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Prevalence of Airflow Obstruction in Smokers and Never Smokers in Switzerland

Results from the SAPALDIA cohort study

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ABSTRACT

We aimed to measure age-specific prevalence of airflow obstruction (AO) in Switzerland in smokers and never smokers using pulmonary function tests and respiratory symptoms from 6126 subjects participating in the Swiss Cohort Study on Air Pollution and Lung Diseases in Adults.

The lower limit of normal of FEV_1/FVC ratio was used to define AO. Severity of AO was graded according to the recommendations of the Global Initiative for Chronic Obstructive Lung Disease.

Prevalence of AO ranged from 2.5% in subjects aged 30-39 to 8.0% in those aged 70 or more. In multivariate analysis, age ($OR_{aged70+ \text{ vs aged } 30-39}$ 2.8), smoking (OR 1.8) and asthma, (OR 6.7) were associated with AO. Never smokers constituted 29.3 % of subjects with AO. Never smokers with AO were younger, male and reported more frequently asthma than obstructive smokers. Obstructive smokers and never smokers had similar level of symptoms and quality of life impairment.

Prevalence of AO in Switzerland is similar in magnitude compared to other developed countries. Never smokers account for a third of the prevalence which is higher than elsewhere. AO in never smokers deserve attention because of its frequency and its similar health impact than in smokers.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a leading cause of death, morbidity and health care cost worldwide[1-3]. The Burden of Obstructive Lung Disease study (BOLD) reports between countries variability in prevalence of stage 2 to 4 COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) definition.[4] For example, in male subjects aged 40 or older, prevalence of GOLD stage 2 or higher varies from 8.5% in Iceland to 18.8% in the Philippines. Country-specific age distributions and smoking prevalence rates contribute most to these disparities. Nevertheless, never smokers are also affected by COPD. Celli et al found an obstruction rate of 9.1 % in adult never smokers in the third National health and Nutrition Examination Survey and never smokers accounted for 23% of the obstruction rate as defined by the Forced Expiratory Volume in 1 sec/Forced Vital Capacity <0.7 (FEV_1/FVC).[5] Older age, male sex, low body mass index and allergy were the strongest risk factors for obstruction in never smokers.[5]. In Austria, Lamprecht et al found that the overall prevalence of GOLD stage 2-4 was 9.5% and that 27.7% of subjects with GOLD stage 2-4 obstruction were never smokers.[6]

So far, no population study examined the prevalence of AO in Switzerland, a developed country characterized with a low level of social inequalities and easy access to health care.[7] The main objectives of the present study are 1) to provide estimates of the prevalence of AO in the Swiss adult population, 2) to examine the prevalence of AO in never smoker and the associated risk factors.

METHOD

Study design and participants

For this study, we included 6126 subjects from the SAPALDIA (Swiss Study on Air Pollution and Lung Diseases in Adults) cohort which has been described in detail elsewhere. [8, 9]. Online **Figure A** depicts the flow chart of SAPALDIA subjects for the present analyses.

Characteristics predictive of participation at SAPALDIA 2 are displayed in **online supplementary table A.**

Because AO develops after long lasting exposure to noxious agents, we based our estimates on data from the follow up survey SAPALDIA 2 [2002] where participants had a median age of 53 years, [range 30-73]).

Definition of airflow obstruction

Pulmonary function tests (PFTs) were performed without bronchodilators by trained technicians according to the American Thoracic Society standards. We defined airflow obstruction according to the lower limit of normal FEV_1/FVC derived from population specific prediction equations. [10] In accordance with the recently published studies on the prevalence of COPD, we report airflow obstruction in presence of FEV_1/FVC <LLN and FEV_1<0.8 predicted (modified stage 2-4 AO).[4] To facilitate international comparisons we also report the prevalence of AO as defined by the fixed GOLD criterion (FEV_1/FVC <0.7). Because respiratory symptoms are important predictors of FEV_1 decline and respiratory care use, we also report prevalence of symptomatic airflow obstruction. [11, 12]

Chronic cough or chronic phlegm or chronic shortness of breath by walking were used to define respiratory symptoms. The underlying questions have been described in detail previously **(Online supplement)**.[12]

Methacholine bronchial challenge tests

Bronchial challenge tests were performed at SAPALDIA 1 with administration of methacholine chloride in subjects who had no contraindication.[9] The test was considered positive if FEV_1 dropped by 20% or more from the pre-test level.

Covariates

Subjects who answered yes to both questions "have you ever had asthma?" and, if yes, "was this confirmed by a doctor?" were classified as having "physician diagnosed asthma". Education level, nationality, comorbid conditions, smoking status, lifetime smoking (packs of cigarettes/day * smoking duration [years]), environmental tobacco smoke exposure and level of physical activity were derived from the questionnaires. Detailed methods regarding the definition of physical activity have been published before.[13] Short Form 36-item (SF-36) was administered to assess health-related quality of life. Respiratory care utilization was considered when inhaler use or emergency room visit or hospitalisation or ambulatory visit (all for respiratory problems) was reported during the year preceding SAPALDIA 2.

Statistical analysis

Multivariate analysis involved mixed logistic regression models, systematically controlling for categories of age and smoking with the study area as a random effect variable. These variables were chosen a priori based on published literature. Covariates potentially associated with obstruction were tested one by one in models controlling for the above mentioned core variables.

Methods to evaluate bias related to non participation are detailed on the online supplement. Statistical analyses were carried out with Stata version 10 (StataCorp, 4905 Lakeway Drive, College Station, Texas 77845 USA).

RESULTS

Prevalence of airflow obstruction

Table 1 compares the prevalence of AO stage 2 or higher as defined by the lower limit of

normal of FEV_1/FVC or the GOLD criterion. Compared to the LLN, the fixed FEV_1/FVC ratio led to higher AO prevalence in older age categories (15.2%$_{GOLD}$ CI95% (11.1 20.3) vs 8.0%$_{LLN}$ CI95% (5.3 11.9)). Overall, stage 2 or higher AO was found in 5.1% CI95% (4.3 5.9) according to the LLN and 7.0% CI95% (6.0 8.3) according to the GOLD criterion.

