



Relationship between environmental Fungi and changes in lung function indices of new referral allergic patients in Ahvaz city under normal and dust conditions

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Abstract

Background Aim of this study was to determine whether any specific fungal spores could be responsible for changes observed in lung function indices.

Materials and methods 1042 new allergic patients were selected from July 2017 to May 2018 in Ahvaz City, Iran. Fungal samples were collected in normal and dusty condition within 5 and 2 min, respectively. Sampling was repeated once every 6 days and also in the dusty days.

Results Average numbers of fungi colony were 639.86 and 836.44 CFU m⁻³ under normal and dusty conditions, respectively. Most common fungi in Ahvaz City air were *Cladosporium sp.*, *Penicillium sp.*, *Aspergillus Niger*, *Aspergillus Flavus* and *Alternaria sp.*. Highest fungal mean concentrations, 392 and 480 CFU m⁻³, were related to *Cladosporium sp.* under normal and dust conditions, respectively. Average total numbers of colony fungal were 614, 483, 1082, 424 CFU m⁻³ and 856, 701, 1418, 418 CFU m⁻³ during the spring, summer, autumn, and winter under normal and dusty conditions, respectively. Patients were evaluated by measured lung function parameters of FEV₁ (L), FEV₁ (%pred), FVC (L), FVC (%pred), and FEV₁/FVC ratio with mean values of 1.85, 58.32, 2.63, 68.18, and 69.43, respectively.

Conclusion Increases in mean total spores of fungi in spring were accompanied by decreases in FEV₁/FVC ratio. Enhanced spores of *Cladosporium sp.* in spring led to reduced FEV₁/FVC ratio. Increase the spores of *Curvularia sp.* in summer decreased by FEF_{25–75%}. The augmented spores of *Drechslera sp.* in summer were associated with declined FEV₁ and FEV₁/FVC ratio. Enhanced fungal spores of *Rhizopus sp.* in spring resulted in lowered FEV₁, FEV₁/FVC ratio, and FEF_{25–75%}.

Keywords Weather · Ambient air pollution · Fungal spores · Respiratory function tests

Introduction

Allergic diseases, the prevalence of which has increased dramatically in recent years, are among chronic diseases. These

diseases significantly affect the quality of life and are considered as the main reasons for referring to health centers [1–3]. An allergy is an immediate deformed reaction to the re-entry of allergenic substances previously triggered by a person's

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immune system [4]. Allergens are defined as any substances capable of causing allergies and susceptibility [5]. Several allergic factors, including inhalant, oral, contact, drug substances, etc. have been already identified [6]. Inhalant allergens are more important than other allergens in allergic events [7, 8]. Airborne fungi and their respective spores are ubiquitous and they constitute the largest proportion of airborne biological particles [9]. Public health concerns regarding the effects of ambient fungal spores on respiratory health have increased since they are known as the possible sources of outdoor allergens since the diameters of most of them (2–10 μm) can make them readily penetrable into the airway through inhalation [10]. The observed effects of ambient fungal spores on respiratory morbidities include the developments of allergic respiratory diseases [11], exacerbations of respiratory symptoms [11, 12], increases in emergency department visits [13], hospitalization for respiratory diseases [14] and decrement of Peak Expiratory Flow Rate (PEFR) among children [15]. According to a study performed in Taiwan that evaluated the effects of ambient particulate matter and fungal spores on lung function in schoolchildren, exposure to fungal spores was associated with decreased vital capacity [16]. Due to air pollution trend in the region and the increasing prevalence of allergic diseases, the number of infected people is constantly increasing [17]. Significant complications and severe symptoms, heavy health costs, and considerable reductions of life quality resulting from these diseases have urged the identification of common allergens in each area to prevent and treat the diseases properly [18].

Air pollution has recently increased in the large industrial area of Ahvaz, Khuzestan Province, Iran, which has a warm and dry climate, due to dust storms; hence, allergic diseases have caused many problems for residents in the city. Since there are no accurate data on common allergens in Ahvaz to specify these allergens, we aim to provide comprehensive data for the preventions, diagnoses, and suitable treatments of the related diseases [19, 20]. Therefore, the current research was conducted to identify the common allergic fungi present in air in Ahvaz and their association with lung functions [21].

