Indoor mould exposure, asthma and rhinitis: findings from systematic reviews and recent longitudinal studies

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Evidence that indoor mould at home increases asthma in children is accumulating but is still insufficient in adults http://ow.ly/nEnt30j7lco

Cite this article as: Caillaud D, Leynaert B, Keirsbulck M, *et al*. Indoor mould exposure, asthma and rhinitis: findings from systematic reviews and recent longitudinal studies. *Eur Respir Rev* 2018; 27: 170137 [https://doi.org/10.1183/16000617.0137-2017].

ABSTRACT Starting from the Institute of Medicine (IOM) and World Health Organization (WHO) reports, this review provides an overview of the literature published from 2006 to 2017 on the associations between indoor mould exposure and asthma and rhinitis separately in children and adults with a focus on longitudinal epidemiological studies.

A systematic search of peer-reviewed literature was performed, including systematic reviews and meta-analyses, longitudinal, incident case–control and panel studies. 61 publications were identified reporting visible mould or mould odour or quantitative assessment of culturable fungi or mould species.

In children, visible mould and mould odour were associated with the development and exacerbations of asthma, providing sufficient evidence of a causal relationship. Results from population-based studies in adults were too few and divergent to conclude at more than a limited level of evidence. Exposure to mould in a work building was associated with the incidence and exacerbations of occupational asthma, and we concluded at a sufficient evidence for an association. Systematic reviews, meta-analyses and longitudinal studies on the relationships between mould exposure and allergic rhinitis provide sufficient evidence of an association.

This review extended the conclusions of the IOM and WHO reports, and highlighted the need for further longitudinal studies on asthma in adults, and on rhinitis.

Introduction

Providing good air quality is a measure with the potential to improve lung and general health [1]. Among preventable risk factors, there is a growing interest in the effect of exposure to dampness and visible mould at home. A recent review estimated the cost to society, corresponding to total economic burden of disease

This article has supplementary material available from err.ersjournals.com

Received: Dec 19 2017 | Accepted after revision: March 15 2018

Provenance: Submitted article, peer reviewed.

with cost of illness, and willingness to pay attributable to dampness and mould in the USA to be USD 15.1 (9.4–20.6) billion for asthma morbidity, and USD 3.7 (2.3–4.7) billion for allergic rhinitis [2].

In 2004, the Damp Indoor Spaces and Health Committee of the Institute of Medicine (IOM) reviewed and summarised the scientific evidences for relationships between indoor air exposure and the development and exacerbations of asthma [3]. It concluded that there was sufficient evidence of an association between damp indoor exposure and certain respiratory health outcomes, but insufficient evidence to determine whether an association exists between the presence of mould and asthma development. In 2009, the World Health Organization (WHO) [4] considered that the level of evidence was sufficient in favour of causality for asthma development and almost sufficient for asthma exacerbation without distinction between children and adults.

In the past decade, several meta-analyses and specific reviews have investigated the associations between indoor exposure to mould and respiratory health. These reviews, and more particularly the meta-analyses have provided useful estimates for the increased risk of asthma or rhinitis associated with exposure to mould. New data available in these reviews led to the conclusion that there was sufficient evidence of an association between qualitative mould exposure in indoor environments and asthma development, especially in children, but the authors emphasised the need for further work [5–10]. Indeed, results from cross-sectional and longitudinal studies were often pooled in these reviews, and thus if an association was observed the temporal sequence could not be ascertained. Furthermore, the analyses used a rather broad definition of exposure: the association was related to mould exposure or to dampness [4]. Finally, studies in adults were not included or were grouped together with studies in children, despite the possible difference in the risk factors of adult-onset and childhood-onset asthma.

The aim of the present review was to provide an overview of papers published from 2006 to 2017 on the effect of indoor mould exposure on asthma and rhinitis specifically. Studies reporting only on the health effect of dampness, with no specific focus on mould exposure, were not included in our review. The review focused on longitudinal studies, with a separation of findings from qualitative and quantitative studies, and from studies in children and adults. The search covered any indoor environment, including the workplace.

Methods

This review is one of the deliverables of a working group of 13 experts commissioned by the French Agency for Food, Environmental and Occupational Health and Safety (ANSES) to give an expertise on the exposure to mould in indoor environment (see detailed information in the online supplementary material). A full report was published in French in August 2016 [11] and a short version of the ANSES opinion is available in English [12].

Taking as a starting point the last report of the French Higher Council for Public Health [13] published in 2006, and the WHO report covering publications up to 2007, a systematic review of publications on the health effect of indoor mould exposure from January 2006 to November 2017 was conducted. The literature search used computerised bibliographic databases (PubMed and Scopus). The analysis of literature was performed in four steps according to the four-phase flow diagram of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement: identification, screening, eligibility and inclusion as illustrated in figure E1. We chose “mold” and “fungi” as keywords not including microbial, moisture or bio-contaminant. For Pubmed, the search was also based on nine MESH terms: “fungi/adverse effects”, “fungi/epidemiology”, “fungi/growth and development”, “fungi/immunology”, “fungi/physiopathology”, “fungi/toxicity”, “fungi/pathology”, “occupational health/epidemiology” and “occupational health/toxicity”. For Scopus, the search was based on three groups of free terms: 1) health*, asthma*, respirat*, atopi*, allerg*, cancer* and psychological*; 2) mold* and fung*; and 3) indoor* and expos*. We identified 4967 records after excluding duplicates.

After screening, 518 records were selected as follows. 1) We selected epidemiological studies investigating home, office, school and hospital as indoor environments; 2) we selected “mould exposure” as qualitative data: visible dampness if combined with mould exposure, mould exposure or mould odour, or quantitative mould species: specific or total culturable fungi, mould components such as extracellular polysaccharides, ergosterol, glucans and molecular tools (quantitative (q)PCR); and 3) we selected the following respiratory health outcomes showing the most comprehensive effect: respiratory symptoms, wheeze, asthma symptoms, exacerbations and development of asthma and allergic and nonallergic rhinitis, not including specific search terms for biomarkers of respiratory health.

We further included only records on symptoms due to mould exposure by inhalation leading to 485 eligible full-text articles.

Final inclusion criteria were longitudinal studies, incident case–control studies, panel studies, systematic reviews and meta-analyses leading to the review of 61 papers.

The working group classified strength of evidence using the same categories as those found in the IOM and WHO reviews. In addition to the studies included in the present review, animal data and toxicological data dealing mainly with potential mechanisms behind the observed health effect were considered in interpreting the evidence of health effect due to mould exposure. A set of criteria was used for the assessment of evidence based on Hill's [14] criteria: strength of association, biological gradient, consistency of association, biological plausibility and coherence and temporally correct association [3, 4]. New findings extended the conclusions of the IOM and WHO reports and are summarised in table E3.

Results

The literature search identified 4967 publications, of which 61 reported relevant exposures and health outcomes in suitable study populations (figure E1). Seven meta-analyses and four systematic reviews were identified [5–10, 15–19]. While in 2007, Fisk *et al.* [15] concluded that there was insufficient evidence of an association between mould and asthma development and sufficient evidence for asthma exacerbations in sensitised asthmatic subjects, subsequent reviews progressively identified new outcomes or specific exposure that led to the conclusion that there was sufficient evidence. Figure 1 shows the odds ratios (ORs) for the association between mould exposures and asthma development derived from the meta-analyses, with the number of studies selected. The strength of evidence for exacerbations of asthma was stronger for associations between indoor dampness and mould with suggestive evidence of causality in children and sufficient evidence in adults [6, 16]. Regarding quantitative exposure, there was limited evidence of an association for culturable fungi [6, 16]. In a meta-analysis, Sharpe *et al.* [17] found that *Aspergillus*, *Penicillium*, *Alternaria* and *Cladosporium* species were present at higher concentrations in homes of patients with asthma symptoms (adjusted (a)OR 1.36, 95% CI 1.02–1.82; I^2=61%), but concluded that more work was needed on the role of fungal diversity.

