



Associations between household airborne culturable fungi and allergies and airway illnesses in childhood in Shanghai, China

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Abstract

Associations of household airborne fungi with allergies in childhood were inconsistent in the epidemiologic studies. During 2013–2014, we conducted a case-control study (phase two), which was nested in a cross-sectional study (phase one) during 2011–2012 in Shanghai, China. We inspected indoor air quality of 454 residences for 5–10 years old children. We defined cases as those children who were reported illnesses in the questionnaire of phase one or phase two and defined controls as those children who were not reported illnesses in both phases. A total of 436 living rooms and 445 bedrooms had valid data of household airborne fungi, and their mean concentrations were 301 cfu/m³ and 310 cfu/m³, respectively. In the multiple logistic regression analyses with adjusting for potential confounders, most associations of 16 studied illnesses with airborne fungi concentration were not statistically significant. Taking children in the 1st quartile that was stratified according to airborne fungi concentration in the living room as reference, only children in the 3rd quartile were significantly associated with a higher odd of lifetime-ever ear infections (adjusted OR, 95% CI 3.05, 1.29–7.21), and children in the 4th quartile were significantly associated with a higher odd of lifetime-ever wheeze (2.72, 1.28–5.75); but children in the 3rd quartile (0.33, 0.17–0.68) and in the 4th quartile (0.47, 0.23–0.97) were significantly associated with a lower odd of rhinitis in the past 12 months prior to the home inspection. Our results indicate that exposures to indoor airborne fungi in low concentrations seemingly have no significant impacts on the risks of most allergic and airway illnesses in childhood. Since families with sick participants might pay more attention to improve indoor air quality, effects of “avoidance behavior” on associations between indoor pollutants and childhood health should be considered in the data analysis and design of the nested case-control study.

Keywords Airborne fungi · Asthma · Childhood · Case-control study · Residence · Threshold

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Introduction

Airborne fungi are ubiquitous in indoor (Cabral 2010). Several epidemiologic studies have investigated associations of indoor airborne fungi and risks of childhood airway diseases (Arshad et al. 2001; Downs et al. 2001; Fan et al. 2017; Halonen et al. 1997; Kanchongkittiphon et al. 2015). But findings in these studies were inconsistent. Some studies suggested that indoor airborne fungi could be associated with asthma, allergic rhinitis, and pneumonia in childhood (Arshad et al. 2001; Downs et al. 2001; Fan et al. 2017; Halonen et al. 1997). A review integrated 69 peer-reviewed articles that were published during 2000–2013 and concluded that household exposures to culturable *Penicillium* and total fungi were strongly associated with the exacerbations of asthmatic symptoms (Kanchongkittiphon et al. 2015). In China, a study performed in 12 homes of case children (children with asthma, pneumonia, or dry cough) and 12 homes of control

children (children without these diseases) indicated that the culturable fungi species were associated with respiratory illness in childhood (Liu et al. 2014). However, a case-control study for 198 cases (children with asthmatic symptoms) and 202 controls (children without these symptoms) in Sweden found that associations of concentration of airborne fungi and childhood allergies were not significant (Holme et al. 2010). A birth cohort study in the Netherlands even suggested that exposures to higher levels of bio-contaminants and dust mite in home were associated with a lower risk of asthma in childhood (Douwes et al. 2006). Another study also reported that home exposure to higher level of dust endotoxin during early lifetime was associated with lower concentration of exhaled nitric oxide (an indicator for airway inflammation) among children in 10 years old (Casas et al. 2013).

Meanwhile, prevalences of asthma, allergies, and airway diseases in childhood rapidly increased in the large cities of China in the past years (Asher et al. 2006; Huang et al. 2015; Zhang et al. 2013a; Zhao et al. 2010). In Shanghai, asthma prevalence in childhood has significantly increased in almost five-fold from 1990 to 2011 (Huang et al. 2015). We suspected that these increases in the prevalences could be substantially associated with changes in indoor environment among children in China (Zhang et al. 2013a, b). However, associations between exposures to indoor airborne fungi which were measured in household air samples and developments of asthma, allergies and airway diseases/symptoms in childhood were still poorly understood in China (Liu et al. 2014; Huang et al. 2015). During 2011–2014, we conducted a cross-sectional study and a nested case-control study (phase one and phase two of the China, Children, Homes, Health (CCHH) study) in Shanghai, China. As part of this CCHH study in Shanghai, we investigated associations between airborne fungi and childhood history of asthma, allergies, and airway illnesses in the present study. We suspected that exposures to higher concentrations of airborne fungi were associated with the increased risks of the studied diseases.

Methods

Study design and health information

From April 2011 to April 2012, we conducted the cross-sectional study in six districts of Shanghai and collected 16,948 valid questionnaires (response rate 84.7%) from parents of preschoolers. These questionnaires provided information regarding the child's health status, dwelling characteristics, and indoor environmental exposures, as well as parents' willingness to cooperate with on-site home inspection.

From March 2013 to December 2014, the case-control study was conducted. We contacted parents who agreed to cooperate with on-site inspection in the cross-sectional study

and conducted an on-site measurement of indoor air quality in 454 selected residences. The selected residences were matched with the following criteria (from last questionnaire investigation to home inspection): (1) home addresses of the families were not changed, (2) homes were not renovated for large area, and (3) families did not purchase large amount of new furniture. The inspection time was ranged from about 8:00 a.m. to about 8:00 p.m. Before the home inspection, an investigator introduced the inspected contents and inspection procedure to parents of children and then signed the informed consent together with parents to obtain their agreement. The case-control study contained household environmental inspection and questionnaire. The parents/guardians of children filled out the same questionnaire in regard to health information of children as in the cross-sectional study. Our previous papers provided additional information about phase one (Liu et al. 2013; Hu et al. 2014; Cai et al. 2016; Wang et al. 2016a) and phase two (Huang et al. 2016; Wang et al. 2016b) of the CCHH study in Shanghai.

