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Mold and dampness exposure and allergic outcomes from birth to adolescence: data from the BAMSE cohort

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Abstract

Background: Exposure to moldy or damp indoor environments is associated with allergic disease in young children, but it is unclear whether the effects persist to adolescence. Our objective was to assess whether exposure to mold or dampness during infancy increases the risk of asthma, rhinitis, or IgE sensitization in children followed from birth to 16 years of age.

Methods: We collected questionnaire derived reports of mold or dampness indicators and allergic outcomes from 3798 children in a Swedish birth cohort (BAMSE). Sensitization was assessed from blood samples in 3293 children. Longitudinal associations between prevalent asthma, rhinitis, and IgE sensitization and mold or dampness indicators were assessed using generalized estimating equations.

Results: Exposure to any mold or dampness indicator was associated with asthma up to 16 years of age (OR 1.31; 95% CI 1.08–1.59), while exposure to mold odor (OR 1.29; 95% CI 1.03–1.62) and visible mold (OR 1.28; 95% CI 1.04–1.58) were associated with rhinitis. Increased risks were observed for nonallergic asthma (OR 1.80; 95% CI 1.27–2.55) and rhinitis (OR 1.41; 95% CI 1.03–1.93). No association was observed between mold or dampness indicators and IgE sensitization. Exposure to any mold or dampness indicator was associated with persistent asthma (OR 1.73; 95% CI 1.20–2.50), but not with early-transient or late-onset asthma.

Conclusion: Exposure to mold or dampness during infancy increased the risk of asthma and rhinitis up to 16 years of age, particularly for nonallergic disease. Early exposure to mold or dampness appeared particularly associated with persistent asthma through adolescence.

Indoor mold and dampness is a major environmental problem globally, with estimates ranging from 18% to 50% of household dwellings (1–3). Efforts to improve household energy efficiency and reduce heat loss can increase the risk of dampness and fungal contamination (4). Excessive indoor dampness fosters microbial proliferation and results in exposure to various microbial agents, like spores and cell fragments containing toxins, inflammatory substances, and allergens (5). These substances have been shown to cause irritation and immunostimulation, and induce inflammatory processes (6). Exposure to mold and dampness has been suggested to increase the risk of asthma and allergic disease, and both allergic and nonallergic pathways have been proposed (7).

In epidemiological studies, exposure to a moldy or damp indoor environment in early life has been associated with atopic diseases such as asthma, rhinitis, and immunoglobulin E (IgE) sensitization in young children (7–10). The most consistent and highest excess risks have been noted for asthma (8) and rhinitis (11), while fewer and less conclusive studies have been conducted for IgE sensitization (6). Studies have attempted to elucidate the association between exposure to moldy indoor environments early in life and allergic health outcomes in school age (10, 12, 13), but the results have been

inconsistent and few prospective studies have followed children beyond 10 years of age (8, 14, 15). Furthermore, the role of dampness and mold for persistence and late-onset asthma is not clear (16).

The purpose of this study was to assess whether exposure to mold or dampness during infancy influences the risk of asthma, rhinitis, or IgE sensitization in children followed prospectively from birth to adolescence. In conjunction, we assessed clinical phenotypes of asthma, looking at the timing of onset and persistence of symptoms.

Methods

Study design and population

This study utilizes data collected within the Swedish BAMSE (Barn/Child Allergy Milieu Stockholm Epidemiology) study, described elsewhere (17). Briefly, 4089 children born in selected areas of Stockholm County between February 1994 and November 1996 were recruited and followed for 16 years. Both urban and suburban areas were represented, with different building construction types and differences in socioeconomic status. When children were a median age of 2 months, parents completed a baseline questionnaire which gathered information on various environmental and behavioral factors including housing characteristics, sociodemographics, and parental history of allergic disease. Subsequent questionnaires were completed by parents at 1, 2, 4, 8, 12, and 16 years of age and included questions concerning children's symptoms of asthma and rhinitis. Follow-up response rates were 96%, 94%, 91%, 84%, 82%, and 78%, respectively.