Most recent reviews emphasise the need for further work. Vesper and Wymer [18] reported the results of six epidemiological studies from United States that used the Environmental Relative Mould Index (ERMI), constructed from dust sample qPCR analysis of 36 indicator moulds [19] and studied its association with asthma: the authors concluded that the ERMI studies do not prove that there is a causal relationship between mould exposure and the development or exacerbation of asthma. Lastly, by focusing on tropical countries, Pei Zam *et al.* [20] underlined that several studies dealing with children's respiratory health were undertaken in China, but were limited in Malaysia and Singapore. This last review indicated that

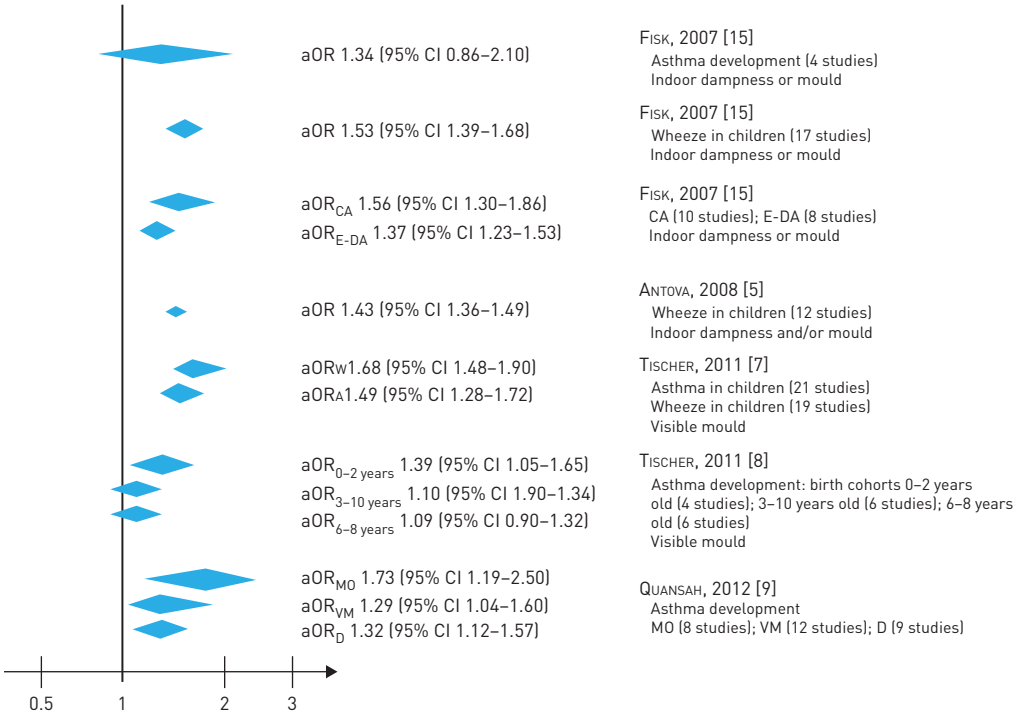

FIGURE 1 Adjusted odds ratios (aOR) and 95% confidence intervals for asthma development and wheeze from the meta-analyses. CA: current asthma; E-DA: ever-diagnosed asthma; W: wheeze; A: asthma; MO: mould odour; VM: visible mould; D: dampness.

TABLE 1 Exposure to moulds using qualitative metrics and asthma occurrence in children (longitudinal studies)

First author, location [ref.]	Study design	Mould exposure	Main outcomes	Results
Pekkanen, Finland [98]	Cases n=121 Controls n=242	Home inspection Visible dampness and mould	Children aged 1–7 years Doctor-diagnosed incident asthma	Main living quarters Dampness: yes *versus* no OR 2.24 (1.25–4.01) Moulds: yes *versus* no OR 2.59 (1.15–5.85)
Karvonen, Finland [99]	Cohort n=396	Home inspection Visible mould and humidity First 6 months of life	Mother's questionnaire at 2, 12 and 18 months	Visible mould: yes *versus* no Doctor-diagnosed wheezing Main living quarters aOR 3.92 (1.54–10) Child bedroom aOR 5.22 (1.48–18.35)
Schroer, USA [100]	Cohort (CCAPS) n=570	Home inspection Visible mould Mould odour First year of life	Parents' ISAAC questionnaire Wheezing at 2 years Persistent wheezing at 1 and 2 years	Visible mould: yes *versus* no Wheezing at 2 years aOR 2.12 (1.25–3.60) Persistent wheezing aOR 2.47 (1.27–4.80)
Dales, Canada [101]	Cohort n=330	Home inspection Visible mould First year of life	Acute and upper respiratory events Birth to 2 years	Visible mould: yes *versus* no NS
Larsson, Sweden [102]	Cohort n=4779 children	Self-reported visible dampness and mould Reported mould odour At birth	Incident asthma at 6–8 years Parents' questionnaire	Mould odour: OR 2.99 (1.50–5.94)
Hwang, Taiwan [103]	1–7 years Cases n=188 Controls n=376	Self-reported mould or mould odour between birth and 1 year	Reported doctor-diagnosed incident asthma 6 years later	Visible mould: yes *versus* no aOR 1.76 (1.18–2.62) Mould odour: yes *versus* no aOR 2.09 (1.30–3.37) Moulds + parent atopy aOR 5.10 (2.80–9.31) Odour + parent atopy aOR 4.11 (2.22–7.64)
Hwang, Taiwan [21]	1–7 years Cases n=188 Controls n=376	Self-reported mould or mould odour between birth and 1 year	Reported doctor-diagnosed incident asthma 6 years later + polymorphisms of interleukin-4 promoter	Visible mould: yes *versus* no CT *versus* TT polymorphism: OR 2.14 (1.05–4.34)
Zhou, France [23]	Cohort n=1765	Self-reported humidity or moulds First year of life	ISAAC questionnaire 0–4, 4–8 and 8–12 months	Humidity and diagnosed asthma + wheeze aOR 2.21 (1.04–4.71) Wheeze aOR 2.12 (1.30–3.46) Diagnosed life-time asthma aOR 2.19 (1.06–4.53)
Wen, Taiwan [24]	Cohort n=19 192	Visible mould during pregnancy Health questionnaire at 0.5, 1.5, 3 and 5 years	Ever doctor-diagnosed asthma in 5-year-old children	Visible mould: yes *versus* no aOR 1.21 (1.01–1.46) Only in females
Shorter, New Zealand [22]	Nested incident cases n=150 Controls n=300	Bedroom wall (electrostatic dust cloth) for 4 weeks Visible mould and odour	Children aged 1–7 years Incident wheezing	Visible mould and mould odour in a dose-dependent manner

Continued

TABLE 1 Continued

First author, location [ref.]	Study design	Mould exposure	Main outcomes	Results
Karvonen, Finland [25]	Cohort n=398	Home inspection Visible mould and humidity First 6 months of life	Ever physician-diagnosed asthma ⩽6 years	Visible mould: yes *versus* no Living room aOR 7.51 (1.49–37.83) Child's bedroom aOR 4.82 (1.29–18.02) Allergic asthma aOR 9.08 (1.95–42.23)
Thacher, Sweden [26]	BAMSE cohort n=3798	Any self-reported mould or dampness indicator (dampness damage, visible mould or mould odour) in infancy (2 months)	Asthma ⩽16 years	Any indicator Asthma OR 1.31 (1.08–1.59) Nonallergic asthma aOR 1.80 (1.27–2.55)

aOR: adjusted odds ratio; CCAPS: Cincinnati Childhood Allergy and Air Pollution Study; ISAAC: International Study of Asthma and Allergies in Childhood; NS: nonsignificant; BAMSE: Barn/Child Allergy Milieu Stockholm Epidemiology.

dampness and mould in buildings were associated with various respiratory symptoms as well as onset of asthma, strongly suggesting moulds as the causal agents.

