Allergic disease and sensitization in Steiner school children

Helen Flöistrup, MSc,[a,b] Jackie Swartz, MD,[c] Anna Bergström, PhD,[a] Johan S. Alm, MD, PhD,[d] Annika Scheynius, MD, PhD,[e] Marianne van Hage, MD, PhD,[f] Marco Waser, PhD,[g] Charlotte Braun-Fahrländer, MD,[g] Dieneke Schram-Bijkerk, MSc,[h] Machteld Huber, MD,[i] Anne Zutavern, MD,[j] Erika von Mutius, MD,[j] Ellen Üblagger, MD,[k] Josef Riedler, MD, PhD,[l] Karin B. Michaels, ScD, PhD,[m] Göran Pershagen, MD, PhD,[a,n] and the PARSIFAL Study Group[o] *Stockholm and Järna, Sweden, Basel, Switzerland, Utrecht and Driebergen, The Netherlands, Munich and Schwarzach, Germany, Salzburg, Austria, and Boston, Mass*

Background: The anthroposophic lifestyle has several features of interest in relation to allergy: for example, a restrictive use of antibiotics and certain vaccinations. In a previous Swedish study, Steiner school children (who often have an anthroposophic lifestyle) showed a reduced risk of atopy, but specific protective factors could not be identified.
Objective: To investigate factors that may contribute to the lower risk of allergy among Steiner school children.
Methods: Cross-sectional multicenter study including 6630 children age 5 to 13 years (4606 from Steiner schools and 2024 from reference schools) in 5 European countries.

Results: The prevalence of several studied outcomes was lower in Steiner school children than in the reference group. Overall, there were statistically significant reduced risks for rhinoconjunctivitis, atopic eczema, and atopic sensitization (allergen-specific IgE ≥0.35 kU/L), with some heterogeneity between the countries. Focusing on doctor-diagnosed disease, use of antibiotics during first year of life was associated with increased risks of rhinoconjunctivitis (odds ratio [OR], 1.97; 95% CI, 1.26-3.08), asthma (OR, 2.79; 95% CI, 2.03-3.83), and atopic eczema (OR, 1.63; 95% CI, 1.22-2.17). Early use of antipyretics was related to an increased risk of asthma (OR, 1.54; 95% CI, 1.11-2.13) and atopic eczema (OR, 1.32; 95% CI, 1.02-1.71). Children having received measles, mumps, and rubella vaccination showed an increased risk of rhinoconjunctivitis, whereas measles infection was associated with a lower risk of IgE-mediated eczema.
Conclusion: Certain features of the anthroposophic lifestyle, such as restrictive use of antibiotics and antipyretics, are associated with a reduced risk of allergic disease in children. (J Allergy Clin Immunol 2006;117:59-66.)

Key words: *Allergy, anthroposophic lifestyle, antibiotics, antipyretics, asthma, biodynamic diet, measles, sensitization, vaccination*

The prevalence of IgE-mediated allergic diseases has increased markedly during the past decades, especially in children,[1,2] although recent reports indicate that the occurrence has stabilized.[3] The causes behind these trends are largely unknown. Factors increasing the risk have received the greatest attention, but in recent years, attention has also focused on possible protective factors, such as living on a farm[4] and specific probiotic strains.[5] To identify protective factors, it is of interest to study groups in the population with a low prevalence of allergy, such as children from anthroposophic families.[6] The anthroposophic lifestyle includes factors like a restrictive use of antibiotics, antipyretics, and vaccinations, and often a biodynamic diet.[6] An earlier study was conducted in a limited community of anthroposophic families, showing a lower prevalence of childhood allergy,[6] but specific protective factors could not be identified.

The aim of this study was to identify possible protective factors for allergy associated with the anthroposophic lifestyle. The study subjects include school children from Steiner schools, who often come from anthroposophic

From [a]the Institute of Environmental Medicine, and [b]the Centre for Allergy Research, Karolinska Institutet, Stockholm; [c]the Vidar Clinic, Järna; [d]Sachs' Children's Hospital, Stockholm Söder Hospital; [e]the Department of Medicine, Clinical Allergy Research Unit, and [f]the Department of Medicine, Clinical Immunology and Allergy Unit, Karolinska Institutet and University Hospital, Stockholm; [g]the Department of Environment and Health, Institute of Social and Preventive Medicine, University of Basel; [h]the Institute for Risk Assessment Sciences, Utrecht University; [i]the Louis Bolk Institute, Driebergen; [j]Dr von Hauner Children's Hospital, University of Munich; [k]the Department of Paediatric Pulmonology and Allergology, Children's Hospital, Salzburg; [l]Children's Hospital Schwarzach; [m]Brigham and Women's Hospital, Harvard Medical School, and Department of Epidemiology, Harvard School of Public Health, Boston, and and [n]the Department of Occupational and Environmental Health, Stockholm County Council.

[o]Göran Pershagen, Tobias Alfvén, Johan Alm, Anna Bergström, Lars Engstrand, Helen Flöistrup, Marianne van Hage, Niclas Håkansson, Gunnar Lilja, Fredrik Nyberg, Annika Scheynius, Jackie Swartz, Magnus Wickman (Sweden); Charlotte Braun-Fahrländer, Marco Waser, Felix Sennhauser, Roger Lauener, Johannes Wildhaber, Alex Möller (Switzerland); Bert Brunekreef, Dieneke Schram-Bijkerk, Gert Doekes, Mirian Boeve, Jeroen Douwes, Machteld Huber, Mirjam Matze (The Netherlands); Erika von Mutius, Marcus R. Benz, Jörg Budde, Markus Ege (Germany); Josef Riedler, Waltraud Eder, Ellen Üblagger, Gertraud Weiss, Mynda Schreuer (Austria); Karin B. Michels (United States).

