



Association between domestic mould and mould components, and asthma and allergy in children: a systematic review

C. Tischer*, C-M. Chen*^{##} and J. Heinrich*

ABSTRACT: Critical reviews over the past 10 yrs have found increased respiratory and allergic health outcomes for children living in damp and mouldy environments. However, recent studies have suggested that early childhood exposure to specific mould components may actually protect children from developing allergy.

We conducted a systematic review of observational studies published in English from January 1980 to July 2010. This review was conducted according to systematic guidelines for Meta-analyses of Observational Studies in Epidemiology (MOOSE). The literature was searched using a computerised bibliographic database, PubMed. In order to increase the quality of the reviewed studies, meta-analyses of the effects of visible mould exposure on allergic health outcomes were performed and we evaluated the findings according to the Bradford Hill criteria for evidence of causation.

The literature search identified 1,398 peer-reviewed scientific publications, and 61 studies that fulfilled the inclusion criteria were included in this review. We observed increased risks of allergic respiratory health outcomes in children exposed to visible mould and mould spores. These findings were confirmed by the results of the meta-analysis and in line with the evaluation criteria according to Bradford Hill. Visible mould was positively associated with asthma (OR 1.49 (95% CI 1.28–1.72)), wheeze (OR 1.68 (95% CI 1.48–1.90)) and allergic rhinitis (OR 1.39 (95% CI 1.28–1.51)). However, there was a tendency of lower risk for allergic health outcomes in children exposed to mould-derived components such as (1,3)- β -D-glucan and extracellular polysaccharides.

These findings suggest that home environments with visible mould and mould spore exposure increase the risk of allergic respiratory health outcomes in children. However, further investigations are needed to examine the effects of exposure to mould-derived components as the current literature is inconclusive. In order to disentangle the different effects of overall microbial exposure on children's health, research should focus on specific microbial markers in the home, in combination with new assessment techniques including molecular methods.

KEYWORDS: Allergy, asthma, biomarkers, moulds, systematic review, wheeze

Numerous studies have analysed the relationship between living in a damp and mouldy environment and effects on respiratory health. Reviews conducted in the past 10 yrs have found an increased risk of respiratory and allergic health outcomes in children with a parent-reported damp and mouldy home environment. A review of the European studies (NORD DAMP) published prior to 1998 concluded that there was strong evidence for an association between dampness at home and increased risk of respiratory and allergic symptoms in children and

young adults [1], which was also confirmed in a subsequent review (EUROEXPO) of studies published from 1998–2000 [2]. In 2004, the Institute of Medicine (IOM) of the US National Academy of Sciences reviewed studies published up to late 2003 and concluded that there is sufficient evidence for an association between exposure to dampness and mould and wheezing symptoms in children. Similar associations were also observed for physician-diagnosed asthma and asthma symptoms [3]. Subsequent epidemiological studies have strengthened the evidence for a positive association

AFFILIATIONS

*Institute of Epidemiology, Helmholtz Zentrum München, German Research Centre for Environmental Health, Neuherberg, and

[#]Dept of Paediatric Pneumology, Allergy and Neonatology, Hanover Medical School, Hanover, Germany.

CORRESPONDENCE

J. Heinrich
Institute of Epidemiology
Helmholtz Zentrum München
German Research Centre for
Environmental Health
Ingolstaedter Landstrasse 1
D-85764
Neuherberg
Germany
E-mail: joachim.heinrich@
helmholtz-muenchen.de

Received:

Nov 30 2010

Accepted after revision:

March 16 2011

First published online:

May 03 2011

This article has supplementary material available from www.erj.ersjournals.com

European Respiratory Journal
Print ISSN 0903-1936
Online ISSN 1399-3003

between home dampness and new-onset asthma in children aged up to 7 yrs [4]. The only meta-analysis to date [5] found a positive association between exposure to dampness or visible mould in the home and wheezing symptoms in children (OR combined estimate 1.53 (95% CI 1.39–1.68)). Recently, the World Health Organization (WHO) presented guidelines for the protection of public health from dampness- and mould-derived risks and concluded that there was sufficient epidemiological evidence that dampness and mould were associated with an increased risk of respiratory symptoms and exacerbation of asthma in children and adults [6]. However, this review was neither systematic nor were combined quantitative effect estimates given.

While the previous reviews and publications focused mainly on self- or parent-reported indoor exposure to dampness, visible mould and mould spores, there are also some recent studies which used measured mould components, such as (1,3)- β -D-glucan and extracellular polysaccharides (EPS) in house dust samples as surrogates for mould exposure [6, 7]. (1,3)- β -D-glucans are nonallergenic water-insoluble structural cell wall components of most fungi. The biological active polyglucose molecule may account for up to 60% of the weight of the fungal cell wall [7]. However, (1,3)- β -D-glucans are also part of the structure of plant materials, including pollen and cellulose, as well as of soil bacteria. Therefore, the level of mould exposure may be overestimated by using (1,3)- β -D-glucan as a surrogate. Fungal EPS are stable carbohydrates secreted or shed during fungal growth and have antigenic specificity at the genus level. In contrast to the findings on visible mould, longitudinal studies have shown that exposure to (1,3)- β -D-glucan and EPS was inversely associated with the development of wheezing symptoms and reported physician-diagnosed asthma in children [8–12]. In addition, one case-control study reported that elevated levels of (1,3)- β -D-glucan and EPS exposure from mattress dust were associated with a lower prevalence of allergic sensitisation in 2–4-yr-old children [13]. The mechanism of these negative associations is not yet understood. It has been hypothesised that exposure to (1,3)- β -D-glucan and EPS may have a similar impact on regulating the development of the infant immune system as does endotoxin exposure during the perinatal period.

Previous investigations (NORDDAMP, EUROEXPO, IOM and WHO) [1–3, 6] have summarised the main findings of the studies reviewed here. However, only the work of FISK *et al.* [5] also provided quantitative summaries. Furthermore, almost all of the previous reviews failed to distinguish between exposure to visible mould at home, measured mould spores and mould-derived components. Finally, several publications have been published since the inclusion deadline for the most recent meta-analysis by FISK *et al.* [5] in 2007.

There is a strong need for a comprehensive and specific review that distinguishes mould and dampness exposure into visible mould, mould spores and measured mould components. Although some investigations have also included endotoxin exposure, we concentrated on mould exposure specifically. Additionally, meta-analyses were used to quantitatively assess the exposure–response relationships. While previous reviews investigated a broad range of health outcomes in adults and children, we have restricted our analysis to children and the development of allergic diseases and symptoms. Lastly, birth cohort and cohort studies with a prospective design were given

more weight than cross-sectional investigations as they can better assign the temporal sequence. To account for the different value of each epidemiological design we have presented the results according to their epidemiological study design.

METHODS

This review was conducted following the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines for meta-analyses of observational studies [14]. The literature was searched using a computerised bibliographic database, PubMed, with the free text search terms listed in table 1.

Inclusion criteria were: observational study, human study population, English, publication date between January 1, 1980 and July 1, 2010, and study population recruited from community. The review included publications that specifically assessed exposure to mould and mould-derived components for children at home. This included inspector- or subject-reported visible mould, measured airborne or dust-borne fungal genera, and measured specific biomarkers of mould species such as (1,3)- β -D-glucan and EPS within the domestic area. Exposure to dampness, and exposure to dampness or mould as well as endotoxin, were excluded from the current review to ensure a specific exposure definition. Studies that did not evaluate asthma or allergic health outcomes were also excluded. Further hand searches were conducted using citations from the previous systematic reviews [3–6] and personal files, published until July 1, 2010.

Longitudinal studies, cross-sectional studies and case-control studies were included. We restricted the health outcomes to physician-diagnosed allergic diseases including asthma, allergic rhinitis or hay fever and eczema, as well as allergic symptoms

TABLE 1 Terms used to search PubMed

- 1) β -glucan
- 2) EPS (extracellular polysaccharides)
- 3) *Cladosporium*
- 4) *Penicillium*
- 5) *Aspergillus*
- 6) *Alternaria*
- 7) Mould spores
- 8) Mould
- 9) Endotoxin
- 10) Visible mould
- 11) Mould components
- 12) Biocontaminants
- 13) Sensitisation
- 14) Allergy
- 15) Asthma
- 16) Wheezing
- 17) Hay fever
- 18) Allergic rhinitis
- 19) Itchy, runny, blocked nose
- 20) Respiratory
- 21) Eczema
- 22) Itchy skin rash
- 23) 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
- 24) 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
- 25) 23 and 24

such as wheezing, itchy, blocked or running nose without having a cold, itchy skin rash and allergic sensitisation to inhalant allergens. Each relevant article underwent standardised data extraction.

