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Asthma & Allergy Development: Contrasting Influences of Yeasts & Other Fungal Exposures

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Abstract

Background—Infancy is a developmental stage with heightened susceptibility to environmental influences on the risk of chronic childhood disease. Few birth cohort studies have detailed measures of fungal diversity data in infants' bedrooms, limiting the potential to measure long-term associations of these complex exposures with development of asthma or allergy.

Objective—We evaluated the relation of home fungal levels in infancy to repeated measures of wheeze and development of asthma and rhinitis by age 13, and sensitization by age 12 years.

Methods—In the Epidemiology of Home Allergens and Asthma prospective birth cohort study, we recruited 408 children with family history of allergic disease or asthma. When children were aged 2–3 months, we measured culturable fungi in bedroom air and dust, and in outdoor air. Main outcomes included ascertainment of symptoms/disease onset by questionnaire from birth through age 13. We estimated hazard ratios and, for wheeze and sensitization, odds ratios for an interquartile increase in log-transformed fungal concentrations, adjusting for other outcome predictors and potential confounders.

Results—Elevated levels of yeasts in bedroom floor dust were associated with reduced: i) wheeze at any age; ii) fungal sensitization; and iii) asthma development by age 13 (hazard ratio

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(HR) = 0.86; 95% confidence interval (CI), [0.75 to 0.98]). Outdoor airborne *Cladosporium* and dustborne *Aspergillus* predicted increased rhinitis. Risk of fungal sensitization by age 12, in response to environmental *Alternaria* and *Aspergillus*, was elevated in children with a maternal history of fungal sensitization.

Conclusions and Clinical Relevance—Despite the irritant and allergenic properties of fungi, early-life elevated dust yeast exposures or their components may be protective against allergy and asthma in children at risk for these outcomes. Ascertainment of fungal components associated with immunoprotective effects may have therapeutic relevance for asthma.

Keywords

Yeast; Mold; Fungi; Damp; Indoor; Outdoor; Wheeze; Asthma; Rhinitis; Allergy; Development; Infants; Children; Housing

INTRODUCTION

Infancy is a susceptible period when exposures may alter the risk of chronic childhood disease (1). Children spend most of their time indoors (2), where they may be exposed to damp conditions and mold. A meta-analysis of eight European birth-cohort studies found that living in visibly damp homes in early-life was associated with asthma development and rhinitis symptoms by age 10 (3). Indoor dampness may favor microbial growth and cause greater exposure to fungi but also endotoxin and dust mites (4), and older studies of home dampness did not differentiate the individual biologic components responsible for the link between dampness and risk of asthma or allergic disease (5).

Few birth cohort studies (6–8) collect detailed data on fungi in infant bedrooms with sufficient follow-up beyond early childhood to measure long-term associations of these complex exposures with subsequent asthma or allergy. While studies of fungal exposures and infant wheeze are mostly focused on adverse outcomes, a small body of literature on fungal components (6, 9–13) and wheeze risk suggest that exposure to some fungal derivatives or certain species (14) may exert protective effects.

In the Boston, Massachusetts Epidemiology of Home Allergens and Asthma prospective birth cohort study of children with parental history of asthma, hay fever or allergy, we evaluated the relation of elevations in infancy (age 2–3 months) culturable fungal and visible home dampness exposures to repeated measures of wheeze and the development of asthma and rhinitis and sensitization by 12 to 13 years of age.

METHODS

Study Protocol

Between September 1994 and June 1996 we recruited 505 children (including six sets of twins) who had at least one parent with hay fever, asthma, or allergies. The recruitment and written informed consent process has been described elsewhere (15). Of the 499 children followed up to age one, 408 had both home indoor air and dust fungal measurements, with complete data for time to first onset of asthma and multiple wheeze assessments. Of the 408

children, 406 had complete data for time to first onset of rhinitis and indoor fungal measurements; 265 had complete data for mold sensitization and fungal measurements. The study was approved by the Institutional Review Board of Brigham and Women's Hospital (ethical approval number BWH 1999P001575).

Early-life fungal exposure assessment has been described previously (16). We collected airborne fungal propagules for 1-minute at 45 lpm using a Burkard portable culture-plate air sampler (Burkard Mfg. Co., Rickmansworth, England) loaded with dichloran glycerol agar (DG18) (17). Outdoor air was sampled 3m from the main entrance, provided temperatures were >36°F (2.2°C). We sampled indoor air 1–1.5m above the area of the bedroom floor demarcated for dust collection. After air sampling, we collected dust for 5-minutes from $2m^2$ of the bedroom floor where the infant slept using a standard portable vacuum (Eureka MightyMite, Peoria, IL), modified with a cellulose dust-collection thimble and culturable fungi were recovered using a dilution series of suspended dust inoculated onto DG18. After room-temperature incubation, all recovered fungal colonies were identified to genus-level using standard mycologic criteria (18, 19). Yeasts were identified only as such and not further characterized. Yeasts are difficult to identify to genus level (when grown only one culture medium), so they were classified as a single group.

