Damp environments and moulds: health effects, mechanisms and causality

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Outline

- Health effects from mould exposure
- Occupational high exposure environments
- Indoor extreme exposure and low exposure environments
- Specific issues in the design of studies on mould exposure
- Conclusions

Awareness that composting might be associated with adverse health risks
Poulsen et al., Sci Total Environm 1995

Poulsen et al. concluded that (separate) waste management resulted in new and poorly described health risks mainly due to exposure to bio-aerosols

	EU/m^3	reference
Grain processing	12-285	Smid et al., 1992
Water sewage treatment	300	Melbostadt et al., 1994
Pig farmers	920	Preller et al., 1995
Chicken farmers	1.300-10.000	Thelin et al., 1984
Garbage handling	**8-25**	**Sigsgaard et al., 1994**




Health effects from bioaerosol emissions from composting facilties: systematic review of occupational and community studies Pearson et al., J Toxicol Environm Health 2015

- Allergic asthma, rhinitis, hypersensitivity pneumonitis (HP)/extrinsic allergic alveolitis, allergic bronchopulmonary aspergillosis (ABPA)

- Toxic non-allergic asthma, rhinitis, mucous membrane irritations (MMI), chronic bronchitis, chronic airway obstruction such as chronic obstructive pulmonary disease (COPD), organic dust toxic syndrome (ODTS), toxic pneumonitis.

- Infectious aspergillosis, zygomycosis; immunocompromised individuals are more susceptible at lower concentrations of the relevant pathogens.

Health effects from bioaerosol emissions from composting facilties: systematic review of occupational and community studies Pearson et al., J Toxicol Environm Health 2015

- 48 exposure studies, 9 health studies, 9 health and exposure studies mostly from Europe

- Respiratory symptoms (most studies)
- Cross-shift lung function changes (Sigsgaard et al., 1994, but not by Muller et al., 2006)
- Reduced lung function (van Kampen et al., 2012; Bunger et al., 2007)
- Nasal obstruction by rhinometry (Heldal et al., 2003)
- Upper airway inflammation in nasal lavage (Heldal et al., 2003; Douwes et al., 1997, 2000, Wouters et al., 2002)

- No differences in specific IgE to environmental molds of currently exposed compost workers (van Kampen et al., 2012; Wouters et al., 2002)

Small and larger scale exposure and cross-sectional and short longitudinal studies
Wouters et al. Toxicol Ind Health 2002, OEM 2002, Annals Occup Hyg 2006; Douwes et al., Am J Ind Med 2000

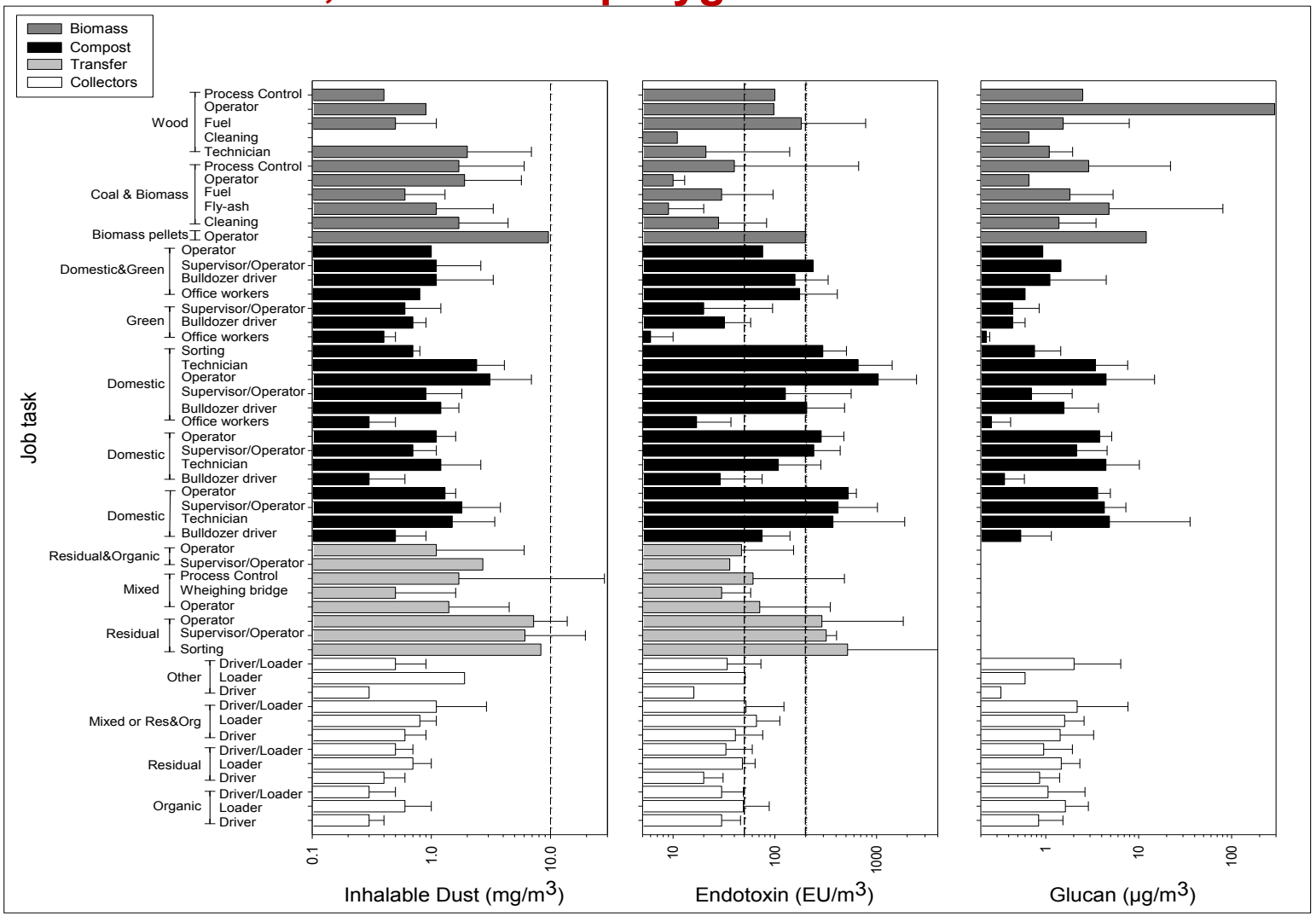
	background	collection	composting
Fungi*	**$2.0*10^3$**	**$0.3\text{-}1.5*10^5$**	**$>10^6$**
Total bacteria*	**$3.0*10^2$**	**$0.4\text{-}1.9*10^3$**	**$>10^4$**
Gram-neg bacteria*	**$6.6*10^1$**	**$1.3\text{-}3.3*10^2$**	**$>10^4$**

Common Fungi (*Aspergillus* and *Penicillium spp.*)

In summer more semi thermophilic fungi, like *A. flavus*

Small and larger scale exposure and cross-sectional and short longitudinal studies

Wouters et al., Annal Occup Hyg 2006

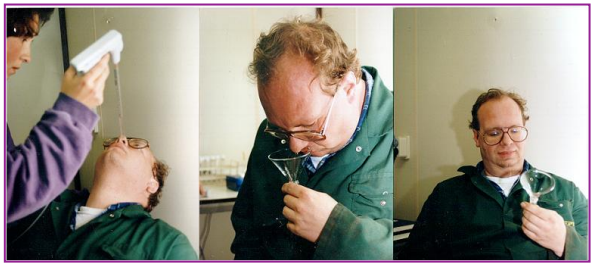


Small and larger scale exposure and cross-sectional and short longitudinal studies
Wouters et al., OEM 2002, Douwes et al., 2000

