Respiratory Medicine (2000) **94,** 668–677
doi:10.1053/rmed.2000.0795, available online at http://www.idealibrary.com on IDEAL®

Trends in bronchial hyperresponsiveness, respiratory symptoms and lung function among adults: West and East Germany

K. Richter*, J. Heinrich†, R. A. Jörres*, H. Magnussen*, H. E. Wichmann† for the INGA Study Group

*Krankenhaus Grosshansdorf, Zentrum für Pneumologie und Thoraxchirurgie, Grosshansdorf and
†GSF-Forschungszentrum für Umwelt und Gesundheit, Institut für Epidemiologie, Neuherberg, Germany

Previous studies have shown higher prevalences of bronchial hyperresponsiveness (BHR), respiratory symptoms and atopic sensitization among adults in Western Germany than in Eastern Germany. One of the aims of the joint project INGA (INdoor Factors and Genetics in Asthma) is to assess incidence, prevalence and trends for asthma, BHR and atopic diseases over a time period of 11 years (1990–2001) in the former West (Hamburg) and East Germany (Erfurt), with special reference to indoor exposure.

INGA was designed as a case-control study following a cross-sectional study performed from 1990 to 1992 within the European Community Respiratory Health Survey (ECRHS). The database consisted of 1159 subjects in Hamburg and 731 subjects in Erfurt from the ECRHS (age 20–44). In 1995–1996, 107 cases (diagnosed asthma, positive specific serum IgE, positive skin prick or $PD_{20}FEV_1 \leq 2{\cdot}0$ mg methacholine at ECRHS) and 106 controls (none of the previous findings) participated in Hamburg (115 cases and 109 controls in Erfurt). The methodology was identical to the ECRHS and dose–response slopes (DRS) of the methacholine challenge were calculated as an index of responsiveness.

In the control group, median values of DRS were 0·028% mg^{-1} (1990–1992) and 0·044 (1995–1996) ($P < 0{\cdot}01$) in Erfurt. Corresponding values for Hamburg were 0·028 and 0·022 (NS). Corresponding values within the case groups were 0·041 and 0·049 (NS) for Erfurt, and 0·069 and 0·052 ($P < 0{\cdot}05$) for Hamburg.

Thus, 4 years after the first survey, we found an increased BHR in the Erfurt control group while the bronchial responsiveness remained unchanged for the Hamburg group. These trends in BHR, which indicate the expected converging tendency between East and West Germany, have to be confirmed within the next INGA-survey in 2000–2001.

Key words: bronchial hyperresponsiveness, lung function, adults, epidemiology, East–West comparison.

Introduction

One of the aims of the joint project INGA (INdoor factors and Genetics in Asthma) is to assess incidence, prevalence and trends for asthma, bronchial hyperresponsiveness and atopic diseases over a time period of 11 years (1990–2001) in former West and East Germany, with special respect to indoor exposure. As part of the European Community Respiratory Health Survey (ECRHS), a previous study clearly revealed that prevalences of respiratory symptoms, atopic sensitization and bronchial responsiveness among adults were higher in West Germany than in East Germany (1). Nicolai *et al.* recently reported similar findings in adults (2). Furthermore, the prevalence of current asthma and hayfever among 9–11-year-old children was found to be significantly higher in West Germany (3). The factors which cause these striking differences remain unclear, even though several explanations have been proposed. Possible factors could be exposure to different allergens or different environmental factors, including outdoor and indoor pollutants (4,5). If these factors really caused higher rates in West Germany one might expect a tendency for increased prevalence rates in the East when the exposure factors in East Germany change towards the conditions met in West Germany. The INGA study is the first study to assess respiratory symptoms, lung function and bronchial

Received 20 August 1999 and accepted in revised form 6 January 2000.
Correspondence should be addressed to: Kai Richter, MD, Krankenhaus Grosshansdorf, Zentrum für Pneumologie und Thoraxchirurgie, Wöhrendamm 80, D-22927 Grosshansdorf, Germany. Fax: +49 4102 601 245. E-mail: k.richter@pulmor-esearch.de

0954-6111/00/070668+10 $35·00/0

responsiveness in relation to indoor allergen exposure in a case-control design among adults in West and East Germany. The aim of this paper is to analyse trends in bronchial hyperresponsiveness, respiratory symptoms and lung function among adults in the two German cities: Erfurt (East Germany) and Hamburg (West Germany) after German re-unification.

Material and methods

STUDY AREA

As part of the European Respiratory Health Survey (ECRHS) the cities of Hamburg and Erfurt participated in this study. The city of Hamburg is mainly a commercial and administrative centre located in the north of former West Germany, about 150 km from the North Sea and 50 km from the Baltic Sea. The population of Hamburg consists of about 1·7 million people. The city of Erfurt is a commercial centre with industrial parts located in a shallow basin in the south-west of the former East Germany, with a total population of about 0·21 million.

STUDY DESIGN

The study was designed as a case-control study following a cross-sectional study performed from 1990 to 1992 within the ECRHS. On the basis of the study results of the first survey in 1990–1992 cases and controls were defined and followed for an average period of 48·6 months. Every subject willing to participate again attended the centre for a detailed questionnaire including respiratory symptoms, spirometry, methacholine or bronchodilator inhalation tests, skin-prick testing and determination of total and specific immunoglobulin E. The study was performed from July 1995 to August 1996. Identical methodology was followed in the two centres. The study protocol had been approved by the local ethics committees and all subjects gave their informed written consent.

