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Characterising non-linear associations between airborne pollen counts and respiratory symptoms from the AirRater smartphone app in Tasmania, Australia: A case time series approach

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ABSTRACT

Pollen is a well-established trigger of asthma and allergic rhinitis, yet concentration-response relationships, lagged effects, and interactions with other environmental factors remain poorly understood. Smartphone technology offers an opportunity to address these challenges using large, multi-year datasets that capture individual symptoms and exposures in real time. We aimed to characterise associations between six pollen types and respiratory symptoms logged by users of the AirRater smartphone app in Tasmania, Australia. We analyzed 44,820 symptom reports logged by 2272 AirRater app users in Tasmania over four years (2015–2019). With these data we evaluated associations between daily respiratory symptoms and atmospheric pollen concentrations. We implemented Poisson regression models, using the case time series approach designed for app-sourced data. We assessed potentially non-linear and lagged associations with (a) total pollen and (b) six individual pollen taxa. We adjusted for seasonality and meteorology and tested for interactions with particulate air pollution ($PM_{2.5}$). We found evidence of non-linear associations between total pollen and respiratory symptoms for up to three days following exposure. For total pollen, the same-day relative risk (RR) increased to 1.31 (95% CI: 1.26–1.37) at a concentration of 50 grains/m^3 before plateauing. Associations with individual pollen taxa were also non-linear with some diversity in shapes. For all pollen taxa the same-day RR was highest. The interaction between total pollen and $PM_{2.5}$ was positive, with risks associated with pollen significantly higher in the presence of high concentrations of $PM_{2.5}$. Our results support a non-linear response between airborne pollen and respiratory symptoms. The association was strongest on the day of exposure and synergistic with particulate air pollution. The associations found with *Dodonaea* and Myrtaceae highlight the need to further investigate the role of Australian native pollen types in allergic respiratory disease.

1. Introduction

Pollen is well established as a trigger of allergic rhinitis and allergic asthma worldwide. Studies from numerous regions show high rates of sensitization to key pollen types amongst the atopic population (Heinzerling et al., 2009; Kam et al., 2016; Lou et al., 2017), and many

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epidemiological studies have found associations between atmospheric pollen concentrations and adverse respiratory outcomes (Erbas et al., 2018; Guilbert et al., 2018; Kitinoja et al., 2020). Collectively, these outcomes constitute a major health and socio-economic burden (Kulthanan et al., 2018; Zuberbier et al., 2014), with the prevalence of allergic rhinitis and allergic asthma climbing in many regions (Pawankar, 2014). In coming years, climate change is predicted to further exacerbate these health risks by increasing pollen season severity and length (Beggs et al., 2019; Ziska et al., 2019).

In this context, there is a strong research imperative to provide policy makers and clinicians with the information they need to better address the impacts of pollen on respiratory health. Concentration-response relationships are crucial to understanding when pollen is likely to pose greatest risk; however the available evidence suggests that these relationships are complex, non-linear, distinct for upper and lower respiratory symptoms, as well as being taxon and location-specific (Caillaud et al., 2012; Damialis et al., 2019; Guilbert et al., 2018; Kitinoja et al., 2020; Tobias et al., 2004). This variability underlines the need for research across a range of pollen types (taxa) and locations to provide the robust, locally-relevant evidence that individuals and health care providers need in order to understand the clinical relevance of pollen data and forecasts.

Particulate air pollution is another airborne hazard that is increasing in association with climate change, especially as a result of severe episodic smoke emissions associated with wildfires. A substantial body of mechanistic and observational epidemiological evidence suggests that particulate pollution exacerbates the impact of pollen on allergic and asthma symptoms: for example by acting as an adjuvant that stimulates IgE-mediated responses, by damaging the pollen cell wall, and/or facilitating the release of small allergen-carrying particles capable of penetrating the lower airways (Reinmuth-Selzle et al., 2017; Sedghy et al., 2018). However, the evidence base is conflicting (e.g. Guilbert et al., 2018; Krmpotic et al., 2011) and further research is needed to enable policy makers and health care providers to understand the implications of combined pollen and particulate exposure. Few studies have investigated interactions between pollen and particulate pollution with non-linear methods.

Smartphone technology provides new opportunities to address these gaps by enabling capture of large datasets of symptom reports submitted by users, collected in near-real time and coupled with geo-located environmental co-variates determined using the smartphone GPS position. Due to the low burden placed on participants, smartphone-based studies can gather data from large cohorts over multiple years (Ambrosini et al., 2018; Chan et al., 2018). They also capture information on day-to-day symptoms that present a substantial health and socio-economic burden (Zuberbier et al., 2014), yet rarely result in hospital or primary care presentations. While smartphone data—particularly when crowd-sourced—are not without analytical challenges (Dorsey et al., 2017), several studies have now demonstrated the capacity of these data to provide useful epidemiological insights into asthma and allergic symptoms (Chan et al., 2018; Jones et al., 2020). New statistical techniques are becoming available to minimize the effects of selection and reporting bias, and maximize the opportunities for obtaining robust and useful insights for public health practice(Gasparrini, in press).

As an exemplar of this technology, we use data from the AirRater smartphone app (Johnston et al., 2018) to assess concentration-response relationships to a range of pollen types in the island state of Tasmania, Australia. Allergic rhinitis affects 22.5% of the adult population in Tasmania, and as such it has amongst the highest rates of asthma and allergic rhinitis in Australia and in the developed world (Australian Institute of Health and Welfare and Australian Bureau of Statistics, 2017; Pawankar et al., 2013). Tasmania is also an ideal location in which to examine interactive effects of pollen and particulate pollution, due to extremely low baseline levels of particulate pollution outside the wood heater and landscape smoke seasons, and extremely low levels of any other types of air pollution. Further, Tasmania has an established pollen and particulate pollution monitoring network that provides a geographically representative coverage of the major population centres.

Our previous research has demonstrated clear associations between AirRater symptom reports and a range of pollen types, including native Australian taxa (Jones et al., 2020). Here we extend on this research base by using a novel method, case time series analysis. We aim to provide robust, locally-relevant knowledge to support public health messaging and advice, and expand knowledge on taxonomic and geographical variability in concentration-response curves. We specifically ask:

a) What are the concentration-response relationships between key pollen taxa and app-logged respiratory symptoms in Tasmania, Australia?
b) Does particulate air pollution modify the association between total pollen concentrations and respiratory symptoms?

