Received: 5 February 2022 | Revised: 15 September 2022 | Accepted: 22 September 2022

DOI: 10.1111/pai.13864

ORIGINAL ARTICLE

WILEY

Early-life residential exposure to moisture damage is associated with persistent wheezing in a Finnish birth cohort

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Funding information
Academy of Finland, Grant/Award Number: 139021, 287675, 338679 and 339666; European Commission, Grant/Award Number: QLK4-CT-2001-00250; EVO- and VTR, Grant/Award Number: no grant number; Finnish Institute for Health and Welfare; Juho Vainion Säätiö; Päivikki ja Sakari Sohlbergin Säätiö; Suomen Kulttuurirahasto; Yrjö Jahnssonin Säätiö

Editor: Jon Genuneit

Abstract

Background and Aims: Moisture damage increases the risk for respiratory disorders in childhood. Our aim was to determine whether early age residential exposure to inspector-observed moisture damage or mold is associated with different wheezing phenotypes later in childhood.

Methods: Building inspections were performed by civil engineers, in a standardized manner, in the children's homes—mostly single family and row houses ($N = 344$)—in the first year of life. The children were followed up with repeated questionnaires until the age of 6 years and wheezing phenotypes—never/infrequent, transient, intermediate, late onset, and persistent—were defined using latent class analyses. The multinomial logistic regression model was used for statistical analysis.

Results: A total of 63% ($n = 218$) had infrequent or no wheeze, 23% ($n = 80$) had transient and 9.6% ($n = 21$) had a persistent wheeze. Due to the low prevalence, results for intermediate (3.8%, $n = 13$) and late-onset wheeze (3.5%, $n = 12$) were not further evaluated. Most consistent associations were observed with the persistent wheeze phenotype with an adjusted odds ratio (95% confidence intervals) 2.04 (0.67–6.18) for minor moisture damage with or without mold spots (present in 23.8% of homes) and 3.68 (1.04–13.05) for major damage or any moisture damage with visible mold in

Abbreviations: ALSPAC, Avon Longitudinal Study of Parents and Children; aOR, adjusted odds ratio; BAMSE, Barn/Child Allergy Milieu Stockholm Epidemiology; CCAAPS, Cincinnati Childhood Allergy and Air Pollution Study; CI95%, 95% confidence interval; LCA, Latent Class Analyses; PASTURE, Protection against Allergy Study in Rural Environments; PIAMA, The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort study.

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a child's main living areas (present in 13.4% of homes). Early-age moisture damage or mold in the kitchen was associated with transient wheezing.

Conclusion: At an early age, residential exposure to moisture damage or mold, can be dose-dependently associated especially with persistent wheezing phenotype later in childhood.

KEYWORDS
childhood, indoor, latent class analysis, moisture damage, mold, wheezing phenotype

1 | INTRODUCTION

Moisture damage and mold growth in buildings increase the risk of asthma exacerbation.[1] Previous reviews[2-4] have also concluded that there is sufficient evidence for the association of moisture damage or mold with asthma development, a finding reported also in the present birth cohort.[5,6] However, asthma itself represents a complex spectrum of phenotypes from early childhood into adulthood. In this context, children might be diagnosed as asthmatics at an early age due to experiencing wheezing symptoms, for instance during respiratory infection episodes, but might lose these symptoms later on, so-called transient wheezing.[7] This may lead to a false positive classification of asthma status in epidemiological studies.

Two analytical approaches have been widely used to identify distinct classifications of asthma and wheezing in birth cohorts: the epidemiological and clinical phenotype definitions.[8] The clinical phenotype definition approach is based on the onset or overall timing of wheezing symptoms and the number of lower respiratory tract illnesses over a certain time period,[9] whereas the epidemiological approach uses hypothesis-free latent class analysis (LCA), utilizing parent-reported respiratory symptoms in different time points.[8,10] Previous studies have differentiated wheezing and asthma phenotypes into six classes by various analytical and data-driven approaches.[9-15]

Previous research has suggested that fungal components including cell fragments or spores released during fungal growth in buildings affected by moisture or mold damage may provoke inflammatory responses,[16,17] and in turn, induce respiratory disorders including wheezing and asthma.[8,18] Due to the heterogeneity of asthma, it is further important to pinpoint those wheezing phenotypes, which may be associated with exposure to moisture damage and mold at an early age.

