ERJ Express. Published on May 3, 2011 as doi: 10.1183/09031936.00184010

Association between Domestic Mould and Mould Components, and Asthma and Allergy in Children: A Systematic Review

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Word Count: 5571

Funding: This work is partly funded by **ENRIECO** (Environmental Health Risks in European Birth Cohorts). A project conducted within the European Union's 7th Framework Programme [Theme 6, Environment (Including Climate Change)], Grant agreement number: 226285

ABSTRACT

Background

Critical reviews over the past 10 years 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.

Objective

We conducted a systematic review of observational studies published in English from 1980 to July 2010.

Methods

This review was conducted according systematic guidelines for meta-analyses of observational studies (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 calculated and we evaluated the findings according to the Bradford Hill criteria for evidence of causation.

Results

The literature search identified 1398 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 (**1.68 (1.48-1.90**)) and allergic rhinitis (1**.39 (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)-ß-D-glucan and Extracellular polysaccharides (EPS).

Conclusion

These findings suggest that home environments with visible mould and mould spore exposure increase the risk for 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 such as recently developed molecular methods.

INTRODUCTION

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 years 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 (NORDDAMP) 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 to 2000 (2). In 2004, the Institute of Medicine (IOM) of the 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 between home dampness and new-onset asthma in children up to the age of 7 years (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 (Odds Ratio combined estimate (CI), 1.53(1.39-1.68)). Recently, The World Health Organization 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 was 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 focus of the previous reviews and publications were 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)-ß-D-glucan and Extracellular Polysaccharides (EPS) in house dust samples as surrogates for mould exposure [6, 7]. (1,3)-ß-D-

glucan are non-allergenic water-insoluble structural cell wall components of most fungi. The biological active poly-glucose molecule may account for up to 60% of the weight of the fungal cell wall (7). However, (1,3)-ß-D-glucan are 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)-ß-D-glucan as a surrogate. Fungal Extracellular Polysaccharides (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 showed that exposure to (1,3)-ß-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)-ß-D-glucan and EPS exposure from mattress dust were associated with a lower prevalence of allergic sensitisation in 2-4 year-old children (13). The mechanism of these negative associations is not yet understood. It has been hypothesized that exposure to (1,3)-ß-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.

A need for a new review

Previous investigations (NORDDAMP, EUROEXPO, IOM and WHO) have summarized the main findings of the studies reviewed here. However, only the work of Fisk and colleagues (2007) also provided summaries quantitatively. 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, Lei-Gomez and Mendell in 2007.

There is a strong need for a comprehensive and specific review which distinguishes mould and dampness exposure into visible mould, mould spores and measured mould components. Although some investigations 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 presented the results according to their epidemiological study design.

METHODS

This review was conducted following the MOOSE guidelines for meta-analyses of observational studies (14). The literature was searched using a computerised bibliographic database, PubMed, with the following free text search terms:

1. ß-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

Inclusion criteria were: observational study, human study population, English, publication date between 1.1.1980 and 1.7.2010, study population recruited from community. The review includes publications which specifically assessed exposure to mould and mould derived components for children at home. This included inspector or subjective reported visible mould, measured airborne or dust-borne fungal genera and measured specific bio-markers of mould species such as (1-3)-ß-D-glucan and Extracellular Polysaccharides 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 ((6) (5),(3, 4)) and personal files.

Longitudinal studies, cross-sectional studies, as well as case-control studies were included. We have restricted the health outcomes to physician-diagnosed allergic diseases including asthma, allergic rhinitis or hay fever and eczema as well as allergic symptoms such as wheezing, itchy, blocked or running nose without having a cold, itchy skin rash and allergic sensitization to inhalant allergens. Each relevant article underwent standardised data extraction.

Statistical analysis:

In order to increase the quality of the reviewed studies, we reported the results of 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 1a-c**. The estimated Odds Ratios (ORs) in bold were used for modelling the summary effect. To summarize 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 (CI) of odds ratios (ORs) and summarize 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).

Table 1a: Risk factor and health outcome definition (Visible mould and asthma, n = 24)