Exposure to moulds using qualitative metrics and asthma occurrence in children (longitudinal studies)

The publications selected addressed the relationship between dampness, visible mould, mould odour and respiratory health. They include two types of studies: birth cohort studies in children with several years of follow-up and studies involving incident asthma [4] (table 1).

We found six newly published studies not referenced in the previous reviews. In the first, incident asthma in older children was associated with reported visible mould and mould odour. This relationship was stronger in children carrying the CT genotype of the interleukin-4 promoter than in those carrying the TT genotype [21]. In the second study, observations of visible mould in New Zealand were strongly associated with new-onset wheezing, in children aged 1–7 years [22]. In the third, parent-reported dampness or moulds were associated with various asthma phenotypes, especially wheeze at 12 months [23]. In the fourth study [24], performed in 19 192 mother–child pairs representative of the population of Taiwan, exposure to visible mould on the walls during pregnancy was independently associated with an increased risk of asthma diagnosed at the age of 5 years in females. In the fifth study, performed in Finland, exposures at an early age to moisture damage and mould in the child's main living room were associated with physician-diagnosed ever-asthma during the first 6 years [25]. In the last study, any self-reported mould or dampness indicator in infancy (2 months) was associated with asthma up to 7 years of age [26].

These studies confirm the review performed by Quansah *et al.* [9], whose findings showed the causal relationship between fungi, mainly in living rooms, and the occurrence of respiratory symptoms, especially asthma. The relationship was progressively stronger with visible mould and mould odour and more marked in children one of whose parents was atopic.

Exposure to moulds using quantitative measured mould species or components and asthma occurrence in children (longitudinal studies)

Analysis of epidemiological data shows that a large variety of methods were used for assessing mould exposure and indicators: mould components from indoor air or settled dust such as (1, 3)-β-D-glucans, extracellular polysaccharides and ergosterol, as previously reported in reviews and meta-analyses. The most recent publications studied the relationship between fungal exposures measured by culture-based methods and molecular techniques and asthma occurrence in children (table E1).

Two fungal culture studies using data from the Boston birth cohort showed that wheezing at 1 year of age was associated with *Alternaria* and *Cladosporium* in dust [27] and asthma at the age of 13 years with airborne *Alternaria* [28]. The study by Rosenbaum *et al.* [29] indicated that *Penicillium* measured in the air

at 3 months was associated with wheezing at 1 year. In contrast, the Boston birth cohort identified a protective effect of yeasts measured in bedroom dust samples taken at the age of 3 months on wheezing at 1 year, and on the development of asthma at 13 years.

In studies using molecular techniques, the risk of asthma was associated with a high ERMI score [19]. In a small case–control study, low fungal diversity was associated with increased risk of asthma development at the age of 7 years, but no significant associations were found with fungal levels [30]. In the LISA German birth cohort [31], exposure to higher fungal diversity in the living room in infancy, assessed using terminal restriction fragment length polymorphism, was associated with reduced risk of developing sensitisation at 6 years and ever-wheezing until the age of 10 years. However, these associations were no more significant in the longitudinal analyses considering the impact of several follow-ups and their correlation with each other. In a case–control incident asthma study performed in 1–7-year-old children in New Zealand, measurements of qPCR microbial levels in the bedroom children using electrostatic dust cloths were not associated with new-onset wheezing, in contrast to observations of visible mould [22].

In conclusion, given the small number of longitudinal studies, and their conflicting and inconclusive results, there is currently insufficient evidence to determine whether an association exists between quantitatively measured mould species or components and the occurrence of asthma.

Exposure to moulds and exacerbations of asthma in children (panel studies)

We found nine studies (table 2), six being already referenced in the recent reviews by Kanchongkittiphon *et al.* [16], Sharpe *et al.* [17], Vesper and Wymer [18], and Pei Zam *et al.* [20]. Five out of the six panel studies investigated the evolution of asthma symptoms or changes in peak expiratory flow in asthmatic children exposed to mould for periods ranging from 2 weeks to 3 years. In these studies, an association, albeit modest, was consistently found between mould exposure in asthmatic children, in particular exposure to *Penicillium*, and an increased variability in peak expiratory flow rate, a higher asthma severity score, or an increase in the number of days with symptoms or in the unplanned hospital visits. Interestingly, in unadjusted analyses in children of unspecified atopic status, Wu *et al.* [32] found that high levels of total culturable fungi in dust were associated with an increased number of urgent care visits only in those with genetic polymorphisms that caused reduced enzymatic breakdown of chitin, an important fungal protein. This study provides biological plausibility for nonallergic mechanisms for exacerbation of asthma in relation to fungal exposures. Overall, these results, from studies performed in children with variable level of severity at baseline, show an increase in asthma activity associated with mould exposure, irrespective of the children's allergic sensitisation to moulds.

Although of small sample size, the first recent study showed an association between indoor *Cladosporium* levels in the child's bedroom and readmissions for asthma [33]. The second one showed that high fungal concentrations in the main living area in which the child spent the most time was associated with asthma severity [34]. After stratification according to atopy, the same association was found significant in nonatopic children. Interestingly, compared to mild asthma, the fungal communities in house dust from atopic children with severe asthma had low compositional variation, whereas no differences were found between homes of nonatopic children with severe compared to mild asthma. Lastly, among 419 children from 25 schools in three European countries, Casas *et al.* [35] found that children with respiratory conditions report fewer symptoms and/or less severe respiratory symptoms during weekends and summer holidays compared with school days, the association being clearer among those attending schools with moisture damage problems.

In summary, all these studies provide strong evidence for associations between indoor mould exposure and exacerbation of asthma in children, with arguments for causality.

Exposure to moulds using qualitative metrics and asthma in adults (longitudinal studies)

To date, few longitudinal studies have investigated the relationships between mould exposure and respiratory health in adults. These studies were either not included in previous reviews or their findings were grouped together with those in children despite the fact that asthma development in adults may result from different risk factors than in children (table E2).

We only identified four longitudinal studies published after 2006. Owing to the scarcity of studies in adults, we decided to include one report that collected data on mould exposure, although only home dampness was included in the longitudinal analyses. Two studies were performed in northern Europe, and two studies were carried out as part of the European Community Respiratory Health Survey (ECRHS).