The aim of the present study was to evaluate prospectively, whether wheezing phenotypes as defined by LCA until the age of 6 years were associated with exposure to building inspection confirmed moisture damage and mold in the home during infancy in a Finnish birth cohort study from the general population.

Highlights

- Exposure to moisture damage is considered a risk factor for respiratory disorders.
- Exposure to moisture damage in infancy was associated especially with persistent wheezing phenotype.
- Persistent wheeze is strongly associated with a later doctor diagnosis of asthma.

Key Message

This is the first study to assess the association of moisture damage and mold observations recorded during standardized building inspections with different asthma phenotypes obtained by latent class analysis in a general population. Early age exposure to moisture damage was associated with persistent wheezing.

2 | MATERIAL AND METHODS

2.1 | Study population and study area

The study population consisted of the Finnish LUKAS birth cohort that has been prospectively followed up from the third trimester of pregnancy.[5] Briefly, the study population includes 442 children that were born between September 2002 and May 2005 in Middle and Eastern Finland. The first half of the study population ($N = 214$) has been recruited from rural areas and is part of a European birth cohort (the Finnish arm of PASTURE),[19] the second half of the cohort comes mainly from suburban areas ($N = 228$).[5] For the current analysis, children whose homes have been investigated for moisture damage and mold at an early age (mostly between 2 and 5 months of age),[5] and who had information on wheezing phenotypes determined by LCA[8] were included ($N = 344$). The ethical permission for the study was granted by the Research Ethics Committee of the Hospital District of Northern Savo, Kuopio, Finland (ORG number: IORG00005196). The number for LUKAS is 299/2017 (33/2002) and for LUKAS2 is 300/2017 (48/2004). Written consent were acquired from the parents of the participating children.

2.2 | Follow-up

Questionnaires at 12, 18, and 24 months of age and thereafter annually,[6] enquired about any wheezing and other symptoms or diseases for the time period after the preceding questionnaire. Confounding factors were asked in the parents' questionnaires and in the 2- and 12-months follow-up questionnaires. Questionnaire-based

information about housing characteristics were collected during the home inspection.

2.3 | Immunoglobulin E (IgE) against inhalant allergens

Venous blood samples have been taken at the age of 6 years and analyzed for specific immunoglobulin E (sIgE) to 19 common allergens by administering the Allergy Screen Test Panel for Atopy (Mediwiss Analytic).[20,21] The cut-off level to define specific sensitization to 13 inhalant allergens was 0.70 kU/L.[5]

2.4 | Home inspection

The method of home inspection has been described earlier.[6,22,23] Briefly, trained civil engineer(s) inspected the homes for moisture damage, including detailed documentation of signs of excess moisture and/or mold on the surfaces and building structures using a pre-designed checklist. In this context, "Children's main living area" encompasses the child's bedroom, the living room, and/or the kitchen. Children were 5 months old on average (mean 5.42 months, SD 6.00) during the home inspection and the results of the home inspection were reported to the parents.

2.5 | Classification of moisture damage

During the building inspection, each sign of excess moisture was graded using a 6-point "need for repair" estimation scale in addition to the area of the damage.[6,23] A description of the exposure assessment has been reported earlier in detail.[5,6] "No damage" was defined as no need for repair or need for repair was only cosmetics (need for repair classes 0 or 1, respectively). "Major damage" was defined in three instances: (A) a repair of surface materials was needed (class 2) with the area of moisture damage ≥1 m^2; (B) a repair of structural components was needed (class 3) with the area of damage ≥0.1 m^2; and (C) a need for repair was more extensive than structural components (classes 4 or 5). Other damage than the above was classified as "minor damage." The presence of mold odor or visible mold was recorded in connection with each damage observation. The variable "Moisture damage or mould in the child's main living areas" was created using combined information on signs of moisture damage and visible mold in the child's bedroom, the home's living room, and kitchen. As in previous publications,[6,24] observation of visible mold only on silicone sealants in the kitchen or in the bathroom was classified as "no mold."