When having filled out the questionnaires, at 4, 8, and 16 years of age, children were invited to participate in a clinical examination, and blood samples were collected. Serological allergy IgE testing was performed in 2605 (63.7%), 2470 (60.4%), and 2547 (62.2%) children at 4, 8, and 16 years of age, respectively.

The BAMSE study and subsequent follow-ups were approved by the Regional Ethical Review Board, Karolinska Institutet, Stockholm, Sweden, and all parents provided informed consent for data collection and analysis.

Definitions of exposure

Data on infant indoor environmental exposures were based on parental questionnaires collected at baseline (2 months). We defined five variables of moisture-related problems from the answers to the following questions.

Mold odor—'Is there, or has there ever been, a smell of mildew in the home?'

Visible mold—'Has there been any visible mold in the home in the past year (prior to the date of the baseline questionnaire)?'

Dampness damage—'Is there, or has there ever been, any type of moisture damage (spots or similar) in the home?'

Any mold or dampness indicator—The presence of any of the three aforementioned exposure indicators.

Exposure score—The sum of mold and dampness indicators (ranging from 0 to 3).

Participants who answered 'I don't know' to the above questions were coded as missing.

Definition of health outcomes

Asthma and rhinitis at 1–16 years of age were based on symptoms reported by parents from questionnaires and were defined as follows:

Asthma—four or more episodes of wheeze in the last 12 months or one or more episode of wheeze in the last 12 months in combination with inhaled steroids (18).

Rhinitis—eye or nose symptoms following exposure to allergens in the last 12 months and/or a doctor's diagnosis of allergic rhinitis (18).

To examine the timing of onset and persistence, asthma was categorized into three distinct clinical phenotypes: early-transient, persistent, and late-onset disease (19). Early-transient asthma was classified as having asthma at 1, 2, or 4 years of age but not again at any subsequent follow-ups. Persistent asthma was classified as having asthma at 1, 2, or 4 years of age and then again at 8, 12, or 16 years of age. Late-onset asthma was defined as having the first incidence of asthma at 8, 12, or 16 years of age.

IgE sensitization was defined as positive if serum antibody levels reached the technical cutoff of $\geq$0.35 kU_A/l for Phadiatop® (mix of pollens of birch, timothy, and mugwort, danders of cat, dog, and horse, mold, and house dust mite) or Fx5® (a mix of cow's milk, hen's egg, soybean, peanut, cod fish, and wheat) (ImmunoCAP System; Thermo Fisher/Phadia AB, Uppsala, Sweden) (20).

To assess the effect of mold or dampness indicators with allergic and nonallergic phenotypes, we constructed categorical variables of asthma and rhinitis combined with and without sensitization, with subjects without asthma/rhinitis and sensitization as the reference category.

Statistical analyses

Differences in the distribution of covariates in relation to any mold or dampness indicator were assessed using the chi-square test. Longitudinal associations of mold or dampness indicators with asthma, rhinitis, and sensitization from birth to 16 years of age were evaluated by generalized estimating equation (GEE) models with an unstructured correlation matrix (21).

Multinomial GEE models were used to assess the associations between mold or dampness indicators and allergic phenotypes of asthma and rhinitis, and logistic regression was used to assess clinical phenotypes of asthma.

