Longitudinal change of prebronchodilator spirometric obstruction and health outcomes: results from the SAPALDIA cohort

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ABSTRACT

Background Understanding the prognostic meaning of early stages of chronic obstructive pulmonary disease (COPD) in the general population is relevant for discussions about underdiagnosis. To date, COPD prevalence and incidence have often been estimated using prebronchodilator spirometry instead of postbronchodilator spirometry. In the SAPALDIA (Swiss Study on Air Pollution and Lung Disease in Adults) cohort, time course, clinical relevance and determinants of seventy stages of obstruction were investigated using prebronchodilator spirometry.

Methods Incident obstruction was defined as an FEV1/FVC (forced expiratory volume in 1 s/forced vital capacity) ratio ≤0.70 at baseline and <0.70 at follow-up, and non-persistence was defined inversely. Determinants were assessed in 5490 adults with spirometry and respiratory symptom data in 1991 and 2002 using Poisson regression controlling for self-declared asthma and wheezing. Change in obstruction severity (defined analogously to the GOLD (Global Initiative for Chronic Obstructive Lung Disease) classification) over 11 years was related to shortness of breath and health service utilisation for respiratory problems by logistic models.

Results The incidence rate of obstruction was 14.2 cases/1000 person years. 20.9% of obstructive cases (n = 113/540) were non-persistent. Age, smoking, chronic bronchitis and non-current asthma were determinants of incidence. After adjustment for asthma, only progressive stage I or persistent stage II obstruction was associated with shortness of breath (OR 1.71, 95% CI 0.83 to 3.54; OR 3.11, 95% CI 1.50 to 6.42, respectively) and health service utilisation for respiratory problems (OR 2.49, 95% CI 1.02 to 6.10; OR 4.17 95% CI 1.91 to 9.13, respectively) at follow-up.

Conclusions The observed non-persistence of obstruction suggests that prebronchodilator spirometry, as used in epidemiological studies, might misclassify COPD. Future epidemiological studies should consider both prebronchodilator and postbronchodilator spirometry measurements and take specific clinical factors related to asthma and COPD into consideration for estimation of disease burden and prediction of health outcomes.
Figure 1 Association of categories of change in severity of obstruction with health service use for respiratory problems at follow-up. Obstruction was defined as forced expiratory volume in 1 s/forced vital capacity (FEV1/FVC) <0.70 based on prebronchodilatation spirometry. Effect estimates are adjusted for: sex, age, smoking (light or heavy ever smoker), chronic bronchitis and shortness of breath at baseline, health service use for respiratory problems at baseline, asthma and wheezing at baseline or follow-up examination, education and area.

Categories of change in obstruction severity during follow-up

Categories of change in severity of obstruction during follow-up were defined as follows: “incident stage I” (normal FEV1/FVC ratio at baseline and stage I at follow-up, n = 683), “incident stage II” (normal FEV1/FVC at baseline and stage II at follow-up, n = 85), “persistent stage I” (stage I at baseline and follow-up, n = 294), “stage I progressing” (stage I at baseline and stage II at follow-up, n = 56), “persistent stage II” (stage II at both examinations, n = 61) and “non-persistent” (stage I or more at baseline and normal FEV1/FVC at follow-up, n = 113). Cases of stage II at baseline but stage I at follow-up (n = 16) were not analysed.

Chronic bronchitis and shortness of breath

Chronic bronchitis was defined as self-report of cough or phlegm during the day or at night on most days for as much as 3 months each year for ≥2 years.

Shortness of breath was defined as an affirmative answer to the question “Are you troubled by shortness of breath when hurrying on level ground or walking up a slight hill?”

Asthma status

Presence of asthma at baseline and follow-up, respectively, was defined by the question “Have you ever had asthma?” Asthma cases reporting attacks during the 12 months before interview or current use of asthma medication were classified as current asthma, the others as non-current. To identify hidden asthma, we considered subjects reporting wheezing without cold in the 12 months preceding each interview.

Smoking status

Ever smokers reported smoking ≥20 packs of cigarettes or ≥360 g of tobacco in their lifetime at baseline, former smokers as quitting smoking at least 1 month before, and current smokers reported active smoking. Smoking intensity was assessed by pack-years smoked up to baseline and classified a priori into ≥15 and <15 pack-years for heavy and light smoking, respectively.