2.6 | Wheezing phenotypes

Wheezing phenotypes in PASTURE ($N = 953$, including the first half of the LUKAS study population) were originally defined using LCA, as defined in more detail in Depner et al.[8] This was done based on repeated parental reports on wheezing symptoms at 12, 18, and 24 months of age and thereafter annually up to the age of 6 years, using the following question: "How often has your child wheezed during the last 12 months?" or during the respective time period. The answer categories were "never," "less than once a month," "once a month," and "at least twice a month." Children with any wheeze at the respective time period were defined as wheezers. In consequence of varying time periods between questionnaires, each follow-up period was recoded to cover a 12 months period. Only those who had no or at most one missing time-point from the wheezing reports were included in the analyses. The Bayesian Information Criterion was used for determining the optimal number of five classes and the children were assigned to their respective classes based on the highest posterior probability of belonging. For the current analysis, the same LCA was repeated, now additionally including the second half of the LUKAS study population ($N = 185$), which resulted in five wheezing patterns as observed in the earlier analysis.[8] LCA was conducted in MPLUS Version 5 (Muthén and Muthén).

2.7 | Statistical analysis

Multinomial logistic regression[25] was used to determine associations between moisture damage with or without mold and the five wheezing phenotypes. All models were adjusted for the following, a priori selected covariates: study cohort, maternal history of allergic diseases (asthma, atopic dermatitis, or allergic rhinitis), gender, number of older siblings (≥2, 1 vs. no siblings), smoking during pregnancy, and living on a farm. A more detailed phenotype description according to disease status and socio-demographics was done in supplementary analyses. Due to the low number of observations in the groups of intermediate and late-onset wheezing, we only report *analytical* findings for moisture damage and mold with no or infrequent wheezing, transient, and persistent wheezing phenotype in the manuscript ($N = 319$). The data were analyzed using SAS 9.3 for Windows (SAS Institute).

3 | RESULTS

3.1 | Descriptive findings

The main population characteristics are shown in Table 1. The low number of children in different subgroups prevented further analyses on the associations between wheezing phenotypes and the association with current disease status (e.g., asthma or atopy at 6 years) and socio-demographic information (Table 1). Minor moisture damage in the child's main living areas was reported for 80 (24%) of the houses and major moisture damage or any moisture damage with visible mold was recorded in 46 homes (13%) (Table 2). During the 6-year follow-up, 63.4% ($n = 218$) of the children were

TABLE 1 Study population characteristics by wheezing phenotype

		Never/infrequent wheeze		Transient wheeze		Intermediate wheeze		Late onset wheeze		Persistent wheeze	
	N	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Farmer											
No	245	145	67	63	79	10	77	9	75	18	86
Yes	99	73	34	17	21	3	23	3	25	3	14
Cohort											
Finnish arm of PASTURE	166	110	51	35	44	9	42	5	41.7	7	33
Extended cohort	178	108	49	45	56	4	58	7	58.3	14	67
Gender											
Girl	173	119	55	33	41	4	31	8	66.7	9	43
Boy	171	99	45	47	59	9	69	4	33.3	12	57
Maternal smoking											
Never	187	125	57	40	50	7	54	5	41.7	10	48
Not during pregnancy	109	68	31	24	30	5	39	5	41.7	7	33
During pregnancy	48	25	12	16	20	1	8	2	16.7	4	19
Maternal history of allergic disease											
No	152	107	49	31	39	5	39	3	25	6	29
Yes	192	111	51	49	61	8	62	9	75	15	71
Paternal history of allergic disease											
No	178	121	56	40	51	3	25	6	50	8	38
Yes	161	95	44	38	49	9	75	6	50	13	62
Number of siblings											
None	120	82	38	26	33	2	15	6	50	4	19
One	115	75	34	27	34	1	8	5	41.7	7	33
Two or more	109	61	28	27	34	10	77	1	8.3	10	48
Maternal education level											
Low	105	62	28	26	33	7	54	2	16.7	8	38
Middle	160	101	46	38	48	4	31	8	66.6	9	43
High	79	55	25	16	20	2	15	2	16.7	4	19
Asthma ever 6 years											
No	281	202	93	65	81	2	15	6	50	6	29
Yes	62	15	7	15	19	11	85	6	50	15	71
Inhalant atopy age 6 year											
No (<0.70 kU/L)	178	120	66	34	55	7	54	7	58	10	59
Yes (≥0.70 kU/L)	109	63	34	28	45	6	46	5	42	7	41

categorized according to no or infrequent wheezing, 23.3% ($n = 80$) transient, 3.8% ($n = 13$) intermediate, 3.5% ($n = 12$) late onset, and 6.0% ($n = 21$) persistent wheezing (Figure 1).