The questionnaire and proposal for the CCHH study was approved by the ethical committee from the School of Public Health, Fudan University. The purpose and proposal of the study was informed to participants by written explanation. Both one inspector and one participant of the inspected families signed an informed consent form before on-site inspection.

In this study, we combined health information of children questionnaires in phase one and phase two. We considered that children had history of the studied diseases or symptoms if parent reported "yes" in questions for these diseases and symptoms in the phase one or phase two questionnaire and defined them as cases. Those children without history of the studied diseases and symptoms both in the phase one and phase two were defined as controls. The studied diseases and symptoms included doctor-diagnosed asthma (lifetime-ever) and wheeze (lifetime-ever and in past 12 months prior to the survey), doctor-diagnosed hay fever (lifetime-ever) and rhinitis (lifetime-ever and in past 12 months prior to the survey), parent-reported eczema (lifetime-ever and in past 12 months prior to the survey), and pneumonia (lifetime-ever). Questions with regard to these diseases were provided in Table 1.

Inspection of indoor airborne fungi

We used Microflow (AQUARIA Inc., Italy) to sample air at a height of about 1 m at the upper floor in the center of the child's bedroom and of living room. Family members kept their normal living habits during on-site inspection. The flow rate of this device was calibrated every month during home inspection. The air sampler was combined with a 60-mm-diameter nutrient agar plate and head with 219 conical holes of 1 mm. For each room, we sampled a total of 1000 L of air for 10 min at the speed of 100 L/min. Then samples were cultivated in 35 ± 1 °C thermostat for 48 h. Colony forming

Table 1 Questions and proportions of cases with respect to various diseases/symptoms

Disease	Question	Case, <i>N</i> (%)
Lifetime-ever		
Wheeze	Has your child ever had wheezing or whistling in the chest at any time in the past?	266 (58.6)
Croup	Has your child had croup (breathing difficulties with severe (dry) cough)?	103 (22.7)
Asthma	Has your child been diagnosed with asthma by a doctor?	261 (57.5)
Pneumonia	Has your child been diagnosed with pneumonia by a doctor?	209 (46.0)
Rhinitis	Has your child ever had a problem with sneezing or a runny or a blocked nose when he/she did not have a cold or flu?	360 (79.3)
Hay fever	Has your child been diagnosed with hay fever or allergic rhinitis by a doctor?	152 (33.5)
Ear infections	Has your child ever had ear infections?	92 (20.3)
Eczema	Has your child ever had an itchy rash (eczema), which was coming and going for at least 6 months?	175 (38.5)
Food allergy	Has the child had allergic irritations such as eczema, nettle-rash, diarrhea, and swollen lips or eyes caused by the listed foods at any time?	133 (29.3)
Dry cough	In the last 12 months before the CCHH (phase one) survey, has your child had a dry cough at night for more than 2 weeks, apart from a cough associated with a cold or chest infection?	181 (39.9)
Common cold (≥ 3 times)	In the past 12 months before the CCHH (phase one) survey, how many times has your child had a cold?	261 (57.5)
In the last year prior to the home inspection (current)		
Wheeze	Has your child had wheezing or whistling in the chest in the last 12 months?	126 (27.8)
Rhinitis	In the past 12 months, has your child had a problem with sneezing or a runny or a blocked nose when he/she did not have a cold or the flu?	188 (41.4)
Eczema	In the past 12 months, has your child had an itchy rash (eczema), which was coming and going for at least 6 months?	61 (13.4)
Dry cough	In the last 12 months, has your child had a dry cough at night for more than 2 weeks, apart from a cough associated with a cold or chest infection?	86 (18.9)
Common cold (≥ 3 times)	In the past 12 months, how many times has your child had a cold?	105 (23.1)

unit (cfu) of airborne fungi was counted by microscopic observation and magnifier. For each group of 10 nutrient agar plates, one of them was randomly selected as a blank.

Statistical analysis

We used two-sample Kolmogorov-Smirnov test to compare differences of airborne fungi concentration between cases and controls. Differences in case proportions among children in different quartiles of airborne fungi were assessed by Pearson's chi-square test. Bivariate and multiple logistic regression models were used to analyze the associations between airborne fungi concentration and the studied diseases. Two approaches were applied to reveal associations of indoor airborne fungi and the studied diseases: (1) we stratified participants according to four quartiles of fungi concentrations and took children in the first quartile as reference, to compare risks of the studied diseases among children in second, third, and fourth quartiles; and (2) we investigated the increased risks of diseases in the increments of the interquartile range (IQR) of airborne fungi concentration. Besides, according to prior literature (Kanchongkittiphon et al. 2015; Fann et al. 2011; Fan et al. 2017) and previous analyses (Liu et al. 2013; Hu et al. 2014; Cai et al. 2016; Wang et al. 2016a), we considered

eight factors as potential confounders. These factors included the child's sex, age, family history of atopy, family annual income, household environmental tobacco smoke (ETS), household dampness-related exposures, and the inspection season. The studied associations were indicated by odds ratio (OR), adjusted odds ratio (AOR), and their 95% confidence intervals (CI). Significances were set at *p* value < 0.05. All statistical analyses were performed by SPSS 19.0 (SPSS Ltd., USA).