Table 1: Airflow obstruction prevalence in SAPALDIA 2 (2002) by age group and sex

Characteristics at SAPALDIA 2 (2002)	$FEV_1/FVC<LLN$, stage 2-4		$FEV_1/FVC<0.7$, stage 2-4	
	Men n=180 %, [CI95%]	**Women** n=127 %, [CI95%]	**Men** n=275 %, [CI95%]	**Women** n=152 %, [CI95%]
Overall, n=6126	6.1 [5.3 7.1]	4.0 [3.3 4.7]	9.4 [8.4 10.5]	4.8 [4.1 5.6]
Age 30-39, n=1109	3.2 [2.0 5.0]	1.9 [0.9 3.4]	3.4 [2.1 5.2]	0.9 [0.4 2.2]
Age 40-49, n=1525	3.2 [3.0 6.0]	4.0 [2.9 5.6]	5.8 [4.3 7.8]	4.0 [2.9 5.6]
Age 50-59, n=1811	6.1 [4.7 7.9]	4.7 [3.5 6.2]	9.2 [7.5 11.3]	5.4 [4.1 7.0]
Age 60-69, n=1378	8.9 [7.0 11.4]	5.0 [3.6 6.9]	15.2 [12.6 18.1]	7.4 [5.7 9.5]
Age 70+, n=303	15.0 [9.9 22.1]	2.4 [0.8 6.1]	26.3 [19.5 34.4]	5.9 [3.2 10.6]
	<0.001	0.029	<0.001	<0.001

* P value from χ^2 test

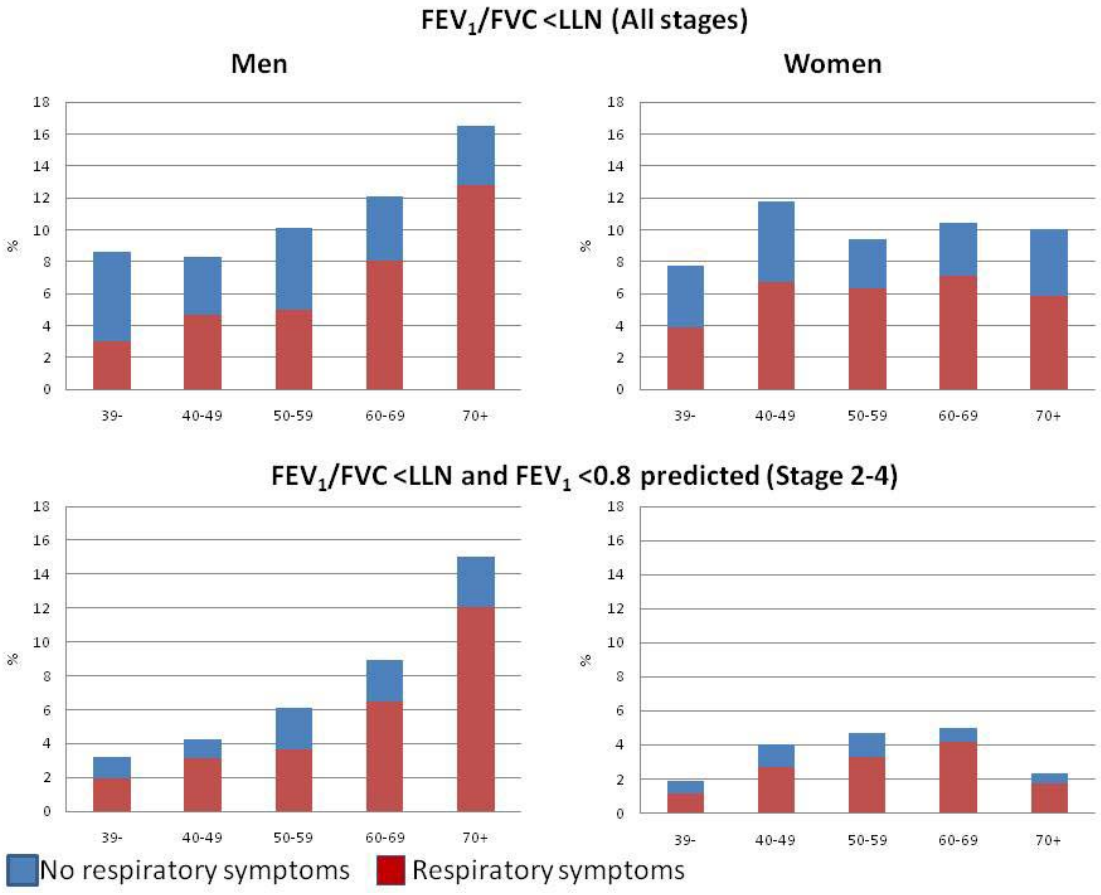
LLN: lower limit of normal of FEV_1/FVC ratio.

Overall, 10.0% (CI95% 8.5% - 11.8%) of the adult population qualified for LLN defined AO. More than half of subjects with stage 1 AO (n total=310) were free of respiratory symptoms (n=166, 53.6%).

Figure 1 provides the prevalence of AO (any stage) and 2-4 AO at SAPALDIA 2 (2002) with percentage reporting respiratory symptoms.

For subjects with FEV_1/FVC below LLN, (all stage) and those with stage 2-4 AO, prevalence increased steadily with age and men were more frequently affected than women. Most subjects with stage 2-4 AO reported one or more chronic respiratory symptoms (lower panel).