3.2 | Analytical findings

3.2.1 | Persistent wheezing

Moisture damage or mold in the child's main living area was dose-dependently associated with an increased risk of persistent wheeze in adjusted analyses (Figure 2; Table 2). The persistent wheezing phenotype tended to be also associated with moisture damage and moisture damage with mold in the living room, in the child's bedroom (Table 2) and in the other main living areas (other than kitchen, living room, and child's bedroom) (Table 3), but due to small numbers confidence intervals are wide. No associations were found between moisture damage or moisture damage with mold in the bathrooms, other interior spaces, or in the whole house and persistent wheezing (Table 3). If children diagnosed with asthma ($n = 45$) were excluded from the current analyses (resulting in 6 persistent wheezers, 65 transient, and 203 no/infrequent wheezers in the model, $N = 274$), the association between moisture damage in the child's main living area and persistent wheeze phenotype showed the same trend. However, due to the small number of persistent wheezers in the model ($n = 6$), a meaningful interpretation of the results is questionable.

TABLE 2 Adjusted associations between different types of moisture damage or mold in the main locations of the home and the risk of transient and persistent wheezing phenotypes. Never or infrequent wheeze is always used as the comparison group.

		Never/ infrequent wheeze		Transient wheeze			Persistent wheeze		
	N	*n*	%	*n*	%	aOR (95% CI)	*n*	%	aOR (95% CI)
Child's main living area (child's bedroom, living room, and kitchen)									
No moisture damage and no mold	200	144	72	46	23	1	10	5	1
Minor damage with/without mold spots	76	48	63	22	29	1.59 (0.85–2.99)	6	8	2.04 (0.67–6.18)
Major/any moisture damage with visible mold	43	26	61	12	28	1.75 (0.78–3.94)	5	11	**3.68 (1.04–13.05), $p = .0435$**
Kitchen									
No moisture damage (reference)	237	170	72	53	22	1	14	6	1
Minor	67	40	60	22	33	**1.93 (1.02–3.68), $p = .0447$**	5	8	1.65 (0.53–5.16)
Major	15	8	53	5	33	2.43 (0.73–8.14)	2	13	3.53 (0.61–20.5)
No moisture damage with mold (reference)	307	213	69	74	24	1	20	7	1
Spots	4	1	25	2	50	4.17 (0.36–48.7)	1	25	5.38 (0.28–104)
Visible mold	8	4	50	4	50	2.62 (0.59–11.7)	0	0	–[a]
Living room									
No moisture damage (reference)	260	177	68	70	27	1	13	5	1
Minor	40	28	70	7	18	0.67 (0.27–1.68)	5	13	2.75 (0.81–9.29)
Major	19	13	68	3	16	0.71 (0.19–2.64)	3	16	**6.24 (1.34–29.0), $p = .0197$**
No moisture damage with mold (reference)	309	212	69	79	26	1	18	6	1
Spots	5	4	80	0	0	–[a]	1	20	2.38 (0.22–26.2)
Visible mold	5	2	4	1	20	1.94 (0.16–23.5)	2	40	**32.3 (2.81–370), $p = .0053$**
Child's bedroom									
No moisture damage (reference)	271	183	68	71	26	1	17	6	1
Minor	40	30	75	8	20	0.76 (0.33–1.78)	2	5	0.78 (0.16–3.69)
Major	8	5	63	1	13	0.69 (0.08–6.41)	2	25	6.91 (0.89–53.6), $p = .0647$
No moisture damage with mold (reference)	305	209	69	79	26	1	17	6	1
Spots	6	4	67	0	0	–[a]	2	33	6.10 (0.85–43.6), $p = .0715$
Visible mold	8	5	63	1	13	0.71 (0.08–6.62)	2	25	5.98 (0.83–42.8), $p = .0752$

Note: Models are adjusted for study cohort, living on a farm, gender, maternal history of allergic diseases (hay fever, atopic dermatitis, and/or asthma), smoking during pregnancy, and the number of siblings. The reference group in phenotypes is Never/Infrequent wheeze and in the exposure group as stated in the table.

[a]Cannot be estimated.

A general estimate of the degree of damage was defined as "need for repair" class of the damage in the whole house.

Bold value indicates significant *p* - value.

3.2.2 | Transient wheezing

Moisture damage or mold in the child's main living area was non-significantly associated with transient wheeze (aOR (95% CI) 1.59 (0.85–2.99)) for minor damage with or without mold spots and 1.75 (0.78–3.94) for major moisture damage or any moisture damage with visible mold (Figure 2; Table 2). This association resulted from exposure to moisture damage or mold in the kitchen because no association was found for moisture damage or mold in the living room or in the child's bedroom (Table 2). No other associations were observed between moisture and mold categories and transient wheezing (Table 3).

