Prevalence of respiratory symptoms, bronchial hyperresponsiveness and atopy among adults: West and East Germany

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ABSTRACT: The prevalence of respiratory symptoms, atopic sensitization and bronchial hyperresponsiveness was compared in a random sample of adults, 20–44 yrs of age, in two cities in West and East Germany, Hamburg and Erfurt, respectively. There were much higher levels of outdoor air pollution due to sulphur dioxide and suspended particulates in Erfurt, and major differences in living conditions during the last 40 yrs.

Within the European Respiratory Health Survey, a short questionnaire was answered by 3,156 (80% response rate) subjects in Hamburg and 3,272 (74%) in Erfurt. A subset of responders to the short questionnaire completed a long questionnaire, spirometry, methacholine or bronchodilator test, skin test, and total and specific immunoglobulin E (IgE) measurements, with a total number of 1,159 participants in Hamburg and 731 in Erfurt.

Six out of 8 questions on respiratory symptoms and diagnoses were answered in the affirmative more frequently in Hamburg than in Erfurt. In Hamburg, mean forced expiratory volume in one second (FEV1) % of predicted was 105 *vs* 107% in Erfurt (p<0.0001), and bronchial hyperresponsiveness was more frequently observed in Hamburg than in Erfurt (25 *vs* 19%; p<0.05). Atopic sensitization was more prevalent in Hamburg than in Erfurt regarding the results of skin tests against grass pollen (24 *vs* 19%; p<0.05), birch pollen (19 *vs* 8%; p<0.0005), cat (10 *vs* 2%; p<0.0005), and *Dermatophagoides pteronyssinus* (14 *vs* 10%; p<0.05). This was reflected by the prevalences of positive specific IgE values, which were higher in Hamburg than in Erfurt for grass (26 *vs* 20%; p<0.05), birch (20 *vs* 10%; p<0.0005) and cat (12 *vs* 8%; p<0.05). In Hamburg, compared to Erfurt, there was: a lower mean number of siblings (p<0.005); a higher degree of childhood and current exposure to environmental tobacco smoke (p<0.005); and a higher frequency of fitted carpets and reported mould or mildew inside the house (p<0.005).

Therefore, these data may support the hypothesis that childhood factors and exposure to indoor allergens and irritants may have been more relevant for the development of asthma and atopy than the potential long-term exposure to high concentrations of sulphur dioxide and particulate matter.
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West and East Germany have experienced different living conditions over the last 40 yrs. The most striking difference was the markedly higher level of ambient air pollution in East Germany as compared to West Germany, mainly due to sulphur dioxide and particulates. In addition, there were differences indoors reflected, *e.g.* by housing, heating and ventilation, and several further factors that influence exposure to pollutants and allergens. On the other hand, these two populations were ethnically identical. The German reunification in 1990 offered the unique opportunity to compare the influence of external factors on respiratory health in two cities in West and East Germany, Hamburg and Erfurt, respectively. Thus, our research examined whether there were differences in the prevalence of atopic sensitization and respiratory diseases in West and East Germany, and to what extent they might be explained by a variety of risk factors with different distributions in the two cities.

Therefore, in both cities, we studied respiratory symptoms, spirometry, airway responsiveness, skin reactivity, and total and specific immunoglobulin E (IgE), as well as a panel of potential risk factors for respiratory diseases, in random samples of adults from the general

population. For this purpose, we followed the protocol of the European Community (EC) Respiratory Health Survey [1].

Material and methods

Study areas

Hamburg is a mainly commercial and administrative centre, located in the flat north of former West Germany about 150 km from the North Sea and 50 km from the Baltic Sea. The total population of Hamburg is approximately 1.67 million. There is a low level of combustion-related air pollution, in contrast to a large amount of traffic. Most of the year, there are predominantly Western coastal winds. Erfurt is an industrial and commercial city, located in a shallow basin in the south-west of the former German Democratic Republic, with a total population of about 210,000 inhabitants. Over the last few decades, only a small amount of traffic was present, but a high level of air pollution due to combustive sources, such as burning of coal with a high content of sulphur in the majority of private households and municipal power plants. In Erfurt, there is normally little wind. Otherwise, climatic conditions are similar between study centres. Within the period from 1985 to 1989, annual mean concentrations of sulphur dioxide and suspended particulates were 31 and 53 $\mu g \cdot m^{-3}$, respectively, in Hamburg as compared to 264 and 137 $\mu g \cdot m^{-3}$ (for suspended particulates in 1988–1989), respectively, in Erfurt. The annual mean concentration of nitrogen dioxide (NO_2) was 38 $\mu g \cdot m^{-3}$ in Hamburg; no data are available for Erfurt.

Subjects

Random samples of 4,500 (Hamburg) and 4,990 (Erfurt) subjects born between 1945 and 1971 were drawn from the lists of the Offices of Population Censuses. Thus, the target population comprised, respectively, 0.6 and 5.8% of the total population aged 20–44 yrs. Only subjects of this age range were included in the data evaluation at each stage, according to the actual age at the time of answer to the questionnaire or measurement. In Hamburg and Erfurt, 3.5 and 0.7% of the subjects under study had been born outside Germany. The study was performed from 1990 to 1992.

Study design

This was a cross-sectional study using a two-step approach. In Stage I, the screening questionnaire standardized within the EC Respiratory Health Survey was mailed. Those subjects who did not respond within a period of 2–4 months received up to two letters to remind them. In Hamburg, all subjects not responding to the mailed questionnaire were contacted by up to five phone calls by trained interviewers at different times, including evenings and weekends. Additionally, in a random 20% sample of subjects not responding to letters and phone calls, up to three attempts at a home visit

were made. In Erfurt, due to lower availability of telephones, all subjects not responding to the mailed questionnaire had to be contacted by home visits, which were made up to three times.

Stage II comprised a detailed questionnaire, spirometric measurements, methacholine or bronchodilator inhalation tests, skin-testing, and determination of total and specific IgE. In Hamburg, all subjects who responded to the Stage I screening questionnaire were invited by phone, letter or home visit to attend subsequent Stage II tests, and in Erfurt, a random sample of the Stage I responders (41%) was invited by letter or home visit to the Stage II tests. The identical methodology of the Stage II tests was followed in the two centres.