Study	Definition exposure	Definition outcome	Age	Nr. of children	Odds ratio central estimate (CI)*	Type of estimate
Antova et al., 2008 (PATY) **combined**	Visible mould Mould every Recent mould	Asthma ever	6-12	57099 (pooled)	**1.35 (1.20 – 1.51)** 1.36 (1.19 – 1.56) 1.23 (1.07 – 1.41)	aOR aOR aOR
Dales et al., 1991, Canada	Nr. of mould sites 0 vs. 1 0 vs. 2	DD asthma	5-8	13495	 1.40 (1.16 – 1.68) **1.67 (1.27 – 2.19)**	 cOR cOR
Dong et al., 2008, China	Visible mould	DD asthma (ever) Current asthma	6-13	10784	1.54 (1.22 – 1.94) **1.69 (1.15 – 2.48)**	aOR aOR
Ponsonby et al., 2000, Tasmania	Mould in child's room i.r. Mould (excl. bathroom) p.r.	Asthma	7	6378	1.26 (0.87 – 1.81) **1.20 (0.96 -1.51)**	aOR aOR
Spengler et al., 2004, Russia	Presence of moulds	DD asthma Asthma symptoms	8-12	5951	**2.82 (1.63 – 4.88)** 1.98 (1.53 – 2.55)	aOR aOR
Freeman et al., 2003, U.S.	Any mould Any mould	DD asthma	8.1-10.9 < 6	4634 240	**1.54 (1.27 – 1.87)** **3.30 (1.57 – 6.97)**	aOR aOR
Brunekreef et al., 1989, U.S.	Mould or mildew (7-11y)	DD Asthma	8-12	4625	**1.27 (0.93 – 1.74)**	aOR
Dong et al., 2008, China	Visible mould	DD asthma Current asthma	1-6	3945	**1.56 (1.13 – 2.16)** 1.89 (1.22 – 2.94)	aOR aOR
Brunekreef, 1992, the Netherlands	Visible mould (6-12y) (1987) Visible mould (6-12y) (1989)	Asthma Asthma	6-12	1051 3344	**1.12 (0.39 – 3.38)** **1.53 (1.04 – 2.28)**	aOR aOR
Warman et al., 2009, U.S.	Visible mould on walls Visible mould on walls, ceilings or windows	DD asthma DD asthma	5-11	1772	**3.26 (2.38 – 4.45)** 2.66 (2.04 – 3.48)	cOR cOR
Chen et al., 2003, Taiwan	Mould patches	DD asthma Asthma symptoms	7-12	1452	**1.55 (0.78 – 3.09)** 1.56 (0.90 – 2.69)	aOR aOR
Li and Hsu, 1996, Taiwan	Visible mould/mildew	DD asthma	8-12	1340	**1.12 (0.72 – 1.74)**	aOR
Zheng et al., 2002, China	Mould or fungi family ceiling child's bedroom	DD Asthma	6-10	1209	 **1.8 (1.1 – 2.9)** 1.8 (1.0 – 3.2)	 aOR aOR
Maier et al., 1997, U.S.	Visible mould	DD asthma	5-9	925	**1.3 (0.9 – 1.9)**	cPR

Dijkstra et al., 1990, the Netherlands	Damp stains and mould	Asthma	6-12	775	**1.56 (0.50 – 4.87)**	cOR
Tischer et al., 2010, Germany and The Netherlands	Visible mould – Germany Visible mould – Netherlands	DD asthma	6	358 332	**1.03 (0.26 – 4.16)** **1.14 (0.48 – 2.70)**	aOR aOR
Verhoeff et al., 1995, 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 and Miller, 1999. Canada	Ever mould / mildew	DD asthma	10	403	**0.91 (0.42 – 1.95)**	aOR
Pekkanen et al., 2007, 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) 1.95 (0.69 – 5.47)	aOR aOR aOR
Fagbule, 1994, Nigeria	Mould growth	Current asthma	5.5	280	**0.48 (0.30 – 0.79)**	aOR
Li and Hsu, 1997, Taiwan	Visible mould	Asthma	7-15	46	**1.02 (0.39 – 2.69)**	aOR

*Figures in **bold** were included within the meta-analysis
DD = Physician-diagnosed asthma
cOR = crude Odds Ratio
aOR = adjusted Odds Ratio

Table 1b: Risk factor and health outcome definition (Visible mould and wheeze, n = 20)