Potential confounders—sex, parental allergic disease (maternal or paternal history of asthma or hay fever), construction year of home (before 1961, 1961–1975, after 1975), type of home (single family, multifamily), older siblings (yes, no), maternal age (<26 years, $\geq$26 years), socioeconomic status (categorized on the basis of parents' occupation as manual and nonmanual workers), maternal smoking during

pregnancy (≥1 cigarette/day at any time during pregnancy), parental smoking during infancy (either parent smoking ≥1 cigarette/day at baseline), exclusive breastfeeding (<4 months, ≥4 months), air pollution from local road traffic [using NO_x as a continuous indicator (22)], furred pets at home (yes, no), birthweight (in grams), children's own smoking at 16 years of age (yes, no), and day care attendance in the first 2 years (yes, no)—were tested using exploratory forward stepwise logistic regression. Dust mite allergen sensitization was also tested as a potential confounder but did not significantly alter effect estimates. Final models were adjusted for putative risk factors based on prior knowledge or covariates leading to more than 5% change in estimates and included sex, socioeconomic status, parental allergic disease, maternal smoking during pregnancy, parental smoking during infancy, maternal age, and older siblings.

We stratified our data based on building construction periods (before 1961, 1961–1975, after 1975) because various building materials and techniques have been used during different periods. In addition, potential effect modification by parental allergic disease was tested by interaction and stratification models.

Children who provided a baseline measure of any mold or dampness indicator and participated in three or more follow-ups were included in the final analyses (N = 3798, 93% of baseline cohort). Children providing at least one blood sample from 4, 8, or 16 years of age were included in analyses of sensitization (N = 3293, 81%).

Associations are presented as odds ratios (ORs) and 95% confidence intervals (95% CIs) and STATA (release 12; Stata Corp., College Station, TX, USA) and R, version 3.2.2 (R Core Team, 2012), were used for statistical analyses.

Results

The 3798 children included in our study population did not differ from the complete cohort (N = 4089) with regard to the distribution of risk factors (Table S1). At baseline, 299 (9.1%) of children were exposed to mold odor, 325 (8.6%) to visible mold, 758 (23.5%) to dampness damage, and 967 (30.4%) to any mold or dampness indicator. The overlap between mold odor, visible mold, and dampness damage is presented in Fig. S1. Dampness damage was the most prevalent mold or dampness indicator, and coincided with both visible mold and mold odor.

Exposure to any mold or dampness was more prevalent among children exposed to maternal smoking during pregnancy, parental smoking during infancy, parental allergic disease, shorter duration of breastfeeding, younger mothers, lower socioeconomic status, pet ownership, having older siblings, and homes constructed 1975 and earlier (Table 1).

At 16 years of age, 199 (6.4%) of children had asthma, 785 (25.4%) had rhinitis, and 1162 (45.9%) were sensitized to any food or aeroallergen.

In longitudinal analyses up to 16 years of age, exposure to mold odor, visible mold, and dampness damage as an infant were all associated with an overall increased risk of prevalent asthma (Fig. 1). Increased risks for prevalent rhinitis through 16 years of age were also observed among children exposed to mold odor (OR 1.29; 95% CI 1.03–1.62) and visible mold (OR 1.28; 95% CI 1.04–1.58), but not for dampness damage. No apparent associations were observed between any mold or dampness indicator and IgE sensitization to airborne or food allergens. Following adjustment for mold and dampness indicators during the follow-up, our findings remained relatively unchanged (Fig. S2).

In exposure–response analyses, we observed a significant trend for increased odds of asthma with increasing exposure score (P_{trend} = 0.002) (Table 2). Children exposed to all three indicators of mold or dampness had an overall increased odds of asthma up to 16 years of age (OR 1.73; 95% CI 1.10–2.74) compared with those unexposed to mold or dampness. A positive trend was also suggested for rhinitis (P_{trend} = 0.14), but not for aeroallergen or food allergen sensitization.