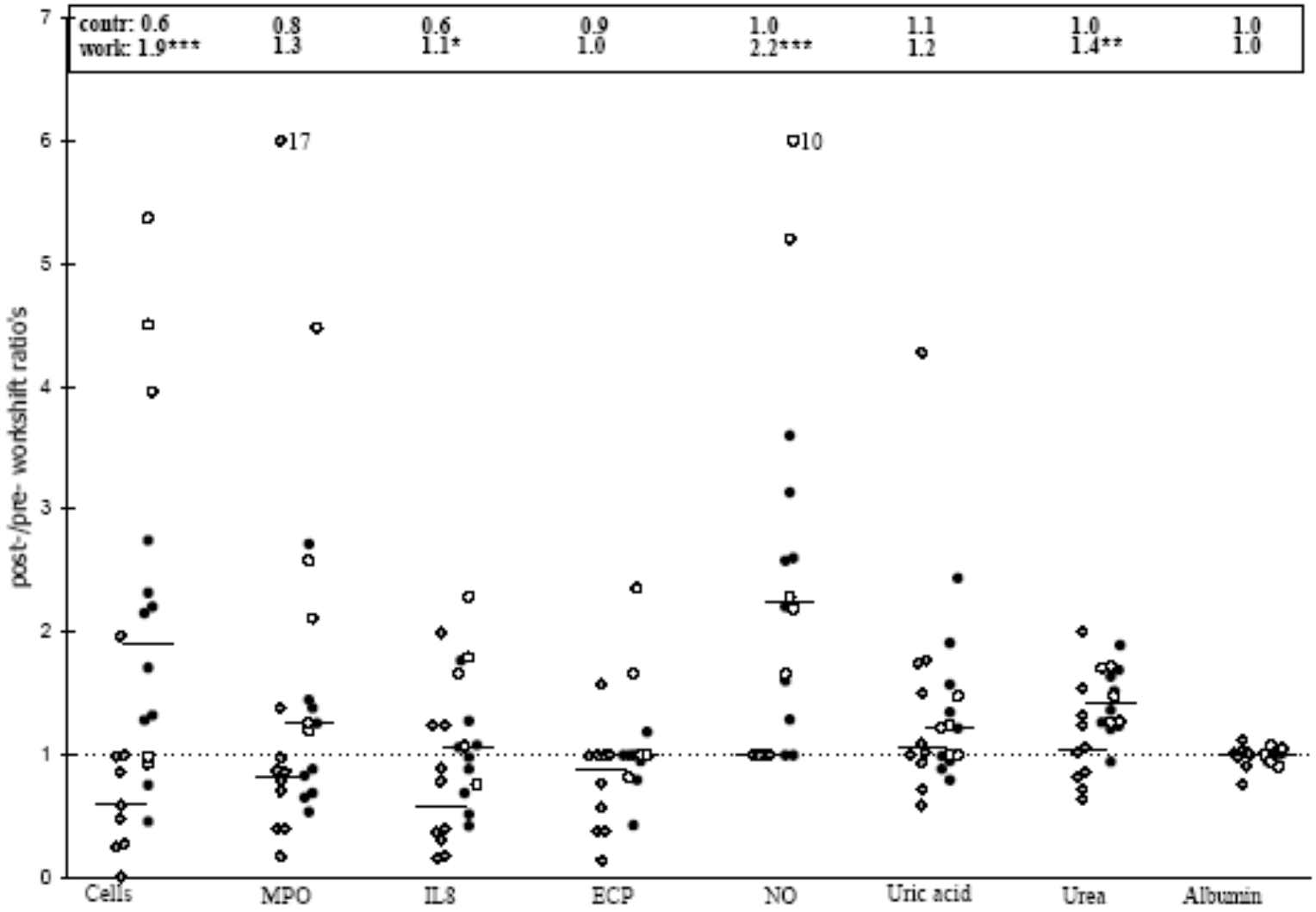
- Serology:
  IgG titers against *A. fumigatus, Aspergillus-4, Pennicillium-4, Cladosporium-3, M. faeni and T. vulgaris* similar for waste collectors and controls

  Rarely positive IgE tests against molds in waste collectors (2%) and compost workers

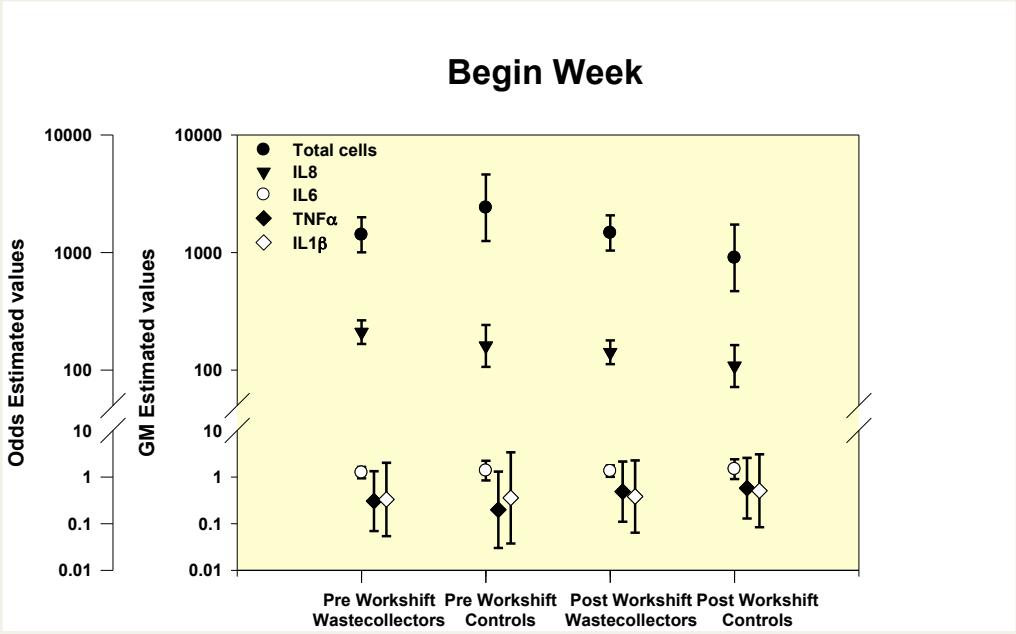
- NAL major cell type:
  neutrophils and epithelial cells

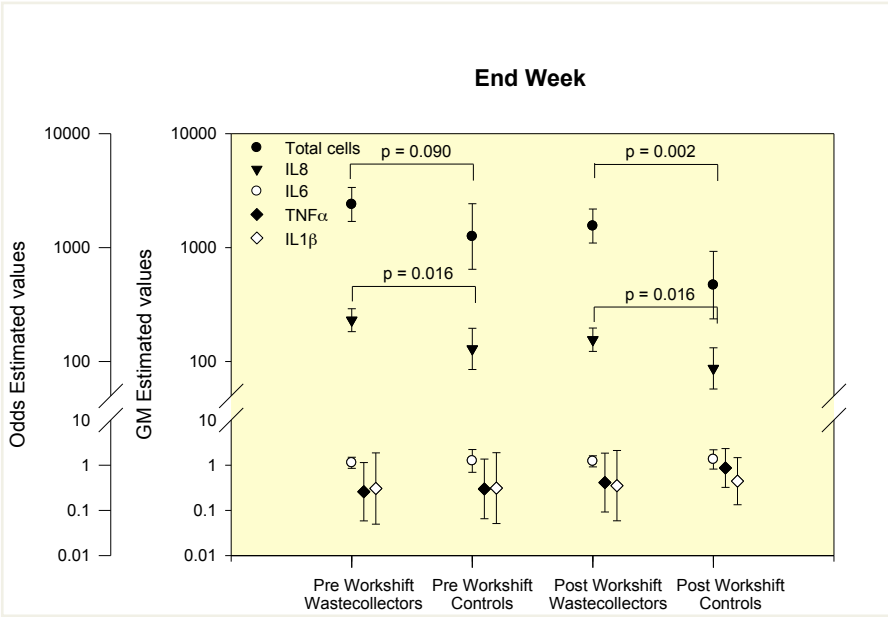


Cross shift changes in 39 composting workers in comparison to 15 controls
Douwes et al., 1997



Cross week changes in 47 waste collectors in comparison to 15 controls
Wouters et al., OEM 2002