Statistical analysis

In order to increase the quality of the reviewed studies, we have reported the results of a quantitative meta-analysis for the exposure–response relationships between exposure to visible mould and asthma, wheeze and allergic rhinitis. The specific risk factor and outcome definitions of each investigation included in the meta-analysis are listed in tables 2–4. To summarise the effect estimates among appropriate studies, we used random effect models to account for the heterogeneity between different studies. The results are presented as forest plots with central point estimates and confidence intervals of odds ratios, and summarise the intensity of increased risk of asthma, wheeze and allergic rhinitis with exposure to visible mould. In order to assess possible publication bias, which may lead to an overestimation of the health effects, funnel plots were performed.

Statistical analyses were performed using the statistical software R, version R 2.9.1 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The literature search identified 1,398 peer-reviewed scientific publications, out of which 36 reported relevant exposures and health outcomes in suitable study populations (fig. 1). Hand searching of previously published reviews and personal files identified 25 additional publications. In total, 61 investigations are included in this review. The funnel plots for the quantitative assessment of the exposure–response relationship between visible mould and asthma showed a symmetric shape. However, there was a higher publication rate for studies that found positive associations between exposure to visible mould and wheeze or allergic rhinitis (see online supplement 1).

Of the 1,398 peer-reviewed scientific publications identified through PubMed, 1,366 were excluded. A large number were background papers such as comments and reviews, laboratory experimental and animal studies or genetic studies ($n=727$). Studies that lacked essential information about the exposure–response relationship, had objectives other than to investigate the relationship between exposure to mould and allergic health outcomes, or that examined only adult study populations were also excluded ($n=622$). Finally, studies that focused solely on exposure to endotoxin were not considered in this systematic review ($n=17$).

Results from the systematic review: birth cohort studies

The birth cohort findings are summarised in online supplement 2. Exposure to domestic visible mould increased the risk for wheezing in children. No effects were observed for allergic rhinitis and allergic sensitisation. The findings also suggested that exposure to higher levels of mould components may decrease the risk of allergic disorders.

Visible mould exposure

Wheeze

Of the nine publications evaluating the longitudinal effect of early exposure to visible mould at home and wheezing in the

first 3 yrs of life, seven studies observed a significant positive association [8, 12, 36, 41, 42, 48, 49]. In one US birth cohort study (the Cincinnati Childhood Allergy and Air Pollution Study) from IOSSIFOVA *et al.* [8], the reported increase in risk was persistent from 1–3 yrs of age. BAKER *et al.* [50] observed no effect of current exposure to visible mould and wheezing at 6 months of age, and TISCHER *et al.* [30] also found no effect in children followed until 6 yrs of age from Germany and the Netherlands.

Other health outcomes

Three studies investigated the effect of exposure to visible mould on allergic rhinitis [30, 45, 46]; one study reported findings on allergic sensitisation [48] and one on physician-diagnosed asthma [30]. However, no significant associations were found.

Exposure to mould spores

Only one birth cohort study reported findings on the association between exposure to mould spores and allergic health outcomes. Exposure to certain dust-borne fungal species such as *Alternaria*, *Aspergillus*, *Aureobasidium* as well as nonsporulating genera and total dust-borne fungal mass were significantly positively associated with physician-diagnosed allergic rhinitis or hay fever at 5 yrs of age [45].

Exposure to mould components

Two European and two US birth cohort investigations studied the effect of exposure to mould components on the risk of allergic health outcomes. IOSSIFOVA *et al.* [12] reported that exposure to low levels of (1,3)- β -D-glucan from children's primary activity room was associated with a higher risk of recurrent wheeze (OR 3.04 (95% CI 1.25–7.38)) in 1-yr-old children, high levels were protective (OR 0.39 (95% CI 0.16–0.93)). However, this could not be confirmed at 3 yrs of age in the same birth cohort [8]. The two European studies did not observe an effect of exposure to (1,3)- β -D-glucan on asthma, wheezing or allergic rhinitis symptoms in school-aged children [9, 30].

The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort study and a follow-up of the European AirAllerg collaboration reported significant inverse effects of exposure to higher levels of EPS on asthma, wheeze and allergic rhinitis in 4–6-yr-old children. Within the PIAMA cohort, there was also an inverse effect on allergic sensitisation status [9, 30].

Results from the systematic review: cohort studies (not recruited at birth)

The cohort study findings are summarised in the online supplement 2. There was no clear exposure–response relationship between exposure to visible mould and asthma. However, the findings did suggest that domestic visible mould may have a harmful effect on wheeze. Exposure to airborne mould spores was associated with wheezing in children aged up to 1 yr.

Visible mould exposure

Asthma

Three studies investigated the relationship between exposure to visible mould and physician-diagnosed asthma, and overall results were inconclusive. Studies from the USA and Finland [21, 51] found no associations, while a second US study

TABLE 2 Risk factor and health outcome definition: visible mould and asthma

First author [ref.]	Location	Definition of exposure	Definition of outcome	Age yrs	Children n	OR central estimate (95% CI)	Type of estimate
ANTOVA [15]	Pollution and the Young Study, multiple locations	Visible mould Mould ever	Asthma ever	6–12	57099 (pooled)	1.35 (1.20–1.51)	aOR
DALES [16]	Canada	Recent mould No. of mould sites 0 versus 1 0 versus 2	DD asthma	5–8	13495	1.36 (1.19–1.56) 1.23 (1.07–1.41)	aOR aOR
DONG [17]	China	Visible mould	DD asthma (ever) Current asthma	6–13	10784	1.40 (1.16–1.68) 1.67 (1.27–2.19)	cOR cOR
PONSONBY [18]	Tasmania, Australia	Mould in child's room i.r. Mould (excl. bathroom) p.r.	Asthma	7	6378	1.54 (1.22–1.94) 1.69 (1.15–2.48)	aOR aOR
SPENGLER [19]	Russia	Presence of moulds	DD asthma	8–12	5951	1.26 (0.87–1.81) 1.20 (0.96–1.51)	aOR aOR
FREEMAN [20]	USA	Any mould Any mould	Asthma symptoms DD asthma	8.1–10.9 <6	4634 240	2.82 (1.63–4.88) 1.98 (1.53–2.55)	aOR aOR
BRUNEKREEF [21]	USA	Mould or mildew (age 7–11 yrs)	DD Asthma	8–12	4625	1.54 (1.27–1.87)	aOR
DONG [22]	China	Visible mould	DD asthma DD asthma Current asthma	1–6	3945	3.30 (1.57–6.97) 1.27 (0.93–1.74) 1.56 (1.13–2.16)	aOR aOR aOR
BRUNEKREEF [23]	The Netherlands	Visible mould (1987) Visible mould (1989)	Asthma Asthma	6–12	1051 3344	1.89 (1.22–2.94) 1.12 (0.39–3.38)	aOR aOR
WARMAN [24]	USA	Visible mould on walls Visible mould on walls, ceilings or windows	DD asthma DD asthma	5–11	1772	1.53 (1.04–2.28) 3.26 (2.38–4.45) 2.66 (2.04–3.48)	aOR cOR cOR
CHEN [25]	Taiwan	Mould patches	DD asthma	7–12	1452	1.55 (0.78–3.09)	aOR
LI [26]	Taiwan	Visible mould/mildew	Asthma symptoms	8–12	1340	1.56 (0.90–2.69)	aOR
ZHENG [27]	China	Mould or fungi Family ceiling Child's bedroom	DD asthma DD Asthma	6–10	1209	1.12 (0.72–1.74)	aOR
MAIER [28]	USA	Visible mould	DD asthma	5–9	925	1.8 (1.1–2.9) 1.8 (1.0–3.2)	aOR aOR
DIJKSTRA [29]	The Netherlands	Damp stains and mould	Asthma	6–12	775	1.3 (0.9–1.9)	cOR
TISCHER [30]	Germany and The Netherlands	Visible mould (Germany) Visible mould (The Netherlands)	DD asthma DD asthma	6	358 332	1.56 (0.50–4.87) 1.03 (0.26–4.16) 1.14 (0.48–2.70)	cOR aOR aOR
VERHOEFF [31]	The Netherlands	Visible mould Living room p.r. Child's bedroom p.r. Living room i.r. Child's bedroom i.r.	DD Asthma ever	6–12	516	2.95 (1.34–6.25) 1.88 (0.74–4.78) 1.83 (0.81–4.13) 0.99 (0.31–3.14)	cOR cOR cOR cOR
DALES [32]	Canada	Ever mould/mildew	DD asthma	10	403	0.91 (0.42–1.95)	aOR
PEKKANEN [33]	Finland	Visible mould Mould spots living room Visible mould living room	DD Asthma	1–7	362	1.24 (0.73–2.11) 4.01 (1.12–14.32)	aOR aOR
FAGBULE [34]	Nigeria	Mould growth	Current asthma	5.5	280	1.95 (0.69–5.47)	aOR
LI [35]	Taiwan	Visible mould	Asthma	7–15	46	0.48 (0.30–0.79) 1.02 (0.39–2.69)	aOR aOR

aOR: adjusted odds ratio; DD: physician-diagnosed; cOR: crude odds ratio; p.r.: parental reported; i.r.: inspector reported. Data in bold were included within the meta-analysis.

