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Article type : Original

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

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/PAI.13526](https://doi.org/10.1111/PAI.13526)

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Funding information

This study was supported by research grants from the Academy of Finland (grants 39021; 287675); the Juho Vainio Foundation (no grant nr); the Foundation for Pediatric Research (no grant nr); Competitive State Research Funding for the Kuopio University Hospital Catchment Area (no grant nr); Päivikki and Sakari Sohlberg Foundation (no grant nr); the Finnish Cultural Foundation (no grant nr).

nr); European Union (grant nr QLK4-CT-2001-00250); and by the Finnish Institute for Health and Welfare (no grant nr).

Competing interest statement

HR is supported by the German Centre of Lung Research (DZL) and the Universities of Giessen and Marburg Lung Center (UGMLC). JP reported grants from EU, grants from Academy of Finland, minor grants from Finnish foundations supporting medical research (Juho Vainio Foundation, Päivikki and Sakari Sohlberg foundation, Finnish cultural foundation). OF reported personal fees from aha! Swiss Allergy Centre, Menarini Switzerland, Novartis Switzerland, ALK Abelló Switzerland, Vifor Switzerland, Milupa/Nutricia Switzerland, Stallergenes Greer Switzerland, and Bencard Switzerland outside the submitted work. All remaining authors have nothing to disclose.

Contributorship statement

AK and JP conceived of the presented idea. CT performed the statistical analysis and wrote the manuscript. CF supported the statistical analysis. All co-authors critically discussed the results and contributed to the final manuscript.

Short title: *Harmful effects of early age moisture damage on FeNO in childhood*

Key words: *asthma, cohort study, exhaled NO, lung function, moisture damage*

ABSTRACT

Background: Exposure to indoor moisture damage and visible mould 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 mould 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 mould in the child's main living areas was significantly associated with increased FeNO levels (>75th percentile) at the age of 6 years (adjusted Odds Ratios, 95% Confidence Intervals, aOR (95%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 mould in the child's main living areas.

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

Word count abstract: 246

Word count text: 3746

Abbreviations: FeNO = Fractional exhaled Nitric oxide, FEV1 = Forced Expiratory Volume in 1 Second, FVC = Forced Vital Capacity, FEV1/FVC ratio, aOR = adjusted Odds ratio, CI = confidence interval, $\alpha\beta$ = adjusted beta, PASTURE = Protection against Allergy Study in Rural Environments

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 mouldy and damp indoor home environment (6, 7) and exposure to indoor moisture damage and visible mould 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, mould or mould 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 mould 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 mould 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.

MATERIAL AND METHODS

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 to 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: 299/2017 (33/2002) and for LUKAS2: 300/2017 (48/2004). Written consents were acquired from the parents of the participating children.

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 mould 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., Füssen, Germany) when the children were 5 months old on average. During the home visit, housing characteristics were assessed (**Online supplement 1**).

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 mould in the child's main living areas, (iii) moisture damage or mould in the child's main living areas and (iv) overall estimate for the need for repair scale in the whole house (**Online supplement 1**).

Health outcome assessment

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 were performed, as described earlier (17, 31). Before spirometry, trained fieldworkers collected exhaled air with an offline kit (EcoMedics AG, Duernten, Switzerland) in triplicate in Mylar-coated bags (Quintron, Cedar Rapids, Iowa) 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).

Lung function

Trained fieldworkers performed spirometry with a mobile spirometer (EasyOne; ndd, Zurich, Switzerland), 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 standardised z-scores to allow international comparisons (34).

Immunoglobulin E (IgE) against inhalant allergens

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

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 mould 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); 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, cut off 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 mould 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 mould in the child's main living areas (no mould N=203, only spots of mould N=5, visible mould N=8) in relation to lung function parameters, 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, Vienna, Austria. URL <https://www.R-project.org/>).

RESULTS

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, cut-off 0.35kU/L) and 18% (19%) were diagnosed with asthma. Early age moisture damage combined with information on the visible mould in the child's main living areas were 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.

