Allergy 2005: 60: 1014–1020

Copyright © Blackwell Munksgaard 2005

ALLERGY
DOI: 10.1111/j.1398-9995.2005.00801.x

Original article

Worm infestation and the negative association with eczema (atopic/nonatopic) and allergic sensitization

Background: Worm infestations may play a role in preventing allergies. There is a lack of epidemiological information from Western countries on the association between worm infestation and eczema.
Objective: To investigate the association between worm infestation and eczema in a proper temporal sequence and under consideration of allergic sensitization.
Methods: Two surveys were performed in East German school children. Questionnaire data included the history of eczema and worm infestation and their time of onset. Specific IgE antibodies to five common aeroallergens were measured and used to define nonatopic and atopic eczema. Logistic regression analyses were performed to control for relevant confounders (age, sex, parental school education and history of allergies). In order to confirm the findings a corresponding conditional regression analysis was applied on cases and controls matched by age and sex.
Results: A total of 4169 children participated (response 75 and 76%) who were, on average, 9.2 years old (47% girls). Overall 17.0% reported a prior worm infestation (Ascaris 44%, Oxyuris 33%) and 18.1% had a history of eczema. Eczema occurred significantly less frequent in children who had a worm infestation (prior to the onset of eczema) compared with children without such a history (8.1% *vs* 16.5%, OR_{adj}: 0.45, 95% CI: 0.33–0.60). The finding was confirmed by the corresponding matched case–control analysis (OR_{adj}: 0.57, 95% CI: 0.41–0.79). Atopic eczema was affected more by a prior worm infestation (OR_{adj}: 0.31, 95% CI: 0.18–0.56) than the nonatopic eczema (OR_{adj}: 0.58, 95% CI: 0.40–0.84). A total of 29.1% exhibited specific IgE antibodies to at least one aeroallergen. Sensitized children gave significantly less frequent a history of worm infestation (14.2% *vs* 18.3%, OR_{adj}: 0.74, 95% CI: 0.60–0.92). Stratified analysis revealed that this effect most pronounced for a sensitization to house dust mite.
Conclusions: A worm infestation is associated with a reduced frequency of subsequent eczema, especially the atopic type. Furthermore allergic sensitization, especially to house dust mite, and worm infestation are negatively associated. The data support the concept that a lack of immune-stimulation by parasitic infections contributes to the development of allergies.

T. Schäfer[1], T. Meyer[1], J. Ring[2,3], H.-E. Wichmann[4,5], J. Heinrich[4]

[1]Institute of Social Medicine, Medical University Lübeck, Lübeck, Germany; [2]Department of Dermatology and Allergy, am Biederstein, Technical University Munich (TUM), Munich, Germany; [3]Division Environmental Dermatology and Allergology GSF/TUM; [4]GSF – National Research Center for Environment and Health, Institute of Epidemiology, Neuherberg, Germany; [5]Chair of Epidemiology, Institute of Medical Data Processing, Biometrics, and Epidemiology, Ludwig-Maximilians-University Munich, Munich, Germany

Key words: allergy; atopic; eczema; epidemiology; helminthic infection; nonatopic; sensitization.

Prof. Dr Torsten Schäfer, MPH
Department of Social Medicine
Medical University Lübeck
Beckergrube 43-47
23552 Lübeck
Germany

Accepted for publication 24 November 2004

It was speculated and proposed as the 'hygiene hypothesis' that a reduced immune-stimulation by infections as a consequence of improved sanitation, antibiotic medication and lifestyle factors including a decreasing family size has contributed to the increasing prevalence of atopic diseases (1, 2). Concerning bacterial and viral infections a dichotomous TH1–TH2 model might be helpful to explain this concept as these infections would shift the balance towards a TH1 stage. Corresponding epidemiological evidence on, e.g. hepatitis A or BCG immunization exists (3). The role of helminthic infestation as an example of a fecal–oral infection has also been discussed in this context. As helminths are a strong TH2 stimulus a more complex immunological model is needed to explain the potentially preventive role of a worm infestation. In this context the function of regulatory T cells is discussed and it is hypothesized that helminths could stimulate regulatory T cells which would then contribute to an anti-allergic environment mainly by the expression of IL10 and TGF-β (2). There are studies supporting hypotheses