Study design

New patients' data and fungal sampling were collected and carried out simultaneously from July 2017 to May 2018 in Ahvaz. Spirometry was performed on all the new referral patients. Before spirometry, a questionnaire was completed for each patient. To perform fungal sampling according to the United States Environmental Protection Agency (USEPA), a sample was taken at 6-day intervals each month [22]. Air pollution was detected daily in addition to the polluted days according to the Hoffmann-Tinel test. When the dust was in the range of 500–2000 $\mu\text{g m}^{-1}$, a fungal sample was taken

from the air on the same day. To study the effective parameters on the concentrations of the spores and their effects on the individuals, three sampling stations were selected including Station 1 in the high-traffic region (Amanyeh), Station 2 in the green area (Ahvaz University of Medical Sciences), and Station 3 in the densely populated residential area (Golestan) (Fig. 1). Sampling was carried out once every six days from 16 to 19 (local time).

Study subjects

From the onset of the study, the patients referring to the private clinic and pulmonary clinic of Imam Khomeini Hospital were screened. This hospital is a referral hospital for all patients with respiratory diseases. The inclusion criteria in this research were as follows: being 18-year-olds and older with at least 5 years of inhabitation in Ahvaz and having no hereditary and familial histories of respiratory diseases, no histories of addiction and smoking, no direct contacts with job-related inhaling pollutants, no history of acute respiratory infections during the previous two weeks, and no usage of bronchodilators and FEV₁/FVC ratio of less than 80%. As a result, 1042 patients were selected.

Outcome measurements

Each patient was tested with a Spirometer while standing (Chestgraph Jr. HI-101, CHEST, Tokyo, Japan) according to the standardization of spirometry made by the American Thoracic Society (ATS) [23]. The values of Forced Vital Capacity (FVC), Forced Expiratory Volume in 1 s (FEV₁), and average expiratory flow over the middle half of FVC (FEF_{25–75%}), as well as the ratio of forced expiratory volume in 1 s over forced vital capacity (FEV₁/FVC), were recorded. According to the ATS standards, at least three acceptable tests were performed on each individual. The device was recalibrated for every three individuals by using a 1-l syringe.

Exposure assessment

During measurements of the patients' lung function indices, fungal sampling was performed every 6 days during normal and dusty days. Air samples for fungi took using a "QuickTake@30" pump. The airflow was 28.3 L min⁻¹. The spores of the fungi were placed in Petri dishes. After sampling, the Petri dishes were immediately transferred to the lab and kept at 25–27 °C for 72–96 h. Then, the colonies formed in the plates were counted and recorded based on sampling flow rates and sampling durations in terms of colony-forming unit (CFU) using the following formula: [24, 25].



Fig. 1 Three sampling points in Ahvaz

CFU m^{-3} was calculated as follows: (Number of colonies $\times$ 1000) / (sampling time $\times$ velocity of air flow).

The fungal samples were identified by an experienced aero-biologist.

Statistical analysis

*We used the *Kolmogorov–Smirnov (K-S)* statistic to optimize the goodness-of-fit of distribution, suggesting the lognormal distribution fitting the observed data.

**Mann-Whitney, ANOVA ONE-WAY, Kruskal-Wallis*, and an independent-sample T-test were utilized for comparing fungi concentrations during different months and seasons and at different locations under normal and dusty conditions.

The Poisson regression model serving as a conventional model in the counting data analysis was employed to determine the relationship between factors affecting the referrals' respiratory conditions and the

number of occurrence of a dust phenomenon. The Poisson regression model is an appropriate model for count response variable explained by explanatory variables. Furthermore, an important feature of the model is providing the equality of the average and variance of the response variable (the number of respiratory problems visit). A failure to this condition, representing inequality of mean and variance that leads to the use of an alternative model, the negative binomial regression model was more prefer.

*A mixed-effect regression model was applied to determine which species fungal spores were most closely related to lung function changes. The varieties of species fungal have existed and in our study, the subset of fungal was examined as a random effect in the model.

The information obtained from the filled questionnaires and the spirometry results were analyzed by using SPSS version 16. A p value of <0.05 was considered as significant level.

Table 1 The distributions of demographic characteristics and lung function of the study subjects

	Demographic characteristics of the study subjects		
	Female $n = 467$	Male $n = 575$	Total $n = 1042$
Age, year ^a	44.81 $\pm$ 15.04	47.37 $\pm$ 15.72	46.22 $\pm$ 15.47
Height, cm ^a	157.94 $\pm$ 7.09	169.89 $\pm$ 8.14	164.53 $\pm$ 9.71
Weight, kg ^a	71.16 $\pm$ 14.19	79.53 $\pm$ 17.28	75.78 $\pm$ 16.49
BMI, kg/m ^{2a}	28.61 $\pm$ 5.90	27.45 $\pm$ 5.23	27.97 $\pm$ 5.57
Lung function ^a			
FEV1, L	1.58 $\pm$ 0.56	2.08 $\pm$ 0.80	1.85 $\pm$ 0.74
FEV1, % of predicted value	58.38 $\pm$ 17.12	58.26 $\pm$ 17.44	58.32 $\pm$ 17.29
FVC, L	2.16 $\pm$ 0.69	3.01 $\pm$ 0.98	2.63 $\pm$ 0.96
FVC, % of predicted value	67.24 $\pm$ 17.34	68.95 $\pm$ 16.96	68.18 $\pm$ 17.15
FEV1/FVC, %	72.18 $\pm$ 9.14	67.19 $\pm$ 10.57	69.43 $\pm$ 10.26
FEF _{(25–75)%} , L/s	41.79 $\pm$ 16.42	41.47 $\pm$ 20.46	41.63 $\pm$ 18.75