Study	Definition exposure	Definition outcome	Age	Nr. of children	Odds ratio central estimate (CI)*	Type of estimate
Antova et al., 2008 (PATY) **combined**	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 aOR aOR
Dales et al., 1991, Canada	Nr. of mould sites 0 vs.1 0 vs.2	Wheeze	5-8	13495	 1.42 (1.26 – 1.59) **1.73 (1.45 – 2.06)**	 cOR cOR
Dong et al., 2008, China	Visible mould	Current wheeze	6-13	10784	**1.65 (1.25 – 2.17)**	aOR
Spengler et al., 2004, Russia	Presence of moulds	Wheeze	8-12	5951	**1.52 (1.19 – 1.94)**	aOR
Brunekreef et al., 1989, U.S.	Mould/mildew (7-11y)	Persistent wheeze (8-12y)	8-12	4625	**1.79 (1.44 – 2.32)**	aOR
Emenius et al., 2004, Sweden (BAMSE)	Visible mould (1y)	Recurrent wheeze (2y)	1-2	4089	**1.5 (1.0 – 2.22)**	aOR
Dong et al., 2008, China	Visible mould	Current wheeze	1-6	3945	**2.07 (1.56 – 2.75)**	aOR
Brunekreef, 1992, the Netherlands	Visible mould (6-12y) (1987) Visible mould (6-12y) (1989)	Wheeze Wheeze	6-12	1051 3344	**1.34 (0.58 – 3.26)** **1.90 (1.41 – 2.54)**	aOR aOR
Li and Hsu, 1996, Taiwan	Dampness and mould	Wheeze	8-12	1340	**1.20 (0.73 – 1.99)**	aOR
Strachan et al., 1990, U.K.	Mould p.r. Mould i.r.	Wheeze	6.5-7.5	1000 330	**3.70 (2.22 – 6.15)** 3.25 (1.60 – 6.60)	cOR cOR
Strachan and Carey, 1995, U.K.	Mould in bedroom	Severe wheeze	13-18	961	**1.25 (0.67 – 2.31)**	aOR
Maier et al., 1997, U.S.	Visible mould	Wheeze	5-9	925	**1.20 (0.70 – 1.90)**	cPR
Alper et al., 2006, Turkey	Dampness and mould (7y)	Persistent wheeze(0-6y) Early wheeze (0-3y) Early transient wheeze Late-onset wheeze (3-6y)	0-7	858	**2.53(1.30 - 4.87)** 2.37(1.52 - 3.69) 2.28(1.34 - 3.87) 2.46(1.29 - 4.66)	cOR cOR cOR cOR
Dijkstra et al., 1990, the	Damp stains and mould	Wheeze	6-12	775	**1.54 (0.59 – 4.00)**	cOR

Netherlands						
Cho et al., 2006, U.S. (CCAAPS)	Mould class 2 vs. 0 (8m)	Recurrent wheeze (1y)	8-12m	640	**2.1 (1.2 – 3.6)**	aRR
Iossifova et al., 2007, U.S. (CCAAPS)	Visible mould (8m) Low vs. none High vs. none	Recurrent wheeze (1y)	8-12m	574	 1.18 (0.73 – 1.91) 4.44 (1.36 – 12.05)	 aOR aOR
Schroer et al., 2009, U.S. (CCAAPS)	Mould exposure (8m)	Wheezing (1y) Wheezing (2y) Persistent wheezing (2y)	8-24m	570	1.22 (0.79 – 1.86) 2.12 (1.25 – 3.60) **2.47 (1.27 – 4.80)**	aOR aOR aOR
Iossifova et al., 2009, U.S., (CCAAPS)	Visible mould (8m) Low vs. none High vs. none	Wheezing with API (3y)	8m-3y	483	 1.68 (0.96 – 2.94) **7.08 (2.22 – 12.60)**	 aOR aOR
Karvonen et al., 2009, Finland (PASTURE)	Mould spots (2m) i.r. Visible mould (2m) i.r. Mould in kitchen (2m) i.r. Mould living area (2m) i.r. Mould child's room (2m) i.r.	DD Wheezing (1y) Wheezing (1y)	2-12m	396	0.99 (0.38 – 2.58) 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)	aOR aOR aOR aOR aOR aOR aOR aOR aOR aOR
Rosenbaum et al., 2009, U.S. (AUDIT)	Visible mould (3m) i.r.	Wheeze (1y)	3-12m	103	**0.90 (0.35 – 2.29)**	cOR

*Figures in **bold** were included within the meta-analysis
cOR = crude Odds Ratio
aOR = adjusted Odds Ratio

Table 1c: Risk factor and health outcome definition (Visible mould and allergic rhinitis, n = 11)