In a population-based incident case–control study in Finland, Jaakkola *et al.* [36] investigated the independent and joint effects of indoor exposure to mould and interior surface material and incident asthma. No independent association was observed for exposure to mould at home or at work. However,

TABLE 2 Exposure to moulds and exacerbation of asthma in children (panel studies)

First author, location [ref.]	Study design	Mould exposure	Main outcomes	Results
Hagmolen of Ten Have, the Netherlands [104]	526 children with asthma (mean age 11 years) Follow-up: 2 weeks (2 visits)	At baseline: positive response to a question on visible mould in the past 2 years	Daily variability of peak flow Daily symptoms: wheezing, cough, BHR at follow-up	No association between mould exposure and symptoms In exposed children: increased peak flow variability: +2.70% (95% CI 0.92–4.47, p=0.003), and higher BHR: aOR: 3.95 (1.82–8.57)
Inal, Turkey [105]	19 children with asthma or rhinitis, and monosensitised to mould (aged 4–13 years) Follow-up: 1 year	Every month: indoor air: MAS-100 Eco 100 L·min^{-1} Culture CFU·m^{-3}: *Cladosporium*, *Penicillium*, *Aspergillus*, *Alternaria* and others (undefined or >1%)	Daily variability of peak flow: morning and evening Daily symptoms (rhinitis and asthma scores)	No association between mean exposure to mould (37.5 CFU·m^{-3}) and daily variability of peak flow or symptoms
Bundy, Western Massachusetts and Connecticut, USA [106]	225 children with asthma (6–12 years old) Follow-up: 2 weeks	At baseline: indoor air: Burkard 1 min 20 L·min^{-1} Culture and classification: 0 CFU·m^{-3}, 1–499 CFU·m^{-3}, 500–999 CFU·m^{-3}, >1000 CFU·m^{-3}, *Cladosporium*, *Alternaria*, *Penicillium* or *Aspergillus*	Daily variability of peak flow: three series of measurements morning and evening performed by children Daily symptoms (wheezing, cough and nocturnal symptoms), drugs reported by the mother	No association between mould exposure and symptoms Associations between *Penicillium* (0 *versus* detectable) and peak flow variability of >18.5% (75th percentile) aOR 2.39 (95% CI 1.19–4.81)
Pongracic, the Inner-City Asthma Study: USA [107]	469 children with mild to severe asthma and at least one positive SPT to mould (aged 5–11 years) Follow-up: 2 years	At baseline and every 6 months: indoor air 2 measurements Burkard 1 min 30.5 L·min^{-1}, 1 m from floor, children's room Outdoor air Culture CFU·m^{-3}: *Cladosporium*, *Alternaria*, *Penicillium* and *Aspergillus* Dust measurements on floor and bed	Call report every 2 months: max number of days (in 2 weeks) with symptoms (wheezing, cough, chest tightness, awakening due to asthma or play activities stopped because of asthma) Number of unplanned visits to hospital or EV in the past 2 months	Association between 10-fold increase in *Penicillium* level and increased number of days with symptoms: 1.19 days per 2 weeks, p<0.03 Association between indoor mould and exacerbations and EV: aOR 1.22 (95% CI 1.05–1.43) and 1.13 (1.01–1.26) Association between *Penicillium* and EV: OR 1.15 (1.05–1.27) (all children), and 1.11 (1.03–1.20) in those SPT– for *Penicillium* 24% (n=95) had high mould dust exposure
Wu, USA [32]	395 children with mild-to-moderate persistent asthma CAMP study (aged 5–12 years) Follow-up: 6 months and 3 years or before in case of moving	At baseline and at the first follow-up (6 months): dust measurements on floor (main living room, bedrooms and kitchen) and on child's bed Vacuum cleaner equipped with a filter (Douglas ReadiVac model): 2 min for each zone of different surfaces Culture and classification: high mould dust exposure: >25 000 CFU·g^{-1} of house dust	Severe asthma exacerbations Hospitalisations or urgent care visits during the 4 years of follow-up (report every 4 months) Polymorphisms (SNPs) in chitinase genes	Number of urgent care visits increased with high mould dust exposure in children with genetic polymorphisms (rs2486953, rs4950936 and rs1417149) in the CHIT1 gene
Gent, Western Massachusetts and Connecticut, USA [108]	1233 school-aged children with asthma (aged 5–10 years) Follow-up: 1 month	At baseline: indoor air: Burkard 1 min 20 L·min^{-1}, culture: CFU·m^{-3} Dust measurements on floor and furniture in the main living room Blood allergens: mould, mites, cat, dog (μg·g^{-1}) and cockroaches (U·g^{-1})	Daily symptoms (wheezing, cough), drugs and severity (five levels) Allergic sensitisation: allergens and IgE	In sensitised children: associations between *Penicillium* and risk of wheezing: aOR 2.12 (95% CI 1.12–4.04), cough: 2.01 (1.05–3.85) and asthma severity score: 1.99 (1.06–3.72)

Continued

TABLE 2 Continued

First author, location [ref.]	Study design	Mould exposure	Main outcomes	Results
Vicendese, Melbourne, Australia [33]	Nested incident case–control study within the MAPCAH study: 44 children (aged 2–17 years) Follow-up: September 2009 to December 2011	Air fungi in the child's bedroom: two-stage Andersen Sampler for 1 min, flow rate: 28 L·min^{-1} Total fungi, *Cladosporium*, *Penicillium/Aspergillus* and *Alternaria*, CFU per 28 L of air	Standardised questionnaires from the ISAAC and NZ Otago studies Incident asthma readmissions	Association between every doubling concentration of CFU of airborne *Cladosporium* (per 28 L of air) in the bedroom and asthma readmission: aOR 1.68 (95% CI 1.04–2.72)
Dannemiller, Western Massachusetts and Connecticut, USA [34]	n=196, subgroup of the 1233 school-aged children with asthma (aged 5–10 years) Follow-up: 1 month	At baseline: indoor air: Burkard 1 min 20 L·min^{-1}, culture: CFU·m^{-3} Dust measurements on floor and furniture in the main living room Total fungi concentration dichotomised at the median (high and low exposure)	Daily symptoms (wheezing, cough), and medication use Asthma severity (five levels) expressed as mild (reference, 0 or 1) or severe (3 or 4), level 2 not included in the analyses Total and specific IgE	Association between high fungal concentration and asthma severity in all children: aOR 2.02 (95% CI 1.14–3.56) and in nonatopic children: aOR 2.40 (95% CI 1.06–5.44), but not in atopic children: 1.69 (0.77–3.75)
Casas, HITEA project: Spain, the Netherlands, Finland [35]	419 children (aged 6–12 years) from 25 schools: 106 children from 8 schools in Spain, 150 children from 11 schools in the Netherlands, 163 children from 6 schools in Finland Follow-up: 1 year	School with or without (reference) moisture damage: number, extent, severity and location of dampness, and moisture damage observations recorded during inspections	Three symptom diaries: a 2-week diary starting before the summer school holiday (May–July 2009), a 3-week diary starting at the end of the summer holiday (August–October 2009) and a 2-week diary during winter and spring (January–May 2010) 16 symptoms in the past 24 h: wheeze, shortness of breath, dry cough during day or at night, phlegm, woken up... and severity (no symptom, slight, moderate or severe)	Holiday and weekends were associated with lower scores Results were heterogeneous across the three countries In Spain, all adjusted IRRs <1 for summer holiday (ref. school day) in schools with moisture damage: lower respiratory symptoms IRR 0.61 (95% CI 0.46–0.81), upper respiratory or allergy symptoms 0.78 (95% CI 0.63–0.93), other symptoms 0.64 (95% CI 0.49–0.83) Similar results in Finland for summer holiday and weekend All random-effect combined IRRs <1

HITEA: Health Effects of Indoor Pollutants: Integrating Microbial, Toxicological and Epidemiological Approaches; BHR: bronchial hyperresponsiveness; aOR: adjusted odds ratio; EV: emergency visit; SPT: skin prick test; SNP: single nucleotide polymorphism; Ig: immunoglobulin; MAPCAH: Melbourne Air Pollen Children and Adolescent Health; ISAAC: International Study of Asthma and Allergies in Childhood; IRR: incidence rate ratio.

combined exposure to mould and wall-to-wall carpet in the workplace was associated with a significant increased risk of incident asthma.

