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Epidemiology of Allergic Disease

Short-term effect of outdoor mould spore exposure on prescribed allergy medication sales in Central France

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Summary

Background: Outdoor moulds are classically associated with exacerbations of asthma.**Objective:** The aim of this paper was to examine nasal allergy morbidity by studying the short-term relationship between mould spore exposure and daily sales of reimbursable anti-allergic treatment in central France.**Methods:** The relationship between daily changes in mould concentrations and daily sales obtained from the national healthcare database was analysed with generalized additive models, taking into account confounding factors such as air pollution, weather conditions, pollen counts, and days of the week.**Results:** During the study, the average total yearly number of treated people was around 10 000 over approximately 230 000 surveyed. The relative risk (95% CI confidence interval) of sales of oral antihistamines with topical treatment associated with an interquartile increase in mould concentration was significant for *Cladosporium* 1.079 [1.019-1.142] and *Aspergillus-Penicillium* (*Asp-Pen*) 1.051 [1.021-1.082] in the whole population. When the influence of age and sex was considered, the relationship was significant only in male children aged 0-12 years and those aged between 13 and 49 years for *Cladosporium*: 1.256 [1.081-1.460] and 1.151 [1.063-1.245], respectively. The relationship was also significant for *Asp-Pen*: 1.038 [1.003-1.075] for those aged between 13 and 49 years and 1.056 [1.007-1.108] for adults over 50 years of age.**Conclusion:** The association between prescribed daily sales of oral antihistamines with topical treatment sales is associated with temporal changes to *Cladosporium* and *Aspergillus-Penicillium* in the whole population. When the influence of age and sex was considered, these two moulds contributed to prescribed medication sales only in the male general population.

KEYWORDS

allergic rhinitis, drug prescription, epidemiology, mould, outdoor

1 | INTRODUCTION

Outdoor moulds are ubiquitous and make up the largest proportion of airborne particles.¹ Spore counts typically exceed pollen countsby 10- to 100-fold. Climate changes may affect the atmospheric concentration and allergenicity of fungal spores.² The most commonly studied outdoor moulds, *Alternaria* and *Cladosporium*, usually peak between spring and autumn, and their quantity is correlated

with weather conditions, including temperature.^{3,4} Therefore, in warmer years, spore production may start earlier and/or finish later in the season.

Systematic recent reviews and meta-analyses⁵⁻⁷ of the relationships between indoor mould exposure and rhinitis provide sufficient evidence of an association, with an odds ratio generally greater than 1.35. In contrast, information about rhinitis and outdoor moulds is still scarce,⁸⁻¹⁰ although many studies have reported a relationship between allergic rhinitis and pollens.¹¹⁻¹⁴ Part of the problem of attributing allergy morbidity to outdoor environmental spore counts is the difficulty in defining a clear-cut window of spore exposure independent of outdoor pollen allergies. Epidemiological studies have failed to demonstrate a direct relationship between allergy morbidity and outdoor fungal exposure.¹⁵

The relationship between exposure to aeroallergens and health can be documented by panel and ecological surveys using appropriate statistical methods such as checking the shapes of concentration responses and controlling for confounders.¹⁶ Unlike for pollens, no temporal ecological study has investigated the relationship between allergy morbidity on the basis of anti-allergic medication prescriptions and outdoor mould spore levels.

We aimed to study the short-term relationship between outdoor mould spore exposure and allergy morbidity by assessing the temporal relationship between anti-allergic drug consumptions in the general population over 6 years old in an urban area in central France.

2 | MATERIAL AND METHODS

2.1 | Health outcome

All individuals prescribed reimbursable anti-allergic treatment living in the Clermont-Ferrand area (pop. 285 000) were included in the study, which ran from May to October for the years 2010 to 2012, from February to October for the years 2013 and 2014 and from March 2015 to October 2015. The population was stable during the study period both in terms of size and of demographics.