Abbreviations: CI, confidence interval (95%); D.pter., *Dermatophagoides pteronyssinus*; HDM, house dust mite; OR, odds ratio; RAST, radioallergosorbent test.

that (i) parasites protect against the development of atopic diseases, that (ii) worms predispose individuals to the development of atopic diseases and that (iii) atopics are protected from parasite infection (4). In summary there is, however, a convincing body of evidence describing a negative association between worm infestation and manifestations of atopy (5–10). Thereby the current literature has focused on outcomes such as asthma and allergic sensitization (11). Little is known on the effect of a worm infestation on eczema. A recent review identified six epidemiological studies on that topic of which only one gave reliable information based on an analytical design (12). This study has analyzed 3110 school children from Taiwan and revealed significant negative associations between an actual pinworm infestation and asthma or allergic rhinitis, but not with eczema (13). No corresponding data are available to date for Europe. Furthermore, there are at least two major methodological questions which have not been addressed adequately so far: due to the cross-sectional design of the studies at hand it was not possible to assure a proper temporal sequence of exposure (worm infestation) and outcome (eczema). This, however, would be necessary in order to test the hypothesis that worm infestation decreases the risk of subsequent eczema. Furthermore, a distinction should be made between nonatopic and atopic type eczema, as only the latter is associated with allergic sensitization and might be affected preferably by a worm infestation.

The following study aims to address these questions in a large sample of school children from East Germany.

Methods

Study design and population

Two repeated cross-sectional studies were performed in three regions of Saxony-Anhalt (East Germany) between September 1995 and July 1996 and between September 1998 and July 1999 to assess various health outcomes including eczema. These studies constitute the second and third survey of a series of three surveys which were performed in this region (14). These two surveys were chosen because they provided detailed data on worm infestation including the time of onset. The study design and results regarding health effects and the body burden of pollutants have been published elsewhere in more detail (15, 16).

Briefly, two of the study regions ('Bitterfeld', 'Hettstedt') were heavily polluted in the past by emissions from large power plants burning brown coal with a high sulfur content (up to 5%), chemical plants, and smelters. The third area (Zerbst) served as a control area with background pollution. Children of three age groups (5–7, 8–10, and 11–14 years) from all schools in Zerbst and Hettstedt were invited to participate. In the larger area of Bitterfeld, schools were chosen to represent each regional district. Parents gave written consent after they had received an informational letter. The examinations took place at schools and kindergartens. Data assessment and analysis always refers to the first or only time of participation. The study protocol was approved by the University of Rostock Ethics Committee.

Outcome assessment

Allergen-specific IgE antibodies. At the beginning of the observation period venous blood samples were drawn and allergen-specific IgE antibodies to five common aeroallergens (*Dermatophagoides pteronyssinus*, grass pollen, birch pollen, cat, and *Cladosporium herbarum*) were determined by standard laboratory procedures (RAST-CAP-FEIA; Pharmacia, Uppsala, Sweden). All analyses were carried out by Pharmacia (Freiburg, Germany) with the same batches of allergen caps per survey. The detection limit for RAST reactivity was set at 0.35 kU/l.

Questionnaire. Standardized instruments were mailed to the parents together with the invitatory letter and checked for completeness at the time of examination. The questionnaire covered basic demographic characteristics, the parental school education as a proxy parameter for socioeconomic status as well as the parental history of atopic eczema.

A positive history of eczema was recorded when the following question was answered positively: Has your child ever had an itchy skin condition of the skin creases such as folds of elbows, behind the knees or front of ankles (neurodermatitis, eczema)? There are no data on the validity of this particular question available. The items however refer to instruments which are validated and used widely in epidemiological studies such as the ISAAC study (17) and the UK refinement of the Hanifin and Rajka criteria (18). According to the latter the sensitivity of an 'itchy skin condition' was determined to be 94.2 and 90% for the affection of the skin creases and 97.5% for the question 'Do you have eczema?'. The corresponding values for specificity are 42.2, 74.5 and 82%, respectively. The German translation on the UK criteria yielded a high sensitivity (88%) and specificity (99%) (19) in school children so that we assume that atopic eczema has been assessed with sufficient validity (20, 21). If this question was answered positively it was further asked at what age these symptoms had appeared for the first time.

