

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 prebronchodilation spirometry instead of postbronchodilation spirometry. In the SAPALDIA (Swiss Study on Air Pollution and Lung Disease in Adults) cohort, time course, clinical relevance and determinants of severity 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 prebronchodilation spirometry, as used in epidemiological studies, might misclassify COPD. Future epidemiological studies should consider both prebronchodilation and postbronchodilation measurements and take specific clinical factors related to asthma and COPD into consideration for estimation of disease burden and prediction of health outcomes.

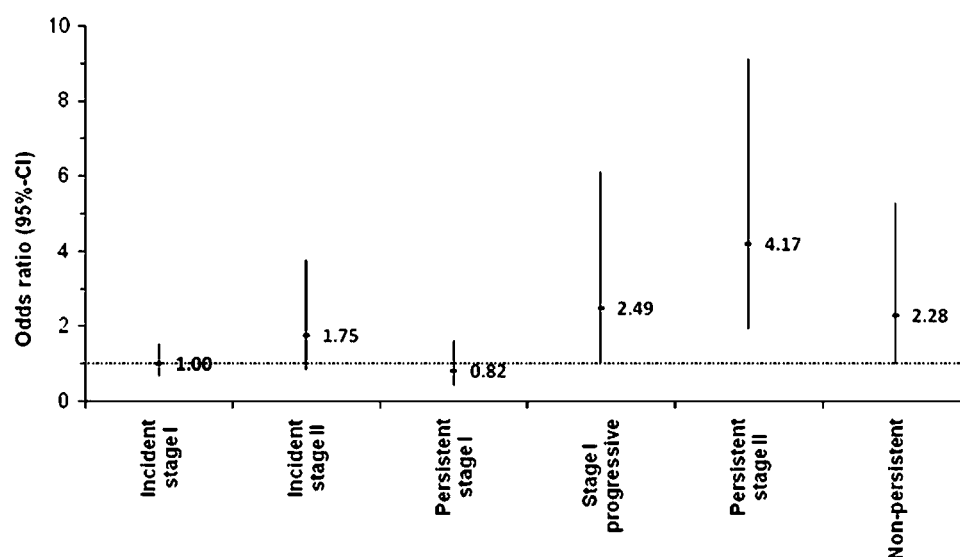
Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and premature mortality worldwide.¹ At diagnosis, often more than half of the lung function has been lost, and subsequent need for medical care is high.² This raises concerns about underdiagnosis, particularly regarding earlier

disease stages^{3–4} which are expected to be more amenable to preventive action and improvement of quality of life. Timely diagnosis may also reduce healthcare costs.⁵ For the clinical identification of early stages, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) provided an international standard for diagnosis based on a forced expiratory volume in 1 s (FEV₁) over forced vital capacity (FVC) ratio <0.70 measured by postbronchodilator spirometry.⁴ Severity classification depends on FEV₁, expressed as a percentage of the predicted value: $\geq 80\%$ mild GOLD stage I, $<80\%$ moderate stage II, $<50\%$ severe stage III, and $<30\%$ very severe stage IV disease.

Population-based epidemiological studies are fundamental to understand the time course and prognostic meaning of COPD GOLD stages in the general population. In recent years, a modified GOLD definition omitting bronchodilation has been widely adopted by these studies.¹ The ease of use and straightforwardness of the FEV₁/FVC cut-off facilitates standardization and comparability of observations,⁶ and overcomes the shortcomings of previous inconsistent case definitions producing a wide range of prevalence and incidence estimates, and complicating evaluation of healthcare needs.⁷ Although prebronchodilation measurements may overestimate COPD prevalence by up to 50%,^{8–9} and might be unreliable when assessing COPD determinants because of reversible airflow obstruction, it is not known whether they perform worse than post-bronchodilator measurements for predicting future health outcomes.¹ So far, GOLD stages II and higher have consistently been associated with mortality and reduced quality of life in epidemiological studies using prebronchodilation spirometry.^{10–13} The picture is less straightforward for stage I, which is most relevant for discussions about underdiagnosis. It has been associated with increased mortality in population studies,^{10–12–14} but partially respiratory symptoms might be responsible for that.^{12–14} Similarly, in the SAPALDIA (Swiss Study on Air Pollution and Lung Disease in Adults) cohort, it recently could be shown that stage I predicted rapid decline in FEV₁, a cardinal feature of COPD,⁴ lower quality of life and increased healthcare utilisation for respiratory problems 11 years later, but only in the presence of respiratory symptoms at baseline.¹⁵

In this current study based on prebronchodilation spirometry data from the SAPALDIA cohort, we investigated the time course and clinical

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 prebronchodilation 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.