The general database of the French public health insurance system that provided the data from anonymous registration numbers contains details of all active or retired employees and their dependents, and is estimated to cover approximately 80% of the French urban population.¹²

Because this study was entirely anonymous, approval from the French Ethics Committee was not required. Professor Caillaud, as a state-employed university teacher, was granted access to the general database of the French public health insurance system.

The health outcome was defined as the number of "cases" per day, whereby a case is defined as the dispensing of an oral antihistamine drug and a topical (nasal or ocular) anti-allergic drug on the same medical prescription. For each year of the study period, all cases who had received at least one reimbursement were identified in the health insurance database from their anonymous registration number. Recurrent prescriptions were counted as new cases whenever an individual received the prescription drugs in a pharmacy.

Reimbursements were also summed on an annual basis for descriptive purposes.

2.2 | Mould and pollen data

Clermont-Ferrand is located in central France and has a temperate climate.

Moulds and pollens were sampled on the rooftop of a building of the University Hospital. Samples for microscopic analysis were collected with a coat paper using a 7-day recording volumetric trap (Burkard Manufacturing Co. Rickmansworth, UK) at a suction rate of 10 L/min. Slides were stained with fuchsin and analysed by microscopy at a magnification of 400 $\times$. For each sample, pollens were identified and counted by the RNSA (National Network for aerobiological monitoring) on two longitudinal fields, as described previously.¹⁷ For fungal spores, only one longitudinal field was analysed.

Identifiable fungal spores were classified into 27 individual taxa, *Alternaria*, *Ascospora*, *Aspergillus-Penicillium* (*Asp-Pen*), *Basidiospore*, *Botrytis*, *Cercospora*, *Chaetomium*, *Cladosporium*, *Didymella*, *Epicoccum*, *Erysiphe*, *Fusarium*, *Fusicladium*, *Ganoderma*, *Helicomyces*, *Helminthosporium*, *Myxomycetes*, *Nigrospora*, *Peronospora*, *Pithomyces*, *Polythrincium*, *Sporobolomycetes*, *Stemphylium*, *Tilletiopsis*, *Torula*, *Uredospore*, *Ustilago* and regrouped into 2 phyla, Ascomycota and Basidiomycota. Daily *Alternaria* and *Cladosporium* data have been identified for 6 years and other taxa or summary phyla data daily for the past 4 years.

2.2.1 | Other data

The average daily concentrations of nitrogen dioxide (NO₂), particulate matter 10 (PM₁₀), and daily maximum 8-hour average ozone concentrations were obtained from the local network for air quality monitoring (ATMO-Auvergne). Highest daily temperature, lowest daily relative humidity, daily maximum wind speed, thunderstorm occurrence and precipitations were provided by the national weather service. Influenza data were obtained from a national network for transmissible disease surveillance.

2.3 | Statistical analysis

Data were analysed by Poisson regression with generalized additive models (GAMs), which are widely used in air pollution studies.¹⁸ By nonparametric smoothing functions, GAMs allow flexible control of the effect of trend and seasonal components, as well as confounding factors with nonlinear relationships to cases, such as pollutants and meteorological factors. They can also visualize the shape (linear or nonlinear) of the curve for every mould studied.

The construction of the model began with the introduction of the long-term trend and seasonal variations, using a cubic smoothing spline of the day of the study. This trend takes into account, *inter alia*, the change in reimbursement over the years of the study. Dummy variables of public holidays, school holidays, days of the week, thunderstorm occurrence (lag 1) and influenza occurrence

(quantitative variable) were then introduced. Quantitative meteorological and pollution variables and total allergenic pollens were introduced as penalized cubic splines, and different lags were tested to take into account a possible delayed effect (lags from 0 to 3 days and mean over several days). Minimization of the Akaike criterion identifies the most appropriate lag for each variable. In the final model, a 0-3 day lag (ie mean of 4 days) was retained for greatest temperature, wind speed and pollens. NO₂ was introduced with a 3 day lag, humidity with a 2 day lag, and precipitations, ozone and particulate matter with a 1 day lag. Finally, the spore, one species per model, was introduced in the form of penalized cubic spline and every lag of spore up to seven 7 days was tested. Lags (single day or mean of several days) were retained after graph inspection. A model with several spores, most related to the outcome, was also built.