Supported by a research grant from the European Union, QLRT 1999-01391, and by funding from the Swedish Foundation for Health Care Science and Allergy Research.

Received for publication May 10, 2005; revised September 8, 2005; accepted for publication September 12, 2005.

Available online November 29, 2005.

Reprint requests: Helen Flöistrup, MSc, Institute of Environmental Medicine, Box 210, Karolinska Institutet, SE-171 77 Stockholm, Sweden. E-mail: Helen.Floistrup@ki.se.

0091-6749/$32.00

doi:10.1016/j.jaci.2005.09.039

Abbreviations used
MMR: Measles, mumps, and rubella
OR: Odds ratio
PARSIFAL: Prevention of Allergy—Risk Factors for Sensitization Related to Farming and Anthroposophic Lifestyle

families, and reference children in 5 European countries, constituting the largest and most coherent study ever performed in this group of children.

METHODS

This work is based on the Prevention of Allergy—Risk Factors for Sensitization Related to Farming and Anthroposophic Lifestyle (PARSIFAL) study, a cross-sectional, multicenter study performed in 5 European countries among children age 5 to 13 years. The design has been described in detail elsewhere.[7] This report focuses on children attending Steiner schools, as well as referents from non-Steiner schools in similar regions. Information about environmental exposures, history of infections, diet, animal contact, anthroposophic lifestyle, and symptoms and diagnoses of allergic diseases was collected through a parental questionnaire. Most of the questions were based on the internationally standardized and validated International Study of Asthma and Allergies in Childhood (ISAAC) phase II protocol,[8] or derived from the earlier Swedish study on anthroposophic children.[6] The fieldwork was performed between October 2000 and May 2002 during overlapping periods in the different countries. The study was approved by local ethics committees in all centers.

A venous blood sample was obtained from children with a completed questionnaire and parental consent. Because of a large number of children included in the questionnaire surveys in Germany and Switzerland, a random sample of eligible children was selected in these countries. In Germany, only Steiner school children whose parents expressed an anthroposophic lifestyle were chosen for blood sampling. Sera were stored at −20°C before analysis. Allergen-specific IgE was measured against a mixture of common inhalant (Phadiatop) and food (fx5) allergens (Pharmacia CAP System; Pharmacia Diagnostics AB, Uppsala, Sweden). All IgE analyses were performed at the Department of Clinical Immunology at the Karolinska University Hospital, Stockholm, Sweden.

All health outcomes were reported by the parents, except sensitization, which was assessed from blood sampling. Current rhinoconjunctivitis symptoms were defined as sneezing, runny nose, nasal block-up, and itchy eyes in the child during the last 12 months without having a cold at the same time. Children diagnosed with hay fever and who ever had symptoms of hay fever were considered to have a doctor's diagnosis of rhinoconjunctivitis. Current wheezing was defined as having wheezing at least once during the last 12 months. Children ever diagnosed with asthma, or obstructive bronchitis more than once, were considered to have doctor's diagnosis of asthma. Current atopic eczema symptoms were present if the child ever had had an itchy rash intermittently for at least 6 months, and if the child had had this rash at any time during the last 12 months. Children with an intermittent itchy rash for at least 6 months and who had ever been diagnosed with atopic eczema were considered to have a doctor's diagnosis of atopic eczema. Atopic sensitization was indicated if the child had at least 1 allergen-specific IgE result of ≥0.35 kU/L against common inhalant and/or food allergens. To achieve a stricter definition of allergic disease, some analyses were performed combining the symptom or doctor's diagnosis–based outcomes with IgE sensitization.[9]

The relation between factors associated with the anthroposophic lifestyle and health outcomes was estimated by using odds ratios (ORs) and 95% CI, computed from logistic regression. Statistical significance was calculated by the Pearson χ^2 test statistic and defined as a P value $\leq .05$. Data were analyzed by using Stata 8.0 software (Stata Corp LP, Collage Station, Tex) and explored in models including only demographic variables—age, sex, and country (crude analysis)—as well as in models including traditional risk factors: maternal smoking during pregnancy, maternal asthma and/or rhinoconjunctivitis, paternal asthma and/or rhinoconjunctivitis, current smoking in the household, older siblings, parental education, and having household pets during first year of life. Furthermore, additional adjustments were made for variables related to the anthroposophic lifestyle[6]: use of antibiotics, use of antipyretics, type of diet, measles infection, and measles, mumps, and rubella (MMR) vaccination. To assess cross-country heterogeneity, separate estimates for each country and a pooled weighted estimate using random-effect meta-analysis were calculated.[10]

RESULTS

Questionnaires were completed for 6 733 children, implying an overall response rate of 68% (Steiner school children, 67%, and reference children, 69%). In total, 103 questionnaires were excluded because the child's age was outside the designated range (5-13 years), missing, or lacking information on group belonging or sex, leaving 6630 (Austria, 11%; Germany, 39%; The Netherlands, 22%; Sweden, 9%; Switzerland, 20%) children to be analyzed. Of these, 4606 were Steiner school children and 2024 reference children.