SUBJECTS

The database consisted of 1159 subjects in Hamburg and 731 subjects in Erfurt who had participated within the European Respiratory Health Survey (ECRHS). Cases for the present study were defined as subjects fulfilling at least one of the following four conditions according to the results from the ECRHS (1990–1992): (i) asthma diagnosed by a physician according to the long questionnaire of the ECRHS (10), (ii) at least one positive specific serum IgE ($> 0{\cdot}35\ \mathrm{kU\,l^{-1}}$; CAP system, Pharmacia, Sweden) against grass, birch, cat, *Dermatophagoides pteronyssinus* or *Cladosporium herbarum*, (iii) at least one positive skin prick test reaction (mean wheal diameter of at least 3 mm) against the allergens mentioned above, (iv) $PD_{20}FEV_1 \leq 2{\cdot}0$ mg methacholine or positive bronchodilator testing. The subjects of the control group did not show anyone of these conditions at the first survey. Based on these criteria, 107 cases and 106 controls were recruited from a random list of 538 cases and 621 controls in Hamburg. Similarly, in Erfurt 115 cases and 109 controls out of 363 cases and 368 controls participated in the INGA study. Table 1 provides a description of the database and subjects' demography. Subjects of the control group were significantly older in Hamburg as compared to Erfurt. Furthermore, the percentages of non-smokers were lower ($P<0{\cdot}05$) in Hamburg in both the control and case group, and also the percentage of ex-smokers was higher in Hamburg within the control group ($P<0{\cdot}01$).

Table 1. Description of database and subjects' demography

	Erfurt		Hamburg	
	Controls	Cases	Controls	Cases
Target population (*n*)	368	363	621	538
Randomly selected (*n*)	109	115	106	107
Questionnaire (%)†	100	100	100	100
Spirometry (%)†	95·4	93·0	100	100
Mch. Challenge (%)†	89·9	77·4	96·2	96·3
Age (years)	37·2	37·9	40·2**	38·0
Gender				
% male	60·6	53·0	49·1	48·6
% female	39·4	47·0	50·9	51·4
Smoking status				
% never	52·3	47·8	31·1**	32·7*
% current	39·5	37·4	31·1	44·9
% ex	8·3	14·8	37·7**	22·4
Higher educational level (%)	45·9	43·5	38·7	37·4

†% of randomly selected (*n*). $^{**}P<0{\cdot}01$, $^{*}P<0{\cdot}05$ as compared to Erfurt.

METHACHOLINE CHALLENGE

Methacholine challenges were performed in all subjects who were willing to participate and able to perform adequate FEV_1 and FVC manoeuvres (showing an FEV_1 above 70% of mean predicted but not below 1·5 l). Subjects who currently were on anti-asthmatic treatment were given an appointment when they had taken their inhalers at least 4 h 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). The output of the dosimeter was checked regularly throughout the study period. β_2-agonists were withheld for at least 4 h before each spirometry test and oral asthma medication at least 8 h. After measuring baseline values and the airway response to the diluent, increasing concentrations of standard methacholine concentrations (Methacholine chloride 171913; Synopharm Co., Barsbüttel, Germany) were given. According to a history of respiratory symptoms, a short protocol with four-fold increases and a long protocol with two-fold increases in methacholine concentrations were used. In either protocol, subjects took a defined number of breaths (1–4), at intervals of 6 sec starting from functional residual capacity, slowly inhaling to total lung capacity, and holding their breath for 3 sec. The FEV_1 manoeuvre was performed 2 min after each dose. Provocation was terminated when FEV_1 had dropped by 20% as compared to post-diluent values or after a maximum cumulative dose of methacholine of 2·0 mg. $PD_{20}FEV_1$ was calculated as the cumulative dose of methacholine necessary to decrease FEV_1 by 20%. In addition, according to Chinn *et al.* (6), the dose–response slope γ was calculated by fitting the line 'fall in FEV_1 = $\delta + \gamma$ dose' using the least-squares method. The dose–response slope was considered as an index of responsiveness. Additionally the transformed dose–response slope (TDRS) was calculated as $TDRS = 1/(\text{slope} + 0{\cdot}1)$. Furthermore a dose–response slope (DRS) of $\geq 0{\cdot}05\%\,\text{mg}^{-1}$ was considered as cut-off value to define mild BHR and a DRS of $\geq 0{\cdot}01$ to define BHR in terms of DRS (7).

Any subject with a baseline FEV_1 below 70% of the mean predicted value received 200 μg of salbutamol by a metered dose inhaler. Spirometry was performed 10 min after administration of the bronchodilator. A more than 12% increase in FEV_1 was considered a positive response.

SPIROMETRY

Spirometric measurements were performed using pneumotachograph-based electronic spirometers (Master Lab 4 in the Hamburg Centre, and PSC-PC in the Erfurt Centre, Jaeger Co., Würzburg, Germany) that met published standards (8). Spirometry was performed according to the ATS standards (9). To account for potential differences between the two devices, additional lung function measurements were performed in a set of 44 volunteers with both devices. We found a statistically significant difference for values of vital capacity (VC), forced expiratory volume in 1 sec (FEV_1) and peak expiratory flow (PEF); no significant difference was found in forced vital capacity (FVC). Subsequently, the Pneumoscope device (PC) was considered as the standard device (independent variable) and the Master Lab 4 device (ML) as a dependent variable. The regression equations (standard errors are given in parenthesis) were:

(1) $VC_{ML} = -0{\cdot}010\ (0{\cdot}088) + 1{\cdot}035\ (0{\cdot}019)*VC_{PC}$
(2) $FEV_{1ML} = 0{\cdot}057\ (0{\cdot}060) + 1{\cdot}037\ (0{\cdot}016)*FEV_{1PC}$
(3) $FVC_{ML} = 0{\cdot}147\ (0{\cdot}077) + 0{\cdot}993\ (0{\cdot}016)*FVC_{PC}$
(4) $PEF_{ML} = 0{\cdot}867\ (0{\cdot}242) + 0{\cdot}891\ (0{\cdot}025)*PEF_{PC}$

All mean values obtained by the Master Lab 4 device were corrected according to these regression equations. This procedure was considered to be statistically allowed as it did refer to similar populations measured under identical conditions.