TABLE 3 Risk factor and health outcome definition: visible mould and wheeze

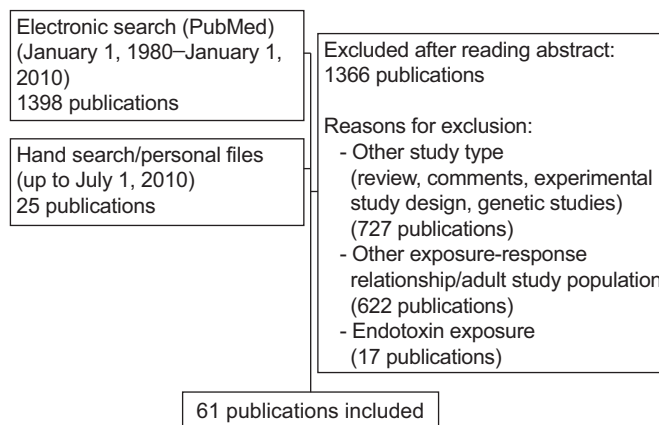
First author [ref.]	Location	Definition of exposure	Definition of outcome	Age [#]	Children n	OR central estimate (95% CI)	Type of estimate
ANTOVA [15]	Pollution and the Young Study, multiple locations	Visible mould Mould ever Recent mould	Current wheeze	6–12	57099	1.43 (1.36–1.49) 1.44 (1.35–1.53) 1.46 (1.31–1.61)	aOR
DALES [16]	Canada	No. of mould sites 0 versus 1 0 versus 2	Wheeze	5–8	13495	1.42 (1.26–1.59) 1.73 (1.45–2.06) 1.65 (1.25–2.17) 1.52 (1.19–1.94) 1.79 (1.44–2.32)	cOR cOR aOR aOR aOR
DONG [17]	China	Visible mould	Current wheeze	6–13	10784		aOR
SPENGLER [19]	Russia	Presence of moulds	Wheeze	8–12	5951		aOR
BRUNEKREEF [21]	USA	Mould/mildew (age 7–11 yrs)	Persistent wheeze (age 8–12 yrs)	8–12	4625		aOR
EMENUS [36]	Sweden (BAMSE cohort)	Visible mould (age 1 yr)	Recurrent wheeze (age 2 yrs)	1–2	4089	1.5 (1.0–2.22)	aOR
DONG [22]	China	Visible mould	Current wheeze	1–6	3945	2.07 (1.56–2.75)	aOR
BRUNEKREEF [23]	The Netherlands	Visible mould (1987)	Wheeze	6–12	1051	1.34 (0.58–3.26)	aOR
LI [26]	Taiwan	Visible mould (1989)	Wheeze		3344	1.90 (1.41–2.54)	aOR
STRACHAN [37]	UK	Dampness and mould	Wheeze	8–12	1340	1.20 (0.73–1.99)	aOR
STRACHAN [38]	UK	Mould p.r.	Wheeze	6.5–7.5	1000	3.70 (2.22–6.15)	cOR
MAIER [28]	USA	Mould i.r.	Severe wheeze	13–18	330	3.25 (1.60–6.60)	cOR
ALPER [39]	Turkey	Visible mould Dampness and mould (age 7 yrs)	Wheeze Persistent wheeze (age 0–6 yrs)	5–9 0–7	961 925 858	1.25 (0.67–2.31) 1.20 (0.70–1.90) 2.53 (1.30–4.87)	aOR cPR cOR
DUKSTRA [29]	The Netherlands	Damp stains and mould	Early wheeze (age 0–3 yrs)		775	2.37 (1.52–3.69)	cOR
CHO [40]	USA (Cincinnati Childhood Allergy and Air Pollution Study)	Mould class 2 versus 0 (age 8 months)	Early transient wheeze Late-onset wheeze (age 3–6 yrs)	6–12 8–12 months	640	2.28 (1.34–3.87) 2.46 (1.29–4.66)	cOR cOR
IOSSIFOVA [12]	USA (Cincinnati Childhood Allergy and Air Pollution Study)	Visible mould (age 8 months) Low versus none High versus none	Wheeze Recurrent wheeze (age 1 yr)	8–12 months	574	1.54 (0.59–4.00) 2.1 (1.2–3.6)	cOR aOR
SCHROER [41]	USA (Cincinnati Childhood Allergy and Air Pollution Study)	Mould exposure (age 8 months)	Wheezing (age 1 yr) Wheezing (age 2 yrs) Persistent wheezing (age 2 yrs)	8–24 months	570	1.18 (0.73–1.91) 4.44 (1.36–12.05) 1.22 (0.79–1.86) 2.12 (1.25–3.60) 2.47 (1.27–4.80)	aOR aOR aOR aOR aOR
IOSSIFOVA [8]	USA (Cincinnati Childhood Allergy and Air Pollution Study)	Visible mould (age 8 months) Low versus none High versus none	Wheezing with API (age 3 yrs)	8 months–3 yrs	483	1.68 (0.96–2.94) 7.08 (2.22–12.60)	aOR aOR aOR
KARVONEN [42]	Finland (Protection Against Allergy: Study in Rural Environments)	Mould spots (age 2 months) i.r. Visible mould (age 2 months) i.r. Mould in kitchen (age 2 months) i.r. Mould living area (age 2 months) i.r. Mould child's room (age 2 months) i.r.	DD wheezing (age 1 yr) Wheezing (age 1 yr) DD wheezing (age 1 yr) DD wheezing (age 1 yr) Wheezing (age 1 yr) DD wheezing (age 1 yr) Wheezing (age 1 yr) DD wheezing (age 1 yr) Wheezing (age 1 yr)	2–12 months	396	0.81 (0.31–2.12) 1.39 (0.57–3.39) 1.98 (0.90–4.35) 1.06 (0.41–2.71) 1.96 (0.89–4.31) 3.92 (1.54–10.00) 1.22 (0.43–3.45) 5.22 (1.48–18.35) 1.92 (0.48–7.60) 0.90 (0.35–2.29)	aOR aOR aOR aOR aOR aOR aOR aOR aOR cOR
ROSENBAUM [43]	USA (Assessment of Urban Dwellings for Indoor Toxics)	Visible mould (age 3 months) i.r.	Wheeze (age 1 yr)	3–12 months	103		

aOR: adjusted odds ratio; cOR: crude odds ratio; p.r.: parental reported; i.r.: investigator reported; API: asthma predictive index; DD: physician-diagnosed. [#]: presented in yrs, unless otherwise stated. Data in bold were included within the meta-analysis.

TABLE 4 Risk factor and health outcome definition: visible mould and allergic rhinitis

First author [ref.]	Location	Definition of exposure	Definition of outcome	Age yrs	Children n	OR central estimate (95% CI)	Type of estimate
ANTOVA [15]	Pollution and the Young Study, multiple locations	Visible mould Mould ever	Hay fever ever	6–12	57099	1.35 (1.18–1.53) 1.48 (1.34–1.62) 1.47 (1.35–1.61)	aOR aOR aOR
DONG [17]	China	Recent mould	DD allergic rhinitis (ever)	6–13	10784	1.21 (0.97–1.50)	aOR
BRUNEKREEF [21]	USA	Mould/mildew (age 7–11 yrs)	Hay fever (8–12 yrs)	7–12	4625	1.57 (1.31–1.87)	aOR
DONG [22]	China	Visible mould	DD allergic rhinitis	1–6	3945	1.20 (0.72–1.99)	aOR
IBARGOVEN-ROTEA [44]	Spain	Mould on walls (age 1 yr)	Allergic rhinoconjunctivitis (age 5–8 yrs)	1–8	3360	1.34 (0.64–2.79)	aOR
CHEN [25]	Taiwan	Mould patches	DD allergic rhinitis	7–12	1452	1.48 (1.03–2.12)	aOR
LI [26]	Taiwan	Visible mould/mildew	Allergic rhinitis symptoms	8–12	1340	1.27 (0.96–1.68)	aOR
BIAGINI [45]	USA (Cincinnati Childhood Allergy and Air Pollution Study)	Visible mould	Allergic rhinitis	1	495	1.2 (0.6–2.5)	aOR
STARK [46]	USA	Low versus none	DD allergic rhinitis or hay fever (age 5 yrs)	1–5	405	3.2 (0.7–14.8)	aOR
KOSKINEN [47]	Finland	High versus none Mould/mildew (age 1 yr)	Rhinitis	≤7	57	1.28 (0.74–2.22) 8.01 (0.77–83.82)	CHR aOR
LI [35]	Taiwan	Mould present Visible mould	Allergic rhinitis	7–15 7–15	147 45	1.77 (0.69–4.53) 3.50 (1.00–12.34)	aOR aOR

aOR: adjusted odds ratio; DD: physician-diagnosed; CHR: crude hazard ratio. Data in bold were included within the meta-analysis.