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 (years), 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*	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 years)	56 / 318 (18%)	40 / 214 (19%)
IgE at 6 years (cut-off 0.35kU/L)	134 / 301 (45%)	92 / 202 (46%)
Recent nitrate consumption (measurements) (6y)	53 / 313 (17%)	33 / 212 (16%)
Asthma medication use past 12 months (6y)	33 / 317 (10%)	26 / 213 (12%)
Steroid use past 12 months (6y)	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 (6y)	109 / 321 (34%)	81 / 215 (38%)
Time spent watching TV on weekdays (6y)		
½ -1 hour	154 / 321 (48%)	107 / 215 (50%)
more than 1 hour	167 / 321 (52%)	108 / 215 (50%)
Type of air conditioning (6y)		
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%)
CO2 living room (measured, parts per million) (6y)		
< 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^s		
No damage	202 / 322 (63%)	142 / 216 (66%)
Minor damage	81 (25%)	51 (24%)
Major damage	39 (12%)	23 (11%)
Moisture damage with visible mould, CMLA		
No mould	299 / 322 (93%)	203 / 216 (94%)
Only spots of mould	10 (3%)	5 (2%)
Visible mould	13 (4%)	8 (4%)
Moisture damage or mould (combined)		
None	202 / 322 (63%)	142 / 216 (66%)
Minor ¹	77 (24%)	49 (23%)

Major ²	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%)

* Breastfeeding “yes” = ≥ 5 months of breastfeeding, [§]CMLA: Child’s main living areas, ¹Minor means minor moisture damage with or without mould spots, ²Major means major moisture damage or any damage (minor/major) with visible mould growth

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

For the main model 1a (**Table 2a**), early age exposure to major moisture damage (i) and major moisture damage or mould (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 2b**, the associations remained significant within all sub-groups in comparison to the main model. Moreover, the models in **Table 2a** and **2b** 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 suggested that harmful effects of early age moisture and/or mould exposure were more pronounced in the group of children classified as atopic as compared to the children without this predisposition (**Table 3**). No significant associations were found for early age exposure to moisture damage with visible mould (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 mould damage in child's main rooms (data not shown).

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

Exposure	Damage	N	n(%) of FeNO >75th percentile	Model 1a* aOR (95 % CI)	N	n(%) of FeNO >75th percentile	Model 1b** 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 mould in the child's main living areas	No visible mould	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 mould	13	5 (38%)	1.49 (0.36-5.29)	4	1 (25%)	1.58 (0.07-18.48)
(iii) Moisture damage or mould (combined) in the child's main living areas	None	202	46 (23%)	1	104	21 (20%)	1
	Minor ¹	77	18 (23%)	1.30 (0.64-2.56)	44	9 (20%)	1.41 (0.46-4.06)
	Major ²	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)

*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 years of age, child's recent nitrate consumption (N=292)

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

¹Minor means minor moisture damage with or without mould spots, ²Major means major moisture damage or any damage (minor/major) with visible mould growth

Table 2b: Adjusted analyses on early age exposure to moisture damage indicators in relation to high FeNO (>75th percentile) levels at the age of 6 years 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* aOR (95 % CI)	N	n(%) of FeNO >75th percentile	No asthma med use* aOR (95 % CI)	N	n(%) of FeNO >75th percentile	Children without DD asthma/asthmatic bronchitis until 6y ^s
(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 mould in child's main living areas	No visible mould	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 mould	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 mould (combined) in child's main living areas	None	195	45 (23%)	1	174	40 (23%)	1	168	42 (25%)	1
	Minor ¹	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 ²	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	Class 0 or 1	88	22 (25%)	1	78	19 (24%)	1	71	19 (27%)	1

(whole house)										
	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)

*No steroid use (N=277), no asthma med use (N=251), and §children without (or less than twice) DD asthma or asthmatic bronchitis until the age of 6 years (N=240):
gender, living on a farm, study cohort, maternal smoking during pregnancy, maternal allergy, older siblings, atopy against any inhalant allergens at 6 years of age, child's recent nitrate consumption

¹Minor means minor moisture damage with or without mould spots, ²Major means major moisture damage or any damage (minor/major) with visible mould growth
Results bolded, if *p-value* <0.05.

