 1783 (57.7) |
| **Stage 1 COPD†** | **No symptom** | 363 | 257 (70.8) | 295 (81.3) | 222 (61.2) |
| | **with symptom‡** | 319 | 173 (54.2) | 224 (70.2) | 156 (48.9) |
| **Stage 2-4 COPD†** | **No symptom** | 37 | 25 (67.6) | 30 (81.1) | 22 (59.5) |
| | **with symptom‡** | 97 | 46 (47.4) | 61 (62.9) | 38 (39.2) |

†: pre-bronchodilator spirometry, ‡: one or more symptoms = report of chronic cough or phlegm or shortness of breath while walking

**Table D: Unadjusted and adjusted long-term outcomes associated with modified GOLD† and symptom categories**

| | | FEV1 decline (ml/year) | |
|---|---|---|---|
| | | **Unadjusted, mean (SD)** | **Adjusted *, mean, (CI95%)** |
| **Normal lung function†** | **No symptom,** | -34 (29) | ref |
| | **with symptom‡** | -37 (30) § | -3.6 (-5.2 ; -2.1) § |
| **Stage 1 COPD†** | **No symptom** | -38 (36) | -3.1 (-6.6 ;+0.5) |
| | **with symptom‡** | -44 (38) § | -8.9 (-13.1 ; -4.6) § |
| **Stage 2-4 COPD†** | **No symptom** | -25 (43) | -12.8 (-23.7 ; -1.9) § |
| | **with symptom‡** | -29 (39) | -9.0 (-17.3 ; -0.70) § |

| | | Respiratory care utilization | | |
|---|---|---|---|---|
| | | **Users, %** | **Unadjusted OR (CI95%)** | **Adjusted OR* (CI95%)** |
| **Normal lung function†** | **No symptom,** | 7.3 | ref | ref |
| | **with symptom‡** | 14.7 | 2.18 (1.84 2.58) § | 1.86 (1.53 2.26) § |
| **Stage 1 COPD†** | **No symptom** | 8.1 | 1.12 (0.73 1.74) | 1.05 (0.63 1.73) |
| | **with symptom‡** | 12.5 | 1.81 (1.20 2.75) § | 1.62 (1.01 2.61) § |
| **Stage 2-4 COPD†** | **No symptom** | 23.4 | 3.86 (1.64 9.07) § | 4.05 (1.59 10.30) § |
| | **with symptom‡** | 34.4 | 6.65 (3.86 11.45) § | 5.67 (2.86 11.22) § |

†: pre-bronchodilator spirometry. *adjusted for age, age squared, gender, baseline $FEV_1$, smoking status, lifetime smoking (pack/yr), baseline BMI, weight change, education level, nationality and study area (random effect). ‡: report of chronic cough or phlegm or shortness of breath while walking. §:P<.05 vs the reference category "Normal lung function, no symptom"

**Table D (cont.d): Unadjusted and adjusted long-term outcomes associated with modified GOLD† and symptom categories**

| | | SF 36 Physical Component Summary | |
|---|---|---|---|
| | | **Unadjusted, mean (SD)** | **Adjusted *, mean, (CI95%)** |
| **Normal lung function†** | **No symptom,** | 53.1 (6.7) | ref |
| | **with symptom‡** | 50.6 (9.1) § | -1.6 (-2.0 -1.1) § |
| **Stage 1 COPD†** | **No symptom** | 51.2 (8.2) § | -0.2 (-1.3 0.8) |
| | **with symptom‡** | 48.7 (10.8) § | -1.6 (-2.9 -0.4) § |
| **Stage 2-4 COPD†** | **No symptom** | 51.4 (4.4) | 0.6 (-2.6 3.8) |
| | **with symptom‡** | 44.2 (12.1) § | -5.2 (-7.8 -2.5) § |

| | | SF 36 Mental Component Summary | |
|---|---|---|---|
| | | **Unadjusted, mean (SD)** | **Adjusted *, mean, (CI95%)** |
| **Normal lung function†** | **No symptom,** | 51.5 (7.7) | ref |
| | **with symptom‡** | 48.7 (9.4) § | -2.6 (-3.2 -2.1) § |
| **Stage 1 COPD†** | **No symptom** | 52.5 (7.6) § | 0.1 (-1.1 1.3) |
| | **with symptom‡** | 48.9 (10.1) § | -3.1 (-4.5 -1.6) § |
| **Stage 2-4 COPD†** | **No symptom** | 53.9 (6.3) | 1.2 (-2.4 4.7) |
| | **with symptom‡** | 50.5 (9.8) | -2.1 (-4.9 0.8) |