Results

Table 2 shows basic demographic data for the inspected children. Numbers of inspected boys and girls were similar. A total of 37.2% participants had family history of atopy. More than half (58.2%) of the children were from urban district, and 76.1% of the inspected children from families who owned the inspected residence. More than half (52.9%) of the children had household ETS exposure, and 83.8% of the inspected children had dampness-related exposures. Numbers of the inspected homes in different seasons had slight differences.

Table 2 Demographic data for the inspected children ($N = 454$)

Items	Sample size, n (%)
Sex	
Boys	234 (51.2)
Girls	220 (48.8)
Age (years old)	
5–6	174 (38.3)
7–10	280 (61.7)
Family history of atopy	
Yes	169 (37.8)
No	278 (62.2)
Family annual income (thousands CNY)	
≤ 200	254 (63.2)
> 200	148 (36.8)
Household environmental tobacco smoke (ETS)	
Yes	235 (52.9)
No	209 (47.1)
Early home dampness-related exposures	
Yes	79 (19.3)
No	331 (80.7)
Current home dampness-related exposures	
Yes	348 (76.8)
No	105 (23.2)
Early antibiotics exposure	
Yes	144 (32.7)
No	297 (67.3)
Early home decoration	
Yes	192 (46.4)
No	222 (53.6)
Inspected season	
Spring	130 (28.6)
Summer	127 (28.0)
Autumn	104 (22.9)
Winter	93 (20.5)

Among 454 participants, 445 children's bedrooms and 436 living rooms were successfully sampled and had concentration data for airborne fungi. The averaged airborne fungi concentrations were 310 cfu/m³ with IQR of 191 cfu/m³ in bedroom and 301 cfu/m³ with IQR of 192 cfu/m³ in living room, respectively (Table 3).

Proportions of cases according to various diseases are presented in Table 1. A total of 35.0%, 23.6%, and 41.4% participants had history of doctor-diagnosed asthma, allergic rhinitis, and pneumonia in lifetime-ever, respectively. A total of 23.8% participants had parent-reported eczema in lifetime-ever. High proportions of the inspected children had wheeze (48.5%) and rhinitis (65.9%) during lifetime-ever. Meanwhile, in the last year before case-control study, a total

of 22.2%, 43.0%, and 13.4% of these children was reported as wheeze, rhinitis, and eczema by parents or guardians.

Table 4 shows comparisons for concentrations of airborne fungi among cases and controls. In the two-sample Kolmogorov-Smirnov test (two-tailed), most differences were not significant in concentrations of airborne fungi between cases and controls. Only case residences for wheeze lifetime-ever had slightly higher concentration in the living room than control residences, and case residences for current rhinitis had significantly lower concentration in the living room than control residences.

Table 5 shows associations of odds of the studied diseases with increment of interquartile range (IQR) for airborne fungi concentration. Most associations were not significant. Only increment of interquartile range for airborne fungi concentration in the living room had significant associations with the decreased odds of food allergy in lifetime-ever (adjusted OR, 95% CI 0.65, 0.45–0.95) and current rhinitis (0.59, 0.42–0.84).

Figures 1 and 2 show associations of different quartiles of airborne fungi concentration with the studied diseases in bedroom and in living room. For bedroom (Fig. 1), all associations between airborne fungi concentration and the studied diseases were not significant. With regard to the living room (Fig. 2), most associations were not statistically significant. Compared with 1st quartile children, 3rd quartile children had significantly higher odd of being reported ear infections (adjusted OR, 95% CI 3.05, 1.29–7.21) during lifetime-ever, and 4th quartile children had significantly higher odd of being reported wheeze during lifetime-ever (2.72, 1.28–5.75); but children in the 3rd quartile (0.33, 0.17–0.68) and in the 4th quartile (0.47, 0.23–0.97) had significantly lower odd of being reported rhinitis after adjusting the potential confounders.

Discussion

In this study, we investigated effects of household airborne fungi concentration on childhood illnesses including asthma, wheeze, hay fever, rhinitis, eczema, pneumonia, and their related symptoms. No significant differences were found on the concentration of airborne fungi among cases and controls except for current rhinitis (lower in case residences). In the logistic regression analyses, most associations were not significant between airborne fungi and the studied illnesses. Only few significant associations existed for airborne fungi in living room.

Our findings are consistent with several previous studies (Holme et al. 2010; Ceylan et al. 2006; Dales et al. 2010; Garrett et al. 1998; Jovanovic et al. 2004). A study compared household environment among 127 asthmatic patients and among 127 healthy controls and reported that no significant differences were found in the means of mold colony counts between patients and controls (Ceylan et al. 2006). During November 1999–March 2000, a study investigated household

Table 3 Mean concentration of airborne fungi in the child's bedroom and in the living room

Inspected room	N (%)	Mean $\pm$ SD (cfu/m ³)	Min (cfu/m ³)	Percentile (cfu/m ³)			Max (cfu/m ³)	IQR (cfu/m ³)
				25%	50%	75%		
Child's bedroom	445 (98.0)	310 $\pm$ 313	6	152	234	343	3184	191
Living room	436 (96.0)	301 $\pm$ 288	19	147	234	339	3044	192

SD standard deviation, IQR interquartile range

levels of airborne fungi for school children in Germany and also did not find significant differences in concentrations and distributions of fungi species between children with and without history of allergic diseases (Jovanovic et al. 2004). A similar study in Sweden inspected 198 children with asthmatic or allergic symptoms (cases) and 202 healthy controls and also reported no significant associations between concentrations of airborne fungi and asthma/allergy in childhood (Holme et al. 2010). Besides, an early study with 148 children 7–14 years old in Australia reported that associations were not significant between the averaged viable and total spore concentrations of airborne fungi and child health (Garrett et al. 1998). A study from the Prince Edward Island of Canada measured the fungal indicators in 357 homes of children and reported that the fungal burden was generally not excessive among these children and was not a risk factor for acute respiratory illness episodes (Dales et al. 2010).