Definition of Fungal and Dampness Predictors

Fungal distributions were skewed, and were therefore natural log (ln) transformed and treated as continuous variables. Total fungi concentrations represent a count of all fungal genera that we identified, including rare taxa. Our working definition for "rare" was not measurable at the 75^{th} percentile. While included in our count of total fungi, these rare taxa were not considered in our analyses as individual predictors of health outcomes. Most of the individual fungal taxa that we considered as exposures were fungi that (a) we evaluated sensitization to and (b) that we had identified as predictors of early-life respiratory outcomes in our cohort (16, 20). We classified exposures as: (1) individual genus; and (2) 'total fungi' [sum of concentrations for all detectable fungi from each location].

Home dampness variables were dichotomized: (1) parent-reported visible mold, water damage, or dampness over the year prior to our 2–3 month home-visit; and annually-assessed parental reports of: (2a) visible mold, water damage, or home dampness; or (2b) water damage in the home or standing water on the basement floor over the past year, until the subject children were 13 years old.

Definition of Other Covariates

We adjusted regression models for potential confounders and independent predictors of our outcomes, as reported in previous publications (4, 15, 21–32). We did not adjust for active or environmental tobacco smoke exposure, as each was rarely reported in our cohort (<1%).

We ascertained maternal sensitivity with serum IgE at birth, which has been described elsewhere (33). Mothers were described as having 'mold atopy' if sensitized to *Alternaria* or *Aspergillus* species, and 'any atopy' if sensitized to ≥1 allergen (mold, cat, dog, ragweed, ryegrass, cockroach, or dust mite), and/or a total IgE ≥200 IU/mL (33).

Definition of Outcome Variables

After written informed consent was obtained, trained research assistants administered a telephone questionnaire to the child's primary caregiver every 2 months, beginning when the child was 2 months old and until the second birthday. Between ages 2 and 13 years, wheeze and asthma were ascertained semi-annually, while allergic rhinitis was assessed annually. For comparability across outcomes, we used a summarized annual assessment, asking whether the child had experienced each outcome over the past year.

A positive wheeze report was defined as ≥1 wheeze episode at any time over the prior year. Secondarily, we categorized wheeze into three age stages: 1) <3 years; 2) ≥3 and <6 years; and 3) ≥6 years, similar to the asthma phenotypes described by Stein *et al*. (2004) (34).

A child was reported to have current (active) asthma if the parent reported a physician's diagnosis of asthma, along with any wheeze symptoms (including with cold air or exercise) in the past year. Current (active) rhinitis was defined as a parental report of physician-diagnosed hay fever and nasal symptoms (runny nose) in the past year.

At ages 7 and 12 years, we ascertained mold sensitization status. A child was defined as mold-sensitive by age 12 if they had a positive skin test (≥3 mm wheal size) or radioallergosorbent test (RAST; Immunoglobulin E (IgE) level ≥0.35 U/mL) to ≥1 of the following genera: *Alternaria*, *Cladosporium*, *Aspergillus*, or *Penicillium*. If missing, we assigned sensitization status based on their age 7 results.

Statistical Analysis

We examined the relationship between early life fungal exposure and respiratory/allergic disease outcomes longitudinally. To determine if fungal exposures were associated with time to onset of asthma or rhinitis, we used Cox proportional hazards regression (35). For the repeated wheeze outcome, we implemented Generalized Estimating Equations (GEE) (36) with exchangeable correlation structures, and inverse probability weighting (IPW) to account for loss to follow-up (37). We also assessed whether annual reports of home dampness predicted wheeze in the same year or in the following year. To assess the relationship between exposures (including maternal fungal sensitization) and mold sensitization by age 12, we used logistic regression (see eMethods). For airborne fungal taxa measurable at but not below the 75th percentile, we conducted sensitivity analyses considering these exposures as discrete categorical variables (e.g. ≥75th percentile vs. below the 75th percentile).

We used SAS 9.2 (SAS Institute, Inc, Cary, NC) for all analyses.