Health service use for respiratory problems

Health service use for respiratory problems was defined as a positive answer to one of the following questions: “Have you visited a hospital casualty department or emergency room because of breathing problems in the last 12 months?” “Have you spent a night in hospital because of breathing problems in the last 12 months?”

relevance of severity of spirometric obstruction according to modified GOLD criteria while controlling for the effects of overt and undiagnosed asthma.

MATERIALS AND METHODS

Study population

The SAPALDIA cohort consists of a random sample of 18- to 62-year-old adults from eight communities. For this study, we included participants with valid spirometry and respiratory symptom data from both baseline (1991) and follow-up (2002) surveys (online figure 1).

The SAPALDIA cohort study complies with the Declaration of Helsinki. Written informed consent was obtained from participants in both surveys. The study was approved by the central ethics committee of the Swiss Academy of Medical Sciences and the respective Cantonal Ethics Committees of the eight study regions.

Spirometry

The spirometry protocol was equivalent to that of the European Community Respiratory Health Survey (ECRHS). No bronchodilatation was applied. Identical spirometers (Sensormedics model 2200, Yorba Linda, California, USA) and protocols were used for both surveys; comparability was assessed before and after each survey. Three to eight forced expiratory lung function manoeuvres were performed, and at least two acceptable measurements of FVC and FEV1 were obtained, complying with American Thoracic Society criteria.

Obstruction to airflow and its severity

Spirometric obstruction was defined as FEV1/FVC <0.7 in prebronchodilatation measurement. An incident case of obstruction was defined as a person with an FEV1/FVC ratio ≥0.70 at baseline, but <0.70 at follow-up examination. Cases of non-persistence were defined inversely.

For measurements with FEV1/FVC <0.7, severity of obstruction was defined analogously to the GOLD guidelines, applying the prediction equation of Quanjer et al. FEV1 values of ≥80% of the predicted value were classified as stage I and values below this threshold as stage II and more, integrating stages III (FEV1 <50% predicted) and IV (FEV1 <30% predicted) into stage II.
the last 12 months,” “Have you been seen by a general practi-
tioner because of breathing problems or because of shortness of
breath in the last 12 months?” and “Have you seen a specialist (chest
physician, allergy specialist, internal medicine specialist, ENT
doctor) because of your breathing problems or shortness of
breath in the last 12 months?”

Health service use for cardiovascular problems
Data from equivalent questions assessing health service use for
cardiovascular problems at follow-up were used for sensitivity
analysis only.

Statistical analysis
Baseline characteristics were compared between the whole
SAPALDIA study population and participants included in the present
study, and analogously between COPD transition
categories.

The incidence rate of spirometric obstruction was estimated
as the number of new cases per total person-years (PY) at risk in
thousands. The non-persistence rate was calculated equivalently.
Rate ratios for both outcomes were estimated using Poisson
regression with the following baseline characteristics: sex, age
(in categories of 18–30, >30–40, >40–50 and >50 years),
smoking status (never smoker, light or heavy ever-smoker),
symptoms of chronic bronchitis at baseline, educational level
and study centre. Variables coding for asthma and wheezing at
baseline and follow-up were included in the models to assess their
independent impact on the outcomes, and to adjust for overt and
hidden asthma. The analysis was repeated using the 5th
percentile (lower limit of normal, calculated as 1.645 residual
standard deviations or more below predicted according to
Quanjer et al23) of the FEV1/FVC ratio distribution to define
obstruction. Logistic regression was used to compare presence of
shortness of breath and healthcare services utilisation for respi-
ratory problems at follow-up between categories of change in
severity of obstruction. Models were adjusted for demographic
characteristics (sex, age, education, examination area), baseline
health service use for respiratory problems (only in health service
utilisation models), smoking habits (light/heavy smoker at
baseline, pack-years between surveys), pre-existing symptoms
(chronic bronchitis, shortness of breath), and asthma or
wheezing at either examination.

