Ragweed pollen and allergic symptoms in children: results from a three-year longitudinal study

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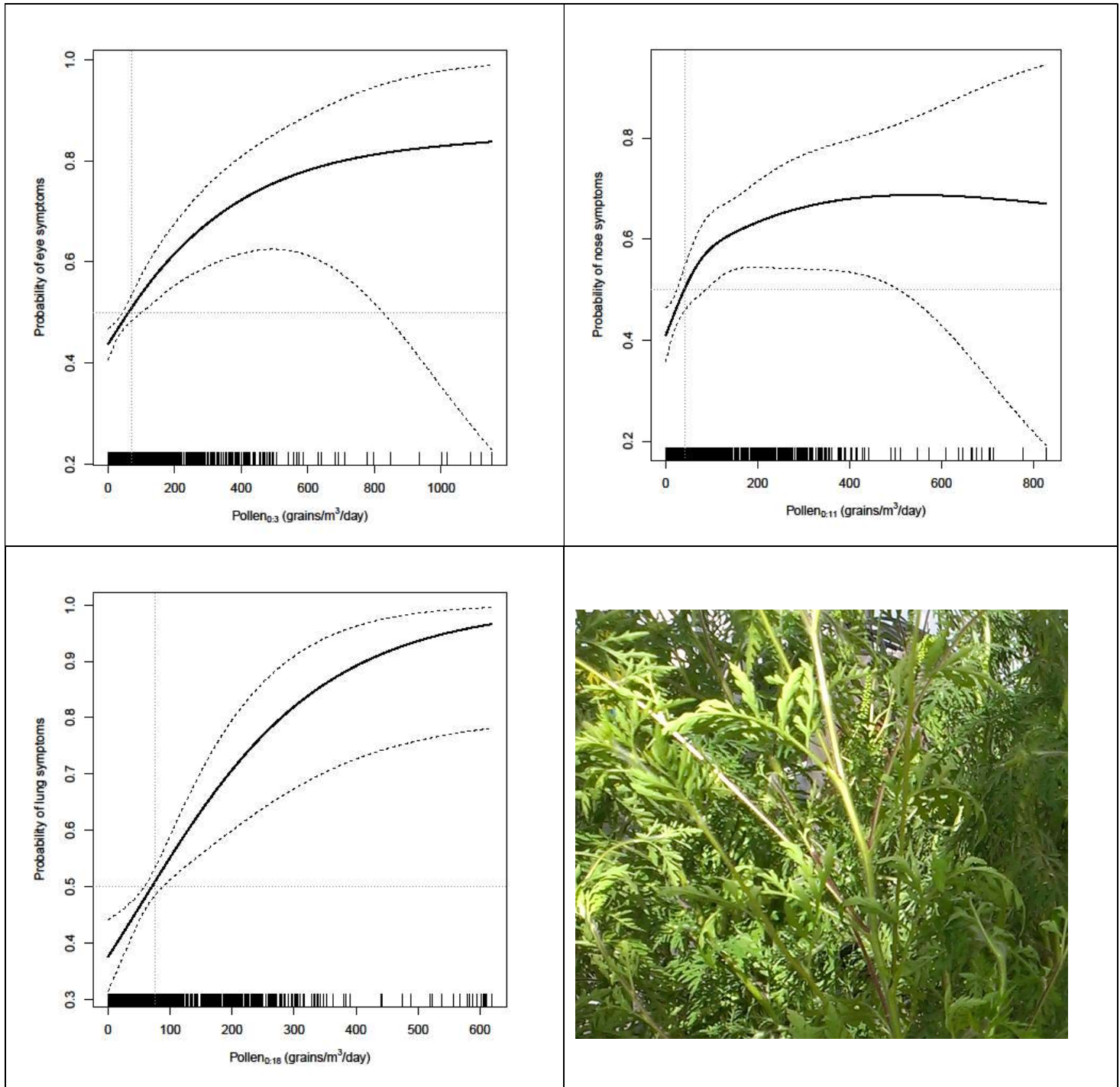[d]Catholic University of Croatia, Ilica 242, 10000 Zagreb, Croatia
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Graphical abstract

Abstract

Common Ragweed is a highly allergenic invasive species in Europe, expected to become widespread under climate change. Allergy to ragweed manifests as eye, nasal and lung symptoms, and children may retain these throughout life. The dose-response relationship between symptoms and pollen concentrations is unclear. We undertook a longitudinal study, assessing the association between ragweed pollen concentration and allergic eye, nasal and lung symptoms in children living under a range of ragweed pollen concentrations in Croatia. Over three years, 85 children completed daily diaries, detailing allergic symptoms alongside daily location, activities and medication, resulting in 10,130 individual daily entries. The daily ragweed pollen concentration for the children's locations was obtained, alongside daily weather and air pollution. Parents completed a home/lifestyle/medical questionnaire. Generalised Additive Mixed Models established the relationship between pollen concentrations and symptoms, alongside other covariates. Eye symptoms were associated with mean daily pollen concentration over four days (day of symptoms plus 3 previous days); 61 grains/m^3/day (95%CI:45,100) was the threshold at which 50% of children reported symptoms. Nasal symptoms were associated with mean daily pollen concentration over 12 days (day of symptoms plus 11 previous days); the threshold for 50% of children reporting symptoms was 40 grains/m^3/day (95%CI:24,87). Lung symptoms showed a relationship with mean daily pollen concentration over 19 days (day of symptoms plus 18 previous days), with a threshold of 71 grains/m^3/day (95%CI:59,88). Taking medication on the day of symptoms showed higher odds, suggesting responsive behaviour. Taking medication on the day prior to symptoms showed lower odds of reporting, indicating preventative behaviour. Different symptoms in children demonstrate varying dose-response relationships with ragweed pollen concentrations. Each symptom type responded to pollen exposure over different time periods. Using medication prior to symptoms can reduce symptom presence. These findings can be used to better manage paediatric ragweed allergy symptoms.

