



Contents lists available at SciVerse ScienceDirect

International Journal of Hygiene and Environmental Health

journal homepage: www.elsevier.com/locate/ijheh



Renovation activities during pregnancy induce a Th2 shift in fetal but not in maternal immune system

Gunda Herberth^{a,*}, Thomas Herzog^a, Denise Hinz^a, Stefan Röder^b, Maik Schilde^b, Ulrich Sack^c, Ulrike Diez^d, Michael Borte^d, Irina Lehmann^{a,b,*}

^a UFZ – Helmholtz Centre for Environmental Research Leipzig, Department of Environmental Immunology, Leipzig, Germany

^b UFZ – Helmholtz Centre for Environmental Research Leipzig, Core facility studies, Leipzig, Germany

^c University of Leipzig, Institute for Clinical Immunology, Leipzig, Germany

^d Children's Hospital, Municipal Hospital "St. Georg", Academic Teaching Hospital of the University of Leipzig, Leipzig, Germany

ARTICLE INFO

Article history:

Received 18 November 2011

Received in revised form 25 May 2012

Accepted 30 June 2012

Keywords:

Renovation

Pregnancy

Cord blood

Th1/Th2 cytokines

Allergic sensitization

IgE

ABSTRACT

The aim of the present study was to investigate to which extent environmental influences like indoor renovation activities affect the immune system of mother and child during the gestation period. Within the LINA (Lifestyle and Environmental Factors and their Influence on Newborn Allergy risk) birth cohort study blood samples of mothers during pregnancy and cord blood samples were analyzed for concentrations of the Th1/Th2 cytokines IL-4, IL-5, IL-13, IFN- γ and IgE. Data on indoor renovation activities (painting, flooring and new furniture) were assessed with questionnaires. Data on cytokine blood concentrations and exposure variables were available for 422 mother/child pairs. Neonates, who were strongly affected by renovation activities (especially floor covering and new furniture) during pregnancy, had significantly higher concentrations of IL-4 and IL-5 in cord blood. Among the single activities, new furniture, particularly flake board, were associated with increased IL-4 levels. Elevated IL-4 levels were also observed in the cord blood of children whose mothers reported wall-to-wall carpeting. Among flooring, polyvinylchloride (PVC) showed the strongest effect with increased IL-5 concentrations. The Th1/Th2 imbalance towards Th2 at birth was related to allergic sensitization in children at the age of one. There were only few and negative associations between renovation activities and Th1/Th2 cytokine concentration in maternal blood. Our study shows that under similar exposure situations the fetal immune system is more susceptible to the influence of environmental factors, in particular renovation products (flake board, wall-to-wall carpets and PVC) compared to the maternal.

© 2012 Elsevier GmbH. All rights reserved.

Introduction

It is common for parents to move or redecorate their home when a baby is expected. However, among others, renovation activities during pregnancy have been identified as risk factors for allergic sensitization and allergic diseases during early childhood (Herberth et al., 2006; Wen et al., 2009). New surface materials, carpets, furniture and paints or adhesives are sources for different groups of chemicals, mainly volatile organic compounds (VOCs). Increased indoor concentration levels of these compounds were found after renovation activities. After recent painting (Rumchev et al., 2004), the use of adhesives or new floor covering (Wilke et al., 2004)

increased indoor VOC concentration levels have been reported. Furthermore, wood and wood-based materials are known as sources for VOC (Jensen et al., 2001). Many VOCs are reported to be associated with airway hyper responsiveness (Billionnet et al., 2011; Jang et al., 2007) or with allergic diseases (Bornehag et al., 2004; Mendell, 2007; Rumchev et al., 2004).

It is well known that allergies and asthma are based on a disturbed immune reactivity at T cell level. Mainly the Th1/Th2 balance directed towards Th2 is responsible for increased IgE production and the development of allergies. In earlier studies we already demonstrated that in children at risk, VOCs exposure was associated with enhanced IgE production and T cell polarization towards Th2 (Lehmann et al., 2001). Furthermore, we showed that prenatal exposure to VOCs also alters the Th1/Th2 balance at birth (Lehmann et al., 2002a). In addition, we found reduced amounts of IFN- γ producing Th1 cells in the cord blood of newborn children whose mothers reported about renovation activities in their home during pregnancy (Lehmann et al., 2002b) and a subsequently enhanced risk for the development of an atopic eczema (Herberth

* Corresponding authors at: UFZ – Helmholtz Centre for Environmental Research, Department of Environmental Immunology, Permoserstrasse 15, 04318 Leipzig, Germany. Tel.: +49 341 235 1547; fax: +49 341 235 1787.

E-mail addresses: gunda.herberth@ufz.de (G. Herberth), irina.lehmann@ufz.de (I. Lehmann).

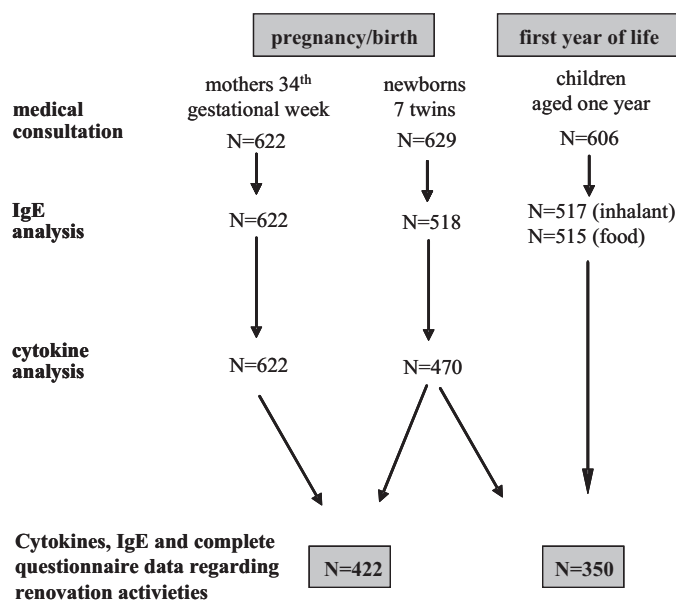


Fig. 1. Flow chart of the study population with the analyzed sub cohort.

et al., 2010). Thus, there is evidence that chemical exposure during pregnancy resulting from renovation activities can contribute to a functional impairment of T cell reactivity in neonates and thereby to an increased risk for the development of allergies in infancy.

