Background: Cystic fibrosis is an inherited disease that predisposes to progressive lung damage. Cystic fibrosis patients are particularly prone to developing pulmonary infections. Fungal species are commonly isolated in lower airway samples from patients with cystic fibrosis. Fungal spores are prevalent in the air.

Methods: We performed environmental air sampling surveillance at the Manchester Adult Cystic Fibrosis Centre, UK (MACFC) over a 14-month period to assess fungal growth inside and outside the CF center.

Results: Airborne counts of fungal spores peaked from May to October, both in outdoor and indoor samples. Collection of meteorological data allowed us to correlate fungal presence in the air with elevated temperatures and low wind speeds. Additionally, we demonstrated patient rooms containing windows had elevated fungal counts compared to rooms not directly connected to the outdoors.

Conclusions: This study suggests that airborne *Aspergillus fumigatus* spores were more abundant during the summer months of the survey period, which appeared to be driven by increased temperatures and lower wind speeds. Indoor counts directly correlated to outdoor *A. fumigatus* levels and were elevated in patient rooms that were directly connected to the outdoor environment via an openable window designed for ventilation purposes. Further studies are required to determine the clinical implications of these findings for cystic fibrosis patients who are predisposed to *Aspergillus* related diseases, and in
INTRODUCTION

Cystic Fibrosis (CF) is a life-long inherited disorder affecting over 10,000 people in the United Kingdom and more than 70,000 people worldwide (Bobadilla et al., 2002; Taylor-Robinson et al., 2018). CF is caused by a mutation in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR) protein (Kerem et al., 1989; Riordan et al., 1989). The CFTR protein is involved in intracellular calcium homeostasis and acts as a cyclic adenosine monophosphate-dependent ion channel, controlling the transport of salts and water across epithelial cell membranes (Grubb and Boucher, 1999). Mutations in the protein leads to defective ion flux, resulting in thickened mucus and impaired mucociliary clearance of particles and pathogens. Patients with CF are predisposed to recurrent and chronic infections which, together with an exaggerated host inflammatory response leads to progressive airway damage and eventually respiratory failure (Cohen and Prince, 2012; Taylor-Robinson et al., 2018).

In recent years, the life expectancy of CF patients has increased dramatically, with a median predicted survival of 49 years (McCormick et al., 2002; Dodge et al., 2007; Taylor-Robinson et al., 2018). Approximately 90% of CF mortality is attributed to respiratory failure secondary to chronic or recurrent infections (Cantin et al., 2015; Beswick et al., 2020). *Aspergillus fumigatus* is commonly isolated from lower respiratory tract samples (Bakare et al., 2003; Armstead et al., 2014) and can cause a range of diseases within CF patients, mainly but not exclusively: allergic bronchopulmonary aspergillosis (ABPA), *Aspergillus* bronchitis, and sensitization (Baxter et al., 2013; King et al., 2016). ABPA results from hypersensitivity to *Aspergillus* spp., occurring in 6–25% of CF patients, most of whom are adolescents or adults (de Almeida et al., 2006; Maturu and Agarwal, 2015). *Aspergillus* bronchitis affects approximately 9% of CF patients, while sensitization can be found in approximately 39% of CF patients (Maturu and Agarwal, 2015; Brandt et al., 2018). However, there is a large variation of reported prevalence of *Aspergillus* infection in CF in the literature, probably due to variable methodologies both for detecting the presence of and host reaction to *Aspergillus* and furthermore inconsistent diagnostic criteria (Mastella et al., 2000; Stevens et al., 2003; Patterson and Strek, 2010).