The study protocol had been approved by the Local Ethics Committees, and written informed consent was obtained from all participants.

Long questionnaire

The long questionnaire, with 71 items, had been developed from pre-existing questionnaires: questions relating to respiratory symptoms and medical history were taken from the International Union Against Tuberculosis and Lung Disease (IUATLD) questionnaire [2–4]; those on smoking from the American Thoracic Society (ATS) questionnaire [5]; and those on occupation and social status from the Office of Population Censuses and Surveys [6]. Questions on housing conditions were based on those used in the Children's Health Study performed at the Harvard School of Public Health. The questionnaire had been translated from the English version into German and, after piloting in 30 volunteers and checking for comprehensibility, back-translated into English.

Spirometry

Spirometric measurements were performed using pneumotachograph-based electronic spirometers (Compact Pneumo Lab, and PSC-PC, Jaeger, Würzburg, Germany) that met published standards [7]. In smokers and subjects using inhaled medication, lung function testing was carried out at least 1 h after the last cigarette had been smoked or 4 h after the use of any inhaler. Subjects carried out five forced vital capacity (FVC) manoeuvres, and the forced expiratory volume in one second ($FEV1$) and FVC of the best two technically satisfactory manoeuvres were recorded. Manoeuvres were accepted as technically satisfactory: if the variation of the two best $FEV1$ values was below 5%; if the back-extrapolated volume was lower than 100 mL or 5% FVC; and if the expiratory time was at least 6 s. If the subjects failed to produce two technically satisfactory manoeuvres after 5 attempts, another four more attempts were allowed.

Methacholine challenge or bronchodilator testing

Methacholine challenges were performed in all subjects who were willing to participate, able to perform

successful FEV1 and FVC manoeuvres (showing an FEV1 above 70% of the mean predicted, not lower than 1.5 L). Subjects who currently were on antiasthma treatment were given an appointment for challenge when they had taken their inhalers at least 4 h beforehand and their oral medication at least 8 h beforehand. Challenges were performed using the Mefar MB3 dosimeter and five individually calibrated dosimeters (Mefar srl Bovezzo, Italy). After measuring baseline values and the airway response to the diluent, increasing concentrations of standard methacholine (Provocholine; Hoffmann La Roche, Basel, Switzerland) were given. According to a history of respiratory symptoms, a short protocol with fourfold increases and a long protocol with twofold increases in methacholine concentrations was used. In either protocol, the subjects took a defined number of breaths (1–4), at intervals of 6 s, starting from functional residual capacity (FRC), slowly inhaling to total lung capacity (TLC), and holding their breath for 3 s. The FEV1 manoeuvre was performed 2 min after each dose. Provocation was stopped when FEV1 had dropped by 20% as compared to post-diluent values or after a maximum cumulative dose of methacholine of 2.0 mg. In this way the cumulative dose of methacholine necessary to decrease FEV1 by 20% (PD20) was determined. In addition, according to CHINN et al. [8], the dose-response slope (γ) was calculated by fitting the line "fall in FEV1 = $\delta + \gamma \times$ dose" using the least-squares method. The dose-response slope was considered as an index of responsiveness.

Any subject with a baseline FEV1 below 70% of the mean predicted value received 200 µg of salbutamol by metered-dose inhaler and volumatic in a standardized fashion. Spirometry was performed 10 min after the administration of the bronchodilator. A more than 15% increase in FEV1 was considered to be a positive response.

Skin-testing

The sensitivity to five common aeroallergens was assessed by skin-testing on the forearms with standardized allergen extracts. The allergens applied were grass, birch, cat, *Dermatophagoides pteronyssinus*, *Cladosporium herbarum*, and *Alternaria alternata*. All allergens, except grass, were supplied on Phazets for the purposes of the EC Respiratory Health Survey by Pharmacia, Uppsala, Sweden [9]. The grass allergen could not be tested by Phazets that were not allowed to be used in Germany, which was also true for some other allergens. Therefore, a batch from Allergopharma, Reinbek, Germany, was used. For the Phazet testing, the respective positive (histamine 10 mg·mL^{-1}) and negative controls (uncoated Phazet) were used. Results were read after 15 min by drawing around the perimeter of the wheal with a ballpoint pen. Using a strip of transparent tape, the prints were transferred to the data sheet. Wheal diameters were read at the widest point and at 90° to the diameter at the midpoint. A skin test was considered positive if a mean wheal diameter of at least 3 mm to at least one allergen was present, and if the wheal diameter to histamine was ≥3 mm, and to uncoated Phazets <3 mm.

Serum IgE

Sera were stored at -20°C until analysed. Total and specific serum IgE against grass, birch, cat, *D. pteronyssinus*, and *C. herbarum* were measured centrally by Pharmacia (Uppsala, Sweden) using the Pharmacia CAP system.

Quality control

All fieldworkers attended a central training seminar prior to the study. Within- and between-fieldworker variability had to be below 5% for FVC and FEV1, and below 30% for mean weal diameters of histamine Phazets. Nebulizer output was checked gravimetrically every month to ensure a comparable and constant output. High performance liquid chromatography analyses of the methacholine solutions were performed in a central laboratory twice during the study. The co-ordinator of the EC Respiratory Health Survey visited the centres and checked that the protocol was followed adequately without deviation.

Statistical analysis

Crude prevalences are given for both populations. In addition, for the subjects tested in Erfurt, prevalence figures have been directly adjusted according to the age and gender distribution in the subjects tested in Hamburg. All statistical comparisons were performed using these adjusted prevalences. Comparisons were made using Student's t-test for continuous variables, and Chi-squared tests to compare prevalences between study populations. In the descriptive tables, only point prevalence estimates are given without confidence intervals, as they were relatively small in this large size study. Multiple logistic regression analysis was performed to estimate the odds ratios of reactor status (positive skin test, positive specific serum IgE, and bronchial hyperresponsiveness) in relation to the two populations, gender, and potential risk factors. The Statistical Analysis System (SAS) and the Statistical Package for Social Sciences (SPSS) software were used for the calculations.