The effect of spores on cases in the short term was expressed as a relative risk (RR) for an increase in an interquartile range of spores.

3 | RESULTS

3.1 | Mould concentrations

The most prevalent individual fungi taxa detected of the total fungi count were (Table 1) *Cladosporium* (70.7%), *Ascospore* (18.4%), *Basidiospore* (5.5%), *Alternaria* (1.3%), *Ganoderma* (0.9%), *Asp-Pen* (0.8%), *Ustilago* (0.6%) and *Myxomycetes* (0.4%). Correlations between the main moulds are shown in Table 2. The evolution of daily *Cladosporium* and *Aspergillus-Penicillium* during the study period is shown in Figures 1 and 2.

3.2 | Antihistamines and topical anti-allergic treatment sales

Mean (SD) daily sales of antihistamines and topical treatments rose from 45.1 (36.6) in 2010 to 56.8 (47.3) in 2015 representing overall sales of nearly 11 000 treatments per year (Table 3).

Between 2010 and 2015, in addition to an oral antihistamine, prescriptions contained a nasal treatment in 63.2% of cases, eye drops in 16.2% and in the remaining 20.6%, the two combined. 60% of deliveries occurred during the mould spore sampling period.

The number of deliveries for cases varied from 1 to 19 for the same individual per year. On average, one individual had two deliveries of an antihistamine with topical treatment per year.

3.3 | Association between medication sales and mould concentrations

In the entire population (Table 4), the RR (95% CI confidence interval) of antihistamine and topical treatment sales associated with an interquartile increase in spore concentration was significant for *Cladosporium* 1.08 [1.02-1.14] and *Aspergillus-Penicillium* 1.05 [1.02-1.08]. Conversely, a significant decrease in the risk of cases was observed for *Ustilago* 0.95 [0.905-0.998].

The shapes (with 95% CIs) of the mould-prescribed allergy medication sales relationships for *Cladosporium* and *Aspergillus-Penicillium* (Figure 3) were fairly linear, up to a saturation point of approximately 5000 and 300 spores/m³, respectively. Above these levels, the effects of mould spores on prescribed allergy medication sales remain relatively constant.

In the GAM multi-mould model, the RR of drug sales associated with an interquartile increase in spore concentration was significant only for two moulds: *Cladosporium* with a higher RR than in the single mould model: 1.15 [1.06-1.24] and *Aspergillus-Penicillium* with an identical RR: 1.05 [1.02-1.09].

When the influence of age and gender was considered (Table 5) in single-mould models, the relationship was significant in men aged 0-49 years for *Cladosporium* and in men older than 13 years for *Aspergillus-Penicillium*. The RR was also elevated in women aged 13-49 years for both moulds, but not significantly.

4 | DISCUSSION

Our ecological study is the first to reveal the relationship between *Cladosporium* and *Asp/Pen* mould spore exposure in the general population and allergy morbidity independently of various confounding factors, such as air pollution, meteorological factors and flu. In particular, the construction of our model makes it possible to distinguish the effects of outdoor mould spores from that of pollens. Although *Ustilago* spores are considered to be allergenic, it is possible that the response to *Ustilago* was dwarfed by the high response to *Cladosporium*, which begins to sporulate a few weeks before *Ustilago* in the studied area.

