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The role of outdoor fungi on asthma hospital admissions in children and adolescents: A 5-year time stratified case-crossover analysis

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ABSTRACT

Background: Some fungal spores can trigger asthma exacerbation but knowledge of which outdoor fungal spores contribute to asthma hospitalisation is limited.
Objectives: To examine the role of outdoor fungal spores in child and adolescent asthma hospitalisations.
Methods: We conducted a bi-directional time-stratified case-crossover study of child and adolescent asthma hospitalisations over 5 years. Conditional logistic regression assessed the role of 20 fungi taxa (Same day [L0] and lagged [L1-3]) adjusted for maximum temperature, humidity and grass pollen. Strata specific effects were explored if there was evidence of effect modification by age, sex, air pollutants or grass pollen. Non-linear effects examined with Generalized Additive Models.
Results: Of 2098 children hospitalised for asthma, 60% were boys; mean age was 5.5 ± 3.7 years. Fungal spore counts peaked during warm months. Regression models found weak associations with *Coprinus* [L0,L1: OR=1.03, 1.01–1.06], *Periconia* [L0: OR=1.03, 1.001–1.07] and *Chaetomium* [L2: OR=1.08, 1.0–1.2]. Sex appeared to act as an effect modifier with girls having stronger associations with *Cladosporium*, *Coprinus* and total fungi. Older adolescent (14–18 years) hospitalisation was significantly associated with *Coprinus* and *Ustilago*/smuts. Air pollutants and grass pollen did not appear to act as effect modifiers. Non-linearity was not detected.
Conclusion: There may be associations between some outdoor fungal spores and asthma hospitalisations. Further research needed to explore whether these findings can be replicated; and examine whether fungal sensitisation and/or human rhinovirus infections are associated with stronger effects. If findings are replicated, then the need to develop predictive models for fungal spore distribution and levels may become more important.

1. Introduction

Asthma is a significant global public health problem (Global Asthma Report, 2014). In Australia, it is the most common chronic condition diagnosed in childhood and is a national health priority (Australian Institute of Health and Welfare). Severe asthma attacks are major causes of childhood hospitalisations and more than half of asthma hospitalisations involve children aged 0–18 years (Australian Institute of Health and Welfare, 2013).

Airborne fungal spores are ubiquitous and are among a number of short-term environmental factors considered to be important in triggering child and adolescent asthma exacerbations that can result in hospitalisation (American College of Occupational and Environmental Medicine, 2003; Denning et al., 2006). The sources of outdoor fungal spores are predominantly fungi growing on trees, plants and grasses (Irga and Torpy, 2015), whereas the sources of indoor fungal spores are related to persistent damp in household structures

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and may also be outdoor spores that have entered through doors and windows (Tischer and Heinrich, 2013). Counts of outdoor fungal spores are consistently much higher than indoor fungal spores (Garrett et al., 1997). Other environmental triggers associated with asthma exacerbations include Human Rhinovirus (HRV) infection (Busse et al., 2010; Erbas et al., 2015), air pollutants (Erbas et al., 2005; Jalaludin et al., 2008) (particulate matter, ozone and nitrogen dioxide) and grass pollen (Erbas et al., 2012a).

Previous observational research that examined associations between total outdoor fungal spore counts and child asthma hospitalisations found significant associations in the UK (Newson et al., 2000), but no associations in the USA (Lierl and Hornung, 2003; Wang and Yousef, 2007). Some studies that categorised fungal spore taxa into phyla (Atkinson et al., 2006; Cakmak et al., 2005; Raphoz et al., 2010) have found increased risk of asthma hospitalisations but their findings were not comparable due to the lack of detail regarding the taxa types that were categorised in phyla. Few studies have examined fungal spores by individual taxa (Chakraborty et al., 2014; Dales et al., 2003; Hanigan and Johnston, 2007; Newson et al., 2000; Pongracic et al., 2010) and these studies also reported inconsistent associations with *Aspergillus* (Dales et al., 2003; Pongracic et al., 2010), *Alternaria* (Chakraborty et al., 2014; Hanigan and Johnston, 2007) and *Cladosporium* (Dales et al., 2003; Raphoz et al., 2010). Only one time series study has reported lagged effects of outdoor fungal spores on child asthma hospitalisations (Raphoz et al., 2010). Two longitudinal time series studies reported that age, sex and air pollution may potentially modify the effects of outdoor fungal spores on child and adolescent asthma hospitalisation (Cakmak et al., 2005, 2012). The findings from these previous time-series, cross-sectional and correlational studies have been limited by the lack of control groups for the cases.

In this study we aimed to build on the findings of previous research and overcome some limitations by examining the associations between a range of outdoor fungal spore taxa and child and adolescent asthma hospitalisations in south-west (SW) Sydney, Australia over a five-year period using a case-crossover design. The objectives were to investigate whether these associations were (a) on the same day as fungal exposure or lagged; and (b) whether associations were modified by sex, age, air pollution or grass pollen.