2. Methods

2.1. Study design and population

We evaluated associations between atmospheric pollen concentrations, particulate air pollution, and symptom reports relating to the eyes, nose and lungs that were logged by users of the free AirRater smartphone app in Tasmania, Australia (Fig. 1, population 535,000). Our study spans the first four years of the app's operation (October 29 2015–October 29 2019) and includes all AirRater users in Tasmania who consented to be study participants (n = 2272). More than 65%, 48% and 34% of participants respectively identify as having allergic rhinitis, asthma or both (Johnston et al., 2018). This research was approved by the Tasmanian Health and Medical Human Research Ethics Committee (Reference: H0015006); all participants provided informed consent via an online form.

2.2. Exposure data

We collected daily pollen concentrations of 27 pollen taxa from six sites across Tasmania as described in Johnston et al. (2018). We used Hirst-type volumetric spore traps (Burkard Manufacturing) and followed Australian standard methods for both counting and sampling (Beggs

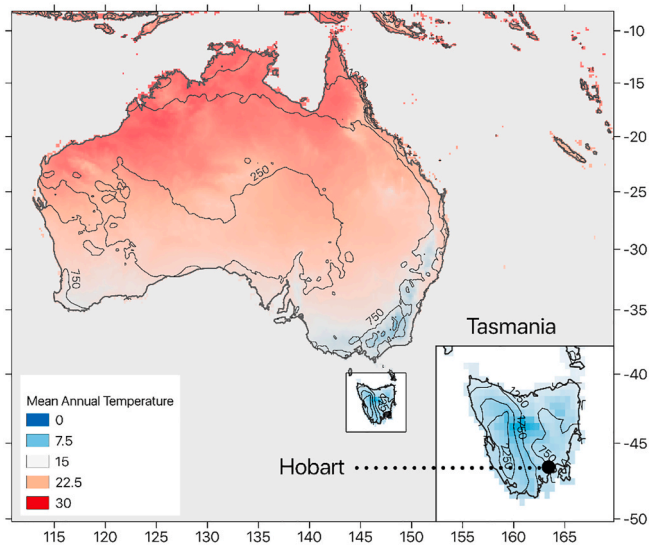

Fig. 1. Map showing the location of Tasmania, Australia and its capital city of Hobart. Approximately 40% of Tasmania's 535,000-strong population reside in Hobart.

et al., 2018). A full list of monitored taxa is available in Supplementary Material (Table S1).

We used meteorological and particulate pollution data as co-variates. These data were sourced from the Base Line Air Network (BLANkET) run by the Environment Protection Authority Tasmania. The BLANkET stations measure particulate matter less than 2.5 μm in aerodynamic diameter ($PM_{2.5}$) using a DustTrak optical analyzer. The stations also sample air temperature, relative humidity, precipitation, barometric air pressure, wind speed and wind direction at 10-min intervals. For each station, we aggregated the meteorological and air quality data into daily observations including: total rainfall (mm), maximum and minimum temperature (°C), mean relative humidity (percentage), and daily average concentration of $PM_{2.5}$ (μg/m^3). There are 35 BLANkET stations dispersed across Tasmanian population centres (Fig. 2).

For all exposures (pollen, air quality, and meteorological variables), each individual was assigned an exposure value based on the operational pollen or air quality station they were closest to on each given day, based on their geolocation as recorded by the app in real time. In some instances, users had disabled background location tracking, for these users, for periods during which they did not use the app (and thus had no location recorded), we used their last recorded geolocation.

The majority of participants are based in Tasmania's major centres, where air quality and pollen monitors are located. In this context a large proportion of symptom reports were made close to a monitor (Fig. 2), allowing for high confidence in the representativeness of the exposure value. The median distance of each symptom report from an air quality station was 3.9 km, while the median distance from a pollen monitor for each symptom report was 7.2 km. Previous literature suggests that pollen exposure estimates can be considered sufficiently representative to a distance of 20–50 km (Silver et al., 2020).

2.3. Outcome data

Symptom data were collected via the AirRater smartphone app (Johnston et al., 2018). The AirRater app allows individuals to report respiratory symptoms in real-time. The interface collects symptoms following a protocol adapted from the Control of Allergic Rhinitis and Asthma Test (CARAT) (Azevedo et al., 2013). The symptom reporting protocol is described in detail in Jones et al. (2020). In brief, if a user wants to report symptoms they are taken to a screen and asked to identify the body region affected (eyes, nose, lungs or other). Here they specify the symptom present and severity for each body region selected. In order to avoid bias, study participants are blinded to the display of environmental conditions in the app until they have submitted a symptom report. They also receive a reminder prompt to log their symptoms (or the absence of symptoms) every six days.

We defined our outcome measure as the count of eye, nose or lung symptoms logged via AirRater on a single day. We conducted both an overall analysis (of eye, nose and lung symptoms combined), and a supplementary stratified analysis, separated into eye/nose and lung symptoms respectively, see below.

2.4. Statistical analyzes

We used case time series analysis (CTS) to evaluate the associations between AirRater-logged symptoms and pollen concentrations, air quality and meteorological variables(Gasparrini, in press). Crowd-sourced app data present challenges for standard epidemiological methods because they are characterized by factors including continuous recruitment, variable drop-out rates, and inconsistent symptom reporting by participants. CTS has been designed to overcome these challenges by combining the longitudinal structure and flexible control of time-varying confounders (typical of aggregated time series), with the individual-level analysis and control of time-invariant between-subject differences typical of self-matched methods (such as case-crossover and self-controlled case series). A preliminary analysis on the AirRater cohort indicated that the study population was well-suited for modelling using CTS methodologies(Gasparrini, in press).

In order to implement CTS, we used AirRater data to build personalized daily time series for each app user. Each time series incorporated symptom reports in addition to the pollen, air quality and meteorological exposures described above. Each individual's time series spanned between when the user first and last accessed the AirRater app on their mobile phone device. We assumed users had no symptoms on days within their time series on which they had not accessed AirRater.

