Thorax Online First, published on May 2, 2006 as 10.1136/thx.2005.052241

BRONCHIAL HYPERRESPONSIVENESS AND THE DEVELOPMENT OF ASTHMA AND COPD IN ASYMPTOMATIC INDIVIDUALS - SAPALDIA COHORT STUDY

MARTIN H. BRUTSCHE[1], SARA H. DOWNS[2], CHRISTIAN SCHINDLER[2], MARGARET W. GERBASE[3], JOEL SCHWARTZ[4], MARTIN FREY[5], ERICH W. RUSSI[6], URSULA ACKERMANN-LIEBRICH[2], PHILIPPE LEUENBERGER[7] FOR THE SAPALDIA TEAM*

[1]Pneumology, University Hospital Basel, Basel, Switzerland,
[2]Institute for Social and Preventive Medicine, University of Basel, Switzerland,
[3]Pneumology, Hôpital Cantonal Universitaire, Geneva, Switzerland,
[4]Harvard School of Public Health, Boston, United States of America,
[5]Klinik Barmelweid, Barmelweid, Switzerland,
[6]Pneumology, University Hospital Zurich, Zurich, Switzerland,
[7]Pneumology, Centre Hôpitalier Universitaire Vaudois, Lausanne, Switzerland.

*SAPALDIA Team

Senior scientific team - Ph. Leuenberger (p) co-dir and U. Ackermann-Liebrich (e) co-dir. J.C. Barthélémy (c), W. Berger (g), R. Bettschart (p)A. Bircher (a), K. Blaser (a), G. Bolognini (p), O. Brändli (p), M. Brutsche (p), L. Burdet (p), S. Downs (e/s), M. Frey (p), J.M. Gaspoz (c), M. W. Gerbase (p), D. Gold (e/c/p), W. Karrer (p), R. Keller (p), B. Knöpfli (p), N. Künzli (e/exp), A. Morabia (e), U. Neu (exp), L. Nicod (p), A.P. Perruchoud (p), M. Pons (p), N. Probst Hensch (g/e), Th. Rochat (p), E. W. Russi (p), C. Schindler (s), P. Schmid-Grendelmeyer (a), J. Schwartz (e), F. Schwarz (p), P. Straehl (exp), J.M. Tschopp (p), A. von Eckardstein, J.P. Zellweger (p), E. Zemp Stutz (e).

Scientific team at coordinating centers - L. Bayer-Oglesby (exp), D. Felber Dietrich (c), M. Imboden (g), D. Keidel (s), P. Städele-Kessler (s), M. W. Gerbase (p), S. Downs (e).

Scientific team at local study sites - C. Burrus, D. Felber Dietrich, U. Egermann, M. Gerbase, R. Gimmi, A. Kick, N. Lutz, R. Keller.

Specialities: (a) allergology, (c) cardiology, (cc) clinical chemistry, (e) epidemiology, (exp) exposure, (g) genetic and molecular biology, (m) meteorology, (p) pneumology, (s) statistics.

Address for correspondence and reprints:

Martin Brutsche, MD, PhD
Pneumologie, University Hospital Basel, Petersgraben 4, CH-4031 Basel, Switzerland
Fax +41 61 265 45 87, Tel. +41 61 265 51 95, e-Mail: mbrutsche@uhbs.ch

Key Words: chronic cough, bronchial challenge, airflow obstruction, epidemiologic study, methacholine

Word count of body text: 3551 (max 3500, introduction to acknowledgment)

Running head: BHR confers risk for asthma & COPD

(ABSTRACT)

Background: Bronchial hyperresponsiveness (BHR) is a common feature of asthma. However, BHR is also present in asymptomatic individuals and its clinical and prognostic significance is unclear. We hypothesized that BHR might play a role in the development of COPD as well as asthma.

Methods: In 1991, respiratory symptoms and BHR to methacholine were evaluated in 7'126 of the 9'651 SAPALDIA cohort study participants. Eleven years later, 5'825 of these participants were re-evaluated of whom 4'852 had spirometry. COPD was defined as $FEV_1/FVC < 0.70$.

Results: In 1991, 17% of participants had BHR, of whom 51% were asymptomatic. Eleven years later the prevalence of asthma, wheeze and shortness of breath in formerly asymptomatic subjects with or without BHR were respectively 5.7% vs. 2.0%, 8.3% vs. 3.4% and 19.1% vs. 11.9% (all $p<0.001$). Similar differences were observed for chronic cough (5.9% vs. 2.3%; $p=0.002$), and COPD (37.9% vs. 14.3%; $p<0.001$). BHR conferred an adjusted OR of 2.9 (95%Cl 1.8-4.5) for wheezing at follow-up among asymptomatic participants. The adjusted ORs for COPD was 4.5 (95%Cl 3.3- 6.0). Silent BHR was associated with a significantly accelerated decline in FEV_1 by 12 (5 -18) mL/y, 11 (5-16) mL/y and 4 (2-8) mL/y in current smokers, former smokers and never smokers at SAPALDIA 2, respectively.

Conclusions: BHR is a risk factor for an accelerated decline in FEV_1 and the development of asthma and COPD irrespective of atopic status. Current smokers with BHR have a particularly high loss of FEV_1.