2. Methods

2.1. Study design

This study used a bi-directional time-stratified case-crossover design which has been shown to be well-suited for studying the effects of transient short-term exposures (fungal spore release, air pollution changes) on the risk of short onset events (asthma hospitalisation) in individuals (Quan et al., 2015). As cases serve as their own controls, there is less risk of confounding due to stable individual characteristics (i.e. age, sex, behavioural factors, genetic factors) (Jaakkola, 2003). The hospital admission date was set as the index case day and referent control dates were the same day of the week within the same month and year as the index case day (Erbas et al., 2012b). This approach reduces potential biases related to possible time or seasonal trends (Janes et al., 2005).

For each admission date (case) and referent control days we compared the daily level of fungal spores, grass pollen, air pollution and meteorological variables. We removed all readmissions within 1–30 days of the previous admission to avoid confusing the definition of case and control days in the case crossover design.

2.2. Asthma hospitalisation data

Daily counts of asthma hospital admissions at Campbelltown, Camden and Liverpool Hospitals for children and adolescents aged 2–18 years between 29 May 2008 and 3 May 2013 (n=1800 days) were obtained from New South Wales Health. Due to coding variations between the hospitals the diagnosis coding definitions included three classification systems: (1) ICD10-AM (Australian Consortium for Classification Development, 2016): Asthma (J45), Status asthmaticus (J46); (2) SNOMED CT-AU (NEHTA, ,2016): Asthma (195967001), Asthma NOS (266365004); (3) ICD-9 (Australian Institute of Health and Welfare, 2016): Extrinsic asthma (493.0); Intrinsic asthma (493.1); Asthma unspecified (493.9); Chronic obstructive asthma (493.2); Other forms of asthma (493.8); Cough variant asthma (493.82).

These individual level data contained hospital, age, sex, date of admission, principal diagnosis, and if readmitted within 28 days.

2.3. Fungal spore data

Daily ambient fungal spores were measured using a Burkard 7-d Volumetric spore trap (Burkard Manufacturing Co. Ltd, Rickmansworth, Herts, England) in accordance with the guidelines of the World Allergy Organisation (Hasnain et al., 2007). The trap was located on the rooftop of the Campbelltown Hospital which is approximately 11 m from the ground and free from obstruction. The collection involved drawing 10 l of air per minute continuously across a microscope slide that had been coated with adhesive. Airborne particles stuck to the slide as it moved past the inlet at 2 mm/h. The fungal spores were identified and counted by a trained technician using a microscope. The fungal spore count is expressed as the number of fungal spores per cubic metre of air (counts/m^3) tested averaged over a 24 h period. Identifiable fungal spores were classified into 21 taxa (Grant Smith, 1990): *Alternaria, Cladosporium, Aspergillus/Penicillium, Epicoccum, Ganoderma, Chaetomium, Ustilago/*smuts, *Polythrincium, Torula, Didymella, Coprinus, Cerebella, Curvularia, Periconia, Puccinia, Drechslera, Stemphylium, Fusarium, Nigrospora, Pithomyces*.

2.4. Grass pollen, air quality and meteorological data

Daily grass pollen counts/m^3 were measured using the same methodology as the fungal spores. We obtained air quality data from the nearest NSW Environment Protection Authority fixed monitoring station which was located at Liverpool (20 km from the Campbelltown Hospital): 24 h average daily concentrations of particulate matter < 2.5 and < 10 μm diameter ($PM_{2.5}$ and PM_{10}) (μg/m^3), daily maximum one-hour average nitrogen dioxide (NO_2) in parts per billion (ppb) and daily maximum four-hour average ozone (O_3) in ppb. We obtained Bureau of Meteorology climate data from Campbelltown weather monitoring station: daily maximum temperature (°C), rainfall (mm), and average daily relative humidity (%).

2.4.1. Age groups

Participants were stratified into age groups 2–13 years and 14–18 years so that age group categorisation was comparable to other outdoor fungi and asthma hospitalisation research (Cakmak et al., 2005; Dales et al., 2004).

3. Statistical methods

We used a conditional logistic regression model for binary outcomes (asthma hospitalisation) (Navidi and Weinhandl, 2002). We assessed the estimated effects of same day (Lag0) and lagged fungal spore exposure up to 3 days (instantaneous Lag1, Lag2, Lag3; and cumulative lag). Maximum temperature, relative humidity and grass pollen were included as a priori confounders in the regression models, as these factors have been shown to be associated with fungal spore production and dispersion (Burge, 2002) and asthma exacerbations (Li et al., 2014). In addition individual fungal spore and asthma hospita-

lisations models were adjusted for air pollutants ($PM_{2.5}$, PM_{10}, NO_2 or O_3), and these were retained in the model if they changed the estimated associations by > 10% or had p-value < 0.05. Spearman's correlations were estimated to determine the levels of correlation between the fungal taxa detected.

We tested sex; age group (2–13 years; 14–18 years); air pollutants; and grass pollen as categorical variables (low ≤90th percentile vs high > 90th percentile) as interaction terms to identify possible effect modification. As the statistical power to test for significant interactions was lower than to test for the main effect, we report strata specific associations if the p-value for the interaction was < 0.1 to avoid missing any important interactions (Kirkwood and Sterne, 2003). Results are presented as odds ratios (OR) and 95% confidence intervals (95% CI) that can be interpreted as the association per increase from the 75th to 90th percentiles of fungal spore counts/m^3calculated for each fungal taxa. In the time series graph, daily counts of asthma hospitalisations were smoothed using LOWESS - Locally Weighted Scatterplot Smoothing. All statistical analyses were performed using Stata IC 13.1 (StataCorp, College Station, Texas).

