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TITLE:

LONGITUDINAL CHANGE OF PRE-BRONCHODILATOR SPIROMETRIC OBSTRUCTION AND HEALTH OUTCOMES – RESULTS FROM THE SAPALDIA COHORT

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Abbreviations: COPD Chronic Obstructive Pulmonary Disease, FEV1 Forced expiratory volume in 1 second, FVC Forced vital capacity, GOLD Global Initiative for Chronic Obstructive Lung Disease

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ABSTRACT

Background: Understanding the prognostic meaning of early COPD stages in the general population is relevant for discussions about under-diagnosis. So far, COPD prevalence and incidence were often estimated using pre- instead of post-bronchodilation spirometry. In the SAPALDIA Cohort we investigated time course, clinical relevance and determinants of severity stages of obstruction using pre-bronchodilator spirometry.

Methods: Incident obstruction was defined as FEV1/FVC ratio ≥0.70 at baseline and <0.70 at follow-up, non-persistence 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 GOLD classification) over 11 years was related to shortness of breath and health service utilization for respiratory problems by logistic models.

Results: Incidence rate of obstruction was 14.2 cases/1'000 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 (0.83-3.54), OR 3.11 (1.50-6.42) respectively) and health service utilization for respiratory problems (OR 2.49 (1.02-6.10), OR 4.17 (1.91-9.13) respectively) at follow-up.

Conclusions: The observed non-persistence of obstruction suggests that pre-bronchodilation spirometry, as used in epidemiological studies, might misclassify COPD. Future epidemiological studies should consider both pre- and post-bronchodilation measurements and take specific clinical factors related to asthma and COPD into consideration for estimation of disease burden and prediction of health outcomes.

INTRODUCTION

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 under-diagnosis, 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 health care 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 second (FEV1) over forced vital capacity (FVC) ratio < 0.70 measured by post-bronchodilator spirometry.[4] Severity classification depends on FEV1, expressed as percentage of the predicted value: ≥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 cutoff 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 health care needs.[7] Although pre-bronchodilation 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 more have consistently been associated with mortality and reduced quality of life in epidemiological studies using pre-bronchodilation 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 cohort we could recently show that stage I predicted rapid decline in FEV1, a cardinal feature of COPD,[4] lower quality of life and increased health care utilization for respiratory problems 11 years later, but only in the presence of respiratory symptoms at baseline.[15]

In this current study based on pre-bronchodilation spirometry data from the SAPALDIA cohort, we investigated the time course and clinical 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 18-62 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 Helsinki Declaration. Written informed consent was obtained from participants at 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 the one of the European Community Respiratory Health Survey (ECRHS).[19] No bronchodilation was applied. Identical spirometers (Sensormedics model 2200, Yorba Linda, USA) and protocols were used at both surveys; comparability was assessed before and after each one.[20, 21] Three to eight forced expiratory lung function maneuvers were performed and at least two acceptable measurements of forced vital capacity (FVC) and forced expiratory volume in the first second (FEV_1) 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 pre-bronchodilation measurement. An incident case of obstruction was defined as a person with FEV1/FVC ratio ≥ 0.70 at baseline, but <0.70 at follow-up examination. Cases of non-persistence were defined inversely.

In 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% or more of the predicted value were classified stage I, 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 analyzed.

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 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 ≥360g of tobacco in their lifetime at baseline,[24] former smokers 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 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 was 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.

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 into 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 health care services utilization 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 utilization models), smoking habits (light/heavy smoker at baseline, pack-years between surveys), preexisting symptoms (chronic bronchitis, shortness of breath), and asthma or wheezing at either examination.