**FIGURE 1.** Flow chart of the study selection process.

reported that current exposure to mildew was significantly inversely related to physician-diagnosed asthma at 12 yrs of age [52]. However, this was only found for children with a wheezing phenotype.

Wheeze

Three cohort studies, all from the USA, investigated the effect of visible mould exposure on wheezing in children. BRUNEKREEF *et al.* [21] reported a significantly positive association between domestic mould and persistent wheeze in 12-yr-old children. BELANGER *et al.* [53] observed an increased risk among 1-yr-old children who were genetically predisposed to allergic diseases, while a second study found no association among children in the same age range (although this may have been due to inadequate power as the study included only 103 children) [43].

Other health outcomes

Reported visible mould during pregnancy was a risk factor for physician-diagnosed atopic eczema in 2–9-month-old Japanese infants without parental allergy [54]. A US study of 12-yr-old schoolchildren reported a significant increased risk of hay fever when exposed to self-reported domestic mould [21].

Exposure to mould spores

Three US studies investigated the relationship between exposure to airborne mould spores and wheezing in 1-yr-old children. GENT *et al.* [55] and ROSENBAUM *et al.* [43] reported an increased risk of wheeze in 1-yr-old infants, when exposed to airborne *Penicillium* ($\geq 1,000$ and 120–1270 cfu·m⁻³, respectively). A subsequent US study on infants found a positive association between exposure to airborne total fungi sampled at 3 months and wheeze at 1 yr [53]. A German cohort study found an increased risk for sensitisation against grass (immunoglobulin E) in 3-yr-old children when exposed to airborne *Aspergillus* genera [56].

Results from the systematic review: case-control studies

There was no clear direction observed for the effect of visible mould or mould spores on measured allergic health outcomes among studies with a case-control design (online supplement 2, case-control studies). However, in studies with a larger sample size, there was a tendency for an increased risk of

asthma when exposed to domestic visible mould. In contrast, the findings suggested that mould component exposure was inversely associated with risk of allergic health outcomes.

Visible mould exposure

Asthma

Five case-control studies investigated the relationship between exposure to visible mould and asthma. One study from China with 1,209 subjects [27], and two studies from Europe [31, 33] reported an increased risk of physician-diagnosed asthma with exposure to visible mould, in children up to school age. This association could not be confirmed by LI and HSU [35] in a small population of 46 Taiwanese school children. A Nigerian case-control study of 5-yr-old schoolchildren reported protective effects on current asthma for mould growth at home [34].

Other health outcomes

Two European studies investigated the effect of visible mould exposure on wheezing [36, 38], but no association was observed. A study of 3-yr-old children from New Zealand also found no association between visible mould exposure and atopic dermatitis [57]. One small study from Taiwan reported a significant increased risk for allergic rhinitis in school-aged children [35].

Exposure to mould spores

Asthma

Four studies investigated the effect of mould spore exposure on physician-diagnosed asthma among children. One small study from Taiwan reported positive associations between exposure to airborne *Cladosporium* and asthma in school-aged children [35]. However, three publications from Europe could not find an association between higher levels of dust-borne fungal species and asthma [58–60].

Allergic rhinitis

One European study from Germany [58] with 272 subjects, reported a higher risk of allergic rhinitis symptoms with exposure to total fungi, *Cladosporium* and *Penicillium* ($>200,000$, $>35,000$ and $>55,000$ cfu·g⁻¹, respectively). A similar finding was observed in a Danish cohort: children sensitised to house dust mites had a significantly higher risk of allergic rhinitis when exposed to dust-borne *Cladosporium* >35 cfu·mg⁻¹ [59]. In contrast, higher levels of airborne *Penicillium* and total fungi measured in summer, were found to be protective against allergic rhinitis in a small Taiwanese study of school-aged children [35].

Other health outcomes

Two studies investigated the effect of dust-borne mould spore exposure on physician-diagnosed eczema and eczema symptoms. While there was no association observed within the German population [58], there was an increased risk for eczema in Swedish children sensitised to house dust mites but not to aeroallergens [59]. Two German studies looked at the association between exposure to domestic mould spores and the risk of allergic sensitisation to inhalant allergens (immunoglobulin E). While JOVANOVIĆ *et al.* [61] found no association, JACOB *et al.* [58] reported a higher risk of sensitisation against inhalant allergens when exposed to *Cladosporium* and *Aspergillus* ($>35,000$ and 0 – $25,000$ cfu·g⁻¹ and above, respectively). No association was

found between exposure to dust-borne mould genera and wheezing phenotype in a German study [58].

Mould components exposure

Three European studies investigated the effect of mould component exposure on allergic disorders. Exposure to EPS was found to significantly reduce the risk of physician-diagnosed asthma [62] and atopic wheeze [10], while exposure to (1,3)- β -D-glucan was significantly inversely related to sensitisation against inhalant allergens among 2–4-yr-old children [13].

Results from the systematic review: cross-sectional studies

A large number of cross-sectional studies reported increased risk of asthma and wheeze when exposed to domestic visible mould. However, the results for other allergic health outcomes such as allergic rhinitis, atopic eczema and atopic sensitisation were less conclusive (online supplement 2, cross-sectional studies). Only two investigations considered the effects of mould component exposure, and they suggested that higher levels of EPS might decrease the risk of allergic health outcomes in children.

Visible mould exposure

Asthma

A total of 30 cross-sectional studies were included, out of which 15 investigated the effect of exposure to visible mould on asthma in school-aged children. There were 10 studies [15–20, 22–24, 63] with sample sizes above 1,500 subjects. Out of these, nine observed a significantly increased risk of asthma. A study from Tasmania, Australia did not observe an association [18], but this may have been due to the young age of the children (7 yrs). No association was found in the remaining studies, which had smaller sample sizes (403–2,720) [25, 26, 28, 29, 32].

Wheeze

The picture with wheeze was similar to that with asthma: nine out of 15 cross-sectional studies found that exposure to mould at home was associated with a higher risk of wheeze in children. This was especially true among studies with a larger sample size [15–17, 19, 22, 23, 37, 39, 64]. However, five studies did not find any association [26, 28, 29, 65, 66]. In one Spanish study, an increased risk of wheezing was observed only in nonatopic schoolchildren [67].

Allergic rhinitis

Two out of eight studies investigated the relationship between visible mould exposure and allergic rhinitis and observed positive associations. The Pollution and the Young (PATY) study reported a significantly increased risk for hay fever in 6–12-yr-old children when exposed to visible mould at home [15]. Two Asian studies from Singapore also reported higher risks for rhinitis and rhinoconjunctivitis among 1–12-yr-old children [25, 65]. The remaining six studies did not observe any statistically significant exposure-response relationships [17, 22, 26, 44, 47].

Atopic eczema

Four studies investigated the relationship between exposure to visible mould and atopic eczema. One German study by SCHÄFER *et al.* [68] observed a significantly increased risk of atopic eczema in a sample of 6-yr-old children. However, no association was observed for the remaining three studies [25, 47, 65].

Atopic sensitisation

Two investigations examined the association between domestic visible mould exposure and atopic sensitisation in school-aged children. ANTOVA *et al.* [15] observed an increased risk of sensitisation against inhalant allergens in a pooled analysis of >58,000 children. In a smaller German study of 1,235 children, exposure to visible mould was found to increase the risk of sensitisation against mugwort, dust mites and cat (assessed by skin-prick test) among 5–7-yr-old children [68].

Exposure to mould spores

Allergic rhinitis

There were only two cross-sectional studies that investigated the effect of mould spores on the risk of allergic health outcomes in childhood. A small study from Australia reported that exposure to airborne *Penicillium* and airborne *Cladosporium* was significantly positively associated with asthma and wheeze, respectively [69]. Exposure to airborne *Penicillium* was significantly related to sensitisation (skin-prick test) to *Penicillium* mix, *Aspergillus* mix, house dust and dog dander. Higher levels of airborne *Cladosporium* were also associated with sensitisation to *Aspergillus* mix and exposure to airborne *Aspergillus* was suggested to increase the risk for sensitisation against inhalant allergens [69]. SALO *et al.* [70] could not find any association between dust-borne *Alternaria alternata* and physician-diagnosed asthma.