We conducted secondary analysis to assess potential nonlinear effects of fungal spore exposure. A Poisson regression model was used to model daily asthma admissions using generalized additive model (GAM) (Hastie and Tibshirani, 1986) where penalized regression splines were used to estimate smoothing spline. To accommodate the case crossover design, the GAM was applied with a mixed effects approach, entailing a random intercept for each participant (Wood, 2013). Smoothing parameters with degrees of freedom up to 10 were automatically determined by Generalized Cross-Validation (GCV). Weather variables and grass pollen were included in the models. The GAMs were explored in three stages: (1) each fungal spore taxa univariately; (2) Each fungal spore taxa with temperature and humidity as confounders; and (3) As in (2) but with grass pollen levels as a further confounder. Diagnostic plots were checked for model fit. All nonlinear analyses were performed using "mgcv" package (Wood, 2006) in R software version 2.15.2 (Available from http://www.R-project.org).

4. Results

There were 2098 children hospitalised once during the study period to any one of the three hospitals. Of these, 60% were male; and mean age was 5.5 ± 3.7 years. The highest number of admissions was at Campbelltown, followed by Liverpool then Camden (Table 1).

The most prevalent fungal taxa detected were *Cladosporium, Aspergillus, Didymella, Coprinus, Periconia, Ustilago/*smuts, and *Alternaria* (Table 2). The total fungi spore count varied greatly, with a range of daily counts between 19 and 10,365. The Spearman correlations indicated that there were weak to moderate correlations between the fungal taxa (see Supplemental Material Table S1); and between the fungal spore taxa and the meteorological variables (see Supplemental Material Table S2).

Table 1
Descriptive statistics of asthma hospitalisations.

	All	Boys	Girls	Differences between boys and girls
N (% of All)	2098	1253 (59.7)	845 (40.3)	p < 0.05*
Mean age (years) ± SD	5.5 ± 3.7	5.3 ± 3.6	5.7 ± 3.9	p=0.02^
Age group				p=0.002ǂ
2–13	1990 (94.9)	1202 (97.1)	788 (94.4)	
14–18	108 (5.1)	51 (2.9)	57 (5.6)	
Hospital n (%)				p=0.5ǂ
Campbelltown	1180 (56.2)	714 (57.0)	466 (55.2)	
Liverpool	885 (42.2)	520 (41.5)	365 (43.2)	
Camden	33 (1.6)	19 (1.5)	14 (1.7)	

*Z-test of proportions; ^*t*-test; ǂX^2 test

During the study period, fungal spore counts were relatively low for most of the year, but for most genera, spore counts peaked during the warmer seasons (September to March). Daily asthma hospitalisations and total fungal spore counts over the study period showed seasonal variation (Fig. 1). The lower fungal spore concentrations in the period September 2009–September 2010 correlated with the end of a major drought (high maximum temperatures and low rainfall) that affected much of south-eastern Australia (see Supplemental Material Fig. S1).

Few associations were seen in the regression models adjusted for maximum temperature, relative humidity and grass pollen; and those associations that were observed were relatively inconsistent across the lag periods examined. There was some evidence for an association between asthma hospitalisations and *Coprinus* at Lag0, Lag1 and cumulative lag; *Cheatomium* at Lag2; *Cerebella* at cumulative lag; and total fungi spores at cumulative lag (Table 3). Air pollutants did not change the effect estimates by more than 10%, so were not included in the final models.

Evidence of interactions with sex and age group were found. Among girls, *Cladosporium* was significant at Lag0 and cumulative lag; *Coprinus* at Lag0, Lag1, Lag2 and cumulative lag; and total fungi spores at Lag0; Lag3; cumulative lag (Table 4).

Among those aged 2–13 years, only *Coprinus* had significantly increased OR at Lag0 and cumulative lag. Among older adolescents (14–18 years), *Coprinus* [Lag0, Lag1 and cumulative lag]; and *Ustilago/smuts* [Lag0] had significantly increased OR. Interestingly, *Stemphyllium*, *Puccina* and *Polythrincium* had significantly reduced OR (Table 4). We found no evidence of effect modification by any air pollutants or grass pollen.

Possible non-linear associations between fungi levels and hospital admission were investigated. Non-linearity was not detected. All fungal taxa seemed to be linearly associated with the odds of asthma hospitalisation.

5. Discussion

This study found evidence of weak associations between some taxa of outdoor fungal spores found in SW Sydney, namely *Coprinus*, *Periconia*, *Chaetomium*, *Ganoderma*, *Cerebella*, and total fungal spores and the children and adolescents who were hospitalised for asthma in this region. There was evidence of same day and lagged effects for these taxa. There was also some evidence that sex and age group were effect modifiers. Girls demonstrated stronger associations with *Cladosporium*, *Coprinus, Chaetomium* and total fungal spores than boys. Older adolescents demonstrated stronger associations with *Coprinus* and *Ustilago/*smuts than the younger age group.