Highlights

- The dose-response between ragweed concentrations and allergy symptoms is unclear
- We used a longitudinal study to determine daily allergy symptoms in 85 children
- Associations between daily symptoms and ragweed concentrations were examined
- Generalised Additive Mixed Models (GAMM) were used for analysis
- Symptom types showed different non-linear associations with ragweed concentration
- Symptom types responded to pollen exposure over differing time periods

1. Introduction

Ambrosia artemisiifolia (hereafter ragweed) is a herbaceous plant native to North America. In Europe, ragweed is an introduced species (Smith *et al.*, 2013) in the process of an ongoing invasion event (Storkey *et al.*, 2014). Each ragweed plant produces over one billion pollen grains (Fumanal *et al.*, 2007) which are highly allergenic (Smith *et al.*, 2013). The concentration of ragweed pollen in the atmosphere varies considerably across Europe, from a total absence up to an annual count of over 25000 pollen grains/m^3/year (Matyasovszky *et al.*, 2018). The ragweed sensitisation rate (the proportion of people developing an allergic reaction to a substance via a skin prick test) is above 2% in all European countries (Burbach *et al.*, 2009), with rates varying from 50-60% in Hungary (Burbach *et al.*, 2009), to 14-20% in Germany (Ruëff *et al.*, 2012) and less than 3% in France, Spain, Italy, Sweden and the UK (Bousquet *et al.*, 2007).

Allergy to ragweed predominantly manifests clinically as allergic rhino-conjunctivitis and allergic asthma (Bass *et al.*, 2000; Salo *et al.*, 2014). The symptoms occur in late summer/autumn and include nasal congestion, ocular redness, itching of the nose or eyes, sneezing, runny nose, coughing, wheezing and dyspnoea. Rhino-conjunctivitis and asthma are commonly co-morbid (Leynaert *et al.*, 2000). The burden of ragweed allergy goes beyond physical symptoms however, with impacts on sleep quality (Meltzer *et al.*, 2009; Nathan, 2007), school attendance (Nathan, 2007; Kay, 2000; Sennhauser *et al.*, 2005), lost workdays (Nathan, 2007) and emotional and social health (Nathan, 2007; Meltzer *et al.*, 2009; Sennhauser *et al.*, 2005), all of which have negative effects on overall quality of life and economic well-being (Meltzer *et al.*, 2009; Sennhauser *et al.*, 2005; Nathan, 2007). Zuberbier *et al.* (2014) have calculated that the economic burden of allergic disease in the EU is between €55 and €151 billion per annum.

Climate change is likely to impact on ragweed allergy in Europe. Under climate change it is expected that the distribution of ragweed in Europe will expand to areas where it is currently not found (Storkey *et al.*, 2014). By 2060, it is predicted that the quantity of ragweed pollen that the population will be exposed to will substantially increase, and the pollen season will lengthen (Lake *et al.*, 2017). Alongside this, by 2060 the rate of sensitisation to ragweed is predicted to more than double across Europe, with rates increasing both in areas where ragweed is currently prevalent and where it is presently uncommon (Lake *et al.*, 2017). Thus, as a result of the increase in pollen concentrations, ragweed pollen allergy will become an increasingly common health problem across Europe (Lake *et al.*, 2017).

Despite this large and growing health problem, very few studies have investigated the associations between ragweed pollen levels and allergy symptoms, and the effect of pollen exposure on childhood rhino-conjunctivitis is largely unknown (Cakmak *et al.*, 2002).   In Italy, Albertini *et al.* (2012) described a correlation between the number of (mainly adult) patients with asthmatic symptoms and the total annual ragweed pollen concentration. In the USA, 24 asthma patients aged 9-64 completed a symptom diary over a two month period, and correlated asthma and rhinitis symptoms with environmental factors. The study found a positive correlation between symptoms and ragweed pollen levels (Newhouse and Levetin, 2004). Studies in Canada have shown an association between ragweed concentration and physician visits for rhinitis in the elderly (Villeneuve *et al.*, 2006) and patients of all ages (Breton *et al.*, 2006). In France, a country where the average total annual ragweed pollen count varies geographically from 4 pollen grains/m^3/year to 5374 pollen grains/m^3/year (Thibaudon *et al.*, 2014), a more extensive longitudinal study using daily diaries over

two years found a significant positive linear relationship between ragweed exposure and daily hay fever symptoms in 30 adults sensitised to ragweed (Caillaud *et al.*, 2014). Despite both laboratory (Naclerio *et al.*, 1983; Solomon, 1984) and clinical (Comtois and Gagnon, 1988; Peternel *et al.*, 2008) studies, no precise ragweed pollen threshold for triggering allergy symptoms has been established (Peternel *et al.*, 2008). To our knowledge there are no longitudinal studies examining the dose-response relationship between ragweed pollen levels and paediatric allergic symptoms, focused on areas with a range of ragweed pollen concentrations including very high levels.