Exposure to mould components

There were only two investigations of one cross-sectional study in Germany, Austria, Switzerland and The Netherlands (the Prevention of Allergy–Risk Factors for Sensitization Related to Farming and Anthroposophic Lifestyle study). KARADAG *et al.* [71] and colleagues found that exposure to EPS from children's mattresses was negatively associated with physician-diagnosed eczema but not with eczema symptoms. In the second investigation by EGE *et al.* [72], EPS was found to significantly decrease the risk of asthma ever and current wheeze. However, there was no effect on atopic sensitisation against inhalant and food allergens. The associations were less conclusive for exposure to (1,3)- β -D-glucan. KARADAG *et al.* [71] found an association with decreased risk of atopic eczema symptoms.

Results of the meta-analysis for the association between visible mould exposure and asthma, wheeze and allergic rhinitis

A total of 21, 19 and 10 publications of different study designs on exposure to domestic visible mould in relation to asthma, wheeze and allergic rhinitis health outcomes, respectively, were included in the meta-analysis. The summary estimates illustrate that exposure to visible mould at home was significantly positively associated with asthma, wheeze and allergic rhinitis (OR 1.49 (95% CI 1.28–1.72), OR 1.68 (95% CI 1.48–1.90) and OR 1.39 (95% CI 1.28–1.51), respectively). Forest-plots in figure 2 illustrate the odds ratios with their 95% confidence intervals and provide a summary estimate for the association between the investigated exposure–response relationships.

Owing to the limited number of studies that investigated the relationship between exposure to mould-derived components

and allergic health outcomes, it was not possible to aggregate the results to perform a meta-analysis.

DISCUSSION

This systematic review included 61 publications. The most commonly reported health outcomes were asthma, wheeze and allergic rhinitis. There was a statistically significant increased risk of asthma (OR 1.49 (95% CI 1.28–1.72)), wheeze (OR 1.68 (95% CI 1.48–1.90)) and allergic rhinitis (OR 1.39 (95% CI 1.28–1.51)) in children when exposed to visible mould. There were fewer studies on exposure to airborne, dust-borne mould spores or measured mould components. While mould spore exposure was found to increase the risk for asthma and wheeze in children at a younger age, our review suggests, however, that mould components such as (1,3)- β -D-glucans and EPS do not increase the risk for allergic health outcomes.

This systematic review on the health impact of visible mould, mould spores and mould-derived components in children provided a comprehensive overview on the literature over the past 30 yrs, which, for the first time, is combined with a quantitative assessment of the reviewed studies. The only previous meta-analysis to examine the health effects of dampness and mould exposure was by FISK *et al.* [5], which reported a significant positive association with wheezing symptoms in children and adults. These prior findings are consistent with those of the present meta-analysis. However, we aimed to go beyond the work of FISK *et al.* [5] and specifically addressed issues such as specificity of exposure, study design, study population, validation criteria and validity of exposure assessment.

Studies after the inclusion deadline for the meta-analysis of Fisk *et al.* [5]

A number of studies were considered here that had not been published in time to be included in the previous meta-analysis of FISK *et al.* [5]. For the association between exposure to mould and wheeze, there were 19 additional publications and for asthma there were 17 additional studies. Furthermore, we identified studies published before 2006 that were not part of the meta-analysis of FISK *et al.* [5], supporting the application of a systematic approach. FISK *et al.* [5] looked at the association between dampness and mould exposure in relation to a number of different upper respiratory tract symptoms, whereas we focused on (physician-diagnosed) allergic rhinitis exclusively. Although we constrained exposure and health outcome definition and limited the analysis to children only, we did reach a higher number of publications than the meta-analysis in 2007 [5].

Specification of type of exposure

Previous investigations, including the work from FISK *et al.* [5], have often assessed dampness, water leakage, mould, mould spores, mould odour and mould-derived exposure as a common exposure type. In order to specify the type of exposure, we defined three different kinds of mould exposure to account for conflicting study results in the past: domestic visible mould, measured airborne fungal species and measured mould-derived components assessed by house dust sampling. While there is a good correlation suggested between visible mould exposure and the concentration of fungal spores [73], recent literature indicated that exposure to mould-derived

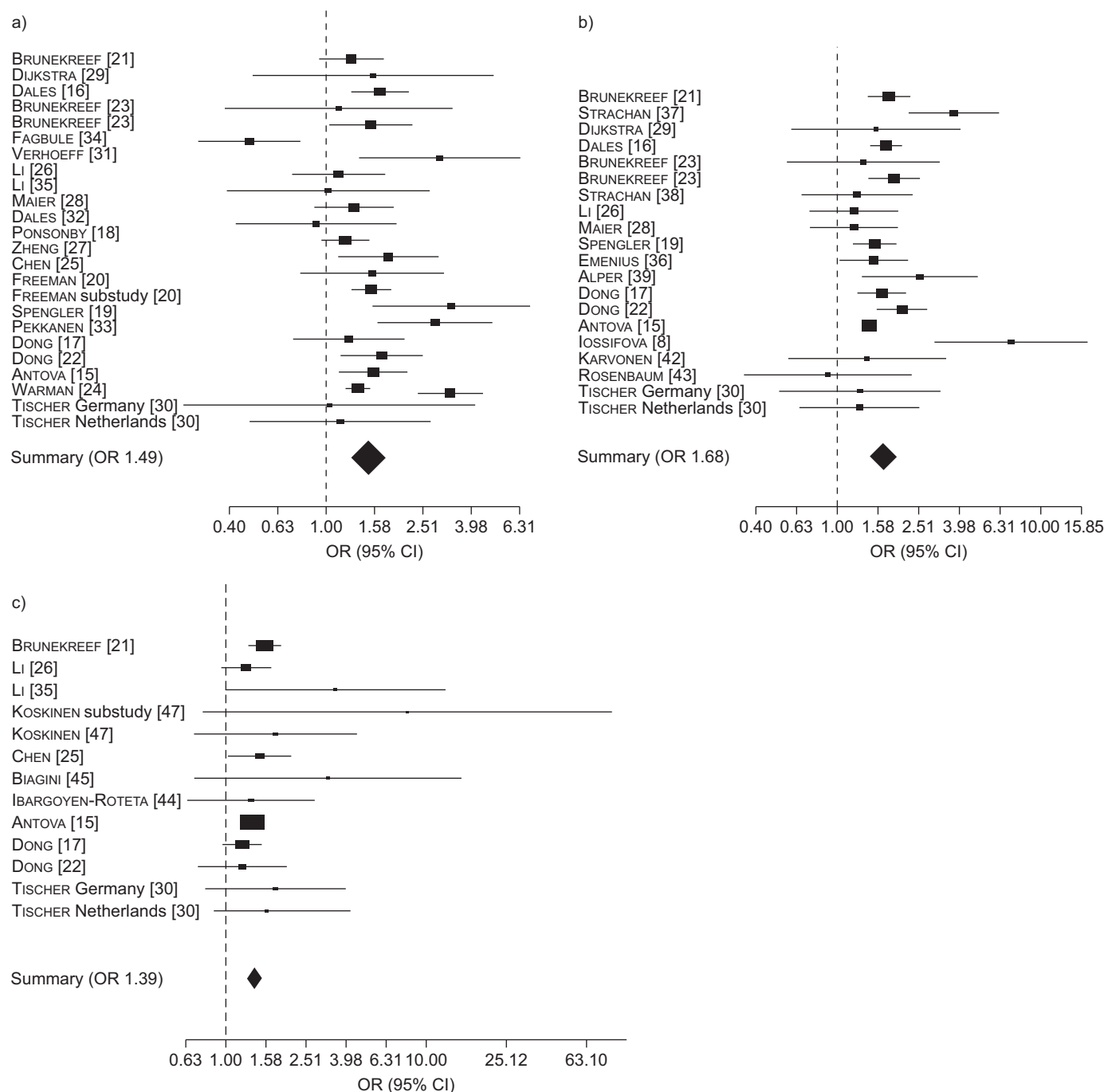


FIGURE 2. Odds ratios and 95% confidence intervals for the association between visible mould and a) asthma, b) wheeze and c) allergic rhinitis from original studies and from a meta-analysis (combined effect) performed using the random effects model. For each study, the size of the box is proportional to the precision (inverse of variance) of the study. The combined estimate from the meta-analysis is indicated by the diamond-shaped box (labelled "Summary") at the bottom of the figure.

components might have a different impact on children's health and may not measure a single kind of exposure. This hypothesis was supported by a US cohort study that did not find a correlation between (1,3)- β -D-glucan exposure and visible mould [8, 12]. This might be partly due to the fact that (1,3)- β -D-glucan is also part of the structure of plant materials, including pollen and cellulose, as well as soil bacteria; therefore, the level of mould exposure may be overestimated by using (1,3)- β -D-glucan as a surrogate [7]. EPS are stable

carbohydrates secreted or shed during fungal growth and have antigenic specificity at the genus level but cannot represent exposures to all of the fungal species in an indoor environment. Furthermore, it has been suggested that mould-derived components such as (1,3)- β -D-glucan or EPS can protect children from developing allergic disorders, as shown in recent longitudinal investigations [8, 9, 12]. A protective tendency of mould-derived components on allergic diseases was also confirmed by this study. It has been proposed that

early exposure to indoor microbial elements may have strong immune-stimulatory properties, as has been suggested for endotoxin in several studies [74–76]. The present review revealed that there are still not enough data on exposure to mould-derived components to perform combined analyses, which would be required to make a more definite statement on the impact of exposure to these components.