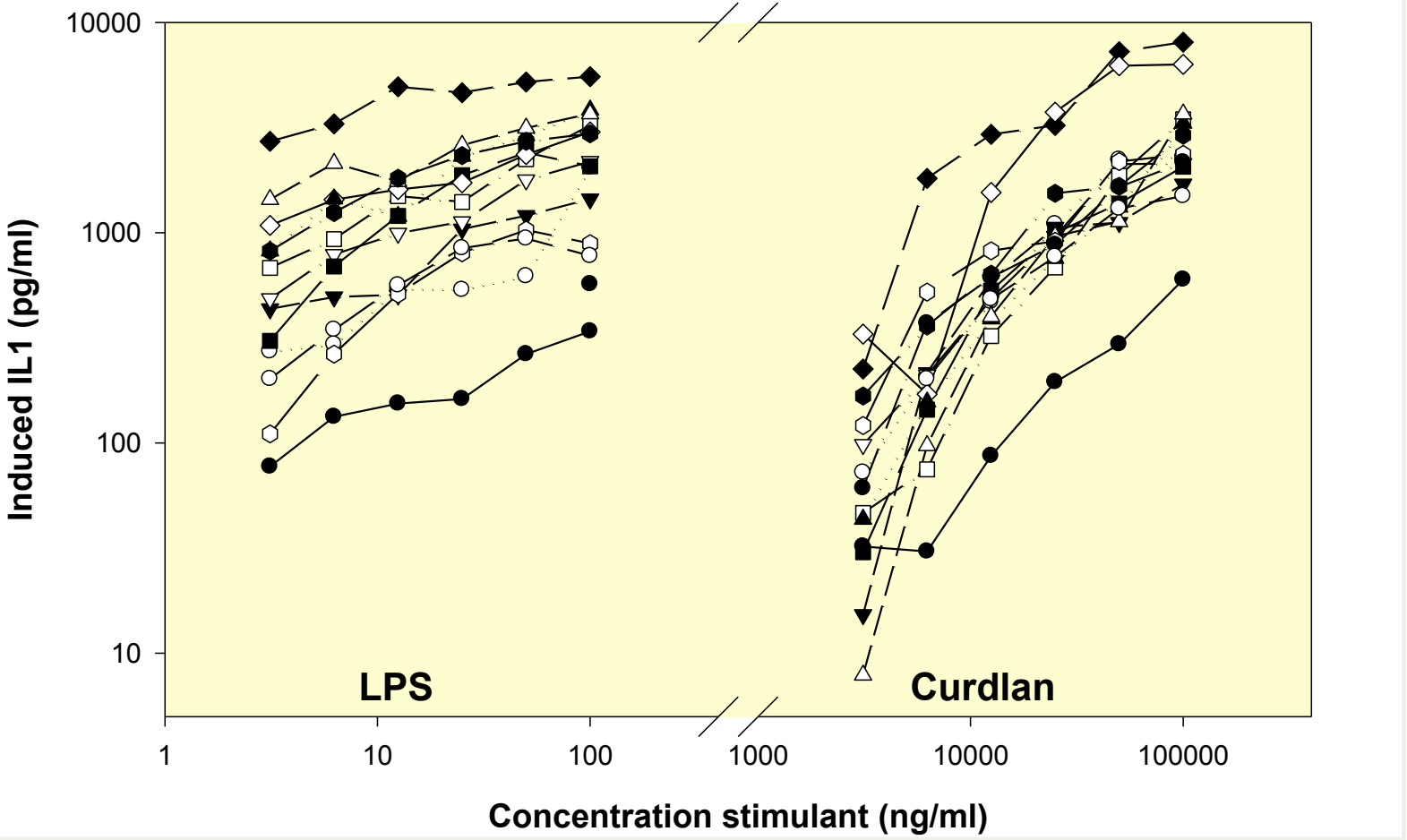




Association between post-shift NAL cell counts and IL8 levels in 166 waste collectors and controls
Wouters et al., OEM 2002

	Cells	IL8
Cough	1.80 #	2.52 **
Cough with phlegm	2.00 #	2.36 *
Wheezing chest	1.33	4.28 *
Dyspnea	0.80	2.44
Shortness of Breath	3.00	2.75
Chest tightness	2.00	1.83
Stuffed nose	1.22	1.71 *
Runny nose	1.50 #	1.59 *
Itchy nose/sneeze	1.47	1.15
Throat irritation	2.33 #	2.14 #

Whole blood assay inter-individual variability in response
Wouters et al., Toxicol Ind Health 2002



Fungal spores: a critical review of the toxicological and epidemiological evidence as a basis for occupational exposure limit setting
Eduard Critical Rev Toxicol 2009

Spores of all tested species induced inflammation in experimental studies

Non-allergic responses dominated

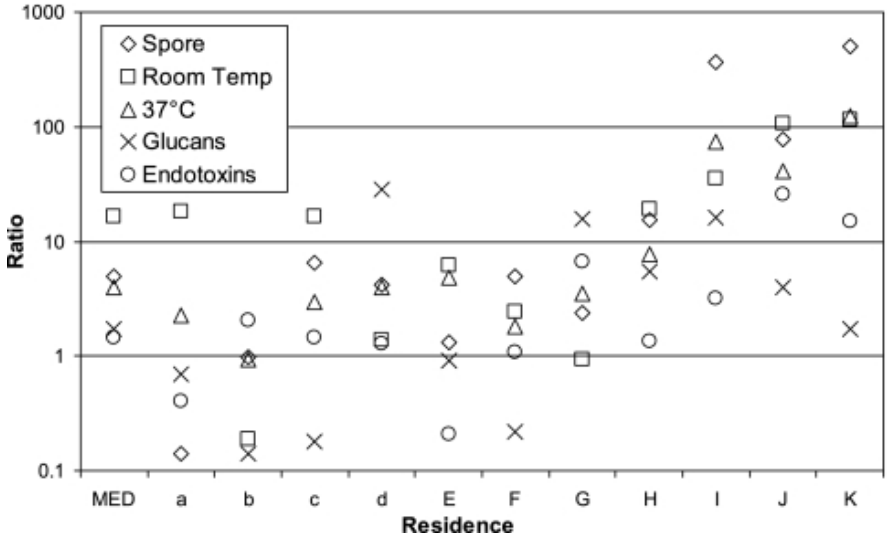
NOELs of 4 x 10^3 - and 8 x 10^3 spores/m^3 for lung function, respiratory symptoms, and inflammatory cells in blood for different species (Trichoderma harzianum Penicillium chrysogenum)

LOELs for reduced airway conductance were lower in asthmatics 1-2 x 10^4 spores/m^3

LOELs In epidemiological studies in highly exposed working populations at exposure levels of 10^5 spores/m^3 for lung function decline, respiratory symptoms and airway inflammation.

Thus, human challenge and epidemiological studies support fairly consistent LOELs of approximately 10^5 spores/m^3 for diverse fungal species in nonsensitised populations.

Extreme indoor mould exposure (post Katrina/Rita flooding Louisiana)
Rao et al., 2007



- Culturable fungi moderately/heavily water-damaged houses (geometric mean=67,000 CFU/m^3) mildly water-damaged houses (geometric mean=3,700 CFU/m^3) (P=0.02).
- The predominant molds found were Aspergillus niger, Penicillium spp., Trichoderma, and Paecilomyces.
- The indoor and outdoor geometric means for endotoxins were 22.3 endotoxin units (EU)/m3 and 10.5 EU/m3, respectively
- (1-->3,1-->6)-beta-D-glucans were 1.7 µg/m3 and 0.9 µg/m3, respectively

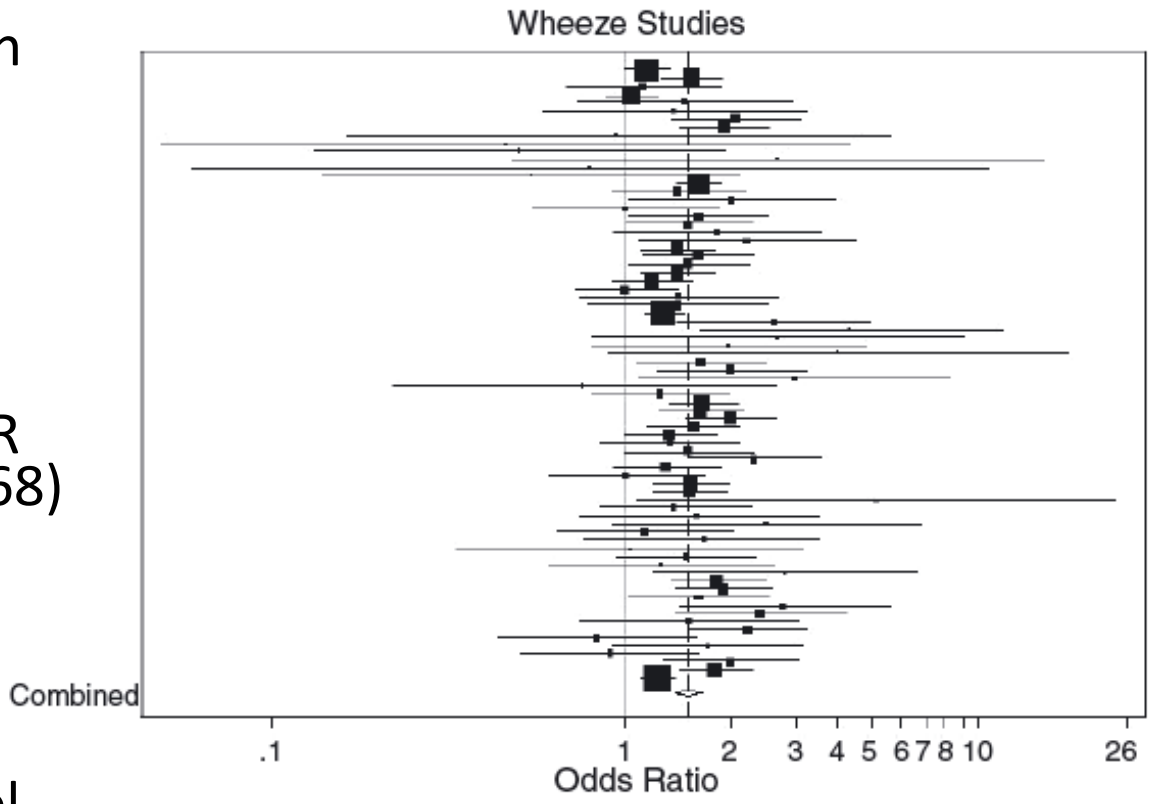
- Barbeau et al. Mold exposure and health effects of following hurricanes Katrina and Rita. Ann Rev Public Health 2010

