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Anthroposophic lifestyle is associated with a lower incidence of food allergen sensitization in early childhood

To the Editor:

Sensitization to food allergens is increasing more rapidly than sensitization to pollen or animal allergens.[1,2] On a population level, development of allergic sensitization commonly begins with food allergen sensitization in early infancy, followed or sometimes replaced by sensitization to animals and later, at 4 to 5 years of age, including sensitization to pollen.

The cause for the onset or development of sensitization to allergens and allergy-related diseases is still not known. Environmental and lifestyle factors are considered to contribute to disease development.[3] Anthroposophy is a holistic philosophy that was founded by the Austrian philosopher Rudolf Steiner (1861-1925) and covers most aspects of life, including education, health care, agriculture, and diet.[4] Previous cross-sectional studies have shown that Steiner school children, who often come from families with an anthroposophic lifestyle, have a lower prevalence of sensitization and allergic disease compared with reference children.[5,6] These observations have been confirmed in the prospective birth cohort Assessment of Lifestyle and Allergic Disease During Infancy (ALADDIN).[7]

In Hesla et al,[8] we report the clinical manifestations up to 2 years of age in the ALADDIN cohort and provide a description of demographics and early lifestyle exposures. We observed that anthroposophic lifestyle was associated with a reduced risk of reported food hypersensitivity and reported recurrent wheeze but not eczema. Moreover, delayed washing of the newborn's whole body (after 7 days of age) was associated with a reduced risk of allergen sensitization, whereas an increased risk was seen for children who had a mother who worked during pregnancy. However, much of the effect of anthroposophic lifestyle on allergen sensitization was unexplained. In this letter we report how the association between lifestyle and sensitization to food, animal, and pollen allergens differs with the child's age.

For complete materials and methodology, see the Methods section in this article's Online Repository at www.jacionline.org. Briefly, this study is based on the Swedish prospective cohort ALADDIN,[7] in which 552 children and their families were followed using questionnaires, examinations, and blood samples. The families were classified into 3 lifestyle groups (anthroposophic, partly anthroposophic, and nonanthroposophic). Blood samples were collected from the children at 6, 12, 24, and 60 months of age. Sensitization to food (hen's egg, cow's milk, and/or peanut), animal (dog and/or cat), and pollen (birch and/or timothy) allergens was determined. IgE values of 0.35 kU_A/L or greater were regarded as being sensitized. Incidence and prevalence of sensitization were determined. The inclusion process and distribution of children and available blood samples are presented in Fig E1 in this article's Online Repository at www.jacionline.org, and prevalences of IgE sensitization for the individual allergens are presented in Table E1 in this article's Online Repository at www.jacionline.org. As described in Hesla et al,[8] several demographic and early lifestyle exposures differed between the lifestyle groups; however, neither parental sensitization nor parental report of allergy-related disease were associated with anthroposophic lifestyle. In addition, parental sensitization was not associated with child sensitization.

Incidence proportions of sensitization for the different allergen categories are presented in Fig 1, *A* to *D*. In the nonanthroposophic group the incidence proportions of food allergen sensitization were high up to 12 months of age: 15% and 16% were first time sensitized for the age periods of 0 to 6 and 6 to 12 months, respectively, and then decreased to 5% from 12 to 24 months to increase again to 16% from 24 to 60 months. In contrast, in the anthroposophic group the incidence proportions of food sensitization were low at up to 12 months of age and similar for the 4 age periods as follows: 1% (0 to 6 months), 1% (6-12 months), 8% (12-24 months), and 9% (24-60 months). In the partly anthroposophic group the incidence proportions of food allergen sensitization were stable, around 7% for all age periods. In all lifestyle groups sensitization to animal and pollen allergens occurred later than to food allergens.