In smokers, spirometry was performed at least 1 h after the last cigarette had been smoked. Subjects had not had an upper respiratory tract infection within the 3 weeks prior to the visit in the laboratory.

QUESTIONNAIRE

The questionnaire used to assess respiratory symptoms such as wheezing, chest tightness and shortness of breath within the last 12 months, medical history, smoking, occupation and social status had been developed according to the validated long questionnaire with 71 items as used in the ECRHS study (10). The validated German version of the original ECRHS questionnaire was shortened to 40 items as compared to the original version, without changing the questions in their wording.

STATISTICAL ANALYSIS

Data were analysed using the PC statistical software Statistica (Release 4·1). Multiple logistic regression analysis was employed for the binary response variables BHR, DRS $\geq$ 0·1 or 0·05. The distribution of DRS was skewed with some negative values. Therefore, we used the reciprocal transformation $1/(DRS + 0{\cdot}1)$ to obtain the transformed dose–response slope (TDRS) (6). Due to the reciprocal transformation, a lower value of TDRS represented a higher methacholine responsiveness. Using this TDRS analysis of trends for bronchial hyperresponsiveness were performed by one-way within subjects (repeated measures) analysis of covariance (ANCOVA).

Baseline lung function data were analysed using multiple linear regression models to assess potential differences between Erfurt and Hamburg in control and case groups. In all logistic and linear regression models, the effect of smoking habits and educational level was studied using categorical variables. In each model, gender, when appropriate, and age were carried as independent variables. Lung function parameters were compared using Student's *t*-test for independent samples. Chi-squared tests were used to compare prevalences between groups.

Results

RESULTS OF QUESTIONNAIRE

Results of the questionnaire are given in Table 2. In the control group there was no statistically significant difference between the Erfurt and Hamburg groups regarding respiratory symptoms, including wheezing, shortness of breath and nighttime symptoms during the last 12 months. When the results of the two surveys were compared within the control group prevalences for wheezing and shortness of breath had slightly increased in Erfurt between 1990/92 and 1995/96, but these differences were not statistically significant. In the case group, at the 1995/96 survey, frequencies of respiratory symptoms were statistically significantly different as compared to Erfurt, with higher prevalences in Hamburg for wheezing and night-time symptoms ($P<0{\cdot}05$). Furthermore, the case group in Hamburg included nearly twice as many subjects who, at the second survey, reported a doctor's diagnosed asthma ($P<0{\cdot}05$) and about five times more current use of asthma medication as compared to Erfurt ($P<0{\cdot}01$). The use of asthma medication increased significantly between 1990/92 and 1995/96 in Hamburg ($P<0{\cdot}01$). All other differences in prevalences between the two surveys were not statistically significant different neither in the control nor in the case groups in Hamburg and Erfurt.

BASELINE LUNG FUNCTION

Lung function parameters are given in Table 3. Mean absolute values of FEV_1 were significantly different between Erfurt and Hamburg for the control groups ($P<0{\cdot}01$) but not for the case groups. FEV_1 (as % predicted) was higher for the control group in Hamburg as compared to Erfurt (109·1% and 102·0%, $P<0{\cdot}01$) In the case group there was no significant difference in FEV_1 (as % predicted) between Erfurt and Hamburg; the mean value of FEV_1 % FVC was lower in Hamburg than in Erfurt (81·7% and 83·9%, $P<0{\cdot}05$). There were no significant differences in FEV_1 FEV_1 (% predicted) and FEV_1 % FVC between the control group and the case group in Erfurt. In contrast, in Hamburg the case group had a significantly lower absolute values of FEV_1 and FEV_1 (as % predicted) ($P<0{\cdot}05$). The mean declines in FEV_1 were significantly lower in Hamburg as compared to Erfurt in the control and the case group. Separate analyses for gender showed that these differences were only significant for men.

BRONCHIAL RESPONSIVENESS

Due to clinical contraindications and refusals by some subjects, methacholine challenges were performed only in 85% of all subjects in Erfurt and 96% in Hamburg, respectively. There were no significant differences between Hamburg and Erfurt for the survey performed in 1995–1996 regarding the months of the year when methacholine challenges were performed. Compared to the months of the year of the first survey in 1990–1992 there was also no significant difference for Hamburg or Erfurt. Results of the methacholine challenges and bronchodilation tests are given in Table 4. Mean values of TDRS (SEM) for both centres and both studies are shown in Fig. 1 for the control group. Mean values of TDRS indicated a significantly higher degree of airway responsiveness for the controls in Erfurt as compared to Hamburg. Compared to the results of the ECRHS, there was a significant decrease in TDRS corresponding to a higher degree of airway hyperresponsiveness in Erfurt for the control group ($P=0.007$, ANCOVA, adjusted for gender, age, smoking status, educational level), whereas the bronchial responsiveness to methacholine did not change significantly between the two studies for the subjects of the control group in Hamburg. Mean values of TDRS 1995–1996 were not statistically significant different between Erfurt and Hamburg for the case groups. However, in Hamburg, the TDRS increased significantly ($P=0.009$, ANCOVA), corresponding to a lower degree of airway hyperresponsiveness for the subjects of the case group compared to the values obtained during the ECRHS. The DRS for the case group in Hamburg decreased significantly only in subjects with asthma medication ($P=0{\cdot}03$), but not in the subjects without asthma medication ($P=0{\cdot}20$). For the case group,