Home dampness and respiratory morbidity in children (Brunekreef et al., Am Rev Respir Dis 1989)

- >4600 US children 7–11 years of age
- Dampness indicators in more than 50% of the homes
- Associations with respiratory symptoms:
  - Mold exposure 1.27 to 2.12
  - Dampness 1.23 to 2.16
  - After adjustment for maternal smoking, age, gender, city of residence, and parental education

Home dampness: a meta-analysis
Fisk et al., 2007

- Meta analysis reports an increase of 30-50% for several asthma related diagnoses for subjects living in damp or moldy homes
- For wheezing a meta-OR of 1.53 (95% CI 1.39–1.68)
- Few studies on asthma
- Most studies cross-sectional or case-control studies and rely on self reported exposure



Respiratory symptoms in damp Dutch homes
Wagemaekers et al., 1989

Dampness classification	Type of home	N	GM CFU (GSD) 
Observer	Damp	24	192 (2.8)
	Dry	8	107 (2.1)
Subjective	Damp	25	214 (2.8)
	Dry	11	91 (1.9)

Home dampness: a meta-analysis Fisk et al., 2007

- Exacerbation of pre-existing asthma and respiratory allergy
- Cause of asthma and allergy?
- Relevant mechanisms:
  - Sensitization
  - Toxic effects (mycotoxins, VOCs)

PEDIATRICS
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

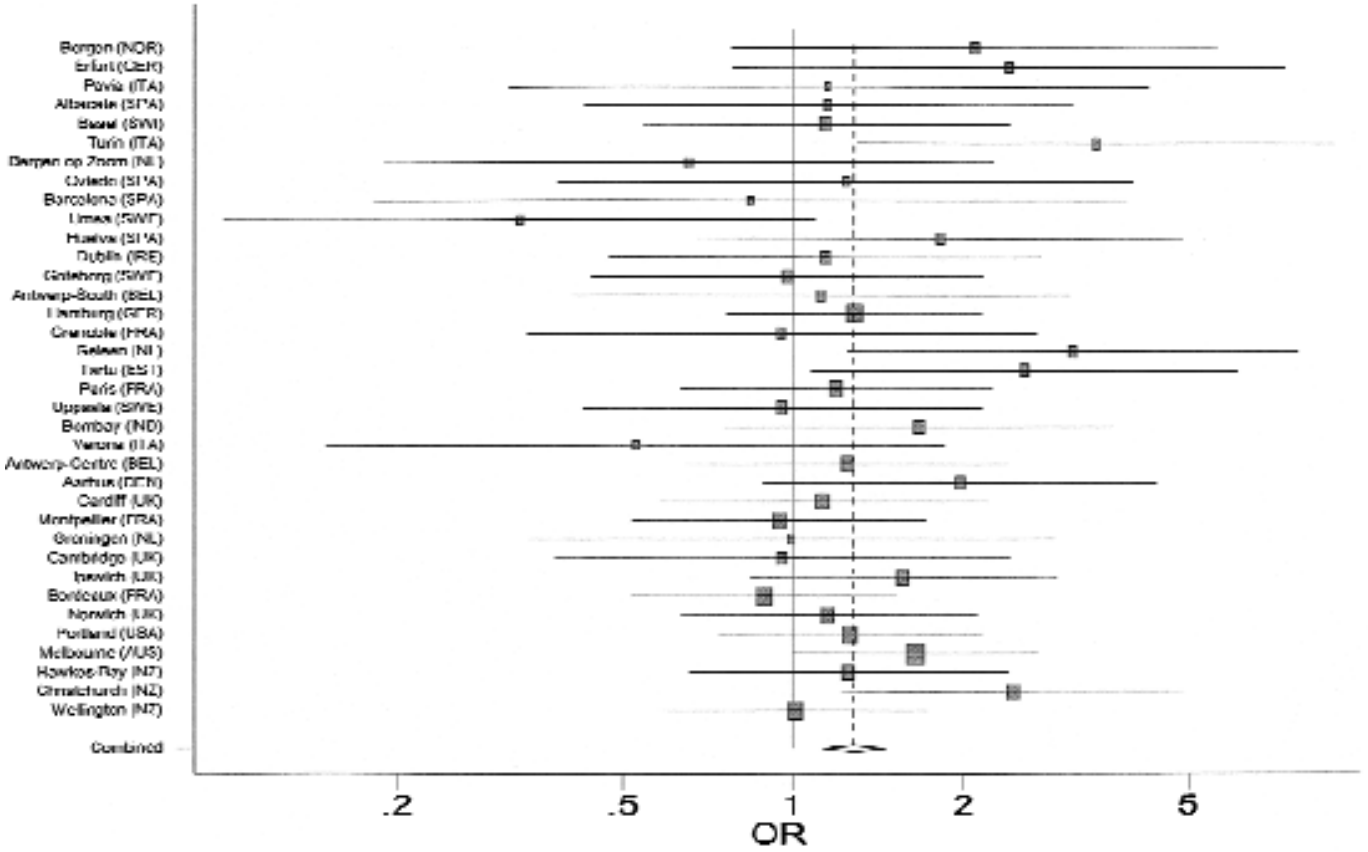
Spectrum of Noninfectious Health Effects From Molds
Lynnette J. Mazur, Janice Kim and the Committee on Environmental Health
Pediatrics 2006;118;e1909-e1926
DOI: 10.1542/peds.2006-2829

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™

Asthma, allergy and building dampness in dwellings. Norbäck et al., Int J Tuberc Lung Dis 1999

- Survey among 98 prevalent asthma cases and 357 controls
- mould allergy prevalence 3.9% among subjects in dwellings without signs of dampness vs 9.3% in dwellings with at least one sign of building dampness
- crude OR 2.6; 95% CI 1.24–5.24

Housing characteristics, reported mold exposure, and asthma in the ECRHS
Zock et al., JACI, 2002



effect was stronger in subjects sensitized to *Cladosporium* species (p=0,004), similar stronger effect for *Alternaria alternata* (but, p=0,33)

Exposure assessment issues

	ρ	k to limit bias to 10%
Total CFU	0.28	35
Aspergillus	0	$+\infty$
Cladosporium	0.23	43
Penicillium	0.8	8
Wallemia	0.05	200

Verhoeff et al., Allergy 1992

	ρ	k to limit bias to 10%
Endotoxin	0.85	3

Noss et al., 2008

- Repeated sampling or longer averaging time
  - Correlations between repeated endotoxin measurements over >6 months (Horick et al., 2006; Abraham et al., 2005) $\rho<0.5$
  - Exposure highly variable over short and longer periods

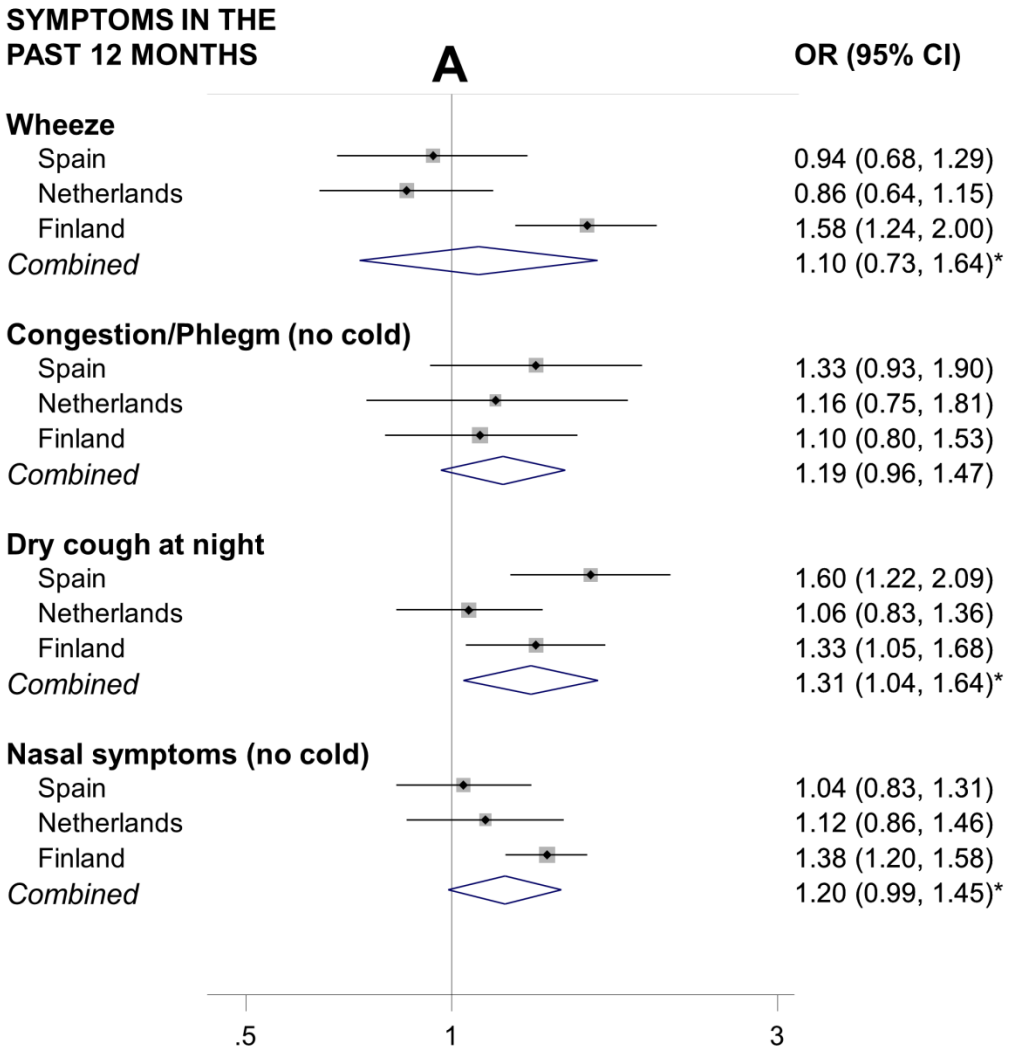
Measured air contaminant exposures and relations to wheeze and persistent cough in the first year of life
Belanger et al. Am J Epid 2003