As sensitivity analysis, confounding by cardiovascular co-
morbidity was assessed for healthcare utilisation for respiratory
problems and respiratory symptoms by including service
utilisation for cardiovascular problems at follow-up. Further-
more, study participants having only baseline spirometry were
compared with the present study sample to predict the proba-
bility of participation for each individual. A dichotomous vari-
able coding participation was regressed on baseline covariates
used in the regression models. Regression analyses were then
repeated using the inverse participation probabilities as
weights.

The statistical analysis was performed using SAS Software,
Version 9.1 (SAS Institute, Cary, North Carolina, USA) and
STATA version 9.2 (StataCorp, College Station, Texas, USA).

RESULTS
Baseline characteristics
Baseline characteristics of SAPALDIA participants and subjects
included in the current analysis are presented in online table O1.
Fifty-three percent of the participants were women and the
average age at baseline was 41.1 years (range 18–62 years).
Thirty percent of the study population was actively smoking at
baseline; 52% had ever smoked. Missing at follow-up examina-
tion was more frequent in participants with higher obstruction
stages (online table O2). As previously described in detail,
women, never smokers, well educated subjects and people with
good respiratory health and no atopy were slightly over-repre-
sented among follow-up participants and therefore in this
study.17

Baseline characteristics according to categories of change in
severity of obstruction are presented in table 1. The proportion of
females was markedly decreased in all categories except “persis-
tently normal” and “incident stage I”. Lung function values
presented a pattern expected from the severity definitions, ex-
citely for categories “persistent stage I” and “non-persistent” which had a
mean FEV1 close to 100% of the predicted value and the highest
FVC values (125.9% and 122.4% predicted, respectively). Both
categories also had the highest absolute FVC values (4.97 and

Table 1 Baseline characteristics according to change in severity of obstruction* during follow-up

<table>
<thead>
<tr>
<th></th>
<th>Persistently normal</th>
<th>Incident stage I</th>
<th>Incident stage II</th>
<th>Persistent stage I</th>
<th>Stage I progressing</th>
<th>Persistent stage II</th>
<th>Non-persistent</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>4181</td>
<td>683</td>
<td>85</td>
<td>294</td>
<td>56</td>
<td>61</td>
<td>113</td>
</tr>
<tr>
<td>Female sex (%)</td>
<td>54.7</td>
<td>54.2</td>
<td>44.7</td>
<td>39.1</td>
<td>33.9</td>
<td>32.8</td>
<td>40.7</td>
</tr>
<tr>
<td>Age in years (mean/SD)</td>
<td>39.2/11.2</td>
<td>45.3/10.3</td>
<td>44.5/11.9</td>
<td>48.8/9.6</td>
<td>48.5/9.2</td>
<td>49.5/9.1</td>
<td>47.0/9.1</td>
</tr>
<tr>
<td>No professional education (%)</td>
<td>12.1</td>
<td>16.4</td>
<td>23.5</td>
<td>15.6</td>
<td>21.4</td>
<td>19.7</td>
<td>8.8</td>
</tr>
<tr>
<td>FEV1 % of predicted value (mean/SD)</td>
<td>109.9/13.6</td>
<td>107.4/12.5</td>
<td>91.3/12.5</td>
<td>101.3/10.9</td>
<td>89.1/7.0</td>
<td>67.4/10.4</td>
<td>99.8/13.5</td>
</tr>
<tr>
<td>FVC % of predicted value (mean/SD)</td>
<td>114.0/0.2</td>
<td>118.2/0.1</td>
<td>110.0/0.1</td>
<td>125.0/0.1</td>
<td>116.0/0.1</td>
<td>96.0/0.1</td>
<td>122.4/0.2</td>
</tr>
<tr>
<td>FEV1/FVC % of predicted value (mean/SD)</td>
<td>100.9/10.1</td>
<td>94.0/0.1</td>
<td>94.0/0.1</td>
<td>84.1/0.0</td>
<td>80.2/0.1</td>
<td>73.0/0.1</td>
<td>84.8/0.0</td>
</tr>
<tr>
<td>Light smoker at baseline (&lt;15 pack-years) (%)</td>
<td>28.7</td>
<td>19.3</td>
<td>13.6</td>
<td>20.9</td>
<td>9.3</td>
<td>11.8</td>
<td>24.5</td>
</tr>
<tr>
<td>Heavy smoker at baseline (&gt;15 pack-years) (%)</td>
<td>18.2</td>
<td>31.8</td>
<td>42.4</td>
<td>38.4</td>
<td>62.5</td>
<td>52.5</td>
<td>28.2</td>
</tr>
<tr>
<td>Shortness of breath at baseline (%)</td>
<td>21.7</td>
<td>25.0</td>
<td>42.4</td>
<td>25.5</td>
<td>44.6</td>
<td>47.5</td>
<td>14.2</td>
</tr>
<tr>
<td>Chronic bronchitis at baseline (%)</td>
<td>7.3</td>
<td>11.6</td>
<td>20.0</td>
<td>13.3</td>
<td>19.6</td>
<td>27.9</td>
<td>9.7</td>
</tr>
<tr>
<td>Wheezing in last 12 months at baseline (%)</td>
<td>4.8</td>
<td>7.8</td>
<td>22.4</td>
<td>9.9</td>
<td>28.6</td>
<td>20.0</td>
<td>8.0</td>
</tr>
<tr>
<td>Non-current asthma at baseline (%)</td>
<td>5.6</td>
<td>10.5</td>
<td>17.6</td>
<td>12.2</td>
<td>21.4</td>
<td>27.9</td>
<td>9.7</td>
</tr>
<tr>
<td>Current asthma at baseline (%)</td>
<td>1.8</td>
<td>3.4</td>
<td>11.8</td>
<td>4.4</td>
<td>16.1</td>
<td>16.4</td>
<td>4.4</td>
</tr>
<tr>
<td>Health service use for respiratory problems at baseline (%)</td>
<td>18.0</td>
<td>22.0</td>
<td>27.1</td>
<td>26.9</td>
<td>33.9</td>
<td>42.6</td>
<td>23.0</td>
</tr>
</tbody>
</table>