We modelled the relationships between symptom reports, pollen,

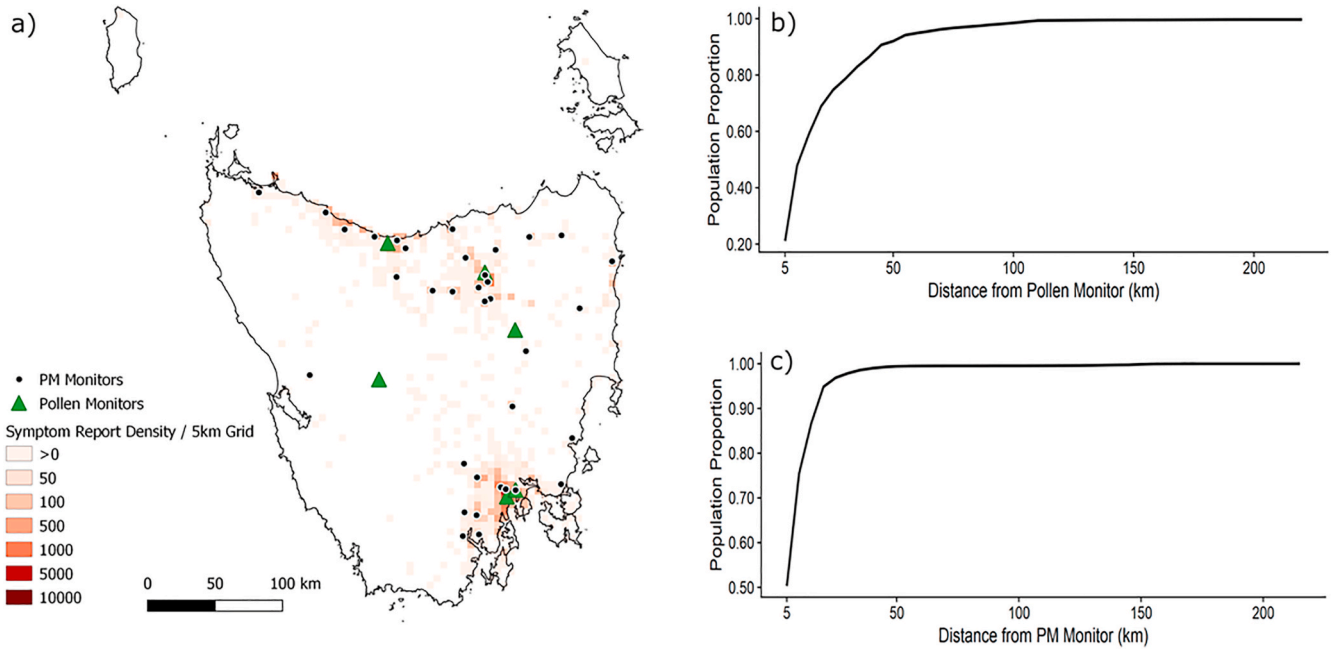

Fig. 2. Meteorological and pollen data for Hobart, Tasmania's capital, over the study period (Oct 29, 2015 to Oct 29, 2019). The pollen taxa have varying y-axes for ease of display. For this study, individuals were assigned exposure-time series matched to their daily location, the Hobart data are provided as a representative exposure time-series only.

particulate pollution and meteorological exposures using a conditional Poisson model over a lag period of 0–3 days. We used an unconstrained distributed lag model for the linear association with $PM_{2.5}$, based on extensive literature supporting a linear association between short-term exposure and respiratory outcomes at the relatively low concentrations observed in our study (Reid et al., 2016; Schwartz et al., 2001). We used bi-dimensional spline distributed lag non-linear models for pollen and meteorological variables, with the evidence suggesting concentration-response relationships are likely to be non-linear (Erbas et al., 2012; Lam et al., 2016; Tobias et al., 2004). Following Gasparrini (in press), we modelled individual-varying baseline risk on top of shared long-term, seasonal, and weekly trends by incorporating natural cubic splines of time (eight degrees of freedom/year), day-of-week variables and subject/month strata intercepts.

Our primary model (**Model 1**) assessed associations between all symptom reports and the six individual pollen taxa most prevalent in Tasmania over the study period: *Betula* (birch), *Allocasuarina* (Australian she-oaks), Cupressaceae (cypress family), *Dodonaea* (hop bush), Myrtaceae (eucalypt family), and Poaceae (grass family). This model included $PM_{2.5}$ and all meteorological and temporal and seasonal factors listed above as co-variates.

A secondary model (**Model 2**) tested for an interaction between total pollen and $PM_{2.5}$. We assessed differences by predicting the risk associated with pollen exposure at a range of daily $PM_{2.5}$ concentrations as follows: baseline (3 μg/m^3), moderate (25 μg/m^3, the Australian national guideline for daily exposure), high (50 μg/m^3) and very high (100 μg/m^3).

We also implemented supplementary stratified analyses to investigate differences in associations between symptom reports related to the eyes/nose (more likely to be associated with allergic rhinitis) and those related to the lungs (more likely to be associated with asthma). These were parametrized in the same way as Model 1.

We performed diagnostic evaluations, including testing for linearity via QQ-plots and testing for multi-collinearity via Pearson correlations. Statistical analyses were undertaken in R (Version 3.5.3), using packages 'dlnm', 'gnm', 'Epi', 'lubridate', 'zoo', 'dplyr', and 'data.table' (Carstensen et al., 2019; Dowle and Srinivasan, 2019; Gasparrini, 2011; Grolemund and Wickham, 2011; R Core Team, 2020; Turner and Firth, 2020; Wickham et al., 2017; Zeilis and Grothendieck, 2005).

For all models we report results as relative risk (RR) between the exposures and the symptom reporting outcome. For individual pollen taxa we display results only up to concentrations of 50 grains/m^3 as concentrations above this are uncommon in Tasmania. We therefore considered findings above 50 grains/m^3 as less robust owing to the low number of data points and being less relevant from a public health perspective.

3. Results

3.1. Symptom reports, pollen and other environmental exposures

We analyzed a total of 36,996 symptom reports from 2272 participants over a total 617,538 user days. Of these, 29,701 were eye/nose related symptoms and 7295 were lung-related symptoms. The mean time series length of a participant was 272 days, with a minimum of 3 and a maximum of 1461 days. The number of reports within each user's time series averaged 19.7 and varied from 1 to 1069. As case time series is a self-matched design based on within-subject comparison, the differential follow-up periods do not affect the estimates.