We used general estimating equation models to study the interaction between age and lifestyle and found that age significantly modified the association between lifestyle and

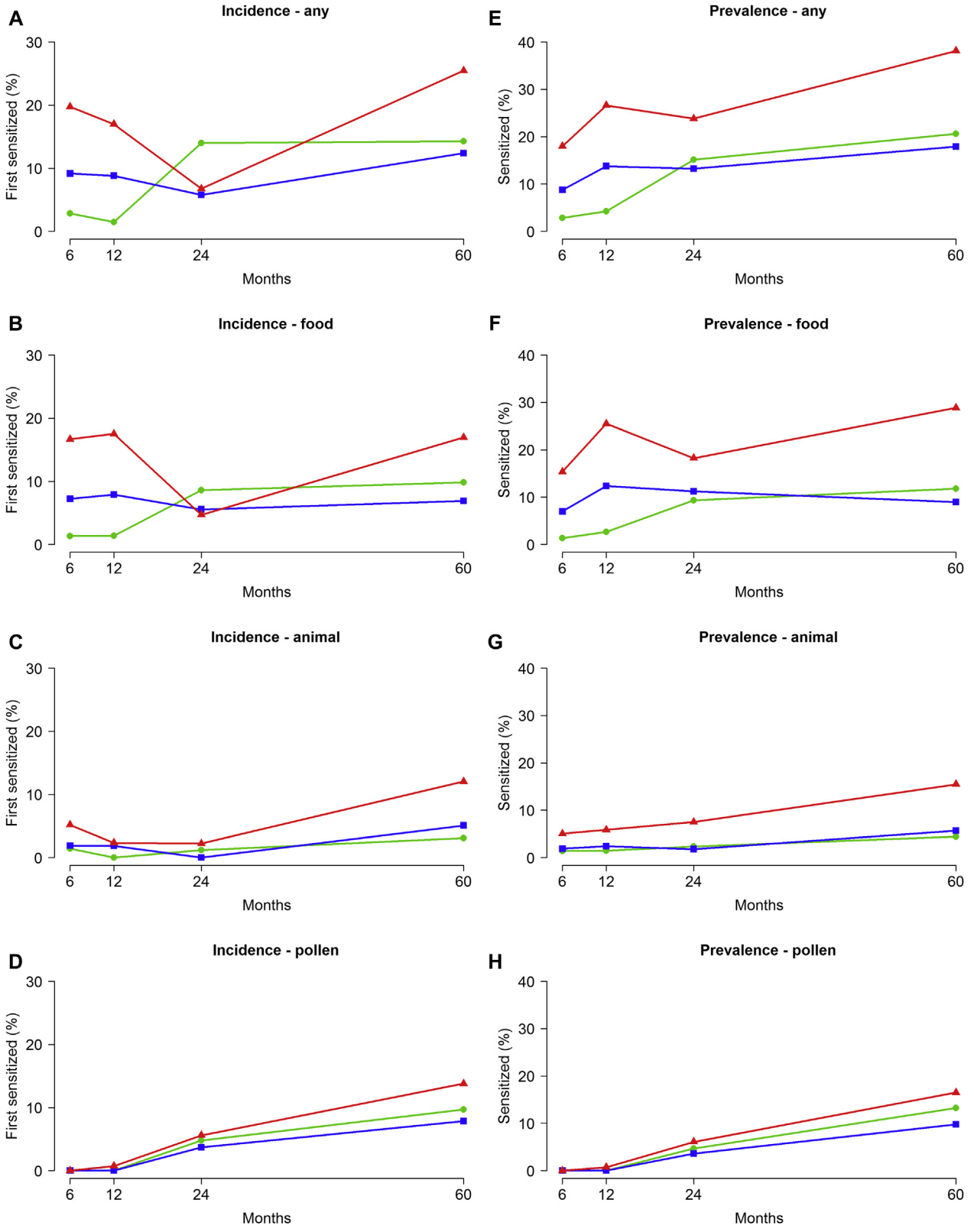

FIG 1. Incidence proportions **(A-D)** and point prevalences **(E-H)** of IgE sensitization (IgE ≥0.35 kU_A/L) to food (cow's milk, hen's egg, and/or peanut), animal (dog and/or cat), and pollen (birch and/or timothy) allergens in children of families with anthroposophic *(green)*, partly anthroposophic *(blue)*, and nonanthroposophic *(red)* lifestyles.