Word count of abstract: 242

INTRODUCTION

Bronchial hyperresponsiveness (BHR) is a common finding in asthma [1] and has also been observed in patients with chronic obstructive airways disease (COPD)[2]. Cross-sectional studies have found significant associations between BHR and respiratory symptoms, including wheezing, cough and shortness of breath.[3] [4] [5] Population-based studies, including the first cross-sectional Swiss study on Air Pollution and Lung Diseases in Adults (SAPALDIA), suggest that between 11 and 20% of individuals have BHR.[4] [6] However, a significant proportion of individuals with BHR do not suffer from respiratory symptoms, asthma or other obstructive airways diseases. It is thought that the proportion of asymptomatic individuals with BHR ranges from 19-62% in the general population.[7] Thus, many subjects with BHR are asymptomatic, or "silent". Although presence of BHR has been positively associated with the development of respiratory symptoms and negatively associated with symptom remission in a longitudinal study of 2'684 adults.[8] [9], the relevance and long-term impact of BHR in the absence of symptoms is not yet fully elucidated.

Prevailing current opinion is that classical asthma is characterised by two main features that occur together: Firstly, (allergic) inflammation with airway thickening and mucus formation,[10] and secondly, airway smooth muscle dysfunction with BHR.[11].BHR or airway inflammation alone are probably not sufficient to cause asthma, but might be independent risk factors for the development of symptomatic airway dysfunction.[12] Indeed, there is good evidence that allergic sensitization is a risk factor for the development of asthma.[13] [14] In a relatively small study of 194 adults Segala et al.[15] found that BHR to methacholine was a predictor of wheezing in a 5-year follow-up study independent of atopic status. In asthmatics prolonged treatment with inhaled or systemic corticosteroids can reduce, but often do not abrogate BHR.[16] Thus, although often associated with airway inflammation,[17] it has not, as yet, been clarified whether BHR is truly an independent risk factor for the development of asthma.

Still less is known about the association between BHR and COPD. The probability of decline of 20% or more in FEV_1 in response to a provoking concentration of <3'000 µmol of inhaled methacholine is partially dependent on baseline lung function,[18]which must be addressed in studying the relation between BHR and COPD. However, apart from its role in the modern dual feature asthma hypothesis, BHR could also be a risk factor for the development and progression of COPD, particularly, in situations where BHR occurs alongside a non-allergic, typically cigarette smoke-induced airway inflammation. The potential interaction between smoking and BHR was documented in the Lung Health Study,[19] a 5-year, randomised, prospective clinical study of 4'201 patients with mild COPD. The study showed that BHR improved after smoking cessation. Along these lines, the European Community Respiratory Health Survey,[20] a large epidemiological study of random population samples of 22 European regions, revealed that smoking was a risk factor for an increase in BHR over time in 3'993 participants. On the other hand, the Normative Aging Study,[21] which studied 435 men and excluded those with symptoms, identified no relation of change in BHR over 3 years to smoking status. In a study of bronchial biopsies, Willemse et al.[22] found that bronchial inflammation was similar in current smokers with COPD and asymptomatic smokers but lower in non-smoking patients with COPD. The authors concluded that the inflammatory effects of current smoking may mask the underlying ongoing inflammatory process pertinent to COPD. Thus, smoking could play the role of an unspecific "amplifier".

The current population-based longitudinal survey investigates the relevance of BHR in asymptomatic adults with respect to a range of prospective clinical outcomes. We hypothesized that asymptomatic BHR in 1991 is a risk factor for the development of respiratory symptoms, and a risk factor for asthma and COPD 11 years later.

METHODS

Study design and population

The methodology and selection of the participants of the SAPALDIA prospective cohort study have been described in detail.[23] [24] The population was a random sample (18-60 years) recruited from eight areas of Switzerland using population registries in 1990. Health examinations were conducted for SAPALDIA 1 in 1991. The second round of health examinations in 2002 (SAPALDIA 2) included identical protocols to those in the first survey. Of the 9'651 participants in 1991, 7'126 had a methacholine challenge. Subjects were included in the present analysis if spirometry and bronchial challenge data were available from SAPALDIA 1 and questionnaire data were available from both surveys (n=5'825). Of these, 4'852 had spirometry done at both surveys. Ethical approval for the study was given by the central ethics committee of the Swiss Academy of Medical Sciences and the Cantonal Ethics Committees for each of the eight examination centres.

Respiratory symptoms, phenotype definitions and smoking habits

Information about respiratory symptoms, smoking habits and other risk factors was gathered through an interview administered questionnaire based on the European Community Respiratory Health Survey (ECRHS) questionnaire.[25] Symptoms examined were 'wheeze without cold in the last 12 months', 'shortness of breath when hurrying on level ground or walking up a slight hill', 'chronic cough – cough during the day or night on most days for as much as 3 months each year for more than 2 years' and 'chronic phlegm – phlegm during the day or night on most days for as much as 3 months each year for more than 2 years'. Asymptomatics were defined as participants without wheeze, shortness of breath, chronic cough, chronic phlegm nor physician-diagnosed asthma at SAPALDIA 1. Participants with a FEV_1/FVC-ratio of less than 0.70 without a physician's diagnosis of asthma were classified as having evidence of chronic obstructive airways disease (COPD).[26] Asthma was defined as physician-diagnosed asthma. Smokers were participants who had smoked ≥20 packs of cigarettes or ≥360 g of tobacco in their lifetime. Former smokers were smokers who had quit smoking at least one month before examination in 2002 and current smokers were participants who reported active smoking at the interview in 2002. Cigarette exposure of participants was assessed by pack-years. Participants were asked not to smoke in the hour before the examination and recent exposure to smoking was validated by the measurement of carbon monoxide (CO) concentration in exhaled air using an EC 50 Micro-Smokerlizer.