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^{16–18} 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).¹⁹ No bronchodilation 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.^{20 21} 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.²²

Obstruction to airflow and its severity

Spirometric obstruction was defined as FEV₁/FVC <0.7 in prebronchodilation 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,⁴ applying the prediction equation of Quanjer *et al*²³: 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.

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,²⁴ 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?”, “Have you been seen by a general practitioner because of breathing problems or because of shortness of breath in the last 12 months?”, “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 al*²³) 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 respiratory 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 comorbidity was assessed for healthcare utilisation for respiratory problems and respiratory symptoms by including service utilisation for cardiovascular problems at follow-up. Furthermore, study participants having only baseline spirometry were compared with the present study sample to predict the probability of participation for each individual. A dichotomous variable coding participation was regressed on baseline covariates used in the regression models. Regression analyses were then repeated using the inversed 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 examination 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-represented 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 “persistently normal” and “incident stage I”. Lung function values presented a pattern expected from the severity definitions, except 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

	Persistently normal n = 4181	Incident stage I n = 683	Incident stage II n = 85	Persistent stage I n = 294	Stage I progressing n = 56	Persistent stage II n = 61	Non-persistent n = 113
Female sex (%)	54.7	54.2	44.7	39.1	33.9	32.8	40.7
Age in years (mean/SD)	39.2/11.2	45.3/10.3	44.5/11.9	48.8/9.6	48.5/9.2	49.5/9.1	47.0/9.1
No professional education (%)	12.1	16.4	23.5	15.6	21.4	19.7	8.8
FEV ₁ % of predicted value (mean/SD)	109.9/13.6	107.4/12.5	91.3/12.5	101.3/10.9	89.1/7.0	67.4/10.4	99.6/13.5
FVC % of predicted value (mean/SD)	114.0/0.2	119.2/0.1	100.6/0.1	125.9/0.1	116.0/0.1	96.0/0.1	122.4/0.2
FEV ₁ /FVC % of predicted value (mean/SD)	100.9/0.1	94.6/0.1	94.9/0.1	84.1/0.0	80.2/0.1	73.3/0.1	84.8/0.0
Never smoker (%)	49.9	44.7	35.3	36.7	19.6	31.1	38.9
Light smoker at baseline (<15 pack-years)† (%)	28.7	19.3	13.6	20.9	9.3	11.8	24.5
Heavy smoker at baseline (≥15 pack-years)† (%)	18.2	31.8	42.4	38.4	62.5	52.5	29.2
Shortness of breath at baseline (%)	21.7	25.0	42.4	25.5	44.6	47.5	14.2
Chronic bronchitis at baseline (%)	7.3	11.6	20.0	13.3	19.6	27.9	9.7
Wheezing in last 12 months at baseline	4.8	7.8	22.4	9.9	28.6	20.0	8.0
Non-current asthma at baseline (%)	5.6	10.5	17.6	12.2	21.4	27.9	9.7
Current asthma at baseline (%)	1.8	3.4	11.8	4.4	16.1	16.4	4.4
Health service use for respiratory problems at baseline (%)	18.0	22.0	27.1	26.9	33.9	42.6	23.0

*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.

Table 2 Incidence rate of obstruction ($FEV_1/FVC < 0.7$) using prebronchodilator spirometry during 11 years of follow-up according to a set of baseline characteristics