Study design

Compared to FISK *et al.* [5], we further addressed different types of study design. Nearly half (41%) of the publications included in this review were cross-sectional studies, and a considerable proportion of these had large sample sizes. In contrast, the proportion of cohort studies and case-control studies is lower (14 and 23%, respectively) and with considerably fewer study subjects. Compared with cross-sectional studies, it was not possible to determine a clear direction of the investigated exposure-response relationships, which might be partly due to lack of power within the original studies. Nevertheless, birth cohort studies and cohort studies not recruited at birth might be given more weight as they can better assign the temporal sequence and presumably the important perinatal exposure window. However, due to the limited number of (birth) cohort studies and short follow-up time, we were not able to quantify them separately in a meta-analysis. In future, combined investigations focused on longitudinal studies exclusively may be able to assess causality over a longer time period. This is currently ongoing in the frame of the Environmental Health Risks in European Birth Cohorts initiative (www.enrieco.org).

Study population

In contrast to previous investigations, the current review focused on studies in children only, as it is suggested that the exposure-response relationship alters with ageing; and the development of allergic diseases and symptoms occurs during early childhood. Furthermore, the incidence of allergic diseases in adults may be provoked by different triggers, for example due to occupational exposure and causing nonallergic rather than allergic responses [76].

Validation criteria

The interpretation of the results from this review is based on systematic, validated criteria in terms of the search for eligible publications and also interpretation and analysis. We performed a reasonable and replicable systematic search using the electronic database PubMed in order to make the process transparent. Until now, there has been no review on the association between mould exposure and allergic health outcomes in children according to systematic search criteria. In addition to the meta-analysis on mould exposure and allergic health outcomes, we evaluated the results of the systematic review according to the Bradford Hill criteria for assessing evidence of causation [77], which are discussed in detail later on.

Validity of exposure assessment

Visible mould exposure at home was assessed mainly by questionnaire. Although this method is convenient and favourable, questionnaire-based methods are difficult to validate against microbial measurements [40, 48]. Numerous studies validated self-reported visible mould questions against

inspector-reported observations [36, 31, 78–81] and did not find any evidence for over- or underreporting of dampness and mould by occupants. Further, against the backdrop of fungal diversity, it is not clear whether the obviously visible mould or unknown, invisible species contribute to the observed effects in children's health [69, 82]. The most ideal exposure assessment for exposure to mould or mould-derived components would be repeated sample collections through a mobile personal air sampler. However, individual biological measurements are costly and therefore usually not feasible, especially in larger (birth) cohort studies. Some studies collected fungal species or mould-derived components by means of settled house dust or air samples. While these methods are generally considered more standardised, in that they follow a protocol and reduce the risk of systematic biases such as reverse causation compared with questionnaire-based methods, there are some shortcomings. To begin with, sampling methods vary considerably between the studies. Dust sampling from floors or mattresses using a vacuum cleaner provides a crude mixture of different particle sizes [10, 83, 84], but some of the dust fraction may never become airborne and might not have an effect on children's health. Hence some investigations sampled specific airborne dust fraction in domestic environments [43, 46, 53, 55, 56, 61]. However, this requires considerable time and cost resources. Recently, new exposure assessment methods have been developed. Passive airborne sampling ("pizza box"), electrostatic dust-fall collector or electrostatic dust clothes [85–87] can be used for a broad range of allergen measurements. These newly developed exposure assessment methods might be a valuable substitute for existing methods in terms of cost and work.

In addition to the meta-analysis on mould exposure and allergic health outcomes, we evaluated the results of the systematic review according to the Bradford Hill criteria [77]. Epidemiological studies typically examine associations between exposure and health outcomes, while the Bradford Hill criteria are suggested to assess the causal nature of an observed association on the basis of nine categories [88, 89]. These nine criteria should not be used as a checklist, but instead highlight important aspects of an investigation. According to these criteria, the evaluation supports the findings of the meta-analysis, especially with regard to aspects such as strength of association, temporal relationship, biological gradient, plausibility and coherence. Further research is needed to examine exposure specification against the backdrop of microbial diversity in indoor environments (see online supplement 3 for an extensive description).

Limitations

The timing of health outcome assessment is crucial in epidemiological studies. Some birth cohorts included in this review were too young to classify wheezing symptoms into transient, persistent and late-onset wheezing. Five out of six studies had an age range of 6 months to 3 yrs. There might be children having transient symptoms of asthma at an early age, but who are not a risk of developing clinical symptoms later during childhood. However, the follow-up time was too short to allow monitoring of disease development over a long period. Therefore, findings from birth cohort studies at younger ages should be interpreted with caution and the results may be of a short-term rather than a long-term character.

Although we specified mould exposure in terms of three different exposure sources, namely visible mould, airborne or dust-borne measurement of mould spores, and measured mould components from settled house dust, a clear assignment to the observed health effects is difficult. While there is a good correlation suggested between visible mould exposure and the concentration of fungal spores [73], exposure to mould-derived components might have different impacts on children's health. Indoor environments consist of a variety of indoor and outdoor sources, not only the measured ones. Visible mould or measured mould spore and mould-derived component exposure might only partly represent the actual microbial pollution at home. A recent study on predictors of bacterial and fungal biomarkers in house dust concluded that home characteristics such as dampness or visible mould explain variation in microbial exposure levels only partially [90]. Moreover, a study from Finland indicated that a considerable part of the measured microbial pollution from mattresses is human-derived (up to 88%) rather than from environmental sources, and varies in addition to that from other sampling locations [91]. Therefore, to draw a causal relationship is complicated by the variability of microbial biomarkers and their suspected effects on children's health. In conclusion, further research measuring specific biomarkers in the home should be emphasised.

Conclusion

The reviewed studies on visible mould exposure indicated an increased risk for allergic respiratory symptoms in children. These findings were confirmed by the meta-analysis results; exposure to visible mould was significantly associated with a higher risk of allergic respiratory disorders including asthma, wheezing and allergic rhinitis in children. Furthermore, the results of this meta-analysis are consistent with the evaluation of causation according to the Bradford Hill criteria. In order to disentangle the different effects of overall microbial exposure in children's health, research on specific microbial markers in the home, in combination with new assessment techniques such as recently developed molecular methods, should be followed. In this context, more weight needs to be given to studies with longitudinal design as they can better assign the temporal sequence; especially studies with a long follow-up and multiple time-point measurements to account for the variation of the complex microbial milieu over time.

SUPPORT STATEMENT

This work is partly funded by Environmental Health Risks in European Birth Cohorts (ENRIECO), a project conducted within the European Union's 7th Framework Programme (Theme 6, Environment (including Climate Change)), grant agreement number 226285.

STATEMENT OF INTEREST

None declared.