Assessment of pulmonary function, bronchial responsiveness and atopy

The same spirometers (SensorMedics 2200 SP Yorba Linda, USA) were used in 1991 and in 2002.[24] [27] The protocol for the measurement of lung volumes and flows was identical to that in the European Community Respiratory Health Survey and complied with American Thoracic Society recommendations.[5] Participants were requested not to use short acting inhalers four hours and long-acting inhalers eight hours prior to the examination appointment.

Participants able to produce technically satisfactory spirometry and who satisfied health inclusion criteria were invited to have a bronchial challenge. Non-specific bronchial responsiveness was assessed by bronchial challenge with methacholine chloride administered by MEFAR aerosol dosimeters.[23] The challenge schedule started with an inhalation of saline followed by increasing concentrations of methacholine up to a cumulative dose of 8.37

μmol. The test was stopped when either the maximum cumulative dose had been reached or FEV_1 had fallen by 20% or more.[6] Bronchial hyperreactivity (BHR) to methacholine was defined as presence of a 20% or greater drop in FEV_1 compared to the highest FEV_1-value measured during the test in response to inhalation of methacholine to the maximum dose and the degree of bronchial reactivity was measured by calculating a dose-response slope.[28] The slope was defined as the ratio between percentage decline in FEV_1 and total cumulative dose administered. Since the distribution of the slopes was skewed, data were transformed using natural logarithms before analysis. A small constant (i.e. 0.01) was added before transformation in order not to loose observations with zero slope.

Skin prick tests were conducted in 1991 in accordance with the ECRHS allergy testing protocol and included testing sensitization to house dust mite (*Dermatophagoides pteronyssinus*), cat, dog, fungi (*Cladosporium* and Alternaria *spp.*), timothy grass, birch and parietaria pollen.[23] [25] Participants were classified as atopic if they developed a skin wheal to one or more of the allergens with a mean diameter exceeding the one of the negative control wheal by at least 3 mm.

Statistical analysis

Univariate and bivariate analyses were conducted initially to provide descriptive statistics. Logistic regression was used to model relations between presence and absence of BHR in asymptomatic subjects in 1991 and new symptoms at follow-up (2002) whilst adjusting for potential confounders. Factors tested as potential confounders included age, sex, atopy, smoking status, pack years, FVC at baseline, height, body mass index at baseline, change in weight, level of education, exposure to environmental tobacco smoke (ETS), exposure to dust and fumes at work and study area. FVC was included as a proxy for lung size and airway caliber.[6] [29] In addition, effect modification of the relation between BHR and new symptoms by sex, atopy and smoking status (current, former or never smoker at SAPALDIA 2) were investigated. The relation between responsiveness to methacholine and symptoms and COPD 11 years later was also examined with responsiveness measured by the continuous variable 'slope'. Potential non-linearities in the associations between methacholine slope at SAPALDIA-1 and outcomes at SAPALDIA-2 were tested by adding the square and the cube of slope as covariates. Percent risks of new symptoms or COPD at follow-up associated with presence of absence of BHR were estimated from the logistic regression models upon adjusting covariates to their population means.

The effect of BHR at baseline on change in FEV_1 was modelled by linear regression adjusting for relevant confounders listed above and for baseline FEV_1. Analyses were conducted using STATA (STATA Corporation, Texas 77845, Special Edition release 8.2). P-values <0.05 and <0.1 were interpreted as statistically significant for main and interaction effects, respectively.

RESULTS

Population characteristics

Of the initial 9'651 participants in SAPALDIA 1, 7'126 underwent a methacholine challenge. Reasons for lack of a challenge included technically poor baseline spirometry, refusal, exclusions on the basis of health criteria including heart disease, epilepsy, pregnancy, lactation and use of beta-blockers [23], and 135 (1.4%) participants were excluded due to a baseline-FEV_1 less than 70 % predicted or lower than 1.5 L [30]. Of the 7'126 participants with a valid bronchial challenge test in 1991, 5'825 were re-evaluated in 2002 and are included in the current analyses. Of these, 4'852 had spirometry and 3'931 were asymptomatic at SAPALDIA 1. A total of 222 participants were excluded from the multivariate analyses because of either inconsistent information about smoking habits between surveys or exhaled carbon monoxide concentrations of more than 10 ppb despite claiming to be a never or former smoker.

Non-participants of the second evaluation in 2002 (n=1'301) were compared to the participants of both evaluations (Table 1). Slightly more males, smokers, persons with low educational background, with professional exposure to fumes and dust, and more individuals with respiratory symptoms were non-participants in the follow-up evaluation.

Table 1. Characteristics of subjects with bronchial challenge at baseline according to whether they participated in both surveys or only in the first one.

Participants	SAPALDIA 1&2	SAPALDIA 1 only	p-value
n=	5825	1301	
Women [%]	50.3	45.5	0.002
Height [cm] (mean ± SD)	169±9	169±9	0.14
Weight [kg] (mean ± SD)	69±13	69±14	0.12
FEV_1 [L/sec] (mean ± SD)	3.6±0.8	3.6±0.8	0.378
FVC [L] (mean ± SD)	4.6±1.0	4.5±1.0	0.284
Atopic [%]	23.5	23.2	0.794
FEV_1/FVC ≥0.70 [%]	92.4	90.8	0.066
Bronchial Hyperresponsiveness [%]	16.7	16.8	0.928
Methacholine dose response slope* [geometric mean]	1.1	1.1	0.860
Severe respiratory infection as an infant [%]	7.5	6.1	0.081
No professional education [%]	13.3	22.0	<0.001
Exposed to dust & fumes at work [%]	31.1	36.2	<0.001
Mother smoked [%]	12.5	15.1	0.012
Father smoked [%]	53.9	56.5	0.085
Current smokers [%]	31.8	40.6	<0.001
Pack-years in current smokers [geometric mean]	11.2	12.8	0.071
Never smokers [%]	45.5	36.3	<0.001
Physician-diagnosed asthma [%]	5.5	6.9	0.050
Wheeze in last 12 months without cold [%]	6.1	8.8	0.001
Shortness of breath while walking [%]	21.8	27.7	<0.001
Chronic cough [%]	4.1	6.0	0.002
Chronic phlegm [%]	5.6	8.6	<0.001

