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Temporal Changes in Total Serum Immunoglobulin E Levels in East German Children and the Effect of Potential Predictors

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Key Words
Allergy · Children · Helminth infection · Immunoglobulin E, total · Trend

Abstract
Background: Elevated total serum immunoglobulin E (IgE) levels are a prominent feature of allergic and parasitic diseases. An epidemiologic study was conducted in East German children to describe trends in the development of total serum IgE levels and analyze the impact of potential determinants. ***Methods:*** The study consisted of three cross-sectional surveys in 1992–1993, 1995–1996 and 1998–1999 and was conducted in three areas of the former German Democratic Republic. In total, 8,051 questionnaires were completed by the parents of children aged 5–14 years, supplying information on allergic symptoms and potential risk factors. A total of 5,918 measurements of total serum IgE and specific IgE to 5 common aeroallergens were available from 4,353 schoolchildren. Generalized estimating equations were applied to data from all children and stratified for atopic and nonatopic children to identify trends and estimate the effect of potential determinants on total IgE. ***Results:*** Total serum IgE levels decreased significantly with a linear trend in East German schoolchildren between 1992 and 1999, the effect being stronger in nonatopic children. The following factors were associated with lower total serum IgE levels: female gender, living in a household with fewer than 4 people, no history of helminth infestation, younger age group (5–7 years), no parental allergy and high socioeconomic status. No association was seen for 'smoking at home' and close contact to pets. ***Conclusion:*** Total serum IgE declined parallel to helminth infestation; however, the latter explained the decrease only in part. Furthermore, total IgE developed in an opposite direction to specific IgE, indicating that it has determinants other than allergic sensitization.

Introduction

In recent decades, the prevalence of allergic diseases has increased worldwide. Atopy-related diseases are the most common chronic disorders in children in Western societies. Allergic sensitization and atopic symptoms are associated with elevated levels of total serum immunoglobulin E (IgE), and increased IgE levels are a risk factor for the development of asthma. IgE is influenced by various environmental factors, including viral, parasitic and bacterial infection [1], indoor air pollution [2], genetic background [3, 4], diet [5], smoking habits [6] and other determinants related to a 'Western lifestyle' [7]. Although

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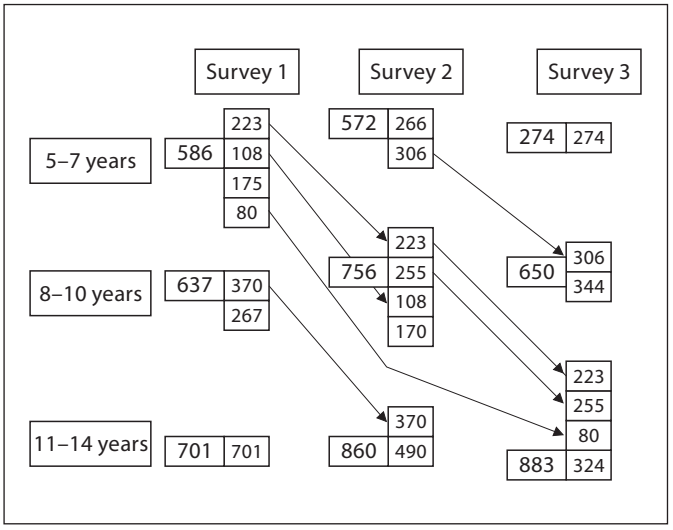

Fig. 1. Three consecutive regional cross-sectional surveys were conducted in 1992–1993, 1995–1996 and 1998–1999. Three areas of East Germany (Zerbst, Hettstedt and Bitterfeld County) were included in each survey.

there is strong evidence for a genetic predisposition to atopic diseases [8, 9], the rapid changes and the huge variation across populations favor environmental explanations [10].

After the German reunification in 1989, several studies conducted in the early 1990s showed a higher prevalence of allergic diseases such as asthma and hay fever in adults and children [11–13] in West Germany (former Federal Republic of Germany) compared to East Germany (former German Democratic Republic). However, total serum IgE levels were found to be higher in East German individuals [12].