The aim of this study is to examine how daily ragweed pollen levels influence a range of allergy symptoms in a cohort of ragweed-sensitised children in Croatia. Croatia is considered one of the most ragweed affected countries in Europe (Rybníček and Jäger, 2001; Peternel *et al.*, 2005; Galzina *et al.*, 2010) with annual pollen counts measuring up to 24801 pollen grains/m^3/year (Peternel *et al.*, 2005) in the most highly infested areas. Given the predicted increase in pollen concentrations across Europe (Lake *et al.*, 2017), it is important to investigate the associations between pollen concentrations and symptoms in areas which already have high pollen concentrations. Children are useful to study as their epidemiological history is less complex than adults, and children who develop symptoms early are likely to retain them later in life (Rhodes *et al.*, 2002; Illi *et al.*, 2006). To our knowledge, this is the first longitudinal study to examine the dose-response relationship between a range of daily allergy symptoms and ragweed pollen in European children.

2. Methods

The purpose of this study is to use an epidemiological study design to explore the relationship between observed levels of pollen in the environment and reported symptoms in children, controlling for a range of confounding variables.

2.1 Study design

Between April 2012 and June 2014, 4015 children were recruited through schools and kindergartens from three areas of Croatia representing a range of ragweed levels: Dalmatia (low pollen: average total annual pollen 422 grains/m^3/year), Zagreb (medium pollen: average total annual pollen 5189 grains/m^3/year) and Slavonia (high pollen: average total annual pollen 13079 grains/m^3/year). Children with chronic immunosuppressant or antihistamine therapy were excluded from participating as these interfere with skin prick tests. Using standard allergy skin prick tests (allergen extract Alyostal ST-IR, Stallegenes S.A. France), children were tested for sensitisation to a palette of aeroallergens including ragweed. From these recruits, 85 children who were sensitised to Ambrosia (defined as a wheal size >2 mm) volunteered to complete a daily symptom diary, developed from a standardised allergy symptom and medication use questionnaire (see www.pollendiary.com; Voukantsis *et al.* (2015)). Altogether 55% of the children were also sensitised to cross-reactive pollens (birch, hazel, pine, olive, grass, and Parietaria pollen). The children (or their parents) recorded their daily symptoms and activity over the pollen season (22nd July to 31st October) for the years 2012 (29 children), 2013 (49 children) and 2014 (24 children). Sixteen children completed diaries on multiple years. Further details of the recruitment and diagnostic tests are detailed elsewhere (Agnew *et al.*, 2018).

2.2 Daily diary, pollen, environment and lifestyle data

The symptom diaries included details of the children's daily allergy symptoms. Eye symptoms (itching, redness, foreign body sensation and watering), nasal symptoms (itching, sneezing, running and blocked nose) and lung symptoms (wheezing, shortness of breath, cough and asthma) were recorded. An overall score for each set of symptoms was produced, indicating the "presence" of any symptom or the "absence" of any symptoms. Altogether three dichotomous symptom measures were generated: reported any eye symptoms (yes/no), reported any nasal symptoms (yes/no) and reported any lung symptoms (yes/no). The daily geographical locations of the children were detailed, indicating whether they were at home or at another location (e.g. on holiday) and where they were located on a two hourly basis each day (home, school, outside). The activities they were participating in on a two hourly basis were also recorded (including sleeping, resting/learning, sport). Any medication the child had taken was noted.

Using Geographical Information Systems (GIS) (ArcGIS 10.2), each child was assigned to their nearest pollen observation site (Croatian Environment Agency). Daily measures of ragweed pollen (grains/m^3) were obtained for the child's location (either home or away) giving each child an individual pollen grain measure for each diary day, based on their location. Figure 1 presents raw data showing the crude relationships between total daily pollen grains/m^3 (in percentiles) and the percentage of days when children reported symptoms. For all three symptoms the percentage of days when children reported symptoms increases with pollen grains/m^3 that day.

Children were allocated to their nearest weather and air quality stations, from where potential confounding variables including daily temperature, rainfall and air quality data (mean concentration of SO_2, PM10, NO_2, O_3) for their daily location was obtained. In addition, a parental questionnaire collected information on the home environment, lifestyle, family/personal medical history and socio-economic information (ISAAC Phase II questionnaire – see http://isaac.auckland.ac.nz/phases/phasetwo/phasetwo.html; Asher *et al.* (1995)). Also using GIS, information on the home environment was determined, such as whether the home was in a rural or urban area, based on CORINE Land cover data (European Environment Agency (2015); see Agnew *et al.* (2018) for more details). The study protocol and informed consent, based on the international Declaration of Helsinki, Declaration on Human Rights and local legislation, were approved by the Local Ethics Committee (Children's Hospital Srebrnjak, Croatia) and the E.U. ATOPICA project Ethics Committee.

2.3 Statistical analysis

Generalised Additive Mixed Models, GAMM (Wood, 2006) with a binomial specification were used to evaluate the potential non-linear and delayed associations between the exposure to ragweed pollen and the presence of symptoms. GAMMs are semi-parametric extensions of generalised linear models where the linear predictor is replaced by a sum of smooth functions (Hastie and Tibshirani, 1986). One advantage of GAMMs is that they automatically estimate the optimal degree of non-linearity of a model directly from the data (Wood, 2006). Separate models were run for reported eye, nasal and lung symptoms. All analyses were undertaken in R version 3.4.4 (R Core Team 2018).