So far, no data exist concerning the impact of the different renovation activities or the used products in pregnancy on the T cell reactivity and the allergy risk of the child. Available information on critical products or activities, however, would help to prevent hazardous exposure situations during pregnancy. In the present study we followed the hypothesis that renovation activities during pregnancy alter the Th1/Th2 status and the IgE levels in expecting mothers and their newborn children. Therefore, we analyzed the impact of different renovation products/activities on Th1/Th2 cytokines during pregnancy and in cord blood and the consequences for children's allergic sensitization at the age of one.

Methods

Study design and subjects

The LINA study (Lifestyle and Environmental Factors and their Influence on Newborn Allergy risk) was designed to investigate the prenatal influence of life style and environmental factors on the maturation of the immune system in neonates and the resulting allergy risk in infancy.

622 mother–child pairs (629 children; 7 twin pairs) were recruited in Leipzig, Germany in the Children's Hospital "St. Georg" between May 2006 and December 2008. In this study cohort 97% of children were of German nationality and participation of other ethnical groups was below 6.2%. Pregnant women were mainly recruited by a study assistant in cooperation with midwives during antenatal classes. Questionnaire data on mothers and fathers history of atopic diseases, smoking behavior, housing conditions, renovation activities, traffic exposure, noise, social stress and disease outcomes were collected during pregnancy and at children's first birthday. Blood samples were taken at the 34th week of pregnancy of the mother and after birth of venous cord blood. At the age of one another blood sample was taken from both, the mother and the child during a clinical visit (Fig. 1). Participation in the study was voluntary. Informed consent was obtained from the parents of

all children. The study was approved by the Ethics Committee of the University of Leipzig (reference number 046-2006).

Blood sampling

Sera (2.5 ml) and heparinized blood (5 ml) were obtained by venous puncture and prepared within 6 h to further analysis. For cytokine measurement heparinized blood samples were incubated for 4 h at 37 °C. Thereafter, samples were diluted 1:1 with RPMI 1640 medium without supplements and centrifuged. Collected cell free supernatants were stored at –80 °C until analysis. Serum samples were stored at –20 °C until IgE measurement.

Measurement of cytokines/chemokines

Concentrations of the cytokines/chemokines IL-4, IL-5, IL-6, IL-8, IL-10, IL-13, MCP-1, IFN- γ , TNF- α were measured by flow cytometry using a cytometric bead array (BD CBA Human Soluble Flex Set system, Becton Dickinson, Heidelberg, Germany) according to manufacturer's instructions. In brief, cytokine specific antibody coated beads were incubated for 1 h with 25 μ l of diluted plasma samples or standard solution. Thereafter, samples were incubated with the corresponding PE labeled detection antibodies for 2 h. After one washing step samples were measured by flow cytometry. Analysis of data and quantification of cytokines were performed using the FCAP Array™ software (Becton Dickinson, Heidelberg, Germany) on the basis of corresponding standard curves. Finally, plasma dilution factor was accounted. Detection limits were 3 pg/ml for all cytokines, excepting IL-5, where the detection limit was 2 pg/ml.

Immunoglobulin E measurement

The concentration of total IgE in maternal and in cord blood was determined by the Phadia CAP System (Phadia GmbH, Freiburg, Germany). Furthermore, in children's samples at the age of one specific IgE against food (Fx5) and inhalant allergens (Sx1) were determined. The allergen multipanel Fx5 consists of hen's egg, cow's milk, wheat, fish, peanut and soy. Sx1 includes timothy, rye, mugwort, birch, house dust mite (*Dermatophagoides pteronyssinus*), cat and dog.

Assessment of renovation activities

A questionnaire was sent to the parents in the 30th week of gestation. Data from completed questionnaires comprised information on smoking behavior of the parents, housing conditions, pet keeping, traffic burden, and renovation activities. Indoor exposure was assessed based on questionnaire information focusing on type of home renovation. Parents were asked whether renovation was performed and if yes, the type of renovation and the used products were specified. First question was "Did you renovate your apartment?", If yes: "Did you paint your apartment?", If yes: "Which paint did you use: emulsion paint, silicate paint, distemper, casein paint, oil paint or eco paint?", "Did you perform a new floor covering in your apartment?", If yes: "Which kind of material did you use: parquet, laminate, wall-to-wall carpets, PVC or others?", "Did you furnished your apartment?", If yes: "Which kind of furniture: wooden, flake board, others". In addition we asked the parents for the point in time they performed the particular activities ("When did you renovate: before gestation, 1st to 13th, 14th to 26th or 27th to 40th week of gestation?").

We generated variables including those cases, which were affected by only one renovation activity (painting, new furniture), respectively by only one material (paints, flake board, wooden. . .). There were no cases of floor covering alone. Therefore, floor covering and the respective materials could only be analyzed in

combination with painting and/or new furniture. Children without any renovation activity served as reference group.

Statistical analysis

We performed descriptive statistics and tested the relation between renovation activities and cytokine concentrations in children's and maternal blood. Chi-square test was used to test the relationship between the analyzed sub cohort and the remaining children of the LINA cohort. The non-parametric Mann–Whitney U-test was applied for crude analysis of the relation between renovation activities, cytokine concentrations and total IgE. After logarithmic transformation of cytokine concentrations, the association with renovation activities was calculated by means ratios (MR), that is the ratio of the geometric mean in the category of study vs. the reference category (no renovation activities). We adjusted for gender, parental history of atopy, low birth weight, cat ownership, ETS exposure during pregnancy, parental education level, nationality (German vs. others) and mold exposure at home. These confounding variables were selected by prior knowledge. The relationship between cytokine concentrations in cord blood and specific IgE at the age of one was calculated by means ratios adjusted for the factors mentioned before.