*Obstruction was defined as FEV1/FVC < 0.70 based on prebronchodilation spirometry.
†Numbers do not add up to 100.0% due to smokers with missing pack-year information.
FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity.
4.84 litres, respectively, online Table O3). The proportion of never smokers was lowest in categories “stage I progressing” (19.6%), “persistent stage II” (51.1%) and “incident stage II” (51.8%).

**Determinants of incidence and non-persistence of obstruction**

To assess determinants of incidence and non-persistence of obstruction, we stratified the study sample by baseline FEV1/FVC (FEV1/FVC < 0.70 vs FEV1/FVC ≥ 0.70).

From the 4945 participants with baseline FEV1/FVC ≥ 0.70, 765 had incident obstruction at follow-up (table 2). This corresponds to a cumulative incidence of 15.5% and an incidence rate of 14.2 cases/1000 person years (PY). Incidence rates were 25.1 and 28.0 cases/1000 PY for participants with non-current and current asthma at baseline, respectively, but only 13.4 cases/1000 PY for subjects without asthma. In participants never reporting asthma or wheezing at either examination, the rate was 12.3 cases/1000 PY. Determinants of incidence were (relative rate (RR) and 95% CI): older age (RR 1.38 per 10 years, 95% CI 1.29 to 1.47), heavy smoking at baseline (RR 1.51, 95% CI 1.29 to 1.77), chronic bronchitis at baseline (RR 1.23, 95% CI 1.00 to 1.51), non-current asthma at baseline (RR 1.39, 95% CI 1.01 to 1.92), current asthma at follow-up (RR 1.68, 95% CI 1.13 to 2.50) and wheezing without cold at follow-up (RR 1.95, 95% CI 1.57 to 2.42). Among participants with FEV1/FVC < 0.70 at baseline (n = 540), 113 (20.9%) presented a normal value at follow-up, giving a non-persistence rate of 19.2 cases/1000 PY (online table O4). Of non-persistent cases, 93.5% were classified as stage I obstruction at baseline. Participants with current asthma at follow-up had a significantly lower rate of non-persistence (4.9 cases/1000 PY). In participants never reporting asthma or wheezing at either examination, the rate was 22.8 cases/1000 PY. Heavy smokers at baseline and wheezers at follow-up showed lower rates of non-persistence (14.0 and 9.8 cases/1000 PY, respectively), but the effects did not reach statistical significance after adjustment for all asthma variables.