REFERENCES

- 1 Bornehag CG, Blomquist G, Gyntelberg F, *et al.* Dampness in buildings and health. Nordic interdisciplinary review of the scientific evidence on associations between exposure to "dampness" in buildings and health effects (NORDDAMP). *Indoor Air* 2001; 11: 72–86.
- 2 Bornehag CG, Sundell J, Bonini S, *et al.* Dampness in buildings as a risk factor for health effects, EUROEXPO: a multidisciplinary review of the literature (1998–2000) on dampness and mite exposure in buildings and health effects. *Indoor Air* 2004; 14: 243–257.
- 3 Institute of Medicine of the National Academies. Damp Indoor Spaces and Health. Washington, National Academies Press, 2004.
- 4 Sahakian NM, Park JH, Cox-Ganser JM. Dampness and mold in the indoor environment: implications for asthma. *Immunol Allergy Clin North Am* 2008; 28: 485–505.
- 5 Fisk WJ, Lei-Gomez Q, Mendell MJ. Meta-analyses of the associations of respiratory health effects with dampness and mold in homes. *Indoor Air* 2007; 17: 284–296.
- 6 World Health Organization. Dampness and Mould. WHO Guidelines for Indoor Air Quality. Copenhagen, World Health Organization, 2009.
- 7 Douwes J. (1→3)- β -D-glucans and respiratory health: a review of the scientific evidence. *Indoor Air* 2005; 15: 160–169.
- 8 Iossifova YY, Reponen T, Ryan PH, *et al.* Mold exposure during infancy as a predictor of potential asthma development. *Ann Allergy Asthma Immunol* 2009; 102: 131–137.
- 9 Douwes J, van Strien R, Doekes G, *et al.* Does early indoor microbial exposure reduce the risk of asthma? The Prevention and Incidence of Asthma and Mite Allergy birth cohort study. *J Allergy Clin Immunol* 2006; 117: 1067–1073.
- 10 Schram-Bijkerk D, Doekes G, Douwes J, *et al.* Bacterial and fungal agents in house dust and wheeze in children: the PARSIFAL study. *Clin Exp Allergy* 2005; 35: 1272–1278.
- 11 von Mutius E, Braun-Fahrlander C, Schierl R, *et al.* Exposure to endotoxin or other bacterial components might protect against the development of atopy. *Clin Exp Allergy* 2000; 30: 1230–1234.
- 12 Iossifova YY, Reponen T, Bernstein DI, *et al.* House dust (1–3)- β -D-glucan and wheezing in infants. *Allergy* 2007; 62: 504–513.
- 13 Gehring U, Heinrich J, Hoek G, *et al.* Bacteria and mould components in house dust and children's allergic sensitisation. *Eur Respir J* 2007; 29: 1144–1153.
- 14 Stroup DF, Berlin JA, Morton SC, *et al.* Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000; 283: 2008–2012.
- 15 Antova T, Pattenden S, Brunekreef B, *et al.* Exposure to indoor mould and children's respiratory health in the PATY study. *J Epidemiol Community Health* 2008; 62: 708–714.
- 16 Dales RE, Zwanenburg H, Burnett R, *et al.* Respiratory health effects of home dampness and molds among Canadian children. *Am J Epidemiol* 1991; 134: 196–203.
- 17 Dong GH, Ma YN, Ding HL, *et al.* Effects of housing characteristics and home environmental factors on respiratory symptoms of 10,784 elementary school children from Northeast China. *Respiration* 2008; 76: 82–91.
- 18 Ponsonby AL, Couper D, Dwyer T, *et al.* The relation between infant indoor environment and subsequent asthma. *Epidemiology* 2000; 11: 128–135.
- 19 Spengler JD, Jaakkola JJ, Parise H, *et al.* Housing characteristics and children's respiratory health in the Russian Federation. *Am J Public Health* 2004; 94: 657–662.
- 20 Freeman NC, Schneider D, McGarvey P. Household exposure factors, asthma, and school absenteeism in a predominantly Hispanic community. *J Expo Anal Environ Epidemiol* 2003; 13: 169–176.
- 21 Brunekreef B, Dockery DW, Speizer FE, *et al.* Home dampness and respiratory morbidity in children. *Am Rev Respir Dis* 1989; 140: 1363–1367.
- 22 Dong GH, Ma YN, Ding HL, *et al.* Housing characteristics, home environmental factors and respiratory health in 3945 pre-school children in China. *Int J Environ Health Res* 2008; 18: 267–282.
- 23 Brunekreef B. Associations between questionnaire reports of home dampness and childhood respiratory symptoms. *Sci Total Environ* 1992; 127: 79–89.

- 24 Warman K, Silver EJ, Wood PR. Modifiable risk factors for asthma morbidity in Bronx *versus* other inner-city children. *J Asthma* 2009; 46: 995–1000.
- 25 Chen WY, Tseng HI, Wu MT, *et al.* Synergistic effect of multiple indoor allergen sources on atopic symptoms in primary school children. *Environ Res* 2003; 93: 1–8.
- 26 Li CS, Hsu LY. Home dampness and childhood respiratory symptoms in a subtropical climate. *Arch Environ Health* 1996; 51: 42–46.
- 27 Zheng T, Niu S, Fan X, *et al.* Childhood asthma in Beijing, China: a population-based case-control study. *Am J Epidemiol* 2002; 156: 977–983.
- 28 Maier WC, Arrighi HM, Morray B, *et al.* Indoor risk factors for asthma and wheezing among Seattle school children. *Environ Health Perspect* 1997; 105: 208–214.
- 29 Dijkstra L, Houthuijs D, Brunekreef B, *et al.* Respiratory health effects of the indoor environment in a population of Dutch children. *Am Rev Respir Dis* 1990; 142: 1172–1178.
- 30 Tischer C, Gehring U, Chen CM, *et al.* Respiratory health in children and indoor exposure to (1,3)- β -D-glucan, EPS mould components and endotoxin. *Eur Respir J* 2011; 37: 1050–1059.
- 31 Verhoeff AP, van Strien RT, van Wijnen JH, *et al.* Damp housing and childhood respiratory symptoms: the role of sensitization to dust mites and molds. *Am J Epidemiol* 1995; 141: 103–110.
- 32 Dales RE, Miller D. Residential fungal contamination and health: microbial cohabitants as covariates. *Environ Health Perspect* 1999; 107: Suppl. 3, 481–483.
- 33 Pekkanen J, Hyvarinen A, Haverinen-Shaughnessy U, *et al.* Moisture damage and childhood asthma: a population-based incident case-control study. *Eur Respir J* 2007; 29: 509–515.
- 34 Fagbule D, Ekanem EE. Some environmental risk factors for childhood asthma: a case-control study. *Ann Trop Paediatr* 1994; 14: 15–19.
- 35 Li CS, Hsu LY. Airborne fungus allergen in association with residential characteristics in atopic and control children in a subtropical region. *Arch Environ Health* 1997; 52: 72–79.
- 36 Emenius G, Svartengren M, Korsgaard J, *et al.* Indoor exposures and recurrent wheezing in infants: a study in the BAMSE cohort. *Acta Paediatr* 2004; 93: 899–905.
- 37 Strachan DP, Flannigan B, McCabe EM, *et al.* Quantification of airborne moulds in the homes of children with and without wheeze. *Thorax* 1990; 45: 382–387.
- 38 Strachan DP, Carey IM. Home environment and severe asthma in adolescence: a population based case-control study. *BMJ* 1995; 31: 1053–1056.
- 39 Alper Z, Sapan N, Ercan I, *et al.* Risk factors for wheezing in primary school children in Bursa, Turkey. *Am J Rhinol* 2006; 20: 53–63.
- 40 Cho SH, Reponen T, Bernstein DI, *et al.* The effect of home characteristics on dust antigen concentrations and loads in homes. *Sci Total Environ* 2006; 371: 31–43.
- 41 Schroer KT, Biagini Myers JM, Ryan PH, *et al.* Associations between multiple environmental exposures and glutathione S-transferase P1 on persistent wheezing in a birth cohort. *J Pediatr* 2009; 154: 401–408.
- 42 Karvonen AM, Hyvarinen A, Roponen M, *et al.* Confirmed moisture damage at home, respiratory symptoms and atopy in early life: a birth-cohort study. *Paediatrics* 2009; 124: e329–e338.
- 43 Rosenbaum PF, Crawford JA, Anagnost SE, *et al.* Indoor airborne fungi and wheeze in the first year of life among a cohort of infants at risk for asthma. *J Expo Sci Environ Epidemiol* 2010; 20: 503–515.
- 44 Ibargoyen-Roteta N, Aguinaga-Ontoso I, Fernandez-Benitez M, *et al.* Role of the home environment in rhinoconjunctivitis and eczema in schoolchildren in Pamplona, Spain. *J Investig Allergol Clin Immunol* 2007; 17: 137–144.
- 45 Biagini JM, LeMasters GK, Ryan PH, *et al.* Environmental risk factors of rhinitis in early infancy. *Pediatr Allergy Immunol* 2006; 17: 278–284.
- 46 Stark PC, Celedon JC, Chew GL, *et al.* Fungal levels in the home and allergic rhinitis by 5 years of age. *Environ Health Perspect* 2005; 113: 1405–1409.
- 47 Koskinen OM, Husman TM, Meklin TM, *et al.* The relationship between moisture or mould observations in houses and the state of health of their occupants. *Eur Respir J* 1999; 14: 1363–1367.
- 48 Cho SH, Reponen T, LeMasters G, *et al.* Mold damage in homes and wheezing in infants. *Ann Allergy Asthma Immunol* 2006; 97: 539–545.
- 49 Jeedrychowski W, Maugeri U, Zembala M, *et al.* Risk of wheezing associated with house-dust mite allergens and indoor air quality among three-year-old children. Krakow inner city study. *Int J Occup Med Environ Health* 2007; 20: 117–126.
- 50 Baker D, Henderson J. Differences between infants and adults in the social aetiology of wheeze. The ALSPAC Study Team. Avon Longitudinal Study of Pregnancy and Childhood. *J Epidemiol Community Health* 1999; 53: 636–642.
- 51 Jaakkola JJ, Hwang BF, Jaakkola N. Home dampness and molds, parental atopy, and asthma in childhood: a six-year population-based cohort study. *Environ Health Perspect* 2005; 113: 357–361.
- 52 McConnell R, Berhane K, Gilliland F, *et al.* Indoor risk factors for asthma in a prospective study of adolescents. *Epidemiology* 2002; 13: 288–295.
- 53 Belanger K, Beckett W, Triche E, *et al.* Symptoms of wheeze and persistent cough in the first year of life: associations with indoor allergens, air contaminants, and maternal history of asthma. *Am J Epidemiol* 2003; 158: 195–202.
- 54 Miyake Y, Ohya Y, Tanaka K, *et al.* Home environment and suspected atopic eczema in Japanese infants: the Osaka Maternal and Child Health Study. *Pediatr Allergy Immunol* 2007; 18: 425–432.
- 55 Gent JF, Ren P, Belanger K, *et al.* Levels of household mold associated with respiratory symptoms in the first year of life in a cohort at risk for asthma. *Environ Health Perspect* 2002; 110: A781–A786.
- 56 Muller A, Lehmann I, Seiffart A, *et al.* Increased incidence of allergic sensitisation and respiratory diseases due to mould exposure: results of the Leipzig Allergy Risk children Study (LARS). *Int J Hyg Environ Health* 2002; 204: 363–365.
- 57 Purvis DJ, Thompson JM, Clark PM, *et al.* Risk factors for atopic dermatitis in New Zealand children at 3.5 years of age. *Br J Dermatol* 2005; 152: 742–749.
- 58 Jacob B, Ritz B, Gehring U, *et al.* Indoor exposure to molds and allergic sensitization. *Environ Health Perspect* 2002; 110: 647–653.
- 59 Wickman M, Gravesen S, Nordvall SL, *et al.* Indoor viable dust-bound microfungi in relation to residential characteristics, living habits, and symptoms in atopic and control children. *J Allergy Clin Immunol* 1992; 89: 752–759.
- 60 Hyvarinen A, Sebastian A, Pekkanen J, *et al.* Characterizing microbial exposure with ergosterol, 3-hydroxy fatty acids, and viable microbes in house dust: determinants and association with childhood asthma. *Arch Environ Occup Health* 2006; 61: 149–157.
- 61 Jovanovic S, Felder-Kennel A, Gabrio T, *et al.* Indoor fungi levels in homes of children with and without allergy history. *Int J Hyg Environ Health* 2004; 207: 369–378.
- 62 Douwes J, van der SB, Doekes G, *et al.* Fungal extracellular polysaccharides in house dust as a marker for exposure to fungi: relations with culturable fungi, reported home dampness, and respiratory symptoms. *J Allergy Clin Immunol* 1999; 103: 494–500.
- 63 Lee YL, Lin YC, Hsiue TR, *et al.* Indoor and outdoor environmental exposures, parental atopy, and physician-diagnosed asthma in Taiwanese schoolchildren. *Paediatrics* 2003; 112: e389.
- 64 Chong Neto HJ, Rosario NA. Risk factors for wheezing in the first year of life. *J Pediatr (Rio J)* 2008; 84: 495–502.
- 65 Tham KW, Zuraimi MS, Koh D, *et al.* Associations between home dampness and presence of molds with asthma and allergic symptoms among young children in the tropics. *Pediatr Allergy Immunol* 2007; 18: 418–424.

