



Original Article

Clinical relevance of *Scedosporium* spp. and *Exophiala dermatitidis* in patients with cystic fibrosis: A nationwide study

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Abstract

An increased prevalence of various filamentous fungi in sputum samples of patients with cystic fibrosis (CF) has been reported. The clinical significance, however, is mostly unclear. The aim of this study was to investigate the clinical relevance of *Scedosporium* spp. and *Exophiala dermatitidis* from sputum samples of patients with CF in the Netherlands. In this cross-sectional study, all CF patients of the Dutch national CF registry who were treated at five of the seven recognized CF centers during a 3-year period were included. We linked clinical data of the national CF registry with the national Dutch filamentous fungal database. We investigated the association between clinical characteristics and a positive sputum sample for *Scedosporium* spp. and *E. dermatitidis*, using logistic regression. Positive cultures for fungi were obtained from 3787 sputum samples from 699 of the 1312 patients with CF. *Scedosporium* spp. was associated with severe genotype, CF-related diabetes, several microorganisms, and inhaled antibiotics. *E. dermatitidis* was associated with older age, female sex, and *Aspergillus* spp. CF patients with and without *Scedosporium* spp. or *E. dermatitidis* seemed comparable in body mass index and lung function. This study suggests that *Scedosporium* spp. and *E. dermatitidis* are probably no major pathogens in CF patients in the Netherlands. Greater understanding of epidemiologic trends, risk factors, and pathogenicity of filamentous fungi in the respiratory tracts of patients with CF is needed.

Key words: cystic fibrosis, filamentous fungi, *Scedosporium*, *Exophiala*, epidemiology.

Introduction

Cystic fibrosis (CF) is the most common lethal autosomal recessive disease among populations with northern European ancestry.¹ It is a multiorgan disorder and mostly affects the lungs. Progressive chronic lung inflammation and infection is responsible for at least 80% of CF-related deaths.^{1,2} The main cause of chronic lung inflammation and infection are bacteria, such as *Staphylococcus aureus*, *Burkholderia cepacia*, *Stenotrophomonas maltophilia*, and *Pseudomonas aeruginosa*.² In addition to bacteria, filamentous fungi are increasingly recovered in respiratory cultures from patients with CF.^{3–5} *Aspergillus fumigatus* is the fungus most frequently cultured in patients with CF. Reported prevalence rates based on sputum cultures vary from 16% to 57% in CF patients.^{3–8} It has been associated with allergic bronchopulmonary aspergillosis (ABPA), hospitalization, and lung function decline.⁷ *Scedosporium* species have been reported as the second most prevalent filamentous fungus isolated in sputa from 2 to 9% of the patients with CF.^{3,5,9,10} Its isolation has been associated with older age, white race, and inhaled antibiotic use.^{10,11} The genus *Scedosporium* is an ubiquitous filamentous fungus present mainly in soil, sewage, and polluted waters.¹² Several species of *Scedosporium* have been reported in CF: *Scedosporium apiospermum*, *Scedosporium boydii*, *Lomentospora prolificans* and *Scedosporium aurantiacum*, *Scedosporium ellipsoideum*, *Scedosporium minutisporum*.¹³ The black yeast *Exophiala dermatitidis* is able to grow as a filamentous fungus in humid environments such as dishwashers and steam baths¹⁴ and has been isolated from a significant percentage (1–16%) of CF patients.^{6,13,15}

The clinical relevance of these two filamentous fungi is unclear, leading to a lack of guidelines for clinical management.¹⁶ Besides *A. fumigatus*, other filamentous fungi are increasingly

reported as well, although mostly in small numbers and in single center studies.^{13,15,17} Whether presence of *Scedosporium* spp. and *E. dermatitidis* in the lungs only causes harmless colonization of the airways, or also constitutes a clinically relevant risk for patients with CF remains a matter of debate.^{10,16,18,19}

The aim of this study was to investigate the clinical relevance of *Scedosporium* spp. and *E. dermatitidis* from sputum samples of patients with CF seen in Dutch CF centres during a 3-year period.

