

DIAGNOSIS

Bronchial Responsiveness, Spirometry and Mortality in a Cohort of Adults

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Objective. Prospective population studies have reported that pulmonary function, measured by forced expiratory volume in one second (FEV₁), is an independent predictor for mortality. Besides, several studies found that death from all causes is higher in asthmatics than in non-asthmatics. However, none of these studies examined whether bronchial hyperresponsiveness (BHR), one of the key features in asthma, can be used as a predictor for mortality. Thus, the aim of this study was to analyze the association between BHR, FEV₁, and all-cause mortality in a population-based cohort of adults. **Methods.** Within the cross-sectional survey ECRHS-I Erfurt (1990–1992), 1162 adults aged 20–65 years performed lung function tests, including spirometry and BHR testing by methacholine inhalation up to a cumulative dose of 2 mg. BHR was assessed from the methacholine dose nebulized at $\geq 20\%$ fall of FEV₁. After circa 20 years of follow-up, the association between baseline lung function, BHR, and mortality was investigated. **Results.** A total of 85 individuals (7.3%) died during a mean follow-up period of 17.4 years (SD = 2.4). FEV₁, but not forced vital capacity (FVC), was a predictor for mortality. In men, BHR increased the mortality risk (OR = 2.6, 95% CI: 1.3–5.3; adjusted for age and BMI). Additional adjustment for asthma did not change the results (OR = 2.4, 95% CI: 1.2–5.0). However, after an additional adjustment for pack years of cigarette smoking or airway obstruction, the association was not statistically significant anymore (OR = 1.8, 95% CI: 0.8–4.0, OR = 1.9, 95% CI: 0.9–4.3, respectively). **Conclusions.** BHR was associated with an increased mortality risk in men. Potential explanatory factors for this association are cigarette smoking, chronic obstructive pulmonary disease (COPD), or asthma. Thus, BHR might be an indirect predictor for all-cause mortality. FEV₁ was an independent predictor for all-cause mortality.

Keywords adults, bronchial responsiveness, ECRHS, epidemiology, mortality, spirometry

INTRODUCTION

Prospective population studies have reported that asthma and pulmonary function are important predictors for mortality. They have demonstrated that poor lung function, measured as forced expiratory volume in one second (FEV₁), is associated with increased mortality from all causes, respiratory diseases, and cardiovascular diseases (1–5). Some studies observed an association between FEV₁ rate of decline and mortality, which was likewise independent of smoking status (3, 6, 7). Thus, smoking seems to be not the only explanation for the association between lung function and mortality. Other important explanatory factors might be inflammatory markers, behavior-related factors like physical inactivity, and chronic diseases (5). However, the mechanisms underlying this association are still unclear. Besides, several studies found that death from all causes is higher in asthmatics than in non-asthmatics (8–10). They could identify several factors associated with death from asthma, such as chronic obstructive pulmonary diseases (COPDs), lung cancer, and smoking. However, none of these studies examined whether bronchial hyperresponsiveness (BHR), one of the key features in asthma, can be used as a predictor for mortality. Furthermore, it is well known that cigarette

smoking is associated with excess mortality risk (11), and several studies suggested that bronchial responsiveness increased among smokers (12–17). However, the results for the relationship between smoking and BHR are conflicting (18, 19), and possible causal pathways by which smoking leads to BHR and predicts mortality are still a matter of debate (20). Moreover, cigarette smoking or asthma might be an explanatory factor for the link between low FEV₁ and BHR.

Thus, our hypothesis is that BHR and FEV₁ are independent predictors for all-cause mortality, and that besides asthma cigarette smoking is one of the causal connections between BHR and mortality. Therefore, the objective in the present study was to determine the predictive values of BHR and FEV₁ for all-cause mortality and to identify potential mechanisms for these associations in a population-based cohort of adults.