When investigating the impact of pollen on allergic symptoms it is common to consider pollen over the consecutive days prior to symptoms, as in epidemiological studies lagged relationships are often found (Breton *et al.*, 2006; Villeneuve *et al.*, 2006; Erbas *et al.*, 2018). It is also suggested that the clinical response to pollen tends to increase as the pollen season develops (Tobias *et al.*, 2004), the

sustained effect of environmental stimuli potentially have cumulative long-lasting effects (Frey and Suki, 2008) and that elevated concentrations of pollen from previous days can have an additive effect, resulting in heightened allergy symptoms (Newhouse and Levetin, 2004). Therefore, to account for lagged and cumulative effects of pollen on symptoms, the influence of pollen on the days previous to the symptom day were examined. Individual associations between symptoms on a day and the pollen concentration on the days previous to the symptoms were examined (see Supplementary Table S1). The continuous days where the individual association between daily pollen concentration and symptoms was p<0.01 were used to compute a mean daily pollen concentration measure. The number of days where pollen had an influence varied for the different symptoms. Four days (day of symptoms plus the three previous days) for eye symptoms (Pollen03), 12 days (day of symptoms plus the 11 previous days) for nasal symptoms (Pollen011) and 19 days (day of symptoms plus the 18 previous days) for lung symptoms (Pollen018). The mean pollen concentrations over these time periods were included in the model as the main pollen measure. Zheng *et al.* (2015) suggest that lags are essential in time-series studies to better determine the effects of outdoor air pollution on asthma outcomes and thus we used matching time lags to account for any potential effect of SO_2, $PM10$, NO_2, and O_3 on the presence of symptoms.

In the development of the models, all variables shown in Agnew *et al.* (2018) to be associated with ragweed sensitised children and the development of allergic disease were included as potential explanatory variables, alongside additional time series measures (day, year and measure of early or late season, child locations, daily symptoms, daily medication, daily activity, weather, air pollutants). A core model was developed including the unique identifier of each child, the unique identifier for each area, mean daily pollen concentration, mean daily temperature ($^{\circ}$C), total daily rainfall (mm/day), gender, age group and year. Also included was the logarithm of the binary symptom scores lagged one day to account for potential temporal correlation in the data (Imai *et al.*, 2015). Any other variables adding to the explanatory power of the model were retained. A full list of potential explanatory variables is shown in Supplementary Table S2. The general algebraic definition of the core model is given by:

$$ln\left[\frac{p}{1-p}\right] = \alpha + ID + Area + ln(S_{t-1}) + Year + Age + Sex + \sum_{p=1}^{P} \beta\,(X) + s(Z_{0:L})$$

where *p* denotes the probability of the symptoms occurring and *0 < p < 1*; *α* is the intercept; *ID* indicates the child specific random effects; Area is the area-specific random effects; *ln(S_{t-1})* is the natural logarithm of the symptoms on the previous day; *Year* is a categorical variable for each year in the records; *Age* corresponds to the age group of the child; *Sex* indicates the gender of the child; *β* is the coefficient of each weather variable (*X*) in the model; and *s* denotes the smooth function of pollen (Z) lagged zero to *L* days.

For each predictor not present in the core model, we iteratively incorporated the predictor leading to the lowest Akaike's information criterion (AIC) until no further variable incorporations lowered the AIC. Supplementary Table S3 shows the change in AIC for each additional variable. Model selection was conducted using the AIC because it performs better than hypothesis-based approaches (Mazerolle, 2006). Notably, the AIC as a value is meaningless by itself and is meaningful only when compared with other AIC values from other models. The model with the lowest AIC is considered the most adequate model (Symonds and Moussalli, 2011). Within the models, some non-significant

variables have been retained when they improve the fit of the model. There were no patterns in the residual plots, confirming these as the most appropriate models.

3. Results

Altogether, 85 children completed diaries over 306 days that covered three ragweed pollen seasons, resulting in 10,130 individual daily diary entries. In total, 38% of the children were girls, their ages ranged from 4 to 12 and 63% lived in the Zagreb area, whilst 29% lived in Slavonia and 7% in Dalmatia. Of the 85 children, 56 (66%) reported eye symptoms, 75 (88%) reported nasal symptoms and 41 (48%) reported lung symptoms. Table 1 summarises the main characteristics of the children in the study.

In the eye model, mean daily pollen concentrations were based on four days (day of symptoms plus previous three days - Pollen03). The dose-response relationship between the mean daily pollen concentration (Pollen03) and the probability of reported eye symptoms is shown in Figure 2. The X axis represents increasing levels of pollen (expressed in grains/m^3/day). The rug (lines) at the bottom indicates the density of observations at each level of pollen. The majority of children were exposed to a mean daily pollen concentration (Pollen03) of less than 500 grains/m^3. The Y axis shows the probability of reported eye symptoms. The smooth line indicates the maximum likelihood estimates for the risk of symptoms, and the dashed lines represent the 95% confidence intervals. The relationship between pollen and the risk of symptoms was non-linear. There was an increase in the probability of symptoms up to around 500 grains/m^3/day after which the relationship flattens; however, the large confidence intervals at pollen levels above 500 grains/m^3/day suggest large uncertainties in the association between reported eye symptoms and pollen at high pollen levels. These large confidence intervals were the result of low numbers of children being exposed to these levels of pollen. The dotted lines indicate the threshold of pollen where 50% of children reported symptoms. For eye symptoms it was 61 grains/m^3/day (95% confidence intervals: 45, 100).

