

Increase of inflammatory markers after indoor renovation activities: The LISA birth cohort study

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There is concern about indoor air quality as a possible cause for health impairment. Exposure to indoor renovation activities has been shown to be associated with airway symptoms and allergic manifestations in children. The aim of this study is to analyse immune markers responsible for disease development in relation to renovation activities. Within the LISApplus (Life style Immune System Allergy) birth cohort study, blood samples of 6-yr-old children were analysed for concentration of the inflammatory markers interleukin (IL)-8, IL-6, tumour necrosis factor- α , MCP-1 and IL-10. Data on indoor renovation activities (painting, flooring, new furniture) were assessed with a questionnaire filled in by the parents. Data on cytokine blood concentrations and exposure variables were available for 250 children. Increased levels of IL-8 and MCP-1 in children's blood were related to renovation activities. In particular, new floor covering was associated with increased inflammatory markers. Among floor covering materials only wall-to-wall carpets were associated with elevated IL-8 and Monocyte Chemoattractant Protein-1 (MCP-1) levels. No association between the single renovation activities painting and furnishing and blood concentration of inflammatory markers has been found. Our data shows that IL-8 and MCP-1 may be suitable markers for monitoring inflammatory reactions in relation with renovation activities. Among renovation activities floor covering seems to induce the strongest inflammatory reactions.

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In developed countries, people spend more than 90% of time indoors. Thus, indoor air quality is of particular relevance for human health. There is concern about the contribution of indoor air pollutants to the risk for the development of inflammatory airway diseases (1), wheezing and (2) allergic manifestations and sensitization (3–7). In this context, it has been demonstrated that chemical pollutants are emitted from building materials after indoor redecoration activities

like painting, flooring and acquisition of new furniture (8–10). In earlier studies, an increase in ocular or upper airway symptoms (11), bronchial hyperresponsiveness (12) and mucosal symptoms (13) was found in recently painted buildings. It is discussed that volatile or semi-volatile organic compounds (VOC or SVOC) that are released in redecorated buildings or apartments may cause inflammatory reactions in the mucosal membranes in the airways which subsequent can lead

to respiratory symptoms. Indeed, enhanced levels of inflammation markers have been detected in nasal lavage in relation to renovation activities. Increased concentrations of eosinophilic cationic protein and lysozyme in the nasal lavage were found in people moved to newly redecorated buildings (1).

The occurrence of allergic disorders and sensitizations in association with renovation activities also refer to additional systemic effects of indoor chemical pollutants. However, only few studies attributed attention to this systemic inflammatory reaction so far. In subjects living in newly painted dwellings enhanced blood eosinophil counts were reported (12). Furthermore, an influence of indoor VOC exposure on T-cell differentiation has been described. T-cell polarization towards the Th2 phenotype in association with VOC exposure has been demonstrated in atopy risk children (6) as well as in newborn children (9). Especially for asthma and wheezing but also in the case of some allergic disorders the inflammatory cytokines/chemokines interleukin (IL)-8 (14), IL-6 (15), tumour necrosis factor (TNF)- α (16), MCP-1 (17) and IL-10 (18, 19) play an important role and might be predictors for disease development. While VOCs have been reported to be associated with adverse respiratory effects (20) and may increase the risk of childhood asthma (21). In the present study, we investigated whether a systemic inflammatory response after renovation activities can be characterized by the analysis of inflammatory cytokines/chemokines in the peripheral blood with the final aim to identify markers of exposure to renovation induced alterations in indoor air.

Methods

Study design and subjects

The Life style Immune System Allergy study (LISA) was designed to investigate the influence of life style and environmental factors on the maturation of the immune system and the allergy risk in early childhood. Only healthy full-term neonates of German descent were included and newborn children whose mothers suffered from autoimmune disease or infectious disorders during pregnancy were excluded. The design of LISA has been described in detail elsewhere (22). Nine hundred and seventy-six neonates born in Leipzig, Germany were recruited between December 1997 and January 1999 as subpopulation of the prospective cohort study. The present investigation refers to data from the 6th yr of life of these children. At the age of 6, 565 cohort

subjects participated in the study and parents answered a questionnaire on health outcomes, life-style factors and the home environment. For 324 of these children parents gave approbation for blood collection.

Participation in the study was voluntary and informed consent was obtained from the parents of all children. This study was approved by the Ethics Committees of the University of Leipzig.

