Meta-analysis of mould and dampness exposure on asthma and allergy in eight European birth cohorts: an ENRIECO initiative


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Keywords
asthma; environment; epidemiology; moulds; pediatrics; rhinitis.

Abstract

Background: Several cross-sectional studies during the past 10 years have observed an increased risk of allergic outcomes for children living in damp or mouldy environments.

Objective: The objective of this study was to investigate whether reported mould or dampness exposure in early life is associated with the development of allergic disorders in children from eight European birth cohorts.

Methods: We analysed data from 31 742 children from eight ongoing European birth cohorts. Exposure to mould and allergic health outcomes were assessed by parental questionnaires at different time points. Meta-analyses with fixed- and random-effect models were applied. The number of the studies included in each analysis varied based on the outcome data available for each cohort.

Results: Exposure to visible mould and/or dampness during first 2 years of life was associated with an increased risk of developing asthma: there was a significant association with early asthma symptoms in meta-analyses of four cohorts [0–2 years: adjusted odds ratios (aOR), 1.39 (95%CI, 1.05–1.84)] and with asthma later in childhood in six cohorts [6–8 years: aOR, 1.09(95%CI, 0.90–1.32) and 3–10 years: aOR, 1.10 (95%CI, 0.90–1.34)]. A statistically significant association was observed in six cohorts with symptoms of allergic rhinitis at school age [6–8 years: aOR, 1.12 (1.02–1.23)] and at any time point between 3 and 10 years [aOR, 1.18 (1.09–1.28)].

Conclusion: These findings suggest that a mouldy home environment in early life is associated with an increased risk of asthma particularly in young children and allergic rhinitis symptoms in school-age children.
Reviews conducted in the past 10 years have found an increased risk of respiratory and allergic health outcomes in children with a parent-reported damp and mouldy home environment (1–5). Although a small number of collaborative investigations have consistently reported increased risks of asthma, wheeze and allergic rhinitis in children exposed to visible mould (6–8), these previous studies have been primarily cross-sectional, comprised different definitions of exposure and health outcome and assessed the health outcome at a single time point. The Environmental Health Risks in European Birth Cohorts (ENRIECO) initiative included only population-based prospective birth cohort studies and allows for investigation into allergic health outcomes from birth to 10 years of age in a large, comprehensive, longitudinal data set from eight European studies. The objective of this investigation was to assess whether early residential exposure to mould/dampness up to 2 years is associated with the development of asthma, symptoms of allergic rhinitis and sensitization in children at different time points between birth and 10 years.

**Methods**

**Birth cohort characteristics**

ENRIECO is a project conducted within the European Union’s Seventh Framework Programme [Theme 6, Environment (Including Climate Change)] focusing on the potential health effects of environmental exposures. For this investigation, eight birth cohort studies with suitable information on

<table>
<thead>
<tr>
<th>Table 1 Descriptive overview of the eight European birth cohorts</th>
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<tbody>
<tr>
<td><strong>Acronym and key reference</strong></td>
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<tr>
<td><strong>Country</strong></td>
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<tr>
<td><strong>N (birth)</strong></td>
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<tr>
<td><strong>Sex (female)</strong></td>
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<tr>
<td><strong>Early mould and/or dampness (0–2 years)</strong></td>
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<tr>
<td><strong>Early asthma (0–2 years)</strong></td>
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<td><strong>School-age asthma (6–8 years)</strong></td>
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<td><strong>Ever asthma (3–10 years)</strong></td>
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<tr>
<td><strong>Symptoms of allergic rhinitis at school-age (6–8 years)</strong></td>
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<tr>
<td><strong>Ever symptoms of allergic rhinitis (3–10 years)</strong></td>
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<tr>
<td><strong>Sensitization to aero-allergens (6–8 years)</strong></td>
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<tr>
<td><strong>Sensitization to mould at early school age (6–8 years)</strong></td>
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<tr>
<td><strong>Parental allergy</strong></td>
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<tr>
<td><strong>Parental education</strong></td>
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<td><strong>Maternal smoking (pregnancy)</strong></td>
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<td><strong>Maternal smoking (pregnancy)</strong></td>
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<tr>
<td><em><em>Early SHS</em> exposure (0–2 years)</em>*</td>
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<tr>
<td><strong>Early day care (1–2 years)</strong></td>
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<tr>
<td><strong>Breastfeeding (24 months)</strong></td>
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</tbody>
</table>

IgE, Immunoglobulin E.