The association between any mold or dampness indicator with allergic and nonallergic phenotypes of asthma and

Table 1 Distribution of selected exposure characteristics in relation to any mold or dampness indicator at baseline among children in the BAMSE birth cohort (n = 3798)

	Exposure to any mold or dampness indicator				
	No n = 2215 (69.6%)		Yes n = 967 (30.4%)		
	n	%	n	%	P-value*
Male sex	1117	50.4	476	49.2	0.53
Maternal smoking during pregnancy†	243	11.0	141	14.6	<0.01
Parental smoking during infancy‡	400	18.2	234	24.4	<0.001
Parental allergic disease§	601	27.3	341	35.6	<0.001
Maternal age < 26 years¶	136	6.1	82	8.5	0.02
Socioeconomic status**					
Manual workers	309	14.1	179	18.8	<0.01
Nonmanual workers	1880	85.9	775	81.2	
Exclusive breastfeeding ≥ 4 months	1777	81.5	732	77.1	<0.01
Furred pets at home**	312	14.1	171	17.7	<0.01
Older siblings**	1056	47.7	505	52.2	0.02
Construction year of home**					
Before 1961	1058	47.8	532	55.1	<0.001
1961–1975	452	20.4	270	28.0	
After 1975	703	31.8	164	17.0	
Type of home**					
Single family	404	18.2	187	19.3	0.63
Multifamily	1810	81.7	779	80.6	

*P-values obtained from chi-square test.
†Mother smoked at least 1 cigarette per day at any point in time during pregnancy.
‡Mother or father smoking at least one cigarette daily.
§Mother or father with history of asthma or hay fever.
¶At birth of the child.
**At baseline.

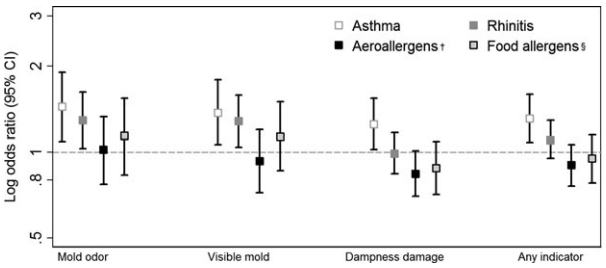

Figure 1 Association between exposure to mold or dampness indicators during infancy and the overall risk of asthma, rhinitis, or sensitization to aero- or food allergens during the first 16 years of life among children in the BAMSE birth cohort ($n = 3798$)*. *Odds ratios (OR) and 95% confidence intervals (CI) obtained from generalized estimating equation (GEE) adjusted for sex, parental allergic disease, socioeconomic status, maternal smoking during pregnancy, parental smoking in the first 2 months, maternal age < 26 years, and presence of siblings. †Sensitization to cat, dog, horse, mite, timothy, birch, mugwort, or mold. §Sensitization to cow's milk, hen's egg, soybean, peanut, cod fish, or wheat.

rhinitis is summarized in Table 3. Among children exposed to any mold or dampness indicator during infancy, increased risks were observed for nonallergic asthma (OR 1.80; 95% CI 1.27–2.55) and nonallergic rhinitis (OR 1.41; 95% CI 1.03–1.93), but no associations were observed for allergic asthma or rhinitis. Similar patterns were observed when exposure to mold odor, visible mold, and dampness damage was analyzed separately (data not shown).

In analyses of clinical phenotypes of asthma, children exposed to any mold or dampness indicator during infancy had an increased odds of persistent asthma (OR 1.73; 95% CI 1.20–2.50), but not early-transient or late-onset asthma (Fig. 2). The association between asthma clinical phenotypes with mold odor, visible mold, and dampness damage provided a similar picture for persistent asthma. Exposure to dampness damage was associated with late-onset asthma (OR 1.41; 95% CI 1.02–1.95).

Comparable odds ratios for asthma were observed across strata of building construction periods (Tables 4 and S2). For rhinitis, somewhat higher odds ratios were suggested among children living in buildings constructed after 1975. However, there were no significant interactions between any mold or dampness indicator and year of construction for either asthma or rhinitis (data not shown).

In addition, exposure to any mold or dampness indicator was associated with comparable odds ratios for asthma among children with (OR 1.49; 95% CI 1.10–2.02) and without (OR 1.21; 95% CI 0.93–1.57) parental allergic disease (Table S3). In an interaction model, no statistical significant interaction was suggested ($P = 0.35$). Likewise, no differences between strata or significant interaction was observed for rhinitis ($P = 0.94$).

