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Early age exposure to moisture and mould is related to FeNO at the age of 6 years

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Abstract

Background: Exposure to indoor moisture damage and visible mold has been found to be associated with asthma and respiratory symptoms in several questionnaire-based studies by self-report. We aimed to define the prospective association between the early life exposure to residential moisture damage or mold and fractional exhaled nitric oxide (FeNO) and lung function parameters as objective markers for airway inflammation and asthma in 6-year-old children.

Methods: Home inspections were performed in children's homes when infants were on average 5 months old. At age 6 years, data on FeNO (n = 322) as well as lung function (n = 216) measurements were collected. Logistic regression and generalized additive models were used for statistical analyses.

Results: Early age major moisture damage and moisture damage or mold in the child's main living areas were significantly associated with increased FeNO levels (>75th percentile) at the age of 6 years (adjusted odds ratios, 95% confidence intervals, aOR (95%

Abbreviations: aOR, adjusted odds ratio; aβ, adjusted beta; CI, confidence interval; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity, FEV1/FVC ratio; PASTURE, Protection against Allergy Study in Rural Environments.

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CI): 3.10 (1.35-7.07) and 3.16 (1.43-6.98), respectively. Effects were more pronounced in those who did not change residential address throughout the study period. For lung function, major structural damage within the whole home was associated with reduced FEV1 and FVC, but not with FEV1/FVC. No association with lung function was observed with early moisture damage or mold in the child's main living areas.

Conclusion: These results underline the importance of prevention and remediation efforts of moisture and mold-damaged buildings in order to avoid harmful effects within the vulnerable phase of the infants and children's immunologic development.

KEYWORDS
asthma, cohort study, exhaled NO, lung function, moisture damage

1 | INTRODUCTION

The global prevalence of allergic diseases has continuously risen for more than half a century. Already now allergies and asthma are among the most common chronic diseases in many parts of world with 30% to 40% of population affected by at least by one or more allergic conditions.[1] Reduced lung function in early childhood is associated with asthma as well as persistent low lung function in young adulthood[2,3] but also with other pulmonary disorders such as chronic obstructive pulmonary disease (COPD) in later adulthood.[4] Environmental exposures in early infancy are particularly important for the development of regulatory mechanisms preventing inflammatory responses.[5]

A considerable proportion of children worldwide are exposed to a moldy and damp indoor home environment[6,7] and exposure to indoor moisture damage and visible mold has been found to be associated with asthma and respiratory symptoms in several studies.[8-12] It has been suggested that microbial components such as cell fragments or spores shed during fungal growth in moisture-damaged buildings may induce inflammatory responses.[13-18] In turn, a chronic inflammatory process within the respiratory tract is considered as a key factor in the pathogenesis of asthma.[19,20]

A major part of previous studies assessed asthma by self-reported questionnaires.[10,11] Literature is scarce and inconclusive on associations between exposure to moisture, mold, or mold-derived components with fractional exhaled nitric oxide (FeNO) or lung function as objective markers for airway inflammation or asthma.[17,21-27] The only longitudinal study in European birth cohorts looking at parental-reported early childhood dampness exposure did not observe any significant associations with FeNO at the age of 10 years.[21] Moreover, to our knowledge, no study has prospectively investigated associations of early age inspector-observed dampness or visible mold in relation to both FeNO and lung function in later childhood. Therefore, the aim of the current study was to evaluate whether inspector assessed exposure to moisture damage or mold in early infancy is prospectively associated with FeNO and lung function parameters (forced expiratory volume in 1 second [FEV1], forced vital capacity [FVC], and their ratio [FEV1/FVC]) as objective markers for airway inflammation and asthma in 6-year-old children.

Key Message

Early age major moisture damage with and without visible mould is associated with elevated FeNO at 6 years of age.

2 | MATERIAL AND METHODS

2.1 | Study population and study area

The study population of 322 children with information on FeNO and of 216 children with information on lung function parameter along with home inspection data consists of a general population-based birth cohort located in the Eastern parts of Finland.[28] Briefly, the first half of the original study population is the Finnish arm of the European birth cohort study PASTURE (Protection against Allergy Study in Rural Environments), recruited between 9/2002 and 5/2004 in rural areas (N = 214).[29] The second half of the study population was recruited between 5/2004 and 5/2005 in mainly sub-urban areas and is its extended cohort (N = 228).[28] The ethical permission of the study was granted by the Research Ethics Committee of the Hospital District of Northern Savo, Kuopio, Finland. The number for LUKAS is 299/2017 (33/2002) and for LUKAS2 is 300/2017 (48/2004). Written consents were acquired from the parents of the participating children.