TABLE 2. Results of the questionnaire (% prevalences)

	Erfurt				Hamburg			
	Controls		Cases		Controls		Cases	
	1990/92	95/96	1990/92	95/96	1990/92	95/96	1990/92	95/96
Diagnosis of asthma	0	0	4·3	5·2	0	0·9	9·4	15·0†
Asthma medication	0	0	0·9	2·6	0	0·9	3·8	13·2*,‡
Wheezing	2·8	4·6	6·1	6·1	4·7	4·8	10·4	15·0†
Shortness of breath	0·9	1·8	6·1	6·1	4·7	3·8	7·5	9·4
Nocturnal awakenings	4·6	0·9	4·3	4·3	2·8	0·9	6·6	13·1†

*$P<0{\cdot}05$ 1990/92 compared to 1995/96, Hamburg as compared to Erfurt 1995/96; †$P<0{\cdot}05$, ‡$P<0{\cdot}01$.

TABLE 3. Results of baseline lung function (mean values [95% CI])

	Erfurt			Hamburg		
	M	F	∑	M	F	∑
Controls (*n*)	65	39	104	52	54	106
Baseline lung function						
FEV_1 (l)	4·24	3·08	3·81	4·54**	3·30**	3·91**
	[4·08–4·41]	[2·94–3·22]	[3·65–3·95]	[4·38–4·71]	[3·17–3·42]	[3·75–4·07]
FEV_1 (% predicted)	101·7	102·5	102·0	109·7**	108·5**	109·1**
FEV_1 % FVC	83·5	84·9	84·0	81·2	83·0	82·1
FEV_1 < 80% predicted (*n*)	3	0	3	0	1	1
FEV_1 1990–1992	4·57	3·34	4·11	4·68	3·47	4·06
	[4·39–4·72]	[3·19–3·48]	[3·94–4·27]	[4·52–4·83]	[3·34–3·59]	[3·91–4·21]
FEV_1 % FVC 1990–1992	82·6	84·1	83·1	81·3	83·1	82·2
Decline FEV_1 (ml)†	313	257	292	132**	170	151**
	[250–376]	[181–334]	[244–341]	[72–192]	[117–222]	[112–191]
Cases (*n*)	59	48	107	52	55	107
Baseline lung function						
FEV_1 (l)	4·16	2·99	3·64	4·25	3·05	3·64
	[4·01–4·32]	[2·84–3·14]	[3·48–3·79]	[4·07–4·43]	[2·91–3·20]	[3·48–3·80]
FEV_1 (% predicted)	102·3	100·9	101·6	103·2	103·4	103·3
FEV_1 % FVC	83·4	84·5	83·9	80·7*	82·7	81·7*
FEV_1 < 80% predicted (*n*)	3	3	6	2	6	8
FEV_1 1990–1992	4·45	3·22	3·90	4·39	3·25	3·80
	[4·30–4·61]	[3·04–3·33]	[3·73–4·06]	[4·23–4·55]	[3·12–3·37]	[3·65–3·95]
FEV_1 % FVC 1990–1992	81·5	82·6	82·0	79·8	82·8	81·4
Decline FEV_1 (ml)†	297	211	259	133**	193	163**
	[216–378]	[134–287]	[202–315]	[55–210]	[141–244]	[118–209]

† Difference in FEV_1 between 1990/92 and 1995/96.
$^{**}P<0{\cdot}01$; $^{*}P<0{\cdot}05$ as compared to Erfurt (adjusted for age, sex, smoking status).

the percentage of subjects with hyperresponsiveness to methacholine decreased from 41·0% in the ECRHS to 27·4% ($P=0{\cdot}01$) in the INGA study in Hamburg. Corresponding values for Erfurt were 32·5% and 30·1%.

Odds-ratios for the different definitions of BHR comparing Hamburg and Erfurt are presented in Table 5. The percentage of subjects with BHR in the control group was higher in Erfurt (13·3%) compared to Hamburg (6·9%) in 1995–1996. Corresponding values for the case group were 31·5% and 28·2% (NS). Furthermore, overall 8·1% (5·6% in Erfurt and 10·3% in Hamburg) of all subjects who showed bronchial hyperresponsiveness to methacholine within the ECRHS, did not show bronchial hyperreactivity within the INGA study. The percentage of subjects who changed from normal responsiveness to hyperresponsiveness between the two studies was 7·1% (10·0% in Erfurt and 5·9% in Hamburg). For comparison, 10·9% of all subjects (10·6% in Erfurt and 11·3% in Hamburg) showed constant bronchial hyperresponsiveness. Table 6 presents the results for the analysis of the shift of BHR using a multi-variate logistic regression model including different factors. Univariate analysis showed that females had a higher risk to show constant BHR as compared to male subjects at both surveys, but when the baseline FEV_1 was taken into account, these differences were abolished. Subjects of the case group in Hamburg showed a significant higher rate of reversion to normal BHR. There were no other significant differences between Hamburg and Erfurt with regard to shift in BHR. Higher age and a non-smoking status proved to be factors for a constant negative BHR at both surveys. Reported respiratory symptoms were strongly associated with a constant positive BHR (odds-ratio 3·2, $P<0{\cdot}01$).