Predictor at baseline	Person-years at risk (in 1000)	No. of cases	Incidence rate (cases per 1000 person years) (95% CI)	Crude incidence rate ratio (95% CI)	Adjusted† incidence rate ratio (95% CI)
All (n = 4945)*	54.00	765	14.17 (13.20 to 15.21)		
Gender:					
Men	24.55	357	14.54 (13.11 to 16.13)	1.00 (Ref)	1.00 (Ref)
Women	29.45	408	13.85 (12.57 to 15.27)	0.95 (0.84 to 1.09)	1.03 (0.90 to 1.18)
Age (years) at baseline					
18–30	11.62	70	6.02 (4.77 to 7.61)	1.00 (Ref)	1.00 (Ref)
>30–40	14.70	165	11.22 (9.64 to 13.07)	1.86 (1.43 to 2.43)	1.72 (1.33 to 2.24)
>40–50	15.81	253	16.00 (14.15 to 18.10)	2.66 (2.08 to 3.40)	2.38 (1.85 to 3.06)
>50	11.86	277	23.35 (20.75 to 26.27)	3.88 (3.05 to 4.93)	3.77 (2.94 to 4.83)
Smoking status at baseline‡:					
Never smoker	28.02	362	12.92 (11.65 to 14.32)	1.00 (Ref)	1.00 (Ref)
Ever smoker:					
<15 pack-years	14.94	153	10.24 (8.74 to 12.00)	0.79 (0.66 to 0.95)	0.87 (0.73 to 1.04)
≥15 pack-years	11.03	250	22.66 (20.02 to 25.65)	1.75 (1.52 to 2.03)	1.51 (1.29 to 1.77)
Chronic bronchitis at baseline:					
Absent	49.62	671	13.52 (12.54 to 14.59)	1.00 (Ref)	1.00 (Ref)
Present	4.38	94	21.45 (17.53 to 26.26)	1.59 (1.30 to 1.93)	1.23 (1.00 to 1.51)
Asthma at baseline					
Absent	50.47	678	13.43 (12.46 to 14.48)	1.00 (Ref)	1.00 (Ref)
Present, but non-current	2.34	54	23.12 (17.70 to 30.18)	1.72 (1.33 to 2.22)	1.39 (1.01 to 1.92)
Present, current	1.18	33	28.02 (19.92 to 39.41)	2.09 (1.51 to 2.88)	0.79 (0.51 to 1.23)
Asthma at follow-up					
Absent	49.75	662	13.31 (12.33 to 14.36)	1.00 (Ref)	1.00 (Ref)
Present, but non-current	2.64	49	18.54 (14.01 to 24.53)	1.39 (1.07 to 1.82)	1.19 (0.85 to 1.65)
Present, current	1.60	54	33.77 (25.86 to 44.09)	2.54 (1.97 to 3.28)	1.68 (1.13 to 2.50)
Wheezing without a cold at baseline					
Absent	50.81	689	13.56 (12.59 to 14.61)	1.00 (Ref)	1.00 (Ref)
Present	2.96	71	23.99 (19.01 to 30.27)	1.77 (1.41 to 2.21)	1.04 (0.81 to 1.35)
Wheezing without a cold at follow-up					
Absent	50.34	655	13.01 (12.05 to 14.05)	1.00 (Ref)	1.00 (Ref)
Present	3.65	110	30.10 (24.97 to 36.29)	2.31 (1.92 to 2.79)	1.95 (1.57 to 2.42)

*Additional reduction of sample size due to exclusion of participants with >120 pack-years at baseline or >150 at follow-up.

†Smoking status at baseline: never smokers: <20 packs of cigarettes and <360 g of tobacco in lifetime.

‡Adjusted for study area, educational level and all predictors listed in the table.

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” (31.1%) and “incident stage II” (31.8%).

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 FEV_1/FVC ratio ($FEV_1/FVC < 0.70$ vs $FEV_1/FVC \geq 0.70$)

From the 4945 participants with baseline $FEV_1/FVC \geq 0.70$, 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 23.1 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 $FEV_1/FVC < 0.70$ 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, 93.8% 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 FEV_1/FVC ratio to define obstruction, lower incidence (7.2 cases/1000 PY) and higher non-persistence (31.5 cases/1000 PY) rates were observed (online table O5). Additionally, female sex was associated with incidence (RR 1.62, 95% CI 1.32 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