Methods

Design and procedures

In this cross-sectional study, all CF patients of the Dutch national CF registry who were treated at five of the seven recognized CF centers between March 22, 2010, and March 27, 2013 were included. Patients with a history of lung transplantation were excluded. We linked the national CF registry with the Dutch CF Fungal Collection Consortium (DCFFCC). Data were pseudonymized prior to analysis. Formal approval from the institutional review board was waived.

National CF registry

The national CF registry was established to support scientific research and improve CF care and treatment.²⁰ It covers 98% of all patients with CF in the Netherlands. The five included centers represent 82% of the patients. The diagnosis of CF disease was based on typical clinical features associated with a positive sweat test (chloride >60 mmol/l) and/or the presence of two known pathogenic cystic fibrosis transmembrane conductance Regulator (CFTR) mutations.

Clinical characteristics

The following parameters were retrieved from the national CF registry: age, sex, body mass index (BMI), CFTR mutation, CF-related diabetes (CFRD), allergic bronchopulmonary aspergillosis (ABPA), lung function (forced expiratory volume in 1 second (FEV₁) % predicted), presence of positive sputum sample(s) for *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, *Staphylococcus aureus*, *Burkholderia cepacia*, nontuberculous mycobacteria, and *Aspergillus* spp., use of inhaled or oral corticosteroids, azithromycin or inhalation antibiotics, and history of lung transplantation. FEV₁ was measured at least 4 times a year during routine visits, and the highest value per year was recorded. A patient receiving daily insulin during at least 1 year of the research period was classified as having CFRD. Continuous inhaled antibiotics or oral azithromycin use was defined as use for more than 3 months during at least 1 year. Sputum cultures of the year 2010 and 2011 were linked to clinical data from the national CF registry of the year 2011, and sputum cultures of the year 2012 and 2013 were linked to clinical data from the national CF registry of the year 2012.

Dutch CF fungal collection consortium

The DCFCC was established to study the epidemiology, microbiological characteristics, and clinical relevance of fungal infection and colonization among patients with CF in the Netherlands. For this aim, we collected all sputum cultures positive for filamentous fungi from patients with CF who were treated at the five participating CF centers in the Netherlands between March 22, 2010, and March 27, 2013. At the local hospital, sputum samples were collected and examined for fungi 4 times a year during routine visits and during hospitalization. Therefore, we considered patients of whom we did not receive a sputum culture as negative. Measurement bias was avoided by excluding the two centers who participated only partially and did not send all positive sputum samples and by using one reference lab for molecular identification.

Fungal culture media and methods

Details on the fungal culture media and methods were previously published.¹³ Briefly, agar plates were provided to the participating laboratories from a central location. Every week, batches of filamentous fungi, recovered at the participating laboratories, were transported to a central microbiology laboratory of Canisius Wilhelmina Hospital Nijmegen on the original plates. Samples were inoculated onto Sabouraud dextrose agar (SDA, Oxoid, Basingstoke, UK) and medium B+ agar plates.²¹ All inoculated plates were incubated aerobically at 30°C for 3 weeks and checked for growth daily in the first week and twice per week in the second and third week. The reference

laboratory identified the isolates with internal transcribed spacer sequencing and registered the fungus in the DCFCC database.²²

Statistical analyses

We compared patients with a positive sputum sample with patients without a positive sputum sample for *Scedosporium* spp. and *Exophiala dermatitidis*, using χ^2 , Fisher exact, and *t* tests. We investigated the association between clinical characteristics and a positive sputum sample for *Scedosporium* spp. and *Exophiala dermatitidis* using logistic regression analysis with adjustment for sex and age. We did a sensitivity analysis comparing patients with more than one positive sputum sample with patients without a positive sputum sample. We used STATA software (version 14; College Station, TX, USA) for all analysis.

Results

During the study period, 699 (53%) of the 1312 patients with CF had at least one positive sputum sample. In total, 3787 samples containing fungal isolates were obtained. A large variety of 107 species of filamentous fungi was encountered in CF patients. The median age was 21 years (range 0–72). The median number of positive sputum samples per patient in this study was three (range 1–35).