^a Values are given as mean $\pm$ standard deviation; Lung function variables given as mean $\pm$ standard deviation

Table 2 Concentration of airborne fungi (CFU m⁻³), measured during normal and dusty event days in Ahvaz

airborne fungi	Time sample	Mean	Std. Dev	P Value
<i>Cladosporium sp.</i>	Normal	392.40	593.22	0.37
	Dusty	480.79	553.03	
<i>Alternaria sp.</i>	Normal	23.34	38.55	0.03
	Dusty	25.19	27.27	
<i>Aspergillus sp.</i>	Normal	10.25	23.51	0.19
	Dusty	9.65	50.49	
<i>Penicillium sp.</i>	Normal	69.91	80.86	0.00
	Dusty	31.41	37.92	
<i>Fusarium sp.</i>	Normal	5.67	12.83	0.41
	Dusty	4.09	10.11	
<i>Curvularia sp.</i>	Normal	1.53	8.98	0.53
	Dusty	0.65	4.37	
<i>Ostilago sp.</i>	Normal	4.69	19.98	0.00
	Dusty	18.98	43.38	
<i>Drechslera sp.</i>	Normal	3.71	12.64	0.08
	Dusty	1.47	7.38	
<i>Rhizopus sp.</i>	Normal	3.60	5.68	0.76
	Dusty	3.27	5.31	
<i>Yeasts sp.</i>	Normal	15.27	33.56	0.08
	Dusty	9.65	21.86	
<i>Ulocladium sp.</i>	Normal	0.65	3.54	0.00
	Dusty	3.93	10.65	
<i>A. niger</i>	Normal	32.94	48.03	0.27
	Dusty	55.95	102.09	
<i>Rhodotorula sp.</i>	Normal	2.73	8.76	0.05
	Dusty	4.58	9.80	
<i>A. flavus</i>	Normal	49.62	125.75	0.11
	Dusty	24.70	40.23	
<i>A. fumigatus</i>	Normal	5.67	13.33	0.57
	Dusty	6.22	19.67	
<i>A. terreus</i>	Normal	1.64	5.21	0.74
	Dusty	2.78	12.42	
<i>Sterile Mycelium sp.</i>	Normal	6.33	17.82	0.01
	Dusty	10.14	16.34	
<i>A. ochraceus</i>	Normal	3.05	9.44	0.33
	Dusty	1.64	5.70	
<i>Monelia sp.</i>	Normal	1.2	4.54	0.05
	Dusty	2.29	5.09	
<i>Total fungi</i>	Normal	639.86	656.11	0.02

Number of total samples collected for normal days: $n = 108$

Number of samples collected for dusty event days: $n = 72$

Results

1042 observations were available for the analysis. The results of the Mann-Whitney test indicated that the referral patients' mean respiratory rates were 463.29 and 603.74 under the normal and dusty conditions, respectively, which was statistically significant ($P < 0.001$). The means and standard deviations of the patients' ages, weights, heights, body mass indices, and lung function indices are presented in Table 1.

We were sampling within a day in three sites during normal condition with 6 days interval. In addition, the sampling was performed in dusty days in three sites. In total, sampling was done in 24 dusty days. We have collected 180 samples, 72 of which were taken in dusty days. We were collected sample carelessly to season and according to schedule.

The distributions of the ambient fungal spores in the air of Ahvaz City under normal and dusty conditions are shown in Table 2. The taxa of *Mucor sp.*, *Tricosporom sp.*, *Stemphylium sp.*, *Nigrospora sp.*, *Acremonium sp.*, *Bipolaris sp.*, *Trichoderma sp.*, *Circenela sp.*, *Monelia sp.*, *Stemphylium sp.*, *Sporotrichum sp.*, and *Paecilomyces sp.* were excluded from further statistical analysis because of their low frequencies and concentrations. Table 3 displays the referral patients' lung function parameters in normal and dusty conditions. No statistically significant correlation was found between lung function index and weather condition.