Results

Participation

With respect to the number of eligible subjects, overall response rates to the Stage I screening questionnaire were 80% in Hamburg and 74% in Erfurt. Defining a Stage II participant as a subject who had completed at least the long questionnaire, the overall participation rates as related to the target population were 37% in Hamburg and 55% in Erfurt (table 1). The distribution of gender and age did not significantly differ between responders to Stage II and the target populations in Hamburg and Erfurt.

Table 1. – Data base in Hamburg and Erfurt

	Hamburg			Erfurt		
	M	F	Σ	M	F	Σ
Local population 20–44 yrs of age (December 31, 1990)	312230	304826	617056	37711	39026	76737
Stage I						
Target population	1907	2027	3934 (0.6)	2126	2303	4429 (6)
Responders	1512	1644	3156 (80)	1523	1749	3272 (74)
Stage II						
Target population	1512	1644	3156 (100)	653	685	1338 (41)
Responders (long questionnaire)	588	571	1159 (37)	376	355	731 (55)
Spirometry	516	455	971	341	312	653
Methacholine challenge	497	437	934	314	279	593
Bronchodilator challenge	1	5	6	0	3	3
Skin test	517	455	972	375	355	730
Serum IgE	403	336	739	373	345	718

Screening questionnaire

According to the screening questionnaire symptom prevalence in Hamburg was higher than in Erfurt for wheezing, being woken up by an attack of coughing, having had an attack of asthma within the previous 12 months, taking asthma medicine, or having nasal allergies including hay fever ($p < 0.0005$ each). At least one out of a combination of questions suggestive of asthma (*i.e.* questions 1.2, 5 and 6) was answered in the affirmative in 14% of the subjects in Hamburg and 8% of those in Erfurt.

Long questionnaire

The most relevant answers from the long questionnaire are given in table 2 (regarding symptom prevalence) table 3 (regarding potential risk factors), and table 4 (symptoms related to exposure).

Respiratory symptoms. The screening questions were also repeated in the long questionnaire. We compared the prevalence of positive answers to these questions between participants in stage I and participants in Stage II. No significant differences were present either in Hamburg or in Erfurt.

Table 2. – Respiratory symptoms according to long questionnaire in Hamburg and Erfurt

		Hamburg			Erfurt				
		M	F	Σ	M	F	Σ	Adjusted[#]	p-value
1.	Have you had wheezing or whistling in your chest at any time in the last 12 months?	20.4	20.7	20.6	8.0	11.3	9.6	9.4	<0.0001
1.1.	Have you been at all breathless when the wheezing noise was present?	6.5	11.0	8.7	4.3	3.9	4.1	3.9	0.0001
1.2.	Have you had this wheezing or whistling when you did not have a cold?	12.8	13.3	13.0	5.6	5.1	5.3	5.1	<0.0001
2.	Have you woken up with a feeling of tightness in your chest at any time in the last 12 months?	8.0	12.8	10.4	6.5	6.8	6.7	6.8	0.0097
3.	Have you been woken by an attack of shortness of breath at any time in the last 12 months?	3.7	5.4	4.6	2.7	3.7	3.1	3.3	0.1767
4.	Have you been woken by an attack of coughing at any time in the last 12 months?	21.5	32.6	26.9	9.8	14.1	11.9	12.0	<0.0001
5.	Have you had an attack of asthma in the last 12 months?	1.2	3.7	2.4	0.5	0.8	0.7	0.6	0.0038
6.	Are you currently taking any medicine (including inhalers, aerosols or tablets) for asthma?	0.7	3.2	1.9	0.3	0.6	0.4	0.4	0.0048
7.	Do you usually bring up any phlegm from your chest first thing in the morning during winter?	10.6	8.9	9.8	12.0	5.9	9.1	9.0	0.5870
8.	Do you have nasal allergies including hay fever?	24.4	24.3	24.4	11.4	13.0	12.2	12.2	<0.0001
	At least one symptom out of questions 1.2, 5 or 6	13.6	14.4	14.0	5.6	5.4	5.5	5.3	<0.0001

Values are percentage positive answers. [#]: adjusted for age and gender distribution in Hamburg. M: male; F: female.

Table 3. – Distribution of potential risk factors for respiratory disease and atopy in Hamburg and Erfurt, according to long questionnaire