As sensitivity analysis, confounding by cardiovascular co-morbidity was assessed for health care utilization for respiratory problems and respiratory symptoms by including service utilization for cardiovascular problems at follow-up. Furthermore, study participants having only baseline spirometry were compared to 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 Inc., 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. 53% of the participants were women and the average age at baseline was 41.1 years (range 18-62 years). 30% 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 overrepresented 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 but '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 (4.97L and 4.84L 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 FEV1/FVC ratio (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 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. 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%-confidence interval (95%-CI)): older age (RR 1.38 per 10 years, 95%-CI 1.29-1.47), heavy smoking at baseline (RR 1.51, 95%-CI 1.29-1.77), chronic bronchitis at baseline (RR 1.23, 95%-CI 1.00-1.51), non-current asthma at baseline (RR 1.39, 95%-CI 1.01-1.92), current asthma at follow-up (RR 1.68, 95%-CI 1.13-2.50), and wheezing without cold at follow-up (RR 1.95, 95%-CI 1.57-2.42). 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). 93.8% of non-persistent cases 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 (31.5 cases/1000 PY) rates were observed (online table O5). Additionally, female sex was associated with incidence (RR 1.62, 95%-CI 1.32-1.98). The effects for the other determinants were comparable to the previous analyses (reported in tables 2 and O4).

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

	Persistently normal	Incident stage I	Incident stage II	Persistent stage I	Stage I progressing	Persistent stage II	Non-persistent
	n=4181	*n=683*	*n=85*	*n=294*	*n=56*	*n=61*	*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**
FEV1 % 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
FEV1/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 PY)[2] (%)	**28.7**	**19.3**	**13.6**	**20.9**	**9.3**	**11.8**	**24.5**
Heavy smoker at baseline (>=15 PY)[2] (%)	**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**

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

[2] Numbers do not add up to 100.0% due to smokers with missing pack-year information

Table 2 Incidence rate of obstruction (FEV1/FVC<0.7) using pre-bronchodilator spirometry during 11 years of follow-up according to a set of baseline characteristics

Predictor at baseline	Person-years at risk (in 1000)	Number of cases	Incidence rate (cases per 1000 person years) (95% CI)	Crude incidence rate ratio (95% CI)	Adjusted[3] incidence rate ratio (95% CI)
All (N=4945) [1]	**54.00**	**765**	**14.17 (13.20 - 15.21)**		
Gender:					
· **men**	24.55	357	**14.54** (13.11 - 16.13)	**1.00** (Ref)	**1.00** (Ref)
· **women**	29.45	408	**13.85** (12.57 - 15.27)	**0.95** (0.84 - 1.09)	**1.03** (0.90 - 1.18)
Age (years) at baseline					
· **18-30**	11.62	70	**6.02** (4.77 - 7.61)	**1.00** (Ref)	**1.00** (Ref)
· **>30-40**	14.70	165	**11.22** (9.64 - 13.07)	**1.86** (1.43 - 2.43)	**1.72** (1.33 - 2.24)
· **>40-50**	15.81	253	**16.00** (14.15 - 18.10)	**2.66** (2.08 - 3.40)	**2.38** (1.85 - 3.06)
· **>50**	11.86	277	**23.35** (20.75 - 26.27)	**3.88** (3.05 - 4.93)	**3.77** (2.94 - 4.83)
Smoking status at baseline[2]:					
· **never smoker**	28.02	362	**12.92** (11.65 - 14.32)	**1.00** (Ref)	**1.00** (Ref)
· **ever smoker:**					
<15 packyrs.	14.94	153	**10.24** (8.74 - 12.00)	**0.79** (0.66 - 0.95)	**0.87** (0.73 - 1.04)
≥15 packyrs	11.03	250	**22.66** (20.02 - 25.65)	**1.75** (1.52 - 2.03)	**1.51** (1.29 - 1.77)
Chronic bronchitis at baseline:					