Blood sampling

Heparinized blood (7 ml) was obtained by venipuncture and prepared within 4 h to further analysis. For cytokine measurement heparinized blood was diluted 1:1 with RPMI1640 medium without supplements and centrifuged at 800 *g* for 5 min at 4°C. Collected cell-free supernatants were stored at -80°C until analysis.

Measurement of inflammatory markers

Concentrations of the inflammatory cytokines/chemokines IL-8, IL-6, IL-10, TNF- α and MCP-1 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 labelled detection antibodies for 2 h. After one washing step samples were measured by flow cytometry. Analysis of data and quantification of cytokines was performed using the FCAP Array™ software (Becton Dickinson) on the basis of corresponding standard curves. Finally, plasma dilution factor was accounted. Detection limits were 3 pg/ml for all cytokines.

Assessment of renovation activities

A questionnaire was sent to the parents at the beginning of the month of the child's 6th birthday. Data from completed questionnaires comprised information on symptoms and diseases of the child, smoking behaviour of the parents, housing conditions, pets keeping, traffic burden and renovation activities. Indoor exposure was assessed based on questionnaire information focusing on type of home renovation ('Did you paint your apartment during the last year?' 'Did you perform a new floor covering in your apartment during the last year?', If yes:

'Which kind of material did you use: parquet, laminate, wall-to-wall carpets or others', 'Did you furnished your apartment during the last year?' If yes: 'Which kind of furniture: wooden, flake board, others').

Statistical analysis

We performed descriptive statistics and tested the relation between renovation activities and cytokine concentrations in children's blood. Chi-square test was used to test the relationship between the analysed subcohort and the remaining children of the LISA cohort from the city of Leipzig. The nonparametric Mann-Whitney *U*-test was applied for the crude analysis of relation between renovation activities and cytokine concentrations that were not normally distributed. The *p*-values from the *U*-test below 0.05 were considered as statistically significant. 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, presence of siblings, cat ownership, smoking in the dwelling and socio economic status assessed as parental education. Cytokine concentrations below the limit of detection were assigned a value of one half of the detection limit and entered calculation. Statistical analysis was performed with STATISTICA for Windows Version 7.0 (Statsoft Inc.), Statsoft (Europe), Hamburg, Germany.

Results

Subjects

Out of the 731 questionnaires that were sent to the LISApplus study participants from the city of Leipzig a total of 565 questionnaires (response rate 77.3%) were returned. For 324 of these children parents agreed with blood collection. Cytokine analyses were performed from 321 of these children. A number of 250 children fulfilled the criteria to have a complete data set including questionnaire data on renovation activities, all confounder variables, and additional cytokine measurements, thus only data from these children are shown.

Basic characteristics of the subset of the study population are given in Table 1. The parental history of atopy was 42.4% (single or double). About three-quarter (77.2%) of the children had one or more siblings, 43.2% of homes had a pet

Table 1. Characteristics of analysed subcohort (n = 250) and remaining children of overall LISA cohort from Leipzig (due to missing information for some characteristics, number of subjects varies between 304 and 315)

Variables	Analysed subcohort n (%) N = 250	Remaining subjects of LISA cohort n (%) N = 315	p-value
Gender			
Male	125 (50)	146 (46.3)	0.64
Female	125 (50)	166 (52.7)	
Parental history of atopy			
None	144 (57.6)	177 (56.2)	0.68
Single positive	78 (31.2)	112 (35.5)	
Double positive	28 (11.2)	26 (8.2)	
Social economic status			
Low	115 (46)	153 (48.6)	0.19
Middle	132 (52.8)	135 (43)	
High	3 (1.2)	16 (5.1)	
Presence of siblings			
None	57 (22.8)	75 (23.8)	0.14
One	156 (62.4)	154 (48.9)	
Two	32 (12.8)	56 (17.8)	
Three or more	5 (2)	23 (7.3)	
Pet			
None	142 (56.8)	164 (52)	0.89
Cats	28 (11.2)	48 (15.2)	
Guinea pigs	29 (11.6)	35 (11.1)	
Rabbits	20 (8)	31 (9.8)	
Others	31 (12.4)	34 (10.8)	
Smoking in the dwelling			
Never	199 (79.6)	235 (74.6)	0.84
Daily	28 (11.2)	39 (12.4)	
Once per week	2 (0.8)	6 (1.9)	
Occasionally	21 (8.4)	32 (10.1)	

and about 20% of parents declared smoking in the dwelling. Regarding to this covariates there was no difference between the analysed subcohort (n = 250) and the remaining children from the LISA cohort from Leipzig (n = 315).