In a sensitivity analysis of movers ($n = 3135$) and nonmovers ($n = 663$), children exposed to visible mold during infancy and moved had increased risks for asthma (OR 1.49; 95% CI 1.14–1.96) and rhinitis (OR 1.41; 95% CI 1.13–1.77) that was not observed in nonmovers (Table S4). Analogous results were seen for mold odor, while an increased risk of asthma was suggested for both movers and nonmovers among children exposed to dampness damage or any indicator.

Table 2 Severity of exposure to mold or dampness indicators* in relation to overall asthma, rhinitis, and sensitization among children in the BAMSE cohort ($n = 3798$)

	Exposure score (crude model†) OR (95% CI)	Exposure score (adjusted model‡) OR (95% CI)
Asthma		
No mold or dampness indicator	Reference	Reference
1 indicator	1.24 (1.00–1.55)	1.16 (0.93–1.44)
2 indicators	1.47 (1.09–2.00)	1.37 (1.01–1.86)
3 indicators	2.00 (1.26–3.16)	1.73 (1.10–2.74)
P-value for trend	<0.001	<0.01
Rhinitis		
No mold or dampness indicator	Reference	Reference
1 indicator	1.09 (1.02–1.21)	1.03 (0.87–1.22)
2 indicators	1.24 (0.97–1.59)	1.18 (0.92–1.52)
3 indicators	1.43 (0.96–2.13)	1.23 (0.82–1.85)
P-value for trend	0.01	0.14
Aeroallergen sensitization§		
No mold or dampness indicator	Reference	Reference
1 indicator	0.94 (0.78–1.14)	0.94 (0.77–1.13)
2 indicators	0.83 (0.62–1.11)	0.85 (0.63–1.14)
3 indicators	1.01 (0.63–1.62)	0.90 (0.55–1.48)
P-value for trend	0.30	0.23
Food allergen sensitization¶		
No mold or dampness indicator	Reference	Reference
1 indicator	0.87 (0.70–1.09)	0.87 (0.69–1.09)
2 indicators	0.99 (0.71–1.38)	1.02 (0.73–1.42)
3 indicators	1.33 (0.80–2.22)	1.22 (0.72–2.07)
P-value for trend	0.93	0.99

*Mold odor, visible mold, or dampness damage.
†Crude odds ratio (OR) and 95% confidence intervals (CI) obtained from generalized estimating equation (GEE).
‡Odds ratio (OR) and 95% confidence intervals (CI) obtained from GEE adjusted for sex, socioeconomic status, parental allergic disease, maternal smoking during pregnancy, parental smoking during infancy, maternal age < 26 years, and presence of siblings.
§Sensitization to cat, dog, horse, mite, timothy, birch, mugwort, or mold.
¶Sensitization to cow's milk, hen's egg, soybean, peanut, cod fish, or wheat.

Discussion

In this prospective birth cohort study, we found that exposure to mold or dampness indicators during infancy increased the odds of asthma through adolescence. An increase in the

Table 3 Exposure to any mold or dampness indicator in relation to allergic phenotypes of asthma and rhinitis up to 16 years of age among children in the BAMSE cohort (n = 3798)

	Any mold or dampness indicator (crude model*) OR (95% CI)	*P*-value	Any mold or dampness indicator (adjusted model†) OR (95% CI)	*P*-value
Asthma				
No asthma and no sensitization‡	Reference		Reference	
No asthma but sensitization	1.13 (0.82–1.57)	0.44	1.02 (0.73–1.41)	0.92
Nonallergic asthma	2.02 (1.43–2.87)	<0.001	1.80 (1.27–2.55)	<0.001
Allergic asthma	0.92 (0.79–1.08)	0.33	0.92 (0.78–1.08)	0.31
Rhinitis				
No rhinitis and no sensitization‡	Reference		Reference	
No rhinitis but sensitization	1.02 (0.82–1.25)	0.89	1.00 (0.81–1.25)	0.97
Nonallergic rhinitis	1.62 (1.19–2.21)	<0.01	1.41 (1.03–1.93)	0.03
Allergic rhinitis	0.91 (0.77–1.07)	0.25	0.88 (0.74–1.05)	0.14