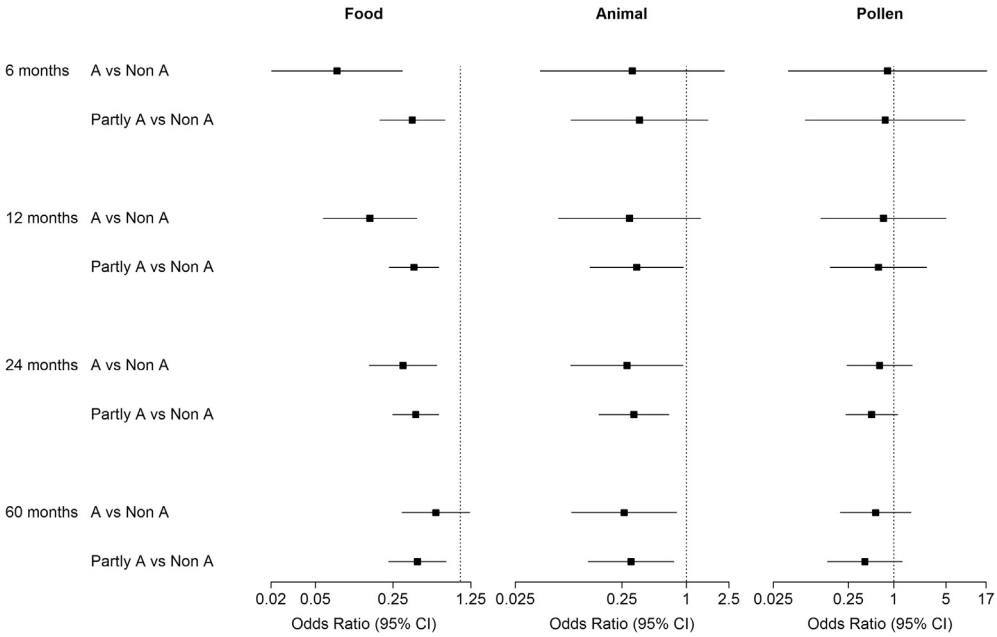

FIG 2. Association between lifestyle and prevalence of food, animal, and pollen allergen sensitization at 6, 12, 24, and 60 months of age in ORs and 95% CIs from a generalized estimating equation model. *A*, Anthroposophic; *Partly A*, partly anthroposophic; *Non A*, nonanthroposophic.

food allergen sensitization ($P = .02$, Fig 2). The inverse association between anthroposophic lifestyle and food allergen sensitization was stronger at 6, 12, and 24 months (odds ratio [OR], 0.16, 0.18, and 0.25, respectively) than at 60 months (OR, 0.58). The association between partly anthroposophic lifestyle and food allergen sensitization was similar at all 4 ages (OR, 0.42, 0.41, 0.40, and 0.35, respectively). No such interaction between age and lifestyle was observed for animal ($P = .89$) or pollen ($P = .91$) allergen sensitization (Fig 2).

The pattern of allergic sensitization, starting with sensitization against food allergens and followed by animal and pollen allergen sensitization, has been described earlier.[9] However, few studies have reported the prevalence of allergen sensitization in early infancy.[2] Tolerance to cow's milk and hen's egg usually develops at 4 to 6 years of age.[9,10] Because the prevalence of animal and pollen sensitization was low in the present study, which is expected at these ages,[9] the association with lifestyle should be interpreted with caution. However, our results are in accordance with earlier studies of school-aged children in which the association with anthroposophic lifestyle was significant only for food but not inhalant allergen sensitization.[5,6]

A higher proportion of families in the anthroposophic group did not consent to blood sampling. However, introduction of selection bias is unlikely because this reluctance to participate in blood sampling was likely to be related to lifestyle and not to sensitization of the child or parent. Consent to blood sampling was made before the parents received any results regarding their own or the child's blood sample analyses.

In conclusion, our findings suggest that the reduced prevalence of allergen sensitization seen among children of families with an anthroposophic lifestyle was largely explained by a low incidence of food sensitization before 1 year of age. This indicates that anthroposophic lifestyle has a greater effect on allergen sensitization during the first year of life.

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Parameters determining the efficacy of CD32 to inhibit activation of FcεRI in human basophils

To the Editor:

The mechanisms that underlie the success of allergen immunotherapy are varied, and the precise details remain unclear. Immune deviation and blocking antibodies are 2 important candidate explanations, and under the category of blocking antibodies are 2 often discussed possibilities: (1) simple competition for allergen between IgG antibodies developed during immunotherapy and IgE antibodies on the mast cell and basophil cell surface (what we are calling stoichiometric blockade) or (2) interaction between IgG antibodies and CD32 (the low-affinity IgG receptor FcγRII) on mast cells[1,2] or basophils,[3-6] leading to inhibition of the IgE-mediated response.