*% decrease in FEV_1 from its maximum level per µmol of methacholine

Demographic characteristics, respiratory symptoms and lung function measured in 1991 in participants without BHR compared to hyperreactive symptomatic or asymptomatic persons are shown in Table 2. In 1991, 970/5'825 (17%) of our study subjects had BHR, of which 492/970 (51%) were asymptomatic. The proportion of females was almost 20% higher than males in both BHR-groups, and symptomatic individuals with BHR were more likely to be current smokers. The prevalence of atopy was higher in subjects with BHR, especially when symptomatic. In individuals with BHR, particularly in those with respiratory symptoms, the proportion with abnormal lung function and the degree of functional impairment was slightly higher. As expected, FEV_1, FEV_1/FVC and methacholine dose response slope showed a trend across categories with the poorest results in individuals with symptomatic BHR.

Table 2. Symptoms and lung function at baseline by presence or absence of bronchial hyperresponsiveness (BHR).

Baseline Measures	no BHR	BHR		p-value*
		Silent	Symptomatic	
n=	4855	492	478	-
Proportion of total population [%]	83	9	9	-
Sex [%, Female]	47	67	64	<0.001
Age [y; mean ± SD]	40±11	40±11	41±12	0.41
Current smokers [%]	31	29	40	<0.002
Never smokers [%]	46	51	38	0.0001
Atopic	20.8	32.3	42.3	<0.001
Physician diagnosed asthma [%]	3.2	-	34.3	-
Wheeze in last 12 months without cold [%]	4.7	-	26.8	-
Shortness of breath while walking [%]	20.3	-	60.0	-
Chronic cough [%]	3.5	-	14.0	-
Chronic phlegm [%]	5.3	-	15.1	-
COPD[†] [%]	5.8	13.4	12.8	<0.001
FEV_1 [%, pred; mean ± SD] [31]	103±11	96±11	93±12	<0.001
FVC [mean ± SD]	102±12	100±12	97±13	<0.001
FEV_1/FVC [mean ± SD]	80±6	78±7	77±8	<0.001
FEV_1/FVC <0.7 [%]	6	13	20	<0.001
Methacholine dose response slope[‡] [geometric mean]	0.7	6.5	10.0	<0.001 <0.001

*Significance test between individuals without BHR and individuals with asymptomatic BHR.

[†]COPD was defined as FEV_1/FVC<0.70 and no physician's diagnosis of asthma at either survey.

[‡]Percent decline in FEV_1 per μmol of methacholine relative to maximum FEV_1.

Longitudinal Results and multivariate Analyses

Longitudinal results are given in Table 3. Reported new symptoms at SAPALDIA 2 in previously asymptomatic participants with and without BHR are compared. Participants with BHR were at greater risk to develop respiratory symptoms, and asthma, as well as COPD.

Table 3. New reports of respiratory symptoms and prevalence of COPD at SAPALDIA 2 in formerly asymptomatic participants with and without BHR at SAPALDIA 1.

Symptoms developed between surveys	Asymptomatic at baseline		p-value
	no BHR	BHR	
Participants	3'439	492	
Physician-diagnosed asthma [%]	2.0	5.7	<0.001
Wheeze in last 12 months without cold [%]	3.4	8.3	<0.001
Shortness of breath while walking [%]	11.9	19.1	<0.001
Chronic cough [%]	2.3	5.9	0.002
Chronic phlegm [%]	4.8	4.9	0.964
COPD* [%]	14.3	37.9	<0.001

*COPD was defined as $FEV_1/FVC<0.70$ and no physician's diagnosis of asthma.

The results of multivariate logistic regression analysis are presented in Table 4 and Figure 1. Participants diagnosed with asthma between 1991 and 2002 were excluded from analyses for chronic cough, phlegm, and COPD allowing us to focus on the role of BHR in the onset of those conditions. Silent BHR conferred an increased risk of newly diagnosed asthma, new symptoms of wheeze, chronic cough and COPD 11 years later. Excluding subjects with COPD in 1991 reduced the association between presence of BHR and COPD in 2002 slightly but a significant association remained (adjusted odds ratio 4.0, 95%CI 2.9-5.6, p<0.001). There was no relation with new reports of chronic phlegm. Despite the differences observed in the prevalence of BHR between sexes at SAPALDIA 1 there was no evidence for interaction by sex in the effect of BHR on symptoms. However, there is some evidence for a gender differences in the association between presence of BHR and the risk of COPD (p=0.087) with slightly lower risks in women (OR 4.1 (95%CI 2.8 to 6.1) than in men (OR 5.4 (95%CI 3.4 to 8.5).

The associations between responsiveness and the clinical phenotypes persisted when responsiveness was quantified by its slope. There were highly significant non-linear relations between methacholine slope and new wheeze, physician's diagnosis of asthma, and COPD (all terms p<0.01), whereas new symptoms of cough, phlegm or shortness of breath were not associated with the degree of bronchial responsiveness. There is a non-linear relation between methacholine slope at SAPALDIA 1 and change in FEV_1/FVC over the follow-up in men and a linear relation in women (p<0.001 for differences between men and women).