The proportions of outdoor fungal taxa reported in this study are similar to surveys in London, UK (Atkinson et al., 2006) and Melbourne, Australia (Mitakakis and Guest, 2001; Tham et al., 2016) that reported fungal spore taxa counts using a similar methodology to this study with predominance of *Cladosporium, Aspergillus, Didymella, Coprinus, Periconia* and *Alternaria*. Lower proportions of *Alternaria* and higher proportions of *Aspergillus* have been reported in an outdoor fungal spore survey in Sydney (54 km from this study site) that used a different sampling methodology (Irga and Torpy, 2015).

The only comparable study from this region was conducted by some authors of this research in another Australian city, Melbourne. In that study of 644 children and adolescents, exposure to outdoor *Alternaria, Leptosphaeria, Coprinus*, and *Drechslera* were significantly associated with asthma hospitalisations with lagged effects up to 3 days. Sex or age group were not significant effect modifiers (Tham et al., 2016). The results from studies conducted elsewhere are mixed. No associations between outdoor fungal spores and asthma hospital attendances have been found in northern Australia (Hanigan and Johnston, 2007), the USA (Lierl and Hornung, 2003; Pongracic et al., 2010; Wang and

Table 2
Fungal spore taxa, grass pollen, weather and air pollutants, 29 May 2008–3 May 2013 (1800 days).

Fungal spore taxa/m^3	n	Mean	SD	Min	25%	Median	75%	90%	Max
Cladosporium	1684	666.2	803.1	0	203	429	814	1442	9153
Aspergillus/Penicillium	1684	92.9	189.8	0	9	41	95	235	3236
Didymella	1684	80.1	141.8	0	5	29	81	217	1263
Coprinus	1684	74.1	206.2	0	5	23	63	163	3941
Periconia	1684	24.8	47.4	0	2	9	27	59	904
Ustilago/smuts	1684	20.7	52.3	0	0	5	18	59	633
Alternaria	1684	20.3	31.2	0	5	9	23	50	344
Epicoccum	1684	13.7	17.7	0	5	9	18	32	253
Ganoderma	1684	10.8	13.2	0	0	7	14	27	145
Fusarium	1684	10.5	22.6	0	0	5	9	27	271
Nigrospora	1684	10.4	44.5	0	0	5	11	23	1681
Cerebella	1684	4.1	17.6	0	0	0	0	9	262
Drechslera	1684	4.0	6.9	0	0	0	5	9	77
Curvularia	1684	3.9	14.9	0	0	0	5	9	276
Torula	1684	3.9	11.9	0	0	0	5	9	253
Puccinia	1684	2.7	6.5	0	0	0	2	9	63
Pithomyces	1684	2.5	4.9	0	0	0	5	9	50
Stemphylium	1684	2.3	4.8	0	0	0	5	9	50
Chaetomium	1684	1.4	3.2	0	0	0	0	5	36
Polythrincium	1684	0.8	2.2	0	0	0	0	5	14
Total spores	1684	1050.0	1015.9	19	418	757	1292.5	2107	10365
Pollen/m^3									
Grass	1516	6.34	12.2	0	0	1	7.5	17	142
Meteorology									
Maximum temperature(°C)	1792	23.7	5.9	11.1	19.1	22.9	27.6	31.4	45.0
Rainfall (mm)	1751	2.0	6.8	0	0	0	0.6	5.8	118.8
Average daily relative humidity(%)	1800	71.2	11.8	0	65.3	72.4	79.1	85.0	99
Pollutants									
$PM_{2.5}$(μg/m3)	1681	66.1	76.8	1	35	58	86	121	2681
PM_{10}(μg/m3)	1624	182.2	401.8	5	113.5	166	221	289	15798
NO_2(ppm)	1663	9.2	5.1	0	5	9	13	16	25
O_3(ppm)	1727	12.5	7.0	0	7	13	17	22	38

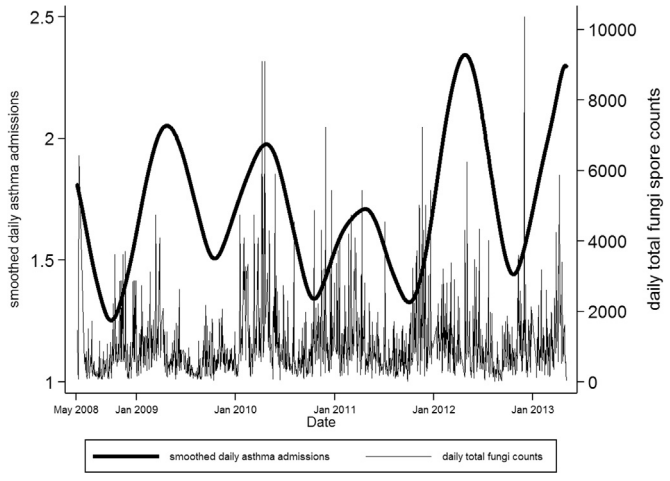

Fig. 1. Daily smoothed asthma hospitalisation counts and daily counts of total fungi.