The distributions of meteorological, air quality and pollen data for Hobart, Tasmania's capital, over the study period are illustrated in Fig. 3. $PM_{2.5}$ is higher on average during winter due to domestic wood heater emissions (Reisen et al., 2013); in summer, $PM_{2.5}$ is generally very low, but with occasional peaks due to wildfires. *Betula* (birch), *Allocasuarina* (she-oak), Cupressaceae (cypress family), *Dodonaea* (hop bush, primarily *D. viscosa*), Myrtaceae (includes *Eucalyptus*, *Leptospermum* and *Melaleuca*) and Poaceae (grasses) were the most commonly represented pollen taxa. No variables met our pre-determined criteria for multicollinearity (>0.8 Pearson correlation). Note that the Hobart data are provided as an example only: as described above, individuals were assigned exposure levels by geolocation. However, all parts of the island have a cool maritime climate, and both $PM_{2.5}$ and pollen taxa show similar seasonal patterns in both the north and the south (Johnston et al., 2018), see Fig. S1 in Supplementary Material for comparative box-plots of all exposure variables in the three major population centres, Hobart (south), Launceston (inland north) and Burnie (coastal north-west). Summary statistics for the overall dataset for all pollen taxa, meteorological variables and $PM_{2.5}$ are available in Supplementary Material, Table S1.

3.2. Associations between symptoms and individual pollen taxa

Our primary analysis **(Model 1)** found non-linear associations between eye, nose and lung symptoms combined and each pollen taxon over lags of 0–3 days (Fig. 4). While there was variation between taxa, concentration response curves were often steeper at lower than at higher pollen concentrations. Apart from *Casuarina*, there was no evidence of a lower threshold below which no association was observed. Same-day associations were consistently stronger than lagged associations for all taxa except Cupressaceae (Fig. 4, Table 1).

With respect to same-day associations (lag 0), Poaceae and Myrtaceae display an initially sharp increase in risk, followed by a slight plateauing of the RR at approximately 30–40 grains/m^3 (see Fig. S2, Supplementary Material). *Betula* and Cupressaceae show similar trends but are closer to being linear. For *Casuarina*, same-day associations were negative at pollen concentrations of 1–25 grains/m^3 but become positive >25 grains/m^3 (Fig. 4, Fig. S2). The same-day RR for *Dodonaea* increased very rapidly to 20 grains/m^3 but then declined. As shown in Table 1, at low (10 grains/m^3) and moderate (30 grains/m^3) pollen concentrations, *Dodonaea* and Poaceae had the highest same-day RR. At high pollen concentrations (50 grains/m^3), *Casuarina* had the highest RR, followed closely by Poaceae and *Betula*. Cumulative risk trends for the three-day lag period were similar in shape to the same-day response curves, but with wider confidence intervals (see Fig. S3).

Results from our supplementary analyses stratified by symptom type (eye/nose only; lungs only) showed that concentration-response curves for eye/nose symptoms closely mirror those for the overall analysis—both in terms of the magnitude and shape of the symptom reporting response (Table S2; Figs. S4-6). Concentration-response relationships for lung symptoms were more variable and had wider confidence interval due to the fewer number of symptom reports for this outcome (Table S3; Figs. S7-9).

Associations between symptoms and $PM_{2.5}$ were positive and linear for all combinations of symptom types (eye/nose symptoms, lung symptoms and all symptoms combined, see Fig. S10). In all cases the association was greatest on the same day.

3.3. Interactions between total pollen and $PM_{2.5}$

We found strong evidence of an interaction between $PM_{2.5}$ and total pollen concentrations. Associations between pollen concentrations and symptom reports were of greater magnitude in the presence of higher $PM_{2.5}$ concentrations. (Fig. 5, for RRs at selected pollen concentrations see Table S4). For example, with an interaction centered at $PM_{2.5} = 100$ μg/m3, the RR for exposure to total pollen of 50 grains/m^3 was 1.54 (1.42–1.66) compared with 1.26 (1.2–1.33) at a baseline $PM_{2.5}$ level of 3 μg/m^3. The same pattern was seen in the stratified analyses, especially with eye/nose symptoms (Fig. S11). For lung symptoms, confidence intervals were wider, but the overall trend was similar (Fig. S12).