However, several previous studies provided supporting evidences on the findings of association between indoor mold or fungi and childhood allergies (Kanchongkittiphon et al. 2015; Liu et al. 2014; Chen et al. 2014; Douwes et al. 1999; Muller et al. 2002; Nambu et al. 2009). A cross-sectional survey was conducted in 44 schools across Taiwan for 6–15 years old schoolchildren and found that the *Aspergillus* or *Penicillium* and spores of airborne fungi were significantly associated with the prevalence of current asthma and asthmatic symptoms (Chen et al. 2014). An early study evaluated the measurement by enzyme immunoassay of extracellular polysaccharides of *Aspergillus* in 31 homes of children and reported that *Penicillium* species in dust (as a marker for fungal exposure) of the living room had significant associations with childhood respiratory symptoms (Douwes et al. 1999). A prospective cohort study with 475 premature and atopic risk newborns found significant associations between respiratory tract

Table 4 Comparison for airborne fungi concentration among cases and controls

Illness	Mean concentration, cfu/m ³					
	Child's bedroom		p value ^a	Living room		p value ^a
	Cases	Controls		Cases	Controls	
Lifetime-ever						
Wheeze	326	287	0.061	308	290	0.954
Croup	301	313	0.346	292	303	0.346
Asthma	324	292	0.370	303	297	0.985
Pneumonia	328	296	0.134	296	304	0.489
Rhinitis	308	318	0.120	302	293	0.997
Hay fever	292	320	0.150	271	316	0.056
Ear infections	289	316	0.101	293	302	0.193
Eczema	322	303	0.166	285	310	0.089
Food allergy	319	307	0.903	297	302	0.508
Dry cough	323	302	0.344	287	310	0.263
Common cold (≥ 3 times)	290	339	0.205	287	319	0.456
In the last year prior to the home inspection (current)						
Wheeze	293	317	0.834	286	306	0.374
Rhinitis	287	310	0.867	277	334	0.001
Eczema	300	312	0.603	257	308	0.066
Dry cough	285	316	0.326	284	304	0.852
Common cold (≥ 3 times)	295	315	0.580	283	306	0.960

^a The two-sample Kolmogorov-Smirnov test (two-tailed) for the concentration differences

Table 5 Associations between airborne fungi and the studied illnesses

Illness	OR, 95% CI (<i>p</i> value)			
	Child's bedroom (increment, 191 cfu/m ³)		Living room (increment, 192 cfu/m ³)	
	Crude	Adjusted	Crude	Adjusted
Lifetime-ever				
Wheeze	1.27, 0.99–1.64 (0.060)	1.32, 0.96–1.82 (0.089)	1.14, 0.87–1.48 (0.345)	1.22, 0.87–1.70 (0.255)
Croup	1.08, 0.81–1.44 (0.616)	1.02, 0.70–1.50 (0.902)	1.07, 0.79–1.44 (0.685)	1.27, 0.86–1.86 (0.231)
Asthma	1.21, 0.94–1.55 (0.136)	1.26, 0.92–1.73 (0.152)	0.99, 0.76–1.28 (0.927)	1.04, 0.74–1.44 (0.836)
Pneumonia	1.08, 0.84–1.38 (0.553)	1.01, 0.74–1.38 (0.947)	0.95, 0.73–1.23 (0.695)	0.98, 0.71–1.36 (0.908)
Rhinitis	1.21, 0.89–1.64 (0.227)	1.14, 0.77–1.67 (0.513)	0.96, 0.70–1.33 (0.818)	0.91, 0.61–1.35 (0.631)
Hay fever	1.02, 0.79–1.32 (0.865)	0.89, 0.63–1.27 (0.529)	0.89, 0.67–1.17 (0.393)	0.90, 0.62–1.30 (0.565)
Ear infections	1.18, 0.88–1.59 (0.274)	1.29, 0.90–1.86 (0.168)	1.06, 0.77–1.46 (0.725)	1.02, 0.69–1.50 (0.937)
Eczema	1.07, 0.82–1.36 (0.671)	0.91, 0.66–1.27 (0.583)	1.08, 0.83–1.40 (0.570)	0.92, 0.65–1.29 (0.614)
Food allergy	1.18, 0.91–1.54 (0.214)	1.22, 0.86–1.71 (0.265)	0.85, 0.64–1.13 (0.271)	<i>0.65, 0.45–0.95 (0.026)</i>
Dry cough	1.04, 0.81–1.33 (0.780)	0.92, 0.68–1.25 (0.610)	0.98, 0.76–1.28 (0.896)	0.84, 0.63–1.21 (0.412)
Common cold (≥ 3 times)	<i>0.75, 0.59–0.96 (0.024)</i>	0.81, 0.59–1.11 (0.182)	0.81, 0.63–1.05 (0.114)	0.89, 0.63–1.24 (0.472)
In the last year prior to the home inspection (current)				
Wheeze	0.88, 0.67–1.15 (0.340)	0.88, 0.62–1.25 (0.477)	0.96, 0.72–1.28 (0.761)	1.01, 0.70–1.45 (0.956)
Rhinitis	1.00, 0.78–1.28 (0.992)	0.91, 0.66–1.24 (0.533)	<i>0.70, 0.53–0.91 (0.008)</i>	<i>0.59, 0.42–0.84 (0.003)</i>
Eczema	1.09, 0.77–1.55 (0.626)	1.19, 0.77–1.84 (0.427)	0.81, 0.55–1.17 (0.277)	0.88, 0.55–1.41 (0.596)
Dry cough	0.88, 0.64–1.20 (0.420)	0.89, 0.61–1.31 (0.562)	0.80, 0.57–1.12 (0.188)	0.76, 0.50–1.14 (0.183)
Common cold (≥ 3 times)	0.90, 0.67–1.21 (0.483)	0.99, 0.69–1.40 (0.931)	0.87, 0.64–1.18 (0.365)	0.94, 0.65–1.36 (0.733)