*DARC: High prevalence of early asthma because of high medication intake (medication prescribed for asthma or bronchitis).
†DARC: Low prevalence of school-age symptoms of allergic rhinitis partly because of different assessment methods.
‡Sensitization to aero-allergens (6–8 years): IgE >0.35 ku/l for at least one of the measured aero-allergens in each birth cohort (cat dander, dog dander, mite, mould, grass and tree pollen).
§Parental allergy: mother or father having at least one of the following allergic dispositions: asthma, hay fever, atopic eczema, pet allergy and house dust mite allergy (ever).
*SHS: second-hand smoke (maternal smoking).
**Breastfeeding (at least 4 months).
exposure and health outcomes were included. The cohorts recruited subjects between 1985 and 2004 with a sample size between 330 and 14 057 children (Table 1). Most studies were single-centre studies, except two German birth cohorts (LISAplus and GINIplus) and a Dutch birth cohort (PIAMA-NHS). All cohorts were population-based except the PIAMA-NHS cohort that over-sampled nonallergic pregnant women in the NHS component. All cohorts obtained ethical approval from their local review boards.

Definition of exposure and health outcomes
Exposure was defined as parent-reported mould and/or dampness in any room of the home during the first 2 years of life (Data S1).

We defined seven health end points, based on the comparability across the birth cohort studies (Data S2): 'Early childhood asthma' (0–2 years), 'school-age asthma' (6–8 years), and 'ever asthma' at any time between 3 and 10 years of life. The asthma definition was based on the ISAAC-related questions (17) and satisfied two of three conditions: physician-diagnosed asthma ever, parent-reported wheezing (last 12 months) and asthma medication (last 12 months). If there was no comprehensive information on 'physician-diagnosed asthma ever', we used 'physician-diagnosed asthma in the past 12 months' for the assessment. School-age and childhood 'symptoms of allergic rhinitis' (6–8 years) were defined as sneezing attacks, runny, blocked and itchy nose without having a cold.

Sensitization against aero-allergens and mould allergens was available for five of the eight cohorts. Sensitization was defined as having specific Immunoglobulin E (IgE) of at least 0.35 kU/l to at least one of the measured aero-allergens (cat dander, dog dander, mite, mould allergens, grass or tree pollen) between 6 and 8 years.

Definition of potential confounders
Individual cohort analyses were adjusted for the following potential confounders: gender, parental atopy, parental educational level at birth (proxy for socio-economic status), maternal smoking during pregnancy, environmental tobacco smoke during the first 2 years of life, breastfeeding (at least 4 months) and early day care attendance. A confounder was considered a risk factor in the adjusted model if it was associated ($\chi^2$-test, $P < 0.1$) with the respective health outcome in at least two birth cohorts.

Statistical analysis
Logistic regression was used to calculate crude odds ratios (OR) and adjusted odds ratios (aOR) to assess the effect of early exposure to mould and/or dampness on the development of allergic disorders including asthma, symptoms of allergic rhinitis and sensitization to aero-allergens individually for each cohort and combined. Meta-analyses with fixed- and random-effect models were applied to account for the heterogeneity between the cohorts. The number of the studies included varies according to the data available from each individual cohort. The results of the meta-analysis are presented as forest plots with central point estimates and 95% confidence intervals (CI). We further stratified the analyses by atopic sensitization status and parental allergy.

Statistical analyses were performed using the statistical software R, version R 2.12.2 (The R Foundation for Statistical Computing).

Results
Study population
There were considerable variations among the European birth cohorts regarding the distribution of most exposure variables and potential confounders. During the first 2 years of life, exposure to residential mould and/or dampness ranged from 13% in Bologna, Italy (CO.N.ER), to 67% in Bristol, UK (ALSPAC). Further, in the Netherlands (PIAMA-NHS), Denmark (DARC) and one German birth cohort (LISAplus), more than one-third of the parents reported exposure to mould and/or dampness at home within the first 2 years of life (Table 1).