In total, 28% of all included children provided a blood sample (1202 Steiner school children and 634 reference children). The resulting distribution of children with blood samples was Austria, 22%; Germany, 20%; Sweden, 26%; Switzerland, 18%; and The Netherlands, 15%. Overall, children who provided a blood sample had similar characteristics and prevalence of allergic disease as all children in the respective group (data not shown). However, although the prevalence of any allergic symptom or doctor-diagnosed disease was similar among those with and without blood samples among the Steiner school children, 30% and 29% respectively, it appeared higher for those with blood samples (36%) than those without (31%) in the Steiner reference group. Differences in symptom/disease rates related to blood samples between Steiner and Steiner reference children tended to be most pronounced in Sweden, Switzerland, and The Netherlands.

Characteristics of Steiner school and reference children are summarized in Table I. Considerable differences were seen comparing the anthroposophic lifestyle factors between the 2 groups. Antibiotics and antipyretics were less often used in the Steiner school children, whereas a diet mainly based on biodynamic food was found almost exclusively in this group. MMR vaccination was about 3 times more common in the reference group, and consequently, the prevalence of measles infection was 33%

TABLE I. Distribution of risk factors for childhood allergy and prevalence of allergic diseases and sensitization in Steiner school children and reference children

Characteristics	Steiner school children %† (n = 4606)	Reference children %† (n = 2024)	*P* value*
Age (y, mean ± SD)	9.1 ± 1.9	8.8 ± 1.8	<.001
Sex (% male subjects)	48.0	49.2	
Traditional risk factors			
Maternal smoking during pregnancy	8.0	13.7	<.001
Current smoking in the household	13.7	26.9	<.001
Maternal asthma and/or rhinoconjunctivitis	26.6	23.8	.015
Paternal asthma and/or rhinoconjunctivitis	25.3	23.2	
≥1 older sibling	60.7	51.3	<.001
Parental education			<.001
Secondary school	30.4	45.7	
University	64.8	37.9	
Household pets during first year of life	36.6	28.2	<.001
Anthroposophic lifestyle factors			
Use of antibiotics			<.001
Never	41.6	15.1	
First use after 12 months of age	38.0	48.1	
First use when 0-12 months old	17.1	30.8	
Use of antipyretics			<.001
Never	42.8	8.3	
First use after 12 months of age	33.4	31.9	
First use when 0-12 months old	20.0	53.0	
Type of diet			<.001
Mainly conventional foods	22.2	72.5	
Mainly biodynamic foods	15.8	1.1	
Other‡	60.6	18.7	
Child had measles	33.4	10.3	<.001
MMR vaccination	26.0	72.4	<.001
Health outcomes			
Current rhinoconjunctivitis symptoms	7.9	10.5	<.001
Doctor's diagnosis of rhinoconjunctivitis	4.7	6.0	.026
Current wheezing	8.6	8.3	
Doctor's diagnosis of asthma	9.1	10.7	.042
Current atopic eczema symptoms	11.4	14.5	.001
Doctor's diagnosis of atopic eczema	11.3	12.2	
Atopic sensitization§	32.3	39.1	.001
Inhalant allergens	21.5	26.5	
Food allergens	1.2	3.3	
Both inhalant and food allergens	9.5	9.3	

*P values are calculated from the Pearson χ^2 test statistic and presented if $P \leq .05$.
†Totals may not add up to 100% because of missing values. Internal nonresponse/missing rates for all children were as follows: maternal smoking during pregnancy (1.7%), current smoking in the household (1.2%), maternal asthma and/or rhinoconjunctivitis (1.1%), paternal asthma and/or rhinoconjunctivitis (2.6%), older siblings (2.8%), parental education (2.8%), household pets during first year of life (0.8%), use of antibiotics (4.2%), use of antipyretics (4.7%), type of diet (3.3%), child had measles (6.6%), and MMR vaccination (17.5%).
‡*Other* refers to a diet mainly based on organic foods or combinations of conventional, organic, and/or biodynamic foods.
§Analyses conducted among children with blood sample; 1202 Steiner school children, 634 reference children. *Atopic sensitization* refers to an allergen specific serum IgE level ≥ 0.35 kU/L.

among the Steiner school children compared with 10% among the reference children. Moreover, parents of Steiner school children had lower smoking rates and higher education. The prevalence of the different health outcomes and atopic sensitization was significantly lower in the Steiner school children compared with the reference children, except for current wheezing and doctor's diagnosis of atopic eczema.

In a model adjusting for traditional risk factors of childhood allergy, we observed 25% to 30% lower ORs for rhinoconjunctivitis (current symptoms and doctor's diagnosis), current atopic eczema symptoms, and atopic sensitization among Steiner school children (Table II). When adjustments were made for prevalence of any allergic disease or symptom, to minimize potential selection bias in blood sampling, the OR and CI for atopic sensitization changed from 0.75 (0.59-0.95) to 0.81 (0.63-1.04). In general, the risks were also lower among Steiner school children when each country was analyzed separately (Fig 1, *A-G*). However, there was some heterogeneity

TABLE II. ORs and 95% CIs for allergic diseases and sensitization in Steiner school children compared with reference children