In temperate climates, *Cladosporium* is the dominant airborne fungus.¹⁹ The size of *Cladosporium* spores varies over a wide range, from 3 to 56 µm.²⁰ The mould *Cladosporium* is generally considered as an outdoor species and to be associated with asthma exacerbations.^{1,20} However, in a Boston birth cohort, outdoor *Cladosporium* measured in the first 3 months of life was associated with an increased risk of developing doctor-diagnosed allergic rhinitis by the age of 5 years.²¹ In addition, some studies have reported associations between *Cladosporium* sensitization and rhinitis. In the Isle of Wight birth cohort, sensitization to *Cladosporium* by the age of 4 years was associated with rhinitis.²² In a clinical study involving outpatients with rhinitis symptoms, nasal provocation tests with moulds were positive with *Cladosporium*, *Aspergillus* and *Penicillium*.²³ In a Polish outpatient study, patients monosensitized to moulds had a greater nasal obstruction than patients with other allergies. Sensitization to *Cladosporium*, *Aspergillus* and *Penicillium* were reported, respectively, in 40%, 36% and 6% of cases.²⁴ It is not possible in these studies to disentangle the effects of outdoor and indoor moulds on sensitization. In Greek²⁵ and Turkish²⁶ panel studies of patients monosensitized to moulds, outdoor *Cladosporium* concentrations were correlated with rhinitis symptom scores.

Aspergillus and *Penicillium* are the two most commonly encountered indoor mould genera. However, in temperate climates, as in

TABLE 1 Outdoor mould concentrations and other environmental factors from April 2012 to October 2015

Fungal spore taxa (number of spores/m ³)	N ^a (days)	Mean (SD)	Min	Q1	Median	Q3	Max
<i>Alternaria</i>	573	11 (139.9)	20	31	62	124	1240
<i>Ascospore</i>	744	1226 (2294.4)	26	217	550	1275	25 699
<i>Asp-Pen</i>	193	198 (338)	26	51	103	2016	3503
<i>Basidiospore</i>	710	384 (500)	25	93	248	496	5808
<i>Botrytis</i>	56	54 (42)	25	31	31	62	217
<i>Cercospora</i>	36	52 (33)	26	31	31	70	154
<i>Chaetomium</i>	20	32 (12)	26	26	26	31	62
<i>Cladosporium</i>	1057	3323 (4426)	20	600	1900	4060	36 263
<i>Didymella</i>	27	45 (28)	26	31	31	62	124
<i>Epicoccum</i>	259	68 (60)	25	26	50	77	437
<i>Erysiphe</i>	247	53 (42)	25	26	31	62	283
<i>Fusarium</i>	37	56 (39)	26	31	31	62	155
<i>Fusicladium</i>	42	47 (40)	26	26	31	51	217
<i>Ganoderme</i>	382	122 (96)	26	51	103	155	558
<i>Helicomyces</i>	158	74 (99)	25	31	31	75	675
<i>Helminthosporium</i>	106	58 (47)	25	31	31	62	283
<i>Myxomycetes</i>	200	101 (164)	26	26	51	103	1388
<i>Nigrospora</i>	55	44 (30)	26	31	31	31	186
<i>Peronospora</i>	92	75 (63)	26	31	41	93	372
<i>Pithomyces</i>	69	62 (108)	25	26	26	31	496
<i>Polythrincium</i>	118	46 (31)	25	26	31	51	180
<i>Sporobolomycetes</i>	31	45 (31)	26	31	31	41	155
<i>Stemphylium</i>	23	29 (9)	25	25	26	26	51
<i>Tilletiopsis</i>	62	49 (34)	25	26	31	51	150
<i>Torula</i>	195	46 (31)	25	26	31	62	231
<i>Uredospore</i>	91	50 (43)	25	26	31	62	334
<i>Ustilago</i>	189	170 (252)	26	31	77	186	1645
Summary phyla							
Ascomycota	1077	4278 (5521)	20	960	2575	5140	50 840
Basidiomycota	724	498 (558)	25	125	360	651	6245
Meteorological variables							
Maximum temperature (°C)	1078	22.2 (6.7)	−2.6	18.1	22.45	26.6	39.8
Relative humidity (%)	1078	43 (13)	10	35	42	50	90
Rainfall (mm)	405	5.0 (7.8)	0.2	0.6	2.0	6.1	58.3
Pollutant							
Ozone (µg/m ³)	1078	87 (20)	31	74	86	100	156
NO ₂	1078	15 (7)	2	10	14	18	49
PM ₁₀ (µg/m ³)	1078	17 (9)	3	12	15	20	83
Total pollens	1038	154 (224.8)	1.1	33.9	89.8	182.7	3195.6

^aDays with detectable levels of each mould during days monitoring.

our study, *Aspergillus-Penicillium* spores are present in outdoor air throughout the year.²⁷

Aspergillus and *Penicillium* are classically associated with asthma. Sensitization to *Aspergillus* is associated with severe persistent adult asthma²⁸ and also with allergic bronchopulmonary aspergillosis.²⁹ In two recent reviews^{30,31} including panel studies in asthmatic children,

an association was consistently found between indoor *Penicillium*, and asthma exacerbations, irrespective of the children's allergic sensitization to moulds.