Variable	Crude model		Adjusting for all but asthma covariates‡		Adjusting for asthma and wheezing at baseline or follow-up	
	RR (95% CI)	p Value	RR (95% CI)	p Value	RR (95% CI)	p Value
Incident stage I (n = 683)	1.59 (1.32 to 1.91)	0.000	1.24 (0.99 to 1.56)	0.056	1.12 (0.89 to 1.41)	0.344
Incident stage II (n = 85)	2.74 (1.74 to 4.30)	0.000	1.43 (0.84 to 2.45)	0.192	1.10 (0.63 to 1.90)	0.743
Persistent stage I (n = 294)	1.48 (1.13 to 1.94)	0.004	1.14 (0.82 to 1.60)	0.428	1.02 (0.73 to 1.44)	0.903
Stage I progressing (n = 56)	3.76 (2.18 to 6.48)	0.000	2.21 (1.10 to 4.45)	0.026	1.71 (0.83 to 3.54)	0.148
Persistent stage II (n = 61)	5.43 (3.15 to 9.37)	0.000	4.38 (2.19 to 8.75)	0.000	3.11 (1.50 to 6.42)	0.002
Non-persistent (n = 113)	1.02 (0.64 to 1.62)	0.947	1.40 (0.80 to 2.44)	0.237	1.39 (0.80 to 2.43)	0.246
Asthma at baseline non-current§					1.08 (0.70 to 1.65)	0.739
Asthma at baseline current§					0.50 (0.27 to 0.91)	0.024
Asthma at follow-up non-current§					1.09 (0.73 to 1.63)	0.667
Asthma at follow-up current§					2.18 (1.28 to 3.72)	0.004
Wheezing without a cold at baseline					1.41 (1.03 to 1.94)	0.034
Wheezing without a cold at follow-up					2.07 (1.55 to 2.75)	0.000

*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.

adjusting for the baseline covariates sex, age, education, smoking, chronic bronchitis, shortness of breath and area, only categories “stage I progressing” and “persistent stage II” remained statistically significant (OR 2.21, 95% CI 1.10 to 4.45 and OR 4.38, 95% CI 2.19 to 8.75, respectively). Adjustment for current or non-current asthma and wheezing without a cold at either examination made the estimate for “stage I progressing” statistically non-significant (OR 1.71, 95% CI 0.83 to 3.54) and decreased effect sizes.

Categories 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 (figure 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 than subjects with normal spirometry. The association with category “non-persistent obstruction” was marginally significant (OR 2.28, 95% CI 0.98 to 5.27, $p = 0.054$) and remained largely unaltered by asthma adjustment.

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 prebronchodila-

tion spirometry) of 14.2 cases per 1000 PY. This estimate is at the higher end of comparable ones^{25–28} which range between 3 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,^{1 6 25–29} and found a significant association with chronic bronchitis, a finding not reported consistently so far.^{27–29} 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,^{25 27–29} but our finding could support the currently debated hypothesis that women are more susceptible to COPD.^{1 30}

Our observation that 20.9% of obstructive cases at baseline did not persist is noteworthy. Two factors probably explain non-persistence. The first is measurement error: like the ECRHS study,²⁸ 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 93.8% of our non-persistent cases were mildly obstructive. Secondly, the use of prebronchodilator 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 (besides self-declared asthma), but hidden non-wheezing asthma cases might still be present.

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 postbronchodilation 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 postbronchodilation measurements and consider characteristics such as medication intake and symptoms for asthma³² or the BODE index for COPD,^{33, 34} 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. Finally, according to weighted regression analyses, loss to follow-up was not a source of bias, although selection for lower stages of obstruction was detectable in our sample.

CONCLUSION

The observed non-persistence of obstruction suggests that prebronchodilation 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 prebronchodilation 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 postbronchodilation spirometry, as well as individual prognostic factors used in today's clinical practice.