Study	Definition exposure	Definition outcome	Age	Nr. of children	Odds ratio central estimate (CI)*	Type of estimate
Antova et al., 2008 (PATY) **combined** 	Visible mould Mould ever Recent mould	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 et al., 2008, China	Visible mould	DD allergic rhinitis (ever)	6-13	10784	**1.21 (0.97 – 1.50)**	aOR
Brunekreef et al., 1989, U.S.	Mould / mildew (7-11y)	Hay fever (8-12y)	7-12	4625	**1.57 (1.31 – 1.87)**	aOR
Dong et al., 2008, China	Visible mould	DD allergic rhinitis	1-6	3945	**1.20 (0.72 – 1.99)**	aOR
Ibargoyen-Roteta, 2007, Spain	Mould on walls (1y)	Allergic rhinoconjunctivitis (5-8y)	1-8	3360	**1.34 (0.64 – 2.79)**	aOR
Chen et al., 2003, Taiwan	Mould patches	DD allergic rhinitis	7-12	1452	**1.48 (1.03 – 2.12)**	aOR
Li and Hsu et al., 1996, Taiwan	Visible mould / mildew	Allergic rhinitis symptoms	8-12	1340	**1.27 (0.96 – 1.68)**	aOR
Biagini et al., 2006, U.S. (CCAAPS) 	Visible mould low vs. none high vs. none	Allergic rhinitis	1	495	 1.2 (0.6 – 2.5) **3.2 (0.7 – 14.8)**	 aOR aOR
Stark et al., 2005, U.S.	Mould / mildew (1y)	DD Allergic rhinitis or hay fever (5y)	1-5	405	1.28 (0.74 – 2.22)	cHR
Koskinen et al., 1999, Finland	Mould present	Rhinitis	≤ 7 7-15	57 147	**8.01 (0.77 – 83.82)** **1.77 (0.69 – 4.53)**	aOR aOR
Li and Hsu et al., 1997, Taiwan	Visible mould	Allergic rhinitis	7-15	45	**3.50 (1.00 – 12.34)**	aOR

*Figures in **bold** were included within the meta-analysis
DD = Physician-diagnosed
cOR = crude Odds Ratio
aOR = adjusted Odds Ratio
cHR = crude Hazard Ratio

RESULTS

The literature search identified 1398 peer reviewed scientific publications, of which 36 articles reported relevant exposures and health outcomes in suitable study populations (**figure 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 which found positive associations between exposure to visible mould and wheeze or allergic rhinitis (see **online supplement 1**).

Of the 1398 peer reviewed scientific publications identified through Pubmed, 1366 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 ones that only examined adult study populations were also excluded (n=622). Finally, studies solely on exposure to endotoxin were not considered in this systematic review (n=17).

Results from the systematic review, grouped by study design and exposure type

BIRTH COHORT STUDIES

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

Visible mould exposure

Wheeze

Of the 9 publications evaluating the longitudinal effect of early exposure to visible mould at home and wheezing in the first three years of life, 7 studies observed a significant positive association ((8, 12, 15-19)). In one U.S. birth cohort study (CCAAPS) from Iossifova and colleagues, the reported increase in risk was persistent from age one to age three (8). Baker et al.((20)) observed no effect of current exposure to visible mould and wheezing at the age of 6 months, and Tischer and colleagues also found no effect in children followed until 6 years from Germany and the Netherlands ((21)).

Other health outcomes

Three studies investigated the effect of exposure to visible mould on allergic rhinitis (21-23); one study reported findings on allergic sensitization (16) and one on physician-diagnosed asthma (21). However, there were no significant associations found.

Mould spores exposure

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 non-sporulating genera and total dust-borne fungal mass

were significantly positively associated with physician-diagnosed allergic rhinitis or hay fever at the age of 5 years ((23)).

Mould components exposure

Two European and two U.S. birth cohort investigations studied the effect of exposure to mould components on the risk of allergic health outcomes. Iossifova and colleagues (12) reported that exposure to low levels of (1,3)-ß-D-glucan from children's primary activity room was associated with a higher risk of recurrent wheeze (**3.04** (**1.25-7.38**)) in 1 year old children, but was protective when exposed to high levels (**0.39** (**0.16-0.93**)). However, this could not be confirmed at the age of three in the same birth cohort ((8)). The two European studies did not observe an effect of exposure to (1,3)-ß-D-glucan on asthma, wheezing or allergic rhinitis symptoms in school age children (9, 21).

The PIAMA birth cohort study and a follow-up of the European AirAllerg collaboration reported significant inverse effects of exposure to higher levels of EPS (Extracellular Polysaccharide) on asthma, wheeze and allergic rhinitis in 4 to 6 year old children. Within the PIAMA cohort, there was also an inverse effect on allergic sensitisation status (9, 21).

COHORT STUDIES (not recruited at birth)

The cohort study findings are summarized 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 an inverse effect on wheeze. Exposure to airborne mould spores was associated with wheezing in children up to 1 year.

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 U.S. and Finland ([27, 28]) found no associations, while a second U.S. study reported that current exposure to mildew was significantly inversely related to physician-diagnosed asthma at the age of 12 years. However, this was only found for children with a wheezing phenotype.

Wheeze

Three cohort studies investigated the effect of visible mould exposure on wheezing in children, all were from the United States. Brunekreef and colleagues (24) reported a significantly positive association between domestic mould and persistent wheeze in 12 year old children. Belanger and colleagues observed an increased risk among 1 year old children who were genetically predisposed to allergic diseases (25), while a second study found no association among children in the same age range - but this may have been due to inadequate power as the study included only 103 children ((26)).