Furthermore, the parents were asked whether the child ever had a worm infestation and if so when this had happened for the first time. The parents were further asked to recall the type of worm (Ascaris, Oxyuris, other) in case they could provide this detailed information.

Statistical analyses

Besides descriptive statistics we used odds ratio (OR) and 95% confidence interval (CI) as measures of association and stability in bivariate and multiple logistic regression analyses. Regression models used eczema (nonatopic/atopic) or allergic sensitization as dependent variables and controlled for age, sex, parental eczema and parental school education when analyzing the association with a history of worm infestation. In order to assure a proper temporal sequence worm infestations which did not occur prior to the onset of eczema were considered to be of no relevance for the question at hand and recoded as 'negative'. The restriction of cases with specific conditions concerning the exposure and outcome (worm prior or after eczema) might lead to a differential effect on a single cell in the 2×2 table which then could bias the effect estimate. Therefore we aimed, as a kind of sensitivity analysis, to confirm the resulting odds ratios of the unconditional logistic regression analyses with a different analytic option and conducted a conditional logistic regression analysis on a subsample matched exactly on age and gender of the children with a 1 : 3 ratio. This procedure yields a second estimate of the OR of primary interest by a more restrictive control for possible confounders which furthermore should not be affected by this potential bias.

As data on the onset of allergic sensitization could not be achieved a similar approach was not possible for the association of allergic sensitization and worm infestation.

All statistical analyses were carried out using the software packages SPSS for Windows 11.0, except for the conditional logistic regression analysis which was performed by EpiInfo 2002.

Results

A total of 4169 children participated, which corresponds to a response of 75% in 1995/96 and 76% in 1998/99. A total of 1515 children attended the 1995/96 survey and 1355 the 1998/99 survey only, whereas another 1299 children took part in both surveys. The participating children were on average 9.18 years old and 46.6% were girls.

A positive history of eczema was obtained in 747 children (18.1%) which was not significantly different for children of the 1995/96 (17.9%) and the 1998/99 (18.7%) survey. Less children suffered from eczema in the control region Zerbst (16.4%), which was, however, not statistically different from the exposed areas Hettstedt (17.2%) and Bitterfeld (19.7%). Of the cases 29.6%occurred within the first year and 41.9% within 2 years. On average the parents reported the onset with 4.2 (median 3.0) years (range 1–13), whereby occurrences within the first year of life were counted as 1 year.

For 682 of 4012 children a prior worm infestation was reported (17.0%). Worm infestation first occurred on average with 4.7 years (median 4.0) and the age of onset ranged between 1 and 13 years. In 79.3% of the cases the parents could specify the type of worm infestation (corresponding to 20.7% unknown) and according to that most children were infected by Ascaris (43.9%) or Oxyuris (33.1%) and the remaining 2.3% by other parasites (not further specified). A worm infestation occurred significantly more often in girls (17.5%) than boys (13.0%) (OR: 1.41, 95% CI: 1.19–1.68). For those children where information on eczema was available ($n = 3983$) a positive history of a worm infestation was given in 15.0%. Data on allergic sensitization were available for 3265 children (78.3% of the participating children) and 29% of these exhibited specific IgE antibodies to at least one of five common aeroallergens. Of the children with eczema 41.2% showed a concomitant allergic sensitization and were classified as suffering from atopic eczema.

Detailed information on basic characteristics is given in Table 1. When comparing children with and without a history of eczema with respect to common confounders on a bivariate level it became clear that significantly more girls and children with a positive parental history of eczema were affected. Furthermore, eczema was more frequent when the parents had a higher school education. Allergic sensitization was on average twice as common in children with eczema.

When taking the temporal sequence of the onset of eczema and time of infestation not into account no significant association was observed (OR_{adj}: 1.12, 95% CI: 0.89–1.39).