In contrast to asthma, studies relating *Aspergillus* or *Penicillium* to rhinitis are scarce. Although the size of *Asp-Pen* is often less than 10 µm, they can form aggregates. The clusters of small *Aspergillus* conidia

TABLE 2 Spearman's correlation coefficients among outdoor moulds, 2010-2015

Moulds	<i>Cladosporium</i>	<i>Alternaria</i>	<i>Asp-pen</i>	<i>Erysiphe</i>
<i>Cladosporium</i>	1			
<i>Alternaria</i>	0.47	1		
<i>Asp-Pen</i>	0.12	0.18	1	
<i>Erysiphe</i>	0.17	0.13	0.03	1
<i>Myxomycetes</i>	0.10	0.18	0.03	0.01

are usually deposited in the nasopharynx, while the small individual spores reach the lower airways.³² *Aspergillus* is classically associated with allergic fungal rhinosinusitis.³³ In the 2005-2006 NHANES survey, sensitization to *Aspergillus* was consistently associated with current hayfever or perennial or seasonal rhinitis symptoms.³⁴

In our study, the relationship between allergy morbidity and mould concentrations was observed only in men. This sex-specific observation could be related to differences in mould exposure, mould sensitization or different genetic susceptibility. Levels of physical activity differ by sex. In the general US population, women and older youths are the least active groups.³⁵ However, in a 10-year study of patients taking medication for allergic rhinitis and airborne pollens performed by our team in the Clermont-Ferrand area, the

sex male/female ratio was 1.4 before the age of 15 years and 0.7 thereafter.¹² In the 2005-2006 NHANES survey, the prevalence of allergic sensitization to *Alternaria* was (%), (SE) 10.1% (0.72) in men and 7.1% (0.54) in women and to *Aspergillus* 8.5% (0.59) in men and 4.5% (0.34) in women.³⁶ One Hungarian study reported a genetic FOXP3 polymorphism protective against allergic rhinitis in women.³⁷

Studies on dose-response relationships between mould concentrations and clinical symptoms are scarce. However, our results show a sharp positive linear trend followed by a plateau. This is consistent with the findings of ecological studies performed with some pollens (although the outcome variable differs). Erbas³⁸ showed in a time-series analysis that grass pollen had an increasing effect on asthma hospital admissions up to a saturation point of 30 grains/m³, with this effect remaining stable thereafter. Tobias et al³⁹ also reported nonlinear short-term effects of airborne grass levels on asthma emergency room admissions in Madrid. Taudorf et al,⁴⁰ using time-series analysis, showed that the association between birch pollen load and symptom severity was nonlinear, with a plateau.

The main strength of the present study lies in its extremely large regionally representative dataset comprising subjects of all ages. All individuals studied in the Clermont-Ferrand area were living less than 15 km from the spore trap. It has been shown that a single collector is representative of spore concentrations within a radius of