Table 2 contains the model for the reported presence or absence of eye symptoms. Predictors which showed significantly lower odds of reported eye symptoms included being ten years or older, being away from home, taking nasal sprays or drops on the day before reported symptoms and increased time spent being active outside. Conversely, reporting symptoms on the day previous, taking nasal sprays or drops on the day, the year 2013 and daily temperature showed significantly higher odds of reported eye symptoms.

In the nasal model, mean daily pollen concentrations were based on 12 days of pollen (day of symptoms plus previous 11 days - Pollen011). Figure 3 shows the dose-response relationship between mean daily pollen concentration (Pollen011) and the probability of reported presence of nasal symptoms. As can be seen from the rug, most children were exposed to a mean daily pollen concentration (Pollen011) of less than 400 grains/m^3. There was a non-linear and positive relationship between the mean daily pollen concentration and the risk of reported nasal symptoms. The increase in the risk of reported nasal symptoms was steeper at levels between 0 and 100 grains/m^3/day after which the relationship gradually started to flatten. For nasal symptoms the threshold for reported symptoms to appear in 50% of children was 40 grains/m^3/day (95% confidence intervals: 24, 87).

The model for the associations with the reported presence or absence of nasal symptoms is shown in Table 3. Being away from home and the rainfall on the day of measurement showed lower odds. Reporting nasal symptoms on the previous day, taking nasal sprays or drops on the day, and mean daily temperature increased the odds of reported nasal symptoms.

In the lung model, mean daily pollen concentration was based on 19 days of pollen (day of symptoms plus previous 18 days - Pollen018). Figure 4 highlights the dose-response relationship between the probability of reported lung symptoms and the mean daily pollen concentration (Pollen018). Most children were exposed to a mean daily pollen concentration below 350 grains/m^3/day. There was a non-linear and positive relationship between pollen concentration and the risk of reported lung symptoms, with the relationship starting to flatten around 300 grains/m^3/day. Approximately 71 grains/m^3/day (95% confidence intervals: 59, 88) was the threshold which triggered the reported appearance of lung symptoms in 50% of children.

Table 4 shows the model for reported lung symptoms. Time spent being active and the year 2014 showed significantly lower odds. Higher odds of reported lung symptoms were significantly associated with reported lung symptoms on the previous day and taking asthma medication on the same day.

4. Discussion

When examining the relationship between ragweed pollen concentration and reported symptoms, lagged and cumulative effects were considered, as in previous studies (Breton *et al.*, 2006; Villeneuve *et al.*, 2006; Erbas *et al.*, 2018). The number of days when ragweed pollen was associated with symptoms varied for the different symptomologies. For eye symptoms, only pollen levels on the day of symptoms plus the three previous days were relevant, suggesting that eye symptoms are an immediate response to ragweed pollen. Nasal symptoms were an longer response, as the ragweed pollen concentration over the day of symptoms plus the 11 previous days were associated with nasal symptoms. Meanwhile, the response of the lungs to ragweed pollen exposure was over the longest period, as the day of symptoms plus the 18 previous days were associated with lung symptoms. To our knowledge, no other studies have investigated the pollen lag structure for self-reported symptoms in children. Where the impact of ragweed pollen on symptoms has been examined, there is little consistency in the length of lags, with studies showing five (Breton *et al.*, 2006), ten (Villeneuve *et al.*, 2006) and 15 (Newhouse and Levetin, 2004) days of pollen impacting on allergic rhinitis (Breton *et al.*, 2006; Villeneuve *et al.*, 2006), and asthma and allergic rhinitis (Newhouse and Levetin, 2004).

There is a non-linear positive dose-response relationship between ragweed pollen concentration and reported eye, nasal and lung symptoms, although this relationship differs for the three types of reported symptoms. Interestingly, Caillaud *et al.* (2014), who investigated both linear and non-linear relationships between hay fever symptoms in adults and ragweed pollen counts, observed a linear relationship, at a lower range of pollen levels (ranging from 0 – 543 grains/m^3/day).

For all reported symptoms, taking medication on the day of symptoms was associated with a significantly greater chance of symptoms occurring, as was found in the French study (Caillaud *et al.*, 2014). It is unclear whether reported medication was taken for prevention or relief of symptoms,