Discussion

Previous results from our follow-up study performed in 1994–1995, using a self-administered questionnaire which was identical to the screening questionnaire of the ECRHS from 1990–1992, indicated that the prevalence of atopic diseases in East and West Germany might already converge (11). Prevalence rates of asthma attacks, asthma medication use, allergic rhinits and wheezing remained stable in Hamburg but increased significantly in Erfurt, approaching those of Hamburg. However, due to the fact that the

TABLE 4. Results of methacholine challenge including transformed dose response slope (TDRS, mean values [95% CI]).

	Erfurt			Hamburg		
	M	F	∑	M	F	∑
Controls (1995/96) (*n*)	61	37	98	50	52	102
BHR[1] (% of *n*)[†]	5 (8·2)	8 (21·6)	13 (13·3)	2 (4·0)	5 (9·6)	7 (6·9)
DRS (%/mg)[†]	0·035 [−0·040–0·213]	0·051 [0·005–0·653]	0·044 [−0·040–0·653]	0·017 [−0·022–0·214]	0·023 [−0·005–1·61]	0·022 [−0·005–1·61]
TDRS	7·45 [6·87–8·03]	6·49 [5·84–7·13]	7·07 [6·64–7·51]	8·57 [8·09–9·05]	7·64 [7·08–8·20]	8·10
1990/92 (*n*)	58	35	93	50	52	102
DRS (%/mg)[†]	0·027 [−0·009–0·075]	0·035 [−0·012–0·093]	0·028 [−0·012–0·093]	0·024 [−0·028–0·092]	0·032 [−0·013–0·095]	0·028 [−0·028–0·095]
TDRS	7·92 [7·60–8·24]	7·60 [7·12–8·06]	7·80 [7·53–8·06]	8·14 [7·70–8·58]	7·66 [7·24–8·08]	7·89 [7·59–8·19]
Cases 1995/96 (*n*)	57	36	93	51	55	106
BHR (% of *n*)*	13 (22·8)	15 (41·7)	28 (30·1)	7 (13·7)	22 (40·0)	29 (27·4)
DRS (%/mg)[†]	0·043 [−0·035–1·05]	0·071 [−0·002–7·53]	0·049 [−0·035–7·53]	0·041 [0·001–2·80]	0·055 [−0·046–18·86]	0·052 [−0·046–18·8]
TDRS	6·71 [6·03–7·40]	5·11 [4·19–6·03]	6·08 [5·52–6·65]	6·62 [5·91–7·32]	6·18 [5·20–7·15]	6·39 [5·79–0·98]
1990/92 (*n*)	51	32	83	48	52	100
DRS (%/mg)[†]	0·036 [−0·007–0·873]	0·109 [0·011–2·46]	0·041 [−0·007–2·46]	0·046 [−0·041–4·57]	0·115 [0–10·85]	0·069 [−0·041–10·85]
TDRS	7·04 [6·51–7·59]	5·04 [4·11–5·97]	6·27 [5·75–6·79]	6·60 [5·75–7·45]	4·62 [3·75–5·49]	5·57 [4·94–6·20]
BHR (% of *n*)*	9 (17·6)	18 (56·3)	27 (32·5)	13 (27·1)	28 (53·9)	41 (41·0)

* Positive bronchodilator test or PD_{20} $FEV_1 \leq 2{\cdot}0$ mg.
[†] Median values [range] given.

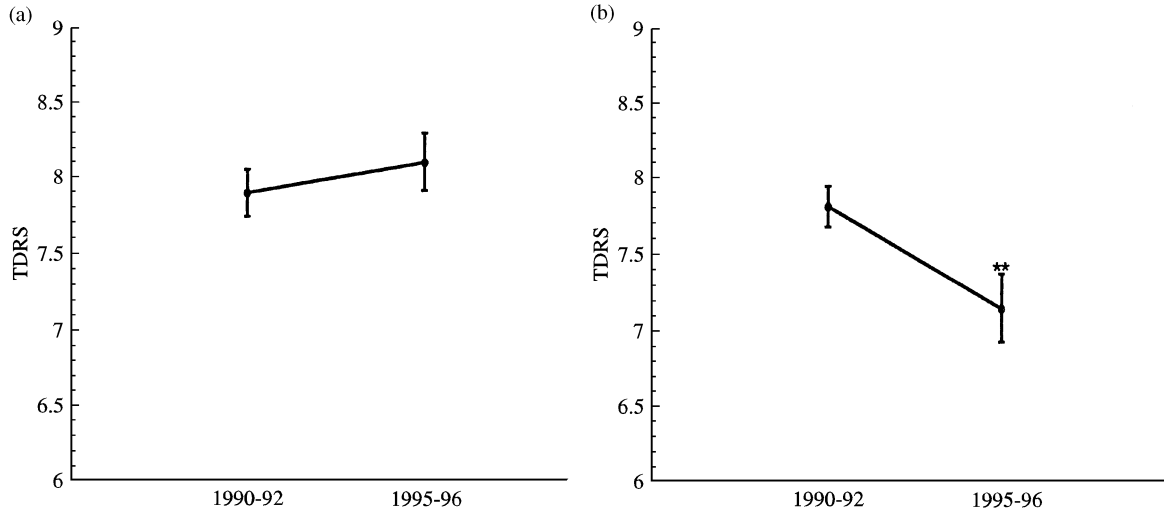

FIG. 1. Transformed dose–response slopes for methacholine (TDRS) of control groups from (a) Hamburg and (b) Erfurt within the ECRHS (1990–1992) and the INGA-study (1995–1996). Mean values ± SEM are given. $^{**}P<0{\cdot}01$.