RESULTS

Cohort and Home Characteristics

Population and home characteristics have been described previously (15, 16, 28). Of the 499 children, 82% were followed through 12 to 13 years of age. The children with complete follow-up were not different to the full cohort with respect to outcomes; the prevalence of "ever presenting with asthma", "rhinitis", or "wheeze" at some point by age 13 did not differ

between the full cohort followed up to age 1 (N=499) and the children with both indoor air and dust fungal exposure assessment who were included in the primary analyses (N=208; Table 1). Lower family income, African American race/ethnicity, and covariates linked to disadvantage were associated with loss to follow-up, which we accounted for in our models.

Compared with the 499 children, the subset of children with measures of sensitization and indoor air/dust measures (N=265) had slightly higher rates of asthma (36% vs. 33%) and rhinitis (40% vs. 36%), but a very similar prevalence of "ever wheeze." The median ages for the first diagnosis of asthma, rhinitis and the first wheeze episode were 5, 7, and 1, year(s), respectively. Twenty percent (52/265) of children were mold-sensitive when measured.

Comparing outdoor and indoor air fungal concentrations, *Cladosporium*, nonsporulating, and total fungal concentrations were greater in outdoor air, while *Aspergillus* and *Penicillium* were greater indoors (Table 2). For total fungi, levels in air and dust were highest in summer/fall and lowest in winter/spring. Outdoor airborne *Alternaria*, *Cladosporium*, and *Penicillium* were highest in summer/fall, whereas outdoor airborne yeasts were lowest in summer/fall (see eFigure 1); this was generally reflected in the indoor air patterns of the specific taxa. Forty-four percent of families reported visible mold, water damage, or home dampness in the 12 months prior to the sampling visit during infancy. Overall from birth through age 13, 54% of children lived in homes with visible mold, water damage or dampness, and 37% lived in homes with reported water damage or standing water on the basement floor.

Mold and Asthma

Elevated levels of dustborne yeasts in infancy were inversely associated with asthma development (hazard ratio (HR) = 0.86; 95% confidence interval (CI), [0.75–0.98]) (Table 3). In contrast, increased concentrations of indoor airborne *Alternaria* (HR=1.48 [0.97–2.26]) and dustborne *Cladosporium* (HR=1.17 [0.97–1.41]) were suggestive risk factors. Early-life visible dampness (HR=0.82 [0.54–1.24]) was not associated with asthma development. In addition, total fungi in indoor air (HR=0.91 [0.62–1.33]), or dust (HR=1.02 [0.79–1.33]) were not associated with asthma development (N=408). In sensitivity analyses considering indoor air *Alternaria*, indoor air *Aspergillus* and indoor air yeasts as discrete categorical variables, results were consistent, with significant protective associations for dust yeasts and a significant risk for *Alternaria* (HR=1.70 [1.01–2.86] for $\geq 75^{th}$ percentile vs. below the 75^{th} percentile) (eTable 1). Results were consistent in the subset with outdoor air measurements (N=317).

Mold and Rhinitis

Higher levels of indoor bedroom dustborne *Aspergillus* (HR=1.39 [1.11–1.74]) in infancy were associated with an increased risk of incident rhinitis (Table 3). In the subset with outdoor air fungal measures (n=316), outdoor airborne *Cladosporium* (HR=2.12 [1.14–3.92]) and nonsporulating fungi (HR=1.41 [0.97–2.06]) were also associated with an increased risk of rhinitis development. However, total fungi were not associated with rhinitis development risk.

Mold and Wheeze

Over the lifetime of the children (birth to age 13), elevated levels of dustborne yeasts were associated with a lower odds of wheeze (odds ratio (OR) = 0.88; 95% confidence interval (CI), [0.80–0.96]) in repeated measures analyses (Table 3). Results were consistent when we limited the data to the subset with outdoor air fungal exposure assessment (OR=0.82 [0.70, 0.96]). Moreover, dustborne yeasts were negatively associated with "any wheeze" at each of 3 age stages {age <3 years (OR=0.86 [0.76–0.97], n=408); ages 3 through <6 (OR=0.83 [0.74–0.94], n=394); and 6 through 13 (OR=0.90 [0.80–1.01], n=379)}. In contrast, there was a suggestion that elevated indoor air yeasts were associated with increased odds of wheeze in repeated measures analyses (OR=1.24 [0.99–1.56]). As with asthma, in sensitivity analyses considering indoor air *Alternaria*, indoor air *Aspergillus* and indoor air yeasts as discrete categorical variables, results were consistent, with significant protective associations for dust yeasts and a significant risk for *Alternaria* (0R=1.47 [0.00–2.14] for ≥75th percentile vs. below the 75th percentile) (eTable 1).