For the analysis of the association of a worm infestation and eczema a restriction was made to eczema cases in which the infestation had occurred prior to the onset of eczema (58 of 134 eczema cases with a history of worm infestation). In these cases eczema has occurred on average at 7.4 years (median 8.0) and the worm infestation with 4.0 years (median 3.0). Here a prior worm infestation was associated with a risk reduction of 55% for eczema. After controlling for relevant confounders the odds ratio of the unconditional logistic regression remained unchanged (OR_{adj}: 0.45, 95% CI: 0.33–0.60).

To investigate the question whether this association differs according to the subtypes of eczema separate unconditional logistic regression models were used for atopic and nonatopic eczema. Thereby it was shown that the association was more pronounced for atopic eczema (OR_{adj}: 0.31, 95% CI: 0.18–0.56) than for nonatopic eczema (OR_{adj}: 0.58, 95% CI: 0.40–0.84). These findings

Table 1. Basic demographic characteristics and prevalence of relevant confounders in the entire sample (merged survey data from 1995/96 and 1998/99) and in comparison of children with and without eczema

Variable, % (*n*)	All, 4169	Eczema, 747/4124 (18.1%)	No eczema, 3377/4124 (81.9%)	OR (95% CI)
Sex (female)	46.6 (4169)	53.1 (4124)	45.1	1.38 (1.18–1.62)
Age (years, mean)	9.18 (4169)	9.10 (4124)	9.19	$P = 0.40$
Parental history of eczema	9.6 (3941)	19.0 (3909)	7.5	2.89 (2.29–3.63)
Parental school education ≥12 years	40.8 (3980)	46.0 (3942)	39.6	1.30 (1.10–1.53)
Sensitization				
Grass pollen	17.9 (3272)	28.5 (3243)	15.6	2.16 (1.75–2.66)
Birch pollen	11.0 (3264)	19.6 (3235)	9.1	2.43 (1.90–3.10)
HDM (D.pter.)	15.7 (3274)	20.9 (3245)	14.5	1.56 (1.24–1.95)
Cat	6.7 (3274)	17.0 (3245)	4.5	4.37 (3.29–5.81)
Cladosporium	3.7 (3270)	10.5 (3241)	2.2	5.24 (3.61–7.60)
Any	29.1 (3265)	41.2 (3236)	26.5	1.95 (1.62–2.35)
History of worm infestation	17.0 (4012)	8.1* (3983)	16.5	0.45 (0.37–0.59)

*Prior to onset of eczema.

Table 2. Unconditional logistic regression on eczema and atopic and nonatopic subtypes (worm infestation occurred prior to onset of eczema, $n = 3606$)

	Eczema ($n = 3606$)		Atopic eczema ($n = 3210$)		Nonatopic eczema ($n = 3294$)	
Variable	OR	95% CI	OR	95% CI	OR	95% CI
Prior worm infestation	0.45	0.33–0.60	0.31	0.18–0.56	0.58	0.40–0.84
Age (years)	1.00	0.97–1.03	0.98	0.93–1.03	0.96	0.92–1.00
Gender (female)	1.39	1.17–1.66	0.83	0.62–1.10	2.15	1.68–2.74
Parental atopic eczema	2.89	2.27–3.67	4.23	3.02–5.93	2.43	1.74–3.41
Parental school education (<9, 9–12, >12 school years)	1.42	1.23–1.65	1.48	1.16–1.89	1.45	1.18–1.77

indicate that an effect on allergic sensitization contributes to the negative association with eczema. On the contrary, it became clear that the prevalence of eczema is reduced by a prior worm infestation independently from a pathway which is mediated by allergic sensitization (Table 2).

As some evidence suggests that an atopic state protects against a secondary helminthic infection the association between eczema and a subsequent worm infestation was also analyzed. In these cases eczema has occurred on average at 2.5 years (median 2.0) and the worm infestation with 4.7 years (median 4.0). A still negative but weaker association was found in this group (OR_{adj}: 0.61, 95% CI: 0.46–0.80) with effects being more pronounced for the nonatopic (OR_{adj}: 0.58, 95% CI: 0.39–0.85) than the atopic (OR_{adj}: 0.70, 95% CI: 0.45–1.08) type.

In order to investigate worm-specific effects the same models were used to analyze the association between prior worm infestation and eczema separately for Ascaris and Oxyuris. Both types of worm infestation showed a negative association which was slightly more pronounced for Oxyuris (OR_{adj}: 0.40, 95% CI: 0.24–0.68) than Ascaris (OR_{adj}: 0.58, 95% CI: 0.39–0.87).