Italics indicates statistical significance (*p*-value <0.05)

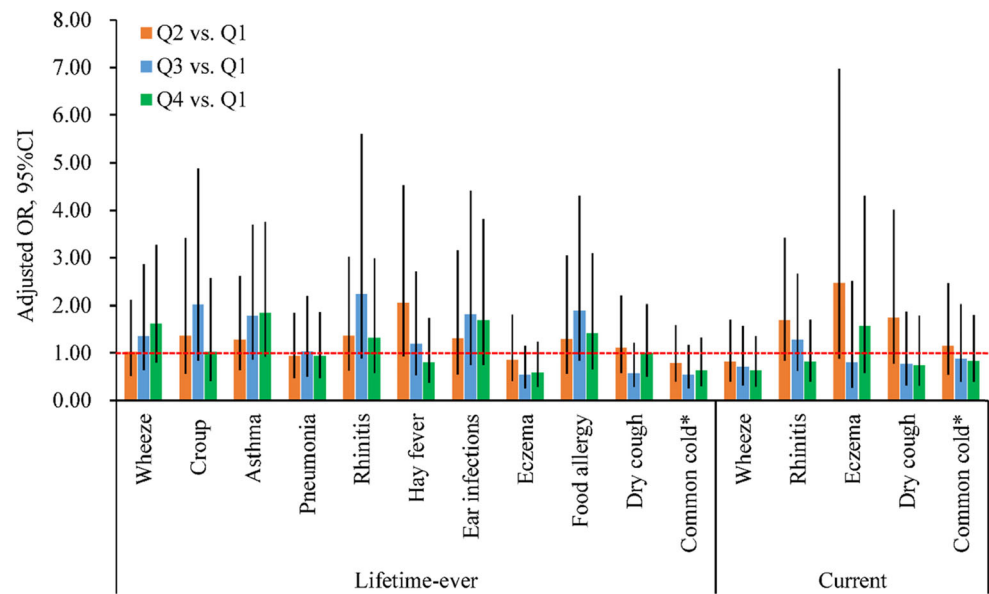
infections and exposures to *Penicillium* spores as well as between rhinitis and its related symptoms and *Aspergillus* exposures (Muller et al. 2002). A study from Japan reported that children with household *Alternaria* exposure had higher levels of alternaria IgE than children without household *Alternaria* exposure (Nambu et al. 2009).

Furthermore, several studies even found inverse associations of exposure to household mold or fungi in early life with children's respiratory diseases (Casas et al. 2013; Celedon et al. 2007; Douwes et al. 1999, 2002, 2006; Douwes 2005). Ege et al. conducted two cross-sectional studies for children living in farms and reported inverse associations of odds of asthma and atopy with diversity of microbial exposures (Ege et al. 2011). A study with on-site inspection and questionnaire on 812 parents of school-age children from Germany, Australia, and Switzerland found that dust endotoxin levels in the child's mattress were inversely associated with hay fever, atopic asthma, and atopic sensitization (Braun-Fahrlander et al. 2002). A series of studies in regard to early indoor microbial exposure with childhood respiratory symptoms also reported that exposure to bacterial endotoxin in the early lifetime was associated with the decreased risk of asthma, airway inflammation and symptoms, and respiratory symptoms including chronic wheeze, chronic cough, attacks of shortness of breath with wheezing, and doctor-diagnosed bronchitis in childhood (Douwes et al. 1999, 2002, 2005, 2006).

In summary, it is still very limited and inconsistent in understanding of exposure or causal agents of indoor airborne fungi in relation to childhood health disorders. In general, our findings in the present study indicate that current exposures to indoor airborne fungi have no consistent and substantial effects on history of allergies and airway illnesses in childhood. The primary possible reason for these differences in associations from various studies might be that different studies had different methodologies for sampling and analysis of airborne mold spore (Holme et al. 2010). There is no standard method to collect the air samples; therefore, findings from the similar studies on associations between indoor airborne fungal and health outcomes could not be consistently compared (Nevalainen et al. 2015).