4 | DISCUSSION

4.1 | Summary of main findings

In this study, we applied LCA to questions about current wheeze from birth until age 6 years, resulting in five wheezing phenotypes; infrequent/no wheeze, transient wheeze, intermediate wheeze, late-onset wheeze, and persistent wheeze. We found that moisture damage and mold observations in the child's main living areas, as determined by building inspections performed during the child's first year of life, were significantly associated especially with the

persistent wheezing phenotype until the age of 6 years. Exposure to moisture damage or mold in the kitchen area was associated with transient wheeze only. No associations were observed for moisture observation in the bathrooms, in the other interior spaces or when considering the entire house.

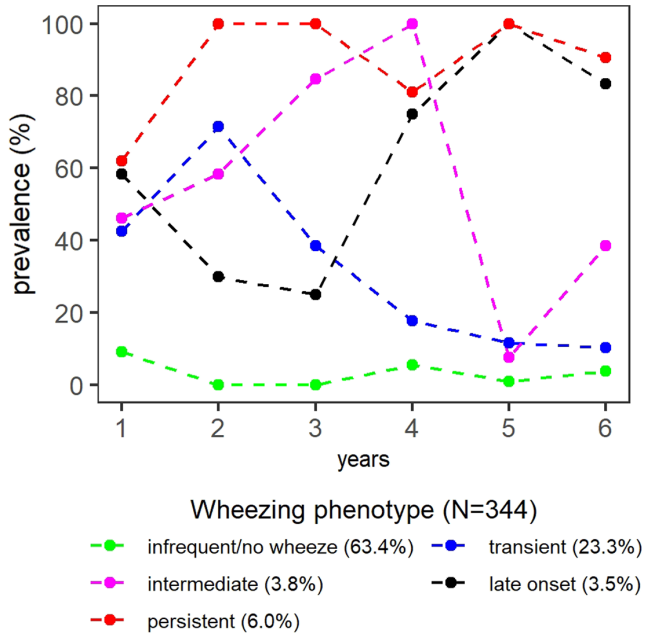

FIGURE 1 Prevalence of wheezing in different time points during the first 6 years of life in five wheezing phenotypes analyzed by latent class analyses (LCA) reproduction.

4.2 | Validation of wheezing phenotype identification

It is crucial to determine the underlying mechanisms to prevent the continuation of symptoms and a subsequent asthma diagnosis later in childhood by targeted intervention measures beforehand.[26] To distinguish between different wheezing phenotypes in early childhood, epidemiological studies including ours, have mostly used a hypothesis-free LCA approach to evaluating long-term trajectories of wheezing outcomes or wheezing classes throughout childhood.[15,27] Martinez and colleagues[9] identified four patterns of early-life wheezing (never wheeze, transient early wheeze, late-onset wheeze, and persistent wheeze) on the basis of clinical observation among children from the Tucson Children's Respiratory Study in 1995. These wheezing patterns have generally been confirmed and further refined in subsequent investigations using clinical and epidemiological approaches.[10,11,13,27] The identified wheezing phenotypes in our study are consistent and similar in magnitude to those obtained in the Tuscon,[9] the ALSPAC (Avon Longitudinal Study of Parents and Children) birth cohort study,[10] and the Melbourne Atopy Cohort Study.[28] In addition, they were identical to those ascertained from the Dutch PIAMA