METHODS

Study Population

ECRHS-I Erfurt. The cross-sectional survey ECRHS-I Erfurt (European Community Respiratory Health Survey) was performed from 1990 to 1992 in Erfurt, Germany. Its design has been described in detail in other studies (21, 22). In a two-step approach, 6291 randomly chosen individuals of the Erfurt population were asked to reply to a short questionnaire on respiratory symptoms which was sent by post (stage I). Afterward a population-based

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random sample of 2500 out of the 4332 stage I responders was invited to attend a clinical examination, to perform lung function measurement, and to answer a detailed questionnaire (stage II). The age range of the local Erfurt study covered subjects between 20 and 65 years and exceeded the range of the international ECRHS study. In stage II, 1282 subjects underwent the clinical examination and answered the detailed questionnaire, and 1162 lung function tests were available. In December 2009, circa 20 years after the baseline survey, a mortality follow-up was performed. Vital status of all 1162 subjects was completed.

The study protocol has been approved by the Local Ethics Committees of the Medical Academy in Erfurt and a written informed consent was obtained from all participants.

Outcome Assessment

Lung Function. All lung function tests were conducted based on the ECRHS protocol (23). Forced vital capacity (FVC) and FEV₁ were determined by spirometry using pneumatograph-based electronic spirometers (Compact Pnemo Lab, and PSC-PC, Jaeger, Würzburg, Germany). Spirometry was performed in all subjects, who did not smoke or did not use inhalers within 1 hour prior to the test. The spirometry protocol was consistent with American Thoracic Society (ATS) guidelines fulfilling the ATS criteria for repeatability (24). Tests were assumed as valid if at least two technically satisfactory maneuvers were obtained within a maximum of nine trials. Based on the best maneuver as defined by the highest sum of FVC and FEV₁, the final values of FVC and FEV₁ were determined. Percent predicted values were calculated according to Quanjer et al. (25). When not meeting any exclusion criteria (acute heart disease during the past three months, taking β -blockers, taking drugs for heart diseases or epilepsy, pregnancy, lactation, an initial FEV₁ value of <70% compared to the index value or a FEV₁ value of <1.5 litres), BHR was also tested for by methacholine provocation. The methacholine challenge, which was carried out with the help of Mefar MB3 dosimeter (Mefar srl Bovezzo, Italy), has been described in detail elsewhere (22, 23). After inhalation of saline as a diluent, increasing doses of aerosol methacholine were given. The provocation was stopped when the FEV₁ value fell by more than 20% compared with the post-saline FEV₁ check value or at a cumulative dose of 2 mg methacholine. For analysis, the dose of methacholine causing a 20% decline in FEV₁ compared with the post-saline value was used (PD₂₀). A cumulative dose of ≤ 2 mg methacholine (PD₂₀ ≤ 2 mg) was defined as BHR according to Abramson et al. (26).

Mortality Rate and Determinants. During the baseline survey anthropometric measurements, standardized face-to-face interviews and questionnaires on lifestyle and health-related factors were performed. The smoking status (never, former, or current smokers) was assessed by self-report. Pack years were calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the person has smoked. Education level

was defined by the highest graduation (less than ordinary level, ordinary level, and more than ordinary level, where ordinary level is equivalent to a secondary school leaving certificate). Furthermore, several pulmonary, cardiac, metabolic, and allergic diseases were inquired. Airway obstruction was defined as FEV₁/FVC < 70%. Blood pressure and total cholesterol levels were measured. Two independent blood pressure measurements were taken with a 5-minute pause after a rest of 5 minutes in a sitting position. The mean of the two measurements was used for the current analyses. Hypertension was defined as blood pressure ≥ 140 mm Hg systolic or 90 mm Hg diastolic or the use any antihypertensive medication. Elevated cholesterol concentrations in the blood were defined as cholesterol ≥ 5.2 mmol/l.

Circa 20 years after the baseline survey ECRHS I, a vital status survey was performed by the residential registration offices. Vital status of all participants of the ECRHS I survey was recorded. Mortality rates were calculated as the number of deaths divided by the number of individuals included in our study population.