	OR (95% CI)	
	Crude*	Adjusted for traditional risk factors*
Current rhinoconjunctivitis symptoms	0.70 (0.58-0.83)	0.71 (0.57-0.88)
Doctor's diagnosis of rhinoconjunctivitis	0.75 (0.59-0.94)	0.74 (0.57-0.96)
Current wheezing	1.06 (0.88-1.28)	1.13 (0.91-1.40)
Doctor's diagnosis of asthma	0.82 (0.69-0.98)	0.84 (0.69-1.02)
Current atopic eczema symptoms	0.74 (0.63-0.86)	0.70 (0.58-0.83)
Doctor's diagnosis of atopic eczema	0.91 (0.77-1.07)	0.90 (0.75-1.08)
Atopic sensitization†	0.76 (0.62-0.93)	0.75 (0.59-0.95)

*From a logistic regression model adjusting for age, sex, and country (crude),or maternal smoking during pregnancy, maternal asthma, and/or rhinoconjunctivitis, paternal asthma and/or rhinoconjunctivitis, older siblings, parental education, current smoking in the household and household pets during first year of life (adjusted for traditional risk factors for childhood allergy).

†Analyses conducted among children with blood sample (n = 1836). *Atopic sensitization* refers to an allergen-specific serum IgE level $\geq$ 0.35 kU/L.

between countries, reaching statistical significance for current wheezing ($P = .02$), current atopic eczema symptoms ($P = .05$), and atopic sensitization ($P = .03$). Results were most consistent in Germany, The Netherlands, and Sweden, whereas in Austria, Steiner school children appeared to have similar or even slightly higher risk compared with reference children. Adjustments for prevalence of any allergic disease or symptom had no major effect on the country specific results regarding atopic sensitization.

Associations between specific anthroposophic lifestyle factors and allergic diseases and sensitization are presented in Table III. In the adjusted model, we observed an increased risk of rhinoconjunctivitis (current symptoms and doctor's diagnosis), current wheezing, doctor's diagnosis of asthma, and atopic eczema (current symptoms and doctor's diagnosis) among children who received antibiotics compared with never-users. In general, ORs were somewhat higher when antibiotics were introduced during first year of life, compared with later. Use of antipyretics was associated with an increased risk of doctor-diagnosed asthma and atopic eczema (current symptoms and doctor's diagnosis) in the adjusted model.

In the crude model, children with a diet mainly based on biodynamic food had a reduced risk of all studied health outcomes compared with the reference group with a diet based on conventional food. This association was no longer present in the fully adjusted model. In a similar manner, the reduced risk among children who had had measles observed in the crude model disappeared in the fully adjusted model. On the other hand, children who had received MMR vaccination had an increased risk of rhinoconjunctivitis (current symptoms and doctor's diagnosis) in all models.

In analyses combining the symptom or doctor's diagnosis–based outcomes with sensitization, associations tended to be weaker than those reported in Table III, with wider CIs, because these analyses were based on less than 30% of the children with questionnaire responses. However, measles infection was related to lower risks for doctor's diagnosis of eczema and current atopic eczema symptoms combined with sensitization (ORs in the order of 0.4-0.5).

In addition, the risk of overall allergic disease—that is, a doctor's diagnosis of rhinoconjunctivitis, and/or asthma, and/or atopic eczema—was studied in relation to the anthroposophic lifestyle factors. We found increased risks for antibiotic use (OR, 1.94; 95% CI, 1.58-2.38) and for antipyretic use (OR, 1.23; 95% CI, 1.01-1.51) during the first year of life, but no clear relation for type of diet (OR, 0.97; 95% CI, 0.76-1.24), measles infection (OR, 1.04; 95% CI, 0.90-1.21), or MMR vaccination (OR, 0.88; 95% CI, 0.72-1.07). When overall allergic disease was combined with IgE sensitization, there was a decreased risk in children having had measles (OR, 0.64; 95% CI, 0.40-1.00).

DISCUSSION

We observed a lower prevalence of both current symptoms and doctor's diagnosis of rhinoconjunctivitis and atopic eczema and also doctor's diagnosis of asthma and atopic sensitization in Steiner school children compared with reference children, confirming the results of Alm et al,[6] although our results were not entirely consistent in all countries. Differences in lifestyle between the study groups in different countries may have contributed to this apparent incoherence. Early use of antibiotics and antipyretics as well as MMR vaccination were associated with increased risks of several allergic symptoms and doctor's diagnoses, whereas an inverse relation was seen for measles infection when combined with IgE sensitization.

Antibiotics use has been associated with asthma in some[11-13] but not all previous studies.[14,15] Similar to our observation, use of antibiotics, especially when introduced during first year of life, has been associated with asthma and wheeze among Steiner school children in New Zealand.[12] The observed relation between antibiotics and asthma could represent a causal association[11]; however, reverse causation may also contribute—that is, if children with asthma symptoms received antibiotics on the presumption that they had a bacterial respiratory infection. An increased risk of atopic eczema associated with use of antibiotics has been observed in previous studies.[12,13]

A possible biological mechanism contributing to these associations might be the influence by antibiotics on the intestinal microflora. Because the intestinal microflora is a major factor driving the maturation of the immune system in newborns,[16] it is plausible that use of antibiotics might