Figure 1: Prevalence of airflow obstruction at SAPALDIA 2*



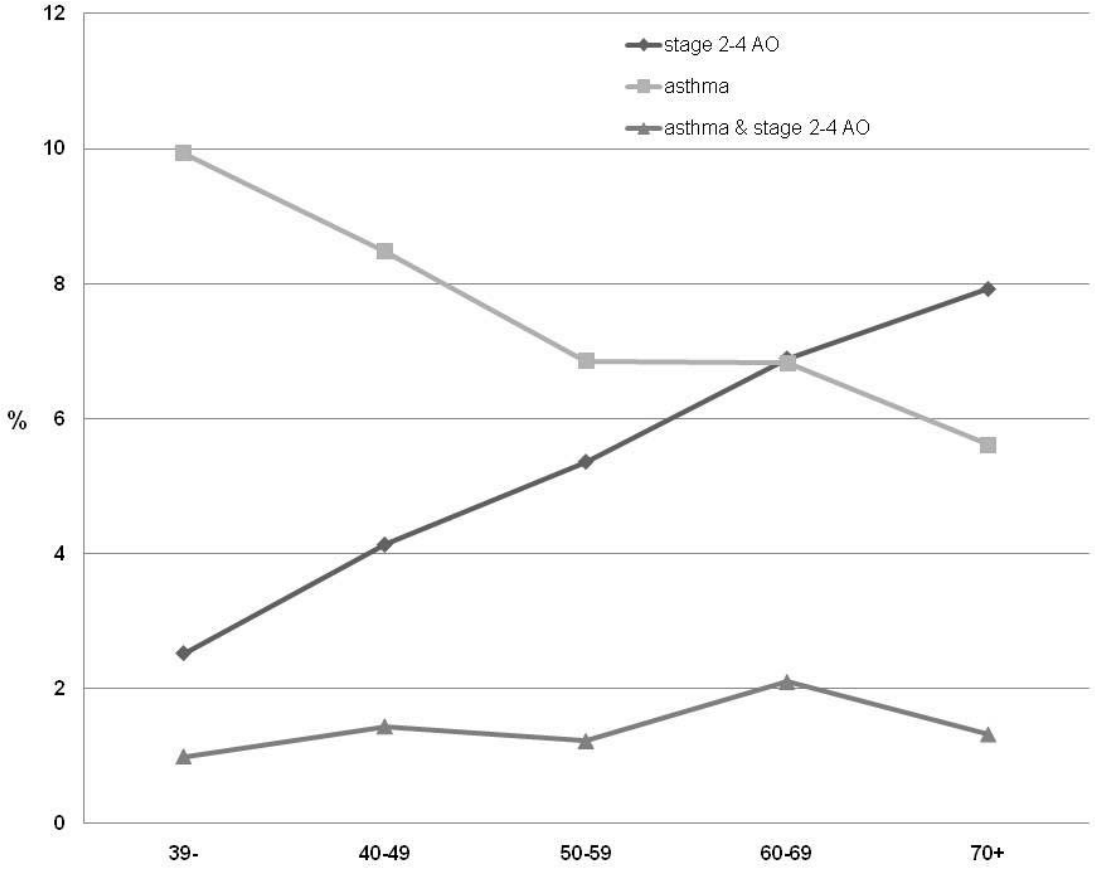
*pulmonary function tests were performed without bronchodilation. Respiratory symptoms: chronic cough or phlegm or shortness of breath by walking.

Physician diagnosed asthma prevalence

Physician diagnosed asthma prevalence is detailed for categories of age in **figure 2.** Asthma

was less frequently reported in older age categories (5.7% [CI95% 3.5%-9.1%] for subjects aged 70 or more) compared to younger age categories (10% [8.1%-12.3%] for subjects aged 30-39). The concomitant presence of asthma and stage 2-4 AO increased with age: up to 2.1% (1.4%-3.0%) for those aged 60 to 69. However in the oldest age group (70 or more, n=303), both conditions were found in 4 subjects only (1.3% [0.5%-3.5%]).

Figure 2: Physician diagnosed asthma, stage 2-4 airflow obstruction and concomitant asthma+AO by age group.



Risk factors for airflow obstruction

Table 2a 2b compare the characteristics of normal subjects (normal spirometry and no report of respiratory symptoms) with a) subjects with respiratory symptoms but no AO, b) stage 1 AO or c) stage 2-4 AO.

Table 2a shows that AO prevalence increases with smoking, environmental tobacco smoke exposure, low education, non-Swiss citizenship and physical inactivity. Ever smokers (men 65.4%; women 49.8%) reported 26.2 pack years (median 20.4, iqr 27.4) for men and 17.0 (median 11.5, iqr 21.0) for women. Environmental tobacco smoke during childhood, professional exposure to dust smoke or fumes or outdoor fine particulate matter exposure were not associated with AO.

Subjects with stage 2-4 AO also reported higher rate of comorbid conditions **(Table 2b)**.

When examining risk factors for stage 2-4 AO as defined using the fixed FEV_1/FVC ratio instead of the LLN ratio, we found that those risk factors were associated in a very similar manner with AO.

Table 2a: Risk factors prevalence by severity of airflow obstruction in SAPALDIA 2 (2002)