Statistical Analyses

Multivariable regression models were applied to study the association between lung function, BHR, and mortality separately in men and women. This separation between the sexes allows to calculate sex-specific associations and to determine whether potential mechanisms for these associations differ between men and women. Additionally, interaction terms between sex and BHR were calculated. Odds ratios (ORs) with 95% confidence intervals (CIs) are given for unadjusted and adjusted models. An adjustment was done for the a priori-defined potential confounding factors age, height, BMI, and pack years of cigarette smoking, as in almost every model on lung function. Furthermore, possible confounding due to several pulmonary, cardiac, and metabolic diseases, like asthma, hypertension, heart attack, stroke, diabetes, and hyperlipidemia, was taken into account by additional adjustment for these confounders, because of its known effect on mortality. Additionally, the association between BHR and mortality was analyzed after stratification for doctor-diagnosed asthma and smoking status.

P-values < .05 were considered statistically significant for all analyses. All statistical analyses were performed with SAS (version 9.13).

RESULTS

Table 1 shows sex-specific characteristics of the 1162 participants with data on lung function tests. Men smoked significantly more and had more often airway obstruction ($p = .02$), hypertension, or elevated cholesterol levels compared to women ($p < .01$ for each comparison). Overall, roughly twice as many men compared to women were current (40.7% vs. 26.4%; $p < .01$) or former (30.2% vs. 17.1%; $p < .01$) smokers. There was no difference in FEV₁ % predicted values, whereas FVC% predicted

TABLE 1.—Characteristics of the study population ECRHS I.

	Men (<i>N</i> = 602)	Women (<i>N</i> = 560)	<i>P</i> -Value*
	Mean ± SD	Mean ± SD	
Age (years)	41.4 ± 12.3	42.4 ± 12.3	.14
Follow-up time (months)	207.2 ± 35.5	210.6 ± 18.5	<.01
BMI (kg/m ²)	25.5 ± 3.6	25.0 ± 4.4	.05
Pack years (years)	16.0 ± 13.0	8.2 ± 7.9	<.01
Lung function			
FEV ₁ (l)	4.1 ± 0.8	3.0 ± 0.6	<.01
FVC (l)	5.1 ± 0.9	3.7 ± 0.6	<.01
FEV1% predicted	106.3 ± 16.6	107.0 ± 15.0	.43
FVC% predicted	108.0 ± 14.3	113.1 ± 14.6	<.01
FEV ₁ /FVC	0.8 ± 0.1	0.8 ± 0.1	.13
	<i>n</i> (%)	<i>n</i> (%)	<i>P</i> -Value*
Died			
Yes	63 (10.5)	22 (3.9)	<.01
BHR			
Positive	75/523 (14.3)	119/429 (27.7)	<.01
Smoking status			
Never	175 (29.1)	316 (56.4)	<.01
Former	182 (30.2)	96 (17.1)	<.01
Current	245 (40.7)	148 (26.4)	<.01
Education level			
High	157 (26.2)	86 (15.4)	<.01
Medium	207 (34.5)	165 (29.6)	.07
Low	236 (39.3)	307 (55.0)	<.01
Pulmonary, cardiac and metabolic diseases			
Asthma ^a	12 (2.0)	11 (2.0)	.97
COPD ^b	53 (8.8)	30 (5.4)	.02
Hypertension ^c	257 (42.8)	169 (30.2)	<.01
Heart attack ^a	27/597 (4.5)	16/553 (2.9)	.15
Stroke ^a	24/596 (4.0)	13/553 (2.4)	.11
Diabetes ^a	37/596 (6.2)	23/553 (4.2)	.12
Elevated cholesterol ^d	419/598 (70.1)	338/556 (60.8)	<.01
Hay fever ^e	60 (10.0)	69 (12.3)	.21
Eczema ^e	144 (24.0)	162 (28.9)	.50

Notes: Mean ± standard deviation values or proportions and corresponding percentages are given.

^aDoctor-diagnosed.

^bCOPD = FEV₁/FVC <70%.

^cHypertension = blood pressure ≥ 140/90 mm Hg or antihypertensive treatment.

^dElevated Cholesterol ≥ 5.2mmol/l.

^eSelf-reported, not necessarily doctor-diagnosed.