Table 3: Adjusted^s analyses on early age exposure to moisture damage indicators in relation to high FeNO (>75th percentile) levels at the age of 6 years – stratified by atopy against inhalant allergies at 6 years (IgE, cut-off 0.35kU/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 mould in the child's main living areas	No visible mould	125	34 (27%)	1	154	32 (21%)	1
	Only spots	4	2 (50%)	2.80 (0.28-27.54)	5	-	n.a.
	Visible mould	5	3 (60%)	3.40 (0.50-28.51)	8	2 (25%)	
(iii) Moisture damage or mould (combined) in the child's main living areas	None	88	21 (24%)	1	103	19 (18%)	1
	Minor ¹	31	9 (29%)	1.43 (0.52-3.76)	39	7 (18%)	0.99 (0.34-2.65)
	Major ²	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)

§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)

¹Minor means minor moisture damage with or without mould spots, ²Major means major moisture damage or any damage (minor/major) with visible mould growth

Associations between early age exposure to moisture damage or mould 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 200ml 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 mould in the child's main living areas in relation to lung function parameters (**Table 4**). 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 4**).

Table 4: Adjusted analyses* on early age exposure to moisture damage indicators in relation to FEV1, FVC and FEV1/FVC ratio(%) at 6 years, both using original lung function values in milliliters and % and when using *GLI z-scores* (*italic*) (34)

Exposure	Damage	N	Unit	FEV1 a β (95%CI), p-value	FVC a β (95%CI), p-value	FEV1/FVC% a β (95%CI), p-value
Moisture damage in the child's main living areas	No damage	142		1	1	1
	Minor damage	51	ml or % <i>z-score</i>	7.39 (-54.30 – 69.08), p=0.81 <i>0.04 (-0.34 – 0.42), p=0.85</i>	3.66 (-60.74 – 68.06), p=0.91 <i>-0.007 (-0.96 – 0.37), p=0.97</i>	0.30 (-1.69 – 2.29), p=0.76 <i>0.03 (-0.25 – 0.31), p=0.84</i>
	Major damage	23	ml or % <i>z-score</i>	18.61 (-65.86 – 103.08), p=0.67 <i>0.10 (-0.42 – 0.62), p=0.71</i>	13.03 (-51.37 – 68.06), p=0.77 <i>0.002 (-0.49 – 0.49), p=0.99</i>	1.11 (-1.63 – 3.85), p=0.43 <i>0.12 (-0.26 – 0.50), p=0.53</i>
Moisture damage or mould (combined) in the child's main living areas	None	142		1	1	1
	Minor ¹	49	ml or % <i>z-score</i>	-5.44 (-68.7 – 57.82), p=0.87 <i>-0.03 (-0.41 – 0.35), p=0.88</i>	-9.93 (-75.66 – 55.80), p=0.77 <i>-0.07 (-0.43 – 0.29), p=0.72</i>	0.22 (-1.82 – 2.26), p=0.84 <i>0.02 (-0.26 – 0.30), p=0.91</i>
	Major ²	25	ml or % <i>z-score</i>	42.47 (-39.62 – 124.56), p=0.31 <i>0.22 (-0.28 – 0.72), p=0.39</i>	34.71 (-50.29 – 119.71), p=0.42 <i>0.11 (-0.36 – 0.58), p=0.64</i>	1.20 (-1.44 – 3.84), p=0.37 <i>0.13 (-0.23 – 0.49), p=0.47</i>
Overall need for repair scale (whole house)	Class 0 or 1	63		1	1	1
	Class 2	86	ml or % <i>z-score</i>	-49.32 (-109.3 – 10.66), p=0.11 <i>-0.32 (-0.69 – 0.05), p=0.09</i>	-51.79 (-113.88 – 10.3), p=0.10 <i>-0.30 (-0.73 – 0.04), p=0.09</i>	-0.44 ($\pm$ 2.00, p=0.66 <i>0.0003 (-0.27 – 0.27), p=0.99</i>
	Class 3 or 4	67	ml or % <i>z-score</i>	-76.27 (-142.8 – -9.75), p=0.03 <i>-0.45 (-0.86 – -0.04), p=0.03</i>	-90.45 (-158.8 – -22.06), p=0.01 <i>-0.48 (-0.86 – -0.10), p=0.01</i>	0.17 ($\pm$ 2.21), p=0.88 <i>0.04 (-0.26 – 0.34), p=0.81</i>