Risk factors for isolation of *Aspergillus* in respiratory samples in CF patients have been attributed to inhaled antibiotics, oral corticosteroid treatment, and exocrine pancreatic insufficiency (Brenier-Pinchart et al., 2009; Hong et al., 2018). Meteorological parameters have been reported to influence fungal contamination in other healthcare settings (van Rijn and Bromley, 2021) but not in CF setting. Higher outdoor mean and maximum temperatures, and also indoor temperatures, are associated with an increased fungal presence (Li and Kendrick, 1995; Singh and Chauhan, 2013; Alshareef and Robson, 2014). As several studies, humidity and rainfall have been correlated to higher fungal load in the atmosphere (Li and Kendrick, 1995; Takahashi, 1997; Brenier-Pinchart et al., 2009). Climate change may also be changing our daily exposure to fungi (van Rijn and Bromley, 2021). Construction and demolition work have been associated with an increased isolation of fungi in air samples (Srinivasan et al., 2002; Curtis et al., 2005; Pilmis et al., 2017; Wirmann et al., 2018). Building works adjacent to healthcare settings are an important risk factor for nosocomial aspergillosis. Preventative measures, such as laminar airflow and HEPA filters, have been explored to attempt to keep indoor fungal loads consistently low during construction work (Streifel et al., 1989; Cornet et al., 1999; Falvey and Streifel, 2007). In this study, we examined the relationship between meteorological factors with environmental load of *A. fumigatus* and other fungi at the MACFC over a 14-month period.

Keywords: *Aspergillus fumigatus*, Penicillium, fungi, air sampling, temperature, cystic fibrosis, climate, weather

MATERIALS AND METHODS

Air Sampling

All sampling took place in the adult CF ward at the Wythenshawe Hospital, Manchester University Hospitals NHS Foundation Trust, which houses both the Manchester Adult Cystic Fibrosis Centre and the National Aspergillosis Centre. The hospital is situated in a mixed residential and rural area of south Manchester. The CF center comprises of a 22-bedded CF inpatient ward on the ground level and outpatient department and offices, situated directly above the ward on the first floor. There is a specific car park for CF patients, located opposite the ward entrance, to prevent patients from having to walk through the main hospital. Sampling was performed in the CF ward at regular intervals at consistent sites: 18 out of 22 inpatient rooms, two sites in the ward corridor, inside an anteroom that provides positive pressure (>10 air changes per hour) to two inpatient rooms, and outside the kitchen on the ward (Figure 1). Samples were also taken in the CF patients’ car park. Air samples were taken using a single headed SAS microbial air sampler (PBI, Milan, Italy), which used impaction onto a malt agar plate (Cherwell labs) and samples 1 m³ air over 10 min. Plates were incubated at 30°C for 4 days and sampled at a height of 1.2–1.5 m (Morris et al., 2000).

Fungal species were determined by macroscopic phenotypic examination and microscopic examination at the Mycology Reference Centre. Lactophenol blue was added to visualize fungal elements. Colony counts are expressed as colony forming units (CFU).
Meteorological Data

Meteorological data was obtained from the Met Office (Met Office, United Kingdom) from the Rostherne No. 2 (Cheshire East) weather station (Lat: 53.336, Long: -2.3833), which is located approximately 6.6 km/4.10 miles away in a straight line from the Wythenshawe Hospital site. In total, 10 different meteorological variables were used: daily maximum, minimum, and mean temperatures (09:00–09:00) in Celsius; daily total rainfall (09:00–09:00) in mm; daily total sunshine (01:00–24:00) in hours; daily mean wind speed and maximum gust (01:00–24:00) in knots (kn); and daily mean, maximum and minimum relative humidity (00:00–23:00) in %. For each variable, values were used for both each sampling date as well as the day before each sample was undertaken.

Data Analysis

Data was analyzed using R and Rstudio, using packages ggplot2, tidyverse, and corrplot (Wickham, 2011; Wei et al., 2017; Wickham et al., 2019). Correlation analysis was performed using multiple non-linear regression, with p <0.05 being deemed statistically significant. The growing season was defined as May to October to subset the data. For the analysis of correlation of meteorological parameters to indoor CFUs, data from the anteroom was excluded. Data is presented as mean (SD) unless stated otherwise.