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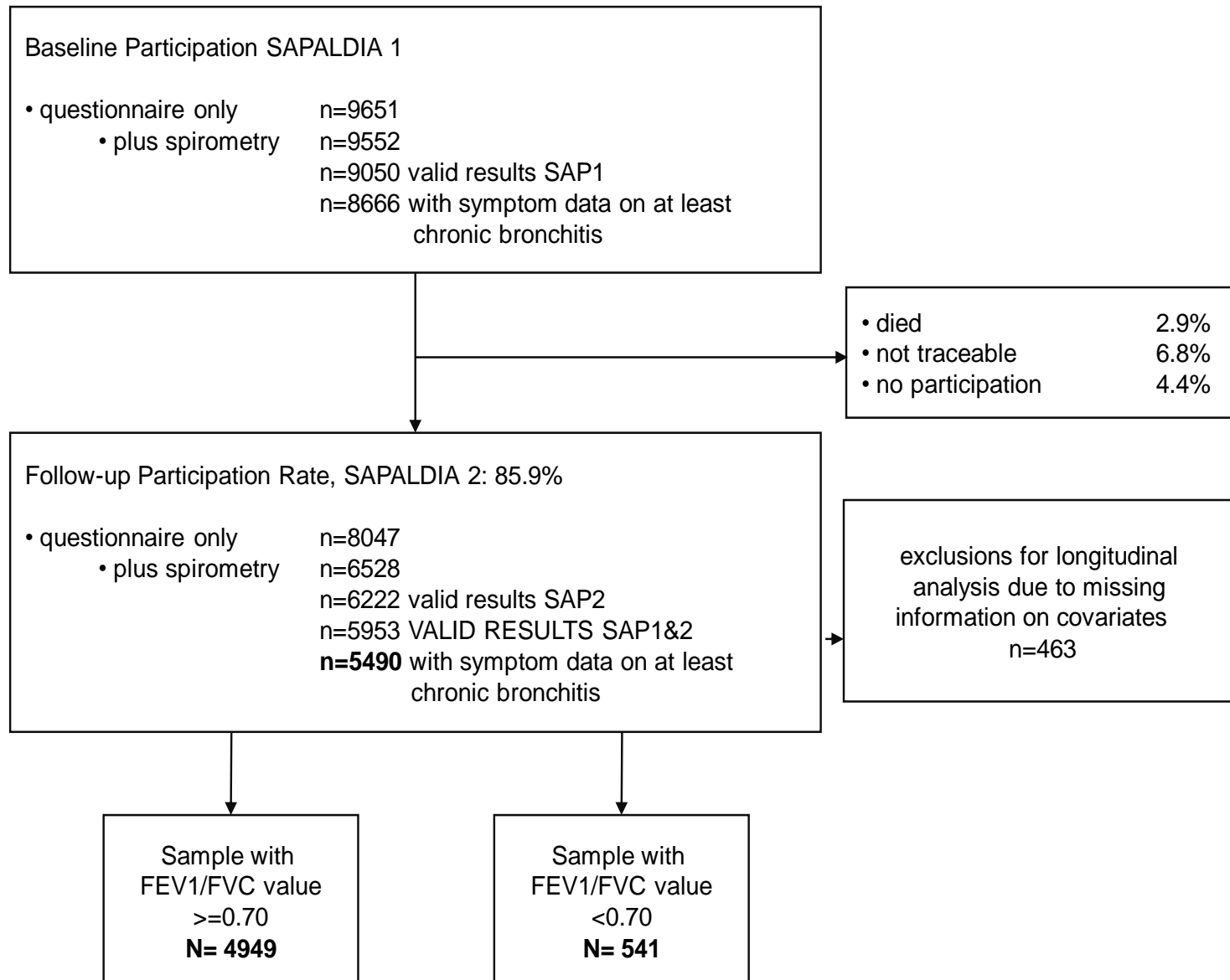
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Online Figure 1. Participation in SAPALDIA 1 (Baseline) and SAPALDIA 2 (Follow-up)



Online Tables

Online Table O1: Baseline characteristics of all SAPALDIA participants and of subjects included in current analysis

Baseline	SAPALDIA 1 participants	SAPALDIA 1 & 2 participants
Characteristics		(included in current analysis)
Total	n=8666	n=5490
Women (%)	51.6	0.5289617
Mean (SD) age (yrs)	41.0 (11.7)	40.9 (11.4)
Mean BMI (SD) (kg/m2)	23.9 (3.8)	23.7 (3.6)
Mean FEV1 (SD) (l/s)	3.54 (0.84)	3.57 (0.82)
Mean FVC (SD) (l)	4.48 (1.04)	4.51 (1.02)
Mean FEV1/FVC (SD)	0.79 (0.08)	0.79 (0.07)
Atopic (%)¹	23.2	22.9
Severe respiratory infection as an infant (%)	7.7	8.3
No professional education (%)	16.2	13.1
Exposed to dust and fumes at work (%)	31.3	30.2
Never smokers² (%)	44	50.7
Former smokers² (%)	22.9	23.4
< 15 pack-years³	62.6	64.5
≥15 pack-years³	32.8	30.9
Current smokers² (%)	33.1	29
< 15 pack-years³	39.3	40.6
≥15 pack-years³	54.5	52.4
Asthma⁴	7.9	7.4
Wheezing without a cold in the 12 months prior to baseline	7.4	6.3

¹ atopy defined as positive skin prick test; available for only n=8326 and 5309 subjects at baseline and follow-up, respectively