Adjustments due to multiple testing were not performed since our analyses were based on an a priori hypothesis (Perneger, 1998). Cytokine concentrations below the limit of detection were assigned a value of one half of the detection limit and entered calculation. *P* values below 0.05 were considered as statistically significant. Statistical analysis was performed with STATISTICA 7.0 for Windows XP (Statsoft Inc. Europe, Hamburg, Germany).

Results

Subjects

A number of 422 children fulfilled the criteria to have a complete data set including questionnaire data on renovation activities, all confounder variables and additional cytokine measurements of mother–child pairs, thus only data from these children are shown. Cord blood samples (*n* = 470, cytokine analysis) do not fully match with blood samples from children at the age of one (*n* = 515, IgE to food allergens). The greatest common subset of children with blood samples at birth and at the age of one was *n* = 388. Out of these participants *n* = 350 had complete questionnaire data regarding renovation variables (Fig. 1).

Basic characteristics of the complete LINA cohort and the analyzed subset are given in Table 1. About two-third (66.8%) of cases had a positive history of atopy (single or double); the parental education level was high in 73.9% of cases. In 17.8% of homes cat keeping has been reported and 85.1% of the parents declared to have never been smoking in the dwelling. Regarding the covariates there was no difference between the analyzed subset (*n* = 422) and the remaining children from the LINA cohort (*n* = 207).

Indoor renovation activities

Reported indoor renovation activities during pregnancy consisted mostly in new furnishing (*n* = 264; 62.6%) and painting (*n* = 232; 55.0%) of the dwellings whereas floor covering was less frequent (*n* = 95; 22.5%). The number of subjects who performed all of the three activities was *n* = 69 (16.4%). A total of 22.0% (*n* = 93) was not affected by any redecoration activity, Table 2. Single renovation activities occurred in *n* = 37 (8.8%) cases for painting and in *n* = 85 (20.1%) for new furniture. There was no case of floor covering alone (Table 2). In Table 3 the types of materials for painting, floor covering and the furniture used are shown.

Table 1

Characteristics of analyzed sub cohort (*N* = 422), the entire LINA cohort and the remaining LINA study population.

Variables	Entire LINA cohort <i>n</i> (%)	Analyzed sub cohort <i>n</i> (%)	Remaining LINA cohort <i>n</i> (%)	<i>P</i> value*
	<i>N</i> = 629	<i>N</i> = 422	<i>N</i> = 207	
Gender				0.661
Male	327 (52.0)	199 (47.2)	104 (50.3)	
Female	302 (48.0)	223 (52.8)	103 (49.7)	
Parental history of atopy				0.668
None	212 (33.7)	140 (33.2)	72 (34.8)	
Single positive	296 (47.1)	194 (46.0)	102 (49.3)	
Double positive	121 (19.2)	88 (20.8)	33 (15.9)	
Parental educational level				0.905
Low	16 (2.5)	10 (2.4)	6 (2.9)	
Middle	144 (22.9)	100 (23.7)	44 (21.3)	
High	469 (74.6)	312 (73.9)	157 (75.8)	
Low birth weight (<2500 g)				0.283
No	608 (96.5)	412 (97.6)	195 (94.2)	
Yes	21 (3.3)	10 (2.4)	11 (5.3)	
Cat ownership				0.912
No	516 (82.0)	347 (82.2)	169 (81.6)	
Yes	113 (18.0)	75 (17.8)	38 (18.4)	
Smoking in the dwelling				0.996
Daily	48 (7.6)	32 (7.6)	16 (7.7)	
At least once a week	4 (0.6)	3 (0.7)	1 (0.5)	
Occasionally	43 (6.8)	28 (6.6)	15 (7.2)	
Never	534 (84.9)	359 (85.1)	175 (84.5)	
ETS outside the dwelling				0.300
Daily	91 (14.5)	61 (14.5)	30 (14.5)	
At least once a week	51 (8.1)	42 (9.9)	9 (4.3)	
Never/rare	487 (77.4)	319 (75.6)	168 (81.2)	

* *P* value from the comparison of the analyzed sub cohort with the remaining cohort of the LINA study, Chi-square test.

In most cases flake board (42.7%), wall-to-wall carpets (9.7%) and emulsion paints (29.1%) were used.

Relationship between cytokine concentrations and renovation activities

Th1/Th2 cytokine as well as total IgE concentrations were measured in maternal blood (34th week of gestation) and in cord blood. Cord blood IL-5 concentrations were increased in children from parents reporting any renovation, arrangement of new furniture, floor covering and the performance of all renovation activities together (data not shown, Mann–Whitney U test). In a linear regression model with and without adjustment for further possible influence of gender, parental history of atopy, low birth weight, cat ownership, ETS exposure during pregnancy, parental education level, ethnicity (German vs. others) and mold exposure at

Table 2

Frequency of combined and single renovation activities.

Variables	Frequency <i>n/N</i> (%)
Any renovation	
Yes	329/422 (78.0)
No	93/422 (22.0)
Renovation activities ^a	
Painting	232/422 (55.0)
Floor covering	95/422 (22.5)
New furniture	264/422 (62.6)
Painting and new furniture and floor covering (all renovation activities)	69/422 (16.4)
Single activities ^b	
Painting	37/422 (8.8)
Floor covering	0/422 (0)
New furniture	85/422 (20.1)

^a Case numbers resulting from questionnaire answers, see Section "Methods".

^b Single activities after excluding cases with multiple renovation activities.

Table 3
Frequency of products used for renovation activities during pregnancy.

Variables	Frequency n/N (%)
Type of new furniture	
Wooden	131/422 (31.0)
– Wooden only	18/422 (4.3)
Flake board	180/422 (42.7)
– Flake board only	30/422 (7.1)
Others	81/422 (19.2)
– Others only	23/422 (5.5)
Type of floor covering	
Parquet	16/422 (3.8)
Laminate	32/422 (7.6)
Wall-to-wall carpet	41/422 (9.7)
PVC	8/422 (1.9)
Others	13/422 (3.1)
Type of paint	
Emulsion paint	123/422 (29.1)
– Emulsion paint only	19/422 (4.5)
Oil-based paint	9/422 (2.1)
– Oil-based paint only	2/422 (0.5)
Eco-paint	32/422 (7.6)
– Eco-paint only	7/422 (1.7)
Silicate paint	0/422 (0)
Distemper	0/422 (0)
Casein paint	0/422 (0)

Floor covering was never performed as single renovation activity.

home these associations remained significant, Table 4. The IL-4 concentrations in cord blood were increased when parents reported about any renovation, new furniture arrangement and when all renovation activities were performed together. Estimates from the adjusted linear regression model revealed that these relationships were significant (Table 4).