2.2 | Questionnaires and Home inspection

General information about the study population was assessed during the third trimester of pregnancy. The exact methodology of the home inspection has been described earlier in detail.[8] In short, the homes were inspected by a civil engineer for the signs of moisture and mold in the surfaces and the structures without opening the

structures using a pre-designed checklist and surface moisture meter (Doser BS2; Doser Messtechnik GmbH & Co.) when the children were 5 months old on average. During the home visit, housing characteristics were assessed (Online supplement 1).

2.3 | Exposure assessment

A detailed description of the exposure assessment has been comprehensively depicted previously.[8,30] For the present analysis, we focused on *four* previously described[16] combined variables due to limited number of cases for the more detailed exposure classifications: (i) moisture damage in the child's main living areas (including living room, child's bedroom, and kitchen), (ii) moisture damage with mold in the child's main living areas, (iii) moisture damage or mold in the child's main living areas, and (iv) overall estimate for the need for repair scale in the whole house (Online supplement 1).

2.4 | Health outcome assessment

2.4.1 | FeNO

During the 6-year study visits [median age 6.1 years, Table 1], fractional exhaled nitric oxide (FeNO) as well as lung function measurements was performed, as described earlier.[17,31] Before spirometry, trained fieldworkers collected exhaled air with an offline kit (EcoMedics AG) in triplicate in Mylar-coated bags (Quinton) and measured FeNO levels within 12 hours by using a rapid-response chemiluminescence analyzer (CLD 88; EcoMedicsAG), according to current guidelines of the ERS and the American Thoracic Society (ATS).[32]

2.4.2 | Lung function

Trained fieldworkers performed spirometry with a mobile spirometer (EasyOne; ndd), according to current ERS/ATS standards,[33] before and after bronchodilator tests (400 mg of salbutamol). Outcomes were (i) forced expiratory pressure in 1 second (FEV1), (ii) forced vital capacity (FVC), and (iii) the FEV1/FVC ratio, in addition to forced expiratory flow between 25% and 75% of FVC. For the present analysis, we will concentrate on FEV1, FVC, and FEV1/FVC lung function parameters. Further, based on the reference equations for spirometry from the Global Lung Function Initiative (GLI, http://www.ers-education.org/guidelines/global-lung-function-initiative.aspx), we calculated standardized z-scores to allow international comparisons.[34]

2.4.3 | Immunoglobulin E (IgE) against inhalant allergens

Venous blood samples were further analyzed for specific immunoglobulin E (sIgE) to 19 common allergens, by using the Allergy Screen Test Panel for Atopy (Mediwiss Analytic).[35] For the determination of specific allergic sensitization, 13 inhalant allergens were included.[28] The cutoff level to define any atopic sensitization was 0.35 kU/L at the age of 6 years.

2.5 | Statistical analysis

Analyses were based on those children with complete data on home inspection at early age and measurements on FeNO (N = 292) and lung function (N = 198, pre- and post-acceptable tests after bronchodilation). As in our previous paper, FeNO levels were dichotomized into two classes: values below and above the 75th percentile (≥ 7.81 ppb).[17] With respect to lung function parameters, a positive bronchodilation response was defined as an increase of more than 12% and more than 200ml in FEV1 and/or FVC, measured after bronchodilation.[36]

Logistic regression models were applied for the association between early age exposures to moisture damage with and without mold in relation to FeNO. Generalized additive models were used in relation to the lung function parameters (FEV1, FVC, FEV1/FVC) in later childhood to take into account the non-linear association between age and height with lung function parameter.

The main regression models for FeNO were adjusted for the following a priori selected confounding factors based on earlier findings:[17] gender, living on a farm, study cohort, maternal smoking during pregnancy, maternal history of allergic diseases (hay fever, atopic eczema and/or asthma), older siblings, atopy against any inhalant allergens at 6 years of age, and child's recent nitrate consumption before FeNO testing (N = 292). Furthermore, we ran the model in a subset of children who never moved home throughout the study period (N = 152); without steroid use in the past 12 months (N = 277); without asthma medication use in the past 12 months (N = 251); and in the group with no doctor-diagnosed asthma or less than 2 attacks of doctor-diagnosed obstructive bronchitis until the age of 6 years (N = 240). Analyses were further stratified by atopy against inhalant allergens (IgE, cutoff 0.35 kU/L) at the age of 6 years. Moreover, the main models were further adjusted for current moisture damage exposure in child's main areas, ever physician-diagnosed asthma as well as other type of exposure including type of ventilation and renovation activities. For significant associations between moisture damage with or without mold exposure in relation to dichotomized FeNO at 6 years, linear models were additionally run with the log-transformed FeNO values (log base 10). The lung function models were adjusted as follows: sex, living on a farm, study cohort, age, height and weight at lung function measurement, maternal smoking during pregnancy, maternal education, breastfeeding, and parental allergy. The z-score models were adjusted for living on a farm, study cohort, weight, maternal smoking during pregnancy, maternal education, breastfeeding, and parental allergy. As the models did not converge for exposure to (ii) moisture damage with mold in the child's main living areas (no mold N = 203, only spots of mold N = 5, visible mold N = 8) in relation to lung function parameters,