Besides, our findings, that most associations were not statistically significant, perhaps had something to do with that overall averaged concentrations of indoor airborne fungi in the present study that are relatively low (Wang et al. 2016b), with consideration of the upper limited value (2500 cfu/m³) of indoor airborne bacterial concentration in the national standard of China for indoor air quality (GAQS 2002). In a previous study, Zhang and colleagues systematically reviewed literature for on-site inspected concentrations of airborne bacteria and fungi and suggested that concentrations of indoor airborne bacteria and fungi should be lower than 1200 cfu/m³ and 700 cfu/m³ (Zhang et al. 2016). The overall averaged concentrations of indoor airborne

Fig. 1 Associations of airborne fungi in the child's bedroom with the studied illnesses. Herein, “current” means “In the last year prior to the home inspection”. Data for different quartiles (Q1 1st quartile, min–25%; Q2 2nd quartile, 25%–50%; Q3 3rd quartile, 50%–75%; Q4 4th quartile, 75%–max) are presented in Table 3. * ≥ 3 times. The detailed ORs and their 95% CIs are presented in the supplemental Table S1



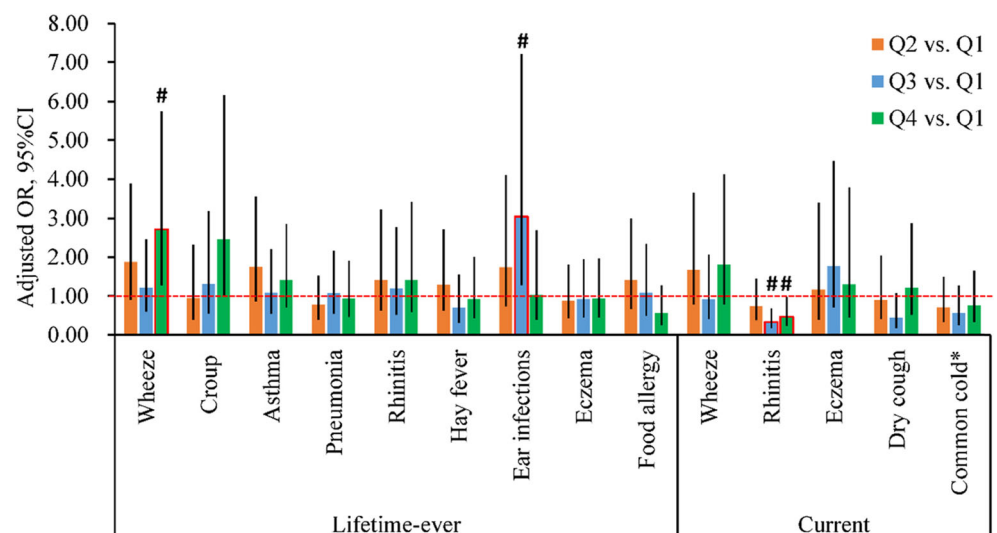
fungi in the living room and bedroom in the present study also were notably lower than the suggested concentrations (Zhang et al. 2016). Besides, we only measured the total quantitative concentration of indoor airborne fungi, but did not identify the specific species of fungi. This may also be one reason why we did not obtain significant associations.

Unexpectedly, we found that exposures to higher level of airborne fungi in the living room were associated with lower odds of food allergy in lifetime-ever and current rhinitis. Generally, exposures to higher level of airborne fungi unlikely decreased risks of these illnesses. A possible explanation could be that those families with sick participants might pay more attention to improve indoor air quality (Wang et al. 2016b). When children were diagnosed with the studied diseases, their parents could be advised to improve indoor air quality by doctors (Huang et al. 2016). Therefore, indoor

airborne fungi level of sick children could be lower than that of healthy children, and negative associations were found between airborne fungi exposure and the studied illnesses. The similar findings for pet-keeping, fast-food consumption, and home cleaning frequency could support this explanation (Bornehag et al. 2003; Huang et al. 2019; Huang et al. 2013; Liu et al. 2015, 2020; Naydenov et al. 2008; Wang et al. 2016a). These findings are warranted to verify by more studies with high-concise measurement and good design.

This study had limitations. First, indoor airborne fungus was sampled once and sampled for 10 min during home inspection. These data may have low validity in representing the long-term levels of indoor pollutants for those inspected residences. Besides, the air flow rate (100 L per minute) for our sampling was higher than the widely used rate, certain sensitive fungi could be inactivated by desiccation stress, and thus fungi

Fig. 2 Associations of airborne fungi in the living room with the studied illnesses. Herein, “current” means “In the last year prior to the home inspection”. Data for different quartiles (Q1 1st quartile, min–25%; Q2 2nd quartile, 25%–50%; Q3 3rd quartile, 50%–75%; Q4 4th quartile, 75%–max) are presented in Table 3. * ≥ 3 times. Red frame and “#” indicate that adjusted odds ratio has statistical significance (p value < 0.05). The detailed ORs and their 95% CIs are presented in the supplemental Table S2



concentrations may be lower than actual concentrations (Zhen et al. 2009). Second, the cultivation-based method has several limitations including lack of reproducibility, selection effect, and underestimation of total number of fungi propagules (Holme et al. 2010). Most fungal species which could not be cultured might also contain allergens to children (Nevalainen et al. 2015). And we only measured the total quantitative concentration of fungi, but did not identify their specific species. Third, data regarding allergic symptoms in children were from parents' questionnaire. Reported errors and bias might exist.

Nevertheless, to our best knowledge, the present study is the first study in China on home environment and airborne fungi using on-site inspection in such large sample sizes. Second, family members were asked to keep their lifestyle behaviors as normal during home inspection. This arrangement could reduce deviation between measured data and real status. Third, our methods for on-site inspection were derived from similar studies in Sweden (Bornehag et al. 2005; Clausen et al. 2012; Hargreaves et al. 2003) and Denmark (Bekö et al. 2011). Our results could be compared with the findings from these studies. Fourth, although the cultivation-based method has limitations, this method still is used widely and could provide a series of benefit conclusions in regard to concentration of airborne fungi and its related factors (Oh et al. 2014; Rajasekar and Balasubramanian 2011; Zhu et al. 2015).