however our findings suggest that taking medication on the day is a response to symptoms, rather than preventative. Our study also showed that taking medication on the previous day was significantly associated with a lower likelihood of reported eye symptoms. In particular, taking nasal sprays or nose drops on the previous day was associated with a lower likelihood of reported eye symptoms. The links between nasal and ocular symptoms remain unclear (Siroux et al., 2018), however, pathways of nasal-ocular communication are thought to increase the risk of inflammation at both sites following allergen exposure (Bielory, 2010) and nasal sprays are used as treatments for ocular symptoms associated with allergic rhinitis (Naclerio, 2008). Thus, the association between the use of nasal sprays and eye symptoms is plausible. Very few children in the study reported the use of eye drops and therefore these were not included in the models. The use of anti-allergy tablets was retained in the lung model because it added explanatory power, although it was not significant. Our findings indicate taking medication on the day before symptoms has a positive effect on reducing eye symptoms, thus it is interesting that, despite the recognised links between nasal medication and ocular symptoms (Naclerio, 2008), many children are not using these medications and are symptomatic for many days. In this cohort, 15 children reported eye symptoms on at least one day and took no nasal sprays or nose drops, while 11 children reported eye symptoms for more than seven days and took no nasal sprays or nose drops. As Croatia has a ragweed pollen forecast system in place (Peternel et al., 2005; Andrija Stampar Teaching Institute of Public Health, 2019) information is available to allow for the commencement of regular treatment in advance of the ragweed pollen season (Scadding, 2015) as a pragmatic approach to current and likely future increasing pollen levels and hence symptoms.

There has long been a question over the impact of physical activity on allergy symptoms (Lucas and Platts-Mills, 2005). Our study shows that being active outdoors is associated with a lower likelihood of reported eye symptoms, while being active either indoors or outdoors was associated with a lower probability of lung symptoms. A Greek investigation has shown a trend towards a reduction in asthma symptoms amongst children who participate in physical activity outdoors (Kosti et al., 2012). However, it has been suggested that children with allergy symptoms are less likely to participate in exercise, sport or playing with friends (Meltzer et al., 2009) and thus those being active may be those who suffer fewer symptoms. Further investigation into the relationship between allergy symptoms and both indoor and outdoor physical activity is required.

Weather also influenced allergic symptoms, independently of the impact of weather on pollen. Higher daily temperature was associated with an increased likelihood of reported eye and nasal symptoms, which supports previous data (Medek et al., 2012). Conversely, rainfall has a protective impact on reported nasal symptoms, which is similar to an Australian study which found that allergy symptoms decreased after rainfall events (Medek et al., 2012) but differs from a European study which found asthma and wheeze to be positively associated with rainfall (Arnedo-Pena et al., 2013). Further investigation is required to determine how temperature and rainfall drive allergic symptoms independently of pollen.

The majority of our study participants who stated they were away from home had travelled from a higher pollen area to a lower pollen area. Being away from home was protective for eye and nasal symptoms, but not for lung symptoms. This effect is seen even controlling for changing pollen levels. This suggests that there is a protective effect on eye and nasal symptoms of moving from an

area with a high ragweed pollen load to an area with a lower load, which is not captured by our mean daily pollen concentrations (Pollen03, Pollen011). The reasons for this are unclear.

We considered whether the day of the week was important, as nasal symptoms have been shown to vary between week days and weekends in adults (Caillaud *et al.*, 2014), but this measure was not significant and did not improve the fit of the model. This may be because we were looking at children rather than adults and because much of the ragweed season occurs during the school holidays, when inter-day activities may be similar.

Our study demonstrates that it is possible to collect extensive self-reported diary data on the allergy symptoms and behaviour of children aged 4 – 12 over a three-year period. Previous studies indicate that the use of personal diaries to collect data on allergy symptoms is valid in adults (Jantunen *et al.*, 2012; Globe *et al.*, 2015) and children (Casas *et al.*, 2017). However, there are limitations to our study. As the symptoms measured were self-reported and not medically determined, it is not possible to assess their clinical importance. However, any self-reported symptoms affecting daily activities might be considered important, and Bousquet *et al.* (2018) have shown that using a simple electronic self-report method can accurately assess nasal symptoms. The children (or their parents) were self-selecting for the overall study and although those invited to participate in the diary element were chosen because of their ragweed sensitisation, they participated voluntarily. This may result in a biased sample, but the analysis focus was differences in symptoms over time and not between children. There was an uneven sampling distribution of participant age (62% aged 7-9), gender (62% male) and geographic location (64% in the Zagreb area). Participant numbers also varied across ragweed seasons, with almost twice as many in 2013 (49) than in 2012 (29) and 2014 (24). However, all these factors were controlled for in the analysis.

Measurements from pollen observation stations may not reflect the levels of pollen to which children are exposed. In this study, children were selected if their school was within 15 km of a ragweed pollen station (Agnew *et al.*, 2018). However, pollen levels will vary within this zone, and additionally, the location of the child's home and daily activities may be outside this zone. Wherever possible if the child was away from home (e.g. on holiday), values from the nearest pollen station to their known location were used, but this may have been greater than 15 km. Therefore, the actual pollen level the child was exposed to may differ from the measured amount. The same limitations hold for the weather and air quality data, where observation networks are sparser.

To our knowledge, this is the first study to examine reported daily allergy symptoms and ragweed pollen in European children living under a range of pollen concentrations, including areas with very high ragweed pollen concentrations. We have examined the influence of daily ragweed pollen on the reported presence or absence of allergy symptoms in Croatian children keeping a daily symptom diary and used these to develop dose-response curves. We have demonstrated lag effects on symptoms, the pollen thresholds needed for symptoms to occur and highlighted how different symptoms respond to different pollen exposure levels. Under future conditions of climate change, it is predicted that the distribution of ragweed will expand throughout Europe (Storkey *et al.*, 2014) and the numbers of people sensitised to this allergen could more than double (Lake *et al.*, 2017). Thus, the numbers of people suffering allergy symptoms due to ragweed exposure is likely to increase. The findings from this study could be used to address this challenge by combining the dose-response curves developed with predictive pollen modelling (such as in Voukantsis *et al.*

(2010)) to develop early warning systems and provide allergy sufferers with adequate information to allow them to better pre-empt and manage allergy symptoms.