Yousef, 2007), Israel (Garty et al., 1998) or UK (Khot et al., 1988), however these studies were conducted over shorter time periods with smaller study samples and may have lacked power to detect effects; none of these studies examined lagged effects or stratified by age groups or sex; and only one study examined individual fungal taxa (Pongracic et al., 2010). Other studies have found associations between some fungal taxa in Canada (Dales et al., 2000, 2003, 2004; Raphoz et al., 2010), the UK (Atkinson et al., 2006; Newson et al., 2000), and India (Chakraborty et al., 2014). The closest comparators are studies that analysed individual fungal taxa rather than by phyla (a subdivision of the Fungal Kingdom that groups fungal taxa based on their reproductive processes, e.g. Basidiomycetes, Ascomycetes and Deuteromycetes).

In the UK, Newson and colleagues (Newson et al., 2000) found significant associations between asthma epidemics involving the age group 0–14 years compared to those aged ≥15 years (which included adults) and hyaline Basidiospores, *Didymella*, *Leptosphaeria*, other coloured Ascospores and *Botrytis* on the same day and one day lag. In addition they found no associations between total fungal spore counts in either of these two age groups. Also in the UK, Atkinson and colleagues (Atkinson et al., 2006) found spores most strongly and consistently associated with emergency department (ED) attendance and hospitalisation included *Alternaria*, *Epicoccum*, *Botrytis*, smuts, hyaline Basidiospores and other coloured Ascospores. They also found *Coprinus* was consistently associated with child asthma emergency department attendance, hospitalisation and visits to the medical practitioner which is similar to our most significant finding. *Coprinus* may be an under-recognised fungal spore taxon in relation to asthma exacerbation that may warrant further investigation.

In an inner city study conducted in multiple cities in the USA, Pongracic and colleagues (Pongracic et al., 2010) detected that outdoor *Alternaria*, *Aspergillus*, *Cladosporium* and *Penicillium* were significantly associated with increased asthma symptoms; and indoor *Aspergillus* was significantly associated with unscheduled visits to the doctor or hospital ED in children aged 5–11 years.

In Montreal, Canada, Raphoz and colleagues (Raphoz et al., 2010) found significant associations between increased asthma emergency department attendances and Basidiomycetes (taxa not defined) and *Cladosporium* at Lag 4 days. A Canadian study that examined the association between thunderstorms and asthma ED attendances found that increases in *Cladosporium*, *Penicillium*, *Aspergillus*, Ascomycetes and total spores were associated with increased asthma ED attendances regardless of whether there was a thunderstorm or not (Dales et al., 2003). Unlike a number of these studies, our study did not find significant associations between asthma hospitalisation and *Cladosporium* (except in girls), *Alternaria* or *Aspergillus*.

Table 3
Adjusted associations, OR (95% CI), between fungal spore taxa and asthma hospitalisation.

Fungi	Lag 0	Lag 1	Lag 2	Lag 3	Cumulative lag
Cladosporium	1.02 (0.98–1.05)	0.99 (0.95–1.03)	1.03 (0.99–1.07)	1.03 (0.99–1.06)	1.01 (0.99–1.03)
Aspergillus/Penicillium	1.02 (0.99–1.05)	1.02 (0.98–1.05)	0.99 0.95–1.02)	1.01 (0.97–1.04)	1.01 (0.99–1.02)
Didymella	0.99 (0.94–1.04)	1.03 (0.99–1.07)	1.03 (0.99–1.08)	1.02 (0.98–1.06)	1.01 (0.99–1.03)
Coprinus	**1.03 (1.01–1.06)***	**1.03 (1.01–1.06)***	1.02 (0.99–1.05)	1.02 (0.99–1.04)	**1.01 (1.01–1.02)***
Periconia	**1.03 (1.001–1.07)***	0.98 (0.95–1.01)	0.98 (0.94–1.01)	1.01 (0.97–1.05)	0.99 (0.98–1.01)
Ustilago/smuts	1.03 (0.98–1.07)	1.00 (0.96–1.04)	0.98 (0.94–1.03)	1.01 (0.96–1.04)	1.01 (0.99–1.02)
Alternaria	0.96 (0.92–1.01)	0.99 (0.95–1.04)	0.99 (0.95–1.04)	0.99 (0.96–1.04)	0.99 (0.97–1.01)
Epicoccum	1.00 (0.97–1.07)	1.03 (0.99–1.06)	1.00 (0.96–1.04)	1.03 (0.99–1.06)	1.01 (0.99–1.03)
Ganoderma	1.02 (0.98–1.07)	1.03 (0.99–1.08)	1.00 (0.96–1.05)	1.03 (0.98–1.08)	**1.02 (1.00–1.04)***
Fusarium	0.98 (0.95–1.02)	0.97 (0.93–1.01)	0.97 (0.93–1.01)	0.97 (0.93–1.01)	0.98 (0.97–0.99)
Nigrospora	0.99 (0.98–1.01)	0.99 (0.99–1.00)	1.00 (0.99–1.01)	1.02 (0.98–1.05)	1.01 (0.99–1.02)
Cerebella	1.01 (0.99–1.02)	1.00 (0.98–1.02)	1.01 (0.99–1.03)	1.01 (0.99–1.03)	**1.01 (1.00–1.01)***
Drechslera	1.02 (0.99–1.05)	0.99 (0.97–1.02)	0.99 (0.97–1.03)	1.01 (0.98–1.03)	1.00 (0.99–1.01)
Curvularia	1.00 (0.99–1.01)	0.99 (0.98–1.01)	0.99 (0.99–1.00)	0.99 (0.99–1.01)	0.99 (0.99–1.00)
Torula	0.99 (0.98–1.02)	0.98 (0.96–0.99)	0.99 (0.98–1.02)	0.99 (0.98–1.02)	0.99 (0.99–1.00)
Puccinia	1.00 (0.95–1.05)	1.00 (0.95–1.06)	0.92 (0.87–0.98)	0.98 (0.92–1.04)	0.98 (0.96–1.01)
Pithomyces	1.01 (0.98–1.04)	1.01 (0.99–1.05)	0.99 (0.96–1.03)	1.01 (0.98–1.04)	1.00 (0.99–1.02)
Stemphylium	0.97 (0.94–1.01)	1.02 (0.98–1.06)	1.00 (0.96–1.05)	0.99 (0.96–1.04)	1.00 (0.98–1.02)
Chaetomium	1.00 (0.93–1.08)	0.96 (0.88–1.05)	**1.08 (1.00–1.16)***	1.05 (0.97–1.13)	1.02 (0.98–1.06)
Polythrincium	0.89 (0.8–0.98)	0.97 (0.88–1.07)	0.97 (0.88–1.07)	1.03 (0.94–1.14)	0.96 (0.99–1.00)
Total spores	1.03 (0.99–1.07)	1.00 (0.96–1.05)	1.03 (0.99–1.07)	1.03 (0.99–1.07)	**1.02 (1.00–1.03)***