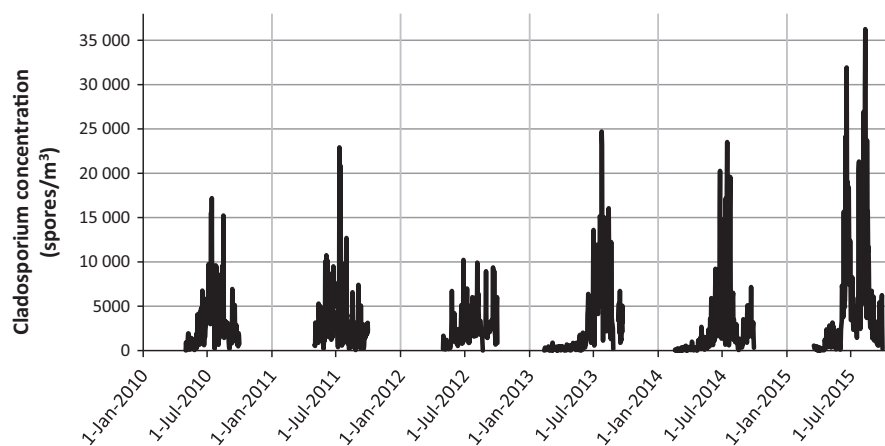
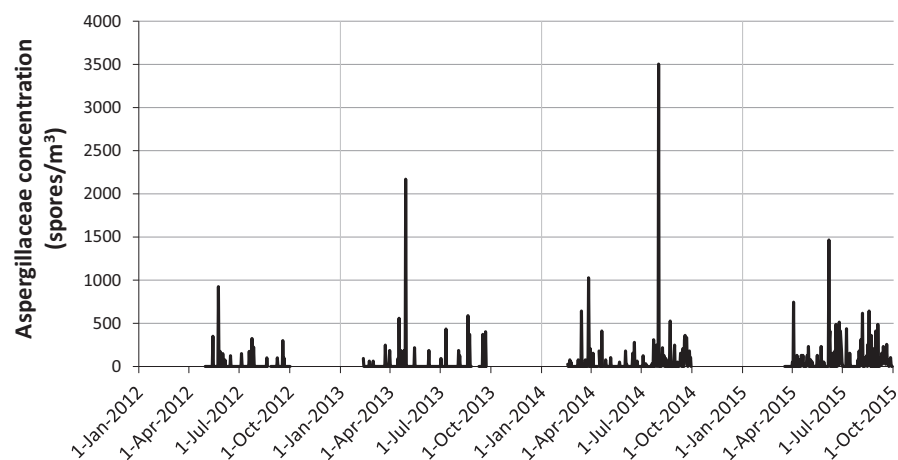
FIGURE 1 Evolution of daily concentration (spores/m³) of *Cladosporium* spores in Clermont-Ferrand (during periods with measures and when moulds are detectable [not zero])**FIGURE 2** Evolution of daily concentration (spores/m³) of *Aspergillus-Penicillium* spores in Clermont-Ferrand (during periods with measures and when moulds are detectable [not zero])

TABLE 3 Oral antihistamines with topical anti-allergic treatment sales, 2010-2015

Year	Yearly treatment sales	Number of treatment sales per day			
		Mean (SD)	Minimum	Median	Maximum
2010	9563	45.1 (36.6)	0	36	167
2011	9442	44.3 (40.0)	0	36	185
2012	10 492	48.3 (42.3)	0	38	271
2013	10 401	48.3 (38.6)	0	41	264
2014	10 871	50.6 (40.1)	0	43	230
2015 ^a	10 834	56.8 (47.3)	0	46	228

^aFrom 1 January to 31 October 2015 (10 months).

TABLE 4 Relative risk (RR) and 95% confidence interval [95% CI] of oral antihistamines with topical anti-allergic treatment sales in the whole population, 2010-2015, estimated for a single mould model associated with a variation equal to an interquartile range (IQR) of mould distribution. Significant results ($P < .05$) are in bold character

Mould	Lag (days)	IQR	RR ^a	95% CI
<i>Cladosporium</i>	2-6	3534	1.08	1.02-1.14
<i>Alternaria</i>	4-6	72	1.01	0.997-1.03
<i>Asp-Pen</i>	6-7	101	1.05	1.02-1.08
<i>Epicoccum</i>	0-7	39	0.97	0.91-1.04
<i>Erysiphe</i>	0-7	23	1	0.9997-1.0003
<i>Ganoderma</i>	0-7	120	0.97	0.90-1.04
<i>Helicomyces</i>	3-5	31	1	0.9996-1.0004
<i>Myxomycetes</i>	0-7	42	0.97	0.93-1.01
<i>Torula</i>	0-7	12	1	0.9998-1.0002
<i>Ustilago</i>	0-7	66	0.95	0.90-0.998
Summary phyla				
Ascomycota	2-6	4641	1.09	0.9996-1.19
Basidiomycota	5	526	1.03	0.99-1.07