Tables

Table 1: Summary characteristics of children

		Number of children (%) (n=85)
Age at entry into study	4	9 (11%)
	5	6 (7%)
	6	7 (8%)
	7	16 (19%)
	8	16 (19%)
	9	21 (25%)
	10	10 (12%)
Gender	Male	53 (62%)
	Female	32 (38%)
Pollen season[a]	2012	29 (34%)
	2013	49 (57%)
	2014	24 (28%)
Home region	Zagreb	54 (64%)
	Slavonia	25 (29%)
	Dalmatia	6 (7%)
Reported symptoms[b]	Eye	56 (66%)
	Nasal	75 (88%)
	Lung	41 (48%)

[a]17 children completed the diary in more than one pollen season
[b]64 children reported more than one symptom type

Table 2: Model showing associations with the reported presence or absence of eye symptoms

		Odds Ratio [CI]	p
	4–7	Ref	
Age	8	0.26 [0.05, 1.31]	0.096
	9	0.16 [0.02, 1.07]	0.054
	10–12	*0.07 [0.01, 0.67]*	*0.019*
Gender	Male	Ref	
	Female	0.68 [0.02, 21.56]	0.825
Location	At home	Ref	
	Away from home	*0.54 [0.30, 0.97]*	*0.036*
Reported eye symptoms on previous day		*45.21 [32.56, 62.78]*	*<0.001*
Self (or parental)-reported allergic rhinitis symptoms in child		1.80 [0.03, 103.28]	0.771
Self (or parental)-reported asthma symptoms in child		0.62 [0.01, 28.24]	0.803
Taking nasal spray or nose drops on day of symptoms		*18.91 [9.48, 37.69]*	*<0.001*
Taking nasal spray or nose drops on previous day		*0.31 [0.16, 0.61]*	*0.001*
Taking anti-allergy tablets on day of symptoms		0.89 [0.04, 22.21]	0.940
Time spent being active outside		*0.85 [0.75, 0.96]*	*0.009*
Monthly Household Income	<€660	Ref	
	€660-€1320	0.30 [0.01, 12.00]	0.517
	>€1320	0.29 [0.01, 15.18]	0.535
Year	2012	Ref	
	2013	*4.48 [2.21, 9.07]*	*<0.001*
	2014	0.90 [0.31, 2.63]	0.842
Mean daily temperature (°C)		*1.09 [1.03, 1.16]*	*0.002*
Daily rainfall (mm)		0.99 [0.97, 1.02]	0.586
Mean SO_2 (μg/m^3) over previous 4 days		0.99 [0.94, 1.03]	0.550
Mean PM10 (μg/m^3) over previous 4 days		1.00 [0.98, 1.03]	0.993
Mean O_3 (μg/m^3) over previous 4 days		1.01 [1.00, 1.03]	0.098

Italics indicate significant findings

Deviance explained 66.7% ; AIC = 1349.82 ; Dispersion parameter = 0.611

Table 3: Model showing associations with the reported presence or absence of nasal symptoms

		Odds Ratio [95% CI]	p
Age	4–7	Ref	
	8	0.60 [0.16, 2.24]	0.440
	9	0.91 [0.19, 4.28]	0.899
	10–12	0.79 [0.13, 4.64]	0.787
Gender	Male	Ref	
	Female	0.61 [0.09, 4.01]	0.602
Location	At home	Ref	
	Away from home	*0.39 [0.22, 0.69]*	*0.001*
Reported nasal symptoms on previous day		*71.45 [50.41, 101.26]*	*<0.001*
Self (or parental)-reported allergic rhinitis symptoms in child		1.79 [0.21, 14.98]	0.586
Self (or parental)-reported asthma symptoms in child		0.73 [0.09, 6.06]	0.767
Taking nasal spray or nose drops on day of symptoms		*10.07 [5.18, 19.55]*	*<0.001*
Monthly Household Income	<€660	Ref	
	€660-€1320	1.08 [0.13, 8.81]	0.942
	>€1320	1.25 [0.13, 12.07]	0.843
Child has been treated by doctor for worms		1.16 [0.03, 42.48]	0.934
Year	2012	Ref	
	2013	*2.87 [1.37, 6.02]*	*0.004*
	2014	0.69 [0.26, 1.79]	0.432
Mean daily temperature (^{o}C)		*1.07 [1.01, 1.14]*	*0.012*
Daily rainfall (mm)		*0.98 [0.96, 1.00]*	*0.037*
Mean SO_2 ($\mu g/m^3$) over previous 12 days		0.99 [0.92, 1.08]	0.870
Mean PM10 ($\mu g/m^3$) over previous 12 days		0.99 [0.96, 1.03]	0.775
Mean O_3 ($\mu g/m^3$) over previous 12 days		0.99 [0.98, 1.01]	0.541

Italics indicate significant findings

Deviance explained 73.1%; AIC = 1230.319 ; Dispersion parameter = 1.020

Table 4: Model showing associations with the reported presence or absence of lung symptoms