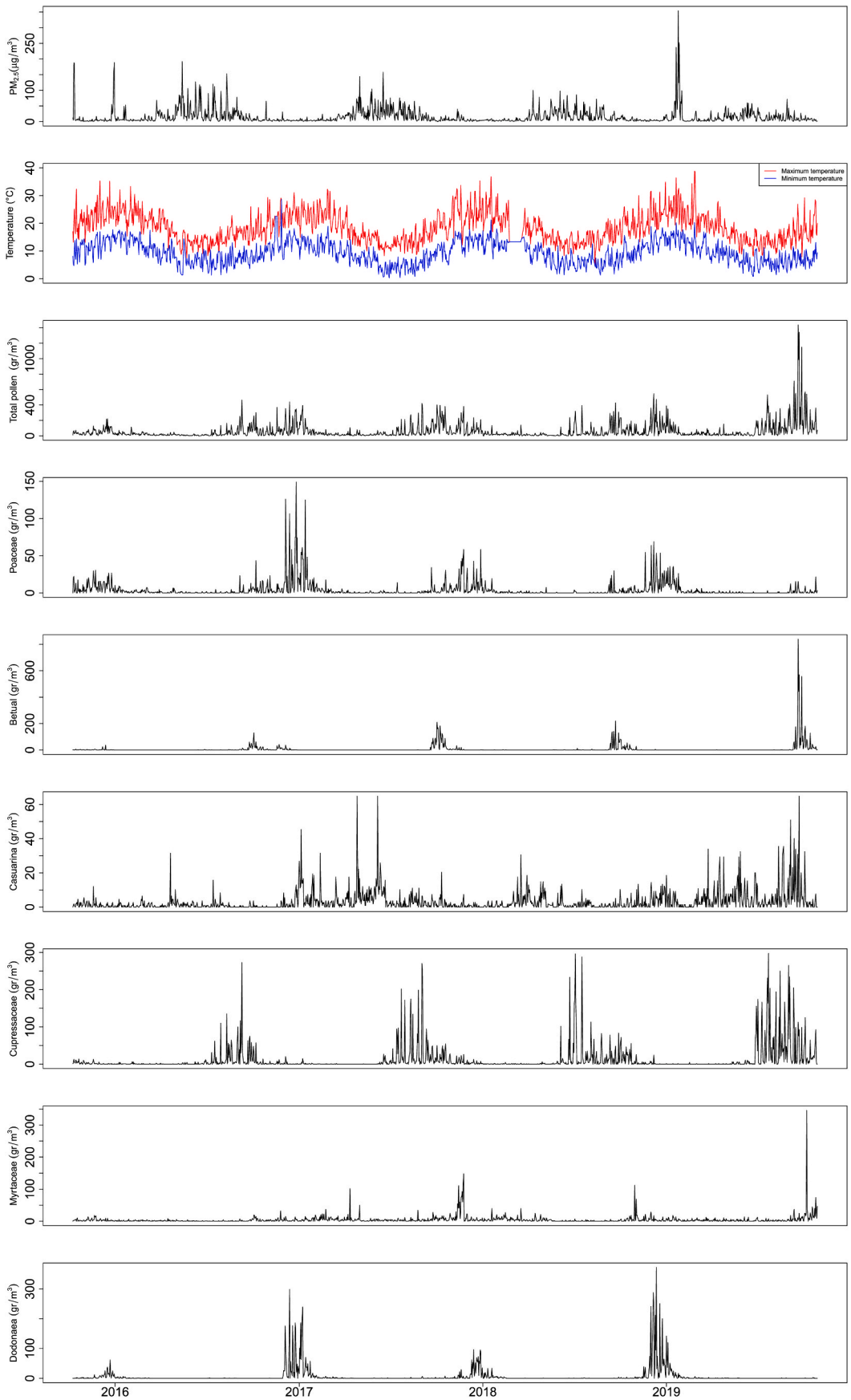

Fig. 3. Associations between AirRater app-user reported eye, nose and lung symptoms (combined), and exposure to the pollen taxa Poaceae, *Betula*, *Casuarina*, Cupressaceae, Myrtaceae and *Dodonaea*, in Tasmania, Australia. Associations are represented as relative risk (RR) and Each panel uses a bi-dimensional risk surface to show the response of symptoms to a given pollen type over a lag of 0–3 days.

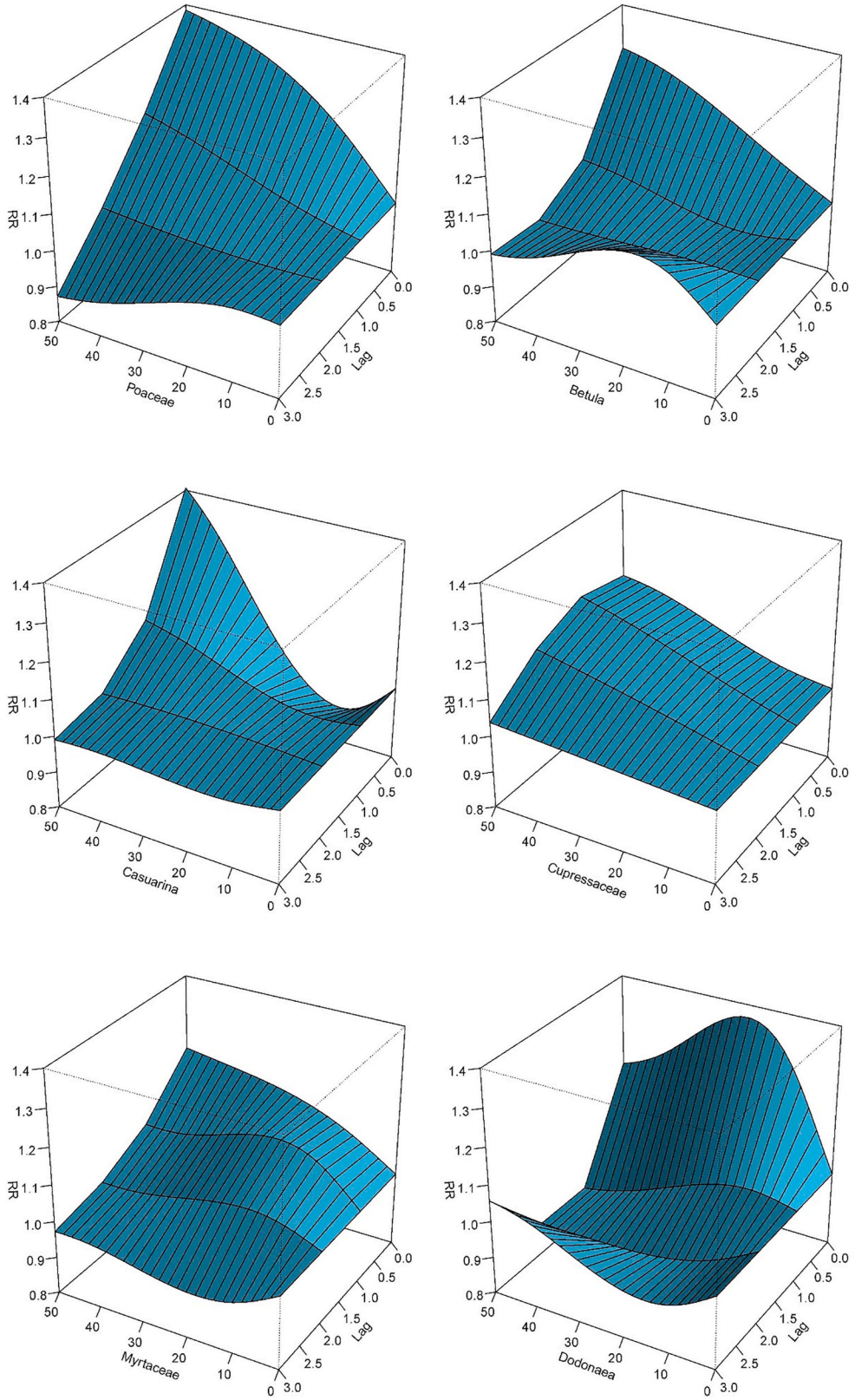

Fig. 4. The effect of an interaction at selected levels of fine particulate matter ($PM_{2.5}$) on the association between total pollen concentration and AirRater app-user reported eye, nose and lung symptoms. The association between total pollen and symptoms is expressed as relative risk (RR) and $PM_{2.5}$ values are in $\mu g/m^3$. Grey shading shows the 95% confidence interval for the association with total pollen without a $PM_{2.5}$ interaction.

Table 1
Relative Risk of AirRater symptom reporting for eye, nose, and lung symptoms (combined) for six pollen taxa over varying levels of exposure and lag periods. Numbers in brackets indicate the 95% confidence interval. Pollen concentrations are in grains/m^3. The model controlled for $PM_{2.5}$, maximum and minimum temperature, relative humidity, and rainfall.