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 ((27)). A U.S. study of 12 year old

school children reported a significant increased risk for hay fever when exposed to self-reported domestic mould ((24)).

Mould spores exposure

Three U.S. studies investigated the relationship between airborne mould spores exposure and wheezing in 1 year old children. Gent and Rosenbaum ((28), (26)) reported an increased risk of wheeze in 1 year old infants, when exposed to airborne *Penicillium* ($\geq$ 1.000 cfu/m^3 and 120-1270 cfu/m^3, respectively). A subsequent U.S. study on infants found a positive association between exposure to airborne total fungi sampled at three months and wheeze at 1 year ((25)). A German cohort study found an increased risk for sensitization against grass (IgE) in three year old children when exposed to airborne *Aspergillus* genera ((29)).

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 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 the risk for 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 1209 subjects, and two studies from Europe reported an increased risk of physician-diagnosed asthma with exposure to visible mould, in children up to school age ([33], (30)),((31)). This association could not be confirmed by Li and Hsu ((32)) in a small population of 46 Taiwanese school children. A Nigerian case-control study of 5 year old school children reported protective effects on current asthma for mould growth at home ((33)).

Other health outcomes

There were two European studies that investigated the effect of visible mould exposure on wheezing (15, 34), but no association was observed. A study of 3 year old children from New Zealand also found no association between visible mould exposure and atopic dermatitis (35). One small study from Taiwan reported a significant increased risk for allergic rhinitis in school age children (32).

Mould spores exposure

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 age children ((32)). However, three publications from Europe could not find an association between higher levels of dust-borne fungal species and asthma ((36), (37), (38)).

Allergic Rhinitis

One European study from Germany (36) with 272 subjects reported a higher risk of allergic rhinitis symptoms with exposure to total fungi, *Cladosporium* and *Penicillium* (> 200.000 cfu/g, > 35.000 cfu/g and > 55.000 cfu/g, respectively). A similar finding was observed in a Danish cohort; children sensitized to house dust mites had a significantly higher risk of allergic rhinitis when exposed to dust-borne *Cladosporium* above 35 cfu per mg ((37)). 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 age children. ((32))

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 (36), there was an increased risk for eczema in Swedish children sensitized to house dust mites, but not to aeroallergens (37). Two German studies looked at the association between exposure to domestic mould spores and the risk of allergic sensitization to inhalant allergens (IgE). While Jovanovic and colleagues ((39)) found no association, Jacob and colleagues ((36)) reported a higher risk of sensitization against inhalant allergens when exposed to *Cladosporium* and *Aspergillus* (> 35.000 cfu/g, 0-25.000 and above, respectively). No association was found between exposure to dust borne mould genera and wheezing phenotype in a German study (36).

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 (40) and atopic wheeze (10), while exposure to (1,3)-ß-D-glucan was significantly inversely related to sensitisation against inhalant allergens among 2-4 year old children (13).

CROSS-SECTIONAL STUDIES

A large number of the 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**). There were only two investigations to consider 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, and 15 of these studies investigated the effect of exposure to visible mould on asthma in school age children. There were 10 studies ((41), (42), (43), (44), (45), (46), (47), (48), (49)) with sample sizes above 1500 subjects and 9 of these observed a significantly increased risk of asthma. However, a study from Tasmania did not observe an association ((50)), but this may have been due to the young age of the children (7 years). No association was found in the remaining studies of smaller sample sizes (403-2720) ([54], (51), (52), (53), (54)).

Wheeze

Similar to asthma, nine out of fifteen cross-sectional studies found that exposure to mould at home was associated with a higher risk of wheeze in children, especially among studies with a larger sample size (41, 43-45, 47, 48, 55-57). However, five studies did not find any association (51-53, 58, 59). In one Spanish study, an increased risk of wheezing was observed only in non atopic school children (60).

Allergic Rhinitis

Two out of eight studies investigated the relationship between visible mould exposure and allergic rhinitis and observed positive associations. The PATY study reported a significantly increased risk for hay fever in 6-12 year old children when exposed to visible mould at home ((41)). An Asian study from Singapore, also reported higher risks for rhinitis and rhinoconjunctivitis among 1-6 year old children (58). The remaining six studies did not observe any statistically significant exposure-response relationships (44, 47, 51, 61-63).

Atopic eczema

Four studies investigated the relationship between exposure to visible mould and atopic eczema. One German study by Schäfer and colleagues ((64)) observed a significantly increased risk of atopic eczema in a sample of 6 year old children. However, no association was observed for the remaining three studies ((58), (62), (63)).