TABLE 5. Comparison of the methacholine challenges between Hamburg and Erfurt. Odds-ratios[‡] [95% CI] Erfurt *vs.* Hamburg have been calculated for the different conditions listed

	Controls		Cases	
	1990/92	1995/96	1990/92	1995/96
BHR	*	3·13 [0·94–10·0]	0·86 [0·47–1·56]	1·18 [0·61–2·27]
Responsiveness				
DRS≥0·1%/mg	*	2·63 [0·90–7·69]	0·83 [0·45–1·54]	1·21 [0·61–2·38]
DRS≥0·05%/mg	1·27 [0·61–2·63]	5·88 [2·50–14·29]	0·69 [0·37–1·25]	0·93 [0·50–1·75]

[‡] Adjusted for sex, age, educational level, smoking status; DRS: dose-response-slope, BHR: positive bronchodilator test or PD_{20} $FEV_1 \leq 2{\cdot}0$ mg.
* Odds-ratios not calculated because all subjects within the control group had negative BHR per definition in 1990–1992.

symptoms were self-reported, this converging tendency might have been the result of an enhanced awareness among the public and health care providers in East Germany. Therefore, long-term follow-up measurements of atopy (e.g. skin-prick testing or IgE-levels), lung function and determination of bronchial responsiveness are needed. Recently published results from von Mutius *et al.* showed increasing prevalences of hayfever and atopy among children in East Germany (12). However, in that group of children (age 9–11 years) there was no significant change in the prevalence of asthma, respiratory symptoms or bronchial hyperresponsiveness.

Any interpretation of results from the INGA study has to take into account that there have been drastic changes towards Western lifestyle in Erfurt within the 5 years between the ECRHS and INGA studies. It is a common belief that environmental factors that may determine the development of atopic sensitization, respiratory symptoms and bronchial hyperresponsiveness, are important predominantly in early life (13,14). From this point of view one might expect that a change in environmental conditions would not drastically influence the prevalence rates for sensitization, symptoms or bronchial responsiveness in adults (age 24–50 years).

There are only few data available about long-term follow-up studies on bronchial hyperresponsiveness. Most of these studies addressed children or adolescents (15,16). Panhuysen *et al.* found that in a 25-year follow-up study in adult patients with diagnosed asthma, about 21% of all subjects did not show bronchial hyperresponsiveness at the second test 25 years later (17). Our data, obtained over a time period of 5 years, show a remission rate for bronchial hyperresponsiveness of about 8% overall. The remission rate was about twice as high in Hamburg as compared to Erfurt. Conversely, the incidence rate for BHR was about twice as high in Erfurt. These results might indicate a converging tendency between Hamburg and Erfurt in terms of bronchial responsiveness. The bronchial reactivity in terms of TDRS decreased in the case group in Hamburg, i.e. subjects were more likely to change from a positive

TABLE 6. Results of the multiple logistic regression analysis of shift in BHR between negative BHR (−) and positive BHR (+) from 1990/92 to 1995/96 for all subjects. Odds-ratios [95% CI] are given (for FEV_1 baseline values means ratios [95% CI] are given).

	BHR 1990–92/ 1995–96			
Factors entered in model	−/−	−/+	+/−	+/+
Female *vs.* male	0·35 [0·22–0·57]**	1·64 [0·75–3·55]	2·02 [0·91–4·50]	3·44 [1·49–7·90]**
Female *vs.* male	0·82 [0·44–1·55]	1·67 [0·51–5·43]	1·14 [0·31–4·26]	1·01 [0·44–2·33]
FEV_1 baseline	2·12 [1·35–3·35]**	1·01 [0·55–1·85]	0·64 [0·26–1·55]	0·33 [0·19–0·59]**
Female *vs.* male	0·69 [0·34–1·42]	1·89 [0·64–5·60]	0·60 [0·14–2·66]	1·08 [0·48–2·46]
FEV_1 baseline	2·01 [1·22–3·32]**	1·03 [0·57–1·86]	0·33 [0·10–1·06]	0·41 [0·19–0·86]*
Hamburg *vs.* Erfurt	1·02 [0·62–1·68]	0·49 [0·22–1·09]	2·90 [1·02–8·26]*	1·07 [0·56–2·03]
Age 30–34 *vs.* 24–29	1·24 [0·50–3·08]	1·56 [0·61–3·95]	0·15 [0·01–5·14]	0·89 [0·12–6·78]
Age 35–39 *vs.* 24–29	1·67 [0·78–3·58]	0·47 [0·14–1·53]	0·27 [0·06–1·25]	1·52 [0·38–6·02]
Age 40–50 *vs.* 24–29	2·15 [1·02–4·54]*	0·50 [0·17–1·41]	0·38 [0·12–1·25]	0·78 [0·18–3·44]
Smokers *vs.* non-smokers	0·53 [0·32–0·88]*	1·51 [0·70–3·24]	1·34 [0·50–1·99]	1·63 [0·91–2·94]
Symptoms *vs.* no symptoms	0·34 [0·17–0·67]**	2·10 [0·81–5·50]	0·57 [0·12–2·68]	3·20 [1·71–6·12]**
Medication *vs.* no medication	0·59 [0·14–2·40]	–	0·13 [0·01–31·6]	3·30 [1·00–10·8]

*$P<0·05$, **$P<0·01$.
†One or more of the following symptoms: wheezing, shortness of breath, nocturnal awakenings.