- 66 Cuijpers CE, Swaen GM, Wesseling G. Adverse effects of the indoor environment on respiratory health in primary school children. *Environ Res* 1995; 68: 11–23.
- 67 Garcia-Marcos L, Castro-Rodriguez JA, Suarez-Varela MM, et al. A different pattern of risk factors for atopic and non-atopic wheezing in 9–12-year-old children. *Pediatr Allergy Immunol* 2005; 16: 471–477.
- 68 Schäfer T, Kramer U, Dockery D, et al. What makes a child allergic? Analysis of risk factors for allergic sensitization in preschool children from East and West Germany. *Allergy Asthma Proc* 1999; 20: 23–27.
- 69 Garrett MH, Rayment PR, Hooper MA, et al. Indoor airborne fungal spores, house dampness and associations with environmental factors and respiratory health in children. *Clin Exp Allergy* 1998; 28: 459–467.
- 70 Salo PM, Arbes SJ Jr, Sever M, et al. Exposure to *Alternaria alternata* in US homes is associated with asthma symptoms. *J Allergy Clin Immunol* 2006; 118: 892–898.
- 71 Karadag B, Ege MJ, Scheynius A, et al. Environmental determinants of atopic eczema phenotypes in relation to asthma and atopic sensitization. *Allergy* 2007; 62: 1387–1393.
- 72 Ege MJ, Frei R, Bieli C, et al. Not all farming environments protect against the development of asthma and wheeze in children. *J Allergy Clin Immunol* 2007; 119: 1140–1147.
- 73 Haas D, Habib J, Galler H, et al. Assessment of indoor air in Austrian apartments with and without visible mold growth. *Atmos Environ* 2007; 41: 5192–5201.
- 74 Douwes J, Zuidhof A, Doekes G, et al. (1→3)-beta-D-glucan and endotoxin in house dust and peak flow variability in children. *Am J Respir Crit Care Med* 2000; 162: 1348–1354.
- 75 Wong GW, von Mutius E, Douwes J, et al. Environmental determinants associated with the development of asthma in childhood. *Int J Tuberc Lung Dis* 2006; 10: 242–251.
- 76 Radon K. The two sides of the "endotoxin coin". *Occup Environ Med* 2006; 63: 73–78.
- 77 Hill AB. The environment and disease: association or causation? *Proc R Soc Med* 1965; 58: 295–300.
- 78 Andrae S, Axelson O, Bjorksten B, et al. Symptoms of bronchial hyperreactivity and asthma in relation to environmental factors. *Arch Dis Child* 1988; 63: 473–478.
- 79 Nafstad P, Oie L, Mehl R, et al. Residential dampness problems and symptoms and signs of bronchial obstruction in young Norwegian children. *Am J Respir Crit Care Med* 1998; 157: 410–414.
- 80 Norback D, Bjornsson E, Janson C, et al. Current asthma and biochemical signs of inflammation in relation to building dampness in dwellings. *Int J Tuberc Lung Dis* 1999; 3: 368–376.
- 81 Williamson IJ, Martin CJ, McGill G, et al. Damp housing and asthma: a case-control study. *Thorax* 1997; 52: 229–234.
- 82 Osborne M, Reponen T, Adhikari A, et al. Specific fungal exposures, allergic sensitization, and rhinitis in infants. *Pediatr Allergy Immunol* 2006; 17: 450–457.
- 83 Fahlbusch B, Koch A, Douwes J, et al. The effect of storage on allergen and microbial agent levels in frozen house dust. *Allergy* 2003; 58: 150–153.
- 84 Schram-Bijkerk D, Doekes G, Boeve M, et al. Exposure to microbial components and allergens in population studies: a comparison of two house dust collection methods applied by participants and fieldworkers. *Indoor Air* 2006; 16: 414–425.
- 85 Noss I, Doekes G, Sander I, et al. Passive airborne dust sampling with the electrostatic dustfall collector: optimization of storage and extraction procedures for endotoxin and glucan measurement. *Ann Occup Hyg* 2010; 54: 651–658.
- 86 Wurtz H, Sigsgaard T, Valbjorn O, et al. The dustfall collector – a simple passive tool for long-term collection of airborne dust: a project under the Danish Mould in Buildings program (DAMIB). *Indoor Air* 2005; 15: Suppl. 9, 33–40.
- 87 Cozen W, Avol E, Diaz-Sanchez D, et al. Use of an electrostatic dust cloth for self-administered home allergen collection. *Twin Res Hum Genet* 2008; 11: 150–155.
- 88 Lucas RM, McMichael AJ. Association or causation: evaluating links between "environment and disease". *Bull World Health Organ* 2005; 83: 792–795.
- 89 Phillips CV, Goodman KJ. The missed lessons of Sir Austin Bradford Hill. *Epidemiol Perspect Innov* 2004; 1: 3.
- 90 Sordillo JE, Alwis UK, Hoffman E, et al. Home characteristics as predictors of bacterial and fungal microbial biomarkers in house dust. *Environ Health Perspect* 2011; 119: 189–195.
- 91 Taubel M, Rintala H, Pitkaranta M, et al. The occupant as a source of house dust bacteria. *J Allergy Clin Immunol* 2009; 124: 834–840.