Table 4. Risk for the development of respiratory symptoms and for the presence of COPD at SAPALDIA 2 related to bronchial hyperresponsiveness in asymptomatic individuals

	Unadjusted odds ratio	Adjusted Odds Ratio (95% CI)*	p-value†
Asthma Phenotypes			
Physician-diagnosed asthma	3.0 (1.9- 4.7)	3.0 (1.8-5.0)	<0.001
Wheeze in last 12 months without cold	2.7 (1.8-3.9)	2.9 (1.8-4.5)	<0.001
Shortness of breath while walking	1.8 (1.4-2.4)	1.3 (0.9-1.8)	0.115
COPD Phenotypes‡			
All subjects			
Chronic phlegm	1.0 (0.7-1.6)	1.2 (0.7-2.0)	0.478
Chronic cough	2.7 (1.7-4.3)	3.0 (1.7-5.2)	<0.001
Chronic bronchitis	3.0 (1.5-6.3)	2.6 (1.1, 6.0)	0.023
COPD§	3.7 (2.9-4.7)	4.5 (3.3- 6.0)	<0.001

*From logistic regression with adjustments for sex, age, FVC in 1991, BMI in 1991, change in weight, exposure to environmental tobacco smoke reported in 2002, smoking status in 2002, pack years in 2002, atopy at baseline, exposure to dust and fumes at work in 2002, level of education at baseline and study area.

†for effect estimates in adjusted analyses.

‡Participants diagnosed with asthma between 1991 and 2002 were excluded from analyses for chronic cough, phlegm, chronic bronchitis and COPD.

§COPD was defined as $FEV_1/FVC<0.70$ and no physician's diagnosis of asthma.

Chronic bronchitis defined as presence of chronic cough or phlegm.

Silent BHR and Decline in FEV_1

In asymptomatic individuals, BHR was associated with an accelerated decline in FEV_1. Our linear regression analyses adjusting for potential confounders (from baseline assessment: FEV_1, age, age squared, height; change between surveys: weight; from the follow-up assessment: exposure to ETS and exposure to dust and fumes at work) revealed that this effect was significantly modified by smoking status (p=0.02), but not by sex (p=0.17). Silent BHR was associated with an additional decline in FEV_1 by 12 (5 -18) mL/y (p=0.038), 11 (5-16) mL/y (p<0.001) and 4 (2-8) mL/y (p<0.001) in current smokers, former smokers and never smokers at SAPALDIA 2 respectively compared to asymptomatic participants without BHR. Figure 2 shows the relationship of the observed annual loss of FEV_1 in function of methacholine response slope. Although the variability of the observed change in FEV_1 over time is significant, the modelled adjusted mean goes along the same lines: Current and former smokers with bronchial hyperresponsiveness show a greater loss in FEV_1 compared to life-long non-smokers.

DISCUSSION

This prospective population-based study confirms that bronchial hyperresponsiveness is associated with the development of respiratory symptoms, asthma and COPD. Active smoking in individuals with BHR conferred a synergistic detrimental effect on the loss of lung function. The effects were observed in a population defined as asymptomatic at baseline.

Interpretation of our results warrants careful consideration. Some selection bias cannot be excluded since participation in the bronchial challenge required fulfilment of health criteria as well as satisfactory spirometry. Non-participants in the follow-up, who had a challenge at baseline, were significantly more likely to be smokers, symptomatic, and of lower educational background; although, they were similar to participants in terms of lung function characteristics.

Definitions for asthma and COPD are controversial, and especially in the context of epidemiologic studies.[26] [32] In order to address the problems of misclassification in reports of new symptoms we used a rather sensitive definition for asymptomatic (i.e. absence of all symptoms) at baseline to exclude as many participants as possible with undetected but existing respiratory symptoms at baseline. On the other hand, we used more specific definitions of symptoms at follow-up, which should have minimized false-positive reports of new symptoms.

In addition, we found significant dose-response relations between new symptoms and bronchial responsiveness as a continuous variable. The coherence of our findings strongly supports the importance of BHR as a risk factor for the development of asthma as well as COPD, and argues against misclassification explaining the results. An additional potential limitation to the study is the fact that we did not measure post-bronchodilator lung function. As a consequence, our definition of COPD may be somewhat imprecise because we may have under-estimated lung volumes in participants with reversible airway obstruction. However, we have tried to address this possible bias by excluding all individuals with physician-diagnosed asthma.[33]

In the current study BHR at baseline was associated with an increased risk of COPD (defined as FEV_1/FVC less than 0.70) at follow-up. This observation confirms the finding of a longitudinal Dutch study.[8] [9] which found a positive association of BHR with the development of respiratory symptoms, and a negative association with the resolution of such symptoms. However, in their study subjects with asthma were not systematically excluded from the primary analyses. In order to reduce the risk of contamination between asthmatic and COPD-phenotypes we excluded subjects with physician-diagnosed asthma when assessing BHR as a predictor for COPD. In the multivariate analyses we also adjusted for FVC, since responsiveness is affected by lung size and airway calibre.[6] [29]

Since individuals with BHR at baseline had an increased risk for COPD at follow-up, BHR may precede the development of COPD, and not just to be a consequence of it. The highest annual losses of FEV_1 were observed in current smokers with BHR, suggesting also that BHR is not only an independent risk factor for the development of COPD, but also increases the detrimental effect of cigarette smoking.