² smoking status at baseline: never smokers: <20 packs of cigarettes and <360 g of tobacco in lifetime; former smokers: stopped smoking ≥1 month before baseline examination; current smokers: active smoking at baseline

³ numbers do not add up to 100% due to missing pack-year information

⁴ asthma defined by self-declaration (not confirmed by a doctor)

Online Table O2: Distribution of severity stages of obstruction at follow-up and rates of missings according to baseline severity stage of obstruction

Severity stage of obstruction at baseline examination (n, %)	Severity stage of obstruction at follow-up examination (n, row%)			
	no obstruction	stage I	stage II or more	missing at follow-up*
no obstruction n=7716 (89.0%)	4181 (54.2%)	683 (8.9%)	85 (1.1%)	2767 (35.9%)
stage I n= 757 (8.7%)	106 (14.0%)	294 (38.8%)	56 (7.4%)	301 (39.8%)
stage II or more n= 193 (2.2%)	7 (3.6%)	17 (8.8%)	61 (31.6%)	108 (56.0%)
Total	4294 (49.5%)	994 (11.5%)	202 (2.3%)	3176 (36.6%)

* p_{χ^2} for difference in missing rates <0.001

Online table O3 Lung function values at baseline and follow-up according to category of change in severity of obstruction¹

	Persistently normal n=4181	Incident stage I n=683	Incident stage II n=85	Non- persistent n=113	Stage I progressing n=56	Persistent stage I n=294	Persistent stage II n=61
FEV1 (L)	3.66	3.42	2.96	3.27	2.92	3.30	2.22
FEV1 follow-up (L)	3.31	2.91	2.14	3.11	2.00	2.87	1.79
FVC (L)	4.49	4.54	3.92	4.84	4.61	4.97	3.87
FVC follow-up (L)	4.25	4.34	3.41	4.23	3.73	4.49	3.28

¹ Obstruction was defined as FEV1/FVC<0.70 based on pre-bronchodilation spirometry.

Online table O4 Rate of non-persistence¹ of spirometric obstruction during 11 years of follow-up according to a set of baseline predictors

Predictor at baseline	Person- years at risk (in 1000)	Number of cases	Non- persistence rate (cases/1000) person-years	(95% CI)	Crude non- persistence rate ratio (95% CI)	Adjusted ⁴ non- persistence rate ratio (95% CI)
All (N=540)²	5.89	113	19.20	(15.97 - 23.09)		
Gender:						
· men	3.62	67	18.49	(14.55 - 23.49)	1.00 (Ref)	1.00 (Ref)
· women	2.26	46	20.35	(15.24 - 27.17)	1.10 (0.79 - 1.54)	1.08 (0.74 - 1.57)
Age (years) at baseline						
· 18-30	0.34	6	17.66	(7.94 - 39.32)	1.00 (Ref)	1.00 (Ref)
· >30-40	0.77	17	21.96	(13.65 - 35.32)	1.24 (0.54 - 2.86)	1.17 (0.48 - 2.82)
· >40-50	1.94	46	23.73	(17.78 - 31.69)	1.34 (0.64 - 2.84)	1.28 (0.57 - 2.89)
· >50	2.83	44	15.53	(11.56 - 20.87)	0.88 (0.40 - 1.93)	0.92 (0.40 - 2.10)
Smoking status at baseline³:						
· never smoker	2.36	50	21.15	(16.03 - 27.91)	1.00 (Ref)	
· ever smoker:						1.00 (Ref)
<15 packyrs.	1.16	30	25.79	(18.03 - 36.88)	1.22 (0.82 - 1.81)	0.98 (0.64 - 1.52)
≥15 packyrs	2.36	33	13.99	(9.95 - 19.69)	0.66 (0.44 - 0.99)	0.66 (0.43 - 1.03)
Chronic bronchitis at baseline:						
· absent	5.00	102	20.42	(16.81 - 24.79)	1.00 (Ref)	1.00 (Ref)
· present	0.89	11	12.37	(6.85 - 22.35)	0.61 (0.35 - 1.06)	0.87 (0.47 - 1.59)
Asthma at baseline						
· absent	4.98	102	20.48	(16.87 - 24.87)	1.00 (Ref)	1.00 (Ref)
· present, but non-current	0.44	6	13.69	(6.15 - 30.48)	0.67 (0.32 - 1.40)	0.89 (0.36 - 2.19)
· present, current	0.47	5	10.70	(4.45 - 25.70)	0.52 (0.23 - 1.17)	1.20 (0.37 - 3.90)