Indoor renovation activities

Reported indoor renovation activities during the last 12 months were mostly painting (n = 107; 42.8%) and new furnishing (n = 96; 38.4%) of the dwellings whereas floor covering was less frequent (n = 46; 18.4%). A total of 40.4% of the study participants (n = 101) were not affected by renovation activities. In the majority of cases more than one renovation activity was performed during the 6th yr of children's life. Occurrence of painting alone was only in 31 families (12.4%) and single new furnishing occurred in 41 households (16.4%). New floor covering was performed only in association with painting and/or new furnishing (Table 2). The type of floor covering material mostly used was wall-to-wall carpet (11.2%). Approximately, 8% of the households parquet or laminate were laid and in 6% other, not further specified materials, were used (Table 3).

Table 2. Frequency of single and combined redecoration activities during the last 12 months before blood analysis

Variables	Frequency n/N (%)
No redecoration	101/250 (40.4)
Single activities	
Painting only	31/250 (12.4)
Floor covering only	0/250 (0)
New furniture only	41/250 (16.4)
Combined activities	
Painting and new furniture	31/250 (12.4)
Painting and/or new furniture and floor covering	46/250 (18.4)

Table 3. Frequency of redecoration activities during the last 12 months before blood analysis

Variables	Frequency n/N (%)
Type of floor covering	
Parquet	5/250 (2)
Laminate	14/250 (5.6)
Wall-to-wall carpet	28/248 (11.2)
Others	15/250 (6)
Type of new furniture	
Wooden	56/249 (20.4)
Flake board	51/249 (20.4)
Others	13/248 (5.2)

Inflammatory markers and renovation activities

Relation between inflammatory markers in blood samples and renovation activities are shown in Table 4. Children, whose parents reported about floor covering in combination with painting and/or new furnishing in the dwelling, had significantly higher blood concentrations of IL-8, IL-6 and TNF- α , and a borderline significance for MCP-1. After adjustment for further possible influences of gender, parental history of atopy, presence of siblings, cat keeping and passive smoking the association between renovation activities and IL-8 (MR 1.44; 95% CI: 1.01–

2.05) and MCP-1 (MR 1.27; 95% CI: 1.00–1.63) remained significant (Fig. 1). Single painting or furnishing had no relation to cytokine concentrations although significant enhanced TNF- α levels in correlation with painting were observed within the crude data analyses.

In addition to the kind of renovation activities we asked for materials used for floor covering and furnishing. Among floor covering materials only new wall-to-wall carpets revealed significant associations to the appearance of inflammatory signals in the blood of the children. Elevated IL-8, IL-6, TNF- α and MCP-1 levels were observed in blood samples of children living in flats with new wall-to-wall carpets (Table 5). After adjustment to the possible confounders again only the association between new wall-to-wall carpets and IL-8 (MR 1.59; 95% CI: 1.03–2.93) or MCP-1 (MR 1.41; 95% CI: 1.05–1.89), respectively, remained significant (Fig. 2).

Regarding to furnishing materials neither crude nor adjusted, associations with renovation activities has been found (data not shown).

Discussion

Indoor air is a dominant exposure for humans. More than half of the body's intake during a lifetime is air inhaled in the home (23). Thus, most illnesses related to the environmental exposures stem from indoor air exposure. An improved understanding of the contribution made by indoor microenvironmental exposures to disease burden in children is essential for the characterization of health risk factors and will give a scientific basis for the development of prevention strategies.