Scedosporium spp. were recovered from 94 (7%) of the 1312 patients with CF and from 225 sputum samples (6%) during the research period (Table 1). The mean age of these 94 patients was 22 years (range 0–56), and the majority was female and had two severe CFTR mutations (class I–III) (Table 2). The median number of sputum samples per patient with *Scedosporium* spp. was 11 (range 1–35).

The clinical characteristics of patients with CF and at least one positive sputum sample of *Scedosporium* spp. compared to those without a positive sputum sample with *Scedosporium* spp. are shown in Figure 1. The two groups were comparable with respect to age and inhaled corticosteroid use. Severe genotype (odds ratio 2.86, 95% confidence interval [CI] 1.42–5.76), CF-related diabetes (1.80, 1.10–2.95), use of inhaled antibiotics (1.60, 1.03–2.48), and coinfection with *Stenotrophomonas maltophilia* (2.47, 1.37–4.45), *Staphylococcus aureus* (1.81, 1.17–2.79), and *Aspergillus* spp. (2.77, 1.77–4.32) were associated with *Scedosporium* spp. CF patients with or without *Scedosporium* spp. had almost a similar mean BMI (1.03, 0.96–1.11) and FEV₁ % predicted (1.00, 0.99–1.01), also when adjusted for age and sex.

Exophiala dermatitidis was cultured from 57 (2%) sputum samples of 31 (2%) of the 699 patients with CF (Table 1). The mean age of the 31 CF patients with *Exophiala dermatitidis* was 28 years (range 10–59), and the majority was female (Table 3). The median number of sputum samples with *Exophiala dermatitidis* per patient was five (range 1–29).

Table 1. Isolation rate of *Scedosporium* spp. and *Exophiala dermatitidis*.

	Patients with CF ^a N = 1312 n (%)	Positive sputum samples N = 3787 n (%)
Total <i>Scedosporium</i> spp.	94 (7)	225 (6)
<i>Scedosporium apiospermum</i>	23 (2)	66 (2)
<i>Scedosporium boydii</i>	16 (1)	55 (2)
<i>Scedosporium ellipsoideum</i>	11 (1)	27 (1)
<i>Scedosporium aurantiacum</i>	11 (1)	19 (1)
<i>Lomentospora prolificans</i>	4 (<1)	8 (<1)
<i>Scedosporium minutisporum</i>	1 (<1)	1 (<1)
<i>Scedosporium</i> spp. – no species identification	45 (3)	49 (1)
<i>Exophiala dermatitidis</i>	31 (2)	57 (2)

^aCystic fibrosis.**Table 2.** Clinical characteristics of patients with *Scedosporium* spp. positive and negative sputum samples.

	<i>Scedosporium</i> spp. positive N = 94 n (%)	<i>Scedosporium</i> spp. negative N = 1218 n (%)	P-value ^a
Demographic factors			
Age, years (mean, SD)	22 (12)	21 (15)	0.345
Sex, female	53 (56)	575 (47)	0.088
BMI, (mean, SD)	20 (3)	20 (4)	0.173
Genotype, severe CFTR mutations ^b	83 (89)	949 (78)	0.010
Disease characteristics			
CF-related diabetes	30 (33)	232 (20)	0.003
ABPA	14 (15)	105 (9)	0.049
Lung function, FEV ₁ (mean, SD)	71 (23)	71 (25)	0.950
Microorganisms			
<i>Pseudomonas aeruginosa</i>	43 (47)	387 (35)	0.020
<i>Stenotrophomonas maltophilia</i>	16 (17)	85 (8)	0.001
<i>Staphylococcus aureus</i>	43 (47)	369 (33)	0.007
<i>Burkholderia cepacia</i>	2 (2)	21 (2)	0.692
Nontuberculous mycobacteria	3 (3)	15 (1)	0.150
<i>Aspergillus</i> spp.	47 (51)	283 (26)	<0.001
Medications			
Inhalation corticosteroids	32 (36)	315 (31)	0.370
Azithromycin	50 (56)	485 (46)	0.071
Inhalation antibiotics	48 (52)	447 (39)	0.012

^aT-test for continuous variables, Chi-2 for binary variables and Fisher's exact for binary variables with less than 10 cases.^bSevere mutations was defined as 2 CFTR mutations from class I-III.ABPA, allergic bronchopulmonary aspergillosis; BMI, body mass index; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; FEV₁, forced expiratory volume in 1 second.