	Exposure level (grains/m^3)	Lag (days)			
		0	1	2	3
Poaceae	10	1.13 (1.08–1.18)	1.03 (0.99–1.06)	1.00 (0.97–1.03)	1.01 (0.96–1.05)
	30	1.31 (1.22–1.40)	1.11 (1.05–1.17)	1.00 (0.95–1.04)	0.94 (0.88–1.00)
	50	1.39 (1.29–1.50)	1.18 (1.11–1.25)	1.01 (0.96–1.07)	0.88 (0.81–0.94)
Betula	10	1.06 (1.00–1.13)	0.98 (0.93–1.02)	1.00 (0.96–1.04)	1.09 (1.03–1.16)
	30	1.20 (1.09–1.31)	1.00 (0.94–1.08)	0.98 (0.93–1.05)	1.07 (0.98–1.17)
	50	1.29 (1.15–1.44)	1.05 (0.96–1.15)	0.98 (0.90–1.06)	0.99 (0.87–1.13)
Casuarina	10	0.90 (0.86–0.95)	0.99 (0.95–1.03)	1.01 (0.97–1.04)	0.98 (0.93–1.03)
	30	1.08 (0.99–1.17)	1.05 (0.98–1.12)	1.02 (0.96–1.08)	0.99 (0.91–1.08)
	50	1.41 (1.23–1.64)	1.13 (1.00–1.26)	1.02 (0.92–1.13)	1.00 (0.87–1.15)
Cupressaceae	10	1.02 (0.97–1.07)	1.04 (1.00–1.08)	1.03 (1.00–1.06)	1.01 (0.96–1.06)
	30	1.10 (1.02–1.18)	1.12 (1.06–1.18)	1.09 (1.03–1.14)	1.02 (0.95–1.10)
	50	1.17 (1.07–1.27)	1.19 (1.11–1.27)	1.14 (1.07–1.21)	1.04 (0.95–1.13)
Myrtaceae	10	1.07 (1.03–1.12)	1.10 (1.07–1.14)	1.05 (1.01–1.08)	0.94 (0.90–0.98)
	30	1.16 (1.08–1.25)	1.11 (1.05–1.18)	1.04 (0.98–1.09)	0.94 (0.88–1.02)
	50	1.20 (1.08–1.34)	1.08 (0.99–1.18)	1.01 (0.93–1.10)	0.98 (0.87–1.09)
Dodonaea	10	1.26 (1.18–1.35)	1.03 (0.98–1.08)	0.94 (0.90–0.98)	0.93 (0.87–0.99)
	30	1.31 (1.20–1.44)	0.97 (0.90–1.03)	0.89 (0.84–0.95)	0.96 (0.89–1.05)
	50	1.16 (1.05–1.28)	0.89 (0.83–0.96)	0.89 (0.83–0.95)	1.05 (0.95–1.15)

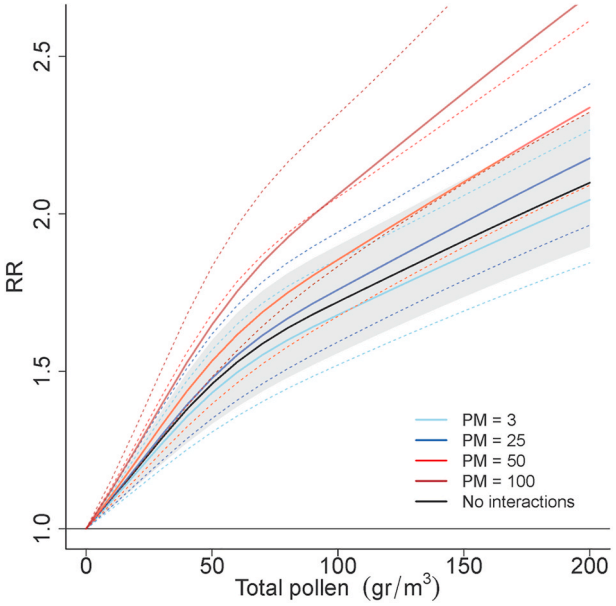

Fig. 5. The effect of interactions centered at selected levels of fine particulate matter ($PM_{2.5}$) on the association between total pollen concentration and AirRater app-user reported eye, nose and lung symptoms. The association between total pollen and symptoms is expressed as the relative risk ratio (RR) and $PM_{2.5}$ values are in μg/m^3. Grey shading shows the 95% confidence interval for the association with total pollen without a $PM_{2.5}$ interaction.

4. Discussion

Drawing on a novel method, case time series analysis, we found non-linear associations between Poaceae, *Betula*, Cupressaceae, *Casuarina* and *Dodonaea* pollen and AirRater-logged respiratory symptoms in Tasmania, Australia. While there was variation between taxa in concentration-response curves, in all cases associations were strongest on the same day. We found some differences in concentration-response curves for upper versus lower respiratory symptoms, and a strong positive interaction with $PM_{2.5}$ pollution, with the effect size doubling from baseline to high (100 μg/m^3) $PM_{2.5}$ concentrations.

4.1. Concentration-response relationships between pollen taxa and allergic symptoms

A key finding to emerge from our data is that for most taxa, with the single exception of *Casuarina*, there was no evidence for a lower threshold pollen concentration below which no associations were observed. This has relevance for clinical advice and practice: it suggests there is no 'safe level' below which symptoms would not be expected in some portions of the vulnerable population.

More broadly, our results emphasize the importance of considering non-linearity in response relationships between pollen concentrations and allergic symptoms (whether upper or lower respiratory tract). The clearly non-linear shape of most of our exposure-response curves accords with multiple studies from Australia and elsewhere, which have demonstrated a non-linear response between pollen concentrations and outcome variables ranging from asthma emergency department presentations to daily diaries that record nasal, bronchial and ocular symptoms (Caillaud et al., 2008, 2012; Erbas et al, 2007, 2012; Tobias et al., 2003). Not all studies have found non-linear patterns—for example, Silver et al. (2020) found a linear relationship between app-logged symptoms and Poaceae pollen in two Australian cities. In Vienna, Bastl et al. (2018) suggest a linear response of app and web-logged symptoms to multiple pollen types. Overall, however, our results add to growing evidence that a non-linear relationship between pollen and health outcomes is more likely.