RESULTS

Outdoor Fungal Spores Correlate With Elevated Temperature and Low Wind Speeds

Environmental surveillance to quantify the abundance of fungal spores in the air was set up in and around the MACFC during November 2014–January 2016. Sampling occurred on a total of 48 dates from November 27, 2014 until January 15, 2016, with samples mostly being taken weekly (mean gap between samples 8.8 ± 4.55 days, median: 7 days (range 6–28 days), with allowances for holidays such as Christmas and Easter (Figure 1 and Supplemental Data 1). Of all the culturable fungi, the most abundant fungal species detected was *A. fumigatus* [mean (SD) 16.23 (25.14) colony forming unites (CFUs)], followed by *Penicillium* species (8.47 (32.42) CFUs) and *Geotrichum* (2.2 (3.99) CFUs). Peak spore counts of *Aspergillus* species occurred during the summer and autumn months (end of May–October), while spores of *Penicillium* species peaked during autumn and winter (October to early January). *Geotrichum* was detected more during spring and negatively correlated with the presence of *A. fumigatus* (R = −0.71, p < 0.05) and *Aspergillus niger* in the air (R = −1, p <0.05) (Figure 2A).

Throughout the year, we were able to positively correlate *A. fumigatus* spore abundance with maximum humidity (R = 0.34), maximum temperature (R = 0.35), and mean temperature (R = 0.31) during the sampling day (Figure 2B and Supplemental Figure 1). Spore abundance was negatively correlated with maximum gust (R = −0.45) and mean wind speed (R = −0.47) on the day of sampling. On the day prior to sampling, a positive correlation was found for *A. fumigatus* spore abundance with maximum temperature (R = 0.36), minimum humidity (R = 0.35), and minimum temperature (R = 0.36). A negative correlation was found for maximum gust (R = −0.34) and mean humidity (R = −0.3). A negative correlation for maximum gust and positive correlation for maximum temperature was found for both sampling day and the day before sampling. For *A. niger* we were able to negatively correlate sunshine on the day before sampling with abundance in air samples (R = −0.52) (Figure 2B).

Temperature was clearly an important factor for *A. fumigatus* abundance and we found a seasonal pattern for all fungi observed. Therefore, we assessed the difference in fungal abundance in air during the growing season (May–October) and non-growing season (October–April). An increase in *A. fumigatus* CFUs during the growing season (mean (SD) 19.93 (23.64) CFUs), compared to non-growing season (mean (SD) 14.25 (25.70) CFUs) was observed (Figure 3A). For other fungal
species this trend was not observed, with consistent CFUs in both growing and non-growing season. *A. fumigatus* CFUs negatively correlated with the maximum gust (R = −0.72) and mean speed of the wind (R = −0.72) during the growing season, no other significant correlation could be found for *A. fumigatus* (Figure 3B and Supplemental Figure 2). However, no significant differences were observed for differences in wind direction (Supplemental Figure 3).

The Presence of *A. fumigatus* Spores in Indoor Air is Determined by Meteorological Factors and the Presence of Windows

Indoor counts of *A. fumigatus* were generally lower compared to outdoor counts (mean (SD) 3.21 (5.04) vs 16.23 (25.15) CFUs, p < 0.0001 Wilcoxon matched-pairs signed rank test) (Figure 4A). Indoor CFUs of *A. fumigatus* peaked from May to November in line with outdoor counts. Indoor and outdoor *A. fumigatus* correlated when matched for their sampling date (R = 0.62, p = 7.9e−06, Spearman Rank) (Figure 4B).

Examining indoor *A. fumigatus* CFUs with meteorological parameters of the sampling day and day before sampling we identified indoor CFUs correlated positively to maximum (R = 0.38) and mean temperature (R = 0.31) to outdoor counts. Also, a negative correlation was found for maximum gust (R = −0.35) and mean wind speed (R = −0.32), in line with our findings for outdoor CFUs (Figure 5A). Maximum and mean temperature correlate with each other (R = 0.95) as well as maximum gust and mean wind speed (R = 0.94) (Figure 5B). *A. fumigatus* CFUs the day before sampling positively correlated with maximum (R = 0.41) and mean temperature (R = 0.31), like the day of sampling, but also with the minimum temperature (R = 0.41) and rainfall (R = 0.41). Rainfall correlated strongly with the maximum (R = 0.91), minimum (R = 0.91), and mean temperature (R = 0.92).

We further explored the correlation between *A. fumigatus* CFUs indoors, outdoors and maximum or mean temperature. Increased maximum temperature correlated with elevated *A. fumigatus* CFUs in outdoor and indoor air (Figure 5C). Similarly, higher mean temperatures resulted in higher *A. fumigatus* CFUs indoors and outdoors with a similar rate (R = 0.31 vs R = 0.31) (Figure 5D). However, indoor sampling resulted in 18 samples with no *A. fumigatus* CFUs detected, unlike outdoors where we could detect *A. fumigatus* in more than 95% of sampling dates (no CFUs in four samples).