· **absent**	49.62	671	**13.52**	(12.54 - 14.59)	**1.00**	(Ref)	**1.00**	(Ref)
· **present**	4.38	94	**21.45**	(17.53 - 26.26)	**1.59**	(1.30 - 1.93)	**1.23**	(1.00 - 1.51)
Asthma at baseline								
· **absent**	50.47	678	**13.43**	(12.46 - 14.48)	**1.00**	(Ref)	**1.00**	(Ref)
· **present, but non-current**	2.34	54	**23.12**	(17.70 - 30.18)	**1.72**	(1.33 - 2.22)	**1.39**	(1.01 - 1.92)
· **present, current**	1.18	33	**28.02**	(19.92 - 39.41)	**2.09**	(1.51 - 2.88)	**0.79**	(0.51 - 1.23)
Asthma at Follow-up								
· **absent**	49.75	662	**13.31**	(12.33 - 14.36)	**1.00**	(Ref)	**1.00**	(Ref)
· **present, but non-current**	2.64	49	**18.54**	(14.01 - 24.53)	**1.39**	(1.07 - 1.82)	**1.19**	(0.85 - 1.65)
· **present, current**	1.60	54	**33.77**	(25.86 - 44.09)	**2.54**	(1.97 - 3.28)	**1.68**	(1.13 - 2.50)
Wheezing without a cold at baseline								
· **absent**	50.81	689	**13.56**	(12.59 - 14.61)	**1.00**	(Ref)	**1.00**	(Ref)
· **present**	2.96	71	**23.99**	(19.01 - 30.27)	**1.77**	(1.41 - 2.21)	**1.04**	(0.81 - 1.35)
Wheezing without a cold at follow-up								
· **absent**	50.34	655	**13.01**	(12.05 - 14.05)	**1.00**	(Ref)	**1.00**	(Ref)
· **present**	3.65	110	**30.10**	(24.97 - 36.29)	**2.31**	(1.92 - 2.79)	**1.95**	(1.57 - 2.42)

[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

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' (odds ratio (OR) 3.76, 95%-CI 2.18-6.48) and 'persistent stage II' (OR 5.43, 95%-CI 3.15-9.37). After adjusting for 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 1.10-4.45 and OR 4.38, 95%-CI 2.19-8.75 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 0.83-3.54) and decreased effect sizes.

Categories of change in severity of obstruction and health service utilization 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 1.02-6.10) and those persistently in stage II 4.2 times (OR 4.17, 95%-CI 1.91-9.13) more likely to utilize 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 0.98-5.27, 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).

Table 3 Association[1] of categories of change in severity of obstruction[2] with shortness of breath while walking at follow-up

	Crude Model		Adjusting for all but asthma covariates[3]		Adjusting for asthma & wheezing at base-line or follow-up	
Variable	**Rel. rate** 95%-CI	**p-value**	**Rel.rate** 95%-CI	**p-value**	**Rel.rate** 95%-CI	**p-value**
Incident stage I	**1.59**	**0.000**	**1.24**	0.056	**1.12**	0.344
(n= 683)	(1.32 - 1.91)		(0.99 - 1.56)		(0.89-1.41)	
Incident stage II	**2.74**	**0.000**	**1.43**	0.192	**1.10**	0.743
(n= 85)	(1.74 - 4.30)		(0.84 - 2.45)		(0.63-1.90)	
Persistent stage I	**1.48**	**0.004**	**1.14**	0.428	**1.02**	0.903
(n=294)	(1.13 - 1.94)		(0.82 - 1.60)		(0.73-1.44)	
Stage I progressing	**3.76**	**0.000**	**2.21**	**0.026**	**1.71**	0.148
(n= 56)	(2.18 - 6.48)		(1.10 - 4.45)		(0.83-3.54)	
Persistent stage II	**5.43**	**0.000**	**4.38**	**0.000**	**3.11**	**0.002**
(n= 61)	(3.15 - 9.37)		(2.19 - 8.75)		(1.50-6.42)	
Non-persistent	**1.02**	0.947	**1.40**	0.237	**1.39**	0.246
(n= 113)	(0.64 - 1.62)		(0.80 - 2.44)		(0.80-2.43)	
Asthma at baseline						
non-current[4]					**1.08**	0.739
					(0.70-1.65)	
current[4]					**0.50**	**0.024**
					(0.27-0.91)	
Asthma at follow-up						
non-current[4]					**1.09**	0.667
					(0.73-1.63)	
current[4]					**2.18**	**0.004**
					(1.28-3.72)	
Wheezing without a					**1.41**	**0.034**
cold at baseline					(1.03-1.94)	

Wheezing without a cold at follow-up	**2.07** (1.55-2.75)	**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, 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.

DISCUSSION

In our general population sample, we observed an incidence of modified GOLD COPD (obstruction based on pre-bronchodilation spirometry) of 14.2 cases per 1000 person years (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 asthmatics. 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 likely 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. Second, the use of pre-bronchodilator measurements prevents the identification of reversible obstruction (mostly undiagnosed asthma). The high FVC and normal FEV1 percent 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.