	Wheeze*		Persistent cough†	
	OR‡,§	95% CI‡	OR§	95% CI
Children whose mothers had asthma (n = 256)				
Measured fungi per 20 colonies	1.23	1.01, 1.49	1.04	0.87, 1.24
Measured nitrogen dioxide per 10-ppb‡ increase	1.10	0.87, 1.40	1.01	0.81, 1.26
Children whose mothers did not have asthma (n = 593)				
Measured fungi per 20 colonies	1.10	0.99, 1.23	0.99	0.89, 1.10
Measured nitrogen dioxide per 10-ppb increase	1.10	0.96, 1.25	1.21	1.05, 1.40

* Categorized as none, <30 days, or ≥30 days in the first year of life.
† Categorized as none, <30 days, or ≥30 days in the first year of life.
‡ OR, odds ratio; CI, confidence interval; ppb, parts per billion.
§ Adjusted for all factors listed in the table as well as for dust mite, cockroach, and cat and dog allergen, maternal education, ethnicity, the gender of the child, and smoking in the home.

Strong signal? False positive finding? Consitency with the literature? Replication?

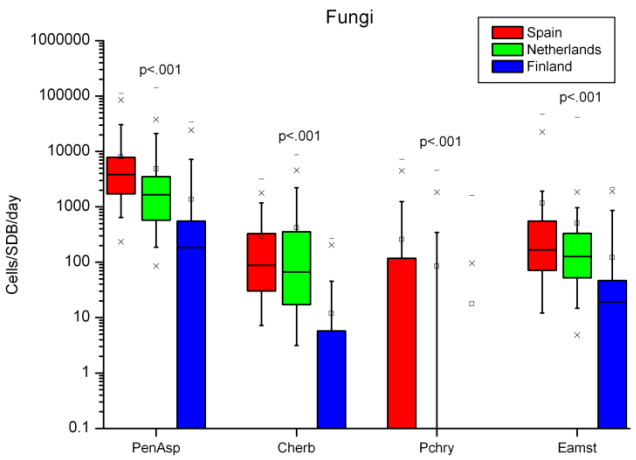
Associations school moisture and symptoms in 9721 children in moisture damage and control schools
Borras Santos et al., 2013

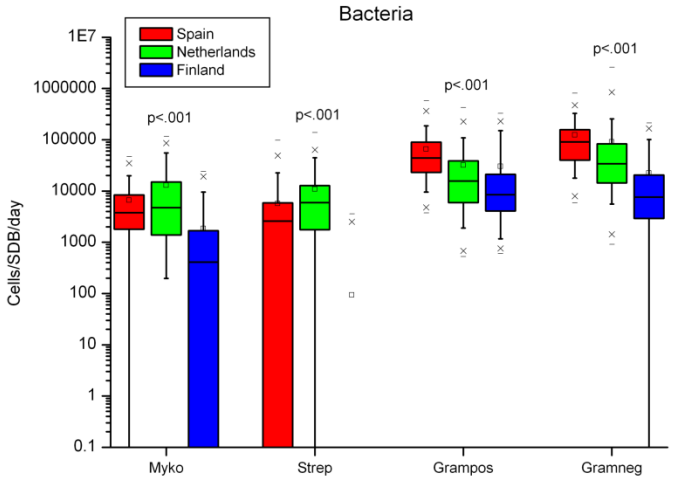


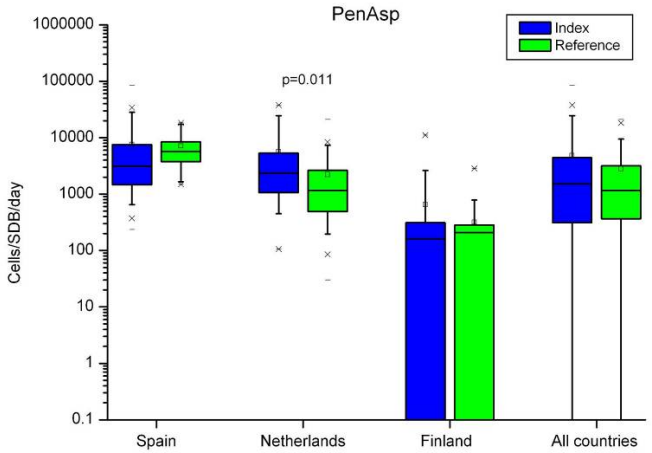
*P for heterogeneity> 0.10

Adjusted for age, gender, home moisture/mold last 12m, parental education

Exposure to microbial molecular markers in 237 class rooms Taubel, in preparation 2016

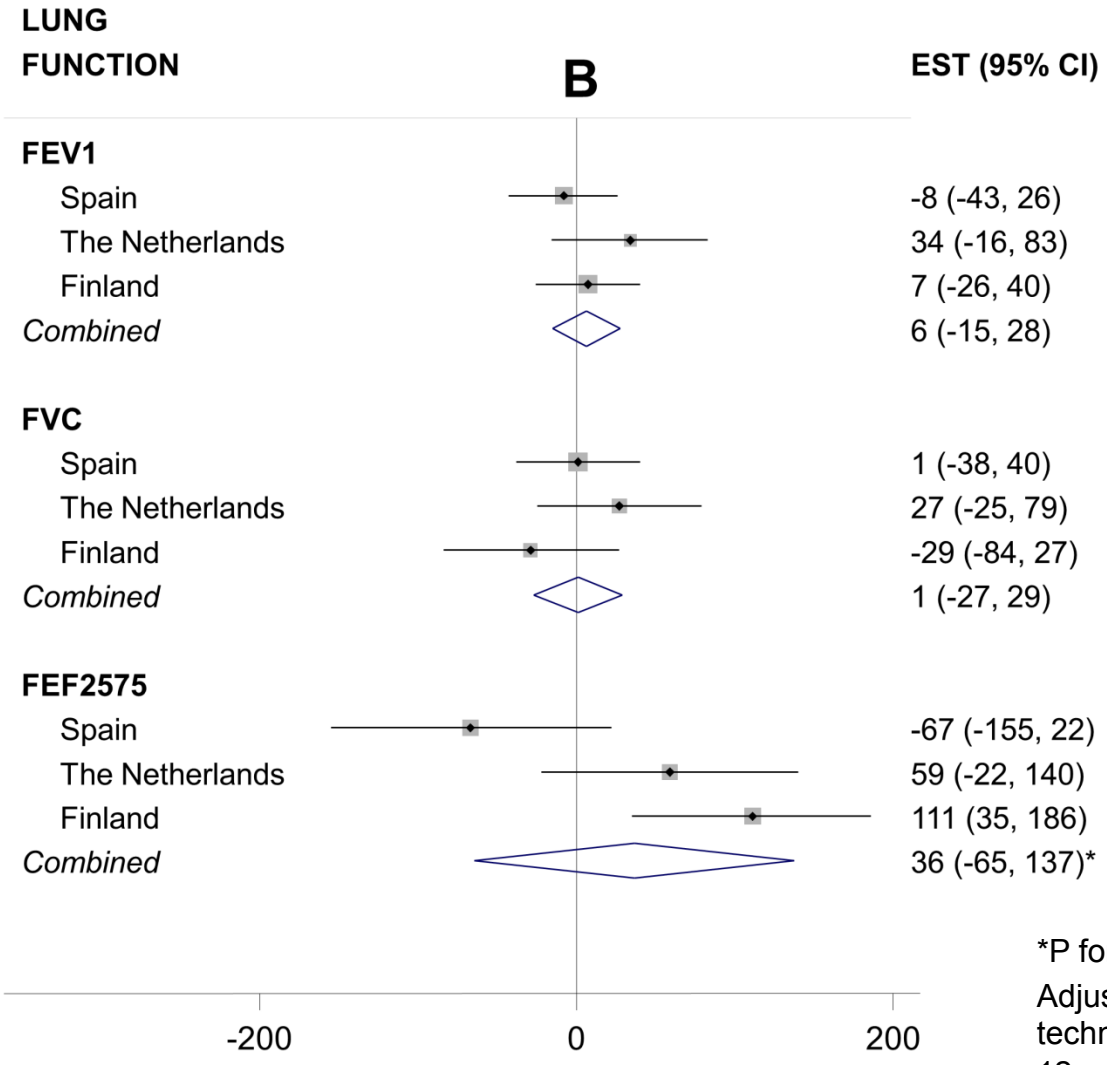






- In Finland levels were lowest (and % ND highest) in particular in winter
- Endotoxin, ergosterol and *Penicillium chrysogenum* levels were higher in classrooms of schools affected by moisture damage and dampness compared to reference schools
- Clearest difference index and reference schools in Dutch schools