Based on the results of the negative binomial regression model at the single-variable level shown in Table 4, there was no statistically significant correlation between the respiratory rates and concentrations of the different fungi, except for *Cladosporium sp.* and *sterile mycelium sp.*. This study examined whether the specific fungal spores could determine any changes in the patients' lung function indices. Based on the results of the mixed-effect regression model, *Cladosporium sp.*, *Curvularia sp.*, *Drechslera sp.*, and *Rhizopus sp.* and the mean of the total fungi were responsible for the main part of the observed changes in health status due to exposure to the fungal spores during the study period. The increases in the mean total spores of the fungi in the spring were accompanied by a decrease in FEV₁/FVC ratio. *Cladosporium sp.* spores were enhanced in the spring by reduced FEV₁/FVC ratio. The increases in *Curvularia sp.* spores in the summer were associated with declined FEF_{25–75%}. The augmented *Drechslera sp.* spores in the summer were associated with lowered FEV₁ pred and FEV₁/FVC ratio. The augmented fungal spores of *Rhizopus sp.* in the spring were accompanied by reduced FEV₁, FEV₁/FVC ratio, and FEF_{25–75%}.

Discussion

In this research, we took a cross-sectional follow-up approach to investigate whether any ambient specific taxa of the fungal spores could be a determinant of the patients' lung function changes. According to the results of this study, there was the number of referral patients under the dusty conditions compared to the normal conditions. In their study conducted from 1994 to 1996, Kwon et al. showed a statistically significant association between the occurrence of a weekly Asian storm in South Korea and deaths resulting from cardiovascular and respiratory diseases [26]. In a study conducted in Ahvaz

Table 3 Parameters of lung function in normal and Dusty conditions

lung function	Weather condition	Mean	Std. Dev	Min	Max	P Value
FEV1(mean L pred)	Normal	1.83	0.72	0.09	4.01	0.3
	Dusty	1.88	0.78	0.4	5.75	
FEV1(mean % pred)	Normal	57.86	17.07	0.66	101	0.3
	Dusty	59	17.62	12	116	
FVC(mean L pred)	Normal	2.62	0.94	0.38	5.88	0.66
	Dusty	2.65	1	0.51	6.76	
FVC(mean % pred)	Normal	67.92	16.83	20	126	0.54
	Dusty	68.58	17.62	23	134	
FEV1.FVC(mean % pred)	Normal	69.21	9.96	36	94	0.4
	Dusty	69.76	10.68	22	96	
FEF _{25.75%} (mean L S ⁻¹)	Normal	40.88	19.48	7	302	0.11

between 2001 and 2009, Shojaei et al. reported increased numbers of patients with cardiovascular and respiratory diseases associated with enhanced frequencies of dust storms [27]. According to the results of the fungi identified during the study period (Table 4), only *Cladosporium sp.* and *Sterile Mycelium sp.* had a significant positive correlation with the number of patients referring to the study clinics [28]. Unlike many other allergens, fungi are impossible to be avoided due to their permanent presence almost in any places. Therefore, susceptibility to fungi can be considered as an important factor

in allergic reactions. Each person generally breathes 22,000 times a day, during which he/she requires about 15 kg of air. As a result, a large number of fungal allergens are inhaled. The effects of fungal spores on the frequency of respiratory tract visits are often unknown. *Cladosporium sp.* is one of the most common fungi existing in polluted air, water, and soil, as well as in decomposing plants. *Cladosporium sp.* species has a high ability to stimulate allergic reactions in sensitive individuals. Long-term contact with large amounts of the spores of this fungus can cause allergic reactions [29]. Reponen et al.

Table 4 Relationship between fungal concentrations (CFU m⁻³) and respiratory tract responses (results of single-variable negative bivariate regression (