Interestingly, the same holds true for asthma: BHR is an independent risk factor for the development of asthma. There is good evidence of an interaction between BHR and airway inflammation, derived from cross-sectional and longitudinal studies, as well as from

pharmacological intervention trials.[34] [35] [36] The prevalence of atopy was higher in subjects with BHR at baseline, especially when symptomatic. However, in our adult study population aged 30 to 72 years, no suggestion of a modification of the effect of BHR by atopy was found. It could be that atopy plays a more important role for the development of respiratory disease in younger adults and children than later in life.[37]

The common mechanism triggering the interaction between BHR and either the (atopic) inflammation leading to asthma, or the smoke-induced inflammation leading to COPD remains speculative. BHR due to an abnormal airflow characteristic might alter the deposition profile of both allergen- and cigarette smoke-derived particles in the central and peripheral airways. Indeed, Kohlhäufl et al.[38] found that women with BHR have an increased fine particle deposition compared to women without BHR independent of their smoking habits. As a consequence of an increased exposure to allergen-derived particles, sensitization to airborne allergens would be more likely. Different studies showed a dose-response relation between allergen exposure and sensitization rates.[39] [40]In addition, once sensitized the ongoing increased exposure fuels atopic airway inflammation.[36] Similarly, increased airway deposition of cigarette smoke-derived particles could increase local toxicity and gradually worsen airway inflammation and dysfunction. There is evidence from studies in bronchial biopsies [41] and sputum markers [42] that even in individuals with asymptomatic BHR there are signs of active inflammation. The dose-response relation between the quantity of cigarettes smoked and BHR,[43] airway inflammation,[44] and the risk for COPD [45] are well-known, and overtly visible in daily clinical practice. In fact, an altered deposition profile would render subjects with BHR more vulnerable to any sort of particulate inhalation irritants. Further investigations are needed to analyze whether subjects with BHR are more vulnerable to air pollutants in general.

Women had a 20% higher prevalence of BHR at baseline, which is in line with the findings of the ECRHS study,[20]. There was no evidence, in this population sample, of a gender difference in the effect from BHR on the development of symptoms 11 years later. However, there were some differences in the effect of BHR on decline in FEV_1/FVC between men and women with slightly stronger effects observed in men.

In conclusion, bronchial hyperresponsiveness is a risk factor for the development of respiratory symptoms, asthma and COPD, and is associated with an increased annual loss of FEV_1. Particularly at risk for COPD are active smokers with BHR. The combination of BHR and smoking confers a detrimental synergistic effect on the decline in FEV_1. Further studies are needed to elucidate the exact pathogenesis underlying this phenomenon.

Acknowledgements

The study could not have been conducted without the help of the study participants, technical and administrative support and the medical teams and field workers at the local centres. We particularly thank the SAPALDIA participants and their continued participation.

Local fieldworkers: Aarau: M. Broglie, M. Bünter, G. Drita Basle: R. Armbruster, T. Damm, M.Gut, L. Maier, A. Vögelin, L. Walter, Davos: D. Jud: Geneva: M. Ares, M. Bennour, B. Galobardes, E. Namer Lugano: B. Baumberger, S. Boccia Soldati, E. Gehrig-Van Essen, S. Ronchetto Montana: C.Bonvin Payerne: S. Blanc, AV Ebinger, ML Fragnière, J. Jordan, Wald: N. Kourkoulos, U. Schafroth.

Software technicians: S. Baur, P. Frankenbach, D. Burkhard.

Administrative assistants: D. Baehler, N. Bauer, R. Nilly.

Financial disclosure

The SAPALDIA-study was supported by the National Science Foundation of Switzerland (grant no.32-65896.01, NF 32-59302.99, 3247B0-102081, the Federal Office for Forest, Environment and Landscape, the Federal Office of Public Health, the Federal Office of Roads and Transport, the Cantons Basel-Stadt, Basel-Land, Geneva, Zurich, Ticino, Aargau, Luzern, the Swiss Lung League and the Lung League of Ticino, Zurich and Basel Stadt/ Basel Landschaft. SAPALDIA Basel is part of the European Respiratory Health Survey.