After renovation activities, the indoor environment reveals increased concentrations of certain substances like VOCs. These organic chemicals are evaporated into the atmosphere

Table 4. Relationships between renovation activities and concentrations (pg/ml) of inflammatory markers (crude data) in blood samples from 6-yr-old children (n = 250)

	Single activities					Combined activities			
	None		p-value	Furniture		Painting and furniture		Painting and/or furniture and floor covering	
	n = 101	n = 31		n = 41	p-value	n = 31	p-value	n = 46	p-value
IL-8	42.2 (23.1–90.4)	51.1 (26.0–112.4)	0.252	43.0 (30.1–79.9)	0.763	49.3 (31.5–90.4)	0.388	67.7 (37.6–137.7)	0.009
IL-6	6.2 (4.1–10.2)	8.7 (4.8–13.4)	0.114	6.7 (5.1–8.7)	0.850	6.9 (5.1–12.8)	0.266	9.5 (5.8–13.8)	0.011
TNF- α	5.8 (4.5–8.8)	8.7 (5.2–14.3)	0.043	5.6 (4.5–8.9)	0.541	7.7 (5.2–11.2)	0.069	6.5 (4.9–12.3)	0.035
MCP-1	84.5 (64.4–118.7)	110.5 (61.0–146.4)	0.194	82.1 (62.3–111.5)	0.822	87.7 (51.5–119.4)	0.640	108.9 (74.4–140.1)	0.058
IL-10	1.5 (1.5–3.0)	1.5 (1.5–3.0)	0.931	1.5 (1.5–3.1)	0.957	1.5 (1.5–2.9)	0.282	2.5 (1.5–3.2)	0.079

The values shown are medians and the 25th–75th percentiles. p-values from the Mann–Whitney *U*-test compared to the group without renovation activities. Limit of detection: 3 pg/ml for all cytokines.

Fig. 1. Relation between renovation activities and cytokine concentrations in blood samples of 6-yr-old children. Data are presented as means ratios (MR) and 95% confidence intervals adjusted for gender, parental history of atopy, presence of siblings, cat ownership, smoking in the dwelling and socio economic status for IL-8, IL-6, TNF- α , MCP-1 and IL-10.

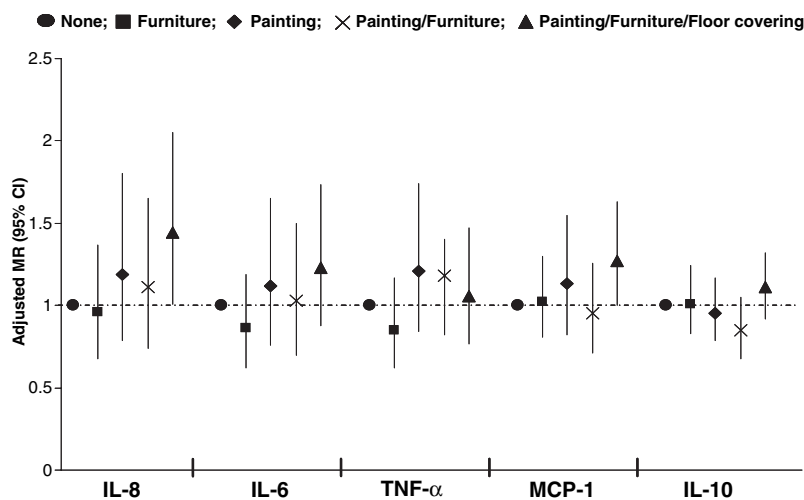
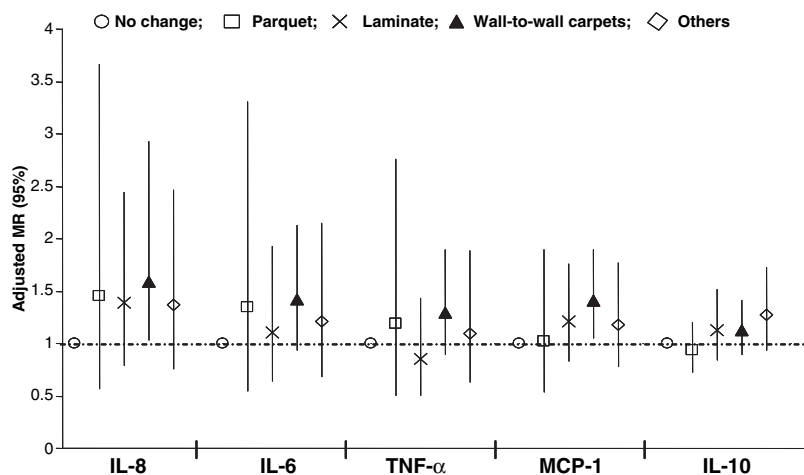


Table 5. Relationships between renovation activities and concentrations (pg/ml) of inflammatory markers in blood samples from 6-yr-old children (n = 250)