Pre-bronchodilatator 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 health care use. While shortness of breath and respiratory care utilization was 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 characterize the modified GOLD stage I category in epidemiological studies. In the past, epidemiological studies have omitted post-bronchodilation 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 post-bronchodilation measurements and consider characteristics such as medication intake and symptoms for asthma[32] 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 pre-bronchodilator 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 pre-bronchodilation 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 pre-bronchodilation spirometry, particularly its longitudinal course, has value in predicting health outcomes on a population level. To accurately identify risk groups, future epidemiological studies will have to consider both, pre- and post-bronchodilation spirometry as well as individual prognostic factors used in today's clinical practice.

FIGURE LEGENDS

Figure 1 Association of categories of change in severity of obstruction with health service use for respiratory problems at follow-up[1]

[1] Obstruction was defined as FEV1/FVC<0.70 based on pre-bronchodilation 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

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Online Tables

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

Baseline Characteristics	SAPALDIA 1 participants	SAPALDIA 1 & 2 participants (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 smokers[2] (%)	44	50.7
Former smokers[2] (%)	22.9	23.4
< 15 pack-years[3]	62.6	64.5
≥15 pack-years[3]	32.8	30.9
Current smokers[2] (%)	33.1	29
< 15 pack-years[3]	39.3	40.6
≥15 pack-years[3]	54.5	52.4
Asthma[4]	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

Severty stage of obstruction at baseline examination (n, %)		**Severty 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%)

*$p_{\chi 2}$ 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 obstruction[1]

	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-persistence[1] 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 baseline[3]:								
· **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**	(0.60 - 1.59)
≥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**	(16.8 1 - 24.7 9)	**1.00** (Ref)		**1.00** (Ref)	
· **present**	0.89	11	**12.37**	(22.3 6.85 - 5)	**0.61** (0.3 5 - 1.0 6)		**0.87** (0.4 7 - 1.5 9)	
Asthma at baseline								
· **absent**	4.98	102	**20.48**	(16.8 7 - 24.8 7)	**1.00** (Ref)		**1.00** (Ref)	
· **present, but non-current**	0.44	6	**13.69**	(30.4 6.15 - 8)	**0.67** (0.3 2 - 1.4 0)		**0.89** (0.3 6 - 2.1 9)	
· **present, current**	0.47	5	**10.70**	(25.7 4.45 - 0)	**0.52** (0.2 3 - 1.1 7)		**1.20** (0.3 7 - 3.9 0)	
Asthma at Follow-up								
· **absent**	4.81	100	**20.81**	(17.1 1 - 25.3 2)	**1.00** (Ref)		**1.00** (Ref)	
· **present, but non-current**	0.47	10	**21.23**	(11.4 2 - 39.4 6)	**1.02** (0.5 7 - 1.8 2)		**1.15** (0.5 3 - 2.4 8)	
· **present, current**	0.61	3	**4.93**	(15.2 1.59 - 8)	**0.24** (0.0 8 - 0.6 7)		**0.26** (0.0 7 - 0.9 0)	
Wheezing without cold at baseline								
· **absent**	5.10	104	**20.40**	(16.8 3 - 24.7 3)	**1.00** (Ref)		**1.00** (Ref)	
· **present**	0.77	9	**11.75**	(22.5 6.11 - 8)	**0.58** (0.3 1 - 1.0 6)		**0.92** (0.4 5 - 1.8 8)	
Wheezing without cold at follow-up								
· **absent**	4.87	103	**21.16**	(17.4 5 - 25.6 7)	**1.00** (Ref)		**1.00** (Ref)	
· **present**	1.02	10	**9.82**	(18.2 5.28 - 5)	**0.46** (0.2 6 - 0.8 3)		**0.69** (0.3 6 - 1.3 2)	

[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 Association[1] of categories of change in severity of obstruction[2] 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**

	(3.65 - 12.70)		
Wheezing without a cold at baseline	**1.32** (0.85 - 2.07)		0.216
Wheezing without a cold at follow-up	**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.

Odds ratio (95%-CI)
10
8
6
4
2
0
1.00
1.75
0.82
2.49
4.17
2.28
Incident stage I
Incident stage II
Persistent stage I
Stage I progressive
Persistent stage II
Non-persistent