BHR to a negative BHR. In contrast, the prevalence of doctor's diagnosed asthma as reported in the questionnaire and the use of asthma medication increased within the case group in Hamburg (odds-ratio 2·9). This finding and the decrease in bronchial hyperresponsiveness might be the result of an improvement in asthma diagnosis and treatment in West Germany. For comparison, bronchial hyperresponsiveness and mild BHR remained unchanged between the two surveys within the control group in Hamburg.

The annual incidence rate of asthma was about 1·2% for the case group in Hamburg as compared to about 0·2% for the case group in Erfurt. Previous studies reported a mean annual cumulative incidence of asthma in adults between 0·2 and 0·5% (18,19) for a general population sample. A direct comparison of these incidence rates is not possible due to the fact that results from the INGA study are based on case-control cohorts, which are not representative of the population in West and East Germany. Irrespective of the differences between Erfurt and Hamburg, out data confirm that a greater airway calibre is associated with less BHR. Previous studies have shown that bronchial hyperresponsiveness occurred more often in females than in males and that these differences were abolished when the lower baseline FEV_1 values were taken into account (7,20,21). Moreover, our data are in line with previous observations that respiratory symptoms are a major risk factor for BHR (22,23).

Regarding the prevalences of respiratory symptoms there were no unique trends in the control or case group from Erfurt and in the control group from Hamburg. A significant increase of respiratory symptoms was only found for the case group in Hamburg. This is in line with the higher prevalence of doctor's diagnosed asthma and of the use of asthma medication. These findings indicate that at least for the case group, adults in West Germany are still at higher risk to develop respiratory symptoms and bronchial asthma. However, the fact that bronchial hyperresponsiveness decreased overall within the case group can only be explained by an effect of asthma medication in the subset of treated subjects in this group.

The higher degree of bronchial responsiveness to methacholine in the 1995–1996 survey as compared to the 1990–1992 survey which we found in the control group in Erfurt, was not accompanied by a significant increase of respiratory symptoms. There was only a weak trend for increased prevalences of wheezing and shortness of breath. However, the absolute number of subjects reporting respiratory symptoms was low in all groups and the power of statistical analyses was therefore limited. It was the additional assessment of indoor exposure within the INGA study (data not shown) which limited the total number of subjects to be studied in Hamburg and Erfurt.

Magnitude of the decline in FEV_1 as found in the case and control groups in Hamburg was compatible with findings of previous studies reporting that the decline of FEV_1 is at an average of $30\,ml\,year^{-1}$ (24) in healthy non-smokers throughout life. The mean rate of decline amongst smokers is approximately twice as high. It is known that 15–20% of smokers demonstrate an increased susceptibility to tobacco smoke with a rate of decline of FEV_1; approximately twice the mean of all smokers (70–$120\,ml\,year^{-1}$) (25). Peat *et al.* found a decline in FEV_1 of $50\,ml\,year^{-1}$ in non-smoking asthmatics as compared to $35\,ml\,year^{-1}$ in healthy subjects (26). Regarding the decline in FEV_1 there were no significant differences between

Hamburg and Erfurt in females. Male subjects however showed a significantly higher rate of decline in FEV_1 in Erfurt. The reasons for these differences remain unclear. At least in the control group these findings might be partly explained by the smoking status with less current smokers and more ex-smokers in Hamburg, but after adjustment for smoking status differences were still significant. In the control groups, baseline FEV_1 was not different between Erfurt and Hamburg at the first survey in 1990–1992. Because of the strong association between airway calibre and bronchial hyperresponsiveness, the significant decrease in transformed dose response slopes which indicated higher bronchial hyperresponsiveness in the control group in Erfurt, was in line with the significantly lower baseline FEV_1 in Erfurt 1995–1996 as compared to Hamburg.

The decrease of the transformed dose response slope in the control group in Erfurt is not likely to be due to changes in methodology because an identical procedure of methacholine challenge has been used in both studies and there was no significant difference in the months of the year when the two surveys were performed. Also, differences in participation rate were small in the control group and therefore are unlikely to have biased the differences in dose–response-slopes for methacholine. This is supported by the fact that there were also no differences in age, gender, or baseline lung function between participants and non-participants.

In conclusion, our data provide objective evidence for the hypothetical possible converging tendency between East and West Germany in terms of bronchial responsiveness. Nevertheless, the reported trends for bronchial hyperresponsiveness should be confirmed within the next INGA-survey which will be performed in the year 2000–2001.

It is policy of the joint project INGA to indicate that further analyses of medical data (e.g. trends for atopy) and the analysis of indoor exposure will be part of separate publications.

Acknowledgements

We would like to thank Mrs S. Janicki, S. Stadler and G. Woelke for their excellent technical work and Mr G. Silbernagl and Mrs U. Gehring for statistical advice. The study was supported by a grant from the Bundesminister für Bildung, Wissenschaft, Forschung und Technologie (BMBF, FKZ 01 EE 9301/6).