CF patients with *Exophiala dermatitidis* had more severe genotypes after adjusting for age and sex (3.31, 1.08–10.12), were slightly older (1.03, 1.01–1.06) and were mostly female (2.45, 1.14–5.26) (Fig. 2). *Aspergillus* spp. coinfection (2.12, 1.01–4.45) was more frequently observed in CF patients with *Exophiala dermatitidis* than in those without (Fig. 2). The frequency of co-infections with bacteria, use of medication did not differ between the two groups. CF patients with *Exophiala dermatitidis* had a weak association with the BMI compared to those without *Exophiala dermatitidis*, however, after adjustment for age and sex, BMI and FEV₁% predicted were

similar in both groups (1.09, 0.98–1.22 and 0.99, 0.98–1.01, respectively).

Our sensitivity analysis showed similar results in patients with more than one positive sputum sample for *Scedosporium* spp. (Table S1, and Fig. S1). CF patients with and without *Scedosporium* spp. had comparable BMI (1.06, 0.96–1.18) and FEV₁% predicted (1.00–0.98–1.01). The number of patients with more than one positive sputum sample for *Exophiala dermatitidis* were too small to do logistic regression, but the comparison of proportions showed similar results as the main analysis (Table S2).

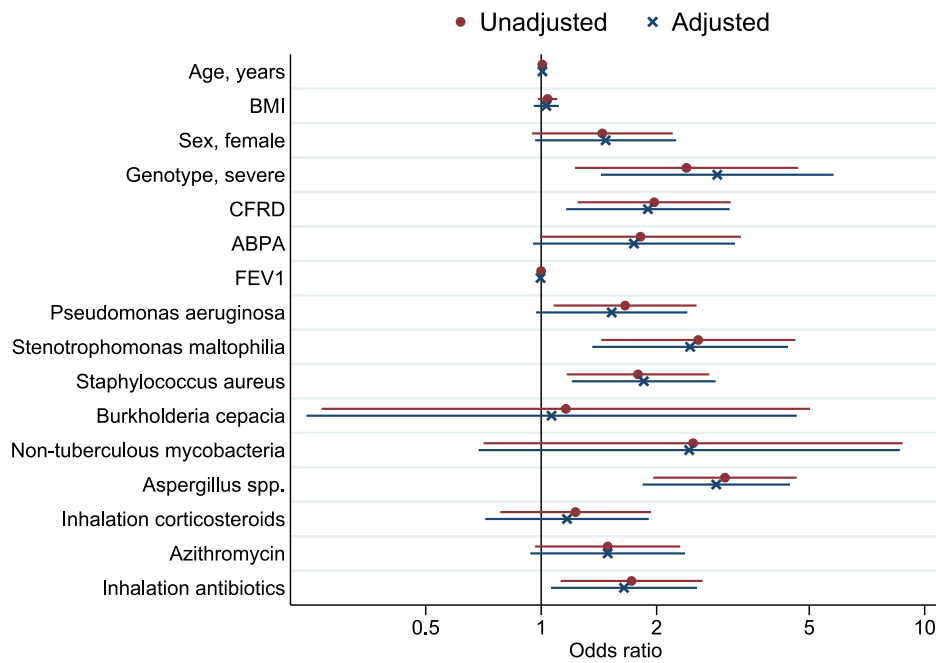


Figure 1. Clinical factors associated with *Scedosporium species*, odds ratio's unadjusted (red dot) and adjusted for age and sex (blue cross) (N = 1312). ABPA, allergic bronchopulmonary aspergillosis; BMI, body mass index; CFRD, cystic fibrosis related diabetes; FEV₁, forced expiratory volume in 1 second. This Figure is reproduced in color in the online version of *Medical Mycology*.