Early exposure to visible mould and/or dampness in relation to allergic health outcomes
The results from the crude and adjusted logistic regression models are presented in Table 2 and Fig. 1.

Among the Danish children, early asthma was reported in 24% when compared to a lower prevalence in the remaining cohorts. In DARC, the question regarding medication intake referred to any respiratory medication, not only asthma medication, which might partly explain the increased prevalence. Further, the prevalence of symptoms of allergic rhinitis at school age was reported for only 3% among the Danish children who were assessed during clinical visits by physicians and not by parent-reported symptoms. Owing to these differences in the assessment, the DARC cohort was excluded from the adjusted analysis of asthma and symptoms of allergic rhinitis to minimize classification bias. However, we performed a sensitivity analysis including the DARC cohort and observed no major changes in the summary effects for asthma [(0–2 years): aOR, 1.33 (95% CI, 1.05–1.69), (6–8 years): aOR, 1.39 (95% CI, 0.90–1.29), (3–10 years): aOR, 1.08 (95% CI, 0.89–1.32) and symptoms of allergic rhinitis (6–8 years): aOR, 1.12 (95% CI, 1.03–1.23) and (3–10 years): aOR, 1.17 (95% CI, 1.08–1.26)]. Because of a similar prevalence of allergic sensitization at school age among the cohorts, the DARC cohort was included in the analysis of early exposure to mould and allergic sensitization status at school age.

Asthma
There was a statistically significant association between early exposure to mould and asthma (<3 years) in adjusted analyses of four cohorts (aOR, 1.39 (95% CI, 1.05–1.84), Fig. 1A). The Leicester cohort showed a reduced risk of school-age
Table 2 Crude and adjusted odds ratios (OR) and 95% confidence intervals (95% CI) of asthma, symptoms of allergic rhinitis and sensitization to aero-allergens, respectively, in relation to early exposure to mould and/or dampness (0–2 years), from random-effect meta-analyses (combined effect) and separately by each cohort.