TABLE 1 Study population and exposure characteristics based on available FeNO and lung function measurements

Population and exposure characteristics	FeNO, N = 322 n / N (%)	Lung function, N = 216 n / N (%)
FeNO min, max, median, IQR ppb	1.8, 30, 6.1, 3.3	2.5, 30, 6.0, 2.9
FEV1 (in milliliter, 1st second): median, IQR	1287, 0.28	1288, 0.27
FVC (in milliliter): median, IQR	1513, 0.32	1510, 0.31
FEV1/FVC% ratio	85.73%	86.02%
Sex (female)	161 / 322 (50%)	103 / 216 (48%)
Age at health measurement (y), median, IQR	6.1, 0.26	6.1, 0.25
Height at health measurement (meter), median, IQR	1.18, 0.06	1.18, 0.06
Weight at health measurement (kilogram), median, IQR	22.4, 4.5	22.5, 4.65
Finnish arm of the PASTURE cohort	168 / 322 (52%)	108 / 216 (50%)
Living on a farm	101 / 322 (31%)	66 / 216 (31%)
Breastfeeding[a]	235 / 307 (77%)	153 / 206 (74%)
Maternal smoking during pregnancy	45 / 322 (14%)	27 / 216 (13%)
Maternal allergy	172 / 321 (54%)	118 / 215 (55%)
Parental allergy	239 / 321 (74%)	166 / 216 (77%)
Maternal education		
Low	98 / 322 (30%)	65 / 216 (30%)
Middle	155 / 322 (48%)	96 / 216 (44%)
High	69 / 322 (21%)	55 / 216 (25%)
Older sibling(s) n / N (%)	217 / 322 (67%)	140 / 216 (65%)
Ever asthma (at the age of 6 y)	56 / 318 (18%)	40 / 214 (19%)
IgE at 6 y (cutoff 0.35 kU/L)	134 / 301 (45%)	92 / 202 (46%)
Recent nitrate consumption (measurements) (6 y)	53 / 313 (17%)	33 / 212 (16%)
Asthma medication use past 12 mo (6 y)	33 / 317 (10%)	26 /213 (12%)
Steroid use past 12 mo (6 y)	15 / 321 (5%)	10 / 215 (5%)
Day-care attendance (year 1)	55 / 315 (17%)	36 / 212 (17%)
Non-movers throughout study period	169 / 224 (75%)	113 / 142 (80%)
Participation in sport's club (6 y)	109 / 321 (34%)	81 / 215 (38%)
Time spent watching TV on weekdays (6 y)		
½-1 h	154 / 321 (48%)	107 / 215 (50%)
More than 1 h	167 / 321 (52%)	108 / 215 (50%)
Type of air conditioning (6 y)		
Natural ventilation	141 / 322 (44%)	94 / 216 (44%)
Mechanical exhaust kitchen/bathroom(s)	114 / 322 (35%)	70 / 216 (32%)
Air conditioning	76 / 322 (21%)	52 / 216 (24%)
CO_2 living room (measured, parts per million) (6 y)		
<700 ppm (good)	41 / 311 (13%)	29 / 211 (14%)
700-1200 ppm (moderate)	181 / 311 (58%)	124 / 211 (59%)
> 1200 ppm (bad)	89 / 311 (29%)	58 / 211 (27%)
Renovation activities		
No	72 / 322 (22%)	50 / 216 (23%)
Only surface materials	159 / 322 (49%)	101 / 216 (47%)
Surface materials and structural repairs	91 / 322 (28%)	65 / 216 (30%)
Exposure		
Moisture damage, CMLA[b]		

(Continues)

TABLE 1 (Continued)

Population and exposure characteristics	FeNO, N = 322 n / N (%)	Lung function, N = 216 n / N (%)
No damage	202 / 322 (63%)	142 / 216 (66%)
Minor damage	81 (25%)	51 (24%)
Major damage	39 (12%)	23 (11%)
Moisture damage with visible mold, CMLA		
No mold	299 / 322 (93%)	203 / 216 (94%)
Only spots of mold	10 (3%)	5 (2%)
Visible mold	13 (4%)	8 (4%)
Moisture damage or mold (combined)		
None	202 / 322 (63%)	142 / 216 (66%)
Minor[c]	77 (24%)	49 (23%)
Major[d]	43 (13%)	25 (12%)
Overall need for repair scale (whole house)		
None / aesthetic repair (class 0 or 1)	91 / 322 (28%)	63 / 216 (29%)
Repair of surface materials (class 2)	126 (39%)	86 (40%)
Repair of structural components (class 3/4)	105 (33%)	67 (31%)

[a]Breastfeeding "yes" = ≥5 mo of breastfeeding.