Three sampling locations were not in rooms that were not directly connected to the outside, and also an anteroom with positive pressure applied, were assessed for *A. fumigatus* CFUs. In these rooms, small numbers of CFUs (maximum detected 28 CFUs) could be detected over the course of 9 months (Figure 6A). In patient rooms that were directly connected to the outside via openable windows showed significantly higher CFUs for *A. fumigatus*, especially during the summer months (p < 0.0001) (Figure 6B). Even though all these rooms were considered identical, we detected variability of *A. fumigatus* CFUs between rooms. For example, in one patient bedroom
(room 14) much lower counts were observed (max count = 25), than another patient bedroom where (room 17) up to 150 CFUs could be detected. A direct comparison of *A. fumigatus* CFUs between rooms that contained windows to the outside and rooms that were not connected to the outside revealed a significant difference (p < 0.0001) (**Figure 6C**). In addition, a significant difference was found between rooms containing windows, rooms containing no windows and the anteroom (p < 0.0001). The anteroom, with >10 air changes/h, *A. fumigatus* CFUs were zero except for four samples (1, 1, 2, and 3 CFUs). For other fungi, no CFUs could be detected in the anteroom or patients rooms adjacent, except in three samples for *Penicillium* (1, 1, and 9 CFUs) (**Supplemental Data 1**).

**DISCUSSION**

Environmental air sampling was performed at the Manchester Adult Cystic Fibrosis Centre over a period of 14 months. Indoors and outdoor areas were sampled for different fungal species. *A. fumigatus* and *Penicillium* were the most dominant species in air samples, in line with previous studies (Shelton et al., 2002).
A. fumigatus presence in the air correlated with days with elevated temperatures (sampling day and day before sampling) and with low wind speed. These data suggest A. fumigatus spores in the air are more abundant during the summer months, which is driven by increased temperatures and lower wind speeds. Indoor counts directly correlated to outdoor A. fumigatus counts and were elevated in rooms that directly connected to the outdoor via a window.

This study has demonstrated a positive correlation between ambient temperature and fungal presence, especially A. fumigatus, in environmental air samples. Other studies have found similar correlations (Li and Kendrick, 1995; Takahashi, 1997; Brenier-Pinchart et al., 2009; Alshareef and Robson, 2014) in different environmental settings. Adding further granularity to these observations, we draw positive correlations with the maximum and mean temperatures on the day of sampling, and also the day before sampling. Wind also appears to play a role in the spread of fungal spores (Grinn-Gofron et al., 2018). Here we identified a negative correlation between wind speed and fungal CFUs. Previous studies have correlated effect of wind speed to fungal load (Takahashi, 1997; Brenier-Pinchart et al., 2009; Grinn-Gofron et al., 2011), but no consistent pattern was found, potentially because the focus of fungal species differed between studies. Sequential events may give rise to increases in fungal counts in air samples. For Coccidioides spp., the “grow and blow” hypothesis has been put forward to facilitate fungal spread. Rainfall promotes growth within the soil, followed by a dry spell with elevated temperatures driving sporulation and aerosolization of spores (Comrie and Glueck, 2007; Tamerius and Comrie, 2011). Undergoing sporulation facilitates adaptation and evolution to environmental conditions (Zhang et al., 2015). Therefore, it is likely that elevated temperatures drive fungal sporulation leading to increased spores in the air. It is currently unclear what climatic factors affect different fungal species. However, temperature has been put forward as a universal driver of fungal proliferation (Alshareef and Robson, 2014; Chaloner et al., 2020). As climate change will drive more days with higher temperatures, this may have drastic effects on fungal loads in air samples (Stott, 2016).