^aFrom model adjusted on trend and seasonal variations, public holidays, school holidays, days of the week, thunderstorm occurrence, influenza occurrence, daily average of NO₂ and PM10, daily maximum 8-h average ozone concentration, highest daily temperature, lowest daily relative humidity, daily maximum wind speed, precipitations and total of allergenic pollen.

50 km.^{41,42} The relationship between drug sales and outdoor spores was examined in terms of individual taxa, a procedure rarely performed in previous studies. Another strength of our study is that it includes a large examination of lags, up to 7 days. For visits for rhinitis, lags may vary substantially. A study in Ottawa found that total fungal spore concentrations appeared to be associated with same day ED visits for rhinitis.⁴³ In Toronto, Canada, physician visits for allergic rhinitis were associated with 10-day average ragweed concentrations.⁴⁴ Lastly, we used appropriate statistical methods, adjusted for pollens, outdoor air pollution and influenza epidemics, to look at the shape (linear or not) of the curve for every mould spore studied.

Our study has a number of limitations, concerning exposure, population and ecological time studies.

As the genera *Aspergillus* and *Penicillium* are morphologically indistinguishable by their conidia, laboratories list them together as *Aspergillus-Penicillium* type. This limits the morphological recognition of these two spores, whose effects on health significantly differ. Also, as several moulds can have a combined effect on allergy morbidity and as only one spore is introduced into each model because some of them are highly correlated with one another, the individual effect of each mould spore could be partially or inadequately assessed. However, the lack of correlation between airborne *Aspergillus-Penicillium* and *Cladosporium* suggests actual differential impacts on allergy morbidity. In addition, the sporulation time of these two moulds is different, with *Aspergillus-Penicillium* being present throughout the year, whereas *Cladosporium* spores peak during summer, as shown in Figures 1 and 2. Exposure assessment could be limited by the absence of data on indoor mould exposure, which can also contribute to rhinitis exacerbations.^{28,29} The complexity of mould exposure should be acknowledged. For example, in a recent paper,⁴⁵ *Aspergillus* and *Penicillium* were detected more frequently indoors than outdoors, in contrast to *Cladosporium* and *Alternaria*, which were detected more frequently outdoors than indoors. Lastly, GAM models using cubic splines do not allow interaction analysis between other exposures and mould spore counts.

Other limitations are that our local study is not representative of the French general population. As our population was urban, the trends observed cannot be extrapolated to rural areas. Another limitation is that the number of affected persons was probably much greater because we did not capture every case. Many individuals with mild allergy morbidity do not seek a physician's diagnosis, but rather self-medicate using over-the-counter antihistamine treatments.⁴⁶ Thus, our analysis likely underestimated the overall contribution of moulds to the use of allergy medication.⁴⁷ However, the definition of our cases, which comprised an oral antihistamine drug and a topical (nasal or ocular) anti-allergic drug on the same physician's prescription, selected a majority of patients with moderate or severe disease.⁴⁸ This definition, although not sensitive, is more specific than the sales of isolated antihistamine drugs, commonly prescribed for allergic rhinitis, but also for other conditions, such as urticarial rashes. This definition has been used as a proxy for allergic rhinitis incidence and prevalence.⁴⁹ The lack of knowledge about mould sensitization in our general population is another drawback. However, in the framework of the European Community Respiratory Health Survey,⁵⁰ sensitization to *Cladosporium* was reported to be very low in the French population (less than 2%). Moreover, several biological factors have been proposed to support the role of mould exposure in respiratory health, involving allergic and irritative mechanisms.⁵¹ The drugs prescribed for rhinitis include oral and local antihistamines, used for allergic diseases, and local nasal corticosteroids, which are anti-inflammatory drugs. We can therefore expect that the combination of these drugs may have both anti-allergic and anti-inflammatory effects.