For the matched analysis 629 eczema cases with complete information could be included of which 49 experienced a worm infestation prior to the onset of eczema. After matching in a 1 : 3 (629 : 1882) modus the entire analysis comprised 2511 children. The conditional logistic regression analysis that was based on the samples matched by sex and age and controlling for parental history of eczema and parental school education yielded an OR_{adj} of 0.57 (95% CI: 0.41–0.79). Thereby this independent analytic approach could confirm the negative association between worm infestation and the subsequent development of eczema.

The association between worm infestation and allergic sensitization was analyzed in more detail. The distribution of relevant confounders in children with and without allergic sensitization is given in Table 3. According to bivariate analyses overall allergic sensitization was significantly negatively associated with a positive history of a worm infestation. With respect to single allergens this association was most pronounced and significant for house dust mite (D.pter.) (Table 4). According to logistic regression analysis a history of worm infestation reduced the risk of allergic sensitization by more than 25% (OR_{adj} 0.73, 95% CI: 0.58–0.91) (Table 5).

Table 3. Basic demographic characteristics and prevalence of relevant confounders in comparison of children with and without allergic sensitization (RAST)

Variable, % (*n*)	Sensitization positive, 29.2% (952/3265)	Sensitization negative, 70.8% (2313/3265)	OR (95% CI)
History of worm infestation	14.2 (3167)	18.3	0.74 (0.60–0.92)
Sex (female)	36.3 (3265)	50.8	0.55 (0.47–0.65)
Age (mean)	9.31 (3265)	8.89	$P < 0.001$ (*t*-test)
Parental history of atopic disease	37.4 (3116)	28.1	1.53 (1.30–1.80)
Parental school education ≥12 years	43.2 (3131)	38.8	1.20 (1.03–1.40)

Table 4. Prevalence (%) of allergic sensitization (RAST) to different aeroallergens by history of worm infestation in children aged 5–14 years

	Prevalence of allergic sensitization		
Variable (%)	Worm infestation ($n = 541$)	No worm infestation ($n = 2626$)	OR (95% CI)
Grass pollen	15.1	18.6	0.78 (0.61–1.01)
Birch pollen	9.1	11.6	0.76 (0.55–1.04)
HDM (D.pter.)	12.2	16.6	0.70 (0.53–0.92)
Cat	5.9	6.9	0.84 (0.57–1.24)
Cladosporium	4.4	3.4	1.31 (0.83–2.07)
Any	24.4	30.4	0.74 (0.60–0.92)

Table 5. Unconditional logistic regression of allergic sensitization (RAST) on a history of worm infestation ($n = 2937$)

Variable	OR	95% CI
History of worm infestation	0.73	0.58–0.91
Age (years)	1.06	1.03–1.10
Gender (female)	0.54	0.46–0.64
Parental atopic disease	1.54	1.30–1.83
Parental school education (>12 school years)	1.09	0.95–1.26

Discussion

In this large population-based study, which was analyzed as retrospective cohort study we were able to show that worm infestation is negatively associated with subsequent eczema and that this association is more pronounced for the atopic type. In this context it was further demonstrated that current allergic sensitization is also negatively associated with a history of worm infestation and that HDM sensitization contributes in particular to this association.

It is worth mentioning that worm infestation in Germany is quantitatively and qualitatively different from that in other, especially developing, countries. In a group of 317 Gabonese school children 46% were infected with Ascaris and 71% with Trichuris (22). Oxyuriasis was diagnosed in 14% of 3107 school children from Taipei (13). An Ascaris infection was present in 51 and 57% of children from two Venezuelan regions (9) and the prevalence of geohelminth infections was also high in a large sample of school children from Ecuador. A total of 63% exhibited an infestation with Ascaris (50%) and Trichuris (44%) being the most important parasites (6). The lifetime prevalence of worm infestation in our study sample was much lower (17%) with Ascaris and Oxyuris being the predominating parasites. Whereas Ascaris seems to be equally important in other countries, Oxyuris does not play that role in contrast to Trichuris which has not a great impact on the overall worm infestation in Germany. Although it is likely that different types of worms have different effects on the immune system we were able to show that the effects of Ascaris and Oxyuris infestations on atopic eczema were quite similar.