<table>
<thead>
<tr>
<th>OR (95% CI)</th>
<th>Summary estimate</th>
<th>LEICESTER</th>
<th>ALSPAC</th>
<th>BAMSE</th>
<th>GIPLUS</th>
<th>PIAMA-NHS</th>
<th>LISAplus</th>
<th>DARC</th>
<th>CO.N.ER</th>
<th>Test for homogeneity (P)</th>
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<tbody>
<tr>
<td><strong>Asthma</strong></td>
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<td>Early (0–2 years)</td>
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<tr>
<td>Crude</td>
<td>1.44 (1.07–1.95)</td>
<td>n.a.</td>
<td>n.a.</td>
<td>1.58</td>
<td>1.27</td>
<td>1.04</td>
<td>DEM</td>
<td>n.i.</td>
<td>2.86</td>
<td>0.0526</td>
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<tr>
<td>Adjusted*</td>
<td>1.39 (1.05–1.84)</td>
<td>n.a.</td>
<td>n.a.</td>
<td>1.52</td>
<td>1.26</td>
<td>1.03</td>
<td>DEM</td>
<td>n.i.</td>
<td>2.73</td>
<td>0.0929</td>
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<tr>
<td>School age (6–8 years)</td>
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<tr>
<td>Crude</td>
<td>1.16 (0.99–1.36)</td>
<td>0.50</td>
<td>1.29</td>
<td>1.30</td>
<td>1.16</td>
<td>0.99</td>
<td>0.93</td>
<td>n.i.</td>
<td>n.a.</td>
<td>0.3048</td>
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<tr>
<td>Adjusted†</td>
<td>1.09 (0.90–1.32)</td>
<td>0.23</td>
<td>1.19</td>
<td>1.20</td>
<td>1.17</td>
<td>1.01</td>
<td>0.83</td>
<td>n.i.</td>
<td>n.a.</td>
<td>0.196</td>
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<tr>
<td>Ever (3–10 years)</td>
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<tr>
<td>Crude</td>
<td>1.16 (0.97–1.39)</td>
<td>0.50</td>
<td>1.32</td>
<td>1.44</td>
<td>1.24</td>
<td>0.94</td>
<td>0.92</td>
<td>n.i.</td>
<td>n.a.</td>
<td>0.0310</td>
</tr>
<tr>
<td>Adjusted‡</td>
<td>1.10 (0.90–1.34)</td>
<td>0.23</td>
<td>1.19</td>
<td>1.35</td>
<td>1.23</td>
<td>0.91</td>
<td>0.95</td>
<td>n.i.</td>
<td>n.a.</td>
<td>0.0275</td>
</tr>
<tr>
<td>Symptoms of allergic rhinitis</td>
<td></td>
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<td>School age (6–8 years)</td>
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<tr>
<td>Crude</td>
<td>1.16 (1.06–1.26)</td>
<td>2.07</td>
<td>1.15</td>
<td>1.24</td>
<td>1.12</td>
<td>1.08</td>
<td>1.14</td>
<td>n.i.</td>
<td>n.a.</td>
<td>0.5183</td>
</tr>
<tr>
<td>Adjusted§</td>
<td>1.12 (1.02–1.23)</td>
<td>1.81</td>
<td>1.12</td>
<td>1.14</td>
<td>1.09</td>
<td>1.09</td>
<td>1.14</td>
<td>n.i.</td>
<td>n.a.</td>
<td>0.8362</td>
</tr>
<tr>
<td>Ever (3–10 years)</td>
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<tr>
<td>Crude</td>
<td>1.22 (1.11–1.34)</td>
<td>2.07</td>
<td>1.19</td>
<td>1.41</td>
<td>1.29</td>
<td>1.13</td>
<td>1.05</td>
<td>n.i.</td>
<td>n.a.</td>
<td>0.0932</td>
</tr>
<tr>
<td>Adjusted¶</td>
<td>1.18 (1.09–1.28)</td>
<td>1.81</td>
<td>1.14</td>
<td>1.33</td>
<td>1.28</td>
<td>1.13</td>
<td>1.04</td>
<td>n.i.</td>
<td>n.a.</td>
<td>0.3184</td>
</tr>
<tr>
<td>Sensitization against Aero-allergens (6–8 years)</td>
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</tr>
<tr>
<td>Crude</td>
<td>1.04 (0.92–1.16)</td>
<td>n.a.</td>
<td>n.a.</td>
<td>0.88</td>
<td>1.14</td>
<td>1.00</td>
<td>1.21</td>
<td>1.16</td>
<td>n.a.</td>
<td>0.3291</td>
</tr>
<tr>
<td>Adjusted**</td>
<td>1.05 (0.89–1.24)</td>
<td>n.a.</td>
<td>n.a.</td>
<td>0.85</td>
<td>1.10</td>
<td>0.97</td>
<td>1.33</td>
<td>1.33</td>
<td>n.a.</td>
<td>0.1215</td>
</tr>
</tbody>
</table>
asthma and asthma between age 3 and 10 in children who were exposed to mould/dampness; however, this result should be interpreted with caution because of the small sample size of the included data set from the Leicester cohort. There was statistically significant heterogeneity between the cohorts in the relationship between visible mould and/or dampness and childhood asthma (3–10 years, \(P < 0.05\)).

Symptoms of allergic rhinitis

The combined OR between early exposure to mould and symptoms of allergic rhinitis during early school age (6–8 years) and childhood (3–10 years) were significantly increased in adjusted analyses [aOR, 1.12 (95% CI, 1.02–1.23) and 1.18 (95% CI, 1.09–1.28), respectively, Fig. 1B). There was no significant heterogeneity between the cohorts observed.

Sensitization to aero-allergens and mould allergens

It was possible to model the relationship between early exposure to mould and sensitization (assessed by specific IgE) against aero-allergens in general and specifically against mould allergens at 6–8 years of age for five cohorts. We observed no association between early exposure to visible mould and/or dampness and sensitization against aero-allergens including mould at early school age in adjusted analyses [aOR, 1.05 (95% CI, 0.89–1.24) and 1.01 (95% CI, 0.69–1.49), respectively (Fig. 1C). Further, we observed no significant heterogeneity between the cohorts.