In addition to the kind of renovation activities, we asked for materials used for furnishing, floor covering and painting. In Table 5 the relation between furnishing material and the Th1/Th2 cytokine and total IgE concentration is presented. After adjustment, a significant association between IL-4 concentrations in cord blood and flake board furnishing (MR 1.37; 95% CI: 1.02–1.84) was observed. Regarding floor covering materials, PVC was associated on crude data level as well as after adjustment with increased IL-5 concentrations in cord blood (adjusted MR 1.56; 95% CI: 1.08–2.28), Table 6. Furthermore, these children had significantly increased IgE levels compared to children without reported renovation activities (0.36 vs. 0.16 kU/l, $P=0.044$, Mann–Whitney U test). In the adjusted regression model, wall-to-wall carpeting was associated with elevated IL-4 concentrations in cord blood (adjusted MR 1.4; 95% CI: 1.08–1.82), Table 6. Neither painting in general nor single painting materials were associated with cytokine concentrations in children's and in maternal blood (data not shown). In maternal blood, only weak associations between IL-5 and reported flooring with laminate (Table 6) as well as when all renovation activities were performed together were observed (Table 4). These relationships were inverse associated compared to data from children.

Relationship between elevated Th2 cytokine concentrations in cord blood and allergic sensitization at the age of one

In order to determine the relevance of elevated Th2 cytokine concentrations observed in cord blood in association to renovation activities we analyzed the relation to allergic sensitization of children and atopic skin manifestations in the first year of life. At age one, 11.9% of the children had IgE antibodies specific for food allergens (fx5) and 2.6% of the children were sensitized against inhalant allergens (sx1). Children with increased IL-4, and IL-13 concentrations in cord blood had increased levels of food allergen specific IgE (fx5) at the age of one, Table 7. These relationships were

stable even after adjustment to the mentioned possible confounding factors (Table 7).

For 9.3% of the children parents reported about symptoms of an atopic dermatitis, a physician diagnosed atopic eczema was developed by 9.5% of the children. A correlation between cord blood cytokine levels and symptomatic or diagnosed eczema was not found (data not shown).

Discussion

Because in developed countries people spend most of their time indoors, the quality of indoor air represents an important risk factor for illnesses related to environmental exposure. In the present study we demonstrate that renovation activities during pregnancy affect the immune response of newborns but not that of corresponding mothers. We observed increased IL-5 and IL-4 concentrations in children exposed to renovation activities like new floor covering and new furniture. In particular, IL-4 in cord blood was increased in association with flake board furnishing and wall-to-wall carpet flooring. Elevated IL-5 concentrations in cord blood were associated with PVC flooring. Furthermore, we found that the Th1/Th2 imbalance towards Th2 at birth was related to allergic sensitization in children at the age of one.

Environmental factors that cause a Th1/Th2 imbalance may contribute to the risk of allergic diseases. In addition, the existence of a physically sensitive window for specific influences from the environment is becoming evident (Herberth et al., 2006). It is now well established that maturation of the adaptive immune system and development of functionally active T cell subsets already starts prenatally (Joerink et al., 2010; Macaubas et al., 2000). Furthermore, it has been proposed that immune programming by environmental influences may also occur at this early developmental stage. Endogenous as well as exogenous exposures may influence the maturation and differentiation of fetal immune cells and may thereby contribute to the development of allergies later in life. For example, it has been shown that prenatal farm exposure is related to the expression of receptors of the innate immunity and protects against atopic sensitization in school-age children (Ege et al., 2006). In addition, farm exposure of mothers during pregnancy seems to affect the number of regulatory T cells in cord blood and may decrease the risk of allergic diseases in offspring (Schaub et al., 2009). Adverse effects on fetal innate immune responses have also been reported in infants of smoking mothers (Noakes et al., 2006; Prescott, 2008). Devereux and colleagues observed that maternal smoking is associated with stronger neonatal allergen-specific responses (Devereux et al., 2002), providing evidence that maternal smoking has effects on fetal cellular immune function. Furthermore, also exposure to volatile organic compounds seems to influence the maturation of the fetal immune system. In a previous study we demonstrated that antenatal exposure to naphthalene and methylcyclopentane was related to elevated percentages of IL-4 producing cord blood T cells whereas exposure to tetrachlorethylene was associated with reduced percentages of IFN- γ producing T cells (Lehmann et al., 2002a). The data of our present study support these previous findings indicating that renovation activities during pregnancy can contribute to the development of a Th2 skewed immune response at birth.

In the present study we compared effects of renovation activities during pregnancy between the maternal and fetal immune system. We found only few associations between maternal blood cytokine concentration in pregnancy and the analyzed renovation activities while the fetal T cell reactivity was stronger affected. Regarding the impact on Th1/Th2 balance the effect was rather protective whereas in children a Th2 biased T cell response was observed in association with renovation activities. These findings might reflect

Table 4
Relationship between renovation activities and concentrations of Th1/Th2-cytokines and IgE in blood samples of mothers in the 34th week of gestation and cord bloods ($n = 422$). Shown are raw and adjusted mean ratios with the 95% CI.