	Hamburg			Erfurt				
	M	F	Σ	M	F	Σ	Adjusted#	p-value
Number of siblings								
One	44.0	39.8	41.9	34.6	35.2	34.9	35.1	0.0031
Two	21.0	20.1	20.6	19.7	20.0	19.8	19.7	0.6718
More than two	14.7	22.2	18.4	26.9	29.9	28.3	28.0	<0.0001
Family history of asthma								
Parents	7.6	9.4	8.5	7.0	10.3	8.6	8.6	0.9467
Siblings	4.4	6.0	5.2	2.9	2.5	2.7	2.9	0.0180
Family history of atopy+								
Parents	23.8	32.1	28.0	17.3	16.3	16.8	16.5	<0.0001
Siblings	22.8	26.8	24.8	12.2	16.1	14.1	14.0	<0.0001
History before 5 yrs of age								
Bedroom sharing with older children	42.7	46.8	44.7	42.0	47.9	44.9	44.6	0.9687
Playschool or nursery	42.6	37.2	40.0	78.3	69.8	74.2	73.7	<0.0001
Serious respiratory tract infection	9.9	10.8	10.3	12.5	12.0	12.3	12.0	0.2681
Environmental tobacco smoke exposure								
Pregnancy and childhood	70.8	72.6	71.7	64.3	64.7	64.5	64.7	0.0014
Current	59.3	61.1	60.2	48.9	48.9	48.9	48.7	<0.0001
Active smoking								
Ever smoked for as long as a year	69.5	65.8	67.7	71.5	56.6	64.3	64.4	0.1351
Current	45.7	42.2	44.0	51.3	36.3	44.0	43.9	0.9733
Ex-smoking	23.9	23.6	23.7	20.2	20.3	20.2	20.5	0.0988
Occupational history								
Exposure to vapours, gas, dust, fumes	56.9	31.5	44.4	59.6	30.5	45.5	45.2	0.7244
Chest tight or wheezy at work	5.7	7.1	6.4	2.8	2.9	2.9	2.8	0.0007
Housing conditions								
Home built before 1960	55.9	61.9	58.8	51.5	39.8	45.8	45.4	<0.0001
Home built 1961–1980	33.8	27.1	30.5	25.6	27.8	26.7	27.4	0.1500
Home built after 1980	10.3	11.0	10.6	22.9	32.4	27.5	27.3	<0.0001
One family house	20.3	20.5	20.4	6.4	5.6	6.0	5.9	<0.0001
Building for 5 or more families	66.8	66.4	66.6	80.6	83.4	81.9	82.1	<0.0001
Heating by open coal, coke or wood fire	5.6	7.5	6.6	40.2	32.7	36.5	36.4	<0.0001
Heating by open gas fire	2.6	3.3	2.9	7.4	3.7	5.6	5.6	0.0038
Cooking by open coal, coke or wood fuel	0.2	0.5	0.3	1.9	0.3	1.1	1.1	0.0541
Cooking by gas	10.4	12.8	11.6	54.0	44.1	49.2	49.1	<0.0001
Fitted carpets in mostly used room	83.8	78.8	81.3	74.7	75.2	75.0	75.2	0.0013
Fitted carpets in bedroom	87.4	88.8	88.1	57.4	54.6	56.1	56.1	<0.0001
Sleep with windows always open in winter	60.6	58.7	59.7	65.7	65.1	65.4	65.5	0.0117
Mould or mildew inside the home	32.8	34.5	33.7	14.6	12.6	13.6	13.6	<0.0001
bathroom	12.3	14.6	13.4	4.6	6.6	5.5	5.5	<0.0001
bedroom	13.7	16.5	15.1	5.9	3.7	4.9	4.7	<0.0001
Cat kept in the house	18.2	19.8	19.0	8.0	7.9	8.0	8.0	<0.0001
Cat in the house during childhood	24.0	26.1	25.0	29.1	31.2	30.1	29.6	0.0289

Values are percentages. #: adjusted for age and gender distribution in Hamburg; +: eczema, skin or nasal allergy or "hay fever"; M: male; F: female.

Family and childhood history. The average number of siblings was higher among the participants from Erfurt than in those from Hamburg (p<0.005). Whereas more subjects in Hamburg reported asthma among siblings (p<0.05), no such difference was reported for their parents' generation. A family history of atopy, however, was more frequently reported among both siblings and parents in Hamburg than in Erfurt (p<0.0005 each). Many more subjects in Erfurt had gone to a playschool or nursery before the age of 5 yrs (p<0.0005), but a similar prevalence was reported for serious childhood respiratory tract infections in both cities.

Active and passive smoking. Although the percentage of current and ex-smokers was similar in either city, more subjects reported childhood and current exposure to environmental tobacco smoke in Hamburg (p<0.005 each).

Occupational history. An occupational exposure to vapours, gas, dust and fumes was reported with similar frequencies in both cities, but more subjects complained of work-related respiratory symptoms in Hamburg than in Erfurt (p<0.005).

Table 4. – Symptoms related to exposure in Hamburg and Erfurt

| | Hamburg | | | Erfurt | | | | |
	M	F	Σ	M	F	Σ	Adjusted#	p-value
Exposure to animals or dust								
Cough, wheeze, tightness, shortness of breath	14.1	20.5	17.3	5.6	7.3	6.4	6.1	<0.0001
Nose or eye symptoms	29.0	36.8	32.8	18.1	20.6	19.3	19.0	<0.0001
Exposure to trees, grass or flowers								
Cough, wheeze, tightness, shortness of breath	9.0	11.2	10.1	1.3	2.8	2.1	2.1	<0.0001
Nose or eye symptoms	28.1	30.8	29.4	10.1	16.1	13.0	12.8	<0.0001
Symptoms after food intake								
Breathlessness	1.2	2.6	1.9	0.3	0.3	0.3	0.3	0.0020
Rash or itchy skin	7.3	10.5	8.9	2.2	2.0	2.1	2.1	<0.0001
Work-related symptoms								
Tightness or wheeze	1.2	2.1	1.7	1.4	0.3	0.9	0.8	0.1428

Values are percentages. #: adjusted for age and gender distribution in Hamburg. M: male; F: female.

Housing conditions. In Hamburg, there was a higher percentage of subjects living in older houses and in smaller housing units (p<0.005 each). Many more subjects in Erfurt reported heating by open coal, coke, or wood fire, and heating or cooking by gas (p<0.005 each). In Hamburg, more people had fitted carpets, and more reported mould or mildew inside the house (p<0.005 each). Whereas slightly more subjects from Erfurt had lived with a cat in the house during childhood (p<0.05), many more people in Hamburg were currently keeping cats in the house (p<0.0005).

Symptoms related to specific exposure. As indicated in table 4, lower and upper respiratory symptoms as well as skin symptoms occurring upon exposure to specific triggers, such as animals, dust, trees, grass, flowers or food, were more frequently reported in Hamburg than in Erfurt (p<0.005 each).

Spirometry

Mean spirometric findings and results of responsiveness testing are presented in table 5. Mean absolute FVC values in Hamburg were slightly higher than in Erfurt (p<0.05), but FEV_1 as (% predicted) was lower in Hamburg (p<0.0005). An FEV_1 below the 5th percentile of the residuals of FEV_1 in a gender-specific linear regression analysis of FEV_1 *versus* age and height for the data sets of both cities was more frequently found in Hamburg than in Erfurt (p<0.005).

Bronchial responsiveness

The percentage of subjects hyperresponsive to methacholine was higher in Hamburg than in Erfurt, and the mean log slope of the dose-response curves for methacholine was higher in Hamburg than in Erfurt (p<0.05 each).

In both centres, hyperresponsiveness was found significantly more frequently in females than in males (p<0.05 each). After introducing absolute values of baseline FEV_1 into a linear regression of the maximum fall of FEV_1 after methacholine, the effect of gender was no longer statistically significant.