More specifically, our results add weight to suggestions that for many pollen taxa, in many locations, the concentration-response relationship attenuates in slope above a particular threshold. Previous studies have reported an attenuation of the concentration-response relationship at higher pollen concentrations for taxa including Poaceae (Caillaud et al., 2012; Erbas et al., 2007), *Betula* (Caillaud et al., 2014), *Platanus* (Caillaud et al., 2015), *Plantago* (Tobias et al., 2004), Cupressaceae (Rakotozandry et al., 2019) and Urticaceae (Tobias et al., 2004). We likewise found that the slope of the concentration-response curve attenuated above a certain threshold for some taxa (*Betula*, Myrtaceae and Poaceae), regardless of whether the outcome was eye/nose, lung or all symptoms combined. We did not necessarily find that the concentration-response relationship reached a complete plateau, nor that the change in slope occurred at similar pollen concentrations as other studies—for example, Caiullard et al. (2014) report rates of nasal, ocular and lung symptoms plateauing at *Betula* pollen concentrations of 110, 70, and 70 grains/m^3 respectively; far above the 30 grains/m^3 at which risk in our study plateaued (see Fig. S4). Contrasting thresholds

have also been reported across the pre-existing literature; for example, for Poaceae (grass), Erbas et al. (2007) suggested plateauing at 30 grains/m^3 in Melbourne, Australia compared to 80–90 grains/m^3 suggested by Cailluard et al. (2012) in France. Although differences in statistical approaches and health outcomes could partly explain these contrasts, overall, it appears that the point at which a plateau becomes evident is population-specific. This may reflect geographical differences in pollen allergen content (e.g. Buters et al., 2015; Jochner et al., 2015), factors such as population rates of pollen sensitization (Tobias et al., 2004), and/or unstable results due to fewer data points and thus higher uncertainty at higher pollen concentrations.

An important caveat to the above discussion is that a flattening in health outcome risk at higher pollen concentrations does not appear to be universal. In our data, this pattern was *not* evident in three of our six study taxa: Cupressaceae, *Dodonaea* and *Casuarina*. Regardless of symptom type stratification, Cupressaceae displayed a linear trend, *Dodonaea* increased sharply before declining, while *Casuarina* was inverse at low pollen concentrations before sharply increasing. It is possible that some details of the concentration-response curves reflect unstable results associated with small datasets, especially for taxa with relatively few data points at higher concentrations. However, previous studies have likewise reported complex concentration-response curves: for example, Tobias et al. (2004), Erbas et al. (2012) and Cailluard et al. (2012) all report asthma outcome responses to Poaceae pollen that increase sharply, plateau or decline, and then increase again. Further, this is not the first study to report varied concentration-response shapes across multiple pollen taxa (e.g. Darrow et al., 2012; Tobias et al., 2004). In this context, our data reinforce the complexity of pollen concentration-response relationships, and the need for more studies using non-linear techniques to unpack the range of within- and between-study variation observed to date.

With respect to lags, our results build on a growing evidence base including symptom diaries (Damialis et al., 2019), over the counter drug sales (Fuhrman et al., 2007) and emergency department presentations (Erbas et al. 2007, 2012), that suggests that pollen exposure has its greatest clinical impact on the day of exposure. This acute impact is also observed with thunderstorm asthma (Silver et al., 2018). However, it is well known that there is often a physiologically biphasic clinical response to aeroallergens and this can produce lagged concentration-response relationships (Sin and Togias, 2011). Studies from some tertiary hospitals support this concept, reporting stronger lagged and/or cumulative multi-day, rather than same day effects (Darrow et al., 2012; Tobias et al., 2004). Similarly, a recent study from Australia found an association between reduced lung function in children with asthma and pollen exposure only after lags of 1–3 days (Lambert et al., 2020). Lagged responses may indicate a compounding of inflammatory responses especially in patients with co-morbidities, and increased sensitivity to pollens as the season progresses (Connell, 1968). Overall, both the timing and severity of clinical responses to pollen exposure are likely to be complex, with geographical and temporal differences in pollen allergenicity (Buters et al., 2015) compounding with individual variations in human physiology.

4.2. Interactions with particulate pollution

Our results show a positive interaction between particulate pollution and total pollen exposure: regardless of whether the outcome measure is eye/nose symptoms, lung symptoms or all respiratory symptoms combined (with the caveat that confidence intervals for lung symptoms were wide). This finding is consistent with a growing body of mechanistic and epidemiological evidence suggesting that particulate pollution can exacerbate the pollen allergy response (Cakmak et al., 2012; Eguiluz-Gracia et al., 2020; Guilbert et al., 2018; Hebbern and Cakmak, 2015; Konishi et al., 2014; Reinmuth-Selzle et al., 2017; Sedghy et al., 2018). This body of literature suggests that interaction between pollen and particulate pollution occurs via several mechanistic pathways: for example, there is evidence that particles can act as adjuvants that stimulate IgE-mediated responses, and alter the immunogenicity of allergenic proteins (Reinmuth-Selzle et al., 2017). Particulate pollution may also damage the pollen cell wall, facilitating the release of small allergen-carrying particles capable of penetrating into the airways (Sedghy et al., 2018). It may also enhance the expression of allergenic proteins in pollen grains (Buters et al., 2015), damage airway tissue and impair mucociliary clearance, enhancing contact between pollen allergens and the immune system, and promoting inflammation and the release of mediators involved in the asthmatic response (Li et al., 2020).

Although not all epidemiological studies have found interactions between pollen and particulate pollution (e.g. see Anderson et al., 1998), this combination of mechanistic pathways provides a compelling rationale for an interactive impact, and our results add weight to the argument that there is an interaction worthy of clinical and public health note. The effect size we found was substantive, particularly at $PM_{2.5}$ levels of 50 μg/m^3 and above.

Although we are not the first epidemiological study to find an interaction between pollen and fine particulate pollution (Bédard et al., 2020; Hebbern and Cakmak, 2015; Konishi et al., 2014), much of the mechanistic literature on air pollution and pollen allergens has focused on diesel exhaust (Eguiluz-Gracia et al., 2020). Diesel is a very minor contributor to particulate pollution in Tasmania and our study reinforces the need to consider particulate pollution more broadly. It is also notable that we found an interaction in the generally clean Tasmanian environment, which experiences episodic spikes of biomass smoke-related pollution, rather than the more consistent mixed-source traffic and industrial pollution typical in larger cities. Our study therefore provides evidence that the relevance of pollen-pollution interactions may extend well beyond highly polluted large urban centres. As noted by Bédard et al. (2020), more large scale, real world studies such as ours are needed to unravel and confirm pollen-particulate interactive effects.