Independent of fungal exposures, in repeated measures analyses, wheeze over the lifetime of the children was not associated with reports of visible dampness in the year prior to the home visit in infancy (OR =1.05 [0.77–1.42]) or in the year of or before the symptom report (results not shown).

All associations for wheeze, asthma and rhinitis were independent of gender, ethnicity, low total annual family income, birth season, Cesarean birth, low birth weight quartile, low-normal gestational age, bottle feeding in bed/crib in first year of life, lower respiratory illness in first year of life, physician diagnosed parental history of asthma, maternal smoking during pregnancy, building type, early-life exposures to cockroach, dust mite, cat, and mouse allergens (as suggested by dust levels); dog ownership; dust endotoxin; and daycare in the first year of life.

Mold Sensitization

Elevated levels of dustborne yeasts were negatively associated with mold sensitization (OR=0.82 [0.66–1.01], (N=265)). All of the children sensitized to mold were sensitized to ≥1 other allergen (cat, dog, mouse, cockroach, dust mite, tree, ryegrass, and/or ragweed), so we were unable to adjust for "any atopy". Total fungi in indoor air (OR=1.13 [0.62–2.07]), and dust (OR=1.16 [0.79–1.70]) were not associated with mold sensitization.

Maternal mold sensitization significantly modified (increased) the odds of mold sensitization by age 12 with exposures to higher fungal dust levels in infancy (OR=4.77 [1.55–14.68] versus OR=1.29 [0.60–2.78]; for *Alternaria*) (OR=1.33 [0.94–1.87] versus OR=1.01 [0.76–1.33]; for *Aspergillus*).

DISCUSSION

Elevated dustborne yeasts levels in infant bedrooms were consistently and strongly associated with lower prevalence of wheeze at every life stage, with lower risk of development of asthma by age 13, and with mold sensitization by age 12. In contrast, increased levels of members of several genera known to be associated with reduced asthma

control in school-aged children (3) (e.g., *Cladosporium*, *Aspergillus*, *Alternaria*) were also risk factors for rhinitis or (more weakly) for asthma development in our cohort. Maternal mold sensitization status at the birth of their child modified the association between elevated early-life dustborne *Alternaria* and *Aspergillus* exposures and mold sensitization by age 12. Occupant-reported dampness was neither associated with fungal concentrations (38) nor was it consistently associated with wheeze, asthma or rhinitis in our cohort.

Ours is one of the most comprehensive birth cohort studies supporting the hypothesis that early-life is a critical period when fungal exposures can influence the development of asthma and allergy up to the teen years. Longitudinal studies of individual fungal genera, rather than total fungi or home dampness, can differentiate potentially protective fungal types from those that increase disease risk. Among the few previous studies on the role of early-life fungi in respiratory disease development beyond early childhood, many were cross-sectional or case-control in design. In the BAMSE longitudinal birth cohort study of 4,089 Swedish children, the odds of recurrent wheezing by age 2-years was associated with early-life (age 2-months) mold odor (OR=2.0 [1.0–3.9]) (7). However, that study relied on parental reports of both exposure and outcome. We did rely on parental report of home dampness but had objective measures of fungi.

In a matched case-control study of 251 cases and their controls from a cohort study of 3,754 Norwegian children, Nafstad *et al.* (1998) found investigator-confirmed dampness to be a significant determinant of bronchial obstruction (OR=3.8 [2.0–7.2]) (39). Although this study adjusted for dust mite exposure, there was no measure of specific species-level fungal concentrations, and children were followed-up to age 2 (39). A Finnish retrospective study of 121 cases and 241 controls aged 1–7 years found that the odds of physician-diagnosed asthma were associated with engineer-reported severity of moisture damage, visible mold or mold odor (40). The principal strength of that study was having objective measures of severity of moisture damage. We relied solely on parental report of dampness, and it is likely that our subjective home dampness reports included a wide range of dampness severity. While chronic dampness in homes is an established risk factor for asthma development in childhood (41, 42), though it is believed to represent a host of microbial exposures and sources of allergens that thrive and multiple in damp conditions. In our cohort, in a number of prior publications, we have demonstrated that, as expected, our metrics of home dampness or its sources are predictors of our exposures of interest—particularly home endotoxin and dust fungal levels (43, 44). However in all of our longitudinal analyses, the microbiota or allergens themselves and not the conditions fostering their growth have been the more robust predictors of a variety of respiratory health outcomes.