People in East Germany quickly adopted a 'Western lifestyle' after German reunification, which included better house insulation and tighter windows with a subsequent increase in dampness and molds [14], fewer homes heated with coal or wood [14], more cars, exotic food [15], fewer infectious diseases, including helminth infestations [16, 17], and more pet-keeping. It was presumed that the prevalence of allergic diseases would rise and approach levels in West Germany, and this trend has actually been observed in several studies in recent years [12, 18–20].

Several known or supposed determinants for total IgE [1, 17, 21] could be considered driving forces behind the temporal changes in total IgE levels in East German children. We decided to evaluate the impact of gender, age, residency, parental education, household size, helminth infection, parental allergy, smoking at home and contact to cats/dogs on total IgE in children.

The objective of this study was to describe trends in total serum IgE levels in East German children and to identify environmental allergic risk factors for high IgE levels in this population.

Methods

Subjects and Setting

This study consisted of three consecutive regional cross-sectional surveys conducted in 1992–1993, 1995–1996 and 1998–1999 [for details, see ref. 22]. Each survey was conducted in three areas of East Germany (Zerbst, Hettstedt and Bitterfeld County) with differing air pollution levels (fig. 1). In each survey, all school entrants (age range 5–7 years), third graders (age range 8–10 years) and sixth graders (age range 11–14 years) who were residents of Zerbst and Hettstedt, and a subgroup of children from Bitterfeld County were invited to participate in this study. All day care centers and schools in Zerbst and Hettstedt counties were contacted. In the larger area of Bitterfeld County, schools and day care centers were randomly selected to represent all children in these age groups. Some of the children were reexamined in the subsequent survey(s). Bitterfeld and Hettstedt counties were heavily polluted in the past by emissions from chemical plants, smelters and power plants burning brown coal with high sulfur content. Zerbst served as a control region with background pollution. The University of Rostock Ethics Committee approved the study protocol. Informed consent was obtained from the parents of all participating children. The data collection and methods have already been described in detail [22, 23].

Questionnaire

Teachers distributed questionnaires to the childrens' parents and collected them a week later. The questionnaire was developed by using questions previously validated in several international studies [24] and contained 78 items adapted to address East German living conditions. It covered questions concerning physicians' diagnoses and typical symptoms of respiratory and allergic disorders, demographic characteristics, parental school education as a proxy parameter for socioeconomic status and possible pathogenic factors. Family history of atopic diseases was considered positive if at least one of the following conditions was present in the mother, father or both: asthma, hay fever, eczema or other forms of allergy. The question regarding whether the child had ever had a helminth infestation and if so at what age was only present in the second and third surveys. For children who participated in the first and second surveys, answers given in the second survey could be used to supplement the 'helminth infestation status'.

Total and Specific IgE

Serum samples were drawn from more than 80% of the children and were immediately frozen and stored at –80°C until the end of the second survey, when they were all analyzed together. The serum samples from the third survey were also stored and analyzed together. Total serum IgE and specific IgE were deter-

mined by an immunoassay and RAST technique, respectively (Pharmacia Diagnostics AB, Uppsala, Sweden). Specific IgE measurements covered grass g6, dust mite *(Dermatophagoides pteronyssinus)* d1, cat e1, *Cladosporium* m2 and birch t3 antigens. Individuals with specific IgE levels greater than or equal to 0.35 kU/l were considered to be sensitized and classified as atopic. Total IgE was determined with a detection limit of 2 kU/l and an upper limit of 2,000 kU/l. As there was no upper limit for total IgE here, all values greater than 2,000 kU/l were set to 2,000 kU/l to make them comparable with those from the first and second survey. All measurements were conducted by a single laboratory (Pharmacia, Freiburg, Germany).

Statistical Analysis

Total serum IgE values were log transformed due to the skewed distribution. The association between log-transformed total IgE and potential determinants, including parental education, number of persons living in the household, helminth infestation, parental allergy, smoking at home, contact to cats or dogs and sensitization to at least one specific IgE (>0.35 kU/l), was calculated using generalized estimating equations with a Gaussian response function. The correlation between repeated measurements in the same individual was assumed to be larger between two successive surveys ($\rho = 0.8$) and smaller between the first and last survey ($\rho = 0.5$). Results are presented as estimated effects of the potential determinants on the log-transformed total IgE level with confidence intervals and p values. Additionally, mean ratios (MRs) are provided to express percentage differences between groups.

