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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

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fungal spores are related to persistent damp in household structures 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