Skin-testing

Prevalences of positive skin tests in the two cities are presented in figure 1a. In Hamburg, higher rates of positive findings were observed for grass (p<0.05), birch (p<0.0005), cat (p<0.0005), and *D. pteronyssinus* (p<0.05),

Table 5. – Lung function and airway responsiveness in Hamburg and Erfurt (mean values)

| | Hamburg | | | Erfurt | | | | |
	M	F	Σ	M	F	Σ	Adjusted#	p-value
Spirometry								
FEV_1/FVC %	81	83	82	82	83	83	83	0.0077
FEV_1 % pred	104	105	105	107	107	107	107	0.0001
Abnormal FEV_1 %	6.6	6.6	6.6	2.6	2.9	2.8	2.8	0.0006
Bronchial responsiveness								
Hyperresponsiveness[†] %	18	33	25	11	27	18	19	0.0059
log (dose-response slope+1)	0.085	0.197	0.138	0.059	0.120	0.088	0.089	0.0005
Slope ≥0.1	14.9	32.1	23.0	8.6	25.8	16.7	17.0	0.0051
Bronchodilation tests[‡]	0/1	3/5		-	2/3			

#: adjusted for age and gender distribution in Hamburg; +: defined by the 5th percentile of the residuals of FEV_1 in a gender-specific linear regression analysis of FEV_1 *versus* age and height for the data sets of Hamburg and Erfurt; †: percentage of subjects with a PD_{20} <2.0 mg or with a positive response to a bronchodilator test; ‡: number of positive bronchodilator tests (ΔFEV_1 ≥15%). M: male; F: female; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; % pred: percentage of predicted value; PD_{20}: provocative dose of methacholine causing a 20% fall in FEV_1; ΔFEV_1: difference in FEV_1.
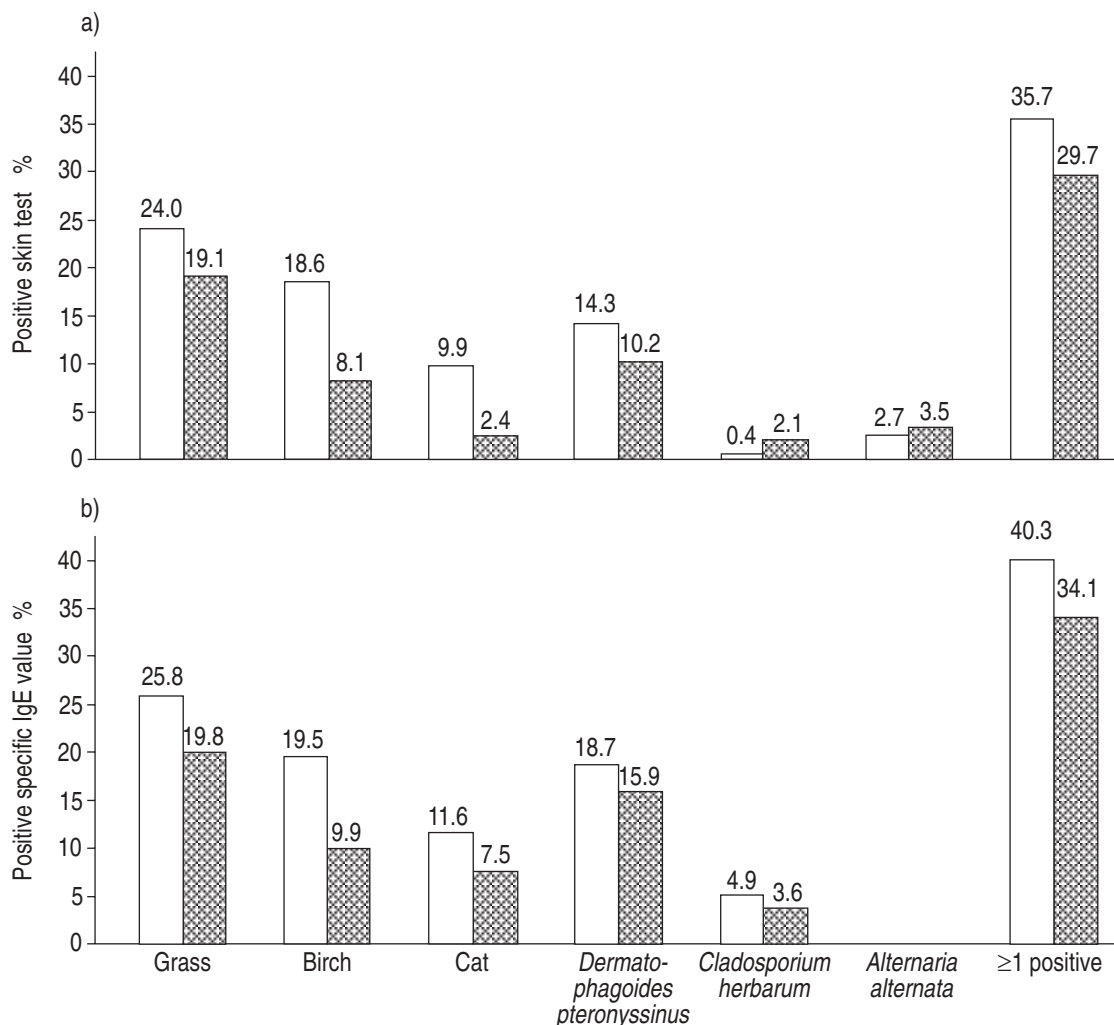
Fig. 1. – a) Prevalence of positive skin test reactions (wheal diameter ≥3 mm); and b) of positive specific immunoglobulin E (IgE) values (>0.35 kU·L^{-1}; radioallergosorbent test (RAST)) in study participants from Hamburg (☐) and Erfurt (▨).

whereas sensitization against *C. herbarum* was more frequent in Erfurt (p<0.005), and no difference was observed for *Alternaria alternata*. At least one positive wheal was present in 36% of the subjects tested in Hamburg and 30% of those in Erfurt (p<0.05).