References

1. Nowak D, Heinrich J, Jörres R, *et al*. Prevalence of respiratory symptoms, bronchial hyperresponsivensess and atopy among adults: West and East Germany. *Eur Respir J* 1996; **9:** 2541–2552.
2. Nicolai T, Bellach B, Mutius E, Thefeld W, Hoffmeister H. Increased prevalence of sensitization against aeroallergens in adults in West compared with East Germany, *Clin Exp Allergy* 1997; **27:** 886–892.
3. von Mutius E, Martinez FD, Fritzsch C, Nicolai T, Roell G, Thiemann HH. Prevalence of asthma and atopy in two areas of West and East Germany. *Am J Respir Crit Care Med* 1994; **149:** 358–364.
4. Wichmann HE. Possible explanation for the different trends of asthma and allergy in East and West Germany. *Clin Exp Allergy* 1996; **26:** 621–623.
5. Nowak D, Wichmann HE, Magnussen H. Asthma and atopy in Western and Eastern communities—current status and open questions. *Clin Exp Allergy* 1998; **28:** 1043–1046.
6. Chinn S, Burney PG, Britton JR, Tattersfield AE, Higgins BG. Comparison of PD_{20} with two alternative measures of response to histamine challenge in epidemiological studies. *Eur Respir J* 1993; **6:** 670–679.
7. Wassmer G, Jörres RA, Heinrich J, Wjst M, Reitmeir P, Wichmann HE. The association between baseline lung function and bronchial responsiveness to methacholine. *Eur J Med Res* 1997; **2:** 47–54.
8. Quanjer PHH, Tammeling GH, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. *Eur Respir J* 1993; **6**(Suppl.)**:** 5–40.
9. American Thoracic Society. Standardization of spirometry: 1994 update. *Am J Respir Crit Care Med* 1995; **152:** 1107–1136.
10. Burney PGJ, Luczynska C, Chinn S, Jarvis D. The European Community Respiratory Health Survey. *Eur Respir J* 1994; **7:** 954–960.
11. Heinrich J, Richter K, Magnussen H, Wichmann HE. Is the prevalence of atopic diseases in East and West Germany already converging? *Eur J Epidemiol* 1998; **14:** 239–245.
12. van Mutius E, Weiland SK, Fritzsch C, Duhme H, Keil U. Increasing prevalence of hay fever and atopy among children in Leipzig, East Germany. *Lancet* 1998; **351:** 862–866.
13. Warner JA, Jones AC, Miles FA, Colwell BM, Warner JO. Maternofetal interaction and allergy. *Allergy* 1996; **51:** 447–451.
14. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. *N Engl J Med* 1995; **332:** 133–138.
15. de Gooijer A, Brend PL, Gerritson J, Koeter GH, Postma DS, Knol K. Changes in respiratory symptoms and airway hyper-responsiveness after 27 years in a population-based sample of school children. *Eur Respir J* 1993; **6:** 848–854.
16. Zhong NS, Chen RC, Yang MO, Wu ZY, Zheng JP, Li YF. Is asymptomatic bronchial hyper-responsiveness an indication of potential asthma? A two-year follow up of young students with bronchial hyperresponsiveness. *Chest* 1992; **102:** 1104–1109.
17. Panhuysen CI, Vonk JM, Koeter GH, *et al*. Adult patients may outgrow their asthma: a 25-year follow up study. *Am J Respir Crit Care Med* 1997; **155:** 1267–1272.
18. Ronmark E, Lundback B, Jonsson E, Jonsson AC, Lindstrom M, Sandström T. Incidence of asthma in adults—report from the obstructive Lung Disease in Northern Sweden Study. *Allergy* 1997; **52:** 1071–1078.

19. Dodge RR, Burrows B. The prevalence and incidence of asthma and asthma-like symptoms in a general population sample. *Am Rev Respir Dis* 1980; **122:** 567–575.
20. Britton J, Pavord I, Richards K, *et al*. *Eur Respir J* 1994; **7:** 881–887.
21. Paoletti P, Carrozi L, Viegi G, *et al*. *Am J Respir Crit Care Med* 1995; **151:** 1770–1777.
22. de Marco R, Bugiani M, Zanolin E, Verlato G, Rijcken B. Doses and models in risk assessment for bronchial hyperresponsiveness. *J Clin Epidemiol* 1998; **51:** 19–28.
23. Rijcken B, Schouten JP, Weiss ST, Speizer FE, van der Lende R. The relationship of nonspecific bronchial responsiveness to respiratory symptoms in a random population sample. *Am Rev Respir Dis* 1987; **136:** 62–68.
24. Sluiter HJ, Koeter GH, de Monchy JGR, Postma DS, de Vries K, Orie NGM. The Dutch hypothesis (chronic nonspecific lung disease) revisited. *Eur Respir J* 1991; **4:** 479–489.
25. Fletcher C, Peto R, Tinker CM, *et al*. The natural history of chronic bronchitis and emphysema. Oxford: Oxford University Press, 1976.
26. Peat JK, Woolcock AJ, Cullen K. Rate of decline of lung function in subjects with asthma. *Eur J Respir Dis* 1987; **70:** 171–179.

Appendix

MEMBERS OF THE INGA STUDY GROUP

GSF National Research Center for Environment and Health, Neuherberg, Germany Institute of Epidemiology (Wichmann HE, Heinrich J, Schneider P, Cyrys J, Gross I, Woelke G. Silbernagl G, Gehring U)
Institute of Ecological Chemistry (Gebefuegi I, Loerinci G)

Friedrich Schiller University, Jena, Germany
Institute of Occupational, Social and Environmental Medicine (Bischof W, Koch A, Witthauer J, Heilemann KJ)
Institute of Clinical Immunology (Jaeger L, Fahlbusch B, Schlenvoigt G)

Hospital Grosshansdorf, Hamburg, Germany
Center for Pneumology and Thoracic Surgery (Magnussen H, Richter K, Jörres RA)

University of Wageningen, The Netherlands
Department of Environmental Health (Brunekreef B, Douwes J)