*Crude odds ratio (OR) and 95% confidence intervals (CI) obtained from multinomial generalized estimating equation (GEE).
†Odds ratio (OR) and 95% confidence intervals (CI) obtained from multinomial GEE adjusted for sex, socioeconomic status, parental allergic disease, maternal smoking during pregnancy, parental smoking during infancy, maternal age < 26 years, and presence of siblings.
‡Sensitization is to any allergen (food or aeroallergens).

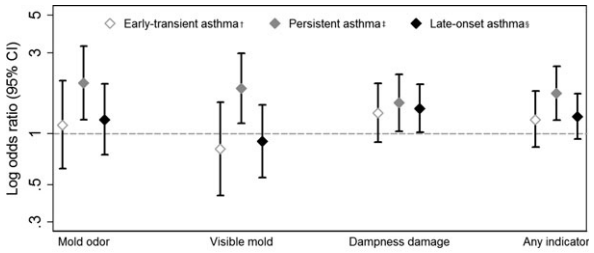

Figure 2 Exposure to mold or dampness indicators at baseline and early-transient, persistent, and late-onset asthma among children in the BAMSE cohort (n = 3798)*. *Odds ratios (OR) and 95% confidence intervals (CI) obtained from logistic regression adjusted for sex, parental allergic disease, socioeconomic status, maternal smoking during pregnancy, parental smoking in the first 2 months, maternal age < 26 years, and presence of siblings. †Early-transient asthma defined as asthma occurrence at age 1, 2, or 4 years of age but not at age 8, 12, or 16 years of age. ‡Persistent asthma defined as asthma occurrence at age 1, 2, or 4 years of age and again at age 8, 12, or 16 years of age. §Late-onset asthma defined as first occurrence of asthma at age 8, 12, or 16 years of age.

number of mold and dampness indicators was associated with a greater risk of asthma. Similarly, infants exposed to mold odor or visible mold had an increased risk of rhinitis. These associations remained following adjustment for mold and dampness indicators throughout follow-up. In analyses of allergic phenotypes, the association was confined to nonallergic asthma and rhinitis. No association was observed between mold and dampness indicators and IgE sensitization to aero- or food allergens. Looking at clinical phenotypes, exposure to mold or dampness was associated with persistent asthma, but not with early-transient or late-onset asthma.

Our results are in line with other studies reporting associations between early mold or dampness exposures and asthma in young children (3, 8, 10, 23). In addition, we demonstrated that exposure to mold or dampness indicators in early infancy was associated with an increased risk of asthma up to 16 years of age. Few prospective studies have been able to examine this association beyond 10 years of age, and a German birth cohort showed no association between exposure to mold in early in life and asthma up to 20 years of age (15).

Our findings for rhinitis are also consistent with recent studies of infants, children, and adults, which found increased risks related to mold or dampness exposure in the home (8, 23, 24). Likewise, a systematic review concluded that the highest risk of rhinitis was among those exposed to mold odor and visible mold (11).

Previous studies of allergic and nonallergic phenotypes of asthma and rhinitis have shown conflicting results (9, 25, 26), but our data support the findings that the association is confined to nonallergic asthma and rhinitis (9). In addition, the lack of association between mold and dampness indicators and IgE sensitization in our study is in line with some (6, 8, 10) but not all previous studies (27–30).

Our study is unique in that we were able to assess clinical phenotypes of asthma and track the onset and persistence of asthma. We show that early exposure contributes to persistent asthma symptoms through adolescence, but not to early-transient asthma. Rhinitis is rather uncommon before school age (31, 32); therefore, we chose not explore clinical phenotypes of rhinitis in the present study.