Models adjusted for maximum temperature, relative humidity and grass pollen; **bold** numbers=statistically significant *p < 0.05.

It is possible that some fungal taxa included in our study were used in the analyses in other studies, but were not individually identified beyond the phylum level so direct comparison cannot be made. The classification of fungal taxa is an important limitation when comparing results from different studies. The fungal classification system was revised in 2006 after improved DNA sequencing resolved fungi into eight phyla, and the phylum Deuteromycetes was discarded with reclassification of these fungal taxa into the phyla Ascomycetes, Basidiomycetes or Zygomycetes. These three phyla contain the majority of fungal taxa that produce airborne allergens (Levetin et al., 2015).

We did not include air pollutants in the final model as they did not change the effect estimates significantly or appear to act as confounding variables. This is consistent with some studies (Atkinson et al., 2006; Dales et al., 2000; Raphoz et al., 2010) but not others (Cakmak et al., 2012). Cakmak et al.'s large study that pooled data from 11 Canadian cities over 13 years found that the relative risk of asthma hospitalisation associated with three fungal phyla increased when air pollutant concentrations were higher (Cakmak et al., 2012). Our five-year study period in one region that may experience lower levels of air pollution compared to Canadian cities may have had insufficient power to detect interactions between fungal spores and air pollutants.

The evidence of lagged effects cannot be definitively explained as we do not know whether the hospitalised children had some delay in experiencing serious asthma symptoms, had previously been to a

Table 4
Adjusted associations, OR (95% CI), between fungi and asthma hospitalisation for: girls; stratified by age group (a) 2–13 years and (b) 14–18 years.

Fungi	Lag 0	p-int	Lag 1	p-int	Lag 2	p-int	Lag 3	p-int	Cumulative lag	p-int
Girls										
Cladosporium	**1.06 (1.01–1.1)***	0.038	1.02 (0.96–1.09)	0.198	1.05 (0.99–1.11)	0.423	**1.06 (1.01–1.11)***	0.116	**1.03 (1.01–1.05)***	**0.020**
Coprinus	**1.07 (1.03–1.11)***	**0.008**	**1.08 (1.04–1.13)***	**0.001**	**1.06 (1.02–1.11)***	**0.01**	1.04 (0.99–1.08)	0.107	**1.03 (1.02–1.05)***	**< 0.001**
Chaetomium	1.02 (0.9–1.15)	0.579	0.99 (0.86–1.14)	0.507	**1.13 (1.01–1.27)***	0.235	1.07 (0.96–1.19)	0.562	1.05 (0.99–1.12)	0.101
Total fungi	**1.08 (1.02–1.14)***	**0.017**	1.04 (0.98–1.11)	0.138	1.05 (0.99–1.11)	0.382	**1.06 (1.01–1.12)***	0.092	**1.04 (1.02–1.06)***	**0.007**
2–13 years										
Coprinus	**1.03 (1.01–1.06)***	**0.002**	1.03 (0.99–1.06)	**0.016**	1.02 (0.99–1.05)	0.511	1.01 (0.99–1.03)	0.550	**1.01 (1.00–1.02)***	**0.003**
Puccinia	0.99 (0.95–1.06)	0.961	0.98 (0.92–1.05)	**0.044**	**0.93 (0.86–0.99)***	**0.048**	0.95 (0.89–1.03)	0.979	0.97 (0.95–1.0)	0.104
Polythrincium	0.87 (0.78–0.98)	0.191	0.95 (0.86–1.07)	**0.007**	0.92 (0.82–1.03)	0.890	1.04 (0.93–1.17)	**0.05**	**0.95 (0.9–0.99)***	**0.002**
14–18 years										
Coprinus	**1.18 (1.08–1.29)***	**0.002**	**1.18 (1.05–1.32)***	**0.016**	1.09 (0.9–1.31)	0.511	1.02 (0.9–1.16)	0.550	**1.06 (1.03–1.09)***	**0.003**
Ustilago/smuts	**1.25 (1.03–1.5)***	**0.074**	0.87 (0.7–1.09)	0.298	0.83 (0.66–1.04)	0.154	0.88 (0.65–1.2)	0.476	0.94 (0.85–1.04)	0.209
Stemphylium	**0.79 (0.63–0.99)***	**0.049**	0.81 (0.58–1.13)	0.147	0.9 (0.72–1.14)	0.528	0.97 (0.8–1.18)	0.830	0.88 (0.99–1.06)	**0.001**
Puccinia	1.03 (0.74–1.4)	0.961	**0.55 (0.31–0.97)***	**0.044**	**0.69 (0.52–0.92)***	**0.048**	0.94 (0.66–1.33)	0.979	0.82 (0.67–1.0)	0.104
Polythrincium	0.54 (0.26–1.1)	0.191	**0.28 (0.12–0.66)***	**0.007**	0.95 (0.52–1.72)	0.890	0.35 (0.12–1.0)	**0.05**	**0.83 (0.74–0.94)***	**0.002**