To improve the comparison of the association between early exposure to mould and asthma outcomes over time, we restricted analyses to those birth cohorts with information at each age category (BAMSE, GINIplus and PIAMA-NHS). The subanalysis revealed similar results – the strongest effect was found for early asthma [0–2 years: aOR, 1.31 (95% CI, 1.03–1.66), 6–8 years: aOR, 1.15 (95%CI, 0.94–1.40) and 3–10 years: aOR, 1.15 (95%CI, 0.90–1.48), respectively].

Stratified analysis

We further stratified the analysis for sensitization against aero-allergens and parental allergy. The estimates showed a positive but not statistically significant association between early exposure to mould and asthma outcomes over time, we restricted analyses to those birth cohorts with information at each age category (BAMSE, GINIplus and PIAMA-NHS). The subanalysis revealed similar results – the strongest effect was found for early asthma [0–2 years: aOR, 1.31 (95% CI, 0.92–1.86), Data S3].

Children with parental allergy and exposure to mould had an increased risk of early asthma symptoms [aOR, 1.49 (95% CI, 1.00–2.22)], school-age asthma [aOR, 1.14 (95% CI, 0.97–1.35)] and asthma diagnoses between 3 and 10 years of age [aOR, 1.28 (95% CI, 1.12–1.47)]. Similar effects were observed for school-age and ever symptoms of allergic rhinitis [aOR, 1.14 (95% CI, 1.02–1.28) and aOR, 1.22 (95% CI, 1.11–1.33), respectively], but there was no association between early exposure to mould in relation to sensitization against aero-allergens in children with parental allergy. For children without parental allergy, no association with aller-
gic, respiratory symptoms was observed; however, there was a significant decreased risk of sensitization against mould allergens at school age [aOR, 0.41 (95% CI, 0.17–0.98), Data S3].

Discussion

Our main findings of the meta-analysis of European birth cohorts indicated that early-life exposure to visible mould and/or dampness significantly increased the risk of allergic rhinitis symptoms up to 10 years of age. We also found a modest and significantly increased risk of asthma (<3 years) and a nonsignificantly increased risk of later asthma outcomes (6–8 and 3–10 years). No association was observed for sensitization against aero-allergens or mould allergens at school age (Fig. 1A–C).

Our results are in agreement with recent studies on mould exposure and respiratory diseases in children (18–20). Collaborative studies observed statistically significant increased risks of asthma for children exposed to mould and dampness at home ranging from adjusted ORs of 1.35–1.56 (6–8). Similar results were reported for wheeze and allergic rhinitis.
This is the largest investigation made into the association of visible mould exposure and allergic disorders, using individual participant data from birth cohorts. The prospective design of these cohort studies is the best approach to assess the temporal sequence between early childhood exposure and health outcomes. Exposure assessment before health outcome
observation strengthens the independence of both measurements. Crude variables from each of the eight birth cohorts were harmonized. A cohort was eligible for the analysis if there was information available for at least one of the seven defined health outcomes. As a result, not all cohorts contributed to all analysis.

Although visible mould has been consistently associated with allergic outcomes, the causal agents have not been identified (5). ‘The enormous diversity of the Fungal Kingdom is well recognized’: in ‘healthy’ indoor environments, the predominant part of fungi is presented by the outdoor air genera Cladosporium, followed by the genera mainly found indoors including Penicillium and Aspergillus (19, 21). Once there is moisture or mould, the composition of the fungal profile is shifting mainly to Penicillium and Aspergillus. Species such as Penicillium chrysogenum, Penicillium expansum, Aspergillus versicolor, Aspergillus penicillioides and also Stachybotris chartarum were reported to be detected typically in moisture damaged environments (22, 23). It has been shown that fungal species induce inflammatory processes (5, 24) and that sensitization to mould allergens is linked to severe asthma (25). In several studies, associations between exposure to spores of Penicillium indoors and an increased risk of respiratory disorders were described (26, 27). However, the epidemiological evidence for the association between exposure to specific fungal spores and asthma and allergy remains inconclusive (5, 28).