Some strengths of this study might be mentioned. In this study 4169 children from the general population could be included, which increases reliability and generalizability of the data. Although several epidemiological studies exist on the association between worm infestation and atopy the association with eczema was rarely studied. Observational and ecologic studies from Malaysia and Venezuela suggested an inverse relationship between worm infestation and eczema (9, 23, 24). These findings, however, are hard to interpret due to several methodological shortcomings. The best cross-sectional study came from Taiwan and could not demonstrate an association between a doctors diagnosed eczema and an actual positive pinworm test (13). According to the actual body of literature the following deficits must be considered:

There is shortage of good epidemiological studies on the association between worm infestation and eczema. Data from Western industrialized countries are basically absent. No study so far could establish the exact temporal sequence of exposure and outcome and furthermore this association was not investigated separately for nonatopic and atopic eczema (12).

As mentioned earlier the model of a TH1–TH2 dichotomy cannot explain these findings, as helminthic infections are a strong TH2 stimulus. The immunological response to a worm infestation seems to involve an initial step which is characterized by the production of specific IgE followed by a phase of polyclonal IgE synthesis. It was postulated that these specific and polyclonal IgE antibodies prevent IgE-mediated allergic diseases by blocking effector cell IgE receptors (25). More recently the TH1–TH2 dichotomy as part of the hygiene hypothesis has been put into context of a more complex anti-inflammatory network. Thereby IL-10 and TGF-β produced by antigen-presenting cells or regulatory T cells play a central role in the downregulation of an allergic inflammatory cascade (2). Recent data from Gabon may confirm this view and interestingly enough parasite-induced IL-10 was able to reduce allergic sensitization to mite (D.pter.) (26) and consequently it was shown that long-term treatment of intestinal helminthes increases the risk of sensitization to mites (22). In our study sensitization to D.pter. was the only one out of five tested aeroallergens which was significantly negatively associated with a history of worm infestation. The strong relationship between worm infestation and mite sensitization, however, needs further elucidation.

An investigation in children of earlier surveys in the Bitterfeld region revealed the presence of Ascaris-specific IgE was associated with a higher total IgE, a higher prevalence of other aeroallergen-specific IgE antibodies as well as allergic rhinitis and asthma (27). The history of a clinical worm infestation, however, was not investigated in this study so that the presence of Ascaris-specific IgE may be interpreted as a characteristic of an atopic child which also exhibits sensitizations to other allergens as well as inhalative allergies.

In retrospective settings like this recall bias is always a concern. A prerequisite would be that the participants are aware of the potential association of interest. This, however, is unlikely because the study was announced in a broader context of environmental influences namely air pollution and their impact on allergies and it can be expected that associations between worm infestations and allergies are not assumed in the public. More important, recall bias basically relies on the fact that diseased persons recall incremental exposure differentially better. In this case of a negative association, however, recall bias would be explanative if healthy subjects had recalled worm infestation differentially more often and vice versa. This seems a rather unlikely explanation. It was suggested and cannot be ruled out completely that for children who developed eczema a subsequent worm infestation was overlooked due to the fact that both disorders are associated with itch.

A causal relationship can hardly be established with the data at hand, however not be excluded either. Some characteristics (consistency, plausibility, temporal sequence) would support a causal relationship. There is concern that a worm infestation is an indicator especially for other infections and an allergy-preventive

environment. We had included parental school education as indicator of social status in all multivariate analyses. Furthermore, family size, pet keeping and the number of infections with fever was tested in the models without affecting the effect estimate for worm infestation (data not shown).

Several studies have assessed the actual exposure by stool examinations. This is certainly a more valid approach than the parental reports we obtained on the children's history of worm infestations. On the contrary, we aimed to assure a proper temporal sequence of exposure and outcome by this retrospective data assessment. Data on stool examinations at the time of the first infestation, however, were not available. As mentioned above recall bias seems an unlikely explanation for the association at hand.