Confounders, including age group, sex and study region, were adjusted in each model. All analyses were performed using R version 2.9.0.

Results

Study Population

In total, 8,051 of 9,630 distributed questionnaires were completed by the childrens' parents. The response rates varied between 68.6 and 92.1% between study areas and surveys (table 1). In all, 6,461 of these responses contained measurements of total serum IgE. A total of 3,155 children participated in one survey, 1,263 in two surveys and 260 in all three consecutive surveys. For this study, we analyzed 5,918 data derived from 4,353 schoolchildren.

Children from the first survey were comparable with those participating in the second and third surveys with regard to sex and parental education. However, due to a general decrease in birth rates in East Germany after German reunification in 1990, the children in the later surveys were slightly older compared to the children from the first survey (average age in the second and third surveys was 9.1 and 9.7 years, respectively, vs. 8.9 years in the first survey).

Temporal Changes in Total Serum IgE Levels and Potential Predictors

The crude geometric means of total serum IgE levels were 66.3 kU/l in the first, 60.9 kU/l in the second and 57.9 kU/l in the third survey (table 1). When adjusted for sex, age group and study region, IgE decreased linearly between the first and the third survey ($p < 0.001$). This overall trend was due to the trend in the number of nonatopic children.

The percentage of children with at least one parent having one or more allergic diseases (asthma, hay fever, eczema or other forms of allergy) increased slightly from 27.0% in the first survey to 33.3% in the third (table 1). The proportion of children living in households with more than 4 persons rose from 17.5% in survey 1 to 21.0% in survey 3. In the first survey, 46.6% of the study population reported close contact to cats and/or dogs, compared to 61.4% in the third survey. The percentage of children with a positive RAST ranged between 29.5 and 32.2% across the three surveys (table 1).

Although the lifetime prevalence of helminth infestations in children increases with age – and the average age rose during the study – the percentage of children with a history of helminth infestation dropped between the second and the third survey. As the information on helminth infection missing in the first survey could only be estimated for those children also participating in the second survey, these data were absent in survey 1 for the third age group (individuals of the third age group were not reconsulted in subsequent surveys). These children from the first survey had higher crude prevalences than other children in their age groups in the following surveys (data not shown). Helminth infection was more frequent in girls than boys (14.9 vs. 11.7% for the three surveys together).

The Role of Potential Predictors

Generalized estimating equations for repeated measurements estimated the effect of the potential determinants shown in table 2 on log-transformed total serum IgE for all children and stratified for atopic and nonatopic children. Atopic children had higher levels of total serum IgE (intercept 4.55) than children in the overall group (intercept 3.87) and nonatopic children (intercept 3.72). Boys had significantly ($p < 0.001$) higher total serum IgE levels than girls (MR 1.40). The gender difference in total serum IgE was smaller when stratifying for the group of atopic (MR 1.32) and nonatopic (MR 1.12) children. IgE levels were generally higher in the age groups 8–10 years and 11–14 years as compared to the age group 5–7 years, even though differences were smaller in

Table 1. Characteristics of the study populations of surveys 1 (1992–1993), 2 (1995–1996) and 3 (1998–1999)

	Survey 1 (n = 1,924)	Survey 2 (n = 2,188)	Survey 3 (n = 1,806)
Median total serum IgE, kU/l	51.9	58.8	62.2
log total serum IgE, kU/l	4.2 ± 1.4	4.1 ± 1.5	4.1 ± 1.4
Study subjects			
Zerbst	677 (35.2)	603 (27.6)	520 (28.8)
Bitterfeld	606 (31.5)	966 (44.1)	742 (41.1)
Hettstedt	641 (33.3)	619 (28.3)	544 (30.1)
Demographic characteristics			
Age, years	8.9 ± 2.6	9.1 ± 2.6	9.7 ± 2.3
Age groups			
5–7 years	586 (30.5)	572 (26.1)	274 (15.2)
8–10 years	637 (33.1)	756 (34.6)	650 (36.0)
11–14 years	701 (36.4)	860 (39.3)	882 (48.8)
Males	972 (48.0)	1,163 (53.2)	957 (53.0)
Parental education			
<10 years of school education	129 (6.7)	172 (7.9)	130 (7.2)
10 years of school education	943 (49.0)	1,104 (50.5)	915 (50.7)
12 years of school education	852 (44.3)	912 (41.7)	761 (42.1)
Potential determinants			
Parental atopy	519 (30.0)	674 (29.6)	601 (33.3)
>4 persons per dwelling	337 (17.5)	408 (18.6)	380 (21.0)
History of helminth infestation	137 (7.1)	398 (18.2)	284 (15.7)
No history of helminth infestation	754 (39.2)	1,777 (81.2)	1,509 (83.6)
Unknown history of helminth infestation	1,033 (53.7)	13 (0.6)	13 (0.7)
Contact to cats and/or dogs	896 (46.6)	1,142 (52.2)	1,109 (61.4)
ETS exposure	897 (46.6)	963 (44.0)	788 (43.6)
Allergic sensitization of the child[1]	614 (31.9)	645 (29.5)	581 (32.2)