In the general population, the analysis of data on dampness retrospectively collected as part of the Respiratory Health in Northern Europe (RHINE) follow-up showed that subjects living in damp homes had a higher risk to develop respiratory symptoms, compared to those living in dry homes [37]. Conversely, the remission of respiratory symptoms was less common in damp homes. As regards asthma, no significant association was observed despite the large sample size and relatively high number of new-onset asthma cases. Questions specifically focusing on mould exposure were only asked at follow-up. The cross-sectional analysis of these data showed a significant relationship between asthma and the presence of visible mould.

Analyses of the ECRHS population-based study of young adults considered "dampness" and "mould" scores calculated as the number of positive answers to the presence of "mould or mildew on any surface inside the home" ever and in the past 12 months both at baseline and follow-up (9 years after baseline) [38, 39]. In addition, 3118 homes were inspected at follow-up for the presence of dampness and mould. Dampness and mould were common at baseline and follow-up (~10% of the sample reported water damage and ~16% reported visible mould in the past 12 months). It is noteworthy that the dampness

score and the mould score showed relatively poor agreement. No significant relationship was found between reported or observed mould exposure and lung function decline [38]. However, other aspects of building dampness (such as water leakage or damp spots) were associated with accelerated lung function decline, but only in females. The reasons why a stronger effect was observed in females are unclear. A greater susceptibility or a longer exposure time in the dwelling for females is speculated. Another study of the same cohort was focused on the risk of asthma onset in subjects without asthma or respiratory symptoms at baseline [39]. There was an excess risk of new asthma onset in subjects reporting mould indoor in the past 12 months at baseline, although no significant relationship was found when considering specifically mould (ever) in the bedroom or in the living room at baseline. A dose–response effect was observed when the score combining exposure at baseline and follow-up was used. No significant interaction by sex was observed, apart for mould exposure in the living room which showed a significant effect only in females. Some heterogeneity was observed between centres. Therefore, this study is one of the first to show a significant relationship between mould exposure in the dwelling and subsequent asthma onset, and to report a dose–response effect. However, the score used for the dose–response relationship combined data from baseline and follow-up.

To summarise the four longitudinal studies identified in our literature review: one study showed an effect of the combined exposure to wall-to-wall carpets and to mould at work, but found no significant effect of visible mould or mould odour at home [36]; one study showed an excess incidence and less frequent remission of respiratory symptoms in individuals living in damp homes, but no significant association with asthma [37]; one study [39] reported a significant relationship between mould exposure in the dwelling and subsequent asthma onset; and the final study showed a significant relationship between lung function decline and various aspects of building dampness, but not with mould exposure when considered specifically [38].

In conclusion, given the small number of longitudinal studies with a particular focus on mould exposure, and the lack of consistent findings, there is limited evidence on the effect of mould exposure on asthma onset in adults from the general population. Further studies are clearly warranted.

Longitudinal studies on occupational asthma related to working in mouldy buildings

Studies on respiratory health in adults working in damp buildings provide additional evidence for the existence of associations between mould exposure and the incidence and morbidity of asthma in adults (table 3).

In Finland, Jaakkola *et al.* [40] had already shown that the risk of incident asthma was related to the presence of visible mould and/or mould odour in the workplace. In a later study a relationship was demonstrated between incident asthma and the combined presence of mould problems and wall-to-wall carpet in the workplace [36]. In this country, indoor moulds from water-damaged buildings have become the most important causative agents of occupational asthma since 2001 [41]. In compliance with compensation policy, most cases referred to the Finnish Institute of Occupational Health are confirmed objectively by specific inhalation challenge tests with mould extracts.

In a first study (table 3), Karvala *et al.* [42] followed 136 patients with "probable" occupational asthma. After 6 months of follow-up, 42% were no longer working, while none of the 13 still exposed reported improvement of symptoms. In a second study [43], 483 patients with asthma-like symptoms related to damp workplaces, but without objective evidence of asthma at inclusion, were followed-up for 3–12 years. The risk of developing asthma was 4.6 times higher in patients still exposed. Additional studies of workers with mould-induced asthma further evidenced impaired quality of life, work disability and a high rate of work withdrawal [44, 45]. In a study of US employees in a water-damaged office, Park *et al.* [46] showed a significant association between asthma with post-occupancy onset and the levels of exposure to mould, especially hydrophilic fungi. In another study [47], the same authors found a dramatic increase in the risk of developing building-related asthma symptoms (OR 7.4, 95% CI 2.8–19.9) in individuals with a high level of both fungal exposure and building-related rhinosinusitis at inclusion. Of note, only the initial mould exposure, but not subsequent exposures, was a significant predictor of building-related asthma symptoms, which suggests that it might be more relevant to understand the historical exposure to dampness rather than focusing on recent exposure. The authors proposed that building-related rhinosinusitis should be considered as a warning for increased risk of developing asthma symptoms and prompt identification of mould problems and timely effective remediation.

In conclusion, these prospective studies provide sufficient evidence of an association between indoor mould exposure at work and the development of asthma, but insufficient evidence for a causal relationship, with further prospective studies in other countries being needed.

TABLE 3 Longitudinal studies on occupational asthma related to working in mouldy buildings

First author, location [ref.]	Study design	Mould exposure	Main outcomes	Results
Park, USA [46]	Nested study Cases n=49 Controls n=152 Employees working in a water-damaged building	Floor and chair dust TCF HF Endotoxins Pet allergens	POA	POA (for increasing IQR) and chair dust Single environmental variable aOR (95% CI) TCF 1.67 (1.07–2.60) HF 1.85 (1.19–2.89) Multiple environmental variables: HF 1.79 (1.12–2.85)
Karvala, FIOH: Finland [42]	Patients assessed between 1995 and 2004 for suspicion of mould-induced OA n=258	Retrospective work exposure: building damage report and microbial analyses	SIC with mould extracts, especially *A. fumigatus*, *C. cladosporioides* and *A. kiliense* Three OA groups: probable, possible, unlikely	Mould duration exposure usually >5 years Sensitisation to moulds: probable: 20.4% possible: 10.7% unlikely: 4.4% Among 133 probable OA (SIC$^+$): *A. fumigatus*: 85 *C. cladosporioides*: 26 *A. kiliense*: 19
Karvala, FIOH: Finland [43]	Longitudinal study over 3–12 years n=483	Exposure: building damage report and microbial analyses	Doctor-diagnosed incident asthma among patients with ALS related to damp workplaces, but without asthma at baseline	Doctor-diagnosed incident asthma No more exposition (ref.) Same remediated OR 2 (95% CI 0.7–5.4) Persistent exposure: OR 4.6 (95% CI 1.8–11.6)
Park, USA [47]	Employees working in a damp building. Baseline n=131 BR-RS without asthma n=361 without BR-RS and asthma at baseline	Floor dust: TCF Ergosterol Endotoxins	BR-AS development	BR-AS development: aOR (95% CI) BR-RS 1.00 (ref.) BR-RS$^+$ 2.24 (1.34–3.72) Baseline TCF 1st tertile 1 (ref.) 2nd tertile 3.59 (1.46–8.83) 3rd tertile: 4.92 (1.90–12.72)
Karvala, FIOH: Finland [44]	Longitudinal study over 3–12 years n=1267	Exposure: building damage report and microbial analyses	Quality of life SF12 physical and mental component scores Four baseline groups n=127 OA n=453 WEA n=483 ALS n=204 URS	SF12, physical component score Mean±SD URS 69.7±28.9 ALS 62.9±29.7 WEA 54.7±30.6 OA 45.4±29.1 p <0.001
Karvala, FIOH: Finland [45]	Longitudinal study over 7–8 years n=1098	Exposure: building damage report and microbial analyses	Self-rated work ability 0: low <scale<10: best Early withdrawal from work owing to disability Four baseline groups n=127 OA n=453 WEA n=483 ALS n=204 URS	Low self-rated work ability (scale <8) %, aOR (95% CI) URS 34%, 1.0 ALS 40%, 1.2 (0.8–1.7) WEA 50%, 1.8 (1.2–2.8) OA 57%, 2.6 (1.4–4.7) Early withdrawal from work %, aOR (95% CI) URS 7%, 1.0 ALS 13%, 1.6 (0.8–3.1) WEA 13%, 1.6 (0.8–3.1) OA 33%, 5.7 (2.8–11.9)