Adjusted for age, maximum temperature, relative humidity and grass pollen p-int=interaction p-value **bold** numbers=statistically significant.
* p < 0.05.

general medical practitioner, but their condition had deteriorated warranting high level care, or whether parents/carers delayed accessing the hospital for any number of reasons. Other possible explanations for the lagged effects may relate to different biological mechanisms that may be taking place. Inspiration of fungal spores into the respiratory system can elicit an allergic response and subsequent bronchoconstriction which is likely to occur rapidly after exposure. Or alternatively, fungal spores can release mycotoxins or volatile organic compounds onto the epithelial lining that cause airway inflammation which may have a cumulative effect over a number of days of exposure, leading to delayed bronchoconstriction. (Denning et al., 2006). Residual confounding from other individual or environmental variables may also contribute to the lagged effects. Further studies of the lagged effects are needed.

Previous research in south-eastern Australia has indicated that, in asthmatic children, prevalence of *Alternaria* sensitisation is approximately 4% in humid, coastal areas and 17% in dry, inland areas (Peat et al., 1993). In a metropolitan area, sensitisation to *Alternaria* is approximately 9%, and sensitisation to either *Alternaria* or *Cladosporium* is approximately 14% (Tham et al., 2016). Although we did not know the sensitisation rates for children in south-western Sydney, if the rates are similar to these other regions then overall fungal sensitisation was quite low and this might contribute to the weak associations we have observed.

We did not have data on the atopic status of each child or adolescent to assess whether atopy had modified the effect of fungal spore exposure on asthma hospitalisation. Understanding of the contribution of fungal allergy to asthma exacerbation is limited. Assessing fungal allergy for the wide range of potentially allergenic fungi has been restricted to focussing on only a few fungal taxa, predominantly *Alternaria, Cladosporium, Aspergillus* and *Penicillium* out of approximately 80 genera that have been shown to induce allergic reactions (Simon-Nobbe et al., 2008). The contribution of atopy as a risk factor for asthma severity is further complicated by the role of cross-reactivity between fungal spore allergens. Cross-reactivity is the ability of the immune system to recognize similarities between different allergens, such that antibodies produced against one allergen will also react against another similar allergen. Fungal allergens that have been identified as potentially cross-reactive due to their protein structures include: *Aspergillus, Alternaria, Cladosporium, Coprinus* and *Penicillium*. Fungal cross-reactivity and its clinical significance require further research using a wider range of fungal allergens (Crameri et al., 2014). Further studies are required to more carefully identify whether allergy to one fungal taxon can increase the risk of allergic sensitisation to other fungal taxa and to investigate other possible mechanisms by which fungal spores can trigger asthma exacerbations. Improving our understanding of these relationships and mechanisms may help to identify high-risk groups for targeted interventions to prevent exacerbations of allergic conditions, such as asthma.

Only one other study examining the contribution of outdoor fungi spores to child asthma hospitalisation analysed differences by sex, and found that boys aged less than 13 years and women older than 15 years were more vulnerable (Cakmak et al., 2005). This contrasts with our finding that in SW Sydney, girls appear to be more vulnerable. The demographics of that large 10-city population study (approximately 350,000) were not reported and hospital readmissions were not explicitly excluded, so our results may not be directly comparable.