Asthma at Follow-up

· absent	4.81	100	20.81	(17.11 - 25.32)	1.00 (Ref)	1.00 (Ref)
· present, but non-current	0.47	10	21.23	(11.42 - 39.46)	1.02 (0.57 - 1.82)	1.15 (0.53 - 2.48)
· present, current	0.61	3	4.93	(1.59 - 15.28)	0.24 (0.08 - 0.67)	0.26 (0.07 - 0.90)

Wheezing without cold at baseline

· absent	5.10	104	20.40	(16.83 - 24.73)	1.00 (Ref)	1.00 (Ref)
· present	0.77	9	11.75	(6.11 - 22.58)	0.58 (0.31 - 1.06)	0.92 (0.45 - 1.88)

Wheezing without cold at follow-up

· absent	4.87	103	21.16	(17.45 - 25.67)	1.00 (Ref)	1.00 (Ref)
· present	1.02	10	9.82	(5.28 - 18.25)	0.46 (0.26 - 0.83)	0.69 (0.36 - 1.32)

¹ Non-persistence of obstruction was defined as FEV1/FVC <0.70 at baseline and ≥0.70 at follow-up based on pre-bronchodilation spirometry

² additional reduction of sample size due to exclusion of participants with >120 pack years at baseline or > 150 at follow-up

³ smoking status at baseline: never smokers: <20 packs of cigarettes and <360 g of tobacco in /lifetime

⁴ adjusted for study area, educational level, and all predictors listed in the table

Table O5 Incidence and non-persistence rates of obstruction as defined by the FEV1/FVC lower limit of normal threshold during 11 years of follow-up according to a set of predictors measured at baseline

Incidence of Spirometric Obstruction (N=5089) ¹					Non-persistence of Spirometric Obstruction (N=396) ¹					
Predictor	Number of cases	Incidence rate (cases/1000 person-years) (95% CI)	Adjusted incidence rate ratio ³ (95% CI)		Number of cases	Non-persistence rate (cases/1000 person-years) (95% CI)	Adjusted non-persistence rate ratio ³ (95% CI)			
All	398	7.16	(6.49-7.90)		136	31.49	(26.62-37.25)			
Gender:										
· men	156	6.02	(5.14-7.04)	1.00 (Ref)	61	27.06	(21.05-34.78)	1.00 (Ref)		
· women	242	8.16	(7.20-9.26)	1.62 (1.32-1.98)	75	36.33	(28.97-45.56)	1.28 (0.95-1.72)		
Age (years) at baseline										
· 18-30	60	5.27	(4.09-6.79)	1.00 (Ref)	16	27.63	(16.93-45.10)	1.00 (Ref)		
· >30-40	107	7.34	(6.08-8.88)	1.17 (0.85-1.59)	31	34.23	(24.07-48.67)	1.10 (0.66-1.83)		
· >40-50	116	7.10	(5.92-8.52)	1.03 (0.76-1.41)	51	36.01	(27.37-47.39)	1.12 (0.70-1.81)		
· >50	115	8.66	(7.21-10.40)	1.32 (0.96-1.80)	38	26.80	(19.50-36.83)	0.87 (0.52-1.46)		
Smoking status at baseline ² :										
· never smoker	173	6.06	(5.22-7.03)		61	33.51	(26.08-43.07)			
· ever smoker:				1.00 (Ref)				1.00 (Ref)		
· <15 packyrs.	79	5.23	(4.20-6.52)	0.87 (0.68-1.13)	39	38.90	(28.42-53.25)	1.09 (0.78-1.54)		
· ≥15 packyrs	146	12.28	(10.44-14.44)	2.02 (1.61-2.54)	36	24.06	(17.36-33.36)	0.67 (0.46-0.97)		

Chronic bronchitis at baseline:

·	absent	335	6.57	(5.90-7.31)	1.00	(Ref)	119	32.92	(27.50-39.39)	1.00	(Ref)
·	present	63	13.79	(10.78-17.66)	1.66	(1.26-2.18)	17	24.17	(15.02-38.88)	1.14	(0.73-1.80)