[b]CMLA: Child's main living areas.

[c]Minor means minor moisture damage with or without mold spots.

[d]Major means major moisture damage or any damage (minor/major) with visible mold growth.

this association won't be reported in the tables. All statistical analyses were performed using the statistical software R, version 4.0.0 (R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing. URL https://www.R-project.org/).

3 | RESULTS

3.1 | Study population characteristics

Characteristics of both study populations (N = 322 FeNO and N = 216 lung function) are shown in Table 1. Of 322 children with FeNO measurements, 210 had also pre- and post-bronchodilation accepted spirometry values (data not shown). Briefly, 31% of the children grew up on farm households and 14% (13% lung function study population) were exposed to maternal tobacco smoking during pregnancy. Over half of the mothers reported to be affected by an allergic disease and about two-thirds of the children had older siblings at birth. Until the age of 6 years, nearly half of the study subjects had any type of atopy against inhalant allergens (IgE, cutoff 0.35kU/L) and 18% (19%) were diagnosed with asthma. Early age moisture damage combined with information on the visible mold in the child's main living areas was classified as "minor" in 24% and "major" in 13% of the inspected homes (23% and 12%, respectively). With respect to the estimate of "overall need for repair scale" in the whole building, no or only aesthetic repair was indicated for 28% (29%) of the homes. Repair of surface materials and repair of structural components were needed to repair for 39% (40%) and 33% (31%) of the inspected homes, respectively.

3.2 | Associations between early age exposure to moisture damage/mold and FeNO at the age of 6 years

For the main model 1a (Table 2), early age exposure to major moisture damage (i) and major moisture damage or mold (iii) in the child's main living areas (including living room, child's bedroom, and kitchen) was significantly associated with higher levels of FeNO at the age of 6 years (adjusted odds ratios, 95% confidence intervals, aOR (95% CI): 3.10 (1.35-7.07) and aOR (95% CI): 3.16 (1.43-6.98), respectively). The associations remained significant in the subset of children who never changed home throughout the study period (aOR (95% CI): 5.01 (1.53-16.75) and 4.93 (1.52-16.43)), respectively. Furthermore, the association between early age exposure to major moisture damage in child's main rooms and elevated FeNO at age 6 years remained significant after additional adjustment for current exposure at 6 years aOR (95% CI): 2.96 (1.07-8.06) and also adjusted for ever physician-diagnosed asthma (data not shown).

We also ran the analyses in three subgroups of children without current steroid medication use, without current asthma medication use and in children without or only a very few symptoms of ever physician-diagnosed asthma and/or asthmatic bronchitis in order to exclude the effect of current asthmatic disease. As shown in Table 3, the associations remained significant within all subgroups in comparison with the main model. Moreover, the models in Tables 2 and 3 have been additionally adjusted for other types of exposure including type of ventilation and renovation activities; however, there were no major changes in the direction and magnitude of the effect estimates (data not shown). Results of the stratified analyses

TABLE 2 Adjusted analyses on early age exposure to moisture damage indicators in relation to high FeNO (>75th percentile) levels at the age of 6 y

Exposure	Damage	N	n (%) of FeNO >75th percentile	Model 1a[a] aOR (95% CI)	N	n (%) of FeNO >75th percentile	Model 1b[b] aOR (95% CI)
(i) Moisture damage in the child's main living areas	No damage	202	46 (23%)	1	104	21 (20%)	1
	Minor damage	81	20 (25%)	1.39 (0.71-2.69)	45	9 (20%)	1.40 (0.46-4.03)
	Major damage	39	15 (38%)	**3.10 (1.35-7.07)**	20	8 (40%)	**5.01 (1.53-16.75)**
(ii) Moisture damage with visible mold in the child's main living areas	No visible mold	299	74 (25%)	1	162	36 (22%)	1
	Only spots	10	2 (20%)	1.02 (0.14-4.84)	3	1 (33%)	2.24 (0.09-29.96)
	Visible mold	13	5 (38%)	1.49 (0.36-5.29)	4	1 (25%)	1.58 (0.07-18.48)
(iii) Moisture damage or mold (combined) in the child's main living areas	None	202	46 (23%)	1	104	21 (20%)	1
	Minor[c]	77	18 (23%)	1.30 (0.64-2.56)	44	9 (20%)	1.41 (0.46-4.06)
	Major[d]	43	17 (40%)	**3.16 (1.43-6.98)**	21	8 (38%)	**4.93 (1.52-16.43)**
(iv) Overall need for repair scale (whole house)	Class 0 or 1	91	23 (25%)	1	42	10 (24%)	1
	Class 2	126	30 (24%)	1.08 (0.53-2.25)	71	16 (23%)	1.82 (0.58-6.51)
	Class 3 or 4	105	28 (27%)	1.17 (0.56-2.49)	56	12 (21%)	1.52 (0.46-2.59)

Significant associations are depicted bold ($P < .05$)

[a] Model 1a: adjusted for gender, living on a farm, study cohort, maternal smoking during pregnancy, maternal allergy, older siblings, atopy against any inhalant allergens at 6 y of age, child's recent nitrate consumption (N = 292).