Our finding that early-life exposure to mold or dampness may play a role for development of asthma and rhinitis is analogous to corresponding associations for other environmental exposures such as air pollution or secondhand tobacco smoke (18, 33, 34). These findings lend support to the hypothesis that early-life exposures contribute to health outcomes later in life.

Early-life exposure to molds could cause recurrent irritation and immune activation in the respiratory tract, inducing prolonged inflammation, prompting the genesis of inflammatory-related diseases, like asthma and rhinitis (10, 23). Certain fungal species are associated with inflammatory

Table 4 Associations between mold or dampness indicators and asthma or rhinitis among children in the BAMSE cohort ($n = 3798$) stratified by building construction year*

	Asthma					
	Before 1961 ($N = 1998$) OR (95% CI)	*P*-value	1961–1975 ($N = 973$) OR (95% CI)	*P*-value	After 1975 ($N = 1115$) OR (95% CI)	*P*-value
Mold odor	1.65 (1.14–2.40)	<0.01	1.34 (0.76–2.36)	0.31	1.34 (0.72–2.50)	0.35
Visible mold	1.47 (1.01–2.14)	0.04	1.14 (0.66–1.99)	0.64	1.59 (0.95–2.69)	0.08
Dampness damage	1.25 (0.91–1.71)	0.16	1.28 (0.88–1.86)	0.20	1.46 (0.95–2.23)	0.08
Any indicator	1.32 (0.98–1.78)	0.06	1.27 (0.88–1.83)	0.21	1.59 (1.09–2.32)	0.02
	Rhinitis					
	Before 1961 OR (95% CI)	*P*-value	1961–1975 OR (95% CI)	*P*-value	After 1975 OR (95% CI)	*P*-value
Mold odor	1.24 (0.91–1.69)	0.17	1.22 (0.76–1.97)	0.40	1.97 (1.20–3.22)	<0.01
Visible mold	1.24 (0.92–1.66)	0.16	1.19 (0.78–1.84)	0.42	1.79 (1.17–2.75)	<0.01
Dampness damage	1.08 (0.86–1.37)	0.51	0.99 (0.72–1.37)	0.97	1.04 (0.72–1.50)	0.84
Any indicator	1.14 (0.92–1.42)	0.24	1.04 (0.77–1.41)	0.80	1.35 (0.99–1.84)	0.06

*Odds ratio (OR) and 95% confidence intervals (CI) obtained from generalized estimating equation adjusted for sex, socioeconomic status, parental allergic disease, maternal smoking during pregnancy, parental smoking during infancy, maternal age < 26 years, and presence of siblings.

processes, and molds may contain substances which have inflammatory effects such as β-1-3-glucans in the cell wall structure, microbial volatile organic compounds (mVOCs), extracellular polysaccharides, and mycotoxins (3, 6, 8, 35). Our results indicate that exposure to any mold or dampness indicator primarily increases the risk of nonallergic asthma and rhinitis, which may speak in favor of irritative rather than allergic inflammatory changes in the airways. Evidence from a case–control study suggests that nonallergic asthmatics have higher nasal and bronchial epithelia sensitivity to nonallergic factors like strong smells, air pollution, cold air, and respiratory viruses, compared with allergic asthmatics (36). Supporting our findings, two mouse models identified fungal glucans [(1→3)-β-D-glucans] and toxic metabolites to influence nonallergic inflammatory respiratory effects, such as increased concentrations of leukocytes and pro-inflammatory cytokines in bronchoalveolar lavage fluid (37, 38).