Dustborne versus Airborne Yeasts

Environmental exposures may have opposing influences on allergic or asthmatic responses, depending on the compartment exposed, the dose received, the timing of the dose or susceptibility of the subject. Yeast exposures are no exception. Dustborne yeasts may have been ingested as well as inhaled by infants in early life. Immune responses in the gut are key to development of immune tolerance (45). Probiotic yeasts (46) and glucans (47) are toll-

like receptor stimulants that may protect against early-life allergen when ingested. In contrast, allergy to baker's yeast is a documented phenomenon (48), and aerosolized yeasts may provoke irritant as well as allergic inflammatory airway responses when inhaled. With hand-to-mouth behaviors in infancy, the children in our cohort may have had gastrointestinal compartment-specific immune responses to the dustborne yeasts in their bedroom, with development of tolerance on ingestion of yeast. Dustborne yeasts were also associated with reduced sensitization, suggesting that their protective association with wheeze and asthma development may have been mediated through reduced allergy. Given the lack of association of airborne yeasts with sensitization, their association with increased wheeze, particularly in early childhood (20) may reflect a compartment-specific irritant rather than an allergic airway response. Level and persistence of dose as well as compartment of exposure may also be responsible for differences in the relation of dust, compared to airborne yeasts, with health outcomes. The 75th percentile of airborne yeasts was equivalent to the lower limit of detection (i.e., 11 CFU/m^3) which could mean that the airborne concentrations of yeasts are not as high (relatively speaking) and as constant as are the exposures to yeasts in dust.

There are over 1500 species of yeasts and yeast-like fungi, a phylogenetically diverse group of mainly unicellular fungi (49). Variability in pathogen-associated molecular patterns (PAMPs) both within yeast species as well as between unicellular (e.g., yeasts) and multicellular fungi may differentially stimulate innate responses (50). Given the diversity of yeasts, it is also feasible in our study that airborne and dustborne yeast communities differed taxonomically, functionally, or structurally in ways that may have influenced their immunologic or physiologic effects (51). Molecular microbiologic studies may elucidate specific components of innate microbiologic stimulants that lead to contrasting effects on respiratory and allergic disease development.

Towards an understanding of protective microbial associations: beyond measurement of total fungal levels

Our study adds specificity to the hygiene hypothesis literature suggesting that microbial organisms or their components may protect against asthma and allergy development (6, 9–13, 52, 53). Tischer *et al* (2011b) found that among children with parental allergy, an increase in (1,3)-β-D-glucan exposure sampled from children's mattresses and living-room floors at age 5 was negatively associated with physician-diagnosed allergic rhinitis (OR=0.58 [0.37–0.91]) at age 6 (8). As well as compartment or timing of exposure, differential levels of biologically-active fungal glucan between genera (54) and different types of yeasts (55) may explain the variable health outcomes associated with early-life fungal exposures (56).

Osborne *et al*. (2006) measured indoor and outdoor air, but not dust, samples for 144 at-risk children, aged between 1 and 3 years (56). They then cross-sectionally tested the association between total fungi and the four most frequent genera with health outcomes in separate logistic regression models. While total airborne fungal concentrations were not associated with increased sensitization, sensitization was associated with higher levels of *Alternaria* and *Penicillium* or *Aspergillus* type spores, but lower levels of *Cladosporium*.

Study Limitations

Our analytical technique required spores be culturable, but non-viable/non-culturable spores and fungal fragments and non-living cellular material can also carry allergens and other immunomodulatory agents. Newer molecular methods may improve fungal exposure assessment (57) and assessment of the functional components of yeasts and other fungi that may be protective against some allergic disease, depending on the timing and mode of exposure. At this time however, the use of community sequencing of diagnostic regions of the fungal rRNA gene remains underexploited for epidemiologic studies.

While we have repeated outcome measures, we are limited by fungal exposures measured only in early-life. Moreover, dust samples may be more representative than single short-term air samples of biologically-relevant long-term exposures to fungi. This was highlighted in an earlier manuscript from our study where we found that concentrations of fungi in duplicate samples were highly correlated for dust samples and to a lesser extent in air samples (38).

There is a growing body of evidence that sensitization to some fungi is associated with a more severe phenotype of asthma (58, 59). We assessed whether early-life fungal exposures were associated with sensitization to species of any of the genera *Alternaria*, *Cladosporium*, *Aspergillus*, or *Penicillium*, rather than to a specific genus. However, children sensitized to fungi tend to be atopic to species in >1 genus, and are also more likely to be sensitized to other aeroallergens (60). With a larger sample size (and non- cross-reactive fungal antigen extracts) we might have been able to evaluate fungal exposure associations with species-specific sensitization. In another analysis of early-life fungi and wheeze by age one (20), we validated models using the Lasso approach (61), reducing the probability of chance findings due to multiple comparisons. Therefore, we evaluated the internal consistency of findings across outcomes and exposures, and the biological plausibility of these joint findings, which helps minimize the probability of type I errors.