REFERENCES

1. Koskela HO, Hyvarinen L, Brannan JD, *et al.* Responsiveness to three bronchial provocation tests in patients with asthma. *Chest* 2003;**124(6)**:2171-7.
2. Magnussen H, Richter K, Taube C. Are chronic obstructive pulmonary disease (COPD) and asthma different diseases? *Clin Exp Allergy* 1998;**28 Suppl 5**:187-94; discussion 203-5.
3. Sparrow D, O'Connor G, Colton T, *et al.* The relationship of nonspecific bronchial responsiveness to the occurrence of respiratory symptoms and decreased levels of pulmonary function. The Normative Aging Study. *Am Rev Respir Dis* 1987;**135(6)**:1255-60.
4. Woolcock AJ, Peat JK, Salome CM, *et al.* Prevalence of bronchial hyperresponsiveness and asthma in a rural adult population. *Thorax* 1987;**42(5)**:361-8.
5. Burney PG, Britton JR, Chinn S, *et al.* Descriptive epidemiology of bronchial reactivity in an adult population: results from a community study. *Thorax* 1987;**42(1)**:38-44.
6. Schwartz J, Schindler C, Zemp E, *et al.* Predictors of methacholine responsiveness in a general population. *Chest* 2002;**122(3)**:812-20.
7. Jansen DF, Timens W, Kraan J, *et al.* (A)symptomatic bronchial hyper-responsiveness and asthma. *Respir Med* 1997;**91(3)**:121-34.
8. Xu X, Rijcken B, Schouten JP, *et al.* Airways responsiveness and development and remission of chronic respiratory symptoms in adults. *Lancet* 1997;**350(9089)**:1431-4.
9. Vestbo J, Prescott E. Update on the "Dutch hypothesis" for chronic respiratory disease. *Thorax* 1998;**53 Suppl 2**:S15-9.
10. Holgate ST. The cellular and mediator basis of asthma in relation to natural history. *Lancet* 1997;**350 Suppl 2**:SII5-9.
11. Roth M, Johnson PR, Borger P, *et al.* Dysfunctional interaction of C/EBPalpha and the glucocorticoid receptor in asthmatic bronchial smooth-muscle cells. *N Engl J Med* 2004;**351(6)**:560-74.
12. Jogi R, Janson C, Boman G, *et al.* Bronchial hyperresponsiveness in two populations with different prevalences of atopy. *Int J Tuberc Lung Dis* 2004;**8(10)**:1180-5.
13. Abramson M, Kutin JJ, Raven J, *et al.* Risk factors for asthma among young adults in Melbourne, Australia. *Respirology* 1996;**1(4)**:291-7.
14. Brutsche M, Britschgi D, Dayer E, *et al.* Exercise-induced bronchospasm (EIB) in relation to seasonal and perennial specific IgE in young adults. *Allergy* 1995;**50(11)**:905-9.
15. Segala C, Korobaeff M, Maccario J, *et al.* Bronchial hyperresponsiveness as a predictor of wheezing in a follow-up study of healthy men. *Respiration* 1996;**63(6)**:352-7.
16. Bateman ED. Using clinical measures of disease control to reduce the burden of asthma. *Pharmacoeconomics* 2001;**19 Suppl 2**:7-12.
17. Jeffery PK, Godfrey RW, Adelroth E, *et al.* Effects of treatment on airway inflammation and thickening of basement membrane reticular collagen in asthma. A quantitative light and electron microscopic study. *Am Rev Respir Dis* 1992;**145(4 Pt 1)**:890-9.
18. O'Connor GT, Sparrow D, Weiss ST. Normal range of methacholine responsiveness in relation to prechallenge pulmonary function. The Normative Aging Study. *Chest* 1994;**105(3)**:661-6.
19. Wise RA, Kanner RE, Lindgren P, *et al.* The effect of smoking intervention and an inhaled bronchodilator on airways reactivity in COPD: the Lung Health Study. *Chest* 2003;**124(2)**:449-58.
20. Chinn S, Jarvis D, Luczynska CM, *et al.* An Increase in Bronchial Responsiveness is Associated with Continuing or Restarting Smoking. *Am J Respir Crit Care Med* 2005.

21. Sparrow D, O'Connor GT, Rosner B, *et al.* Predictors of longitudinal change in methacholine airway responsiveness among middle-aged and older men: the Normative Aging Study. *Am J Respir Crit Care Med* 1994;**149(2 Pt 1)**:376-81.
22. Willemse BW, ten Hacken NH, Rutgers B, *et al.* Association of current smoking with airway inflammation in chronic obstructive pulmonary disease and asymptomatic smokers. *Respir Res* 2005;**6(1)**:38.
23. Martin BW, Ackermann-Liebrich U, Leuenberger P, *et al.* SAPALDIA: methods and participation in the cross-sectional part of the Swiss Study on Air Pollution and Lung Diseases in Adults. *Soz Praventivmed* 1997;**42(2)**:67-84.
24. Ackermann-Liebrich U, Kuna-Dibbert B, Probst-Hensch NM, *et al.* Follow-up of the Swiss Cohort study on Air Pollution and Lung Diseases in Adults (SAPALDIA 2) 1991-2003: Methods and characterisation of participants. *Soz Praventivmed* 2005;**50(4)**:245-263.
25. Burney PG, Luczynska C, Chinn S, *et al.* The European Community Respiratory Health Survey. *Eur Respir J* 1994;**7(5)**:954-60.
26. Pauwels RA, Buist AS, Calverley PM, *et al.* Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. *Am J Respir Crit Care Med* 2001;**163(5)**:1256-76.
27. Kuna-Dibbert B, Künzli N, Keidel D, *et al.* Longitudinal validity of spirometers - a challenge in lung function follow-up studies. *Swiss Med Wkly* 2005;**135(33-34)**:503-508.
28. O'Connor G, Sparrow D, Taylor D, *et al.* Analysis of dose-response curves to methacholine. An approach suitable for population studies. *Am Rev Respir Dis* 1987;**136(6)**:1412-7.
29. Paoletti P, Carrozzi L, Viegi G, *et al.* Distribution of bronchial responsiveness in a general population: effect of sex, age, smoking, and level of pulmonary function. *Am J Respir Crit Care Med* 1995;**151(6)**:1770-7.
30. Quanjer PH, Tammeling GJ, Cotes JE, *et al.* Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir J Suppl* 1993;**16**:5-40.
31. Brandli O, Schindler C, Kunzli N, *et al.* Lung function in healthy never smoking adults: reference values and lower limits of normal of a Swiss population. *Thorax* 1996;**51(3)**:277-83.
32. Pekkanen J, Pearce N. Defining asthma in epidemiological studies. *Eur Respir J* 1999;**14(4)**:951-7.
33. Vestbo J. COPD in the ECRHS. *Thorax* 2004;**59(2)**:89-90.
34. Rabe KF. Mechanisms of immune sensitization of human bronchus. *Am J Respir Crit Care Med* 1998;**158(5 Pt 3)**:S161-70.
35. Bootsma GP, Dekhuijzen PN, Festen J, *et al.* Comparison of fluticasone propionate and beclomethasone dipropionate on direct and indirect measurements of bronchial hyperresponsiveness in patients with stable asthma. *Thorax* 1995;**50(10)**:1044-50.
36. Henriksen AH, Sue-Chu M, Holmen TL, *et al.* Exhaled and nasal NO levels in allergic rhinitis: relation to sensitization, pollen season and bronchial hyperresponsiveness. *Eur Respir J* 1999;**13(2)**:301-6.
37. O'Donnell AR, Toelle BG, Marks GB, *et al.* Age-specific relationship between CD14 and atopy in a cohort assessed from age 8 to 25 years. *Am J Respir Crit Care Med* 2004;**169(5)**:615-22.