Only data without missing values were included here. Values represent means ± SD or numbers of subjects with percentages in parentheses, as appropriate.

[1] Defined as IgE ≥0.35 kU/l.

nonatopic children. Children living in households of more than 4 persons had significantly higher IgE levels than children living in households with up to 4 (MR 1.23; $p < 0.001$). In the stratified analysis according to atopic disease status, the effect was stronger for the group of nonatopic children (MR 1.32) compared to the group of atopic children (MR 1.26). Children with a history of helminth infestation had higher IgE levels than those without (MR 1.13; $p < 0.05$), but this effect was most pronounced in nonatopic children (MR 1.22; $p < 0.001$), while it was lower and not significant in the group of atopic children. An opposite effect was seen for parental education; children of parents with school education of 10–12 years or more than 12 years had lower total IgE levels compared to those with parental school education of less than 10 years (MR 0.86 and 0.85, respectively; $p < 0.05$), and this effect was strongest in nonatopic children (MR 0.82 and 0.77, respectively; $p < 0.05$). Parental allergy was associated with significantly higher values of IgE (MR 1.11; $p < 0.01$), but this lost its impact after stratification for sensitization of the children.

The effects on total serum IgE of environmental tobacco smoke (ETS) exposure and close contact to cats and/or dogs were negligible in all groups.

Discussion

We analyzed 5,918 data for total IgE levels in a population of 4,353 schoolchildren in East Germany in three surveys performed at time intervals of 3 years. We found a linear trend towards lower total serum IgE levels over time, in particular for nonatopic children. Living in households of more than 4 people, history of helminth

Table 2. Results of the generalized estimating equations with log-transformed total serum IgE as the independent variable and survey as an additional fixed effect