Characteristics at SAPALDIA 2 (2002) n=6126	$FEV_1/FVC \geq LLN$		$FEV_1/FVC < LLN$, stage 1		$FEV_1/FVC < LLN$, stage 2-4	
	no symptoms (reference) n=3342	with symptoms n=2161	All n=310	With symptoms n=144	All n=307	With symptoms n=216
Tobacco smoking exposure						
Ever smoker (2002) n (%)	1786 (53.5)	1265 (58.6)	191 (61.6)	99 (68.8)	217 (70.7)	161 (74.5)
P value		<0.001	<0.001	<0.001	<0.001	<0.001
Pack year (ever smokers), median (iqr)	10.0 (20.9)	16.0 (28.9)	16.2 (28.7)	20 (27.0)	31.2 (41.2)	35.0 (42.0)
P value		<0.001†	<0.001†	<0.001†	<0.001†	<0.001†
Environmental tobacco smoke exposure						
Not exposed, n (%)	2633 (78.8)	1536 (71.1)	229 (73.9)	98 (68.1)	212 (69.3)	147 (68.4)
≤ 3 hours/week	443 (13.3)	373 (17.3)	55 (17.4)	29 (20.1)	54 (17.7)	40 (18.6)
> 3 hours/week	265 (7.9)	250 (11.6)	26 (8.4)	17 (11.8)	40 (13.1)	28 (13.0)
P value		<0.001	0.077	0.009	<0.001	0.001
Socio-educational level						
Low education, n (%) missing n=6	129 (3.9)	190 (8.8)	22 (7.1)	15 (10.4)	26 (8.5)	21 (9.7)
P value		<0.001	<0.001	<0.001	<0.001	<0.001
Non Swiss nationals, n (%)	390 (11.7)	341 (15.8)	30 (9.7)	16 (11.1)	50 (16.5)	35 (16.4)
P value		<0.001	0.290	0.834	0.015	0.038
Physically active, n (%) missing n=64	1053 (31.8)	518 (24.2)	105 (34.4)	47 (33.1)	75 (24.8)	45 (21.2)
P value		<0.001	0.347	0.746	0.011	0.001

All statistical comparisons [χ^2 test or †Wilcoxon rank sum test] made with "$FEV_1/FVC \geq LLN$ & no respiratory symptoms" (reference group).

Table 2b: Prevalence of self-reported comorbid conditions by severity of airflow obstruction in SAPALDIA 2 (2002)

Characteristics at SAPALDIA 2 (2002) n=6126	$FEV_1/FVC \geq LLN$		$FEV_1/FVC < LLN$		$FEV_1/FVC < LLN$, stage 2-4	
	no symptoms (reference) n=3342	with symptoms n=2161	All n=310	With symptoms n=144	All n=307	With symptoms n=216
Diabetes, n (%) missing n=6	71 (2.1)	84 (3.9)	4 (1.3)	2 (1.4)	16 (5.2)	10 (4.6)
P value		0.001	0.406	0.360	0.001	0.017
Hypertension, n (%) missing n=9	429 (12.8)	471 (21.8)	45 (14.5)	28 (19.4)	62 (20.2)	49 (22.7)
P value		<0.001	0.402	0.022	<0.001	<0.001
Cardiac disease, n (%) missing n=5	152 (4.6)	220 (10.2)	13 (4.2)	6 (4.2)	26 (8.5)	22 (10.2)
P value		<0.001	<0.775	0.831	0.002	<0.001
BMI <21 kg/m^2, n, (%)	223 (6.7)	127 (5.9)	20 (6.5)	8 (5.6)	16 (5.2)	12 (5.6)
BMI 21 – 24.9 kg/m^2 n, (%)	1520 (45.5)	740 (34.2)	146 (47.1)	66 (45.8)	96 (31.4)	61 (28.4)
BMI 25 – 29.9 kg/m^2 n, (%)	1233 (36.9)	813 (37.6)	108 (34.8)	46 (31.9)	124 (40.5)	88 (40.9)
BMI 30+ kg/m^2 n, (%) missing n=19	366 (11.0)	481 (22.3)	36 (11.6)	24 (16.7)	70 (22.9)	54 (25.1)
P value		<0.001	<0.895	0.159	<0.001	<0.001
Atopy with rhinitis‡, n (%) missing n=601	487 (14.6)	288 (13.5)	37 (12.1)	14 (9.8)	50 (16.5)	33 (15.6)
P value		0.226	0.202	0.103	0.394	0.726
Physician diagnosed asthma, n (%) missing n=4	132 (4.0)	215 (10.0)	39 (12.6)	30 (20.8)	88 (28.7)	72 (33.3)
P value		<0.001	<0.001	<0.001	<0.001	<0.001

All statistical comparisons [χ^2 test or †Wilcoxon rank sum test] made with "$FEV_1/FVC \geq 0.7$ & no respiratory symptoms" (reference group).
‡:presence of atopy (positive phadiatop and rhinitis [2002]) BMI: body mass index

Table 3 details the adjusted odds ratios (OR) of stage 2-4 and stage 1 AO at SAPALDIA 2 for different exposures. Smoking was the strongest risk factors for all stages of AO and age played a role for stage 2-4 AO. However, odds ratio of stage 2-4 AO in association with smoking were higher than for stage 1(OR $_{\text{stage 2-4}}$ 1.25 [CI95%1.19-1.30] vs OR $_{\text{stage 1}}$ 1.12[CI95%1.05-1.30] for each ten unit pack-year increase). Obesity or physical inactivity were not associated with AO. Physician diagnosed asthma was associated with AO for stage 1 and stage 2-4.

In a sensitivity analysis, when examining these exposures for stage 2-4 AO as defined using the fixed ratio of FEV_1/FVC instead of the LLN definition, we found a strong association between ageing and AO for stage 1 and 2-4.