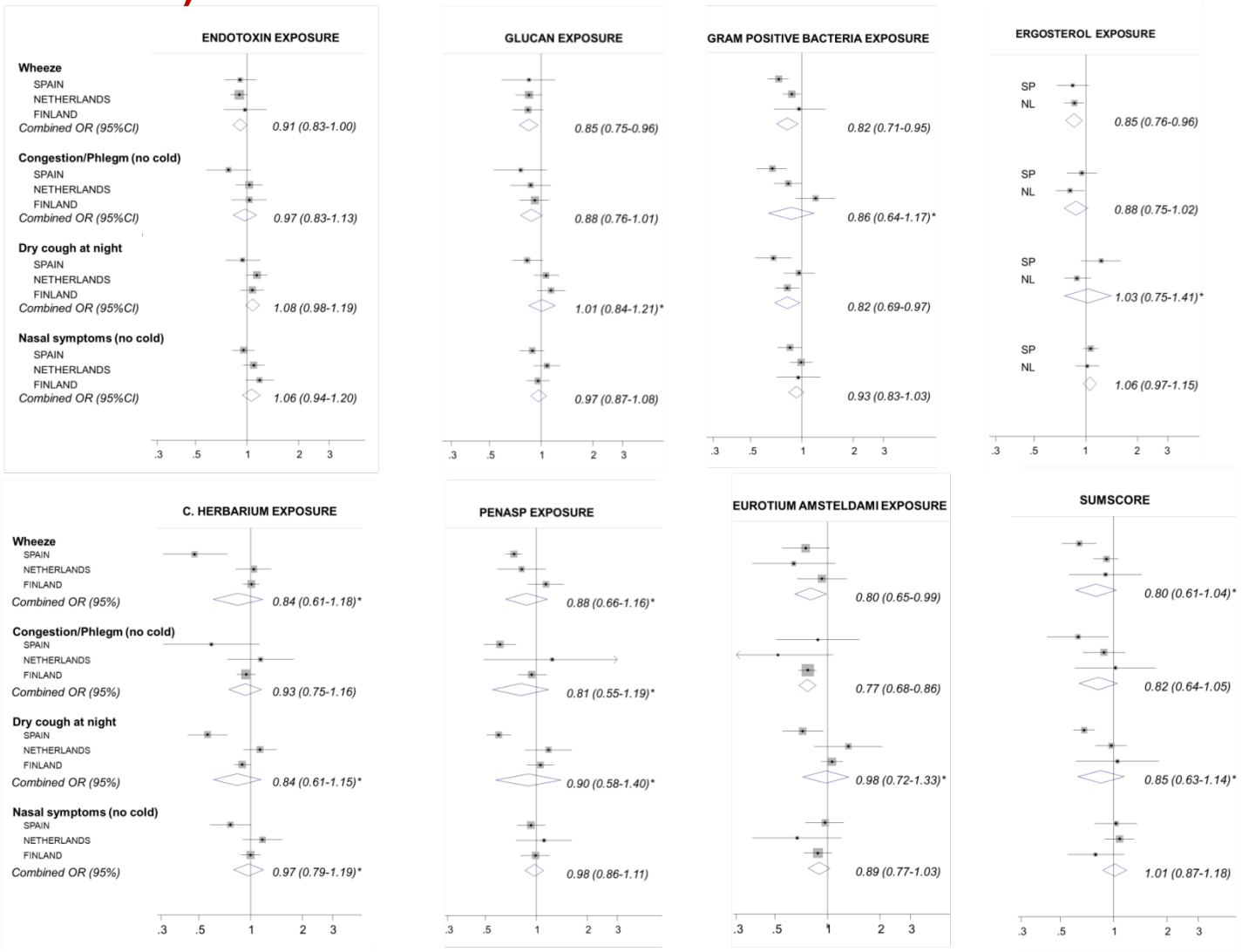
Associations moisture and lung function in 2746 children Jacobs et al., Occup Environ Med 2015



*P for heterogeneity> 0.10

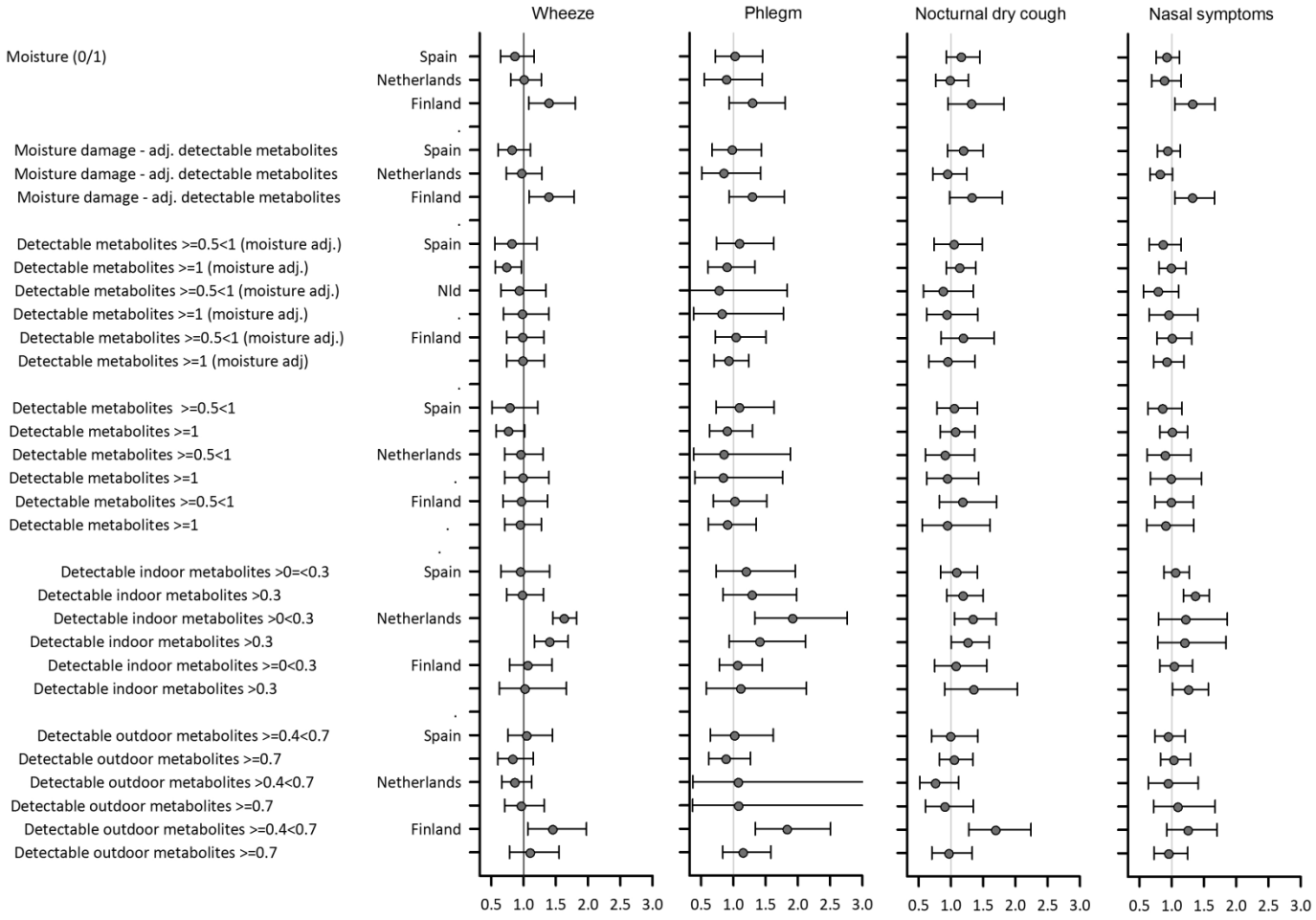
Adjusted for age, sex, height, lung function technician, ETS, home moisture/mold last 12m, parental education