Patients with CF are at risk of Aspergillus related pulmonary complications (Hong et al., 2018) but it is not known if there is a seasonal influence on incidence of ABPA or other Aspergillus related conditions in the CF population. Studies have reported seasonal influences on rates of pulmonary infections caused both by viruses and Pseudomonas aeruginosa in CF patients (Collaco et al., 2011; Flight et al., 2014). P. aeruginosa acquisition in young
children with CF is more observed during summer months (Psoter et al., 2013). However, in a Danish retrospective study chronic infections were more common during winter months (Johansen and Høiby, 1992). P. aeruginosa and A. fumigatus can cause co-infection in CF and have been identified simultaneously in up to 60% of CF patients (Bakare et al., 2003; Paugam et al., 2010; Reece et al., 2017). In addition, increased air pollution is considered a risk factor for pulmonary exacerbations in cystic fibrosis patients (Goss et al., 2004). Elevated air pollution and temperature have a synergistic effect on each other (Ren et al., 2006). However, it is unclear how increased temperature has an effect on exacerbations caused by fungal spores.

Our data demonstrate that rooms with windows have significantly higher A. fumigatus counts compared to rooms without windows or with positive ventilation. It was unclear during our sampling; which windows were opened and the frequency of therefore should be monitored for future studies. Other interventions such as HEPA filters and laminar air flow systems in rooms have been proposed to keep the air free of fungi (Cornet et al., 1999; Hahn et al., 2002; Araujo and Cabral, 2010; Garnaud et al., 2012). At the MACFC, rooms with positive pressure (>10 ACHs) did not reach high levels of fungal spores (9 CFUs maximum). With the exception of four samples no fungal CFUs could be detected at all in these rooms. Increased presence of fungi in the air has been directly linked to the incidence of invasive aspergillosis in patients with other health conditions (Alberti et al., 2001; Brenier-Pinchart et al., 2011).

Our study consists of samples taken over 18 months. Longer sampling would allow assessing yearly seasonal variability and the relation with fungi in the air, which has not been studied in much detail (Calvo et al., 1980; Adhikari et al., 2004; Alshareef and Robson, 2014). We were able to detect and identify A. fumigatus, Penicillium species, Geotrichum candidum, and a mixed population of non-sporulating environmental filamentous fungi. Air samples were incubated at 30°C, which might bias towards fungi with their optimum growth at this temperature (Robert et al., 2015). Lastly, fungal CFUs were correlated to meteorological data collected from the weather station. However, we are unable to assess what parameters are directly causing increased fungal CFUs in the air. Further studies are required to find causative proof of climate and weather affecting fungal proliferation.

In summary, this study demonstrates that A. fumigatus spores in the air are more abundant during the summer months, which is driven by increased temperatures and lower wind speeds. Indoor counts directly correlated to outdoor A. fumigatus

![FIGURE 6](image-url)
counts and were elevated in rooms that directly connected to the outdoor via a window. Further studies are required to determine the clinical implications of these findings for cystic fibrosis patients who are predisposed to Aspergillus related diseases, and in particular whether there is seasonal influence on incidence of Aspergillus related conditions and if screening for such complications such be increased during summer months and precautions intensified for those with a known history of Aspergillus related disease.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

NR, JC, LC, CM, MR, RB-T, and AJ contributed to the article and approved the submitted version.

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FUNDING

This research was funded by the Wellcome Trust, grant number 219551/Z/19/Z.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcimb.2021.759944/full#supplementary-material

Supplementary Figure 1 | Correlation of fungal CFUs on the sampling day and the day before sampling with all measured meteorological parameters. Spearman’s rank correlation of CFUs from fungi in outdoor air samples to meteorological parameters collected on the day of sampling or the day before sampling. Statistically significant (P < 0.05) correlations are shown in circles, with blue showing positive correlations and red negative correlations. Correlation values are shown and the size of the circle corresponds to this value.

Supplementary Figure 2 | Correlation of fungal CFUs during the growing season with all measured meteorological parameters. Spearman’s rank correlation of CFUs from fungi in outdoor air samples to meteorological parameters during the growing season. Statistically significant (P < 0.05) correlations are shown in circles, with blue showing positive correlations and red negative correlations. Correlation values are shown and the size of the circle corresponds to this value.

Supplementary Figure 3 | A. fumigatus CFUs are not associated with wind direction. A. fumigatus CFUs are shown for the wind direction during sampling.
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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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