Table 3. Clinical characteristics of patients with *Exophiala dermatitidis* positive and negative sputum samples.

	Exophiala dermatitidis positive N = 31 n (%)	Exophiala dermatitidis negative N = 1281 n (%)	P-value ^b
Demographic factors			
Age, years (mean, SD)	28 (13)	21 (14)	0.005
Sex, female	21 (68)	607 (47)	0.025
BMI, (mean, SD)	22 (3)	20 (4)	0.003
Genotype, severe CFTR mutations ^a	27 (87)	1005 (78)	0.246
Disease characteristics			
CF-related diabetes	6 (19)	256 (21)	1.000
ABPA	4 (13)	116 (9)	0.529
Lung function, FEV ₁ (mean, SD)	65 (19)	71 (25)	0.167
Microorganisms			
<i>Pseudomonas aeruginosa</i>	11 (37)	420 (36)	0.950
<i>Stenotrophomonas maltophilia</i>	3 (10)	98 (8)	0.733
<i>Staphylococcus aureus</i>	10 (33)	404 (34)	0.926
<i>Burkholderia cepacia</i>	1 (3)	22 (2)	0.442
Non-tuberculous mycobacteria	1 (3)	17 (1)	0.364
<i>Aspergillus spp.</i>	15 (50)	314 (27)	0.005
Medications			
Inhalation corticosteroids	15 (48)	330 (31)	0.044
Azithromycin	18 (58)	512 (47)	0.208
Inhalation antibiotics	14 (45)	483 (40)	0.551

^aSevere mutations was defined as 2 CFTR mutations from class I-III.

^bT-test for continuous variables, Chi-2 for binary variables and Fisher's exact for binary variables with less than 10 cases.

BMI: body mass index, CFTR: Cystic fibrosis transmembrane conductance regulator, CF: Cystic fibrosis, ABPA: allergic bronchopulmonary aspergillosis, FEV₁: forced expiratory volume in 1 second.