Ecological studies also have inherent limitations. Ecological time-series studies estimate the association between short-term changes in mould levels and health events in the general population, such as

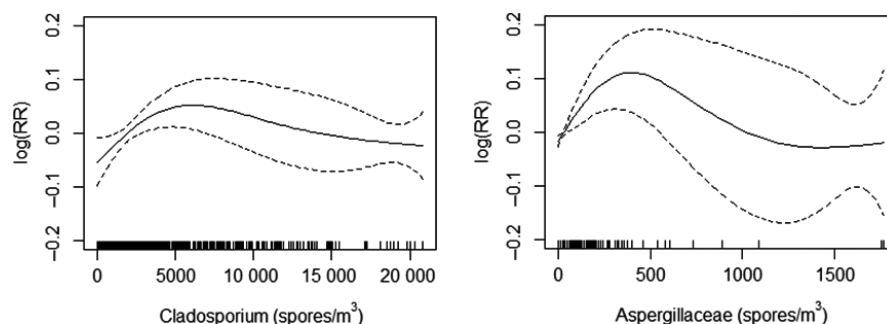


FIGURE 3 Shape of the mould-prescribed allergy medication sales curves from the GAM models for *Cladosporium* and *Aspergillus-Penicillium* in the whole population (adjusted for time trend, outdoor air pollution and meteorological variables). The mould-prescribed allergy medication sales relationship (expressed as natural logarithm of the relative risk [Log (RR)] can be read as the prescribed allergy medication sales increase on the y-axis for a mould increase on the x-axis

TABLE 5 Relative risk (RR) of oral antihistamines with topical anti-allergic treatment sales and 95% confidence interval [95% CI] by age and sex group, 2010-2015, estimated for a single-mould model associated with a variation equal to an interquartile range (IQR) of mould distribution. Significant results ($P < .05$) are in bold character

Mould	Lag (days)	IQR	Sex	0-12 years of age RR ^a [95% CI]	13-49 years of age RR ^a [95% CI]	Over 50 years of age RR ^a [95% CI]
<i>Clado sporium</i>	2-6	3534	M	1.26 [1.08-1.46]	1.15 [1.06-1.24]	1.04 [0.97-1.11]
			F	1.00 [0.99-1.004]	1.07 [0.98-1.16]	1.01 [0.91-1.11]
<i>Asp-Pen</i>	6-7	101	M	1.09 [0.92-1.29]	1.04 [1.003-1.075]	1.06 [1.01-1.11]
			F	1.00 [0.97-1.02]	1.04 [0.998-1.08]	1.03 [0.998-1.06]

^aFrom model adjusted on trend and seasonal variations, public holidays, school holidays, days of the week, thunderstorm occurrence, influenza occurrence, daily average of NO₂ and PM10, daily maximum 8-h average ozone concentration, highest daily temperature, lowest daily relative humidity, daily maximum wind speed, precipitations and total pollen.

hospitalization for asthma or anti-allergic drug consumption. In contrast, clinical studies relate measurements of mould concentrations to symptom severity at an individual level in individuals sensitized to fungi, monitored over time. However, ecological studies can be performed on a huge number of events for a long period of time, whereas clinical studies are performed on a limited number of individuals for a shorter period of time for practical reasons. Lastly, the time periods included in the study differed from year to year, but these variations are attenuated by the fact that several years were analysed.

In conclusion, daily sales of antihistamines and topical treatments are associated with temporal changes to *Cladosporium* and to *Asp-Pen* in the general population. When sex and age are considered, these moulds contribute to rhinoconjunctivitis in the male general population.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

DC, MC and BE contributed to the design, data analyses, and drafted the manuscript. SM and CS contributed to the design, statistical script and data analysis. ND and MT provided mould data. All authors participated in revision of the study manuscript and approval of the final version. All authors had full access to all the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. Because the study was entirely anonymous, approval from the French Ethics Committee was not required.

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