Table 3 Adjusted odds ratio of stage 2-4 airflow obstruction*

Characteristics at SAPALDIA 2 (2002) n=6126	$FEV_1/FVC<LLN$, stage 1 n=310/5819‡	$FEV_1/FVC<LLN$, stage 2-4 n=307/6126
Age 30-39	ref	ref
Age 40-49	0.95 (0.68 1.32)	1.37 (0.87 2.17)
Age 50-59	0.69 (0.48 0.98)	1.62 (1.05 2.51)
Age 60-69	0.70 (0.48 1.02)	2.09 (1.34 3.25)
Age 70+	0.82 (0.46 1.47)	2.76 (1.55 4.91)
Women (vs men)	1.67 (1.31 2.13)	0.82 (0.64 1.05)
Tobacco smoke exposure		
Ever smoker (2002) (vs never)	1.42 (1.11 1.80)	1.76 (1.36 2.28)
Pack year (per 10 unit increase)∫	1.12 (1.05 1.19)	1.25 (1.19 1.30
Environmental tobacco smoke exposure		
Not exposed	ref	ref
≤ 3 hours/week	1.08 (0.79 1.49)	1.09 (0.79 1.51)
> 3 hours/week	0.79 (0.52 1.21)	1.25 (0.86 1.80)
ETS† during childhood (maternal exposure)	1.44 (1.04 1.99)	0.82 (0.55 1.21)
Socio-economical status		
Low education (vs high)	1.11 (0.66 1.85)	1.28 (0.78 2.11)
Non Swiss nationals (vs Swiss)	0.80 (0.54 1.18)	1.25 (0.89 1.73)
Professional exposure to dust, smoke or fumes,	1.01 (0.76 1.36)	0.91 (0.68 1.22)
Physical activity	1.29 (1.00 1.67)	0.88 (0.67 1.17)
Associated conditions		
Atopy with rhinitis‡‡	0.90 (0.63 1.28)	1.67 (1.21 2.31)
Physician diagnosed asthma	2.10 (1.47 3.00)	6.70 (5.04 8.91)
BMI <21 kg/m^2	ref	ref
BMI 21 – 24.9 kg/m^2	1.26 (0.77 2.05)	0.80 (0.46 1.39)
BMI 25 – 29.9 kg/m^2	1.12 (0.67 1.87)	0.91 (0.52 1.60)
BMI 30+ kg/m^2	0.85 (0.48 1.52)	1.14 (0.64 2.05)

*adjusted for age, sex, smoking exposure and study area †ETS: environmental tobacco smoke. ∫: Lifetime smoking for ever smokers (per 10 pack-year increase) BMI: body mass index**.** ‡ subjects with stage 2-4 were excluded. ‡‡ at SAPALDIA 1

Quality of life and respiratory care utilization for subjects with airflow obstruction

Table 4 details the quality of life scores of normal subjects and subjects with obstruction. Out of 6126 subjects, 5278 (86.2%) filled the SF-36. AO and symptomatic AO were systematically associated with lower health-related quality of life and more so for those with stage 2-4 AO and symptoms. Respiratory care utilization increased with severity of AO and symptoms.

Table 4: Quality of life scores and respiratory health care utilisation in normal subjects, subjects with airflow obstruction and/or respiratory symptoms in SAPALDIA 2 (2002)

Characteristics at SAPALDIA 2 (2002)	$FEV_1/FVC \geq LLN$		$FEV_1/FVC < LLN$ & Stage 1		$FEV_1/FVC < LLN$ & Stage 2-4	
	no symptoms (reference) n=2897	With symptoms n=1842	All n=279	With symptoms n=129	All n=258	With symptoms n=182
SF-36 scores, mean (SD)						
Physical Functioning	93.7 (12.9)	84.2 (19.4)*	89.2 (15.7)*	84.5 (16.6)*	80.6 (20.2)*	78.3 (19.2)*
Role Physical	92.3 (21.8)	82.6 (31.4)*	88.4 (27.5)*	83.2 (33.1)*	81.1 (33.1)*	80.3 (32.5)*
Bodily pain	85.4 (21.1)	73.9 (24.3)*	80.0 (23.6)*	74.5 (25.1)*	76.8 (25.2)*	75.0 (25.1)*
General Health	65.0 (11.4)	61.1 (13.1)*	63.5 (12.9)†	61.7 (13.0)*	59.8 (13.5)*	58.2 (13.5)*
Vitality	67.5 (15.0)	59.0 (17.1)*	63.9 (17.3)*	59.6 (18.8)*	59.5 (18.4)*	58.2 (18.1)*
Social Functionning	90.3 (16.1)	82.5 (20.4)*	85.8 (20.9)*	79.5 (24.4)*	83.8 (19.7)*	82.8 (19.2)*
Role Emotional	92.1 (21.7)	82.6 (31.2)*	86.8 (29.7)*	78.3 (36.4)*	82.9 (32.2)*	81.6 (32.7)*
Mental Health	77.6 (13.7)	70.9 (16.6)*	74.6 (16.6)*	70.6 (18.8)*	72.8 (15.4)*	71.9 (15.7)*
Physical component summary	53.3 (6.5)	50.1 (9.4)*	52.0 (8.0)*	50.6 (8.8)*	48.6 (9.6)*	48.0 (9.1)*
Mental component summary	51.7 (7.5)	48.5 (9.3)*	50.1 (9.5)*	47.5 (11.4)*	49.8 (8.8)*	49.4 (9.1)*
Respiratory care utilisation#	206/3344 (6.2%)	405/2161 (18.7%)*	50/310 (16.1%)*	36/144 (25.0%)*	92/307 (30.0%)*	81/216 (37.5%)*

All statistical comparisons [χ^2 test or t-test for unequal variances] made with reference group "$FEV_1/FVC \geq LLN$ & no respiratory symptoms". *: $P<0.001$ †:$P=0.06$ #Report of emergency room visit, hospitalisation, ambulatory visit (all for respiratory problems) or report of inhaler use during the year preceding SAPALDIA 2 (2002).

Airflow obstruction in never smokers

Of 307 subjects with stage 2-4 AO at SAPALDIA 2, 90 (29.3%) were never smokers. Examined by smoking status, prevalence of stage 2-4 AO was 6.3% [CI95% 5.3% – 7.6%] for ever smokers and 3.4% [CI95% 2.7% – 4.3%] for never smokers. **Table 5** reports the distribution of various risk factors and covariates for stage 2-4 AO in subjects without or with smoking history. Never smokers with stage 2-4 AO were younger (p=0.003) and more often women (52.2% vs 36.9%, p=0.013). A third of never smokers with stage 2-4 AO reported asthma at SAPALDIA 1 (34.8% vs 18.0% for smokers with similar AO severity, p=0.001). Atopy was more frequent in never-smoker with AO. Chronic cough and phlegm were similarly distributed and health-related quality of life equally impaired in smokers and never smokers with AO. Respiratory care utilization tended to be more frequent in never smokers with AO (36.7% vs 27.2%, P=0.099) despite higher rate of reported shortness of breath in smokers.