Atopic sensitisation

Two investigations examined the association between domestic visible mould exposure and atopic sensitisation in school age children. Antova and colleagues observed an increased risk of sensitisation against inhalant allergens in a pooled analysis of over 58000 children (41). In a smaller German study of 1235 children, exposure to visible mould was found to increase the risk for sensitization against mugwort, dust mites and cat (assessed by Skin Prick Test) among 5-7 year old children (64).

Mould spores exposure

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 (65)). Exposure to airborne *Penicillium* was significantly related to sensitization (SPT) to Penicillium mix, Aspergillus mix, house dust and dog dander. Higher levels of airborne *Cladosporium* were also associated with sensitization to Aspergillus mix and exposure to airborne *Aspergillus* was suggested to increase the risk for sensitization against inhalant allergens ((65)). Salo and colleagues could not find any association between dust-borne *Alternaria alternata* and physician diagnosed asthma ((66).

Mould components exposure

There were only two investigations of one cross-sectional study in Germany, Austria, Switzerland and the Netherlands (PARSIFAL). Karadag and colleagues found that exposure to EPS from children's mattresses was negatively associated with physician-diagnosed eczema but not with eczema symptoms (67). In the second investigation by Ege and colleagues (59), EPS was found to significantly decrease the risk of ever asthma 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)-ß-D-glucan. Karadag and al. 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 (**1.49** (**1.28-1.72**), **1.68** (**1.48-1.90**) and **1.39** (**1.28-1.51**), respectively). Forest-plots in **Figure 2** illustrate the ORs with CIs and provide a summary estimate for the association between the investigated exposure-response relationships.

Due to the limited number of studies which 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 common reported health outcomes were asthma, wheeze and allergic rhinitis. There was a statistically significant increased risk of asthma (**1.49** (**1.28-1.72**), wheeze (**1.68** (**1.48-1.90**) and allergic rhinitis (**1.39** (**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, this review suggested, however, that mould components such as (1,3)-ß-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 years, 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 and colleagues in 2007, which reported a significant positive association with wheezing symptoms in children and adults (5). These prior findings are consistent with those of the present meta-analysis. However, we aimed to go beyond the work of Fisk et al. and specifically addressed issues such as specificity of exposure, study design, study population, validation criteria and validity of exposure assessment.

Studies after inclusion deadline for the meta-analysis of Fisk et al.

A number of studies were considered here that were unavailable for the previous meta-analysis of Fisk et al. due to publication date. For the association between exposure to mould and wheeze there were 19 additional publications and for asthma there were 17 additional studies. Further, we identified studies published before 2006 that were not part of the meta-analysis of Fisk and colleagues, supporting the application of a systematic approach. Fisk and colleagues looked at the

association between dampness and mould exposure in relation to a number of different upper respiratory tract symptoms (URT), whereas we focused on (physician-diagnosed) allergic rhinitis exclusively. Although we restrained exposure and health outcome definition and limited the analysis to children only, we did reach a higher number of publications compared to the meta-analysis in 2007.

Specification of type of exposure

Previous investigations, including the work from Fisk and colleagues, 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 kind 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 (68), recent literature indicated that the exposure to mould derived components might have different impacts on children's health and may not measure the same kind of exposure. This hypothesis was supported by a U.S. cohort study which did not find a correlation between (1,3)-ß-D-glucan exposure and visible mould (8, 12). This might be partly due to the fact that (1,3)-ß-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)-ß-D-glucan as a surrogate (7). The Extracellular Polysaccharides (EPS) are stable carbohydrates secreted or shed during fungal growth and have antigenic specificity at the genus level but cannot represent the exposures to all of the fungal species in indoor environment. Furthermore, mould derived components such as (1,3)-ß-D-glucan or Extracellular Polysaccharides (EPS) are suggested to 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 was suggested for endotoxin in several studies. (69-71). This review revealed among others, that there is 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 mould derived components.

Study design

Compared to Fisk and colleagues, we further addressed different types of study design. Nearly half of the publications (41%) included in this review were cross-sectional study design and a considerable portion 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 to cross-sectional based 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. Combined investigations in the future focused on longitudinal studies exclusively may be able to assess causality over a longer time period, which is currently ongoing in the frame of the ENRIECO initiative (www.enrieco.org).

Study population

In contrast to previous investigations, this 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 non-allergic rather than allergic responses (71).

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 is 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 (72) which are discussed in detail later on.