	Any renovation $n = 329$		Painting $n = 37$		New furniture $n = 85$		Floor covering ^a $n = 69$		Painting and furniture and floor covering $n = 95$	
	Raw [pg/ml]	Adjusted [pg/ml]	Raw [pg/ml]	Adjusted [pg/ml]	Raw [pg/ml]	Adjusted [pg/ml]	Raw [pg/ml]	Adjusted [pg/ml]	Raw [pg/ml]	Adjusted [pg/ml]
IL-4	0.99	0.97	0.99	0.86	1.02	1.03	0.99	0.94	0.96	0.93
Mother	(0.84–1.18)	(0.82–1.15)	(0.72–1.35)	(0.62–1.2)	(0.82–1.27)	(0.82–1.29)	(0.8–1.22)	(0.76–1.17)	(0.76–1.22)	(0.73–1.18)
Child	1.15	1.2*	1.21	1.35	1.3*	1.3*	1.15	1.21	1.22	1.26*
	(0.97–1.37)	(1.01–1.42)	(0.9–1.64)	(0.97–1.89)	(1.05–1.61)	(1.06–1.6)	(0.93–1.42)	(0.98–1.49)	(0.97–1.54)	(1–1.59)
IL-5	0.96	0.96	0.95	0.91	1.02	1.03	0.92	0.9	0.9	0.88*
Mother	(0.89–1.05)	(0.88–1.0)	(0.82–1.1)	(0.77–1.07)	(0.91–1.14)	(0.92–1.15)	(0.82–1.03)	(0.8–1.01)	(0.79–1.01)	(0.77–1)
Child	1.12*	1.15*	1.04	1.06	1.18*	1.18*	1.17*	1.21*	1.23*	1.26**
	(1–1.26)	(1.02–1.29)	(0.85–1.27)	(0.85–1.33)	(1.02–1.37)	(1.02–1.38)	(1.01–1.35)	(1.04–1.39)	(1.05–1.43)	(1.08–1.47)
IL-13	1.02	1	0.94	0.9	1.13	1.16	0.98	0.96	0.93	0.91
Mother	(0.85–1.22)	(0.83–1.2)	(0.69–1.28)	(0.64–1.26)	(0.89–1.44)	(0.91–1.49)	(0.78–1.23)	(0.76–1.21)	(0.73–1.19)	(0.7–1.18)
Child	1.04	1.07	1	1.02	1.13	1.16	0.98	1.01	1.08	1.05
	(0.82–1.32)	(0.85–1.36)	(0.66–1.53)	(0.64–1.63)	(0.83–1.54)	(0.85–1.59)	(0.72–1.34)	(0.74–1.37)	(0.77–1.52)	(0.75–1.48)
IFN- γ	1.05	1.02	1.09	1	1.06	1.06	0.99	0.94	0.97	0.92
Mother	(0.85–1.29)	(0.83–1.26)	(0.76–1.56)	(0.67–1.49)	(0.8–1.4)	(0.8–1.41)	(0.76–1.29)	(0.72–1.23)	(0.73–1.3)	(0.69–1.24)
child	1.04	1.05	1.02	0.95	1.07	1.08	0.89	0.91	0.96	0.92
	(0.83–1.3)	(0.84–1.33)	(0.69–1.51)	(0.62–1.47)	(0.79–1.45)	(0.8–1.45)	(0.67–1.19)	(0.68–1.21)	(0.7–1.31)	(0.67–1.26)
IgE	1.04	1.04	1.03	1.16	1.17	1.17	0.84	0.88	0.91	0.88
Mother	(0.74–1.46)	(0.75–1.45)	(0.57–1.87)	(0.6–2.22)	(0.75–1.82)	(0.75–1.84)	(0.54–1.31)	(0.57–1.37)	(0.56–1.49)	(0.54–1.44)
Child [kU/l]	1.17	1.25	1.22	1.38	1.14	1.14	1.02	1.11	1	1.03
	(0.86–1.61)	(0.92–1.71)	(0.74–2)	(0.81–2.34)	(0.75–1.73)	(0.75–1.73)	(0.71–1.48)	(0.77–1.61)	(0.67–1.51)	(0.69–1.55)

P values from the multiple linear regression model adjusted for gender, parental history of atopy, low birth weight, cat ownership, ETS exposure during pregnancy, parental education level, nationality (German vs. others) and mold exposure at home.

^a Floor covering and/or painting and/or new furniture.

* P values < 0.05.

** P values < 0.005.

Table 5
Relationships between furnishing materials and concentrations of Th1/Th2 cytokines and IgE in blood samples of mothers in the 34th week of gestation and cord bloods (n = 422). Shown are raw and adjusted mean ratios with the 95% CI.

	Wooden only n = 18		Flake board only n = 30	
	Raw [pg/ml]	Adjusted [pg/ml]	Raw [pg/ml]	Adjusted [pg/ml]
IL-4	0.96	1.05	0.82	0.81
Mother	(0.64–1.42)	(0.69–1.59)	(0.59–1.13)	(0.59–1.13)
Child	1.43	1.27	1.31	1.37*
	(0.98–2.08)	(0.88–1.83)	(0.96–1.79)	(1.02–1.84)
IL-5	1.02	1.03	0.94	0.95
Mother	(0.84–1.25)	(0.83–1.27)	(0.8–1.11)	(0.8–1.12)
Child	1.24	1.16	1.21	1.23
	(0.96–1.61)	(0.89–1.51)	(0.98–1.49)	(0.99–1.52)
IL-13	0.95	0.96	1.2	1.23
Mother	(0.63–1.42)	(0.63–1.48)	(0.85–1.71)	(0.85–1.76)
Child	1.57	1.47	1.06	1.08
	(0.91–2.73)	(0.84–2.58)	(0.67–1.67)	(0.68–1.69)
IFN-γ	0.96	1.01	0.83	0.83
Mother	(0.59–1.55)	(0.61–1.68)	(0.55–1.23)	(0.55–1.24)
Child	1.43	1.27	0.97	0.98
	(0.84–2.41)	(0.75–2.15)	(0.63–1.49)	(0.63–1.51)
IgE	1.32	1.06	1.24	1.29
Mother	(0.59–2.95)	(0.46–2.44)	(0.67–2.31)	(0.68–2.44)
Child [kU/l]	1.03	0.87	1.3	1.36
	(0.52–2.06)	(0.43–1.77)	(0.74–2.29)	(0.78–2.39)

P values from the multiple linear regression model adjusted for gender, parental history of atopy, low birth weight, cat ownership, ETS exposure during pregnancy, parental education level, nationality (German vs. others) and mold exposure at home.
* P values <0.05.

the fact that the fetal immune system is more susceptible for environmental influences.