FIOH: Finnish Institute of Occupational Health; TCF: total culturable fungi; HF: hydrophilic fungi; POA: post-occupancy asthma; IQR: interquartile range; aOR: adjusted odds ratio; OA: occupational asthma; SIC: specific inhalation challenge; *A. fumigatus*: *Aspergillus fumigatus*; *C. cladosporioides*: *Cladosporium cladosporioides*; *A. kiliense*: *Acremonium kiliense*; ALS: asthma-like symptoms; BR: building-related; RS: rhinosinusitis; AS: asthma symptoms, WEA: work-exacerbated asthma; URS: upper respiratory symptoms; SF12: 12-item short form survey.

Recent reviews, meta-analyses and longitudinal studies on rhinitis

Several meta-analyses have covered the relationships between mould or dampness exposure and rhinitis (table 4). In 2007, combining data from 13 cross-sectional and longitudinal studies, Fisk *et al.* [15] showed a significant relationship between exposure to mould and/or dampness and upper respiratory tract symptoms, with no evidence of publication bias. In the Pollution and the Young (PATY) consortium [5], consisting of seven cross-sectional studies in children from different areas, visible mould was associated with an increased risk of hay fever.

In their review, Mendell *et al.* [6] concluded that there was sufficient evidence for the existence of an association between home dampness or mould exposure and risk of upper respiratory tract symptoms and allergic rhinitis, but insufficient evidence of a causal relationship, because of insufficient evidence with regards to causal microbial exposure or dose–response relationships to define "safe" levels of exposure.

Tischer *et al.* [7] performed a systematic review in children, considering more specific criteria for mould exposure and giving more weight to longitudinal studies. However, their meta-analysis included both cross-sectional and longitudinal studies. They concluded that exposure to visible mould was associated with an increased risk of allergic rhinitis in children, and that the results were consistent with the evaluation of causation according to Hill's criteria. However, the authors also reported findings showing a tendency towards a lower risk of allergic health outcomes in children exposed to mould-derived components [7]. In addition, they found some suggestion of moderate publication bias.

In another study, pooling data from six European birth cohorts, Tischer *et al.* [8] showed that exposure to visible mould and/or dampness during the first 2 years of life was associated with an increased risk of allergic rhinitis later in childhood. It is the largest longitudinal study to show relationships between exposure to dampness and the development of allergic rhinitis. However, its focus was not specifically on mould exposure.

A more recent meta-analysis by Jaakkola *et al.* [48] included findings published up to August 2012. The authors considered various criteria to define mould exposure**.** For allergic rhinitis, the highest effect estimate was obtained when the exposure concerned mould odour. A significant and relatively homogeneous association was observed with visible mould. However, most of the studies were cross-sectional. Because the risks of rhinitis and allergic rhinitis were similarly increased, the authors suggested that other mechanisms than allergic ones could also play a role.

Few longitudinal studies have focused on mould exposure (table 4), and only two were not referenced in the systematic reviews. In the Boston birth cohort [28], children with higher levels of *Aspergillus* in bedroom floor dust in infancy were more likely to develop rhinitis, but no association was observed for total fungi. In the BAMSE (Barn/Child Allergy Milieu Stockholm Epidemiology) cohort, visible mould and mould odour in infancy were associated with an increased risk of rhinitis up to the age of 16 years [26]. It is noteworthy that exposure to any mould or dampness indicator during infancy was associated with a significant increased risk of nonallergic rhinitis and with a nonsignificant decreased risk of allergic rhinitis at age 16 years.

To summarise, systematic reviews and meta-analyses published since 2006 on the relationships between mould exposure and allergic rhinitis provide sufficient evidence of an association, with an odds-ratio generally >1.35 (table 4). However, most of the studies that specifically focused on exposure to mould are cross-sectional studies, while the longitudinal studies considered "exposure to mould and/or dampness". Conversely, some studies have suggested there is a possible decreased risk of allergic rhinitis in individuals exposed to mould-derived components. Moreover, the few longitudinal studies to date do not provide consistent evidence. Further longitudinal studies are needed to specifically study the associations between mould exposure and allergic rhinitis, nonallergic rhinitis and rhinitis severity to yield conclusive evidence of the differential effect of the various fungal components related to home dampness.

Discussion

We reviewed data from literature published between January 2006 and November 2017 on the associations between mould exposure and asthma and rhinitis by studying children and adults separately. New findings extended the conclusions of the IOM and WHO reports (table E3). In children, we concluded for the first time that there was a sufficient evidence of a causal relationship between exposure to indoor moulds and the development and exacerbation of asthma. In adults, we concluded that there was a sufficient evidence of an association for asthma in relation to work in a mouldy and damp building, and a limited level of evidence in the general population due to insufficient data. Based on the findings from systematic reviews and meta-analyses, we concluded for the first time on a sufficient level of evidence for an association for allergic rhinitis. This review highlights the areas where further studies are still needed.