Validity of exposure assessment

Visible mould exposure at home was mainly assessed by questionnaire. Although this method is convenient and favourable, questionnaire based methods are difficult to validate against microbial measurements (16, 73). Numerous studies validated self-reported visible mould questions against inspector reported observations (15, 30, 74-77) 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 if the obviously visible mould or rather an unknown, invisible species are contributing to the observed effects in children's health (65, 78). 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 standardized, following a protocol and reducing the risk of systematic biases such as reverse causation compared to questionnaire based methods, there are some shortcomings. To begin with, sampling methods vary considerably across

the studies. Dust sampling from floors or mattresses using a vacuum cleaner provides a crude mixture of different particle sizes (10, 79, 80), 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 (23, 25, 26, 28, 29, 39). However, this requires considerable time and cost resources. Recently, new exposure assessment methods have been developed. Passive airborne sampling ("pizza box"), electrostatic dustfall collector (EDC) or electrostatic dust clothes (81-83) can be used for a broad range of allergen measurements. These newly developed exposure assessment methods might be a valuable substitute to existing methods in terms of cost and work amount.

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" (72). 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 (Lucas and McMichael, 2005, Phillips and Goodman, 2004). These nine criteria should not be used as a checklist, but instead highlight important aspects of an investigation. According to Hill's criteria, the evaluation supports the findings of the meta-analysis, especially with regard to aspects such as strength of an 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 (online supplement 3 for the extensive description).

Limitations

The timing of health outcome assessment is crucial in epidemiologic 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 from 6 months to 3 years. There might be amount of children who are not at risk of developing asthma, because the follow-up time was too

short and the age of the cohort members was still too young to develop asthma. Therefore, findings from birth cohort studies at younger age 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 three different exposure sources such as 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 (68), the 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 to some extent (84). 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 (85). Therefore, to draw a causal relationship is complicated by the variability of microbial biomarkers and their suspected distinguishing effects on children's health. In conclusion, further research measuring specific biomarkers in the home should be emphasized.

Conclusion

The reviewed studies on visible mould exposure indicated an increased risk for allergic respiratory symptoms in children. These findings were confirmed by results of the meta-analyses; 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 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 complex microbial milieu over time.