38. Kohlhaufl M, Brand P, Scheuch G, *et al.* Increased fine particle deposition in women with asymptomatic nonspecific airway hyperresponsiveness. *Am J Respir Crit Care Med* 1999;**159(3)**:902-6.
39. Sporik R, Holgate ST, Platts-Mills TA, *et al.* Exposure to house-dust mite allergen (Der p I) and the development of asthma in childhood. A prospective study. *N Engl J Med* 1990;**323(8)**:502-7.
40. Lau S, Illi S, Platts-Mills TA, *et al.* Longitudinal study on the relationship between cat allergen and endotoxin exposure, sensitization, cat-specific IgG and development of asthma in childhood - report of the German Multicentre Allergy Study (MAS 90). *Allergy* 2005;**60(6)**:766-73.
41. Laprise C, Laviolette M, Boutet M, *et al.* Asymptomatic airway hyperresponsiveness: relationships with airway inflammation and remodelling. *Eur Respir J* 1999;**14(1)**:63-73.
42. Betz R, Kohlhaufl M, Kassner G, *et al.* Increased sputum IL-8 and IL-5 in asymptomatic nonspecific airway hyperresponsiveness. *Lung* 2001;**179(2)**:119-33.
43. Rijcken B, Schouten JP, Mensinga TT, *et al.* Factors associated with bronchial responsiveness to histamine in a population sample of adults. *Am Rev Respir Dis* 1993;**147(6 Pt 1)**:1447-53.
44. Hogg JC. Pathophysiology of airflow limitation in chronic obstructive pulmonary disease. *Lancet* 2004;**364(9435)**:709-21.
45. Lindberg A, Jonsson AC, Ronmark E, *et al.* Ten-Year Cumulative Incidence of COPD and Risk Factors for Incident Disease in a Symptomatic Cohort. *Chest* 2005;**127(5)**:1544-52.

Figure Legends

Figure 1. Adjusted risk for subsequent respiratory symptoms, asthma and COPD among subjects having been symptom-free at baseline according to presence or absence of BHR. .

Estimates are derived from a logistic regression model upon adjusting covariates listed in the footnote of Table 4 to their means. Participants diagnosed with asthma between 1991 and 2002 were excluded for the analysis of chronic cough, chronic phlegm, chronic bronchitis and COPD.

Figure 2. Relative annual change in FEV_1 (expressed as percentage of baseline) and responsiveness to methacholine in 1991.

The scatter plot shows unadjusted relative annual change in FEV_1 in participants with a bronchial challenge at baseline and spirometry at both surveys. The line plot shows mean annual change in FEV_1 by methacholine slope adjusting for FEV_1 at baseline, sex, height, pack years, exposure to ETS, area, weight change and occupation exposure to dust and fumes by smoking status at SAPALDIA 2. The vertical line indicates a PD20 at 2 mg of methacholine and, thus, separates participants with and without bronchial hyperresponsiveness to methacholine.

Figure 1.

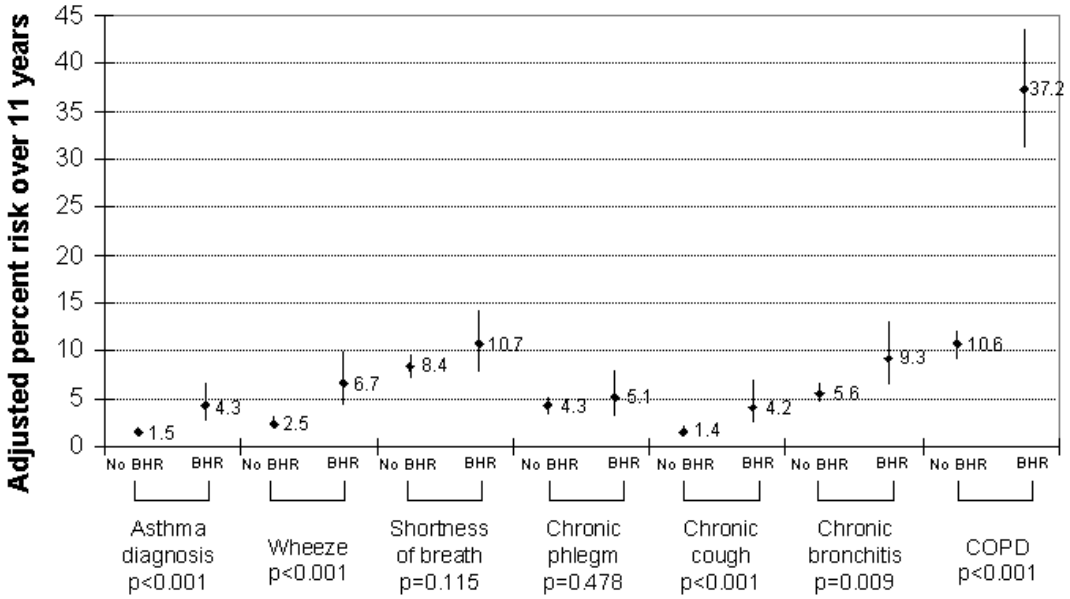

Figure 2.