Conclusions

In one of the most comprehensive longitudinal birth cohort studies following children through age 13 and controlling for loss to follow-up, visible reports of home dampness, and other indoor environmental exposures, we have highlighted the role of early-life fungal exposures in the development of wheeze, asthma, rhinitis, and sensitization. While several specific genera were risk factors, dustborne yeasts appeared protective of early-onset and persistent wheeze, asthma development by age 13, and mold sensitization by age 12. The influences of fungi may vary by form, taxonomically patterned functional differences, by timing, dose, or mode of exposure, or by inherited susceptibility factors. Molecular microbiologic studies may elucidate specific components of innate microbiologic stimulants that lead to contrasting effects on disease development.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

AED	aerodynamic equivalent diameter
A_w	water activity (the ratio of the vapor pressure of water in a material to that of pure water) is a measure of the free water available for fungal growth
Bla g 1 and Bla g 2	Major allergens from *Blattella germanica* (German cockroach allergen)
CFU	colony-forming unit
CI	confidence interval
DG18	dichloran-glycerol agar medium
EPS-*Pen/Asp*	extracellular polysaccharides from *Penicillium* or *Aspergillus*
EU	endotoxin unit, a standard measure of pyogenic potency in a test material relative to that of *Escherichia coli* endotoxin
ICAS	Inner-City Asthma Study
IgE	immunoglobulin E
Inc	incorporated company
IQR	interquartile range
lpm	liters per minute
LRI	lower respiratory illness
Ltd	limited company
r	correlation coefficient
SD	standard deviation
Th1	type 1 T-helper cell
Th2	type 2 T-helper cell

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Table 1

Subject characteristics

	All children (N=499) n (%)	Subset with indoor air and dust fungal measures and assessment of: Asthma/wheeze (N=408) n (%)	Mold sensitization (N=265) n (%)
Health outcomes by age 13			
Ever asthma	168 (33.7)	136 (33.3)	96 (36.2)
Ever wheeze	390 (78.2)	317 (77.7)	204 (77.0)
Ever rhinitis	181 (36.3)	146 (35.8)	106 (40.0)
Male sex	266 (53.3)	215 (52.7)	150 (56.6)
Ethnicity			
Caucasian	375 (75.2)	308 (75.5)	218 (82.3)
African American	59 (11.8)	49 (12.0)	22 (8.3)
Hispanic	30 (6.0)	19 (4.7)	8 (3.0)
Asian	28 (5.6)	26 (6.4)	12 (4.5)
Other	7 (1.4)	6 (1.5)	5 (1.9)
Family income <$30k	43 (8.6)	32 (7.8)	11 (4.2)
Parental history of asthma	256 (51.3)	211 (51.7)	131 (49.4)
Maternal smoking during pregnancy	32 (6.4)	29 (7.1)	21 (7.9)
Birth season			
winter	123 (24.7)	104 (25.5)	62 (23.4)
spring	144 (28.9)	113 (27.7)	76 (28.7)
summer	111 (22.2)	89 (21.8)	61 (23.0)
fall	121 (24.3)	102 (25.0)	66 (24.9)
Cesarean birth	116 (23.3)	92 (22.6)	60 (22.6)
Low birthweight quartile	107 (21.4)	83 (20.3)	53 (20.0)
Low-normal gestational age (≤38.5wks)	104 (20.8)	87 (21.3)	55 (20.8)
Building type			
1-family detached	266 (53.3)	214 (52.5)	140 (52.8)
1-family attached	24 (4.8)	20 (4.9)	13 (4.9)
2-family	94 (18.8)	83 (20.3)	63 (23.8)
≥ 3 apartments	114 (22.9)	90 (22.1)	48 (18.1)
Elevated early-life (2–3mths) exposures			
Home dampness	219 (43.9)	180 (44.1)	119 (44.9)
Cockroach allergen (*≥2 U/g max Bla g 1 or 2 in living room dust*)	109 (21.8)	78 (19.1)	44 (16.6)
Endotoxin (≥ *median of measured samples = 81.3 EU/mg, in living room dust*)	202 (40.5)	162 (39.7)	111 (41.9)
Dust mite allergen (*≥10μg/g Der p or f 1 baby's bed*)	46 (9.2)	40 (9.8)	28 (10.6)
Cat allergen (*≥8μg/g Fel d 1 home max*)	130 (26.1)	109 (26.7)	76 (28.7)
Detectable mouse urinary protein (*living room dust*)	139 (27.9)	114 (27.9)	73 (27.6)