When using the lower limit of normal of the FEV1/FVC ratio to define obstruction, lower incidence (7.2 cases/1000 PY) and higher non-persistence (51.5 cases/1000 PY) rates were observed (online table O5). Additionally, female sex was associated with incidence (RR 1.62, 95% CI 1.52 to 1.98). The effects for the other determinants were comparable with the previous analyses (reported in table 2 and online table O4).

**Categories of change in severity of obstruction and shortness of breath at follow-up**

All transition categories except “non-persistent obstruction” were associated with shortness of breath at follow-up in the crude model (table 3). The association was strongest for categories “stage I progressing” (OR 3.76, 95% CI 2.18 to 6.48) and “persistent stage II” (OR 5.43, 95% CI 3.15 to 9.37). After
Table 3  Association* of categories of change in severity of obstruction ‡ with shortness of breath while walking at follow-up

<table>
<thead>
<tr>
<th>Variable</th>
<th>Crude model RR (95% CI)</th>
<th>p Value</th>
<th>Adjusting for all but asthma covariates ‡ RR (95% CI)</th>
<th>p Value</th>
<th>Adjusting for asthma and wheezing at baseline or follow-up RR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incident stage I (n = 683)</td>
<td>1.59 (1.32 to 1.91)</td>
<td>0.000</td>
<td>1.24 (0.99 to 1.56)</td>
<td>0.056</td>
<td>1.12 (0.89 to 1.41)</td>
<td>0.344</td>
</tr>
<tr>
<td>Incident stage II (n = 85)</td>
<td>2.74 (1.74 to 4.30)</td>
<td>0.000</td>
<td>1.43 (0.84 to 2.45)</td>
<td>0.192</td>
<td>1.10 (0.63 to 1.90)</td>
<td>0.743</td>
</tr>
<tr>
<td>Persistent stage I (n = 294)</td>
<td>1.49 (1.13 to 1.94)</td>
<td>0.004</td>
<td>1.14 (0.62 to 1.90)</td>
<td>0.428</td>
<td>1.02 (0.73 to 1.44)</td>
<td>0.903</td>
</tr>
<tr>
<td>Stage I progressing (n = 56)</td>
<td>3.76 (2.18 to 6.48)</td>
<td>0.000</td>
<td>2.22 (1.10 to 4.45)</td>
<td>0.026</td>
<td>1.71 (0.83 to 3.54)</td>
<td>0.148</td>
</tr>
<tr>
<td>Persistent stage II (n = 61)</td>
<td>5.43 (3.15 to 9.37)</td>
<td>0.000</td>
<td>4.38 (2.19 to 8.75)</td>
<td>0.000</td>
<td>3.11 (1.50 to 6.42)</td>
<td>0.002</td>
</tr>
<tr>
<td>Non-persistent (n = 113)</td>
<td>1.02 (0.64 to 1.62)</td>
<td>0.947</td>
<td>1.40 (0.80 to 2.44)</td>
<td>0.237</td>
<td>1.39 (0.80 to 2.43)</td>
<td>0.246</td>
</tr>
</tbody>
</table>

*Reference category: persistently without obstruction to the airflow.
‡Obstruction was defined as FEV1/FVC (forced expiratory volume in 1 s/forced vital capacity) <0.70 based on prebronchodilation spirometry.
§Covariates adjusted for were: sex, age, smoking (light or heavy ever smoker), chronic bronchitis, shortness of breath while walking at baseline, education and area.
¶Current asthma was defined as presence of asthma attacks in the 12 months prior to assessment or current asthma medication. Non-current asthma cases were defined as self-declared asthma without attacks or asthma medication.