There is no doubt that the immune responsiveness of newborns is different from that of adults. Mainly a Th2 driven T cell response characterized by a reduced capability to produce IFN-γ and a reduced IFN-γ/IL-4 ratio or, in other words a Th2 driven Th1/Th2 balance, was reported in newborns compared to adults (Halonen et al., 2009; Prescott et al., 1998; Schaub et al., 2008). Within our LINA study we were able to confirm these findings by directly comparing mother–child pairs (Herberth et al., 2011). The defective neonatal T cell, and in particular IFN-γ response, seems to be a result of the dysfunction of antigen-presenting cells and an altered innate immune response (Kollmann et al., 2009; Roduit et al., 2011). It has been debated that due to the physiological

differences between the adult and neonatal immune system the later one might be more susceptible to environmental exposure. Although it has been shown that microbial as well as chemical exposure during pregnancy can alter the Th1/Th2 balance in the newborn child (Lehmann et al., 2002a,b; Roduit et al., 2011) there was no real evidence so far for a difference in sensitivity between the adult and the neonatal immune system. With the present study we show such a difference for the first time.

A skewed programming of CD4+ T cells towards a Th2 phenotype is a primary cause of allergic diseases and sensitization and the prenatal period, during development of the immune system, seems to be a critical window of programming. In this regard, maternal exposure to ETS, traffic pollutants, renovation activities have been shown to increase the risk of allergic diseases and asthma in

Table 6
Relationships between furnishing materials and concentrations of Th1/Th2 cytokines and IgE in blood samples of mothers in the 34th week of gestation and cord bloods (n = 422). Shown are raw and adjusted mean ratios with the 95% CI.

	Parquet n = 16		Laminate n = 32		Wall-to-wall carpet n = 41		PVC n = 8	
	Raw [pg/ml]	Adjusted [pg/ml]	Raw [pg/ml]	Adjusted [pg/ml]	Raw [pg/ml]	Adjusted [pg/ml]	Raw [pg/ml]	Adjusted [pg/ml]
IL-4	1.09	1.04	0.89	0.85	1	0.93	1.29	1.24
Mother	(0.72–1.67)	(0.67–1.62)	(0.65–1.22)	(0.61–1.17)	(0.76–1.33)	(0.7–1.23)	(0.73–2.26)	(0.7–2.21)
Child	1.03	1.16	1.07	1.13	1.29	1.4*	1.26	1.29
	(0.69–1.55)	(0.79–1.72)	(0.78–1.47)	(0.82–1.55)	(0.99–1.69)	(1.08–1.82)	(0.72–2.19)	(0.75–2.23)
IL-5	0.84	0.82	0.87	0.83*	0.95	0.94	1.23	1.22
Mother	(0.68–1.04)	(0.66–1.03)	(0.74–1.02)	(0.71–0.99)	(0.82–1.1)	(0.81–1.09)	(0.93–1.63)	(0.91–1.64)
Child	1.1	1.17	1.16	1.19	1.14	1.19	1.55*	1.56*
	(0.84–1.44)	(0.89–1.55)	(0.94–1.42)	(0.96–1.47)	(0.94–1.38)	(0.98–1.44)	(1.08–2.22)	(1.08–2.28)
IL-13	1.02	0.98	0.87	0.89	0.9	0.86	1.13	1.12
Mother	(0.67–1.55)	(0.62–1.53)	(0.63–1.22)	(0.62–1.26)	(0.67–1.2)	(0.64–1.16)	(0.64–2.01)	(0.61–2.07)
Child	0.97	0.97	1.16	1.21	1.06	1.11	1.08	1.01
	(0.54–1.74)	(0.54–1.76)	(0.75–1.8)	(0.78–1.89)	(0.7–1.59)	(0.74–1.67)	(0.48–2.42)	(0.45–2.29)
IFN-γ	1.25	1.28	0.99	0.99	0.84	0.74	0.93	0.9
Mother	(0.75–2.07)	(0.76–2.16)	(0.67–1.44)	(0.66–1.47)	(0.59–1.2)	(0.52–1.06)	(0.47–1.84)	(0.44–1.85)
Child	0.98	0.89	0.73	0.69	0.86	0.9	0.78	0.65
	(0.57–1.69)	(0.51–1.55)	(0.48–1.1)	(0.45–1.05)	(0.59–1.25)	(0.62–1.3)	(0.37–1.65)	(0.3–1.38)
IgE	0.83	0.92	0.98	0.97	0.7	0.77	1.11	1.39
Mother	(0.37–1.88)	(0.39–2.16)	(0.51–1.88)	(0.5–1.89)	(0.4–1.25)	(0.43–1.37)	(0.36–3.41)	(0.43–4.52)
Child [kU/l]	0.81	1.1	1.07	1.17	0.95	0.96	2.28	2.28
	(0.4–1.63)	(0.53–2.25)	(0.62–1.82)	(0.68–2)	(0.59–1.54)	(0.59–1.55)	(0.87–5.97)	(0.87–5.93)

* P values <0.05, P values from the multiple linear regression model adjusted for gender, parental history of atopy, low birth weight, cat ownership, ETS exposure during pregnancy, parental education level, nationality (German vs. others) and mold exposure at home.

Table 7

Relationships between concentrations of Th1/Th2 cytokines in cord blood and IgE concentrations in children's blood at 1 year. Shown are raw and adjusted mean ratios with the 95% CI.

Cord blood cytokines	Inhalant allergens Sx1		Food allergens Fx5	
	Raw	Adjusted	Raw	Adjusted
IL-4	0.97 (0.88–1.07)	0.95 (0.86–1.05)	1.25* (1.04–1.51)	1.21* (1–1.47)
IL-5	0.92 (0.79–1.06)	0.9 (0.77–1.04)	1.3 (0.98–1.73)	1.29 (0.96–1.72)
IL-13	1.05 (0.98–1.13)	1.04 (0.97–1.12)	1.17* (1.02–1.35)	1.16* (1–1.33)
IFN- γ	0.99 (0.92–1.06)	0.98 (0.91–1.05)	1.02 (0.88–1.18)	1 (0.87–1.16)

* P values < 0.05, P values from the multiple linear regression model adjusted for gender, parental history of atopy, low birth weight, cat ownership, ETS exposure during pregnancy, parental education level, nationality (German vs. others) and mold exposure at home.

their children (Dietert and Zelikoff, 2008; Herberth et al., 2006; Keil et al., 2009). The mechanism by which maternal exposure during pregnancy might modulate the fetal immune response is poorly understood. According to our data it is obvious that the same exposure induced a Th2 shift only in the fetal immune system. However, the exact causal agents and the exposure mechanisms warrant further investigation.