4.3. Strengths and limitations

The strengths of this study include our large dataset (4820 symptom reports from 2272 participants), and our capacity to control for a wide variety of environmental co-variates. Our four-year time series, unusual in epidemiological studies, means our results are robust to inter-annual variation in pollution and pollen exposures. We chose a method—case time series analysis—explicitly designed to handle the characteristics of app-sourced data, allowing us to benefit from the advantages of crowdsourcing (including large datasets with low participant burden), while minimising the disadvantages (such as inconsistency in participant reporting) and controlling for factors such as age, ethnicity and gender via the within-person analytical design. A related strength is our use of real-time symptom reporting as our outcome measure: app-logged symptom reports provide for close temporal matching of environmental exposures to health outcomes and capture the ubiquitous lower severity impacts of allergic rhinitis and asthma that rarely result in a reportable health system outcome. Both aspects of app-reported symptom data provide substantive benefits when attempting to understand concentration-response relationships for aeroallergens such as pollen.

A number of limitations should, however, be considered. First, although the majority of symptom reports were made within a reasonable distance of a monitoring station, there are factors that limit our ability to accurately estimate individual exposures, including varying land use types, emission source distributions and meteorological conditions. Second, the number of taxa tested raises the issue of multiple comparisons; however the core patterns in our data appear consistent and robust. Third, we only assessed concentration-response relationships up to 50 grains/m^3 for individual pollen taxa. While this threshold is appropriate given the low number of days in Tasmania with concentrations above 50 grains/m^3, this means that our analysis does not provide information about more extreme exposures. Finally, we did not

assess differences in concentration response curves at different points in the season, nor investigate geographic differences in concentration-response relationships across Tasmania (for example, related to altitude or proximity to coast): both factors which have been suggested to impact concentration-response relationships through mechanisms such as priming and altered pollen potency (Buters et al., 2015; Caillaud et al., 2012; De Weger et al., 2011; Tobias et al., 2003). These spatial and temporal dimensions of concentration-response relationships are highly worthy of further research effort. In this study, however, our core aim was to use a large data set to provide baseline knowledge on concentration-response curves in an under studied region—a pre-requisite before unpacking these nuances through more targeted research.

More broadly, a limitation of using crowd-sourced data is that our study cohort is self-selected and hence our results cannot be generalized to a broader population. Our results may, however, be applicable to those with a history of asthma or allergic rhinitis, given that most users of the app identify as having one or both of these conditions (Johnston et al., 2018). We were not able to control for the presence of other potential symptom triggers (such as animals, mould or dustmite), or the use of symptom-reducing medications. Notwithstanding these limitations, our use of CTS ensures our results provide a robust representation of real-life, real-world concentration-response relationships to a range of well-studied (Poaceae, *Betula*, Cupressaceae) and novel (Myrtaceae, *Casuarina*, *Dodonaea*) pollen types.

4.4. Implications for policy and practice

From a public health perspective, a key implication of our findings is that notable health impacts may occur even at modest pollen concentrations. For several taxa, we observed increases in risk over pollen concentrations of 0–20 grains/m^3 that were statistically significant (at $p \leq 0.05$) on the same day. This suggests that susceptible individuals may respond to pollen levels even within this range, which is typically considered low (e.g. Silver et al., 2020). Although in conflict with some literature, which has suggested 'threshold' levels below which there is no notable increase in symptom risk (e.g. Kiotseridis et al., 2013), our findings of significant responses even at low levels accord with several other studies. For example, Dellavalle et al. (2012) report statistically significant responses of asthmatic children to grass pollen at levels $\geq$2 grains/m^3 and weed pollen levels of 6–9 grains/m^3. Caiullard et al. (2012) and (2014) likewise found increases in symptom risk at low levels of Poaceae and *Betula* pollen in France (with the exception of birch pollen at the onset of the season). Overall, rather than a threshold at which pollen becomes clinically relevant, we suggest a situation similar to particulate pollution, where there is no 'safe level' but rather a gradient over which more and more individuals begin to respond. This has important implications for risk communication, and suggests that individualized approaches will be more effective than attempts to set population-scale thresholds. The AirRater smartphone app is one example of a service that allows individuals to determine their own sensitivity thresholds (Johnston et al., 2018).

Finally, another important implication stems from our finding of a positive association between symptoms and a number of Australian native pollen types—*Casuarina*, *Dodonaea* and Myrtaceae. All three taxa are widespread across Australia and in many other regions, including parts of South Asia, America and Europe. None are commonly considered key allergens; however our study adds to incipient evidence that all three taxa may be substantive contributors to the pollen allergy burden. With respect to Myrtaceae, although a US study concluded that Myrtaceae was not an important aeroallergen (Stablein et al., 2002), clinical studies in Australia and India have found high rates of sensitization to *Eucalyptus* pollen amongst asthmatic or atopic subjects (Boral and Bhattacharya, 2000; Gibbs, 2015). In Darwin, Australia, Hanigan and Johnston (2007) found an association between Myrtaceae pollen and asthma-related hospital admissions. With respect to *Casuarina*, clinical studies in India, Florida, Spain and Australia have reported positive skin prick and/or bronchial provocation challenge responses to this taxon, amongst a small (2.85%) to large (>80%) proportion of the test cohort (Agashe et al., 1994; Bucholtz et al., 1987; Garcia et al., 1997; Gibbs, 2015; Zivitz, 1940). Adeniyi et al. (2018) reported an association between *Casuarina* pollen exposure and wheezy cough in Nigeria, while Lambert et al. (2020) found an association between *Casuarina* and reduced lung function in children at risk of asthma in Sydney, Australia. Little evidence is available for *Dodonaea*, but positive skin prick tests have been reported in India (Singh and Kumar, 2003), and the positive association we found here is consistent with our previous epidemiological analysis of AirRater symptom data (Jones et al., 2020). Given that these taxa, particularly Myrtaceae and *Casuarina,* can comprise a substantial proportion of the pollen load in diverse locations (Agashe et al., 1994; Boral and Bhattacharya, 2000; Haberle et al., 2014; Phillips et al., 2010; Prakashkumar et al., 2009), we suggest a clear need for further investigation of their allergenicity.

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Ethics declaration

This research was approved by the Tasmanian Health and Medical Human Research Ethics Committee (Reference number: H0015006).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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