The prevalence of a prior worm infestation in this sample of school children from East Germany was 17.0% and seems to be high compared with other industrialized regions including West Germany (28). Other independent investigations confirm a rather high prevalence of worm infestations in the former GRD. This has helped to achieve a sufficient degree of exposure variability and raises further questions on worms as a possible explanation for the higher frequency of allergies in West Germany (29–31). In contrast, the frequency of eczema was consistently found to be higher in East compared with West Germany, which could be attributed to a higher percentage of the nonatopic type (32). A stronger increase of the lifetime prevalence of eczema in East compared with West Germany was observed over a 10-year period. However, this trend is not confirmed by data based on an actual examination or reported symptoms. Therefore, reliable data supporting the hypothesis that the decreasing trend of worm infestations in East Germany is accompanied by an increasing trend of eczema are lacking. Overall it seems, however, reasonable to believe that a comparably low frequency of worm infestations is part of the so-called Western lifestyle which has been discussed as being responsible for the increasing trend of allergies (33).

Acknowledgments

We wish to thank all parents and children for their participation. The fieldwork of this study was supported by a governmental funding source, the Federal Environmental Agency (Umweltbundesamt), Grant No. FKZ 298 61724. The data analysis was funded by the GSF-National Research Center for Environment and Health.

References

1. Strachan D. Allergy and family size: a riddle worth solving (Editorial). Clin Exp Allergy 1997;**27**:235–236.
2. Yazdanbakhsh M, Kremsner P, van Ree R. Allergy, parasites, and the hygiene hypothesis. Science 2002;**296**:490–494.
3. Liu A, Murphy J. Hygiene hypothesis: fact or fiction? J Allergy Clin Immunol 2003;**111**:471–478.
4. Pritchard D. Atopy and helminthic parasites. Int J Parasitol 1993;**23**:167–168.
5. Scrivener S, Yemaneberhan H, Zebenigus M, Tilahun D, Girma S, Ali S et al. Independent effects of intestinal parasite infection and domestic allergen exposure on risk of wheeze in Ethiopia: a nested case–control study. Lancet 2001;**358**:1493–1499.
6. Cooper P, Chico M, Bland M, Griffin G, Nutman T. Allergic symptoms, atopy, and geohelminth infections in a rural area of Ecuador. Am J Respir Crit Care Med 2003;**168**:313–317.
7. Cooper P, Chico M, Rodrigues L, Ordonez M, Strachan D, Griffin G et al. Reduced risk of atopy among school-age children infected with geohelminth parasites in a rural area of the tropics. J Allergy Clin Immunol 2003;**111**: 995–1000.
8. Dagoye D, Bekele Z, Woldemichael K, Nida H, Yimam M, Hall A et al. Wheezing, allergy, and parasite infection in children in urban and rural Ethiopia. Am J Respir Crit Care Med 2003;**167**:1369–1373.
9. Lynch N, Hagel I, Palenque M, Di Prisco M, Escudero J, Corao L et al. Relationship between helminthic infection and IgE response in atopic and nonatopic children in a tropical environment. J Allergy Clin Immunol 1998;**101**:217–221.
10. Perzanowski M, Ng'ang'a L, Carter M, Odhiambo J, Ngari P, Vaughan J et al. Atopy, asthma, and antibodies to Ascaris among rural and urban children in Kenya. J Pediatr 2002;**140**:582–588.
11. van Hertzen L, Haahtela T. Asthma and atopy – the process of affluence. Allergy 2004;**59**:124–137.
12. Flohr C. Dirt, worms and atopic dermatitis. Br J Dermatol 2003;**148**: 871–877.
13. Huang S, Tsai P, Yeh Y. Negative association of Enterobius infestation with asthma and rhinitis in primary school children in Taipei. Clin Exp Allergy 2002;**32**:1029–1032.
14. Heinrich J, Hoelscher B, Frye C, Meyer I, Pitz M, Cyrys J et al. Improved air quality in reunified Germany and decreases in respiratory symptoms. Epidemiology 2002;**13**:394–401.
15. Heinrich J, Hoelscher B, Wichmann H. Decline of ambient air pollution and respiratory symptoms in children. Am J Respir Crit Care Med 2000;**161**:1930–1936.
16. Meyer I, Heinrich J, Lippold U. Factors affecting lead, cadmium, and arsenic levels in house dust in a smelter town in Eastern Germany. Environ Res 1999;**81**:32–44.
17. Keil U, Weiland S, Duhme H, Chambless L. The international study of asthma and allergies in childhood (ISAAC): objectives and methods; results from German ISAAC centres concerning traffic density and wheezing and allergic rhinitis. Toxicol Lett 1996;**86**:99–103.
18. Williams H, Burney P, Pembroke A, Hay R. The U.K. working party's diagnostic criteria for atopic dermatitis. III. Independent hospital validation. BJD 1994;**131**:406–416.