Microbial exposure and symptoms in settled dust samples (IQR increase) in 3843 children



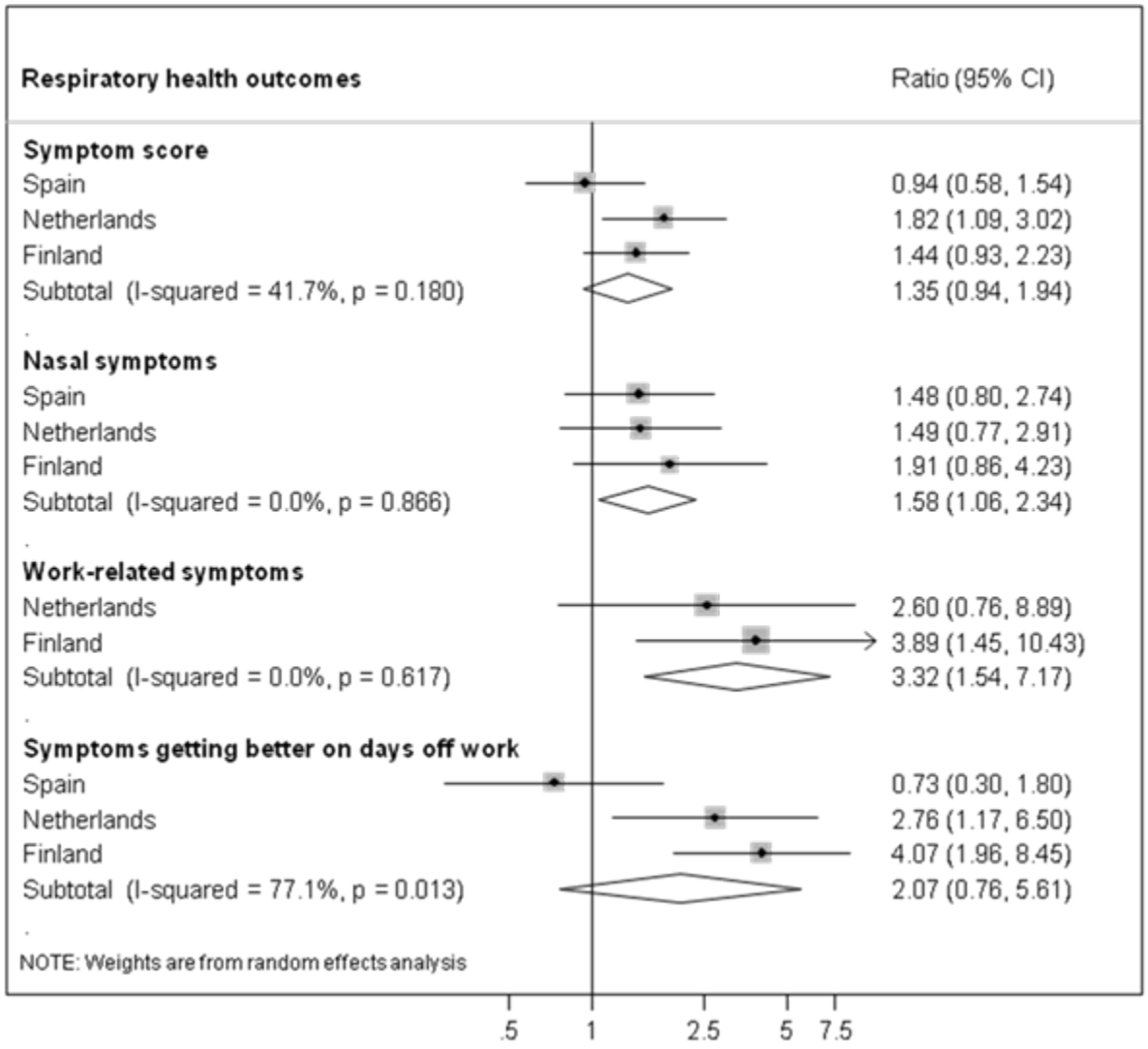
Adjusted for age, gender, moisture/mold at home last 12m, parental education and moisture status school

Mycotoxin exposure and respiratory symptoms for 188 mycotoxins using liquid chromatography/mass spectrometry in settled dust Jacobs et al., 2016 in preparation



Adjusted for age, gender, moisture/mold at home last 12m, parental education and moisture status school

Longitudinal study among 164 teachers over the summer holidays: Questionnaire survey (cross-sectional analysis) Zock et al., 2016 in preparation



Longitudinal study among 164 teachers over the summer holidays: Cross-summer holiday changes
Zock et al., 2016 in preparation

Health outcome	All teachers (n=164)	Teachers from damp schools (n=93)	Teachers from reference schools (n=71)	*P* for difference between damp and reference (adjusted model)
FeNO (ppb)	-2.4*	-2.2*	-2.7	n.s.
Lung function indices				
FEV_1 (mL)	+33*	+20	+50*	<0.1
FVC (mL)	+54*	+47†	+64*	n.s.
$FEF_{25-75\%}$ (mL/s)	+5.6	-37	+63	n.s.

HITEA

Longitudinal study among 164 teachers over the summer holidays: Cross-summer holiday changes
Zock et al., 2016 in preparation

Health outcome	All teachers (n=164)	Teachers from damp schools (n=93)	Teachers from reference schools (n=71)	*P* for difference between damp and reference (adjusted model)
Biomarkers in nasal lavage				
GM-CSF (pg/mL)	-0.05*	-0.05*	-0.05	n.s.
IFN-γ (pg/mL)	-0.36	-0.66	+0.08	n.s.
IL-10 (pg/mL)	-0.05	-0.50	+0.60	n.s.
IL-12P70 (pg/mL)	+0.01	+0.01	+0.01	n.s.
IL-1ß (pg/mL)	-5.96*	-2.67	-10.7*	n.s.
IL-2 (pg/mL)	-0.03*	-0.03*	-0.02*	n.s.
IL-6 (pg/mL)	-1.14	-2.87	+1.37	n.s.
IL-8 (pg/mL)	-78.7†	-54.6	-114*	n.s.
TNF-α (pg/mL)	-0.02	-0.18	+0.23*	n.s.

HITEA

Conclusions from the HITEA study

- Moisture at schools: more respiratory symptoms
Strongest associations in Finland

- Lowest microbial levels in Finland in particular in winter.
Does the intermittant exposure pattern play a role?

- Microbial/mycotoxin classroom levels do not seem to explain associations between moisture and symptoms

- No associations between moisture, microbial levels and lung function

Remediating buildings damaged by dampness and mould for preventing or reducing respiratory tract symptoms, infections and asthma
Sauni et al., Cochrane Database Syst Rev 2015

- 12 RCTs (2)/cluster-RCT (1), controlled before-after studies (9) were included

- effects of remediating dampness and mould in a building on respiratory symptoms, infections and asthma

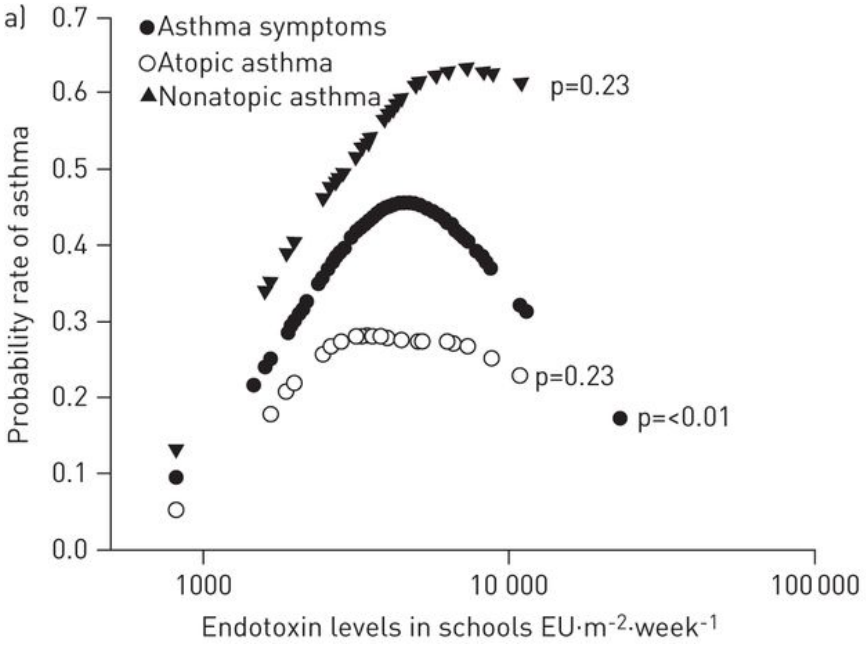
- moderate to very low-quality evidence that repairing mould-damaged houses and offices decreases asthma-related symptoms and respiratory infections compared to no intervention