[b] Model 1b: never moved house/home throughout study period (N = 152), adjusted for variables in Model 1a.

[c] Minor means minor moisture damage with or without mold spots,

[d] Major means major moisture damage or any damage (minor/major) with visible mold growth.

suggested that harmful effects of early age moisture and/or mold exposure were more pronounced in the group of children classified as atopic as compared to the children without this predisposition (Table 4). No significant associations were found for early age exposure to moisture damage with visible mold (ii) or overall need for repair (whole house) (iv) in relation to FeNO at 6 years of age.

Continuous FeNO values showed a right-skewed distribution; therefore, linear regression models were performed on logarithmic-transformed data. With respect to log-transformed continuous FeNO values, only in the subset of children who did not move throughout the study period, significant associations were observed for exposure to minor moisture damage and minor moisture or mold damage in child's main rooms (data not shown).

3.3 | Associations between early age exposure to moisture damage or mold in relation to FEV1, FVC and FEV1/FVC lung function parameters at the age of 6 years

Valid lung function measurements with accepted pre- and post-bronchodilation test values were available for 216 children with complete information for 198 children. For the statistical analyses, pre-bronchodilation test lung function values were used. In general, there were no associations between early age moisture damage exposure and a positive bronchodilation response defined as an increase of more than 12% and more than 200 ml in FEV1 and/or FVC (data not shown). There was no significant association between the early age exposure to moisture damage with or without visible mold in the child's main living areas in relation to lung function parameters (Table 5). However, the need for repair of structural components in the whole house was associated with decreased FEV1 and FVC but not the FEV1/FVC ratio in adjusted analyses. Comparable results were observed for the GLI z-scores (Table 5).

4 | DISCUSSION

In the current study, inspector-observed early age exposure to major moisture damage or visible mold in the child's main living areas including child's bedroom, living room, and kitchen was significantly associated with increased FeNO levels at the age of 6 years. In stratified analyses by atopic status, significant effects of major moisture damage and mold exposure were only visible in atopic children. For the remaining moisture or mold damage-related exposure categories, associations with FeNO did not reach statistical significance. Within the subgroup of children with information on lung function, major damage within the whole home was significantly associated with a decrease in FEV1 and FVC at 6 years of age, but this was not seen with moisture damage or mold in the child's main living areas. The regression models calculated for the association between moisture damage with and without mold and GLI z-scores yielded similar results as when using original lung function values.

Harmful effects of moisture damage and mold on childhood asthma have been demonstrated in a number of cross-sectional and

TABLE 3 Adjusted analyses on early age exposure to moisture damage indicators in relation to high FeNO (>75th percentile) levels at the age of 6 y in three subgroups of children: no steroid use, no asthma medication use, and no or few asthma symptoms

Exposure	Damage	N	n (%) of FeNO >75th percentile	No steroid use[a] aOR (95% CI)	N	n (%) of FeNO >75th percentile	No asthma med use[a] aOR (95% CI)	N	n (%) of FeNO >75th percentile	Children without DD asthma/asthmatic bronchitis until 6 y[b]
(i) Moisture damage in child's main living areas	No damage	195	45 (23%)	1	174	40 (23%)	1	168	42 (25%)	1
	Minor damage	75	17 (23%)	1.14 (0.55-2.27)	69	15 (22%)	1.12 (0.53-2.31)	63	15 (24%)	1.22 (0.57-2.53)
	Major damage	36	15 (36%)	**3.25 (1.40-7.55)**	35	15 (43%)	**3.25 (1.38-7.66)**	31	13 (42%)	**3.07 (1.27-7.42)**
(ii) Moisture damage with visible mold in child's main living areas	No visible mold	286	70 (24%)	1	260	64 (25%)	1	247	64 (26%)	1
	Only spots	9	2 (22%)	1.02 (0.14-4.82)	7	1 (14%)	0.54 (0.03-3.66)	7	2 (29%)	1.31 (0.17-7.26)
	Visible mold	11	5 (45%)	1.99 (0.46-7.83)	11	5 (45%)	1.88 (0.44-7.35)	8	4 (50%)	2.69 (0.58-12.79)
(iii) Moisture damage or mold (combined) in child's main living areas	None	195	45 (23%)	1	174	40 (23%)	1	168	42 (25%)	1
	Minor[c]	71	15 (21%)	1.04 (0.48-2.12)	65	13 (20%)	1.02 (0.46-2.16)	60	13 (22%)	1.08 (0.48-2.30)
	Major[d]	40	17 (43%)	**3.29 (1.47-7.38)**	39	17 (44%)	**3.26 (1.44-7.41)**	34	15 (44%)	**3.32 (1.43-7.82)**
(iv) Overall need for repair scale (whole house)	Class 0 or 1	88	22 (25%)	1	78	19 (24%)	1	71	19 (27%)	1
	Class 2	120	29 (24%)	1.19 (0.58-2.53)	110	27 (25%)	1.18 (0.55-2.64)	105	27 (26%)	1.07 (0.50-2.35)
	Class 3 or 4	98	26 (27%)	1.15 (0.53-2.50)	90	24 (27%)	1.15 (0.51-2.62)	86	24 (28%)	1.07 (0.47-2.42)