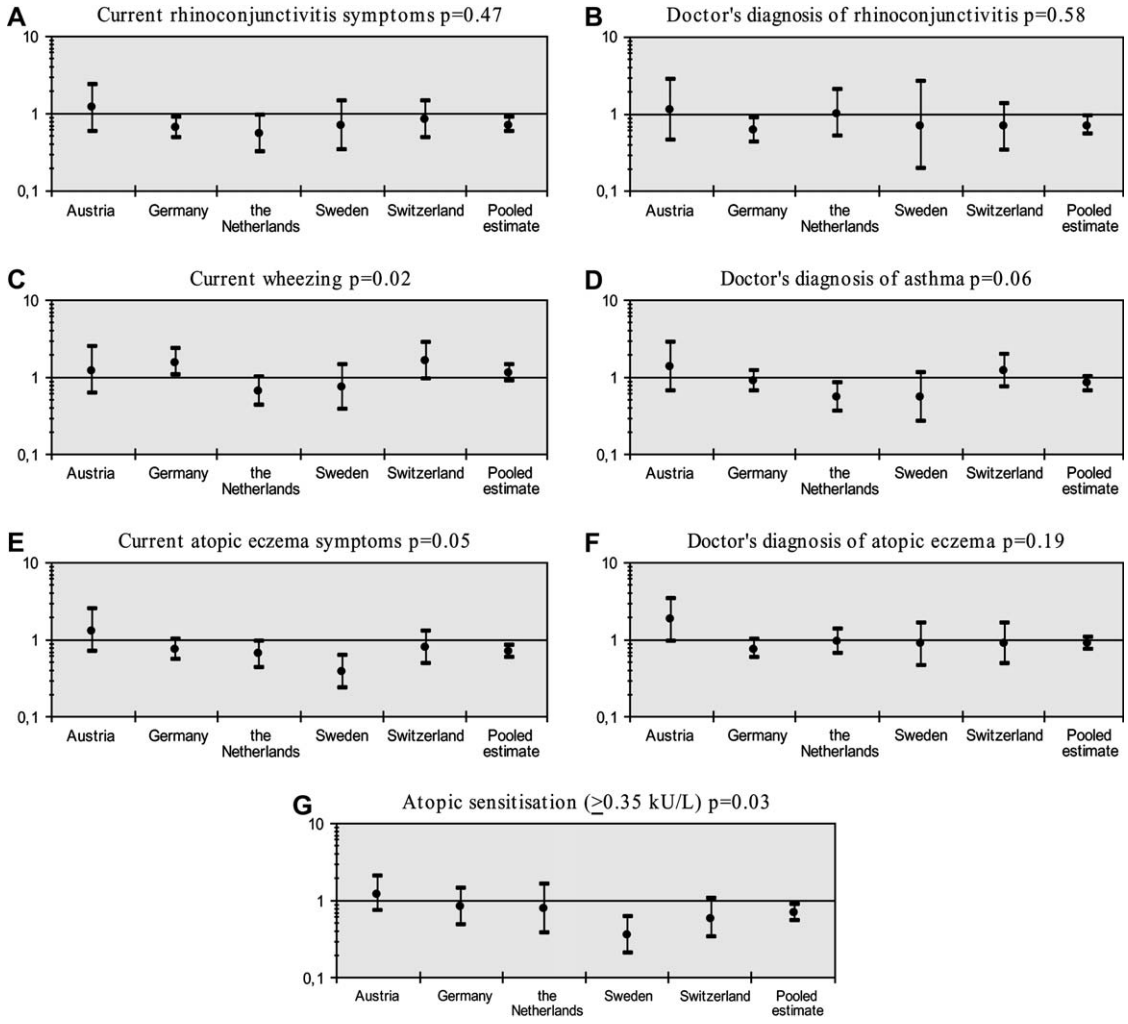

FIG 1. A-G, Country specific and pooled OR and 95% CI estimates for different allergic diseases and sensitization, comparing Steiner school children with reference children. *P* values refer to the test of homogeneity. Adjustments are made for traditional risk factors for childhood allergy.

affect this development negatively.[17] This would be in line with our observation of stronger association with antibiotics use during the first year of life compared with later. It has been shown that the intestinal flora differs between allergic and healthy children[18,19] and that anthroposophic lifestyle factors—for example, consumption of fermented vegetables and antibiotic use—may be related to the intestinal flora in infants.[20]

The association between antipyretics and asthma is supported by a previously reported dose-response relation between paracetamol intake and asthma severity in young adults.[21] Moreover, a strong correlation between paracetamol consumption and the incidence of atopic diseases in children has been reported.[22] In our study, the effect of antipyretics use remained statistically significant also after adjustment for antibiotic use, speaking in favor of an independent effect. Possible mechanisms explaining a role of antipyretics in asthma include depletion of pulmonary glutathione and oxidative stress.[23]

It has been hypothesized that measles infection and/or MMR vaccination could affect the development of atopic disease, but data are inconclusive. Measles infection has been reported to accompany atopic diseases,[24] but also to decrease the risk of atopy[25] and improve atopic dermatitis symptoms.[26] In our study, measles infection was associated with a lower risk of eczema (current symptoms and doctor's diagnosis) combined with IgE sensitization. Furthermore, an increased risk of rhinoconjunctivitis was found among children who had received MMR vaccination. A previous study found an inverse association between allergic diseases and MMR vaccination,[27] whereas in a Danish study, measles infection and MMR vaccination were both associated with an increased risk of atopic dermatitis.[28] One explanation for the apparently discrepant findings between studies may be differences in outcome definitions.