19. Möhrenschlager M, Schäfer T, Williams H, Werth der van J, Krämer U, Behrendt H et al. Übersetzung und Validierung der britischen Diagnosekriterien des atopischen Ekzems bei acht- und neunjährigen Schulkindern in Augsburg 1998. Allergo J 1998;**7**:375–377.
20. Williams H, Burney P, Hay R, Archer C, Shipley M, Hunter J et al. The U.K. working party's diagnostic criteria for atopic dermatitis. I. Derivation of a minimum set of discriminators for atopic dermatitis. BJD 1994;**131**:383–396.
21. Williams H, Burney P, Strachan D, Hay R. The U.K. working party's diagnostic criteria for atopic dermatitis. II. Observer variation of clinical diagnosis and signs of atopic dermatitis. BJD 1994;**131**:397–405.
22. van den Biggelaar A, Rodrigues L, van Ree R, van der Zee J, Hoeksma-Kruize Y, Souverijn J et al. Long-term treatment of intestinal helminths increases mite skin-test reactivity in Gabonese schoolchildren. J Infect Dis 2004;**189**:892–900.
23. Larrick J, Buckley C, Machamer C, Schlagel G, Yosts J, Blessign-Moore J et al. Does hyperimmunoglobulinemia-E protect tropical populations from allergic diseases? J Allergy Clin Immunol 1983;**71**:184–188.
24. Lynch N, Lopez R, Isturiz G, Tenias-Salazar E. Allergic reactivity and helminthic infection in Amerindians of the Amazon Basin. Int Arch Allergy Appl Immunol 1983;**72**:369–372.
25. Lynch N, Goldblatt J, Le Souef P. Parasite infections and the risk of asthma and atopy. Thorax 1999;**54**:659–660.
26. van den Biggelaar A, van Ree R, Rodrigues L, Lell B, Deelder A, Kremsner P et al. Decreased atopy in children infected with *Schistosoma haematobium*: a role for parasite-induced interleukin-10. Lancet 2000;**356**:1723–1727.
27. Dold S, Heinrich J, Wichmann H, Wjst M. Ascaris-specific IgE and allergic sensitization in a cohort of school children in the former East Germany. J Allergy Clin Immunol 1998;**102**:414–420.
28. Behrendt H, Krämer U, Dolgner R, Hinrichs J, Willer H, Hagenbeck H. Elevated levels of total serum IgE in East German children: atopy, parasites or pollutants? Allergo J 1993;**3**:31–40.
29. Schäfer T, Vieluf D, Behrendt H, Krämer U, Ring J. Atopic eczema and other manifestations of atopy: results of a study in East and West Germany. Allergy 1996;**51**:532–539.
30. Krämer U, Behrendt H, Dolgner R, Ranft U, Ring J, Willer H et al. Airway diseases and allergies in East and West German children during the first five years after reunification: time trends and the impact of sulphur dioxide and total suspended particles. Int J Epidemiol 1999;**28**:865–873.
31. Heinrich J, Hölscher B, Frye C, Meyer I, Wjst M, Wichmann H. Trends in prevalence of atopic diseases and allergic sensitisation in children in East Germany. Eur Resp J 2002;**19**:1040–1046.
32. Schäfer T, Krämer U, Vieluf D, Abeck D, Behrendt H, Ring J. The excess of atopic eczema in East Germany is related to the intrinsic type. Br J Dermatol 2000;**143**:992–998.
33. Wichmann H. Environment, life-style and allergy: the German answer. Allergo J 1995;**6**:315–316.