We further questioned the consequence of a Th2 directed neonatal immune status. Early programming of T cell reactivity towards Th2 (IL-4, -5, 13 producing cells) is considered to increase allergic responsiveness, while programming toward Th1 reactivity (IFN- γ , TNF- α producing cells) is considered to protect against allergic responsiveness (Herberth et al., 2010). In the present study, we demonstrated that children with elevated IL-4, IL-5 and IL-13 concentrations in cord blood were sensitized to food allergens at the age of one whereas children with low IFN- γ concentrations were sensitized to inhalant allergens. Although by now we did not find a relation of these cytokines to allergic diseases at the age of one (data not shown), the association to allergic sensitization might represent the first step toward the development of allergic manifestations later in life.

Of all parents in this study, 78% had performed at least one of the three renovation activities and 16.4% carried out all three activities (painting, floor covering and new furniture) during pregnancy. The frequency of prenatal renovation activities observed in this study is comparable to other studies (Herberth et al., 2006; Lehmann et al., 2001, 2002b). Thus, a large number of children are potentially affected by an antenatal exposure to emitted chemicals from renovation materials. The results from this study suggest that painting seems to have no influence on T cell priming and IgE generation, whereas furnishing and floor covering have to be considered as potentially activities of risk in pregnancy in terms of allergy development. Regarding the used products, flake board and wall-to-wall carpets as well as of polyvinylchloride (PVC) flooring have to be considered in detail. At least for PVC products a role in the development of asthma and allergies has been reported (Jaakkola and Knight, 2008). Particularly plasticizers like phthalates are emitted from PVC materials into air and have become ubiquitous environmental contaminants (Wormuth et al., 2006). Furthermore, it has been demonstrated that high levels of phthalates from PVC products can modulate the murine immune response to an allergen (Dearman et al., 2009). Our results regarding PVC flooring may support these data indicating a Th2 skewed immune response and increased IgE levels in exposed children.

The strength of our study is that for the first time we had the opportunity to analyze immune responses of mother–child pairs around birth having the same environmental exposures. The

renovation activities were evaluated in a setting of a large birth cohort with the assessment of immune markers. Thus, the study gives a possible explanation for the immunological background of allergic manifestations after exposure to redecoration materials. Since immune dysregulation in childhood may have an impact on disease development later in life it is of great interest to identify influencing factors. However, our study has also some limitations. The number of exposed children for certain types of floor covering was low, thus the obtained results have to be carefully interpreted. A weakness of the LINA study in general is the potential bias by high rates of participating atopic parents (66.8%). Obviously, since LINA is focussed on allergic diseases, the interest in taking part in this study was higher in pregnant woman with an own atopy history or having a partner with history of atopy. We have considered this point by always including the parental atopy history as confounding variable in the regression models. A further weakness might be the strong focus on renovation activities without including all the other possible relevant exposures.

This study shows for the first time, that under comparable exposure situations the fetal immune system is more susceptible to the influence of environmental exposure, in particular renovation products, compared to the maternal. Furthermore, we were able to specify the type of renovation (floor covering, new furniture) and the used products (flake board, wall-to-wall carpets, polyvinylchloride (PVC) flooring) regarding their adverse impact on T cell development during the prenatal period. Since an impaired T cell response at the time of birth was shown to increase the risk for later allergy development, the here identified activities and products should be avoided during pregnancy.

Conflict of interest statement

The authors declare that they have no conflict of interest.

Acknowledgments

We thank all families for their participation in the LINA study and Anne Hain for excellent technical assistance. The study was supported by Helmholtz institutional funding.

References

- Billionnet, C., Gay, E., Kirchner, S., Leynaert, B., nnesi-Maesano, I., 2011. Quantitative assessments of indoor air pollution and respiratory health in a population-based sample of French dwellings. *Environ. Res.* 111, 425–434.
- Bornehag, C.G., Sundell, J., Weschler, C.J., Sigsgaard, T., Lundgren, B., Hasselgren, M., et al., 2004. The association between asthma and allergic symptoms in children and phthalates in house dust: a nested case–control study. *Environ. Health Perspect.* 112, 1393–1397.
- Dearman, R.J., Betts, C.J., Beresford, L., Bailey, L., Caddick, H.T., Kimber, I., 2009. Butyl benzyl phthalate: effects on immune responses to ovalbumin in mice. *J. Appl. Toxicol.* 29, 118–125.
- Devereux, G., Barker, R.N., Seaton, A., 2002. Antenatal determinants of neonatal immune responses to allergens. *Clin. Exp. Allergy* 32, 43–50.
- Dietert, R.R., Zelikoff, J.T., 2008. Early-life environment, developmental immunotoxicology, and the risk of pediatric allergic disease including asthma. *Birth Defects Res. B Dev. Reprod. Toxicol.* 83, 547–560.
- Ege, M.J., Bieli, C., Frei, R., van Strien, R.T., Riedler, J., Ublagger, E., et al., 2006. Prenatal farm exposure is related to the expression of receptors of the innate immunity and to atopic sensitization in school-age children. *J. Allergy Clin. Immunol.* 117, 817–823.
- Halonen, M., Lohman, I.C., Stern, D.A., Spangenberg, A., Anderson, D., Mobley, S., et al., 2009. Th1/Th2 patterns and balance in cytokine production in the parents and infants of a large birth cohort. *J. Immunol.* 182, 3285–3293.
- Herberth, O., Fritz, G.J., Rehagen, M., Richter, M., Roder, S., Schlink, U., 2006. Association between indoor renovation activities and eczema in early childhood. *Int. J. Hyg. Environ. Health* 209, 241–247.
- Herberth, G., Heinrich, J., Roder, S., Figl, A., Weiss, M., Diez, U., et al., 2010. Reduced IFN- γ and enhanced IL-4-producing CD4+ cord blood T cells are associated with a higher risk for atopic dermatitis during the first 2 yr of life. *Pediatr. Allergy Immunol.* 21, 5–13.