	All children	Subset with indoor air and dust fungal measures and assessment of:	
		Asthma/wheeze	Mold sensitization
	(N=499)	(N=408)	(N=265)
	n (%)	n (%)	n (%)
First year of life factors			
Daycare attendance	240 (48.1)	199 (48.8)	130 (49.1)
Bottle fed	139 (27.9)	111 (27.2)	64 (24.2)
Lower respiratory illness	133 (26.7)	108 (26.5)	72 (27.2)
Pet dog ownership	82 (16.4)	63 (15.4)	43 (16.2)

Table 2

Distributions of fungal exposures (Statistics calculated for all measured samples, including values below the limit of detection)

Fungi	# samples	# detectable	25th percentile (log_e*)	median	75th percentile (log_e*)	IQR (log_e-transformed*)
Alternaria						
outdoor air - CFU/m^3	384	139	0.0 (0.0)	0.0	11.1 (2.5)	2.5
indoor air - CFU/m^3	494	124	0.0 (0.0)	0.0	11.1 (2.5)	2.5
bedroom floor dust - CFU/g	412	236	0.0 (0.0)	454.5	3846.2 (8.3)	8.3
Cladosporium						
outdoor air - CFU/m^3	384	344	33.3 (3.5)	161.1	466.7 (6.1)	2.6
indoor air - CFU/m^3	494	384	11.1 (2.5)	44.4	211.1 (5.4)	2.9
bedroom floor dust - CFU/g	412	322	434.8 (6.1)	3779.8	8485.7 (9.0)	2.9
Aspergillus						
outdoor air - CFU/m^3	384	131	0.0 (0.0)	0.0	11.1 (2.5)	2.5
indoor air - CFU/m^3	494	311	0.0 (0.0)	11.1	33.3 (3.5)	3.5
bedroom floor dust - CFU/g	412	374	1304.3 (7.2)	4791.3	14264.2 (9.6)	2.4
Penicillium						
outdoor air - CFU/m^3	384	287	0.0 (0.0)	22.2	66.7 (4.2)	4.2
indoor air - CFU/m^3	494	423	11.1 (2.5)	33.3	88.9 (4.5)	2.0
bedroom floor dust - CFU/g	412	368	1200.0 (7.1)	3846.2	9523.8 (9.2)	2.1
Yeasts						
outdoor air - CFU/m^3	384	120	0.0 (0.0)	0.0	11.1 (2.5)	2.5
indoor air - CFU/m^3	494	172	0.0 (0.0)	0.0	11.1 (2.5)	2.5
bedroom floor dust - CFU/g	412	367	2600.6 (7.9)	8496.2	25000.0 (10.1)	2.2
Nonsporulating						
outdoor air - CFU/m^3	384	353	22.2 (3.1)	77.8	266.7 (5.6)	2.5
indoor air - CFU/m^3	494	373	11.1 (2.5)	22.2	88.9 (4.5)	2.0
bedroom floor dust - CFU/g	412	380	2390.5 (7.8)	6451.6	19139.2 (9.9)	2.1
Total						
outdoor air - CFU/m^3	384	382	211.1 (5.4)	533.3	972.2 (6.9)	1.5
indoor air - CFU/m^3	494	492	100.0 (4.6)	300.0	588.9 (6.4)	1.8

Fungi	# samples	# detectable	25th percentile (log_e*)	median	75th percentile (log_e*)	IQR (log_e-transformed*)
bedroom floor dust - CFU/g	412	412	24791.3 (10.1)	71633.3	137416.7 (11.8)	1.7

Definition of abbreviations: IQR = interquartile range

*log_e-transformed = log_e (untransformed concentration + 1); addition of 1 CFU/m^3 or/g for values below the limit of detection

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Table 3

Associations between Early-Life Fungi and Dampness with Development of Asthma & Rhinitis, Repeated Measures of Wheeze by Age 13 and Sensitization by Age 12 (Analyses evaluate associations of home dampness and all listed fungal genera jointly)