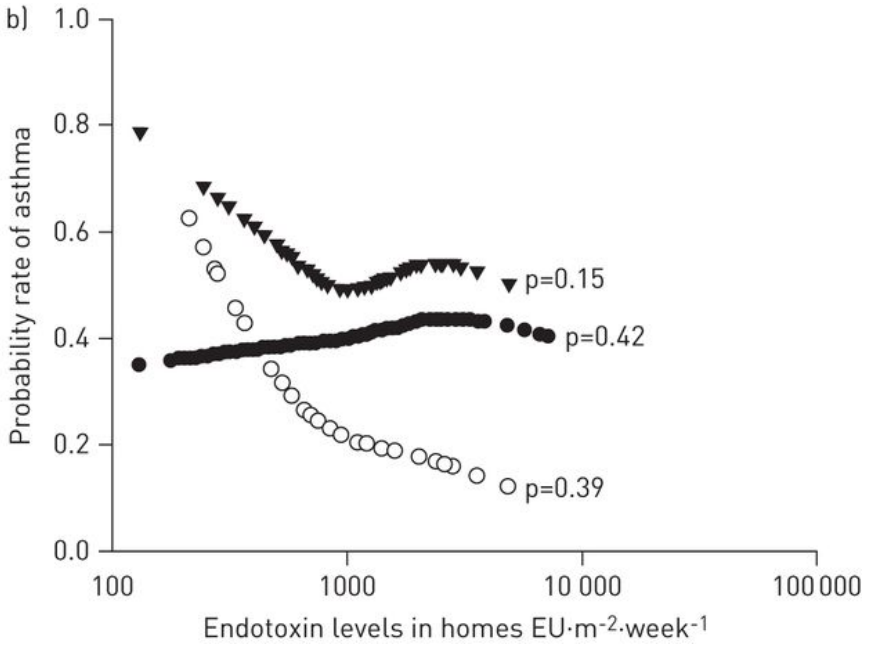
- Better research is needed

Endotoxin at school and at home
Jacobs et al., ERJ

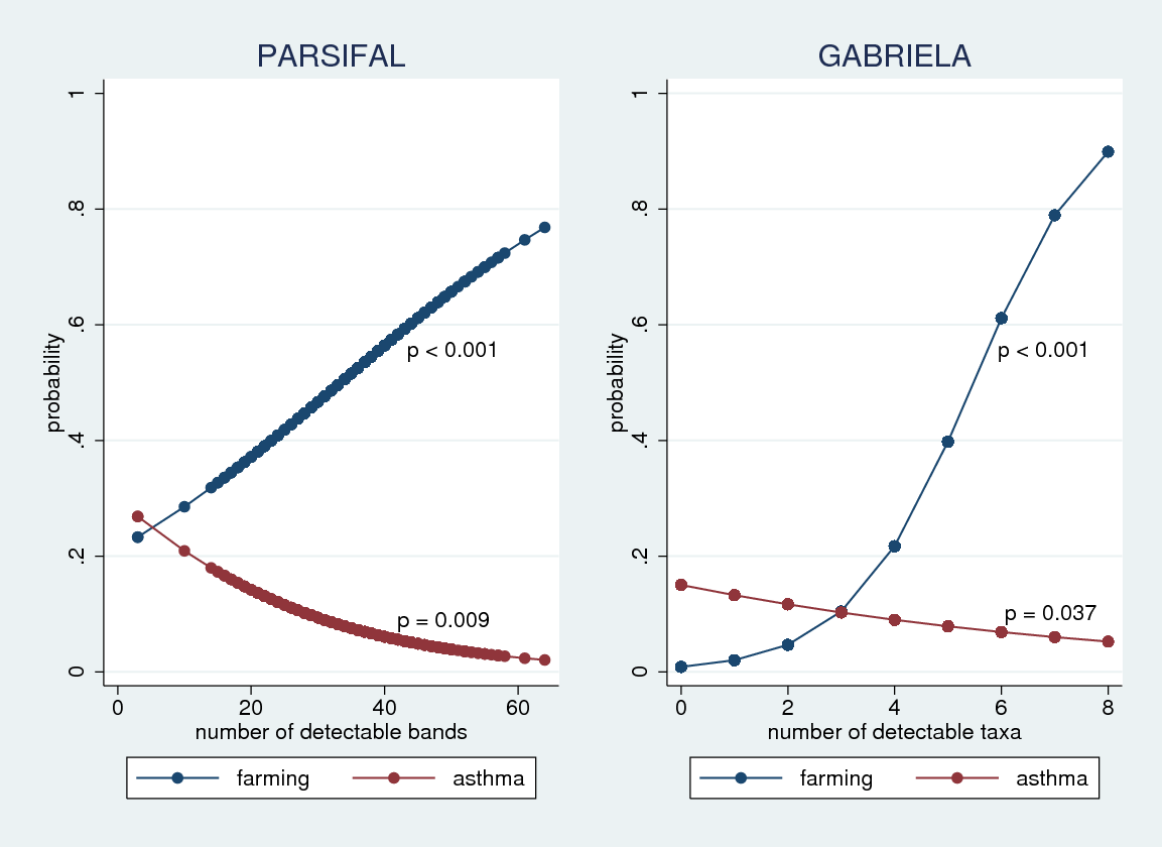
Average endotoxin levels in schools ranged from 2178 to 6914 endotoxin units (EU)·m^{-2} per week compared with 462–1285 EU·m^{-2} per week in homes.

School endotoxin was positively associated with non atopic asthma (OR 1.11, 95% CI 0.97–1.27), while no associations with endotoxin in homes were found.





Microbial diversity in exposure and its relation with atopy and asthma in children
Ege et al., New Engl J Med 2011



Sensitization to common allergens and occupational exposure to endotoxin: a pooled analysis
Basinas et al., 2012

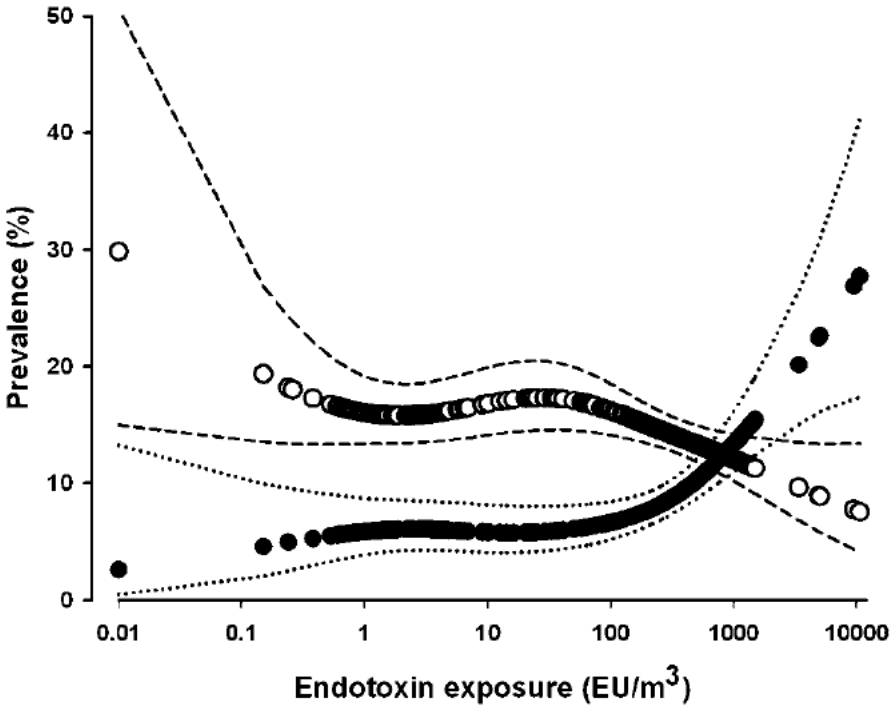


Figure 1 Smoothed relationships between endotoxin exposure, chronic bronchitis and hay fever for the pooled study population. Filled circle, chronic bronchitis; circle, hay fever; dotted line, ±95% CIs for chronic bronchitis; dashed line, ±95% CIs for hay fever. Results are adjusted for gender, age, farm childhood, atopic predisposition, smoking habits and participating study.

Conclusions

- Health effects:
  - exposure dependent inflammation, most prominent at high exposure levels
  - seems to be mediated by (innate) immune responses resulting in inflammation
  - Susceptible populations (asthmatic, hyper-responders)
- Poor exposure assessment has complicated interpretation of studies (false negative results?)
- Almost all studies are single environmental compartiment studies (home, school, office, work environment)
- Exposure assessment problematic: new molecular tools for measuring moulds have been applied only to a limited extent

Pilot study results EDC pyrosequencing

collaborative project UMU, IC, UU

- Between 8 (blanks) and 715 (bedroom air sample) amplicons after denoising on EDCs from indoor samples