Table 6 shows the adjusted OR of stage 2-4 AO associated with various risk factors in never smokers and smokers. Positive methacholine challenge was a risk factor for both categories. However, for never smokers, male sex and asthma at SAPALDIA 1 were stronger risk factors of AO than for smokers. In contrast with never smokers, smokers were older and more exposed to ETS. Interestingly in smokers, asthma was not associated with development of AO at SAPALDIA 2 after adjustment for covariates.

We found a significant interaction between smoking status and asthma (p=0.044).

Table 5: Characteristics of never-smokers and smokers with stage 2-4 airflow obstruction at SAPALDIA 2

Characteristics at SAPALDIA 2 (2002) n=307	$FEV_1/FVC<LLN$, stage 2-4		P value
	never smokers n=90	ever smokers n=217	
Age, mean (SD)	52.4 (12.3)	56.8 (9.7)	0.003†
Age 30-39, n (%)	15 (16.7)	13 (6.0)	
Age 40-49, n (%)	26 (28.9)	37 (17.1)	
Age 50-59, n (%)	18 (20.0)	79 (36.4)	<0.001
Age 60-69, n (%)	26 (28.9)	69 (31.8)	
Age 70+, n (%)	5 (5.6)	19 (8.8)	
Men, n (%)	43 (47.8)	137 (63.1)	0.013
Women, n (%)	47 (52.2)	80 (36.9)	
Environmental tobacco smoke			
ETS* not exposed, n (%)	74 (83.2)	137 (63.1)	
≤ 3 hours/week, n (%)	10 (11.2)	44 (20.3)	0.003
> 3 hours/week, n (%)	5 (5.6)	35 (16.1)	
Asthma and atopy at SAPALDIA 1			
Physician diagnosed asthma, n (%)	31/89 (34.8)	39/217 (18.0)	0.001
Physician diagnosed asthma at SAPALDIA 2, n (%)	33/90 (36.7)	55/217 (25.4)	0.046
Atopy with rhinitis, n (%)	24/88 (27.3)	26/215 (12.1)	0.001
Atopy (positive phadiatop or positive prick test), n (%)	50/85 (58.8)	74/195 (38.0)	0.001
Positive phadiatop, n (%)	43/85 (50.6)	64/195 (32.8)	0.005
Seasonal rhinoconjonctivitis, n (%)	28/89 (31.5)	35/215 (16.3)	0.003
Total IgE (n, geometric mean with [CI 95%])	47 [34-66] n=81	53 [44-65] n=187	0.643‡
Positive methacholine challenge, n (%)	25/43 (58.1)	67/110 (60.9)	0.753
Respiratory symptoms at SAPALDIA 2			
Any respiratory symptoms n, (%)	55 (61.1)	161 (74.2)	0.022
Chronic cough n, (%)	12 (13.3)	39 (18.0)	0.320
Chronic phlegm n, (%)	17 (18.9)	50 (23.0)	0.423
Chronic shortness of breath n, (%)	33 (36.7)	116 (53.5)	0.007
SF-36 scores at SAPALDIA 2	n=73	n=185	
Physical component summary, mean (SD)	49.6 (9.4)	48.2 (9.7)	0.305†
Mental component summary, mean (SD)	49.5 (8.4)	49.8 (9.0)	0.806†
Respiratory care utilisation#, %	33 (36.7)	59 (27.2)	0.099

*ETS: environmental tobacco smoke, †:unequal variances t-test ‡: Wilcoxon rank sum test, #Report of emergency room visit, hospitalisation, ambulatory visit (all for respiratory problems) or report of inhaler use during the year preceding SAPALDIA 2 (2002).

Table 6: Adjusted odds ratio of stage 2-4 airflow obstruction in never smokers and smokers

	FEV_1/FVC<LLN, stage 2-4 in never smokers n=42*/2065	**FEV_1/FVC<LLN, stage 2-4 in ever smokers n=110*/2718**
Age (per one year increase)	1.01 (0.98 1.03)	1.03 (1.01 1.05)
Age 30-39	ref	ref
Age 40-49	1.38 (0.58 3.30)	1.86 (0.68 5.12)
Age 50-59	0.72 (0.27 1.96)	2.34 (0.87 6.29)
Age 60-69	1.34 (0.52 3.45)	3.74 (1.37 10.20)
Age 70+	1.59 (0.40 6.27)	3.57 (0.96 13.22)
Men	ref	ref
Women	0.45 (0.23 0.87)	0.92 (0.59 1.43)
Environmental tobacco smoke		
Not exposed at SAPALDIA 2	ref	ref
≤ 3 hours/week	0.91 (0.30 2.71)	1.10 (0.64 1.91)
> 3 hours/week	1.54 (0.44 5.32)	1.87 (1.05 3.31)
Characteristics at SAPALDIA 1		
Positive methacholine challenge	8.20 (4.16 16.17)	9.64 (6.20 15.02)
Physician diagnosed asthma	3.25 (1.45 7.31)	1.32 (0.67 2.56)

Adjusted for age (categorical), sex, methacholine challenge test, environmental tobacco smoke (categorical), smoking, physician diagnosed asthma at SAPALDIA 1 and study area (random effect). P-value of goodness of fit test for never smokers (P=0.92) and ever smokers (P=0.22)