Note: Results bolded, if *P*-value <.05.

[a]No steroid use (N = 277), no asthma med use (N = 251),

[b]Children without (or less than twice) DD asthma or asthmatic bronchitis until the age of 6 y (N = 240): gender, living on a farm, study cohort, maternal smoking during pregnancy, maternal allergy, older siblings, atopy against any inhalant allergens at 6 y of age, child's recent nitrate consumption.

[c]Minor means minor moisture damage with or without mold spots,

[d]major means major moisture damage or any damage (minor/major) with visible mold growth.

TABLE 4 Adjusted[a] analyses on early age exposure to moisture damage indicators in relation to high FeNO (>75th percentile) levels at the age of 6 y—stratified by atopy against inhalant allergies at 6 y (IgE, cutoff 0.35 kU/L)

Exposure	Damage	N	n (%) of FeNO >75th percentile	Atopics aOR (95% CI)	N	n (%) of FeNO >75th percentile	Non-atopics aOR (95% CI)
(i) Moisture damage in the child's main living areas	No damage	88	21 (24%)	1	103	19 (18%)	1
	Minor damage	33	11 (33%)	1.69 (0.65-4.30)	41	7 (17%)	0.93 (0.32-2.47)
	Major damage	13	7 (54%)	**4.77 (1.32-18.0)**	23	8 (35%)	2.22 (0.71-6.66)
(ii) Moisture damage with visible mold in the child's main living areas	No visible mold	125	34 (27%)	1	154	32 (21%)	1
	Only spots	4	2 (50%)	2.80 (0.28-27.54)	5	-	n.a.
	Visible mold	5	3 (60%)	3.40 (0.50-28.51)	8	2 (25%)	
(iii) Moisture damage or mold (combined) in the child's main living areas	None	88	21 (24%)	1	103	19 (18%)	1
	Minor[b]	31	9 (29%)	1.43 (0.52-3.76)	39	7 (18%)	0.99 (0.34-2.65)
	Major[c]	15	9 (60%)	**5.64 (1.68-20.45)**	25	8 (32%)	1.95 (0.63-5.72)
(iv) Overall need for repair scale (whole house)	Class 0 or 1	37	9 (24%)	1	45	10 (22%)	1
	Class 2	50	18 (36%)	2.02 (0.74-5.81)	70	10 (14%)	0.50 (0.17-1.47)
	Class 3 or 4	47	12 (26%)	1.31 (0.45-4.02)	52	14 (27%)	1.09 (0.38-3.20)

Significant associations are depicted bold ($P < .05$)

[a]Adjusted for gender, living on a farm, study cohort, maternal smoking during pregnancy, maternal allergy, older siblings, and child's recent nitrate consumption (children classified as atopic N = 134, children not classified as atopic N = 167).

[b]Minor means minor moisture damage with or without mold spots,

[c]Major means major moisture damage or any damage (minor/major) with visible mold growth.

prospective studies.[9-11] In the presented study population, early age exposure to moisture damage and mold in the child's main living areas has previously been shown to be associated with the risk of developing physician-diagnosed asthma (ever and persistent) during the first 6 years of life.[8] In the current study, we confirmed adverse respiratory effects of early life exposure to moisture damage and mold by using objective, measurable markers at 6 years of age, with effects in particular visible among children classified as atopic. Emphasizing the importance of early life priming, no statistically significant associations were found in cross-sectional analyses between inspector-observed confirmed moisture damage and/or visible mold in relation to FeNO levels at age 6 years in the same study population.[17] In contrast, although suggested by this cross-sectional analysis,[17] early life moisture and/or mold exposure was not associated with subclinical systemic inflammation in later childhood.[11]