†: pre-bronchodilator spirometry. *adjusted for age, age squared, gender, baseline $FEV_1$, smoking status, lifetime smoking (pack/yr), baseline BMI, weight change, education level, nationality and study area (random effect). ‡: report of chronic cough or phlegm or shortness of breath while walking. §:P<.05 vs the reference category "Normal lung function, no symptom"

**Table E (online supplement): Sensitivity analysis including subjects with physician diagnosed asthma. Adjusted $FEV_1$ decline difference*, respiratory care utilization and quality of life over 11 years, stratified by modified GOLD† and symptom categories at SAPALDIA 1 (1991)**

| | | $FEV_1$ decline (ml/year) mean, (CI95%) n= 5759 | Respiratory care utilization, OR (CI95%) n=6051 | PCS mean, (CI95%) n= 5172 | MCS mean, (CI95%) n= 5172 |
|---|---|---|---|---|---|
| **Normal lung function†** | **No symptom,** | ref | ref | ref | ref |
| | **with symptom‡** | -3.6 (-5.1 , -2.0) | 2.1 (1.7 , 2.5) | -1.6 (-2.1 , -1.2) | -2.7 (-3.2 , -2.2) |
| **Stage 1 COPD†** | **No symptom** | -3.1 (-6.5 , +0.4) | 1.2 (0.8 , 1.9) | -0.1 (-1.2 , +0.9) | -0.2 (-1.3 , 1.0) |
| | **with symptom‡** | -11.2 (-15.2 , -7.3) | 2.5 (1.7 , 3.7) | -1.9 (-3.1 , -0.7) | -2.8 (-4.1 , -1.5) |
| **Stage 2-4 COPD†** | **No symptom** | -12.6 (-22.9 , -2.4) | 4.1 (1.8 , 9.5) | +0.7 (-2.3 , 3.7) | +0.8 (-2.5 , 4.1) |
| | **with symptom‡** | -8.4 (-15.4 , -1.4) | 9.6 (5.5 , 16.7) | -5.3 (-7.6 , -3.1) | -3.2 (-5.7 , -0.8) |

*adjusted for age, age squared, gender, baseline FEV1, smoking status, lifetime smoking (pack/yr), baseline BMI, weight change, education level, nationality and study area (random effect). †: one or more symptoms = report of chronic cough or phlegm or shortness of breath while walking. †: pre-bronchodilator spirometry, ‡: report of chronic cough or phlegm or shortness of breath while walking. see online supplement for detailed questions

**Table F: Sensitivity analysis for emergency room visit or hospitalization for respiratory during the year preceding SAPALDIA 2, stratified by modified GOLD† and symptom categories at SAPALDIA 1 (1991)**

| | | Emergency room visit or hospitalizations | | |
|---|---|---|---|---|
| | | n, (%) | Unadjusted OR (CI95%) | Adjusted OR* (CI95%) |
| **Normal lung function†** | **No symptom** | 28 (0.8) | ref | ref |
| | **with symptom‡** | 39 (1.6) | 2.1 (1.3 – 3.4) | 1.9 (1.1 –3.5) |
| **Stage 1 COPD†** | **No symptom** | 5 (1.7) | 2.2 (0.8 – 5.8) | 0.8 (0.2 – 3.7) |
| | **with symptom‡** | 7 (3.1) | 4.1 (1.8 – 9.6) | 2.8 (1.0 – 8.0) |
| **Stage 2-4 COPD†** | **No symptom** | 0 | - | - |
| | **with symptom‡** | 6 (9.8) | 14.0 (5.6 – 35.2) | 4.7 (1.2 –18.2) |

†: pre-bronchodilator spirometry. *adjusted for age, age squared, gender, baseline $FEV_1$, smoking status, lifetime smoking (pack/yr), baseline BMI, weight change, education level, nationality and study area (random effect). ‡: report of chronic cough or phlegm or shortness of breath while walking. §:P<.05 vs the reference category "Normal lung function, no symptom"