TABLE 4 Mould exposure and rhinitis: findings from meta-analyses, longitudinal studies and birth cohorts

First author [ref.]	Study design	Mould exposure	Main outcomes#	Results
Fisk [15]	Meta-analysis 13 cross-sectional + longitudinal studies Children and adults	Dampness and/or mould	Upper respiratory tract symptoms	OR 1.70 (95% CI 1.44–2.00)
Antova [5]	Pooled analysis of seven cross-sectional studies as part of the PATY study Children aged 6–12 years	Visible mould	Hay fever	OR 1.35 (95% CI 1.18–1.53) p-value from test for between-country heterogeneity p=0.20
Tischer [7]	Meta-analysis 11 cross-sectional + longitudinal studies Children	Visible mould	Allergic rhinitis or hay fever	OR 1.39 (95% CI 1.28–1.51)
Tischer [8]	Pooled analysis of six birth cohorts as part of the ENRIECO initiative	Early exposure to mould	Allergic rhinitis	In early school age (6–8 years) aOR 1.12 (95% CI 1.02–1.23) In childhood (3–10 years) aOR 1.18 (95% CI 1.09–1.28) No significant heterogeneity between the cohorts
Jaakkola [48]	Cross-sectional, case–control and cohort studies in children or adults (31 studies overall)	Water damage, dampness, visible mould and mould odour	Allergic rhinitis	EE (95% CI) Dampness: (6 studies) mild heterogeneity 1.50 (1.38–1.62) All EEs >1; 6/6 EEs significant Visible mould: (12 studies) no heterogeneity 1.51 (1.39–1.64) All EEs >1; 6/12 EEs significant Mould odour: (3 studies) strong heterogeneity 1.87 (0.95–3.68) All EEs >1; 2/3 EEs significant
Biagini, USA [109]	Birth cohort (CCAPS) with at least one parent with positive SPT n=495 infants with SPT at the age of 1 year	Visible mould during home visit	URTI (sinus or ear infection and antibiotic use) reported in diary Allergic rhinitis = rhinitis symptoms + at least one positive SPT	Visible mould: aOR (95% CI) for URTI (*versus* ref.= no visible mould) Low 1.5 (1.01–2.3) High 5.1 (2.2–12.0) aOR (95% CI) for allergic rhinitis Low 1.2 (0.6–2.5) High 3.2 (0.7–14.8)
Osborne, USA [110]	Birth cohort (CCAPS) with at least one parent with positive SPT n=144 children aged 1–3 years	Long-term air sampling and total fungal spore enumeration in the 8 months around clinical examination	SPT to two food allergens and 15 aeroallergens Questionnaire for parents on rhinitis (sneezing, runny or stuffy nose, when you did not have a cold?)	Positive associations between rhinitis and: total concentration (p=0.10), *Ganoderma* (p=0.06), basidiospores (p=0.01) Negative associations between rhinitis and: *Alternaria* (p=0.10) Positive associations between positive SPT and *Alternaria* (p=0.01), *Penicillium/Aspergillus* type (p=0.01) Negative associations between positive SPT and *Ganoderma* (p=0.10), basidiospores (p=0.09) and *Cladosporium* (p=0.04)
Inal, Turkey [105]	19 children aged 4–13 years with asthma or rhinitis, and monosensitised to mould Follow-up 1 year	Monthly sampling of indoor air	Daily symptom score of rhinitis in diary	No association between exposure to mould (total or *Cladosporium*, *Alternaria*, *Penicillium* or *Aspergillus* concentration CFU·m^{-3}) and daily symptom score

Continued

TABLE 4 Continued

First author [ref.]	Study design	Mould exposure	Main outcomes#	Results
Jaakkola, Finland [111]	Population-based prospective cohort n=1863 children aged 1–7 years, free of allergic rhinitis at baseline in 1991 (n=246 incident cases)	Visible mould, wet spots, water damage and indicator of "any" exposure	Development of allergic rhinitis (incident cases) (history of or current physician-diagnosed allergic rhinitis during the 6-year follow-up period)	OR for allergic rhinitis incidence (compared to ref=no exposure) Visible mould at baseline 1.06 (0.51–2.21); at follow-up 1.98 (1.32–2.99) Mould odour at baseline 0.94 (0.36–2.45); at follow-up 1.45 (0.89–2.37) Any exposure at baseline 1.55 (1.10–2.18); at follow-up 1.62 (1.21–2.18); at baseline and follow-up 1.96 (1.29–2.98)
Behbod, USA [28]	Prospective birth cohort 408 children with family history of allergic disease or asthma followed-up to age 13 years	Parental report of home dampness and culturable fungi in bedroom air and dust, and in outdoor air when children were aged 2–3 months Indoor air: Burkard DG18: 1 min 45 $L \cdot min^{-1}$ Culture: identification of fungal genus	Symptoms/disease onset from birth to age 13 years For rhinitis: parental report of physician-diagnosed hay fever and nasal symptoms (runny nose) Mould sensitisation status tested at ages 7 and 13 years (in n=285)	HR (95% CI) for rhinitis onset Home dampness 1.11 (0.73–1.68) Dust (bedroom floor) *Alternaria* 0.79 (0.51–1.22) *Cladosporium* 0.91 (0.77–1.08) *Aspergillus* 1.39 (1.11–1.74) *Penicillium* 1.04 (0.89–1.21) Yeasts 1.06 (0.92–1.22) Nonsporulating fungi 1.05 (0.88–1.25) Measures in indoor air: no significant association observed
Thacher, Sweden [26]	Birth cohort (BAMSE) n=3798 children with follow-up data at age 16 years	Parental report when the child was 2 months, of mould odour ever in the home, visible mould in the home in the past year or moisture damage in the home	Rhinitis: eye or nose symptoms following exposure to allergens in the past 12 months and/or a doctor's diagnosis of allergic rhinitis (+/- positive Phadiatop test) at age 16 years	OR (95% CI) for rhinitis at age 16 years Visible mould 1.28 (1.04–1.58) Mould odour 1.29 (1.03–1.62) Any mould or dampness indicator for nonallergic rhinitis 1.41 (1.03–1.93); allergic rhinitis 0.88 (0.74–1.05)

PATY: Pollution and the Young; ENRIECO: Environmental Health Risks in European Birth Cohorts; aOR: adjusted odds ratio; EE: effect estimate; CCAPS: Cincinnati Childhood Allergy and Air Pollution Study; SPT: skin prick test; URTI: upper respiratory tract infection; BAMSE: Barn/Child Allergy Milieu Stockholm Epidemiology. #: other outcomes are considered in the articles cited.

We focused on longitudinal studies, whose design allows the ascertainment of temporality by assessing exposure before the onset of the disease and which are less subject to biases encountered in cross-sectional studies. In addition, we reviewed the results of seven meta-analyses that included cross-sectional studies. This approach provides a broad spectrum of asthma definition, based or not on standardised and validated questionnaires, including self- (or parent-) reports of wheezing, especially in children, in whom asthma is difficult to diagnose, and self-reports of asthma symptoms or doctor-diagnosed asthma. We limited our review to respiratory symptoms and have not included specific terms for identifying studies using biomarkers in our search. Studies using biomarkers provide evidence of the effect of mould in the inflammatory response, and are very useful in identifying underlying pathways. However, these studies were not included in the present review which summarises the effect on asthma incidence and exacerbation at the population level in children and adults, and on rhinitis. Biomarker measurements are valuable complements to symptom registrations, rather than recommended as core asthma outcomes [49]. Their measurements are mostly reported in cross-sectional studies, and more rarely in longitudinal studies on large sample sizes; no consensus exists on the biomarker to use [50]; their added value in the management of asthma is strongly associated with specific asthma profile [51]; and omics technologies remain at an early stage [52].

Our review focused on exposure to moulds alone or in association with dampness, but did not include studies considering dampness alone. Our search focused on mould and fungi as keywords, without

including specifically microbial, moisture or bio-contaminant. Indeed, mould and dampness exposures are often concomitant, leading to increased fungal growth and related factors, such as fungal spores, hyphae, fragments [53], microbial volatile organic compounds [54, 55], mycotoxins [56], house dust mite allergens [57] and endotoxins [58–60]. Endotoxins can have both additional and synergistic effects on respiratory health [46]. It is possible that inhalation of these agents, singly or in unknown combinations, induces inflammatory [61] and/or immunosuppression responses that result in the development or exacerbation of respiratory illnesses. One of the current challenges for researchers is to understand how the interactions between fungi and these other micro-organisms will impact health [62]. Mould exposure was defined either qualitatively or quantitatively, which includes a wide range of exposures. In the current state of knowledge concerning dose–response relationships, it is not possible to define a threshold below which no effect on health is expected for the general population [11, 62]. On the one hand, there is a wide range of exposure indicators linked to health effects, which has given rise to conflicting results, and on the other, it is difficult to identify the mechanisms of action involved and the underlying susceptibility of individuals in the case of respiratory symptoms (in particular immuno-allergic predispositions). Nevertheless, we consistently observed some associations, and posit the existence of a causal relationship for the development and exacerbation of asthma in children.