Conclusions

The averaged concentrations of indoor airborne fungi in the present study are lower than the upper limited value (2500 cfu/m³ for indoor airborne bacteria) in the national standard for indoor air quality in China. Exposures to indoor airborne fungi in low concentrations seemingly have no substantial effects on the risks of most allergic and airway illnesses. "Avoidance behavior" in indoor pollutants among families with sick children should be considered in the data analysis and design of the nested case-control study.

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Compliance with ethical standards

The questionnaire and proposal for the CCHH study was approved by the ethical committee from the School of Public Health, Fudan University.

Competing interests The authors declare that they have no conflict of interest.

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Supplemental materials for

Associations between Household Airborne Culturable Fungi and Allergies and Airway Illnesses in Childhood in Shanghai, China

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Content

Table S1. Associations of airborne fungi in the child's bedroom with the studied illnesses.

Table S2. Associations of airborne fungi in the living bedroom with the studied illnesses.

Table S1. Associations of airborne fungi in the child's bedroom with the studied illnesses.

Illness	OR, 95%CI (p-value)					
	Q2 ^a (Reference: Q1)		Q3 ^a (Reference: Q1)		Q4 ^a (Reference: Q1)	
	Crude	Adjusted ^b	Crude	Adjusted ^b	Crude	Adjusted ^b
<i>Lifetime-ever</i>						
Wheeze	0.90, 0.53-1.52 (0.687)	1.03, 0.51-2.11 (0.929)	0.88, 0.52-1.49 (0.631)	1.35, 0.64-2.86 (0.427)	1.34, 0.78-2.29 (0.291)	1.62, 0.80-3.27 (0.182)
Croup	1.14, 0.61-2.15 (0.683)	1.37, 0.56-3.41 (0.492)	1.37, 0.74-2.55 (0.315)	2.02, 0.84-4.88 (0.119)	0.90, 0.47-1.74 (0.764)	1.03, 0.41-2.57 (0.954)
Asthma	1.23, 0.73-2.08 (0.438)	1.29, 0.64-2.61 (0.477)	1.45, 0.86-2.47 (0.165)	1.78, 0.86-3.70 (0.120)	1.45, 0.86-2.47 (0.165)	1.85, 0.92-3.75 (0.086)
Pneumonia	1.16, 0.69-1.97 (0.574)	0.94, 0.47-1.85 (0.847)	1.02, 0.61-1.73 (0.930)	1.04, 0.50-2.19 (0.909)	1.14, 0.68-1.93 (0.618)	0.94, 0.47-1.86 (0.852)
Rhinitis	0.97, 0.52-1.79 (0.919)	1.37, 0.63-3.02 (0.428)	1.55, 0.80-3.01 (0.195)	2.23, 0.89-5.60 (0.087)	1.29, 0.68-2.44 (0.443)	1.32, 0.58-2.98 (0.507)
Hay fever	1.19, 0.69-2.06 (0.535)	2.05, 0.93-4.52 (0.076)	0.96, 0.55-1.67 (0.880)	1.20, 0.53-2.71 (0.658)	1.04, 0.60-1.81 (0.889)	0.80, 0.37-1.74 (0.574)
Ear infections	1.08, 0.55-2.11 (0.823)	1.31, 0.55-3.15 (0.542)	1.20, 0.62-2.31 (0.595)	1.82, 0.75-4.41 (0.186)	1.47, 0.78-2.80 (0.238)	1.69, 0.74-3.82 (0.211)
Eczema	0.99, 0.58-1.69 (0.982)	0.86, 0.41-1.81 (0.697)	0.69, 0.40-1.18 (0.175)	0.54, 0.25-1.15 (0.110)	1.10, 0.65-1.86 (0.736)	0.59, 0.28-1.24 (0.165)
Food allergy	1.19, 0.66-2.15 (0.560)	1.30, 0.56-3.05 (0.545)	1.46, 0.82-2.60 (0.201)	1.90, 0.84-4.31 (0.123)	1.46, 0.82-2.60 (0.201)	1.42, 0.65-3.09 (0.379)
<i>In the last year prior to the home inspection (current)</i>						
Wheeze	0.93, 0.53-1.63 (0.801)	0.82, 0.40-1.70 (0.822)	0.67, 0.37-1.20 (0.174)	0.71, 0.32-1.57 (0.395)	0.67, 0.37-1.20 (0.174)	0.63, 0.29-1.35 (0.235)
Rhinitis	1.39, 0.82-2.36 (0.226)	1.69, 0.84-3.42 (1.693)	1.13, 0.67-1.93 (0.643)	1.29, 0.62-2.66 (0.501)	0.94, 0.55-1.61 (0.814)	0.82, 0.40-1.70 (0.596)

Eczema	2.00, 0.95-4.21 (0.067)	2.47, 0.88-6.97 (0.087)	0.71, 0.29-1.73 (0.445)	0.80, 0.26-2.51 (0.704)	1.45, 0.67-3.14 (0.349)	1.57, 0.58-4.30 (0.376)
Dry cough	1.34, 0.71-2.54 (0.372)	1.75, 0.77-4.01 (0.183)	1.01, 0.52-1.96 (0.981)	0.77, 0.32-1.87 (0.567)	0.73, 0.36-1.47 (0.376)	0.74, 0.31-1.79 (0.506)
Common cold (≥3 times)	1.44, 0.79-2.62 (0.235)	1.15, 0.54-2.46 (0.714)	0.87, 0.46-1.64 (0.658)	0.88, 0.39-2.02 (0.768)	0.97, 0.52-1.81 (0.914)	0.84, 0.39-1.80 (0.651)

^a Data for different quartiles (Q1: 1st quartile, min~25th percentile; Q2: 2nd quartile, 25th~50th percentile; Q3: 3rd quartile, 50th~75th percentile; Q4: 4th quartile, 75th percentile ~max) were presented in Table 3. OR, odds ratio; AOR, Adjusted odds ratio. ^b Adjusted for sex, age, family history of atopy, family annual income, household environmental tobacco smoke (ETS), household dampness-related exposures, early antibiotics exposure, early home decoration, and the inspected season.