There is conflicting information about the role of CD32 in this reaction in human subjects. One possible issue is whether human mast cells even express CD32b, the inhibitory IgG receptor. Other issues relate to the relative ability of different IgG subclasses to interact with CD32b or CD32a[7] and whether CD32a, which is normally considered an activating IgG receptor, acts in an inhibitory capacity in the context of CD32b or cell type.[4,5]

Human basophils express both CD32a and CD32b,[3-6] and it has been clearly demonstrated that CD32 can mediate inhibition of the IgE-dependent reaction. However, there are a variety of studies that have demonstrated that not all IgG subclasses bind to CD32a or CD32b.[7] Also, there are polymorphisms in CD32 that influence binding and/or function to certain subclasses.[7,8] Furthermore, immunotherapy generates different increases in IgG subclasses, and for a variety of reasons, studies have focused on IgG_1 and IgG_4 and very infrequently examine IgG_2 or IgG_3. However, binding studies have shown that IgG_4 does not interact with CD32a or CD32b.[7] What remains unclear is the relative ability of IgG_1, IgG_2, and IgG_3 to interact with CD32 and the potential for polymorphisms to further differentiate binding.

Using partially enriched human basophils (see the Methods section in this article's Online Repository at www.jacionline.org) and a series of transfectoma antibodies all using the same complementarity determining region specific for nitrophenyl (NP) but varying the heavy chain subclass (IgE, IgG_1, IgG_2, IgG_3, and IgG_4), the ability of the various IgG subclasses to inhibit IgE-mediated release from basophils sensitized with NP-specific IgE was examined. Three reaction designs were examined, holding IgG constant and varying antigen (which is presumably that natural situation), holding allergen constant and varying IgG, and a third approach presented in the Results section in this article's Online Repository (see also Fig E1 in this article's Online Repository at www.jacionline.org for a schematic of the experimental design). Fig 1 shows results using the first 2 methods.

By using the first method, the amount of inhibition by IgG was titrated to approximately 50% to detect alteration of the response in either the positive or negative direction when including blockade of CD32 and to not bias the reaction to complete stoichiometric blocking (see the Results section in this article's Online Repository). To block CD32 and therefore test the involvement of CD32-mediated inhibition rather than simple stoichiometric blockade, an engineered high-affinity anti-CD32b antibody and a commercial anti-CD32a antibody were used. The densities of CD32a and CD32b were also monitored by using flow cytometry. The results, focusing on the highest concentrations of antigen and antibody (Fig 1, *A-F*), indicate that it was difficult to detect functional interaction with CD32b when IgG_1 was used, but IgG_2 and IgG_3 effectively engaged CD32b (the degree of CD32b involvement was measured by the extent of reversal of inhibition when including the CD32b-blocking antibody Ab10523). At lower concentrations of antigen, only stoichiometric inhibition is observed. Fig E2 in this article's Online Repository at www.jacionline.org shows the importance of absolute antigen concentration and the importance of IgG/allergen ratios.

In the second design shown in Fig 1, *G* (holding antigen constant and varying IgG), it can be again observed that IgG_1 did not engage CD32b, whereas IgG_2 and IgG_3 did. As shown in Fig E3 in this article's Online Repository at www.jacionline.org, IgG_4 did not cause inhibition. These results also demonstrated that IgG_3 was 10-fold more efficacious in interacting with CD32b than IgG_2, such that only 1 IgG_3 per 20 antigen molecules was necessary to mediate inhibition, whereas approximately 0.5:1 ratios were needed for IgG_2. Fig 1, *B*, *D*, and *F*, also examined the ability to further reverse inhibition through inclusion of CD32a blockade with antibody AbIV.3 (see the Results section in this article's Online Repository). There was some further reversal by addition of AbIV.3, although the best reversal occurred with CD32b blockade. As discussed in the Results section in this article's Online Repository, heterogeneity in the relative participation of CD32 was correlated with CD32 expression (see Table E1 in this article's Online Repository at www.jacionline.org), and reversal of IgG_2 and IgG_3 was correlated. Furthermore, as shown in Fig E4, polymorphisms in CD32a and CD32b did not influence the relative participation of CD32. As a low-affinity IgG receptor, CD32 is not thought to engage monomeric IgG effectively, but concentrations of IgG in plasma are very high, and therefore the ability of nonspecific IgG (nsIgG) to inhibit participation of CD32 (by using nsIgG as a substitute for Ab10523) was examined. Fig E5 in this article's Online Repository at www.jacionline.org shows that reversal of CD32's effects occur at an inhibitory concentration of 50% of 150 μg/mL nsIgG.