Asthma at baseline

·	absent	354	6.81	(6.13-7.56)	1.00	(Ref)	118	34.13	(28.50-40.88)	1.00	(Ref)
·	non-current	25	10.51	(7.10-15.55)	1.37	(0.86-2.18)	9	22.81	(11.87-43.84)	1.28	(0.66-2.49)
·	current	19	16.13	(10.29-25.28)	0.68	(0.36-1.29)	9	19.26	(10.02-37.03)	1.23	(0.52-2.92)

Asthma at Follow-up

·	absent	343	6.69	(6.02-7.44)	1.00	(Ref)	118	35.83	(29.91-42.91)	1.00	(Ref)
·	non-current	21	7.82	(5.10-11.99)	0.98	(0.60-1.60)	11	25.67	(14.21-46.35)	0.63	(0.32-1.22)
·	current	34	21.10	(15.08-29.54)	2.07	(1.17-3.67)	7	11.73	(5.59-24.60)	0.47	(0.20-1.08)

Wheezing without cold at baseline

·	absent	352	6.73	(6.06-7.47)	1.00	(Ref)	122	34.12	(28.57-40.75)	1.00	(Ref)
·	present	43	14.26	(10.58-19.23)	1.15	(0.81-1.62)	14	19.69	(11.66-33.25)	0.76	(0.45-1.28)

Wheezing without cold at follow-up

·	absent	331	6.39	(5.74-7.12)	1.00	(Ref)	119	34.90	(29.16-41.77)	1.00	(Ref)
·	present	67	17.80	(14.01-22.62)	1.92	(1.42-2.58)	17	18.71	(11.63-30.09)	0.71	(0.45-1.11)

¹ additional reduction of sample size due to exclusion of participants with >120 pack years at baseline or > 150 at follow-up

² smoking status at baseline: never smokers: <20 packs of cigarettes and <360 g of tobacco in /lifetime

³ adjusted for study area, educational level, and all predictors listed in the table

Online Table O6 Association¹ of categories of change in severity of obstruction² with health service use for respiratory problems at follow-up

Variable	Crude Model		Adjusting for all but asthma covariates ³		Adjusting for asthma & wheezing at base-line or follow-up	
	Rel. rate (95%-CI)	p-value	Rel.rate (95%-CI)	p-value	Rel.rate (95%-CI)	p-value
Incident stage I (n= 683)	1.40 (0.98 - 1.99)	0.063	1.46 (0.99 - 2.15)	0.054	1.00 (0.66 - 1.54)	0.982
Incident stage II (n= 85)	4.57 (2.52 - 8.29)	0.000	3.97 (2.10 - 7.54)	0.000	1.75 (0.82 - 3.75)	0.149
Persistent stage I (n=294)	1.20 (0.70 - 2.06)	0.508	1.33 (0.73 - 2.41)	0.349	0.82 (0.41 - 1.61)	0.558
Stage I progressing (n= 56)	5.01 (2.48 - 10.12)	0.000	5.21 (2.38 - 11.40)	0.000	2.49 (1.02 - 6.10)	0.046
Persistence stage II (n= 61)	10.47 (5.85 - 18.76)	0.000	10.07 (5.17 - 19.62)	0.000	4.17 (1.91 - 9.13)	0.000
Non-persistent obstruction (n= 113)	1.49 (0.68 - 3.26)	0.315	2.26 (1.00 - 5.13)	0.050	2.28 (0.98 - 5.27)	0.054
Asthma at baseline						
non-current ⁴					0.47 (0.23 - 0.94)	0.032
current ⁴					2.10 (1.01 - 4.37)	0.048
Asthma at follow-up						
non-current ⁴					1.56 (0.86 - 2.81)	0.141
current ⁴					6.81	0.000

Wheezing without a cold at baseline	(3.65 - 12.70) 1.32	0.216
Wheezing without a cold at follow-up	(0.85 - 2.07) 2.55 (1.75 - 3.71)	0.000

95%-CI: 95%-confidence intervals; PY: pack-years

¹ Reference category: persistently without obstruction to the airflow

² Obstruction was defined as FEV1/FVC<0.70 based on pre-bronchodilation spirometry.

³ Covariates adjusted for were: sex, age, smoking (light or heavy ever smoker), chronic bronchitis, shortness of breath while walking at baseline, health service use for respiratory problems at baseline, education and area.

⁴ 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.