According to our knowledge, there is only one prospective study and one cross-sectional study among pediatric populations on the subject. Casas and colleagues found that parental-reported exposure to dampness within the first 2 years of life in three European birth cohorts was not associated with FeNO levels at 10 years of age.[21] Similar, in cross-sectional analyses, self-reported home dampness had no significant effect on FeNO levels of school-aged children.[18] As compared to our results, both available studies reported non-significant findings. Several reasons might be thinkable for the discrepancies in comparison with our study results. One reason might be due to differences in the exposure assessment (parental-report versus inspector-assessed) or the study design as such (cross-sectional versus longitudinal). In fact, for the cross-sectional analysis among the same study population between current moisture exposure damage with or without mold in relation to FeNO at 6 years, no significant findings have been obtained.[17] Further, taking into account different confounding factors might also play a role. In the current study, we observed that effects were also visible in the absence of a current asthma-related disease. Moreover, the association between early age exposure to major moisture damage in child's main living areas and elevated FeNO at age 6 years seemed not to be affected by current exposure at 6 years or by adjusting for additional exposure characteristics such as type of ventilation and renovation activities within the home. Therefore, the observed effects in the present investigation can be assumed to be stable. Finally, for our main models, we used dichotomized FeNO with a 75th percentile as cutoff as compared to quartiles by Casas et al[21] and continuous FeNO levels by Kovesi and Dales,[18] respectively. In order to compare the results with those of previous investigations, we additionally ran the models with continuous FeNO levels (log-transformed) for those associations significant with the dichotomized outcome. However, only exposure to minor moisture and minor moisture or mold damage in child's main living areas was significantly associated with increased levels of log-transformed FeNO in the subset of children who did not move throughout the study period. A possible explanation could be that the use of log-transformed FeNO emphasizes the association with low FeNO levels. The levels of FeNO were low in the present study population and also lower as compared to Casas et al [21] and Kovesi and Dales.[18] Higher FeNO levels are more likely to be relevant indicators of lung health, and therefore, significant associations are more likely to be

TABLE 5 Adjusted analyses[a] on early age exposure to moisture damage indicators in relation to FEV1, FCV, and FEV1/FVC ratio(%) at 6 y, both using original lung function values in milliliters and % and when using *GLI z-scores* (italic)[34]

Exposure	Damage	N	Unit	FEV1 aβ (95% CI), *P*-value	FVC aβ (95% CI), *P*-value	FEV1/FVC% aβ (95% CI), *P*-value
Moisture damage in the child's main living areas	No damage	142		1	1	1
	Minor damage	51	ml or % *z-score*	7.39 (−54.30-69.08), *P* = .81 *0.04* (*−0.34-0.42*), *P* = *.85*	3.66 (−60.74-68.06), *P* = .91 *−0.007* (*−0.96-0.37*), *P* = *.97*	0.30 (−1.69-2.29), *P* = .76 *0.03* (*−0.25-0.31*), *P* = *.84*
	Major damage	23	ml or % *z-score*	18.61 (−65.86-103.08), *P* = .67 *0.10* (*−0.42-0.62*), *P* = *.71*	13.03 (−51.37-68.06), *P* = .77 *0.002* (*−0.49-0.49*), *P* = *.99*	1.11 (−1.63-3.85), *P* = .43 *0.12* (*−0.26-0.50*), *P* = *.53*
Moisture damage or mold (combined) in the child's main living areas	None	142		1	1	1
	Minor[b]	49	ml or % *z-score*	-5.44 (−68.7-57.82), *P* = .87 *-0.03* (*−0.41-0.35*), *P* = *.88*	−9.93 (−75.66-55.80), *P* = .77 *−0.07* (*−0.43-0.29*), *P* =*.72*	0.22 (−1.82-2.26), *P* = .84 *0.02* (*−0.26-0.30*), *P* = *.91*
	Major[c]	25	ml or % *z-score*	42.47 (−39.62-124.56), *P* = .31 *0.22* (*−0.28-0.72*), *P* = *.39*	34.71 (−50.29-119.71), *P* = .42 *0.11* (*-0.36-0.58*), *P* = *.64*	1.20 (−1.44-3.84), *P* = .37 *0.13* (*−0.23-0.49*), *P* = *.47*
Overall need for repair scale (whole house)	Class 0 or 1	63		1	1	1
	Class 2	86	ml or % *z-score*	-49.32 (−109.3-10.66), *P* = .11 *-0.32* (*−0.69-0.05*), *P* = *.09*	−51.79 (−113.88-10.3), *P* = .10 *−0.30* (*−0.73-0.04*), *P* = *.09*	−0.44 (±2.00, *P* = .66 *0.0003* (*−0.27-0.27*). *P* = *.99*
	Class 3 or 4	67	ml or % *z-score*	**-76.27 (−142.8-−9.75)**, *P* = .03 ***-0.45 (−0.86-−0.04)***, *P* = *.03*	**−90.45 (−158.8-−22.06)**, *P* = .01 ***−0.48 (−0.86-−0.10)***, *P* = *.01*	0.17 (±2.21), *P* = .88 *0.04* (*−0.26-0.34*), *P* = *.81*

Significant associations are depicted bold (*P* < .05)

[a]Adjusted for: gender, living on a farm, study cohort, age, height and weight at lung function measurement, maternal smoking during pregnancy, maternal education, breastfeeding, and parental allergy (N = 198).