Variable	All children (n = 5,918)					Atopic children (n = 1,840)					Nonatopic children (n = 4,078)				
	Est.	LCL	UCL	p	MR	Est.	LCL	UCL	p	MR	Est.	LCL	UCL	p	MR
Intercept															
Intercept	3.871	3.69	4.05	0.000		4.55	4.23	4.86	0.000		3.72	3.52	3.92	0.000	
Survey															
Survey 1	ref.					ref.					ref.				
Survey 2	–0.091	–0.16	–0.02	0.009	0.91	0.09	–0.03	0.21	0.133	1.09	–0.12	–0.20	–0.04	0.003	0.88
Survey 3	–0.182	–0.29	–0.08	0.001	0.83	0.10	–0.07	0.27	0.236	1.10	–0.24	–0.36	–0.13	0.000	0.78
Gender															
Male	ref.					ref.					ref.				
Female	0.336	0.25	0.42	0.000	1.40	0.28	0.15	0.41	0.000	1.32	0.12	0.03	0.21	0.010	1.12
Age group															
5–7 years	ref.					ref.					ref.				
8–10 years	0.214	0.15	0.28	0.000	1.24	0.22	0.11	0.34	0.000	1.25	0.12	0.04	0.19	0.003	1.13
11–14 years	0.220	0.12	0.32	0.000	1.25	0.22	0.06	0.37	0.006	1.24	0.05	–0.05	0.16	0.322	1.06
Study location															
Zerbst	ref.					ref.					ref.				
Bitterfeld	0.084	–0.02	0.19	0.107	1.09	–0.12	–0.28	0.05	0.158	0.89	0.10	–0.01	0.20	0.081	1.10
Hettstedt	0.019	–0.09	0.13	0.729	1.02	–0.22	–0.39	–0.05	0.010	0.80	–0.06	–0.17	0.06	0.334	0.94
Parental education															
<10 years	ref.					ref.					ref.				
10–12 years	–0.151	–0.30	–0.00	0.045	0.86	0.17	–0.08	0.42	0.176	1.19	–0.20	–0.36	–0.04	0.016	0.82
>12 years	–0.164	–0.31	–0.01	0.033	0.85	0.16	–0.09	0.40	0.223	1.17	–0.27	–0.43	–0.10	0.002	0.77
Household size															
≤4 persons	ref.					ref.					ref.				
>4 persons	0.208	0.11	0.30	0.000	1.23	0.23	0.07	0.40	0.006	1.26	0.28	0.17	0.38	0.000	1.32
Helminth infection															
No	ref.					ref.					ref.				
Yes	0.126	0.02	0.23	0.021	1.13	0.11	–0.08	0.30	0.252	1.11	0.20	0.08	0.32	0.001	1.22
Unknown	0.053	–0.07	0.18	0.399	1.05	0.08	–0.11	0.27	0.421	1.08	0.08	–0.05	0.22	0.234	1.08
Parental allergy															
No	ref.					ref.					ref.				
Yes	0.107	0.03	0.18	0.005	1.11	0.05	–0.07	0.17	0.455	1.05	0.02	–0.06	0.10	0.579	1.02
Smoking at home															
No	ref.					ref.					ref.				
Yes	0.032	–0.04	0.11	0.393	1.03	–0.01	–0.13	0.11	0.847	0.99	0.08	–0.01	0.16	0.068	1.08
Contact to cats/dogs															
No	ref.					ref.					ref.				
Yes	–0.017	–0.08	0.05	0.616	0.98	0.02	–0.09	0.12	0.724	1.02	0.04	–0.03	0.12	0.261	1.04

Est. = Estimate; LCL = lower confidence limit; UCL = upper confidence limit; MR = means ratio; ref. = reference.

infestation, parental allergy and higher age of the children were associated with higher IgE levels. Higher parental education was associated with lower IgE values. Significantly higher total serum IgE levels were seen in boys as compared to girls. In the group of nonatopic children, there was no longer a gender effect.

Summarizing the potential influences of temporal changes in predictors of total IgE levels, we found only the decline of helminth infestations consistent with the decreasing trend for total IgE levels. Although several other potential risk factors for total IgE, such as parental atopy, crowding and contact to cats and dogs, tended to increase, the total IgE levels decreased over time.

Behrendt et al. [25] determined total serum IgE levels in children (mean age 6.4 years) from four towns in East Germany in 1991 and calculated a geometric mean of 51.4 kU/l. Using a similar method, we found slightly higher IgE levels (geometric mean: 66.3 kU/l in 1992–1993 and 57.9 kU/l in 1998–1999), which was partly due to the higher average age in our survey (geometric mean for the 6-year-old children in our study was 52.2 kU/l). In addition, our study covered a more rural area. IgE levels in a comparable group of children in West Germany were clearly lower (geometric mean 20.3 kU/l) [25]. In contrast, the geometric mean of total IgE in a study of schoolchildren in rural Ecuador was as high as 1,004 kU/l [26].

In line with our study findings, other studies have described higher values of total serum IgE for male children [27] and adults [6, 28] as compared to females. Kulig et al. [1] found significantly higher values in boys, also in a group of nonatopic children. However, our data suggest that in our study population, the gender difference in the overall group is partly due to a higher prevalence of atopy among boys than girls (37.5 vs. 24.1%) and higher total serum IgE levels in atopic boys compared to atopic girls, as in the stratified analysis, there was no gender effect in the group of nonatopic children. Similar sex-specific differences in prevalence rates of allergic sensitization assessed by skin prick tests have been described by Sherrill et al. [29], with 39.2% for boys and 26.4% for girls in a population of 6-year-old children in Tucson, Ariz., USA.