Assessing mould exposure is difficult and complex, and the analysis of samples of air and dust varies across studies and is based on different methods [62]. In many studies, fungal exposure is often reduced to a qualitative measurement such as "visible mould". Future research should include simple and validated metrics of mould and dampness with inclusion of mould odour (reflecting hidden moulds) and study on dose–response effects in order to provide health protective thresholds [63]. More recent sampling and measurement methods should be validated and developed in future years. Usual collecting mould air sampling is very short (1–5 min) in order to avoid excessively high density of colonies on Petri dishes, which makes counting impossible. Thus, the representativeness of these short sampling times is disputable, due to limited repeatability [64]. Electrostatic dust collectors applied for extended periods of time can overcome these caveats because they are indicative of longer time exposure [65]. However, mould colony counting on Petri dishes are limited by definition to those that will grow on the media selected. The culturable fungi might be unrelated to a specific health effect, even if these methods inform on the global mould contamination of a room. Real-time qPCR can detect nonculturable fungi or nonviable fungal spores that may have health impacts [66]. The ERMI scale measures the mould burden of a large number of fungal species and is widely used in current research. Initially developed in the United States [67], it was remodelled for use in other countries, such as Finland [68]. One challenge with qPCR is to decide which of the relevant assays should be applied, as this method is selective in the sense that only moulds that are targeted by the assays will be detected [62]. If nonselective assays, often described as "panfungal", are used, the risk is to amplify the most frequent fungal species because of the competitive nature of the amplification process, and not the most clinically relevant [66]. Metataxonomic and metagenomic approaches are still under evaluation for investigating complex environmental samples [69]. These new techniques should be confronted to qualitative studies, and demonstrate they are more valid exposure tools than observed mould/dampness exposure.

Mould exposure is one piece of a larger exposure, including co-exposure to fungi and bacteria. There is increasing evidence that microbial or fungal diversity might show a stronger effect than the level of any single component [30, 70]. One hypothesis is that the increase in the prevalence of asthma observed in the last few decades is attributable in part to declining exposure to environmental micro-organisms [70], and the "hygiene hypothesis" goes some way to explain this global change [71]. Indeed, low prevalence of allergic diseases and inverse associations between exposure to fungi and asthma development have been observed in children living on traditional farms, where there is a high diversity of fungi and bacteria, and intense and sustained exposure to microbes [72–74]. Last, but not least, the role of outdoor exposure to pollutants such as fungal spores [75] and pollen in respiratory health [76] was not included in the present review. Future epidemiological studies should assess as best as possible the exposure to moulds, but also collect co-exposures in order to identify exposure profiles through clustering methods as done in the study by Madureira *et al.* [77], and in the Elfe cohort study [78].

In addition to co-exposures, various factors related to the built environment can contribute to variation in fungal diversity and load such as adequate heating, opening windows or use of extractor [79], property type and age and the extent of household insulation [80]. Differences between the built environment [81], geographic areas and/or climates [82] and factors related to the behaviour of occupants [83] or specific to the population under study, such as sex, age, socioeconomic status, atopy, rhinitis, health status, genetic susceptibility and gene by mould exposure interaction [21, 84, 85] can also modify the associations. The epidemiological studies reviewed in the present article tried, as best as possible, to take into account these confounders or effect modifiers. In many studies, the participants were mono- or polysensitised or with a

family history of allergic diseases or asthma. Overall, although investigating the associations between indoor fungal exposures and respiratory health is highly complex [86], all these factors should be taken into account in future studies. Results from longitudinal epidemiological studies in children without sensitisation or family history of allergic diseases or asthma would be a valuable contribution to ongoing research.

Several biological mechanisms have been proposed to support the role of mould exposure in respiratory health [87] involving allergic and nonallergic mechanisms [88, 89], such as toxicity from mould by-products [90]. Interestingly, a recent paper by Zhang *et al.* [91] found that fungi have potent immunomodulatory properties, independent of fungal sensitisation, and promote progression of allergic asthma to severe steroid-resistant asthma characterised by mixed T-helper type 2 or 17 responses. The measurement of antibodies to specific mould has scientific merit but the precise recognition of species-specific IgE sensitisation to fungal allergens remains challenging [92]. In the near future, the use of recombinant mould allergens should improve the diagnosis of fungal allergy [93]. Before having a clear framework of the biological mechanisms, and hence the appropriate medication or treatment, another way to tackle the problem is to remove exposure to mould [94]. A Cochrane review found very low- to moderate-quality evidence that remediation of dampness and mould in homes decreases asthma-related symptoms [95]. More recently, Le Cann *et al.* [96] performed a systematic review of home environmental interventions implemented to improve health of patients with respiratory diseases, including measures to reduce mould exposure. Reduced levels of fungal spores were observed in some studies after home interventions, particularly in single-family homes where the baseline levels of fungal exposure were considerably higher than in apartments. Some studies showed a reduction in asthma morbidity after interventions aiming at reducing mould exposure in asthmatic children living in homes with documented mould problems. However, other studies showed limited or no significant change in respiratory outcomes after interventions [96, 97]. New randomised controlled trials with careful measurements of exposure and respiratory outcomes are needed to document the causality and effectiveness of real-world environmental interventions in mouldy buildings.

In conclusion, we reviewed the literature between 2006 and 2017 on the associations between exposure to moulds, alone or in combination with dampness and asthma and rhinitis. Longitudinal epidemiological data in children were analysed separately from those of adults. New findings extend the previous conclusions established in 2007. In particular, sufficient evidence of a causal relationship for asthma development and exacerbation in children, and sufficient evidence of an association with allergic rhinitis were found, but additional evidences are needed from longitudinal studies among adults, especially population-based studies.

Acknowledgements: The members of the ANSES "Moisissures dans le bâti" working group are as follows: S. Roussel (CHU, Besançon, France), C. Ashan-Leygonie (Université Lyon 2, Lyon, France), V. Bex (SPSE, Paris, France), S. Bretagne (APHP, Paris, France), D. Caillaud (CHU, Clermont-Ferrand, France), A.C. Colleville (SPF, Saint-Maurice, France), E. Frealle (CHRU, Lille, France), S. Ginestet (INSA, Toulouse, France), L. Lecoq (IMT, Nantes, France), B. Leynaert (INSERM, Paris, France), R. Nadif (INSERM, Villejuif, France), I. Oswald (INRA, Toulouse, France), G. Reboux (CHU, Besançon, France), and T. Bayeux (ANSES), C. Fourneau (ANSES) and M. Keirsbulck (ANSES).

Author contributions: D. Caillaud, B. Leynaert and R. Nadif were members and M. Keirsbulck was the coordinator of the ANSES working group. All authors wrote the paper, participated in revision of the manuscript and gave approval of the final version.

Conflict of interest: None declared.

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