Serum IgE

Mean total serum IgE was significantly lower in Hamburg than in Erfurt (25.5 *vs* 41.6 kU·L^{-1}; p<0.0005). Mean percentage of subjects with positive specific IgE values are given in figure 1b. In Hamburg, sensitization defined by a specific IgE level above 0.35 kU·L^{-1} was more frequent than in Erfurt with respect to all allergens tested, the differences being significant for grass (p<0.05), birch (p<0.0005) and cat (p<0.05). No significant difference was observed for *D. pteronyssinus* and *C. herbarum*. In subjects with a positive response in the methacholine challenge, total IgE was higher than in subjects with a negative methacholine challenge (53.5 *vs* 22.9 kU·L^{-1} in Hamburg and 46.5 *vs* 38.9 kU·L^{-1} in Erfurt).

Multiple logistic regression analysis

Table 6 contains the results of nine regression models that test the influence of location, gender, and potential risk factors on the prevalence of positive skin tests and bronchial hyperresponsiveness. The respective figures on positive specific IgE values as outcome variables are not given separately, since in the respective models they essentially provided the same information as the skin test data. The study area of Hamburg and female gender were significantly associated with increased bronchial responsiveness in all the models. However, the study location was no longer a predictor of positive skin tests or positive specific IgE values when a positive family history of atopy (model IV) or a history of heating (model VII) or cooking (model VIII) by open coal, coke or wood fire or gas were taken into account. Current exposure to passive smoke but not smoke exposure during pregnancy and childhood was a significant predictor of bronchial hyperresponsiveness but not of atopic sensitization (model V). The same was true for current active smoking (model VI). These two variables, however, had no major influence on the odds

Table 6. – Results of the logistic regression analyses with positive skin test reaction and bronchial responsiveness, respectively, as dependent variables

Model No.	Factor entered in the model	Positive skin-prick test[#]			Bronchial responsiveness[†]		
		OR	95% CI	p-value	OR	95% CI	p-value
I	Region: Hamburg	1.29	(1.05–1.59)	0.0154	1.46	(1.13–1.90)	0.0039
	Gender: female	0.80	(0.65–0.98)	0.0315	2.47	(1.92–3.17)	<0.0001
II	Region: Hamburg	1.25	(1.01–1.54)	0.0365	1.45	(1.12–1.88)	0.0053
	Gender: female	0.82	(0.67–1.01)	0.0561	2.49	(1.94–3.20)	<0.0001
	Siblings: one	0.89	(0.67–1.18)	0.4079	0.95	(0.67–1.34)	0.7785
	two	1.03	(0.74–1.41)	0.8779	0.81	(0.54–1.21)	0.3030
	more than two	0.64	(0.46–0.89)	0.0076	0.84	(0.56–1.24)	0.3722
III	Region: Hamburg	1.28	(1.04–1.58)	0.0197	1.40	(1.08–1.82)	0.0116
	Gender: female	0.81	(0.66–1.00)	0.0508	2.51	(1.95–3.24)	<0.0001
	Family history of asthma: parents	1.02	(0.71–1.47)	0.9194	1.15	(0.75–1.77)	0.5191
	siblings	1.26	(0.77–2.08)	0.3613	2.67	(1.58–4.51)	0.0002
IV	Region: Hamburg	1.16	(0.93–1.43)	0.1896	1.39	(1.06–1.81)	0.0164
	Gender: female	0.77	(0.62–0.95)	0.0132	2.52	(1.95–3.26)	<0.0001
	Family history of atopy: parents	1.71	(1.34–2.18)	<0.0001	1.16	(0.87–1.54)	0.3260
	siblings	1.63	(1.27–2.10)	0.0001	1.23	(0.91–1.66)	0.1714
V	Region: Hamburg	1.26	(1.02–1.55)	0.0311	1.37	(1.04–1.79)	0.0226
	Gender: female	0.80	(0.65–0.99)	0.0368	2.74	(2.11–3.56)	<0.0001
	Smoke exposure: pregnancy or as child	0.96	(0.77–1.20)	0.7476	0.96	(0.73–1.27)	0.7791
	Current	1.20	(0.97–1.48)	0.0898	1.37	(1.05–1.78)	0.0187
	Positive skin test[#]				2.73	(2.11–3.53)	<0.0001
VI	Region: Hamburg	1.30	(1.06–1.60)	0.0120	1.40	(1.08–1.83)	0.0126
	Gender: female	0.79	(0.64–0.97)	0.0246	2.79	(2.15–3.61)	<0.0001
	Active smoking: current	0.92	(0.73–1.15)	0.4520	1.44	(1.08–1.92)	0.0136
	ex	0.73	(0.55–0.97)	0.0278	1.21	(0.86–1.72)	0.2743
	Positive skin test[#]				2.68	(2.07–3.46)	<0.0001
VII	Region: Hamburg	1.24	(0.99–1.55)	0.0568	1.58	(1.20–2.09)	0.0013
	Gender: female	0.80	(0.65–0.98)	0.0295	2.51	(1.95–3.23)	<0.0001
	Heating by open coal, wood or wood fire	0.88	(0.66–1.16)	0.3532	1.25	(0.89–1.76)	0.2021
	Heating by open gas fire	0.99	(0.60–1.66)	0.9835	1.65	(0.92–2.95)	0.0928
VIII	Region: Hamburg	1.19	(0.95–1.49)	0.1400	1.57	(1.18–2.08)	0.0021
	Gender: female	0.80	(0.65–0.98)	0.0299	2.48	(1.93–3.19)	<0.0001
	Cooking by open coal, wood or wood fuel	1.94	(0.55–6.78)	0.2997	4.21	(1.05–16.89)	0.0427
	Cooking by gas	0.78	(0.61–1.01)	0.0621	1.12	(0.82–1.53)	0.4627
IX	Region: Hamburg	1.27	(1.03–1.56)	0.0226	1.45	(1.12–1.88)	0.0049
	Gender: female	0.80	(0.65–0.98)	0.0287	2.47	(1.92–3.17)	<0.0001
	Sleep with windows always open in winter	0.76	(0.62–0.94)	0.0096	0.87	(0.68–1.12)	0.2832

[#]: at least one wheal diameter from the six allergens tested ≥3 mm; [†]: PD_{20} ≤2.0 mg or positive response to a bronchodilator test. OR: odds ratio; 95% CI: 95% confidence interval; PD_{20}: provocative dose of methacholine causing a 20% fall in forced expiratory volume in one second. P-values result from testing the hypothesis that OR=1.

ratios of the three dependent variables between the two study locations. If all variables given in table 6 were entered into the model simultaneously, female gender, being an ex-smoker and sleeping with the windows open in winter were associated with a lower risk of a positive skin test, whereas a family history of atopy was associated with a higher risk. Bronchial hyperresponsiveness was positively associated with female gender, having siblings with asthma, and a positive skin test, whereas in this combined model, living in Hamburg was only marginally significant as a risk factor.