*Obtained from chi-square test when comparing frequencies and from the Kruskal–Wallis test when comparing mean values.

values were higher in women compared to men ($p < .01$). Moreover, more women had BHR than men (27.7% vs. 14.3%; $p < .01$). A total of 85 individuals (7.3%) died during a mean follow-up period of 17.4 years (SD = 2.4). There was a significant difference in the mortality rate between men (10.5%) and women (3.9%).

The application of multivariable regression models revealed that FEV₁, but much less FVC, was a predictor for mortality after adjusting for sex, age, height, BMI, and pack years of cigarette smoking (OR = 0.49, 95% CI: 0.32–0.77) (Table 2). An additional adjustment for hypertension, heart attack, stroke, diabetes, elevated cholesterol levels, asthma, airway obstruction, and BHR did not change this result (data not shown).

BHR increased the crude mortality risk substantially in men (OR = 3.73, 95% CI: 1.98–7.01), but not in women (Table 3). After adjusting for age and BMI, the association between BHR and mortality in men remained significant

(OR = 2.59, 95% CI: 1.27–5.28). An adjustment for asthma did not change the results (OR = 2.41, 95% CI: 1.17–5.00), and stratification for asthma did not show an association between BHR and mortality in asthmatic men.

TABLE 2.—Association between lung function and mortality—results of the multivariable regression analysis.

Mortality	Men		Women		Total	
	OR	95% CI	OR	95% CI	OR	95% CI
Crude model						
FEV ₁ (l)	0.28	0.20–0.39	0.16	0.07–0.33	0.50	0.38–0.65
FVC (l)	0.35	0.26–0.49	0.19	0.09–0.38	0.68	0.55–0.86
Adjusted model 1 ^a						
FEV ₁ (l)	0.54	0.33–0.88	0.36	0.12–1.12	0.49	0.32–0.77
FVC (l)	0.73	0.47–1.14	0.44	0.15–1.28	0.66	0.44–1.00

Note: ^aAdjusted for age, height, BMI, pack years, and additionally for sex in “Total”.

TABLE 3.—Association between bronchial hyperresponsiveness (BHR) and mortality—results of the multivariate regression analysis.

Mortality	Men		Women		Total	
	OR	95% CI	OR	95% CI	OR	95% CI
Crude model						
BHR	3.73	1.98–7.01	0.87	0.17–4.35	2.01	1.15–3.52
Adjusted model 1 ^a						
BHR	2.59	1.27–5.28	0.73	0.14–3.81	2.06	1.08–3.93
Adjusted model 2 ^b						
BHR	2.41	1.17–5.00	0.51	0.08–3.19	1.86	1.00–3.61
Adjusted model 3 ^c						
BHR	1.93	0.88–4.26	0.87	0.17–4.53	1.65	0.81–3.35
Adjusted Model 4 ^d						
BHR	1.77	0.78–3.98	0.84	0.16–4.51	1.47	0.71–3.04

Notes: ^aAdjusted for age, BMI, and additionally for sex in "Total".

^bAdjusted for age, BMI, asthma, and additionally for sex in "Total".

^cAdjusted for age, BMI, COPD, and additionally for sex in "Total".

^dAdjusted for age, BMI, pack years, and additionally for sex in "Total".

TABLE 4.—Association between pack years, smoking status, and mortality—unadjusted models.

Mortality	Men		Women		Total	
	OR	95% CI	OR	95% CI	OR	95% CI
Pack years	1.06	1.04–1.07	0.96	0.88–1.05	1.05	1.04–1.07
Smoking (current or ex)	3.62	1.62–8.12	0.47	0.18–1.23	2.07	1.27–3.39