[b]Minor means minor moisture damage with or without mold spots,

[c]Major means major moisture damage or any damage (minor/major) with visible mold growth *z-scores* adjusted for: living on a farm, study cohort, weight at lung function measurement, maternal smoking during pregnancy, maternal education, breastfeeding, and parental allergy.

visible when using dichotomized outcomes with a higher cutoff. It should be noted that the 75% cutoff (7.81 ppb) used in the present study was still clearly lower than what is recommended to be used in clinical practice (>20 ppb).[37] For the analysis in relation to lung function, only exposure to the overall estimate for need for repair scale in the whole house was significantly associated with lower FEV_1 and FVC. Until now, there is no other prospective study on inspector-observed and confirmed moisture damage and/or mold in relation to lung function parameters in children. Only recently, a prospective study observed that early life parental-reported home dampness or mold exposure may induce forced vital capacity (FVC) growth deficits in adolescence.[25] Although reported effect sizes were small, the authors assumed that these could accumulate over time. Within a study among 330 Danish schoolchildren, inspector-observed high classroom dampness, but not parent-reported bedroom dampness was associated with a decline in FEV1 and FVC.[18] A recent meta-analysis on dampness and mold exposure in schools on respiratory health concluded that there is evidence for harmful effects on respiratory health in children.[19] Unfortunately, the literature on objective measurements such as lung function was not able to give unequivocal evidence as yet.[19]

In general, although there is a large body of evidence on harmful effects of exposure to dampness with our without mold in homes on pediatric asthma,[26] asthma itself is a complex disease and the clinical assessment can be a challenge as every method corresponds to a particular aspect of this disease.[38] Therefore, objective methods of exposure and health outcomes measurements are favored in order to obtain valid findings. In contrast to lung function, no significant associations of exposure to the overall estimate for the need for repair scale in the whole house in relation to elevated FeNO at 6 years have been obtained which is in line with previous findings among the same study population.[8,30] There might be several reasons for these results. First, damage in the whole house includes damages also in, for example, the attic, cellar, and other less used areas of the house, which are likely to cause less exposure. Second, FeNO and lung function are not measuring the same aspects of asthma and respiratory health, which again underlines the importance of objective and specific exposure and health outcome assessment. Third, the high dependence of spirometry testing on the performance of the operator[39] and the smaller sample size of children with lung function measurements reduce the statistical robustness of the adjusted analyses with respect to the lung function parameters. Given all these considerations, we consider the findings in relation to lung function values and this particular exposure less reliable.

Nevertheless, apart from the need for further objectively designed studies, the results of the current study along with previous findings underline the importance of remediation and prevention efforts of especially clearly moisture and mold damaged environments. This concerns in particular homes, where infants spend most of their time indoors[40] during their vulnerable phase of immunologic and lung development. In addition, one might speculate how the projected climate change with increased rain, wind, and flooding has the potential to increase the risk of moisture damage or visible mold within the home environment.[41]

A key strength of this study is the objective and extensive inspector-based report of moisture damage and mold within the homes by using standardized methods. Moreover, this is one of the few available prospective studies looking at early age exposure to moisture damage and mold in relation to FeNO and lung function as objective markers for airway inflammation and asthma. A limitation of the study was the reduced sample size in particular for the models looking at early age exposure to moisture damage with visible mold. As a result, we were not able to look into the health effects of early age exposure to moisture damage with visible mold in specific location of the house where the child is most likely to be exposed. In addition, for some of the models, the estimates may be unstable due to the low number of children and the results have to be interpreted with caution. This concerns in particular the sub-study among children with valid lung function measurements.

5 | CONCLUSION

In conclusion, early life exposure to inspector-reported major but not minor moisture damage or visible mold and identified damage of structural components within the home may increase levels of fractional exhaled nitric oxide. These results underline the importance of prevention and remediation efforts of moisture and mold damaged buildings in order to avoid harmful effects within the vulnerable phase of the infants and children's immunologic development.

CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Christina Tischer: Formal analysis (equal); Writing-original draft (equal). **Anne Karvonen:** Conceptualization (equal); Supervision (equal); Writing-review & editing (equal). **Pirkka Kirjavainen:** Writing-review & editing (supporting). **Claudia Flexeder:** Formal analysis (supporting); Writing-review & editing (supporting). **Marjut Roponen:** Writing-review & editing (supporting). **Anne Hyvärinen:** Writing-review & editing (supporting). **Harald Renz:** Writing-review & editing (supporting). **Urs Peter Frey:** Writing-review & editing (supporting). **Oliver Fuchs:** Writing-review & editing (supporting). **Juha**

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PEER REVIEW

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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