- Herberth, G., Hinz, D., Roder, S., Schlink, U., Sack, U., Diez, U., et al., 2011. Maternal immune status in pregnancy is related to offspring's immune responses and atopy risk. *Allergy* 66, 1065–1074.
- Jaakkola, J.J., Knight, T.L., 2008. The role of exposure to phthalates from polyvinyl chloride products in the development of asthma and allergies: a systematic review and meta-analysis. *Environ. Health Perspect.* 116, 845–853.
- Jang, A.S., Choi, I.S., Koh, Y.I., Park, C.S., 2007. Volatile organic compounds contribute to airway hyperresponsiveness. *Korean J. Intern. Med.* 22, 8–12.
- Jensen, L.K., Larsen, A., Molhave, L., Hansen, M.K., Knudsen, B., 2001. Health evaluation of volatile organic compound (VOC) emissions from wood and wood-based materials. *Arch. Environ. Health* 56, 419–432.
- Joerink, M., Oortveld, M.A., Stenius, F., Rindsjo, E., Alm, J., Scheynius, A., 2010. Lifestyle and parental allergen sensitization are reflected in the intrauterine environment at gene expression level. *Allergy* 65, 1282–1289.
- Keil, T., Lau, S., Roll, S., Gruber, C., Nickel, R., Niggemann, B., et al., 2009. Maternal smoking increases risk of allergic sensitization and wheezing only in children with allergic predisposition: longitudinal analysis from birth to 10 years. *Allergy* 64, 445–451.
- Kollmann, T.R., Crabtree, J., Rein-Weston, A., Blimkie, D., Thommai, F., Wang, X.Y., et al., 2009. Neonatal innate TLR-mediated responses are distinct from those of adults. *J. Immunol.* 183, 7150–7160.
- Lehmann, I., Rehwagen, M., Diez, U., Seiffart, A., Rolle-Kampczyk, U., Richter, M., et al., 2001. Enhanced in vivo IgE production and T cell polarization toward the type 2 phenotype in association with indoor exposure to VOC: results of the LARS study. *Int. J. Hyg. Environ. Health* 204, 211–221.
- Lehmann, I., Thoeleke, A., Rehwagen, M., Rolle-Kampczyk, U., Schlink, U., Schulz, R., et al., 2002a. The influence of maternal exposure to volatile organic compounds on the cytokine secretion profile of neonatal T cells. *Environ. Toxicol.* 17, 203–210.
- Lehmann, I., Thoeleke, A., Weiss, M., Schlink, U., Schulz, R., Diez, U., et al., 2002b. T cell reactivity in neonates from an East and a West German city—results of the LISA study. *Allergy* 57, 129–136.
- Macaubas, C., Prescott, S.L., Venaille, T.J., Holt, B.J., Smallacombe, T.B., Sly, P.D., et al., 2000. Primary sensitization to inhalant allergens. *Pediatr. Allergy Immunol.* 11 (Suppl. 13), 9–11.
- Mendell, M.J., 2007. Indoor residential chemical emissions as risk factors for respiratory and allergic effects in children: a review. *Indoor Air* 17, 259–277.
- Noakes, P.S., Hale, J., Thomas, R., Lane, C., Devadason, S.G., Prescott, S.L., 2006. Maternal smoking is associated with impaired neonatal toll-like-receptor-mediated immune responses. *Eur. Respir. J.* 28, 721–729.
- Perneger, T.V., 1998. What's wrong with Bonferroni adjustments. *BMJ* 316, 1236–1238.
- Prescott, S.L., 2008. Effects of early cigarette smoke exposure on early immune development and respiratory disease. *Paediatr. Respir. Rev.* 9, 3–9.
- Prescott, S.L., Macaubas, C., Holt, B.J., Smallacombe, T.B., Loh, R., Sly, P.D., et al., 1998. Transplacental priming of the human immune system to environmental allergens: universal skewing of initial T cell responses toward the Th2 cytokine profile. *J. Immunol.* 160, 4730–4737.
- Roduit, C., Wohlgensinger, J., Frei, R., Bitter, S., Bieli, C., Loeliger, S., et al., 2011. Prenatal animal contact and gene expression of innate immunity receptors at birth are associated with atopic dermatitis. *J. Allergy Clin. Immunol.* 127, 179–185.
- Rumchev, K., Spickett, J., Bulsara, M., Phillips, M., Stick, S., 2004. Association of domestic exposure to volatile organic compounds with asthma in young children. *Thorax* 59, 746–751.
- Schaub, B., Liu, J., Hoppler, S., Schleich, I., Huehn, J., Olek, S., et al., 2009. Maternal farm exposure modulates neonatal immune mechanisms through regulatory T cells. *J. Allergy Clin. Immunol.* 123, 774–782.
- Schaub, B., Liu, J., Schleich, I., Hoppler, S., Sattler, C., von, M.E., 2008. Impairment of T helper and T regulatory cell responses at birth. *Allergy* 63, 1438–1447.
- Wen, H.J., Chen, P.C., Chiang, T.L., Lin, S.J., Chuang, Y.L., Guo, Y.L., 2009. Predicting risk for early infantile atopic dermatitis by hereditary and environmental factors. *Br. J. Dermatol.* 161, 1166–1172.
- Wilke, O., Jann, O., Brodner, D., 2004. VOC- and SVOC-emissions from adhesives, floor coverings and complete floor structures. *Indoor Air* 14 (Suppl. 8), 98–107.
- Wormuth, M., Scheringer, M., Vollenweider, M., Hungerbuehler, K., 2006. What are the sources of exposure to eight frequently used phthalic acid esters in Europeans? *Risk Anal.* 26, 803–824.