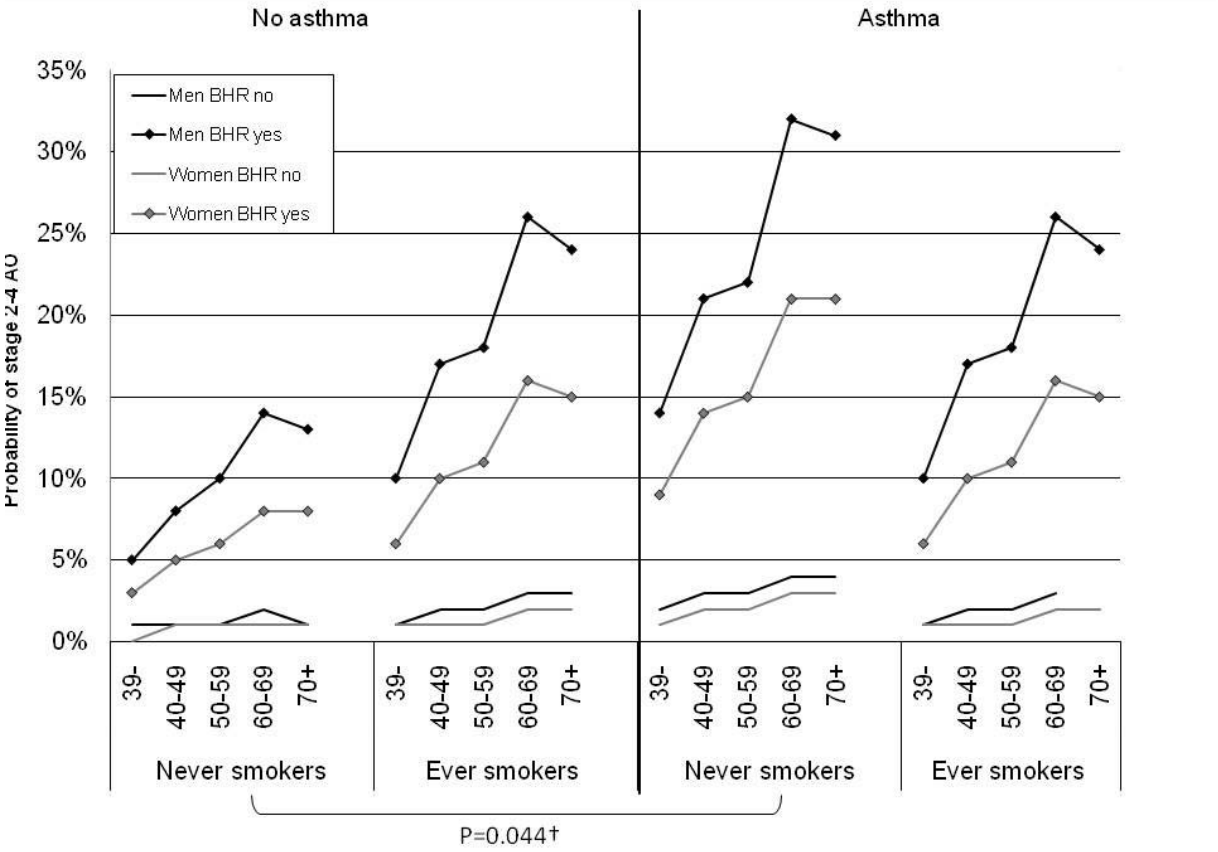
These analyses were repeated after exclusion of subjects with FEV_1 <80% of predicted value at SAPALDIA 1 because they may already have AO. We observed similar relationship between risk factors and AO in this restricted analysis compared to the ones in table 6. Interaction between asthma and smoking status remained significant.

In order to isolate potential risk factors associated with AO in never smokers without asthma in 1991, we repeated these analyses after excluding subjects with asthma. Age, positive methacholine challenge test were still significantly associated with obstruction, while atopy was not **(online supplementary table B)**.

Figure 3 shows the probability estimates of stage 2-4 obstruction stratified on asthma and smoking status. Probabilities of stage 2-4 AO were highest in males, aged 60 or higher with

asthma and positive methacholine challenge in 1991. In both sexes, for smokers and never smokers, positive methacholine challenge and asthma predicted a high risk of AO, (P value for interaction 0.044).

Figure 3: Probabilities of stage 2-4 obstructive lung disease at SAPALDIA 2 (2002) by categories of asthma and smoking status*



*controlled for age, sex, methacholine challenge test, environmental tobacco smoke and study area. No asthma/asthma relates to « physician diagnosed asthma » at first survey (1991).

BHR: methacholine bronchial hyper-reactivity.

†: P value for interaction between smoking status and asthma

Sensitivity analysis

The effect of non-participation at SAPALDIA 2 on the prevalence of AO is estimated in **online supplement table C**. Using our logistic regression models weighting each

observation by the inverse of the propensity of participation, we found only slightly higher prevalence of AO among older subjects (see **online supplement table A** for variables entered into the model) .

We also repeated our analyses using the European Respiratory Society reference values and the NHANES reference values. We found a slightly lower prevalence of stage 2-4 AO using our population specific reference values compared to the NHANES reference, mainly because some subjects move from stage 2 disease to stage 1 AO. However, proportion of subjects with airflow obstruction as defined with the LLN ratio, proportion of never smokers in subjects with AO and risk factors for AO were not sensitive to changes in reference values.

DISCUSSION

The present study is the first one to provide population-based estimates of the prevalence of airflow obstruction in Switzerland as defined by lower limit of normal FEV_1/FVC ratio and FEV_1 <.8 predicted. We found that AO prevalence steadily increases from 3.2 % of the Swiss male adult population aged 30-39 to 8.9% for those aged 60-69 and 15.0% in those aged 70 or more. Women were less affected with prevalence growing from 1.9% for those aged 30-39 to 5.0% for those aged 60-69. One third of subjects with stage 2-4 AO had never smoked. Prevalence of stage 2-4 AO was 6.3% in smokers and 3.4% in never smokers.