	CURRENT ASTHMA** Cox Proportional Hazards Regression (n = 408)		**CURRENT RHINITIS**** Cox Proportional Hazards Regression (n = 406)		**ANY WHEEZE**† Generalized Estimating Equations (baseline n = 408; total obs. = 4809)		**MOLD SENSITIZATION**‡ Logistic Regression (n = 265)	
	HR*	**95% CI**	**HR***	**95% CI**	**OR***	**95% CI**	**OR***	**95% CI**
HOME DAMPNESS								
asked at early-life home visit	0.82	(0.54, 1.24)	1.11	(0.73, 1.68)	1.05	(0.77, 1.42)	1.66	(0.84, 3.28)
ALTERNARIA								
Indoor air (log_e CFU/m^3)	1.48	(0.97, 2.26)	1.07	(0.70, 1.65)	1.29	(0.95, 1.76)	1.03	(0.51, 2.07)
Dust - bedroom floor (log_e CFU/g)	1.17	(0.74, 1.84)	0.79	(0.51, 1.22)	0.96	(0.70, 1.32)	1.57	(0.75, 3.27)
CLADOSPORIUM								
Indoor air (log_e CFU/m^3)	0.97	(0.64, 1.45)	0.82	(0.54, 1.25)	0.94	(0.71, 1.26)	1.08	(0.56, 2.09)
Dust - bedroom floor (log_e CFU/g)	1.17	(0.97, 1.41)	0.91	(0.77, 1.08)	1.10	(0.97, 1.24)	1.11	(0.82, 1.51)
ASPERGILLUS								
Indoor air (log_e CFU/m^3)	1.19	(0.79, 1.78)	1.08	(0.72, 1.63)	1.20	(0.88, 1.63)	0.64	(0.34, 1.23)
Dust - bedroom floor (log_e CFU/g)	0.99	(0.83, 1.19)	**1.39**§	**(1.11, 1.74)**	1.05	(0.92, 1.20)	1.04	(0.79, 1.38)
PENICILLIUM								
Indoor air (log_e CFU/m^3)	0.90	(0.69, 1.17)	1.01	(0.76, 1.33)	0.95	(0.79, 1.14)	0.88	(0.58, 1.33)
Dust - bedroom floor (log_e CFU/g)	0.92	(0.80, 1.07)	1.04	(0.89, 1.21)	1.00	(0.90, 1.11)	1.08	(0.84, 1.39)
YEASTS								
Indoor air (log_e CFU/m^3)	1.13	(0.82, 1.56)	0.73	(0.51, 1.04)	1.24	(0.99, 1.56)	0.95	(0.54, 1.66)
Dust - bedroom floor (log_e CFU/g)	**0.86**§	**(0.75, 0.98)**	1.06	(0.92, 1.22)	**0.88**§	**(0.80, 0.96)**	0.82	(0.66, 1.01)
NONSPORULATING FUNGI								
Indoor air (log_e CFU/m^3)	0.90	(0.71, 1.15)	1.15	(0.90, 1.46)	0.95	(0.80, 1.12)	1.13	(0.78, 1.64)
Dust - bedroom floor (log_e CFU/g)	1.04	(0.86, 1.24)	1.05	(0.88, 1.25)	1.11	(0.97, 1.28)	1.04	(0.77, 1.41)

* Hazard or odds ratios for the presence of home dampness or an inter-quartile increase in the log-transformed fungal concentration.

[**] Models for asthma and rhinitis adjust for male gender (yes/no), African American ethnicity (yes/no), low total annual family income (<$30k), birth season (4 categories, ref: winter), Cesarean birth (yes/no), low birthweight quartile (yes/no), low-normal gestational age (≤38.5wks), bottle fed in bed/crib in first year of life (yes/no), lower respiratory illness in first year of life (yes/no), physician diagnosed parental history of asthma (yes/no), maternal smoking during pregnancy (yes/no), building type (1-family detached/1-family attached/2-family/≥ 3 apartments), and missing indicators for family income (3.2%) and parental asthma (1.2%).

[†] Model for wheeze also adjusts for age, age^2, gender, and their interactions, in addition to covariates in models for asthma and rhinitis.

[‡] Model for sensitization adjusts for birth season (4 categories, ref: winter), low-normal gestational age (≤38.5wks), maternal sensitivity to mold (*Alternaria*/*Aspergillus*) at birth (yes/no), lower respiratory illness in first year of life (yes/no), and building type (1-family detached/1-family attached/2-family/≥ 3 apartments).

NOTE: All associations are independent of, and not confounded by high early-life (2–3mths) cockroach allergen (≥2 U/g max Bla g 1 or 2 in living room dust), endotoxin (≥ median of measured samples = 81.3 EU/mg, in living room dust), dust mite allergen (≥10μg/g Der p or f 1 baby's bed), cat allergen (≥8μg/g Fel d 1 home max), detectable mouse urinary protein (living room dust), and daycare attendance or pet dog ownership in the first year of life.

Definition of abbreviations: HR = hazard ratio; OR = odds ratio; CI = confidence interval; obs. = observations.

[§] $p \leq 0.05$