Discussion

In this study, we compared different measures of respiratory health and atopic status between two cities in West and East Germany. For more than four decades, there had been major differences in housing and living conditions and environmental pollutants between the two cities [10, 11]. We found a higher prevalence of most respiratory symptoms, lung function impairment, bronchial hyperresponsiveness, and atopic sensitization against a variety of allergens in the Western than in the Eastern city. The latter was consistently true both for the skin test results and specific IgE values against indoor allergens, such as cat and house dust mite, as well as outdoor allergens, such as grass and birch. In addition, symptoms upon exposure to animals, dust, trees, grass, or flowers were more frequently reported in Hamburg than in Erfurt.

Therefore, our findings in adults resemble what has been observed in children. VON MUTIUS *et al.* [12],

studying a total of 7,653 children 9–11 years of age, found a higher prevalence of doctor-diagnosed asthma and hay fever among those living in cities in West Germany as compared to East Germany. In addition, a higher prevalence of bronchial hyperresponsiveness as assessed by cold air challenge was found in West than in East Germany. Atopic sensitization to grass and birch pollen, cat, mite, and hazel pollen was more frequently found in West than in East Germany. In a study on 2,054 preschool children, BEHRENDT et al. [13] reported slightly, but not significantly, higher prevalences of doctor-diagnosed allergy and hay fever in West than in East Germany. The prevalence of positive radio allergosorbent test (RAST) results against birch were higher in the Western than in the Eastern areas, but this was not true for grass or house dust [13]. In this study, however, the difference in total IgE, with higher mean values in East than in West Germany, was even more pronounced than the difference observed in the present study subjects. The higher prevalence of allergic sensitization in West Germany is further supported by the data on IgE antibodies against indoor allergens, such as house dust mite and cat, which have been obtained in 901 vocational pupils from West and East Germany. No such differences were found in sensitization against outdoor allergens, such as rye, timothy grass, birch and mugwort [14]. BRABÄCK et al. [15], in a comparison of atopic sensitization and respiratory symptoms among Swedish and Polish school children, reported that children living in urban Sweden, as compared to urban Poland, were more frequently diagnosed as being asthmatic by a doctor, and had higher prevalences of positive skin-prick test reactions against mugwort, timothy, birch and cat.

Several studies have indicated a rising trend in atopic diseases and asthma over time both in children [16–21] and adolescents [2, 22, 23]. Most authors suggest that this is not simply due to improved diagnostic trends. The reasons are only partly known [24, 25], but among those being discussed are number of siblings [26], dietary factors [27], exposure to outdoor allergens [28], ozone [29], nitrogen dioxide [30] and sulphur dioxide [31], and the combination of the latter [32], as well as indoor exposure to environmental tobacco smoke [33] and mites [34].

It may, therefore, be speculated that similar factors are responsible for the geographical differences and the rising trend over time, both factors sometimes being illustrated as "Westernization". Regarding the time trend, there is only limited scientific evidence for an increasingly "toxic" or "allergenic" environment [35], thus leaving the reasons responsible for the observed time trends mostly unknown.

In our study, a positive family history of atopy among parents and siblings was a strong risk factor for a positive skin-prick test. If it was taken into account, the difference in sensitization rates between the two cities was no longer significant (table 6, model IV). This is not surprising, given the well-known hereditary component in atopy. However, this association adds little to the interpretation of "external" risk factors.

The differences described in our cross-sectional study in Hamburg and Erfurt should be discussed in view of potential risk factors in the two cities. The average number of siblings in East Germany was higher than in West Germany, thus supporting the observation of VON MUTIUS et al. [26], who described a decreasing trend of atopic sensitization with an increasing number of siblings. Although subjects from Eastern Germany had more frequently attended a playschool or nursery, no significant differences were reported regarding serious respiratory tract infections which may predispose to impaired lung function [36], but not necessarily to atopy [37]. Since adjusting for the number of siblings did not significantly alter the odds ratio of positive skin tests, specific IgE values or bronchial hyperresponsiveness between the two cities, this does not seem to be a relevant confounder for the observed difference.

Both previous and current exposure to environmental tobacco smoke exposure were more frequently reported in Hamburg than in Erfurt. Current passive smokers had a higher degree of bronchial responsiveness when adjusting for region, sex and positive skin test. Although environmental tobacco smoke exposure during childhood [38] and adulthood [39] may predispose to asthma, the comparatively small difference in self-reported environmental tobacco smoke exposure makes a major contribution to the considerable difference in asthma prevalence unlikely.

Housing conditions differed strikingly between West and East Germany, e.g. heating by open coal, coke or wood fire as well as cooking by gas were four- to sixfold more frequently reported in the East than in the West. This may have led to higher indoor concentrations of sulphur dioxide, particulate matter and nitrogen dioxide, which have been linked to an impairment of respiratory health, especially in children [30, 31]. However, no indoor measurements of these pollutants are available, and it is unknown whether there were systematic differences between cities in reporting potential risk factors. Interestingly, cooking by open coal, coke or wood fuel was related to higher levels of bronchial responsiveness, and was a better predictor of a positive skin test than was living in Hamburg. In the respective statistical model, the odds ratio in sensitization rates between the two cities was no longer significant.