International comparisons

Compared to the multinational BOLD or the Spanish EPI-SCAN studies, which used post-bronchodilation GOLD criteria to define and grade COPD, prevalence of AO in Switzerland appears in the lower range both for men and for women, despite the fact that no post-bronchodilators PFTs were performed in SAPALDIA[4, 15]. In particular, prevalence of

stage 2-4 AO in Switzerland is lower for subjects aged 60+ compared to age specific strata of the BOLD study. This finding remained valid when the fixed FEV1/FVC ratio instead of the LLN ratio was used. For example, in Salzburg (Austria) post-bronchodilator stage 2-4 AO prevalences are 22.3% and 25.0% for men and women 70+, in SAPALDIA these rates were 15.0% for men and 2.4% for women of similar age groups. Lower prevalence of smoking and smaller pack-years for smokers in SAPALDIA than in the BOLD study may explain part of these differences. Other factors could contribute to the lower prevalence of COPD in Switzerland: high household income, easy access to health care, low exposure to fumes from wood stove or organic dust [7].

In accordance with previously published literature on COPD, ageing, smoking, male sex and low education were all associated with AO[4, 16, 17].

Airflow obstruction in never smokers

One third of subjects with airflow obstruction are never smoker. From a different perspective, 3.4% of never-smokers have clinically significant (FEV_1 <80%) obstruction. The proportion of never smokers in subjects with AO is higher than described in other population-based study. In epidemiologic studies from developed countries, this percentage varies from 12.2% to 27.7% [5, 6, 18-21]. It is likely that the proportion of never smokers among subjects with COPD will increase in the future, since the proportion of COPD attributable to smoking will slowly decrease in parallel with tobacco consumption, at least in developed countries[22].

Risk factors of obstruction differ in smokers and never smokers[23]. Air pollution has been associated with respiratory symptoms, adult onset asthma and lung function decline[24-26]. Environmental tobacco smoke may lower quality of life and trigger respiratory symptoms in never smokers[27]. However, in this study, air pollution or ETS were not associated with stage 2-4 AO in never smokers. Behrendt et al or Celli et al, both using the NHANES

population were also not able to identify ETS as a risk factor for COPD[5, 28]. This contrasts with two recent Chinese studies, which found an association between ETS and obstruction in never-smokers[29, 30]. Such an association might be missed if subjects with obstruction succeed to avoid exposure to ETS. Interestingly, we found that ETS was an independent predictor of obstruction in smokers after controlling for smoking history. This suggests that ETS exerts indeed a negative effect on lung function when it cannot be avoided.

We found that positive methacholine challenge test was associated with AO in smokers and never smokers with AO. Asthma and bronchial hyper-reactivity play a specific and important role in increasing the risk of AO in never smokers. A previous SAPALDIA publication extensively described this association[31] and asthma was found to be associated with COPD in never smokers before[28, 32]. The finding that bronchial hyper-reactivity is a marker and a risk factor COPD has been described as the "Dutch hypothesis"[33]. This hypothesis is supported by recent genetic association studies. Genetic single nucleotide polymorphism variants appear to reduce both the risk of asthma or COPD in subjects exposed to smoking[34, 35]. But so far, no similar genetic variants have been described to explain the risk of AO in never smokers. Interestingly, when analysing the risk factors for AO after excluding subjects reporting asthma at SAPALDIA 1, we found a similar role of bronchial hypereactivity. Under reporting of asthma could explain this association as suggested by other studies. [36]

Erroneous classification of COPD as asthma in SAPALDIA 1 could have biased our estimates of AO caused by asthma in SAPALDIA 2. To rule out this possibility, we excluded subjects with low FEV_1 (more likely to have AO) at SAPALDIA 1 and found that asthma still predicted AO at SAPALDIA 2. This provides strong evidence that asthma is a risk factor for future AO, as suggested by other longitudinal studies[32, 37-39].

Airflow obstruction in never smokers is important for several reasons. First, symptoms are equally present, quality of life similarly altered and respiratory care utilization tends to be higher in never smokers compared to smokers with AO. Domingo-Salvany et al showed that symptoms and quality of life are strong predictors of mortality in COPD[40]. Second the common diseases associated with COPD in smokers are also reported in never smokers with COPD. For example, Turner et al found an increased risk of lung cancer (hazard ratio 1.66) for never smokers with COPD compared to those without COPD. Other studies reported an association between low FEV_1 and incident cardiovascular disease independently of smoking [41, 42].

Strengths and limitations

Our estimates of airflow obstruction among adult living in Switzerland are likely to be accurate because the SAPALDIA study is a large representative sample of the population [8]. For instance, the prevalence of smoking in the SAPALDIA cohort is very close to the one having been determined in a larger population-based survey in Switzerland[43].

Limitations deserve mention too. First, our pulmonary functions tests were performed without bronchodilators. Lack of bronchodilation may overestimate the prevalence of AO. CITE Perez-padilla [44]. Misclassification due to absence of bronchodilation has been shown to be greater among younger subject and those with normal FEV_1. Median age of our cohort is 53 and we focused our analyses on subjects with FEV1 < 80% predicted. In addition, we integrated respiratory symptoms in our report to further reduce overdiagnosis. Second, differential loss for follow up might in turn lead to an underestimation of the prevalence of obstruction at SAPALDIA 2. Nonetheless, our weighted analysis taking into account the factors linked to non-participation at follow up study, provided estimates closed to the actual results.

Conclusions

In summary, prevalence of symptomatic stage 2-4 airflow obstruction in Switzerland steadily increases from 3.2% and 1.9% in young men and women respectively to 15.0% and 5.0% in older age categories. These prevalences appear at the lower range compared to other regions of the world with similar age distribution. One third of subjects with obstruction are never smokers who frequently report a history of asthma and have positive methacholine challenge test. Awareness of airflow obstruction in never smokers deserves attention, because it appears to be frequent and has similar health impact than in smokers.

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