*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), ¹Minor means minor moisture damage with or without mould spots, ²Major means major moisture damage or any damage (minor/major) with visible mould 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

DISCUSSION

In the current study, inspector-observed early age exposure to major moisture damage or visible mould 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 mould exposure were only visible in atopic children. For the remaining moisture or mould damage related exposure categories, associations with FeNO did not reach statistical significance. Within the sub-group 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 mould in the child's main living areas. The regression models calculated for the association between moisture damage with and without mould and GLI z-scores yielded similar results as when using original lung function values.

Harmful effects of moisture damage and mould on childhood asthma has been demonstrated in a number of cross-sectional and prospective studies (9–11). In the presented study population, early age exposure to moisture damage and mould 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 mould 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 mould 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 mould 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 paediatric populations on the subject. Casas and colleagues found that parental-reported exposure to dampness within the first two 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 to 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 mould 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 cut-off 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 mould 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 emphasises 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 visible when using dichotomized outcomes with a higher cut-off. It should be noted that the 75% cut-off (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 FEV₁ and FVC. Until now, there is no other prospective study on inspector-observed and confirmed moisture damage and/or mould in relation to lung function parameters in children. Only recently, a prospective study observed that early life parental-reported home dampness or mould 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 mould 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 or without mould in homes on paediatric asthma (9, 11, 12) and on lung function in adults (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 favoured 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 e.g. 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 mould damaged environments. This concerns in particular homes, where infants spend most of their time indoors (40) during their vulnerable phase of immunological 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 mould within the home environment (41).

A key strength of this study is the objective and extensive inspector-based report of moisture damage and mould 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 mould 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 mould. As a result, we were not able to look into the health effects of early age exposure to moisture damage with visible mould 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.

Conclusion

In conclusion, early life exposure to inspector-reported major but not minor moisture damage or visible mould 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 mould damaged buildings in order to avoid harmful effects within the vulnerable phase of the infants and children's immunological development.

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Online supplement 1: Detailed description of moisture damage and mould characterization

A detailed description of the exposure assessment has been comprehensively depicted previously (1,2). Briefly, “no damage” corresponded to “need for repair” classes 0 and 1, which was defined as no need for repair or only aesthetic repair, respectively. “Minor damage” referred to the “need for repair” class 2 (repair of surface materials needed and with an area of damage $\leq 1\text{m}^2$) or to the “need for repair” class 3 (a repair of structural components needed and with an area of damage $\leq 0.1\text{m}^2$). “Major damage” has been defined as “need for repair” class 2 with an affected area of damage of $> 1\text{m}^2$ or as “need for repair” class 3 with an area of damage of $> 0.1\text{m}^2$ or as “need for repair” class 4 (more extensive repair needed on structural components). In the presence of several areas of damage in a given room or area, the areas of damage with the same need for repair estimation were summarized.

In addition, the presence of “visible mould” was recorded for each moisture damage observation and “moisture damage with visible mould” was categorized into three classes: “no mould”, “only spots of mould” and “visible mould” growth. Mould growth, which was detectable on silicone sealants in the kitchen or in the bathroom, was classified as “no mould”.

A combination variable “moisture damage or mould (combined)” in the child’s main living areas had three classes, defined as follows: “none” (no moisture damage and no mould), “minor” (minor moisture damage with or without mould spots) and “major” (major moisture damage or any moisture damage with visible mould). Child’s main living areas consisted living room, kitchen and child’s bedroom.

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