These and our previous studies[6] suggest that there are several important parameters, possibly 5 dimensions, which determine whether it is possible to observe the inhibitory function of CD32 on basophils (see also the Discussion section in this article's Online Repository at www.jacionline.org). These results place some constraints on how to explore the role of CD32 in the basophil reaction during immunotherapy, and the variability in the

METHODS

Study population

This study is based on the prospective birth cohort ALADDIN.[E1] The families were recruited between September 2004 and November 2011 from anthroposophic and conventional maternal-child health care centers (MCHCs) in Stockholm and Järna, a village situated south of Stockholm with a community of anthroposophic followers. Parents were informed about the study at their MCHC, and families interested in participation were enrolled. A total of 552 families were recruited, of whom 444 were recruited during pregnancy and 108 shortly after birth. Preterm infants (born before gestational week 36) and miscarriages were excluded. The parents answered detailed questionnaires about their daily life, health, and food, and the children were examined repeatedly.[E2] Inclusion criteria for children in the present study were having a lifestyle classification (see below) and at least 1 (of 4) blood samples taken (Fig E1). The study was approved by the local ethics committee in Stockholm, and written informed consent was obtained from all parents.

Categorization into lifestyle groups

The families were classified into 3 lifestyle groups (anthroposophic, partly anthroposophic, and nonanthroposophic) based on their choice of MCHC and based on answers to 3 questionnaire questions: (1) "What kind of preschool/school will your newborn child probably go to?"; (2) "Has either of the parents, no matter which type of school you have planned for your child, an anthroposophic view of life?"; and (3) "Is the family's everyday life influenced by an anthroposophic view of life?" Families answering "anthroposophic school" to question 1 and yes to questions 2 and 3 and also attending anthroposophic MCHCs were defined as being anthroposophic. Families answering "conventional" or any other nonanthroposophic type of school to question 1, no to questions 2 and 3, and attending conventional MCHCs were defined as being nonanthroposophic. Families with any other combination of answers were defined as being partly anthroposophic.

Determination of allergen sensitization

Blood samples were collected in sodium heparin tubes from parents at the time of inclusion and from the children at 6, 12, 24, and 60 months of age. Plasma was stored at −20°C. Parental sensitization was determined by using ImmunoCAP Phadiatop (Thermo Fisher Scientific, Uppsala, Sweden) for IgE levels to a set of 11 inhalant allergens. Sensitization at 6, 12, and 24 months of age was determined by using ImmunoCAP (Thermo Fisher Scientific) for IgE levels to hen's egg, cow's milk, peanut, dog, cat, birch, and timothy. Sensitization at 5 years of age was determined by using Phadiatop and a food mix of cow's milk, hen's egg, fish, wheat, soybean, and peanut (fx5, Thermo Fisher Scientific). Subjects with allergen-specific IgE levels of 0.35 kU_A/L or greater were regarded as being sensitized. Allergens were divided into 3 categories: food, animal, and pollen allergens. The analysis at 60 months was restricted to the same 7 allergens used at earlier time points to obtain a comparable longitudinal observation of the development of sensitization.

Statistical analysis

Incidence and prevalence were depicted graphically for the 3 allergen categories, as well as for any sensitization, by lifestyle. Prevalence was calculated as the number of sensitized children at each age through the number of nonmissing observations at the respective age. Incidence proportions were calculated as the number of first time–sensitized children (cases) during the time period divided by the number of children at risk. The children with missing previous samples were considered at risk for that time period, as long as they had not previously been sensitized and had a nonmissing value for age at the end of the time period. To evaluate whether the association between lifestyle and prevalence of sensitization of the respective categories of allergens varied with age, we used generalized estimating equation models with an unstructured correlation matrix and included an interaction term between lifestyle and age as a continuous variable. The significance level was set at .05 (2-sided). Statistical analyses were performed with R v3.1.3 (R Foundation for Statistical Computing, Vienna, Austria) and SAS v9.4 (SAS Institute, Cary, NC) software.