6. Strengths and limitations

This study has analysed five years of daily fungal spore count data at the taxa level which is unique in the Australasian region. The case-crossover design is well suited for studying the effects of transient short-term environmental exposures on the risk of asthma exacerbations in individuals. As cases serve as their own controls, there is reduced risk of confounding due to stable individual characteristics i.e. age, sex, fungal sensitisation or behavioural factors. The selection of bidirectional control periods allows adjustment for seasonal trends. This method is an improvement on previous studies that have utilised time-series and correlational designs that could not be adjusted for differences in individual characteristics. Our study was limited by lack of data on whether the children and adolescents hospitalised for asthma were also infected with any type of respiratory virus. It is well documented that human rhinovirus is strongly associated with child asthma hospitalisations (Busse et al., 2010; Erbas et al., 2015; Tham et al., 2016) and should be controlled for in analyses. However, our previous research in Melbourne found that asthma hospitalisations were associated with a number of fungal taxa independent of human rhinovirus infection (Tham et al., 2016).

Our study used generalized additive models (GAM) rather than generalized linear models (GLM) as the GAM allows a smooth non-linear functional form between the exposure and outcome compared to a GLM which specifically fits a linear combination of the explanatory variables (Guisan et al., 2002). Given the scarcity of evidence on these tested associations, we chose not to make assumptions about any potential linearity in the relationships. Some exposures could be specified as linear, but this is dictated from the data relationship between the exposures and the outcome. A GAM also has the advantage of allowing a combination of linear and smooth terms for the predictors.

Although our effect estimates do not appear to be strong, geographic and demographic variables unique to Sydney may have contributed. Firstly, Campbelltown, Liverpool and Camden are classified as a national growth area (http://www.ngaa.org.au/) with the largest population group being aged < 20 years and increasing in size (Australian Bureau of Statistics, 2011). The overall socioeconomic status of Campbelltown and Liverpool is considered lower than the national average, but within this there are areas that are high and some very low (South West Sydney Local Health District, 2014b, 2014c). The overall socioeconomic status of Camden is considered higher (South West Sydney Local Health District, 2014a). In 2008 current child (aged 2–15 years) asthma rates in this region were the third highest in New South Wales after the Hunter-New England and Greater Western (lowest socio-economic area) regions with significantly more boys affected than girls (Centre for Epidemiology and Research, 2010). Additionally it is an area of urban development of farming land that is nestled alongside a national park. The vegetation was a major source of the outdoor fungal spores recorded in this study. As Campbelltown is located 61 km and Liverpool 35 km from Sydney city centre, we expected that most children with asthma exacerbations would attend the nearest hospital. However, Sydney has two well established children's hospitals, one of which is located west of Sydney at Parramatta. It is possible that some parents of asthmatic children were prepared to travel to this specialised hospital and these children were excluded from our study. Also our sample size being limited to one region of a large city may have limited our ability to detect stronger associations or we may be seeing a Type I statistical error resulting in some possible false positive associations. The lower socioeconomic status in parts of this region increases the risk of asthma exacerbation possibly related to exposure to other environmental triggers, such as indoor air pollution, environmental tobacco smoke, and building conditions.

We should also consider exposure misclassification as a contributor to these findings. We cannot be certain that each child or adolescent was exposed to the same levels of fungal spores, pollen or pollution exposures counted at this single site and it is therefore impossible to gauge the generalisability of exposure. However we did limit the inclusion of hospital admissions to within 30 km of the fungal spore trap to reduce the variability of outdoor exposures with changing vegetation types and densities and climatic variations. In a previous study in inland New South Wales, Mitakakis and colleagues (Mitakakis et al., 2000) reported that the levels of *Alternaria* spores counted in a

Burkard trap (located in similar position as this study – on the roof of a rural hospital) were similar to those counted in personal air monitors. They also found that fungal spores and pollen were inhaled at higher levels when participants (adults and children) were outdoors or active indoors compared to periods of rest.

As we are considering outdoor exposure, misclassification of fungal exposure is likely to be non-differential, hence it should bias the risk estimates towards null. The absence of indoor fungal spore measurements may limit our exposure assessment and the possible contribution of these spores to asthma exacerbation. The concentrations and diversity of indoor fungal spores appears to be related to mould presence inside and the levels of outdoor fungal spores that enter the indoor environment through doors and windows (Weikl et al., 2016). To overcome potential confounding from outdoor fungal spores that migrated indoors we controlled for the climatic variables that most influence fungal spore production (maximum temperature and relative humidity). However, as we could not account for household mould some asthma exacerbations attributed to outdoor fungal spores may be over-estimated or the contribution of indoor fungal spores to asthma exacerbations may be underestimated. However, if indoor and outdoor fungal spores have the same effect on hospitalisation risk then this would most likely lead to non-differential misclassification and a bias toward the null.

7. Conclusion

Our findings indicate that there may be associations between some outdoor fungal spore taxa and child and adolescent asthma hospitalisations in this region. This calls for further research to explore whether these findings can be replicated; and to examine whether fungal sensitisation and/or human rhinovirus infections are associated with stronger effects. If these findings are replicated, then the need to develop predictive models for fungal spore distribution and levels may become more important.

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Competing financial interests declaration

M.J.Abramson holds investigator initiated grants from Pfizer and Boehringer-Ingelheim for unrelated research. He has undertaken an unrelated consultancy for AstraZeneca. He has received assistance with conference attendance from Boehringer-Ingelheim and Sanofi. All other authors declare no conflict of interest.

Ethics

Ethics approvals were obtained from South West Sydney Local Health District Human Research Ethics Committee (LNR/13/LPOOL/189).

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.envres.2016.12.016.

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