Fitted carpets, which were more frequently used in Hamburg than in Erfurt, especially in bedrooms, may predispose to growth of mites, as VAN STRIEN et al. [40] found 6–14 times higher D. pteronyssinus antigen I (Der p I) concentrations in dust from carpeted floors than in dust from floors with a smooth floor covering. Furthermore, in the present study, mould or mildew was reported two- to threefold more frequently in Hamburg than in Erfurt. In the study by DEKKER et al. [41], living in a damp home and exposure to environmental tobacco smoke were significantly associated with increased reports of physician-diagnosed asthma in children, and BRUNEKREEF [42] reported a positive association of damp stains or mould growth with asthma in male adults. It is noteworthy that higher Der p I concentrations were observed in homes with reported or observed signs of dampness [40]. Thus, the higher rates of sensitization against D. pteronyssinus in Hamburg may, in part, reflect a climate more comfortable for mites under "Western" housing conditions.

The higher cutaneous sensitization rates against cat

allergen, which were observed in Hamburg, cannot be easily explained as a consequence of cats being more frequently kept in the house, since specific IgE values against cat allergen did not differ significantly between the two cities. However, in addition to the current or previous presence of a cat in the home, high indoor humidity and the presence of wall-to-wall carpets have been shown to increase the risk for high exposure to cat allergen [43].

Likewise, the higher prevalence of positive skin tests and specific IgE values against birch might reflect a higher exposure to birch allergen in Hamburg than in Erfurt. No comparable data on pollen counts are available, however.

Parasitic infection may be a factor contributing to the observed difference in atopy between the two cities. Parasites may trigger IgE production [44], and there may be an inverse correlation between parasitic IgE and atopic disease [45]. In immigrants to Sweden with decreasing parasite contact, IgE levels lowered, but prevalence of sensitization against birch pollen increased [45]. In the study by BEHRENDT et al. [13], up to 30% of East German children versus only 5% of West German children reported ever having had a parasitic infection. It has been speculated that stimulation of naive resting helper T-cells by worm-like antigens may stimulate type 2 T-helper (Th2) responses, leading to elimination of worms but enhancing viral immunopathology, whereas virus-like antigens stimulate type 1 T-helper (Th1) responses, thus, leading to antiviral immunity but at the cost of allowing worms to persist [46]. However, no data on the frequency of helminthic infestation are available in West and East Germany to clarify the role of worms in the prevalence of atopy within this setting.

Although we observed no major gender differences with respect to most symptoms or to parameters of atopic sensitization in either centre, bronchial hyperresponsiveness was found significantly more frequently in females than in males. Taking the absolute values of baseline FEV_1 into account, the gender difference disappeared. This phenomenon has been described previously by others [47], supporting the view that the smaller the airway calibre, the greater the likelihood of bronchial hyperresponsiveness. From this observation, it may be suggested that the definition of bronchial hyperresponsiveness should take baseline airway calibre into account. Since there was no statistically significant difference in absolute FEV_1 values between Hamburg and Erfurt, the geographical difference in bronchial hyperresponsiveness is unlikely to be biased by geometrical factors of the airways.

In an epidemiological study like ours, several aspects of possible bias and confounding have to be addressed. Both in Stage I and Stage II, age and gender distribution did not differ from those of the target population. In addition, we tried to assess the possible Stage I bias due to nonresponding by comparing the prevalence of symptoms between subjects responding quickly and those responding after reminders. There was a decrease in symptom rates between Stage I and II for several symptoms, e.g. wheeze and hay fever, as has been described in other centres of the EC Respiratory Health Survey [48]. This effect did not differ significantly between Hamburg and Erfurt (data not shown). On the other

hand, the percentage of subjects not responding was similar in both centres. Therefore, a major bias due to nonresponding in Stage I is unlikely. Although infomation on respiratory symptoms was missing in 20–30% of the eligible population sample, there were no significant differences in age and sex distribution between eligible subjects and Stage I responders.

A potential Stage II bias was addressed in several ways. Firstly, among the participants in Stage II tests, we found that the percentages of positive answers asked in Stage I and Stage II were not significantly different in either city. Secondly, we compared the consistency of the relationship between symptoms and objective measurements between both study centres. The percentage of subjects answering the questions related to asthma in the affirmative among those with bronchial hyperresponsiveness was considerably higher in Hamburg than in Erfurt, and the same was true for the percentage of subjects reporting allergic rhinitis among those with any positive skin test. Therefore, although it is unlikely that symptomatic subjects tended to be more willing to participate in the Stage II tests, diagnostic labelling of symptoms appeared to differ between centres (data not shown) which prevented us from defining the "true" prevalence of, e.g. asthma, beyond the information collected in the questionnaires. However, this does not critically affect the interpretation of our figures on atopic sensitization, as these depend on highly standardized methods not prone to bias by differential interpretation. In view of the uncertainties of the relationship between symptoms and functional impairment, we preferred not to perform any extrapolation from data collected in Stage II to those obtainable in Stage I.

The recruitment of subjects, the questionnaires and the instruments for determining bronchial responsiveness and atopy, as well as the procedures for quality control, followed the protocol of the EC Respiratory Health Survey [1]. The questionnaires had been validated in several previous investigations [2–6], and the instruments for measurements had been standardized and validated within the multinational survey. Skin-testing was performed with Phazets, whenever they were allowed to be used in Germany, since the precision of that method is superior to other puncture tests [49]. Due to the strict quality control, comparability of the present results with those obtained in other centres of the survey is ensured. However, one has to be careful in drawing conclusions from the comparison of only two centres, since the populations studied may differ in several aspects not recognized in this survey, and the reliability of an exposure-response gradient depending only on two points is limited. Although the only methods available for demonstrating causation between environmental factors on the one hand and atopy and asthma on the other are randomized, controlled interventions or longitudinal studies carefully monitoring all suspected factors, we feel that this type of cross-sectional study can provide some evidence for risk factors on which we need to focus our attention.

One observation from the present study is that long-term exposure to high concentrations of sulphur dioxide and particulate matter appears not to primarily facilitate the development of asthma, airway hyperresponsiveness and atopy. Childhood factors and exposure to indoor

allergens and irritants may be more likely to be responsible for the differences observed between the two cities. However, it has to be kept in mind that the study was not designed to examine indoor influences in-depth. To investigate the causal role of risk factors of indoor environment or East/West lifestyle, further investigations are necessary.

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