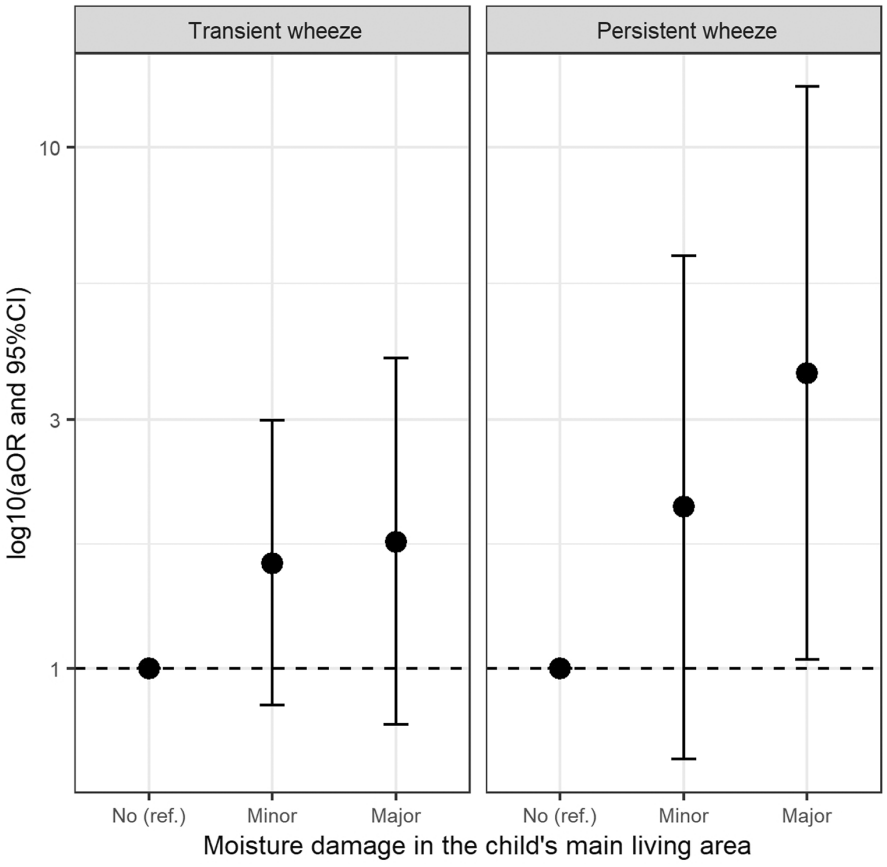

FIGURE 2 Adjusted associations between moisture damage in the child's main living area and transient or persistent wheezing phenotypes compared to no or infrequent wheezing phenotype. No moisture damage (reference category) = no damage or mold in the child's main living areas (minor = minor moisture damage with or without mold spots; major = major moisture damage or any moisture damage with visible mold. Multinomial logistic regression models are adjusted for study cohort, living on a farm, gender, maternal history of allergic diseases (hay fever, atopic dermatitis, and/or asthma), smoking during pregnancy, and the number of siblings. *$p < .05$.

TABLE 3 Adjusted associations between characteristics of moisture damage or mold in further locations of the home and transient as well as persistent wheezing phenotypes compared with never or infrequent wheeze.

		Never/infrequent wheeze		Transient wheeze			Persistent wheeze		
	N	*n*	%	*n*	%	aOR (95% CI)	*n*	%	aOR (95% CI)
Other main living areas (other than the kitchen, living room, and child's bedroom)									
No moisture damage (reference)	243	166	68	66	27	1	11	5	1
Minor	45	32	71	7	16	0.58 (0.24–1.42)	6	13	**3.59 (1.08–10.9), $p = .0368$**
Major	31	20	65	7	23	0.87 (0.33–2.29)	4	13	3.59 (0.90–14.3), $p = .0690$
No moisture damage with mold (reference)	293	200	68	76	26	1	17	6	1
Spots	9	6	68	1	11	0.41 (0.05–3.60)	2	22	3.72 (0.58–23.9)
Visible mold	17	12	71	3	18	0.74 (0.19–2.84)	2	12	1.91 (0.34–10.8)
Bathrooms									
No moisture damage (reference)	127	85	67	35	28	1	7	6	1
Minor	97	68	70	22	23	0.84 (0.44–1.62)	7	7	1.56 (0.49–4.98)
Major	95	65	68	23	24	0.99 (0.50–1.95)	7	7	1.84 (0.55–6.12)
No moisture damage with mold (reference)	285	192	67	74	26	1	19	7	1
Spots	11	8	73	2	18	0.46 (0.09–2.30)	1	9	0.92 (0.10–8.42)
Visible mold	23	18	78	4	17	0.45 (0.14–1.45)	1	4	0.35 (0.04–3.08)
Other interior spaces									
No moisture damage (reference)	240	160	67	63	26	1	17	7	1
Minor	15	12	80	3	20	0.75 (0.20–2.87)	0	0	–[a]
Major	64	46	72	14	22	0.95 (0.47–1.93)	4	6	1.08 (0.32–3.68)
No moisture damage with mold (reference)	289	194	67	75	26	1	20	7	1
Spots	3	3	100	0	0	–[a]	0	0	–[a]
Visible mold	27	21	78	5	19	0.64 (0.22–1.85)	1	4	0.49 (0.06–4.18)
Whole house									
Need for repair scale: Class 0 or 1 (reference)	93	64	67	25	27	1	4	4	1
Class 2	119	81	68	29	24	0.98 (0.51–1.89)	9	8	2.21 (0.61–7.92)
Class ≥3	107	73	68	26	24	1.00 (0.50–2.01)	8	8	2.31 (0.60–8.81)
No moisture damage with mold (reference)	202	138	68	52	26	1	12	6	1
Only spots	46	32	70	9	20	0.63 (0.27–1.48)	5	11	1.37 (0.41–4.58)
Visible mold	71	48	68	19	27	1.17 (0.58–2.37)	4	6	1.03 (0.28–3.82)