airborne fungi	Estimate	Std. Error	RR	95% Confidence Interval		P Value
				Lower Bound	Upper Bound	
<i>Cladosporium sp.</i>	0	0	1	1	1	0.04
<i>Alternaria sp.</i>	0.01	0	1.01	1	1.02	0.07
<i>Aspergillus sp.</i>	0	0.01	1	0.99	1.02	0.45
<i>Penicillium sp.</i>	0	0	1	1	1	0.92
<i>Fusarium sp.</i>	0.02	0.02	1.02	0.99	1.05	0.22
<i>Curvularia sp.</i>	−0.02	0.03	0.98	0.92	1.04	0.45
<i>Ostilago sp.</i>	0	0.01	1	0.99	1.02	0.47
<i>Drechslera sp.</i>	−0.02	0.02	0.98	0.94	1.02	0.28
<i>Rhizopus sp.</i>	0.02	0.04	1.02	0.94	1.09	0.67
<i>Yeasts sp.</i>	0	0.01	1	0.98	1.01	0.71
<i>Ulocladium sp.</i>	0	0.03	1	0.94	1.06	0.95
<i>A. niger</i>	0	0	1	0.99	1	0.09
<i>Monelia sp.</i>	0.03	0.05	1.03	0.94	1.13	0.53
<i>Rhodotorula sp.</i>	0.01	0.02	1.01	0.97	1.05	0.71
<i>A. flavus</i>	0	0	1	0.99	1	0.28
<i>A. fumigatus</i>	0	0.01	1	0.97	1.02	0.89
<i>A. terreus</i>	0.02	0.03	1.02	0.96	1.08	0.56
<i>Sterile Mycelium sp.</i>	0.03	0.01	1.03	1	1.05	0.04
<i>A. ochraceus</i>	−0.04	0.02	0.96	0.92	1	0.07
Total fungi	0	0	1	1	1	0.11

found the lung function responses to *Cladosporium sp.* observed might reflect the allergic characteristics of the fungus and by its spore size. The small particle size of *Cladosporium sp.* in the atmosphere (aerodynamic diameter range of 1.75–1.87 μm) [30] suggests its potential to penetrate and be deposited into the Lower Respiratory Tract (LRT) of humans [31]. In their annual survey of airborne fungi in Zagreb city, Croatia, Despot et al. reported the association of air fungi with respiratory diseases [32]. In their study entitled “The Relationship between Fungi and Severe Asthma,” conducted in the United Kingdom, Denning et al. showed that there was a correlation between asthma and such allergic fungi as *Aspergillus sp.*, *Cladosporium sp.*, *Alternaria sp.* and *Penicillium sp.* in the urban environment [33]. They believed that diseases like depression, disability, and severe asthma and even death are increasing due to the presence of the mentioned bio-aerosols. Considering the presence of these four fungi in Ahwaz City air, there is a greater necessity for studying and evaluating asthma prevalence and frequencies of allergy to these allergic fungi in the involved people. In this research, *Cladosporium sp.*, *Curvularia sp.*, *Drechslera sp.*, and *Rhizopus sp.* and their average total spores during the study period were responsible for the main part of the observed changes in health status. Chen et al. reported that the increase of *Cladosporium sp.* leads to decrease in FVC and FEV₁. They stated that lung function responses to *Cladosporium sp.* may be due to the spore size and allergenicity of this fungus [34]. Vicencio et al. showed that nearly 60% of patients with severe asthma have evidence of fungal allergy and require potent anti-fungal treatments [35]. The sample size did not provide with sufficient statistical power to analyze data. This could be attributed to relatively our study population small sample size. However, our findings suggested that before being treated for the observable effects of symptomatic attacks, the patients had had any exposure to fungal spores probably affecting their lung functions. We assumed that the participating patients had been exposed to similar levels of airborne fungal pollutants. Several limitations to this study can be considered as follows: First, personal information on the times spent indoors and outdoors or for exercising, which might have modified exposures to fungal spores, was not available. Second, pollen levels were not measured in this research.

There were high concentrations of the fungi during the whole study period in the dusty conditions compared to the normal conditions. The dominant and identified fungal sexes in the whole study period were almost the same. *Alternaria sp.*, *Penicillium sp.*, *Ostilago sp.*, *Ulocladium sp.*, *Monelia sp.*, *Rhodotorula sp.*, and *Sterile Mycelium sp.* were observed more frequently under the dusty compared to the normal conditions. Only *Cladosporium sp.* and *Sterile Mycelium sp.* were associated with the number of patients referring to the study clinics. The mean number of referring patients was higher in

dusty conditions. The patients’ lung function indices decreased with the increasing concentrations of *Cladosporium sp.*, *Curvularia sp.*, *Drechslera sp.*, and *Rhizopus sp.* It can be concluded that sensitivity to fungi is one of the most common causes of respiratory allergies in Ahvaz City. Therefore, more accurate identification of the existing allergens in the region can be an important step to be taken for providing the involved patients with suitable advice on controlling and preventing their respiratory diseases probably triggered by airborne fungal spores. Based on our findings we suggest that people (especially susceptible persons) should protect themselves in autumn against fungi spores by using suitable masks and other protective measures. .

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflicts of interest.

Ethics approval and consent to participate This study was approved by the Ethics Committee of Ahvaz University of Medical Sciences, Ethics Code: IR.AJUMS.REC.1396.814. All participants signed a consent form before enrolling into the study.

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