Somewhat higher risks of rhinitis were suggested among children living in homes built after 1975 compared with children living in homes constructed prior to 1961. This is in line with a previous study in Swedish adults that indicated higher risks of current rhinitis among those living in homes constructed from 1976 to 1985 (39). Buildings constructed from 1976 to 1985 were influenced by energy saving constraints due to the rapid rise in oil prices in 1974, and utilized novel building materials and techniques (40). Furthermore, in Sweden from 1977 to 1983 a self-leveling mortar containing the protein casein was utilized, but has since shown to emit certain chemicals such as ammonia and sulfhydryl compounds when exposed to dampness (39).

In analyses stratified on moving status, visible mold or mold odor was associated with an increased risk of asthma and rhinitis among children who had ever moved, but not among the nonmovers. One could speculate that among families that moved, some may have done so due to a suspected or apparent mold problem. However, as 83% of the cohort moved during follow-up, the numbers are low among nonmovers, and no reasons for moving were queried, so these results cannot be ruled out as spurious findings.

The prospective design, large number of participants, high retention rate, and repeated assessments of allergic disease at six different time points are significant strengths of our study. The longitudinal design allowed us to investigate the temporal sequence between early-life exposure and health outcomes up to adolescence, and to study the timing of onset and persistence of these allergic diseases.

Several limitations to our study should be acknowledged. Exposure to mold and dampness were ascertained by parental questionnaires, and some exposure misclassification is probable. Questionnaire-based data are subjective and lack sensitivity and specificity. For example, perceived mold odor in the home may in fact be from chloroanisoles, which are produced by microbes that methylate chlorophenols in wood preservatives in moist conditions, but which do not necessarily indicate major problems with dampness and molds as the odor thresholds of some common chloroanisoles are extremely low (41). Home inspection is a more standardized way of assessing exposure, but it is not often feasible to perform with a large number of participants and homes, and interinspector variation is common (5, 42). In the BAMSE birth cohort, a subset of 540 children's homes were inspected between the child's age of 1 and 2 years for dampness and mold indicators. The overall agreement between the parental reported and inspector noted signs of mold and dampness was rather weak, but increased odds of recurrent wheezing in infancy were observed for both exposures (43). Parents and inspectors reported at different times, so remediation of dampness or mold problems could have occurred prior to the inspector's visit. In this subset of our cohort, families with parental allergic disease more often reported problems with

mold or dampness, and also had a tendency toward higher measured values of indoor humidity (43). In the present analyses, risk estimates for asthma and rhinitis were elevated both among children with and without parental allergic disease. Outcome misclassification can be a concern when analyzing data collected by questionnaires, but the definitions of asthma and rhinitis used in this study were modified based on the validated ISAAC questionnaire (44) and have been used in prior publications (18, 31).

In conclusion, our findings indicate that exposure to mold or dampness during infancy increases the risk of asthma and rhinitis through 16 years of age, particularly for disease without IgE sensitization. Early exposure to mold or dampness may be particularly associated with persistent asthma up to adolescence.

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Author contributions

JDT, OG, GP, EM, JCL, IK, and AB contributed to the design and planning of this study, participated in the interpretation of the findings, and critically revised the manuscript. JDT performed the data analyses and drafted the initial manuscript. All authors approved the final manuscript as submitted.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Distribution and proportional relationship of mold odor, visible mold, and dampness damage exposure at baseline among children in the BAMSE cohort (n = 2983).

Figure S2. Association between exposure to mold or dampness during infancy and the overall risk of asthma, rhinitis, or sensitization during the first 16 years of life after adjustment for exposure during follow-up among children in the BAMSE cohort (n = 3798).*

Table S1. Distribution of selected exposure characteristics among all children in the BAMSE cohort (N = 4089) and children included in the current analyses (n = 3798).

Table S2. Associations between mold or dampness indicators and asthma or rhinitis among children in the BAMSE cohort (n = 3798) stratified by building construction year.*

Table S3. Association between any mold or dampness exposure and asthma or rhinitis among children in the BAMSE cohort (n = 3798) stratified by parental allergic disease.*

Table S4. Associations between early mold or dampness and allergy stratified by ever movers and non-movers.*

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