In contrast, an adjustment for airway obstruction showed a not statistically significant association between BHR and mortality in men (OR = 1.93, 95% CI: 0.88–4.26). Furthermore, after an adjustment for pack years of cigarette smoking the association was also not statistically significant (OR = 1.77, 95% CI: 0.78–3.98). A further sensitivity analysis regarding interaction terms between sex and BHR did not show an effect modification by sex. However, both sex and BHR showed individually strong effects on mortality. Stratification for smoking status showed that BHR was associated with an increased mortality risk only in current or former smokers, but not in nonsmokers. Furthermore, both current or former smoking and pack years of cigarette smoking were associated with BHR. However, these associations were not significant in women. A further sensitivity analysis showed that pack years of cigarette smoking (OR = 1.05, 95% CI: 1.04–1.07 and OR = 1.06, 95% CI: 1.04–1.07) and current or former smoking (OR = 2.07, 95% CI: 1.27–3.39 and OR = 3.62, 95% CI: 1.62–8.12) increased the mortality risk in the total study population and in men, but not in women (Table 4).

DISCUSSION

Our results indicate that BHR is associated with an increased risk for mortality in men, which might be due to asthma, COPD, or cigarette smoking, as possible causal connection. This might suggest that BHR is an indirect predictor for all-cause mortality. Moreover, we could

demonstrate that FEV₁ is a marker for all-cause mortality independent of age, BMI, pack years of cigarette smoking, and several pulmonary, cardiac, and metabolic diseases.

The predictive effect of FEV₁ on all-cause mortality of this study is in agreement with previous reports demonstrating that reduced lung function is associated with increased mortality even after adjusting for smoking, cardiovascular risk factors, or diseases (2–4, 27, 28). The NHANES (National Health and Nutrition Examination Survey Epidemiologic Survey) Follow-up Study, for example, indicated that reduced FEV₁ is a marker for future cardiovascular morbidity and mortality independent of age, gender, smoking status, and Framingham risk score (2). The Whitehall II Cohort Study could demonstrate that inflammatory markers explain a great part of the association between FEV₁ rate of decline and mortality (5). This is again in line with the inflammatory hypothesis which proposes that inflammation plays a possible role in the relation between lung function and other comorbidities leading to death (29). Overall, it is highly probable that multiple processes link lung function and mortality.

Furthermore, several studies showed that asthma is associated with an increased mortality rate (8–10). However, all these studies used a questionnaire-based diagnosis of asthma. But, none of them investigated, whether BHR, a well-established outcome measure in epidemiological studies on asthma (30), can be used as an independent predictor for mortality.

Our data indicated that BHR is an indirect marker for mortality. Potential explanatory factors for the association between BHR and mortality are cigarette smoking, COPD, or asthma. So it has been shown that BHR is a key feature in asthma and it is also related to the development of COPDs (30). However, the mechanisms between increased bronchial responsiveness and the development of chronic airway obstruction are, to a wide extent, still unclear. Besides, there is a substantial overlap between symptoms of asthma and COPD (31). Thus, BHR might be an indicator for the development of either asthma or COPD and might therefore reflect the mortality risk due to these respiratory diseases. However, after stratification for asthma we could not show an association between BHR and mortality in asthmatics. This might be due to the small number of asthmatics in our study population, which does not provide the adequate statistical power to detect a relationship between BHR and mortality in asthmatics. Furthermore, it has to be considered that one exclusion criterion for the methacholine provocation was an initial FEV₁ value of less than 70% predicted, which is a characteristic of mild COPD. This might indicate that BHR independent of COPD is associated with an increased mortality risk. However, after an additional adjustment for airway obstruction the association between BHR and mortality was not statistically significant anymore. Thus, one should take into account that BHR is an early marker for the later development of asthma or COPD. This means even though BHR seems to be an independent predictor for mortality in the beginning, subjects with BHR will probably develop asthma or COPD later on.