Categorisation of change in severity of obstruction and health service utilisation for respiratory problems at follow-up

The only two transition categories significantly associated with health service use for respiratory problems at follow-up were “stage I progressing” and “persistent stage II”, irrespective of covariates included in the logistic model (fig 1; online table O6). After adjustment for sex, age, education, area, baseline health service use for respiratory problems, smoking, baseline respiratory symptoms (chronic bronchitis, shortness of breath) as well as asthma, subjects progressing from stage I to stage II obstruction during follow-up were 2.5 times (OR 2.49, 95% CI 1.02 to 6.10) and those persistently in stage II 4.2 times (OR 4.17, 95% CI 1.91 to 9.13) more likely to utilise health services for respiratory problems, smoking, baseline covariates included in the logistic model (data not shown).

Sensitivity analysis

Inclusion of health service use for cardiovascular problems at follow-up did not alter the associations of categories of change in obstruction severity with health service use for respiratory problems or respiratory symptoms at follow-up. Weighted regression analyses yielded the same determinants of incidence and non-persistence, and the same associations between longitudinal obstruction categories and shortness of breath or health service use for respiratory problems at follow-up (data not shown).

DISCUSSION

In our general population sample, we observed an incidence of modified GOLD COPD (obstruction based on prebronchodilation spirometry) of 14.2 cases per 1000 PY. This estimate is at the higher end of comparable ones which range between 5 and 16 cases/1000 PY depending on age distribution, smoking prevalence, follow-up time and inclusion of those with asthma. This high incidence could only partly be explained by these factors. We replicated associations with age and smoking from previous studies, and found a significant association with chronic bronchitis, a finding not reported consistently so far. Female sex was significantly associated with incidence only when the FEV1/FVC ratio lower limit of normal was used to define disease. Previous evidence regarding gender differences in obstruction rates is inconsistent, but our finding could support the currently debated hypothesis that women are more susceptible to COPD.

Our observation that 20.9% of obstructive cases at baseline did not persist is noteworthy. In the second and third stages, we observed that FEV1/FVC values close to the 0.70 cut-off are predictive of both incidence and non-persistence (data not shown) and 95.8% of our non-persistent cases were mildly obstructive. Secondly, the use of postbronchodilator measurements prevents the identification of reversible obstruction (mostly undiagnosed asthma). The high FVC and normal FEV1, percentage predicted values in our non-persistent cases support this possibility. Also, category “non-persistent obstruction” was marginally associated with health service use for respiratory problems irrespective of asthma adjustment. We captured reversible obstruction as far as possible by considering wheezing without a cold at baseline or follow-up (data not shown).

Prebronchodilator measurements in epidemiological studies might thus misclassify COPD, especially in mild GOLD I stages, but our results suggest their longitudinal course may predict future health events on a population level independently of pre-existing symptoms, smoking or healthcare use. While shortness of breath and respiratory care utilisation were particularly high in participants progressing from stage I to stage II obstruction or persisting in stage II, those remaining in stage I did not have increased risks for either outcome at follow-up.

There is thus a need to better characterise the modified GOLD stage I category in epidemiological studies. In the past, epidemiological studies have omitted postbronchodilator spirometry due to time and resource constraints, or in favour of...
broncho-challenge testing. The procedure is, however, essential to differentiate asthma from COPD in clinical practice. Future epidemiological studies will thus additionally need longitudinal postbronchodilator measurements and consider characteristics such as medication intake and symptoms for asthma or the BODE index for COPD, which are important prognostic factors on the individual level, to define groups at high risk for adverse health outcomes or increased use of health services. Such extended assessments are foreseen in the third examination of SAPALDIA.

Our study benefited from stringent quality control in spirometry and detailed information on lifestyle factors. As discussed above, a limitation is the use of prebronchodilator measurements. The associations of change in severity of obstruction with health service use for respiratory problems or shortness of breath were robust to cardiovascular co-morbidity. The observed non-persistence of obstruction suggests that shortness of breath were robust to cardiovascular co-morbidity.

CONCLUSION

The non-persistence of obstruction suggests that prebronchodilator spirometry at only two time points in epidemiological studies might misclassify COPD. Still, our findings regarding shortness of breath and health service use for respiratory problems show that prebronchodilator spirometry, particularly its longitudinal course, has value in predicting health outcomes on a population level. To identify risk groups accurately, future epidemiological studies will have to consider both prebronchodilation and postbronchodilator spirometry, as well as individual prognostic factors used in today’s clinical practice.

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