Table S2. Associations of airborne fungi in the living bedroom with the studied illnesses.

Illness	OR, 95%CI (p-value)					
	Q2 ^a (Reference: Q1)		Q3 ^a (Reference: Q1)		Q4 ^a (Reference: Q1)	
	Crude	Adjusted ^b	Crude	Adjusted ^b	Crude	Adjusted ^b
<i>Lifetime-ever</i>						
Wheeze	1.30, 0.76-2.21 (0.341)	1.88, 0.91-3.89 (0.087)	0.98, 0.58-1.67 (0.950)	1.22, 0.60-2.46 (0.584)	1.86, 1.07-3.23 (0.028)	2.72, 1.28-5.75 (0.009)
Croup	1.11, 0.59-2.11 (0.744)	0.95, 0.39-2.32 (0.908)	0.96, 0.50-1.84 (0.894)	1.32, 0.55-3.17 (0.536)	1.47, 0.79-2.75 (0.223)	2.46, 0.98-6.17 (0.056)
Asthma	1.26, 0.73-2.16 (0.409)	1.76, 0.87-3.55 (0.114)	0.76, 0.45-1.29 (0.312)	1.09, 0.54-2.21 (0.813)	1.20, 0.70-2.07 (0.509)	1.42, 0.70-2.86 (0.332)
Pneumonia	0.90, 0.53-1.52 (0.685)	0.78, 0.40-1.52 (0.474)	0.88, 0.52-1.49 (0.632)	1.08, 0.54-2.17 (0.822)	0.98, 0.58-1.67 (0.939)	0.94, 0.46-1.91 (0.857)
Rhinitis	1.48, 0.77-2.87 (0.244)	1.42, 0.63-3.22 (0.397)	1.10, 0.58-2.06 (0.776)	1.20, 0.52-2.77 (0.671)	1.43, 0.74-2.78 (0.287)	1.42, 0.59-3.42 (0.430)
Hay fever	0.85, 0.49-1.48 (0.575)	1.29, 0.62-2.71 (0.497)	0.53, 0.30-0.95 (0.034)	0.70, 0.31-1.55 (0.375)	0.93, 0.54-1.61 (0.792)	0.93, 0.43-2.01 (0.860)
Ear infections	1.28, 0.64-2.54 (0.485)	1.74, 0.74-4.10 (0.204)	1.52, 0.78-2.99 (0.223)	3.05, 1.29-7.21 (0.011)	1.32, 0.66-2.64 (0.426)	1.03, 0.39-2.69 (0.954)
Eczema	0.65, 0.37-1.13 (0.125)	0.89, 0.43-1.81 (0.741)	0.84, 0.49-1.44 (0.525)	0.93, 0.45-1.94 (0.848)	1.13, 0.66-1.94 (0.651)	0.94, 0.45-1.97 (0.871)
Food allergy	0.81, 0.46-1.43 (0.471)	1.42, 0.67-3.00 (0.363)	0.72, 0.41-1.28 (0.262)	1.09, 0.50-2.35 (0.833)	0.67, 0.38-1.20 (0.181)	0.56, 0.25-1.28 (0.168)
<i>In the last year prior to the home inspection (current)</i>						
Wheeze	1.00, 0.56-1.79 (1.000)	1.68, 0.78-3.64 (0.185)	0.62, 0.33-1.15 (0.128)	0.92, 0.41-2.06 (0.845)	1.14, 0.64-2.03 (0.667)	1.81, 0.79-4.13 (0.158)
Rhinitis	0.90, 0.53-1.52 (0.686)	0.75, 0.38-1.45 (0.388)	0.43, 0.25-0.75 (0.003)	0.33, 0.17-0.68 (0.002)	0.70, 0.41-1.19 (0.188)	0.47, 0.23-0.97 (0.041)

Eczema	0.63, 0.29-1.37 (0.241)	1.17, 0.40-3.39 (0.775)	0.82, 0.39-1.72 (0.591)	1.77, 0.70-4.47 (0.225)	0.90, 0.43-1.87 (0.775)	1.31, 0.45-3.78 (0.624)
Dry cough	0.81, 0.43-1.53 (0.514)	0.91, 0.41-2.04 (0.820)	0.48, 0.23-0.97 (0.041)	0.44, 0.18-1.08 (0.072)	0.79, 0.41-1.51 (0.474)	1.22, 0.52-2.88 (0.652)
Common cold (≥3 times)	0.72, 0.39-1.32 (0.282)	0.71, 0.34-1.49 (0.363)	0.55, 0.29-1.04 (0.064)	0.57, 0.26-1.27 (0.172)	0.74, 0.41-1.37 (0.339)	0.76, 0.34-1.65 (0.482)

^a Data for different quartiles (Q1: 1st quartile, min~25th percentile; Q2: 2nd quartile, 25th~50th percentile; Q3: 3rd quartile, 50th~75th percentile; Q4: 4th quartile, 75th percentile ~max) were presented in Table 3. OR, odds ratio; AOR, Adjusted odds ratio. ^b Adjusted for sex, age, family history of atopy, family annual income, household environmental tobacco smoke (ETS), household dampness-related exposures, early antibiotics exposure, early home decoration, and the inspected season.