	Type of floor covering									
	No change		Parquet		Laminate		Wall-to-wall carpet		Others	
	n = 101		n = 5	p-value	n = 14	p-value	n = 28	p-value	n = 15	p-value
IL-8	42.2 (23.1–90.4)		70.3 (65.2–137.7)	0.079	69.3 (36.5–126)	0.114	79.1 (42.6–152.1)	0.013	74.9 (45.4–135.4)	0.060
IL-6	6.2 (4.1–10.2)		10.6 (9.5–10.9)	0.036	8.4 (5.4–10.8)	0.239	9.6 (5.9–15.5)	0.005	9.5 (5.6–13.8)	0.130
TNF-α	5.8 (4.5–8.8)		8.7 (5.2–14.3)	0.478	6.3 (3.1–8.2)	0.894	7.6 (5.6–12.3)	0.042	6.4 (4.0–13.1)	0.627
MCP-1	84.5 (64.4–118.7)		110.5 (61.0–146.4)	0.556	111.5 (82.2–150.2)	0.109	111.5 (81.7–143.2)	0.020	107.3 (67.7–157.6)	0.323
IL-10	1.5 (1.5–3.0)		1.5 (1.5–2.4)	0.731	2.8 (1.5–3.5)	0.092	2.5 (1.5–3.4)	0.056	2.7 (2.2–3.0)	0.087

Values shown are medians and the 25th–75th percentiles. p-values from the Mann-Whitney *U*-test compared to the group without renovation activities. Limit of detection: 3 pg/ml for all cytokines.

Fig. 2. Relation between type of floor covering materials and cytokine concentrations in blood samples of 6-yr-old children. Data are presented as means ratios (MR) and 95% confidence intervals adjusted for gender, parental history of atopy, presence of siblings, cat ownership, smoking in the dwelling and socioeconomic status for IL-8, IL-6, TNF- α , MCP-1 and IL-10.



at room temperature (24) and may occur indoors at health relevant concentrations over a period of time. For example, in a Swedish study increased indoor concentrations of aliphatic compounds (C₈–C₁₁) were observed in newly painted dwellings (12). Comparable results were found in the Leipzig Allergy Risk Children Study (LARS) study performed from 1995 to 1996 in Germany.

In contrast to painting, which is mostly related with the emission of aliphatic compounds, floor covering may lead to the additional release of aromatic compounds (3).

It is discussed that the volatile or VOC or SVOC that are released in redecorated buildings or apartments may cause inflammatory reactions in the airway mucosal membranes which

subsequently lead to respiratory symptoms. The appearance of inflammation markers in nasal lavage in relation to renovation activities confirm the development of local inflammatory reactions in the mucosal membranes of the airways (1). But obviously the inflammatory response is not restricted to the mucosal membranes of the respiratory tract. First evidence for that was given by the detection of higher blood eosinophil counts among subjects living in newly painted dwellings (12). Our results may also confirm the occurrence of systemic effects in children exposed to renovation activities. Elevated concentrations of the inflammatory chemokines IL-8 and MCP-1 were found in blood samples of children whose parents reported about floor covering in combination with painting and/or new furnishing during the last 12 months prior to blood analysis. Since painting and new furnishing alone did not affect the analysed inflammatory markers, we conclude that floor covering was responsible for the increased chemokine levels in the blood of the exposed children. Unfortunately, this can not be further verified since floor covering alone has not been performed.

Before adjustment for further possible confounders also IL-6 and TNF- α showed a significant correlation to floor covering in combination with other renovation activities. Within the same cohort, we observed that exposure to environmental tobacco smoke is also related with the appearance of enhanced concentrations of inflammatory markers (IL-6, IL-8, MCP-1 and TNF- α) in the blood of the affected children (unpublished data). We suggest that while passive smoking induces also IL-6 and TNF- α the effect of a renovation activity (in particular floor covering) is more restricted to IL-8 and MCP-1.

MCP-1 is a chemokine which plays an important role in inflammatory disorders of the lung (17). There are a number of reported mechanisms to which MCP-1 might modulate the development of allergic airway diseases, including induction of histamine and leukotriene release, increase in Th2 polarisation, and mediation of localization of effector cells to the airways or other lung compartments (17). Thus, an induction of MCP-1 release after new floor covering could indeed contribute to the development of associated airway diseases. We assume that the release of MCP-1 might be induced by solvents emitted from adhesives used in floor covering. For example, adhered wall-to-wall carpets were found to be associated with elevated styrene concentrations in indoor air (3). Styrene and other aromatic hydrocarbons (toluene, xylene) are often used as organic solvents. Within an

experimental study, we exposed human lung epithelial cells with aromatic hydrocarbons and have shown that styrene, chlorobenzene and xylene induce the release of MCP-1 and IL-8 from lung epithelial cells (25).