The strength of our study is its large size and multinational design. PARSIFAL is the largest study ever

TABLE III. ORs and 95% CIs for allergic diseases and sensitization associated with use of antibiotics, use of antipyretics, type of diet, having had measles infection, and having received MMR vaccination among Steiner school children and reference children

	Reference	Crude*		Adjusted for traditional risk factors and anthroposophic lifestyle factors*	
Use of antibiotics	Never	First time at >12months of age	First time at 0-12months of age	First time at >12months of age	First time at 0-12months of age
Current rhinoconjunctivitis symptoms	1.0	1.58 (1.27-1.97)	1.81 (1.41-2.31)	1.31 (0.97-1.78)	1.60 (1.12-2.29)
Doctor's diagnosis of rhinoconjunctivitis	1.0	1.73 (1.30-2.32)	2.27 (1.65-3.11)	1.41 (0.95-2.10)	1.97 (1.26-3.08)
Current wheezing	1.0	1.55 (1.25-1.94)	2.08 (1.64-2.65)	1.41 (1.06-1.87)	2.05 (1.48-2.85)
Doctor's diagnosis of asthma	1.0	2.02 (1.61-2.30)	3.56 (2.81-4.52)	1.63 (1.23-2.17)	2.79 (2.03-3.83)
Current atopic eczema symptoms	1.0	1.49 (1.24-1.79)	1.93 (1.57-2.37)	1.30 (1.02-1.66)	1.61 (1.21-2.15)
Doctor's diagnosis of atopic eczema	1.0	1.33 (1.10-1.60)	1.65 (1.34-2.03)	1.22 (0.96-1.55)	1.63 (1.22-2.17)
Atopic sensitization‡	1.0	1.27 (1.00-1.60)	1.07 (0.81-1.41)	1.15 (0.84-1.58)	0.91 (0.60-1.37)
Use of antipyretics	Never				
Current rhinoconjunctivitis symptoms	1.0	1.45 (1.16-1.82)	1.59 (1.27-2.00)	1.05 (0.77-1.44)	0.94 (0.65-1.36)
Doctor's diagnosis of rhinoconjunctivitis	1.0	1.30 (0.96-1.76)	1.93 (1.45-2.57)	0.95 (0.62-1.43)	1.14 (0.72-1.80)
Current wheezing	1.0	1.04 (0.83-1.29)	1.22 (0.98-1.52)	0.98 (0.73-1.31)	0.86 (0.61-1.21)
Doctor's diagnosis of asthma	1.0	1.21 (0.96-1.52)	2.00 (1.62-2.48)	1.09 (0.81-1.46)	1.54 (1.11-2.13)
Current atopic eczema symptoms	1.0	1.43 (1.17-1.74)	1.70 (1.40-2.07)	1.42 (1.09-1.85)	1.59 (1.17-2.15)
Doctor's diagnosis of atopic eczema	1.0	1.33 (1.09-1.62)	1.49 (1.22-1.82)	1.32 (1.02-1.71)	1.30 (0.96-1.76)
Atopic sensitization‡	1.0	1.17 (0.92-1.50)	1.08 (0.84-1.38)	1.05 (0.75-1.47)	1.08 (0.71-1.63)
Type of diet†	Conventional	Biodynamic	Other	Biodynamic	Other
Current rhinoconjunctivitis symptoms	1.0	0.53 (0.38-0.73)	0.75 (0.62-0.90)	0.86 (0.55-1.33)	0.99 (0.75-1.33)
Doctor's diagnosis of rhinoconjunctivitis	1.0	0.58 (0.38-0.88)	0.81 (0.64-1.03)	0.96 (0.56-1.67)	1.06 (0.75-1.45)
Current wheezing	1.0	0.74 (0.53-1.01)	0.99 (0.82-1.20)	0.81 (0.53-1.24)	1.06 (0.81-1.38)
Doctor's diagnosis of asthma	1.0	0.70 (0.52-0.94)	0.87 (0.73-1.04)	1.14 (0.77-1.69)	1.11 (0.86-1.43)
Current atopic eczema symptoms	1.0	0.59 (0.45-0.78)	0.85 (0.73-1.00)	0.76 (0.53-1.10)	0.88 (0.70-1.10)
Doctor's diagnosis of atopic eczema	1.0	0.79 (0.60-1.02)	0.92 (0.78-1.08)	0.91 (0.64-1.30)	1.01 (0.80-1.27)
Atopic sensitization‡	1.0	0.78 (0.55-1.09)	0.87 (0.70-1.08)	0.86 (0.54-1.38)	0.87 (0.64-1.20)
Child had measles	Never	Yes		Yes	
Current rhinoconjunctivitis symptoms	1.0	0.71 (0.57-0.88)		0.88 (0.65-1.21)	
Doctor's diagnosis of rhinoconjunctivitis	1.0	0.68 (0.52-0.90)		0.94 (0.63-1.40)	
Current wheezing	1.0	1.19 (0.98-1.46)		1.20 (0.91-1.58)	
Doctor's diagnosis of asthma	1.0	0.97 (0.80-1.18)		0.99 (0.75-1.30)	
Current atopic eczema symptoms	1.0	0.88 (0.74-1.06)		1.15 (0.90-1.47)	
Doctor's diagnosis of atopic eczema	1.0	1.04 (0.86-1.24)		1.23 (0.96-1.56)	
Atopic sensitization‡	1.0	0.83 (0.66-1.05)		0.77 (0.56-1.07)	
MMR vaccination	Never				
Current rhinoconjunctivitis symptoms	1.0	1.80 (1.48-2.20)		1.43 (1.04-1.96)	
Doctor's diagnosis of rhinoconjunctivitis	1.0	1.92 (1.48-2.48)		1.58 (1.05-2.38)	
Current wheezing	1.0	0.87 (0.71-1.06)		0.75 (0.55-1.02)	
Doctor's diagnosis of asthma	1.0	1.20 (0.99-1.45)		0.77 (0.57-1.03)	
Current atopic eczema symptoms	1.0	1.25 (1.06-1.48)		0.89 (0.69-1.16)	
Doctor's diagnosis of atopic eczema	1.0	1.04 (0.87-1.23)		0.81 (0.62-1.06)	
Atopic sensitization‡	1.0	1.21 (0.96-1.51)		0.91 (0.63-1.31)	