Worldwide, there is a striking pattern of allergic diseases with a strong gradient from developing and rural to industrialized and urban areas [30] with region-specific temporal changes [31, 32]. One obvious difference in living conditions between developing and industrialized regions besides socioeconomic status consists of lower hygienic standards and greater exposure to parasitic and other infections in developing areas. The 'hygiene hypothesis' [33] claims that the maturing immune system of children in westernized wealthy regions is less challenged by infectious diseases and is therefore more likely to develop an imbalance between the Th1/Th2 immune responses. This results in a tendency to target Th2-dependent reactions on ubiquitous harmless antigens, as observed in atopic individuals [33]. This hypothesis has been taken further by many researchers to develop a model claiming that early chronic or long-lasting parasitic infections lead to the activation of a regulatory network of the immune system that has anti-inflammatory effects on Th1 as well as Th2 responses [34].

A higher prevalence of helminth infestation has been suggested as one explanation for higher IgE levels but a lower prevalence of allergic diseases in East Germany. In our study, 14.9% of the girls and 11.7% of the boys reported a history of helminth infestation, which is higher than comparable data from West Germany, such as the 5% lifetime prevalence reported by Behrendt et al. [25]. Our study showed that children with a history of helminth infestation have higher IgE. In the nonatopic group, that effect was even stronger. During the observation period of the study, IgE levels as well as the lifetime prevalence of helminth infestation decreased, and average age at the time of the first helminth infection rose from 4.2 years in the second survey to 5.0 years in the third survey. The decline in helminth infestation is consistent with the observed decreasing levels of total IgE during the 1990s. However, adjustments for helminth infestation did not completely explain the declining total IgE levels. The reasons for the modest effect of helminth infestation might have been underreporting on the questionnaire because it was too long ago or parents did not recognize it. Also, an infestation from several years previously may have lost its impact on IgE levels.

Strachan [33] found that hay fever was inversely related to the number of children in the household at age 11 and suggested that with an increasing number of people per household, infection rates in childhood also rise due to frequent contact with pathogens and chains of reinfection. It has also been reported that total serum IgE levels increase with the number of people per dwelling [2]. Our analysis further supports this hypothesis. Interestingly, Behrendt et al. [25] only found a significant effect of household size on IgE in East German and not in West German children. In our study, the effect of household size of more than 4 people on IgE decreased between 1993 and 1999. This trend may be another manifestation of a converging tendency of lifestyle factors between East and West.

Although an enhancing effect on IgE production has been reported for cigarette smoking [6, 35], the impact of ETS on serum IgE levels is controversial [36, 37]. In this study, there was no association between ETS and IgE.

In our study, the percentage of children having close contact to cats or dogs increased clearly between 1993 and 1999 from 46.6 to 61.4% but its impact on IgE was not significant and was close to nil in all three groups.

One of the strengths of the present study is that identical methods, including an identical questionnaire, were used in all three surveys. This study used a large data set of total IgE measurements, with intra- and interassay coefficients of variation being 7%. However, there are also limitations of the study that should be addressed.

A possible limitation lies in the lower participation rates in the second and third surveys, although they did not lead to a selection bias regarding parental education. The survey question regarding whether the child had ever had a helminth infection and if so at what age was not present in the first survey. Therefore, this information was extrapolated for the cohort that answered the question in the second survey. Retrospective assessment of the childrens' age at first helminth infestation by parents might have led to misclassification of children in the first survey.

Overall, IgE levels decreased over time in our study population, while the prevalence of strong sensitization (at least one specific IgE $\geq$17.5 kU/l) and allergic diseases (except for hay fever) increased [18]. In part this could be understood as a loss of parasite-induced immunomodulatory counterregulation due to decreasing helminth infestation. Schäfer et al. [17] proved a negative association between helminth infestation and subsequent allergic sensitization in our study population.

Nickel et al. [27] have shown that IgE values of children aged 5 years and older correlate well with IgE levels later in life, while in earlier childhood, IgE levels vary considerably and are not predictive for the future development of IgE. In our study, the intraindividual correlation for IgE levels was also high (0.84 between surveys 1 and 2, 0.83 between surveys 2 and 3, and 0.72 between surveys 1 and 3). Therefore, the results of this study based on a population of school-aged children (5–13 years) are likely to be predictive for the future development of IgE levels in these individuals.

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