Regarding to particular floor covering materials in our present study only in association to wall-to-wall carpeting enhanced blood levels of IL-8 and MCP-1 were found. Emissions from wall-to-wall carpeting might mainly result from the used adhesives (26). In addition to primary released VOCs, the formation of secondary emissions from wall-to-wall carpets (aldehydes and organic acids) was observed starting 1 month after floor covering (10). Concluding from this, wall-to-wall carpeting may have additional long lasting effects on mucosal respiratory cells and may induce the observed systemic inflammatory effect on immune cells. New parquet and laminate seem not to provoke an inflammatory response in exposed children. If one assume that parquet and laminate are solvent-free low-emission materials and are laid without adhesives this result may confirm the above-mentioned arguments.

The occurrences of enhanced IL-8 and MCP-1 levels in association with wall-to-wall carpeting may support the suggestion, that floor covering and in particular wall-to-wall carpeting is among the renovation activities, the most important factor with an effect on inflammatory markers. Again, due to overlapping renovation measures, we were not able to distinguish between wall-to-wall-carpeting alone and further renovation activities (painting, new furnishing). Despite the fact, that wall-to-wall carpeting cannot be separated from other kinds of activities, it nevertheless, shows a strong correlation to IL-8 and MCP-1 blood levels. This result may give further evidence that painting and new furnishing are less important in terms of the induction of inflammatory parameters.

High levels of IL-8, IL-6 and MCP-1 have been found in the bronchoalveolar lavage (BAL) fluid of subjects with allergic asthma (16, 27). Moreover, enhanced concentrations of these inflammatory markers were found not only in the BAL fluid but also in the serum of asthmatic patients. Here, IL-8 and TNF- α are discussed to be markers of 'systemic' inflammation in severe asthmatics, in conjunction with augmented circulating neutrophils, suggesting the involvement of neutrophil-derived cytokine pattern in severe asthma (14). Concluding from these findings, it is assumable that the induction of IL-8 and MCP-1 after renovation activities described here, can

contribute to the development of allergic asthma or other airway diseases.

Given that eczema, allergic symptoms and sensitizations also have been associated with renovation activities (5, 6), it implicates that not only inflammatory reactions but also T-cell differentiation may be affected by exposure to chemical indoor air contaminants. The primary induction of inflammatory reactions in the mucosal membranes by inhaled volatile chemicals could result in an additional recruitment of further immune cells to the sight of inflammation and among them also T cells. Locally released inflammatory mediators from different cell types at the sight of inflammation may enter the blood stream being systemically distributed in low but nevertheless detectable concentrations. On the other hand, VOCs released during redecoration work enter the body through the lungs and can be absorbed by the blood (28). Thus, these chemicals themselves or metabolites of them become also systemically distributed and thereby may have direct influences on immune cells outside mucosal membranes. However, so far all that is speculative and requires further clarification.

The strength of this study is that for the first time 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 respiratory manifestations after exposure to redecoration materials. While immunological dysregulation in childhood may have an impact on disease development, later in life it is of great interest to identify influencing factors. To our knowledge, our study demonstrates for the first time an association between renovation activities and systemic inflammatory alterations in children.

However, our study has some limitations. The number of exposed children for certain types of floor covering was very low ($n = 5$ for parquet). Unfortunately, the questionnaire did not comprise a detailed question on the type of painting or the type of carpets (synthetic vs. natural/wool). Thus, in future studies a more detailed investigation of the used renovation materials is advised.

Summarizing our results, we could show that renovation activities are associated with increased levels of inflammatory markers in the blood. As these cytokines are reported to be involved in the pathomechanism of bronchial hyper-reactivity, one can conclude that the chemicals released in indoor air through renovation activities may act via these cytokines. The

analysed inflammatory markers are IL-8 and MCP-1, therefore are suitable to characterize exposure related effects in affected people. Among renovation activities, floor-covering and in particular wall-to-wall carpets are related with the above described alterations in immune parameters. Especially for the redecoration of children's room, these findings should be considered.

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