In this investigation, mould exposure was defined as parent-reported visible mould and/or dampness within the home. This common approach in epidemiological studies might lead to misclassification if moulds were not reported in spite of being present (e.g. hidden behind furniture) or not aerosolized and therefore not relevant to inhaled exposure. As the appearance of visible mould might not be sensitive enough, some studies measured mould exposure via settled house dust or air sampling to reflect the potential inhaled amount (29–31). This objective method is often not realizable in large cohort populations. However, the correlation between visible mould and the airborne concentration of fungal spores seemed to be good (32), and slightly higher indoor spore concentrations were reported for buildings with apparent mould problems (33, 34). In summary, the presence of visible mould serves as a good indicator that the indoor environment is out of balance (19).

Our meta-analysis showed that early exposure to mould was significantly associated with asthma, especially in young children. However, this positive effect could be masked by uncertainties of the diagnosis in the first 2 years of life and therefore might be of a transient character. Nevertheless, owing to the asthma definition used in our investigation, satisfying at least two of three allergic conditions implies a more serious health disorder rather than transient symptoms arising from a common cold, and adverse effects of mould exposure on asthma were also observed at later ages.

Although the risk of allergic respiratory disorders was increased in children exposed to mould/dampness, we found no association with allergic sensitization at the same age – which is considered to be a major risk factor (35, 36). Moreover, after stratifying children by their atopic status, there was a positive, not-statistically-significant association for non-IgE-mediated asthma compared with the nonallergic and nonsymptomatic children. In approximately 80% of childhood asthma cases, allergy seems to be mediated by IgE antibodies (37), but it is unclear whether the tested aero-allergens are causal agents. The mechanisms of nonallergic asthma result from similar inflammatory changes, but are suggested to be driven by the production of antibodies mainly of the IgG, IgA and IgM isotype after inhalation of large amounts of protein as in mould (37, 38). We further observed an increased risk of visible mould exposure in relation to asthma and symptoms of allergic rhinitis in children with parental allergy, but not in children without this hereditary component. In addition, early exposure to mould was observed to decrease the risk of sensitization to mould allergens in children without parental allergy; however, because of the small sample size, these findings should be interpreted with caution. Nevertheless, allergic parents are well advised to ensure healthy indoor air quality and to both remove visible mould or signs of moisture and actively prevent its formation in the first place.

Conclusion

The results of the first collaborative effort of European birth cohorts with regard to mould and/or dampness indicated an increased risk of subsequent allergic respiratory symptoms in children spending their first years of life in homes with visible mould and/or dampness. To draw a causal relationship is hindered by the variability of microbial components in indoor air. Assessment techniques such as molecular methods and measurements of airborne enzyme activity are considered both highly sensitive and specific and may help to identify patterns of causal agents in relation to asthma and allergy.

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Author contribution

Christina G. Tischer (first author) carried out statistical analysis, manuscript preparation and revision; Joachim Heinrich designed the study and provided data and commented on the draft; Cynthia Hohmann prepared data (common data base) and commented on the draft; Thomas Keil (MAS), Elisabeth Thiering (LISAplus), Olaf Herbarth (LISAplus), Andrea Müller (LISAplus), John Henderson (ALSPAC), Raquel Granell (ALSPAC), Maria Pia Fantini (CO.N.ER), Lorenza Luciano (ALSPAC), Anna Bergström (BAMSE), Inger Kull (BAMSE), Elke Link (GINplus), Andrea von Berg (GINplus), Claudia E. Kühni (LEICESTER), Marie-Pierre F. Strippoli (LEICESTER), Ulrike Gehring (PIAMA-NHS), Alet Wijs (PIAMA-NHS), Esben Eller (DARC) and Carsten Bindslev-Jensen (DARC) provided data, commented on
the manuscript and participated in the critical revision of the manuscript.

Conflict of interest
The authors declare no conflict of interest.

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References
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Data S1. Definition of early mould and/or dampness exposure in each participating birth cohort.

Data S2. Definition of health outcomes in each participating birth cohort.

Data S3. Mould and/or dampness exposure in relation to asthma and allergy, stratified by sensitization and parental allergy.

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