*From a logistic regression model; adjusted only for age, sex, and country (crude), or in addition for maternal smoking during pregnancy, maternal asthma and/or rhinoconjunctivitis, paternal asthma and/or rhinoconjunctivitis, older siblings, parental education, current smoking in the household, household pets during first year of life, use of antibiotics (not in analysis of antibiotics), use of antipyretics (not in analysis of antipyretics), child had measles (not in analysis of measles), type of diet (not in analysis of diet), and MMR vaccination (not in analyses of MMR vaccination) (adjusted for traditional risk factor for childhood allergy and anthroposophic lifestyle factors).

†A *biodynamic diet* refers to a diet mainly based on biodynamic foods. Other types of diets are mainly based on organic or combinations of conventional, organic, and/or biodynamic foods. The reference group consists of children whose diet mainly is based on conventional foods.

‡Analyses conducted among children with blood sample (n = 1836). *Atopic sensitization* refers to an allergen-specific serum IgE level $\geq$ 0.35 kU/L.

conducted among Steiner school children, covering 5 European countries, and the heterogeneity of the anthroposophic lifestyle between the countries. This heterogeneity may contribute to the differences in country specific results. Selection bias is a possible limitation of the study. Although the participation rates varied between the countries, similar proportions of the invited Steiner school children and reference children were included in all countries. We cannot exclude that nonresponse might affect the observed prevalence rates, but the prevalence of allergic symptoms among the reference children was comparable to a previous report covering the countries under study.[29]

The cross-sectional design is a potential limitation, because disease occurrence may have affected exposure or the reporting of exposure.[30] However, it is unlikely that misclassification of exposure would entirely explain the differences between Steiner school children and reference children. Parental interpretation of the child's symptoms might lead to misclassification of disease, but several health outcomes included a doctor's diagnosis and/or serological analysis, which should decrease misclassification and potential bias. To strengthen the definition of allergic disease,[9] analyses were also performed combining questionnaire responses with determinations of IgE sensitization. As these analyses only included children who left a blood sample (28%), the statistical power was reduced. Further, there might be a selection bias in results based on blood sample data because the prevalence of allergic disease tended to be higher among reference children who provided a blood sample compared with children who did not. To minimize this problem, we adjusted for having any doctor's diagnosis or symptom of allergic disease, which resulted in only a small change of the OR. Considering also that this represents an overadjustment, it speaks against a major effect by selection bias.

It may be concluded that certain factors in the anthroposophic lifestyle, such as restrictive use of antibiotics and antipyretics, are associated with the lower risk of allergic disease in children. However, the lifestyle factors investigated in our study represent only a selection of various characteristics of the anthroposophic lifestyle. Therefore, we cannot exclude that other factors need to be considered to understand completely the background for this lower risk.

The authors thank all fieldworkers and other PARSIFAL team members, especially Stina Gustafsson, Eva Hallner, André Lauber, Wiveka Lundberg, Helena Svensson, Anki Wigh, Annika Zettergren, Anne-Charlotte Öhman-Johansson (Sweden), Susanne Löhliger, Remo Frey (University Children's Hospital Zurich), Marianne Rutschi, Stefan Worminghaus (study center support), Michaela Glöckler (head of the medical section of the Goetheanum in Dornach, Switzerland), Anja Strengers, Siegfried de Wind, Marieke Siekmans, Patricia Jansen-van Vliet, Janneke Bastiaanssen, Marieke Dijkema, Siegfried de Wind, Jack Spithoven, Griet Terpstra, Gert Buurman (The Netherlands), Helmut Egger, Martina Burger, Bernadette Burger, and Elisabeth Buchner (Austria). We also like to thank all school doctors and teachers and all children and parents who contributed to this study.