Note: Models are adjusted for study cohort, living on a farm, gender, maternal history of allergic diseases (hay fever, atopic dermatitis, and/or asthma), smoking during pregnancy, and the number of siblings. The reference group in phenotypes is Never/Infrequent wheeze and in the exposure group as stated in the table.

[a]Cannot be estimated.

The general estimate of the degree of damage was defined as "need for repair" class of the damage in the whole house, *p*-value ^<.1, *<.05.

Bold value indicates significant *p* - value.

birth cohort.[11] Consensus over the identification of wheezing phenotypes is important as previous findings indicate that in particular persistent and recurrent wheezing during early childhood years is associated with an asthma diagnosis and lung function decline throughout later childhood.[29,30] In our study, early age exposure to moisture damage and visible mold in the child's main living areas (living room, kitchen, and child's bedroom) was most notably associated with the persistent wheezing phenotype. This underlines the importance of measures to repair moisture damages at home and helps to target those efforts.

4.3 | Results in comparison with previous findings

In line with the present findings, we reported previously from the same study population that early age exposure to residential

moisture damage and mold in the child's main living area was associated with an increased risk of asthma ever and asthma at the age of 6 years.[6] The latter is likely to remain symptomatic until adulthood.[31] Accordingly, excluding asthmatics from the analyses still showed the same trend, however, a meaningful interpretation was hampered due to the small numbers.

In the current study, moisture damage or mold in the child's main living areas further tended to be associated with the transient wheezing phenotype, mainly driven by associations with moisture observations in the kitchen. We have reported earlier that moisture damage or mold in the kitchen was associated with asthma or asthmatic bronchitis in the first 18 months of life,[5] but was not associated with persistent asthma at the age of 6 years.[6] We can only speculate about the possible reasons for this specific finding, in addition to small numbers. Depending on the age of the child, their occupancy patterns with respect to time spent in different rooms of the apartment are likely to change. Transient wheezing was associated with wheezing that occurs at an early age when children typically spend more time with their parents, including in the kitchen when the parents prepare food. At the later age of the child, this aspect might become less important and the kitchen, for example, might no longer be as relevant with respect to exposure duration. In contrast, if the moisture damage or mold is located in the main living areas, such as the child's bedroom or the living room, the exposure time can be assumed to remain somewhat similar throughout childhood. In addition, it has been suggested that atopic children might be more affected by environmental exposures and thus prone to persistent wheezing. Compared to that, transient wheezing is often associated with early life respiratory infections, thus less affected by the environment.[11,28]

To the best of our knowledge, this is the first study looking at *objectively* assessed early age moisture and mold exposure in relation to different wheezing phenotypes obtained by hypothesis-free LCA in a general population. A very similar study protocol was followed in an atopic cohort (the Cincinnati Childhood Allergy and Air Pollution Study, CCAAPS), which used home investigation for moisture damage and mold at an early age, but used clinical asthma phenotypes defined by parental-reported records instead of hypothesis-free LCA.[32] Similarly, they observed that children had a significantly increased risk of persistent wheezing until the age of 7 years upon exposure to objectively observed severe moisture and mold damage in the home at an early age.[32] However, the weakness of the study was that the results were not as generalizable due to the nature of an atopic cohort as compared to the results from our cohort. In another birth cohort study (Barn/Child Allergy Milieu Stockholm Epidemiology, BAMSE) with the follow-up up to the age of 16 years, parents reported mold odor, visible mold, or dampness in the whole home at an early age, and clinical asthma phenotypes defined by parental-reported records was used.[33] Among children exposed to any parent-reported mold or dampness at an early age, a significantly increased risk was observed for persistent, but not for the transient or late-onset asthma phenotype, as was found in our cohort with shorter follow-up time. Among 18 months old children from the PARIS (Pollution and Asthma Risk: An Infant Study) birth cohort, three wheezing phenotypes were identified by LCA.[34] Parent-reported visible mold and/or moldy smell in the home was a risk factor for the atopic severe phenotype, which was associated with recurrent wheezing, other respiratory as well as allergic symptoms and an increased usage of medical and hospital-based care. Due to the short follow-up period, it is hard to separate children from early transient wheezing phenotype to persistent phenotype.