Besides, it is well known that cigarette smoking is associated with excess mortality risk mainly due to lung cancer and cardiovascular diseases (11). It is one of the most important causes leading to chronic airway obstruction and to the development of COPD. Furthermore, it has been demonstrated that cigarette smokers have reduced values of lung volumes or forced expiratory flows compared to that of nonsmokers (32, 33). For BHR, however, the results are conflicting. Several studies suggested that bronchial responsiveness is increased among smokers (12–17), whereas two historical studies did not find any relationship between smoking and BHR (18, 19). These discrepancies may be due to the small sample size and the not population-based subject selection in the studies which failed to show an association. Our results of a large population-based sample could show that current or former smoking is associated with increased bronchial responsiveness, and that the effect of cigarette smoking is dose-related. This is in line with other findings showing that pack years of cigarette smoking is correlated with the number of positive BHR test in current smokers (12). Furthermore, a study on determinants of change in BHR indicated that continuing smokers and restarters have the greatest increase in BHR compared to recent or long-term quitters and nonsmokers (15). All these findings indicate that there is probably a strong association between smoking and BHR. Thus, BHR, an indicator of the susceptibility to asthma and chronic airway obstruction, might predict the mortality risk of COPD or asthma caused by cigarette smoking.

Another interesting result of our study is that BHR was associated with an increased mortality risk in men, but not in women. One reason for this might be that too few women died during the follow-up period to provide the adequate statistical power to detect a relationship between BHR and mortality in women. Apart from that there were clear sex differences in smoking habits. Smoking was much more common among men and men smoked considerably more cigarettes per day compared to women. This might imply that smoking is a major cause of the excess mortality in men, which is consistent with a review indicating that half of the sex difference in total mortality is attributable to smoking (34). Moreover, the relationship between BHR and excess mortality could be demonstrated only in current or former smokers, but not in nonsmokers. This might indicate that BHR is an indirect marker for mortality caused by cigarette smoking.

The main strengths of this study are the large sample size, the population-based setting, and the international standardized methods of data collection. Because of the long follow-up time of approximately 20 years, the observed mortality rate was high enough to provide adequate statistical power for our analysis. Moreover, the detailed information on health behaviors and risk factors enabled us to adjust for a large number of potential confounders of the association between BHR, lung function, and all-cause mortality. However, the number of deceased people was too small to calculate cause-specific effects. One possible limitation of this study could be the limited representative status of the population sample included in

our analysis. However, responders and nonresponders did not differ concerning asthma attacks during the last 12 months and concerning the use of asthma medication. Besides, selection bias might play a minor role in association analyses compared to prevalence studies. Moreover, there were several exclusion criteria for the methacholine challenge test. Thus, only subjects without a poor lung function performed the test, which might imply that current or former smokers, who probably have a reduced lung function, were excluded. However, when comparing the smoking status and the number of performed methacholine challenges, we could show that although 70% of the males were current or former smokers, BHR was tested in 87% of males. This indicates that at least for the smoking status, our results of the methacholine challenge are mostly transferable to the general population. Cigarette smoking, one of the most important risk factors for mortality, was only assessed by self-report and not independently validated with biomarkers. Nevertheless, this possible information bias which is probably characterized by underreporting of smoking would only lead to an underestimation of the true association between BHR and increased mortality. Besides, possible confounding due to the use of inhalers has to be considered. Thus, using inhalers is likely to have an effect on lung function or BHR, even though it was forbidden for at least one hour before the test. However, it is important to consider the direction, in which this possible bias might change the results. As some participants might not be classified as BHR, because they were protected by the medication, the true mortality risk associated with BHR is probably underestimated. Moreover, only 0.8 % of the participants were taking anti-asthma medication and an additional sensitivity analysis excluding all participants taking anti-asthma medication did not change our results. Thus, the possible effect of inhalers on lung function or BHR is negligibly small in our analysis.

CONCLUSIONS

Our study demonstrates that BHR is associated with an increased mortality risk in men. Potential explanatory factors for the association between BHR and mortality are cigarette smoking, COPD, or asthma. This might indicate that BHR can be used as an indirect predictor for all-cause mortality. Furthermore, we could confirm previous findings that FEV₁ is an independent predictor for all-cause mortality.

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DECLARATION OF INTEREST

The authors report no conflicts of interest.

AUTHORS' CONTRIBUTIONS

EB was responsible for data analysis, interpretation of data, and manuscript preparation. JH assisted in interpretation and critical revision of the results. GW was responsible for the data. All authors read and approved the final article.

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