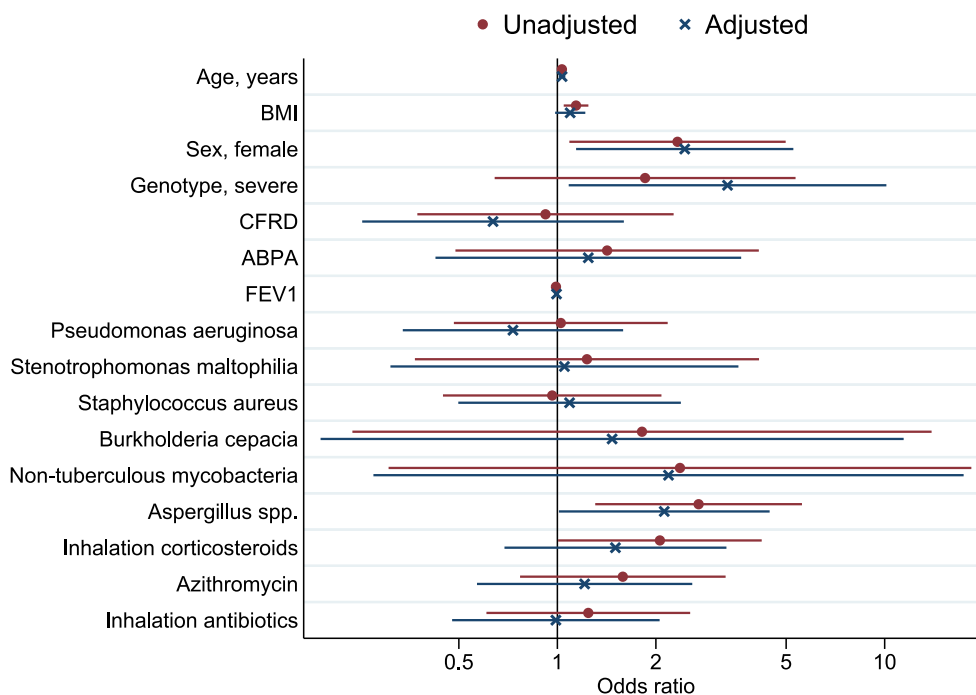


Figure 2. Clinical factors associated with *Exophiala dermatitidis*, odds ratio's unadjusted (red dot) and adjusted for age and sex (blue cross) (N = 1312). ABPA, allergic bronchopulmonary aspergillosis; BMI, body mass index; CFRD, cystic fibrosis related diabetes; FEV₁, forced expiratory volume in 1 second. This Figure is reproduced in color in the online version of *Medical Mycology*.

Discussion

We describe the clinical relevance of two species of non-*Aspergillus* filamentous fungi in a national cohort of Dutch CF patients. Our results showed that CF patients with and without *Scedosporium* spp. or *Exophiala dermatitidis* were comparable with regard to BMI and lung function. *Scedosporium* spp. was associated with severe genotype, CF-related diabetes, several microorganisms, and inhaled antibiotics. *Exophiala dermatitidis* was associated with older age, female sex, severe genotype, and *Aspergillus* spp.

Only one other multicenter study determined clinical factors associated with *Scedosporium* spp. isolation in patients with CF.¹⁰ This American retrospective cohort study found that FEV₁% predicted was not associated with *Scedosporium* spp. isolation (odds ratio 0.99, 95% CI 0.96–1.04), which is in line with our findings (1.00, 0.99–1.01).¹⁰ An Australian single centre study did not find a difference in FEV₁ between patients with and without *Scedosporium* spp. either.¹⁷ In the study by Hong et al., higher BMI was associated with lower probability of *Scedosporium* spp. in adults (0.90, 0.87–0.91) but not in children (0.96, 0.91–1.01). In comparison, we did not find a difference in BMI in our age-adjusted model (1.03, 0.96–1.11).

Our finding that inhaled antibiotic treatment was associated with positive sputum cultures for *Scedosporium* spp. (1.60, 1.03–2.48) is in line with findings by Hong et al. (2.01, 1.61–2.52) and Blyth et al.^{10,17} Both previous studies also found this association with other fungi such as *Aspergillus*, suggesting that the

widespread use of broad-spectrum antibiotics has favored the selection and opportunities of growth and colonization of fungi in the respiratory tract.⁵

Blyth et al. and Kaur et al. both suggested that *Scedosporium* colonization/infection occurs less frequently in patients colonized by mucoid *Pseudomonas aeruginosa*.^{17,23} In contrast, we found an indication that *Pseudomonas aeruginosa* occurred more frequently in patients with a positive sputum culture for *Scedosporium* spp. which is in line with Hong et al.¹⁰ Synergistic or antagonistic interactions within the polymicrobial flora colonizing the airways in CF patients have been described, especially for *Aspergillus fumigatus*.⁷ An association between fungi, colonizing bacteria, and antimicrobial use has been observed for *Aspergillus fumigatus*, with increased risk for colonization of *Aspergillus* in combination with *Pseudomonas aeruginosa* and *Burkholderia cepacia*.⁷ The association of *Burkholderia cepacia* co-colonization was not found in our study for *Scedosporium* spp. due to very few *Burkholderia cepacia* co-colonizations, which is in line with Hong et al.¹⁰ We found an association between the presence of *Stenotrophomonas maltophilia* and a positive sputum sample for *Scedosporium* spp., which has also been found with *Aspergillus fumigatus* in a French single center study.³

Exophiala dermatitidis has been studied less, which could be due to the fact that routine isolation techniques are insufficient to detect this slow growing fungus in specimens from CF patients and that it needs a prolonged incubation time (of up to

4 weeks).⁶ Lebecque et al. did not find any associations between treatment with continuous antibiotic treatment and colonization with *Exophiala dermatitidis* and neither did we.¹⁵

It was also suggested that *A. fumigatus* coinfection is associated with an increased risk of *Exophiala dermatitidis* and that *Pseudomonas aeruginosa* is less frequently found in patients with *Exophiala dermatitidis*.^{15,24} In our study, a slight indication was found for the latter. A possible explanation could be that *Pseudomonas aeruginosa* has been reported to inhibit fungal growth by certain extracts from the extracellular mucus.⁶

A strength of this study is that it utilizes data of a large CF cohort followed for 3 years. Many other studies of fungal infection in CF patients have been limited by small sample size, short study time, or lack of correlating clinical details. Using data from a multicenter study improves the external validity of the study. Due to the reference laboratory, uniformity in the culturing, molecular typing and detection of filamentous fungi was assured.