Based on the evidence from our study and others, early age exposure to moisture damage and mold is associated specifically with a more severe, partly atopic wheezing phenotype, characterized by persistency and frequent episodes. In addition, there are a few studies looking at the association between wheezing phenotypes and exposure to moisture and/or mold without using an a priori data-driven approach. According to Civelek et al.,[32] current but not early age exposure to mold and dampness was associated with frequent wheezing in a multi-center cross-sectional analysis among over 6000 elementary school children in Turkey. Finally, Lezmi and colleagues showed in a French multicenter observational cohort that exposure to residential mold was significantly associated with severe recurrent wheezing in preschoolers that were at high risk of asthma.[35] Taken together, the findings of our and previous investigations consistently suggest that exposure to moisture damage and mold in early and throughout infancy are associated in particular with persistent and recurrent wheezing, which in turn is a risk factor for later asthma outcomes.

4.4 | Strengths and limitations

Our study used information on moisture damage and mold observations from a home inspection carried out by trained civil engineers following standardized protocols, which is a more objective assessment compared to for instance parent reports. Due to detailed records of the observations, we were able to estimate the dose of the exposure using mostly three-level indicators and information on location. We also collected the information on wheezing prospectively, and thus, neither recall bias nor the well-known difficulties with asthma diagnoses—that is, asthma diagnoses at an early age may lead to a false positive classification of asthma—could have affected our results. As mentioned, this is the first study investigating inspector observed early age exposure to moisture damage and mold in relation to wheezing phenotypes ascertained by latent class analyses in population-based birth cohorts. Although there are limitations due to a limited sample size, our work confirmed earlier findings from similar studies in different geographical regions, underlining that moisture and mold damage in early infancy might contribute to later asthma outcomes. However, due to the low numbers of observations in the individual phenotypes in our study, some estimates may be unstable and the results need to be interpreted with caution.

5 | CONCLUSION

Our results add to earlier findings that exposure during infancy to moisture damage and mold in the child's main living areas in the home, increases the risk of especially persistent wheezing, thereby potentially contributing to asthma outcomes later in life. These findings emphasize the importance of providing a healthy home environment free of major moisture damages during early childhood, in an effort to reduce the risk of later asthma.

AUTHOR CONTRIBUTIONS

Martin Taubel: Writing – review and editing (equal). **Pirkka Kirjavainen:** Writing – review and editing (equal). **Martin Depner:** Writing – review and editing (equal). **Anne Hyvärinen:** Writing – review and editing (equal). **Eija Piippo-Savolainen:** Writing – review and editing (equal). **Juha Pekkanen:** Conceptualization (lead); funding acquisition (lead); writing – review and editing (equal). **Anne Karvonen:** Conceptualization (lead); formal analysis (lead); methodology (lead); writing – review and editing (supporting).

ACKNOWLEDGMENTS

We gratefully acknowledge the contribution of our fieldworkers Raija Juntunen, Riikka Juola, and Seija Antikainen, civil engineers Juho Halla-aho and Jari Koivisto, as well as Timo Kauppila and Asko Vepsäläinen, for help with data management. We further like to thank Dr. Sabina Illi for her help and support in the statistical analysis. Ultimately, we would like to thank the families for their participation in the study.

FUNDING INFORMATION

This study was supported by research grants from the European Union QLK4-CT-2001-00250; EVO- and VTR-funding; the Academy of Finland (grant 139021, 287675, 338679, 339666); the Juho Vainio Foundation; the Yrjö Jahnsson foundation; Päivikki and Sakari Sohlberg foundation; the Finnish Cultural Foundation; and by the Finnish Institute for Health and Welfare, Finland.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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How to cite this article: Tischer C, Täubel M, Kirjavainen PV, et al. Early-life residential exposure to moisture damage is associated with persistent wheezing in a Finnish birth cohort. *Pediatr Allergy Immunol*. 2022;33:e13864. doi:10.1111/pai.13864