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Figure 1

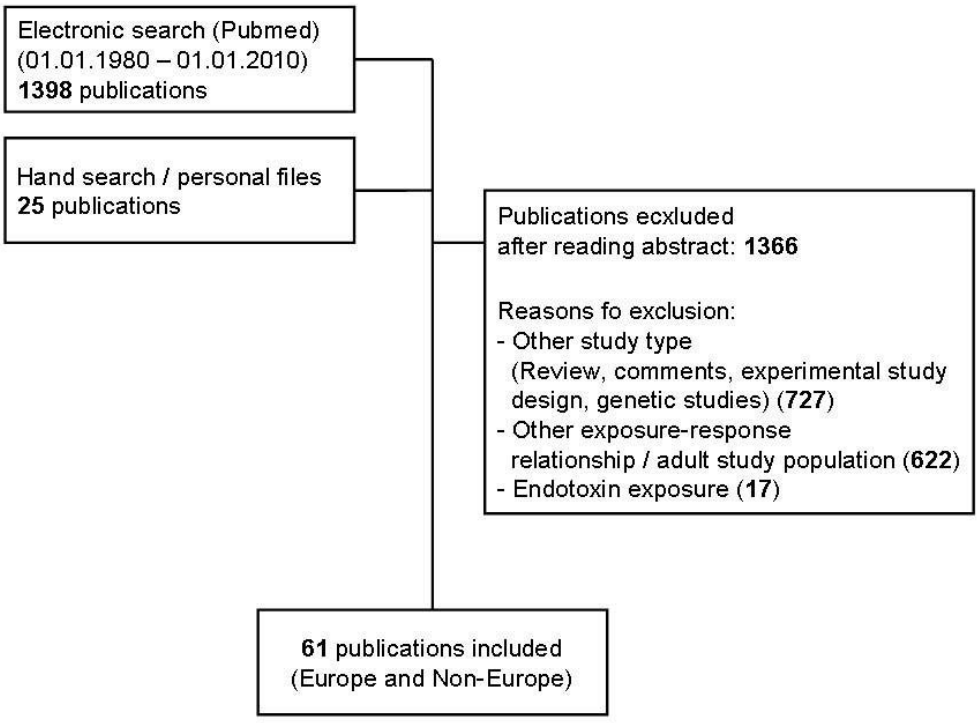

Figure 1: Flow chart for study selection process

Figure 2

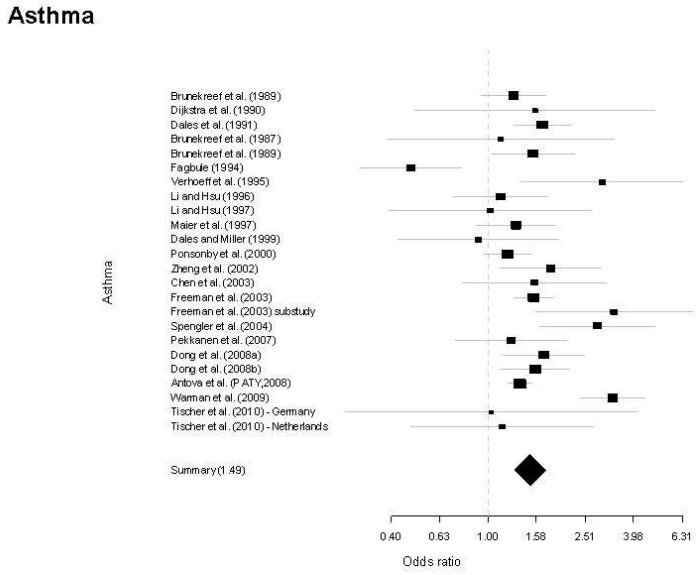

Figure 2-A: Odds Ratios and 95% confidence intervals (95% CI) for the association between visible mould in relation to asthma, wheeze and allergic rhinitis from original studies and from a meta-analysis (combined effect) performed using the random effects model. For each study, the size of the boxes 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. Studies are listed according to their publication year (from 1989 to 2010).

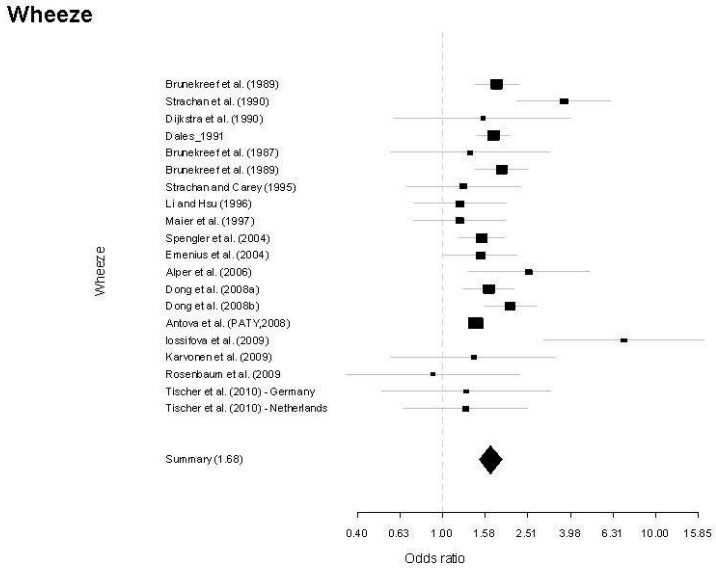

Figure 2-B: Odds Ratios and 95% confidence intervals (95% CI) for the association between visible mould in relation to asthma, wheeze and allergic rhinitis from original studies and from a meta-analysis (combined effect) performed using the random effects model. For each study, the size of the boxes 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. Studies are listed according to their publication year (from 1989 to 2010).

Allergic Rhinitis

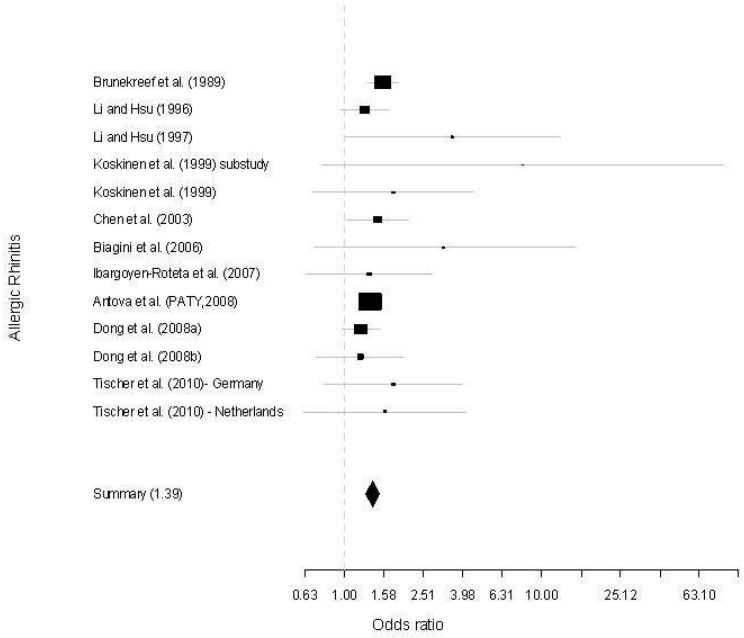

Figure 2-C: Odds Ratios and 95% confidence intervals (95% CI) for the association between visible mould in relation to asthma, wheeze and allergic rhinitis from original studies and from a meta-analysis (combined effect) performed using the random effects model. For each study, the size of the boxes 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. Studies are listed according to their publication year (from 1989 to 2010).