One limitation of the study is that we did not use a *Scedosporium*-selective medium, such as the Scesel + medium, which might have led to an underestimation of the *Scedosporium* spp. positive sputum samples.^{25,26} In our study, we used medium B+, which has better bacterial inhibition than the routinely used Sabouraud followed by polymerase chain reaction based identification. We did not have clinical data from the national CF registry for the whole study period. Therefore, we used clinical data from 2011 and 2012 as a proxy. This could have led to misclassification bias. In patients with CF, the lung function and BMI usually decrease over time, because disease progresses. Therefore, the clinical parameters (such as lung function) of 2011 are likely to be worse for the cases with *Scedosporium* spp. and *Exophiala dermatitidis* identified in 2010, than they actually were in 2010, so the impact of a positive sputum culture could be overestimated in these patients. Only three new cases with *Scedosporium* spp. were identified in 2013, so this will have had little impact. Detection bias may have occurred in sicker patients who had more respiratory tract cultures per quarter compared to other patients. Increased respiratory sampling in this group may have led to a higher fungal yield, providing an overestimation of the association between decreased lung function and filamentous fungi. We aimed to correct for differences in the number of (outpatient) clinic visits by analysing unique patients instead of analysing the number of sputum samples. Finally, it could be that the number of patients with *Scedosporium* spp. or *Exophiala dermatitidis* was not big enough to show slight differences.

In clinical practice, although there was no association with FEV₁ and BMI, *Scedosporium* spp. or *Exophiala dermatitidis* may still be important at an individual level. For example, *Scedosporium apiospermum*, *Scedosporium prolificans*, and *Scedosporium auranticum* were suggested as emerging pathogens among immuno-compromised patients and in immuno-competent patients with a chronic lung disease.^{11,27,28} It has also been suggested that the presence of *Scedosporium*

apiospermum in the respiratory tract is clinically relevant because it may trigger an inflammatory response that can manifest as an allergic bronchopulmonary disease.⁹ Furthermore, *Scedosporium* species are reportedly difficult to treat because of their resistance to antifungal agents, with *Scedosporium prolificans* being the most resistant.^{22,29} However, since the prevalence of filamentous fungi is very high among patients with CF and resistance is a serious problem, it becomes increasingly important to identify the individual patient who requires antifungal treatment.¹³ A careful selection of patients is necessary to avoid unintentional selection of more viable but resistant fungi in the respiratory system.³⁰ We believe that watchful waiting in the case of positive cultures with *Scedosporium* spp. and *Exophiala dermatitidis* in CF is warranted because starting, switching, and stopping azole therapy has the potential risk of selecting for resistant fungal species with wild-type fitness.³⁰

Our study showed that CF patients with and without *Scedosporium* spp. or *Exophiala dermatitidis* were comparable in terms of clinical parameters, that is, BMI and lung function, suggesting that *Scedosporium* spp. and *Exophiala dermatitidis* are probably no major pathogens for CF patients on a population level. These findings should be confirmed in a larger study.

As the prevalence of filamentous fungi in the sputum of patients with CF is very high, greater understanding of epidemiologic trends, risk factors, and pathogenicity of filamentous fungi in the respiratory tracts of patients with CF is needed to develop evidence based management guidelines. This study suggests that in general, it seems wise to withhold antifungal treatment when encountering *Scedosporium* spp. or *Exophiala dermatitidis* in patients with CF.

Supplementary material

Supplementary data are available at [MMYCOL](http://www.mmycol.org) online.

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Declaration of interest

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