REFERENCES

1. Maziak W, Behrens T, Brasky TM, Duhme H, Rzehak P, Weiland SK, et al. Are asthma and allergies in children and adolescents increasing? results from ISAAC phase I and phase III surveys in Munster, Germany. Allergy 2003;58:572-9.
2. Downs SH, Marks GB, Sporik R, Belosouva EG, Car NG, Peat JK. Continued increase in the prevalence of asthma and atopy. Arch Dis Child 2001;84:20-3.
3. Braun-Fahrländer C, Gassner M, Grize L, Takken-Sahli K, Neu U, Stricker T, et al. No further increase in asthma, hay fever and atopic sensitisation in adolescents living in Switzerland. Eur Respir J 2004;23:407-13.
4. Riedler J, Braun-Fahrländer C, Eder W, Schreuer M, Waser M, Maisch S, et al. Exposure to farming in early life and development of asthma and allergy: a cross-sectional survey. Lancet 2001;358:1129-33.
5. Kalliomäki M, Salminen S, Arvilommi H, Kero P, Koskinen P, Isolauri E. Probiotics and prevention of atopic disease: a randomised placebo-controlled trial. Lancet 2003;357:1076-9.
6. Alm JS, Swartz J, Lilja G, Scheynius A, Pershagen G. Atopy in children of families with an anthroposophic lifestyle. Lancet 1999;353:1485-8.
7. Alfvén T, Braun-Fahrlander C, Brunekreef B, von Mutius E, Riedler J, Scheynius A, et al. Allergic diseases and atopic sensitisation in children related to farming and anthroposophic lifestyle—the PARSIFAL study. Allergy 2005; E-pub September 15, 2005; doi:10.1111/j.1398-9995.2005.00939.X.
8. Asher MI, Keil U, Anderson HR, Beasley R, Crane J, Martinez F, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. Eur Respir J 1995;8:483-91.
9. Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, et al. Revised nomenclature for allergy for global use: report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. J Allergy Clin Immunol 2004;113:832-6.
10. Rothman K, Ahlbom A, Andersson T. Episheet, meta-analysis. Available at: http://members.aol.com/krothman/ 'Meta-Analysis'!A1 2004. Version of November 10, 2004. Accessed November 2004.
11. Cohet C, Cheng S, MacDonald C, Baker M, Foliaki D, Huntington N, et al. Infections, medication use, and prevalence of symptoms of asthma, rhinitis, and eczema in childhood. Epidemiol Commun Health 2004;58:852-7.
12. Wickens K, Pearce N, Crane J, Beasley R. Antibiotic use in early childhood and the development of asthma. Clin Exp Allergy 1999;29:766-71.
13. Farooqi IS, Hopkin JM. Early childhood infection and atopic disorder. Thorax 1998;53:927-32.
14. Cullinan P, Harris J, Mills P, Moffat S, White C, Figg J, et al. Early prescriptions of antibiotics and the risk of allergic disease in adults: a cohort study. Thorax 2004;59:11-5.
15. Celedon JC, Fuhlbrigge A, Rifas-Shiman S, Weiss ST, Finkelstein JA. Antibiotic use in the first year of life and asthma in early childhood. Clin Exp Allergy 2004;34:1011-6.
16. Hooper LV, Gordon JI. Commensal host-bacterial relationships in the gut. Science 2001;292:1115-8.
17. Van Vlem B, Vanholder R, De Paepe P, Vogelaers D, Ringoir S. Immunomodulating effects of antibiotics: literature review. Infection 1996;24:275-91.
18. Fukuda S, Ishikawa H, Koga Y, Aiba Y, Nakashima K, Cheng L, et al. Allergic symptoms and microflora in schoolchildren. J Adolesc Health 2004;35:156-8.
19. Kirjavainen PV, Apostolou E, Arvola T, Salminen SJ, Gibson GR, Isolauri E. Characterizing the composition of intestinal microflora as a prospective treatment target in infant allergic disease. FEMS Immunol Med Microbiol 2001;32:1-7.
20. Alm JS, Swartz J, Björkstén B, Engstrand L, Engström J, Kuhn I, et al. An anthroposophic lifestyle and intestinal microflora in infancy. Pediatr Allergy Immunol 2002;13:402-11.
21. Shaheen SO, Sterne JA, Songhurst CE, Burney PG. Frequent paracetamol use and asthma in adults. Thorax 2000;55:266-70.
22. Newson RB, Shaheen SO, Chinn S, Burney PG. Paracetamol sales and atopic disease in children and adults: an ecological analysis. Eur Respir J 2000;16:817-23.
23. Eneli I, Sadri K, Camargo C Jr, Barr RG. Acetaminophen and the risk of asthma: the epidemiologic and pathophysiologic evidence. Chest 2005;127:604-12.
24. Paunio M, Heinonen OP, Virtanen M, Leinikki P, Patja A, Peltola H. Measles history and atopic diseases: a population-based cross-sectional study. JAMA 2000;283:343-6.
25. Shaheen SO, Aaby P, Hall AJ, Barker DJ, Heyes CB, Shiell AW, et al. Cell mediated immunity after measles in Guinea-Bissau: historical cohort study. BMJ 1996;313:969-74.
26. Kondo N, Fukutomi O, Ozawa T, Agata H, Kameyama T, Kuwabara N, et al. Improvement of food-sensitive atopic dermatitis accompanied by reduced lymphocyte responses to food antigen following natural measles virus infection. Clin Exp Allergy 1993;23:44-50.

27. Roost HP, Gassner M, Grize L, Wuthrich B, Sennhauser FH, Varonier HS, et al. Influence of MMR-vaccinations and diseases on atopic sensitization and allergic symptoms in Swiss schoolchildren. Pediatr Allergy Immunol 2004;15:401-7.
28. Olesen Brae A, Juul S, Thestrup-Pedersen K. Atopic dermatitis is increased following vaccination for measles, mumps and rubella or measles infection. Acta Derm Venereol 2003;83:445-50.
29. ISAAC Steering Committee. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Lancet 1998;351:1225-32.
30. Pershagen G. Challenges in epidemiologic allergy research. Allergy 1997;52:1045-9.