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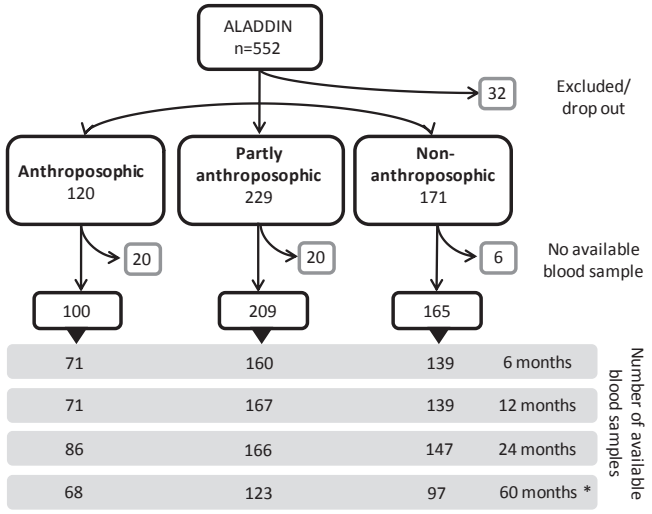

FIG E1. Flowchart of inclusion and number of available blood samples at each time point for the children in relation to lifestyle. *At the time of this study, 6 anthroposophic, 32 partly anthroposophic, and 21 nonanthroposophic children had not turned 5 years of age.

TABLE E1. Point prevalence of IgE sensitization against different allergens at 6, 12, 24, and 60 months of age in children from families with anthroposophic, partly anthroposophic, and nonanthroposophic lifestyles

	Anthroposophic, n/N (%)	Partly anthroposophic n/N (%)	Non-anthroposophic, n/N (%)
Sensitization at 6 mo			
Any allergen*	2/71 (2.8)	14/160 (8.8)	25/139 (18)
Food*	1/75 (1.3)	12/172 (7.0)	22/143 (15.4)
Milk*	0	5	15
Egg	1	9	11
Peanut	0	3	2
Animal	1/71 (1.4)	3/160 (1.9)	7/139 (5.0)
Cat	1	2	4
Dog	0	1	3
Pollen	0/73 (0)	0/162 (0)	0/140 (0)
Birch	0	0	0
Timothy	0	0	0
Sensitization at 12 mo			
Any allergen*	3/71 (4.2)	23/167 (13.8)	37/139 (26.6)
Food*	2/75 (2.7)	21/170 (12.4)	37/145 (25.5)
Milk*	0	11	17
Egg*	2	12	24
Peanut	0	7	6
Animal	1/70 (1.4)	4/167 (2.4)	8/137 (5.8)
Cat	1	2	5
Dog	0	2	5
Pollen	0/74 (0)	0/167 (0)	1/137 (0.7)
Birch	0	0	1
Timothy	0	0	1
Sensitization at 24 mo			
Any allergen*	13/86 (15.1)	22/166 (13.3)	35/147 (23.8)
Food	8/86 (9.3)	19/169 (11.2)	27/148 (18.2)
Milk	8	16	19
Egg*	3	8	16
Peanut	0	8	7
Animal*	2/86 (2.3)	3/167 (1.8)	11/147 (7.5)
Cat	2	2	8
Dog*	0	3	8
Pollen	4/86 (4.7)	6/166 (3.6)	9/148 (6.1)
Birch	4	5	6
Timothy	0	2	5
Sensitization at 60 mo			
Any allergen*	14/68 (20.6)	22/123 (17.9)	37/97 (38.1)
Food*	8/68 (11.8)	11/123 (8.9)	28/97 (28.9)
Milk*	5	7	22
Egg*	6	3	14
Peanut*	2	3	9
Animal*	3/68 (4.4)	7/123 (5.7)	15/97 (15.5)
Cat*	3	5	12
Dog*	2	5	11
Pollen	9/68 (13.2)	12/123 (9.8)	16/97 (16.5)
Birch	8	9	9
Timothy	5	10	13

*Differences were significant at P values of less than .05.