		Odds Ratio [95% CI]	p
Age	4–7	Ref	
	8	0.39 [0.03, 4.54]	0.443
	9	1.55 [0.11, 21.81]	0.741
	10–12	4.06 [0.20, 83.29]	0.354
Gender	Male	Ref	
	Female	1.00 [0.04, 27.43]	0.999
Location	At home	Ref	
	Away from home	0.83 [0.32, 2.10]	0.683
Reported lung symptoms on previous day		*35.40 [21.42, 58.48]*	*<0.001*
Self (or parental)-reported allergic rhinitis symptoms in child		0.84 [0.01, 61.43]	0.936
Self (or parental)-reported asthma symptoms in child		12.91 [0.28, 595.87]	0.182
Taking asthma medication on day of symptoms		*3.57 [1.86, 6.88]*	*<0.001*
Time spent being active		*0.78 [0.64,0.96]*	*0.014*
Monthly Household Income	<€660	Ref	
	€660-€1320	0.14 [0.00, 6.63]	0.311
	>€1320	0.23 [0.00, 14.33]	0.473
Child has an asthmatic parent		8.03 [0.14, 454.72]	0.302
Type of area child lives in	Rural area	Ref	
	Urban area	24.67 [0.41, 1468.70]	0.117
Year	2012	Ref	
	2013	0.45 [0.15, 1.32]	0.138
	2014	*0.16 [0.03, 0.88]*	*0.032*
Mean daily temperature (°C)		1.01 [0.94, 1.08]	0.837
Daily rainfall (mm)		0.97 [0.94, 1.01]	0.101
Mean SO_2 (μg/m^3) over previous 19 days		0.99 [0.85, 1.15]	0.911
Mean PM10 (μg/m^3) over previous 19 days		1.01 [0.94, 1.09]	0.737
Mean O_3 (μg/m^3) over previous 19 days		1.00 [0.98, 1.03]	0.762

Italics indicate significant findings

Deviance explained 77% ; AIC = 636.663; Dispersion parameter = 0.4246
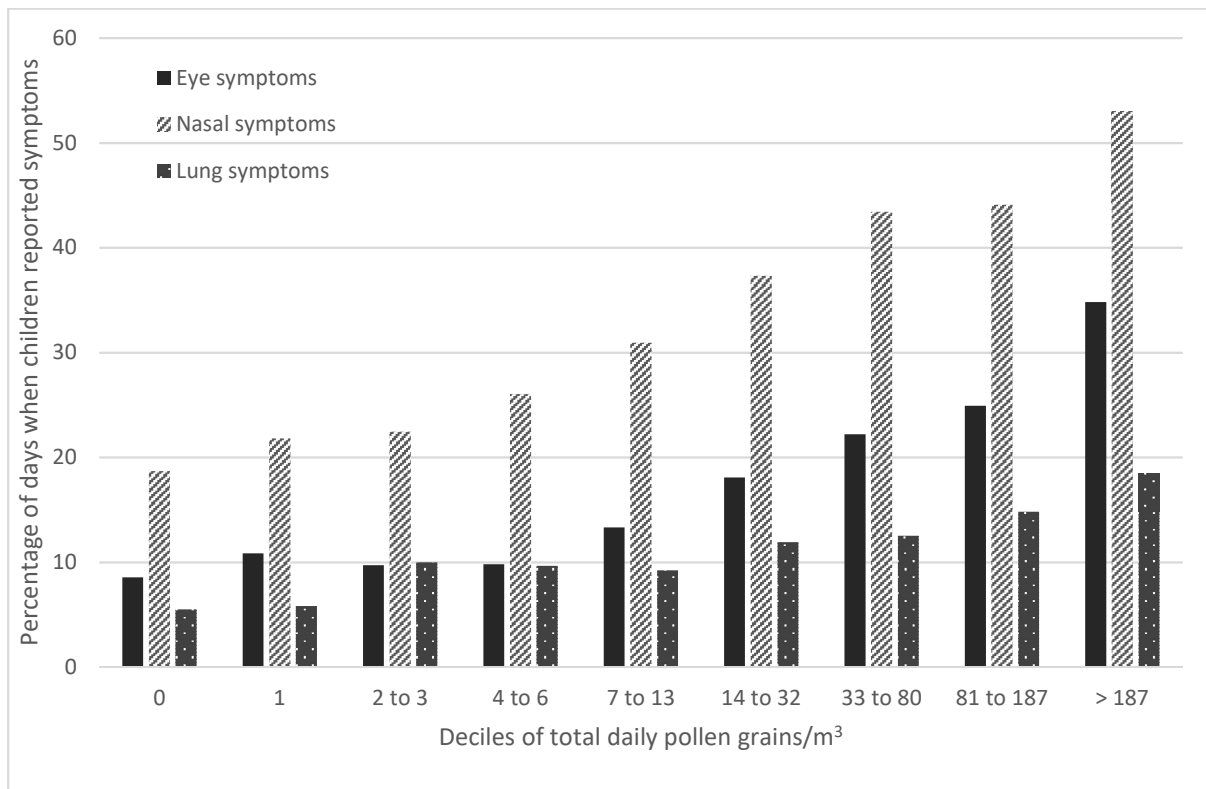
Figures

Figure 1: Relationship between total daily pollen grains/m³ and percentage of days when children reported symptoms.
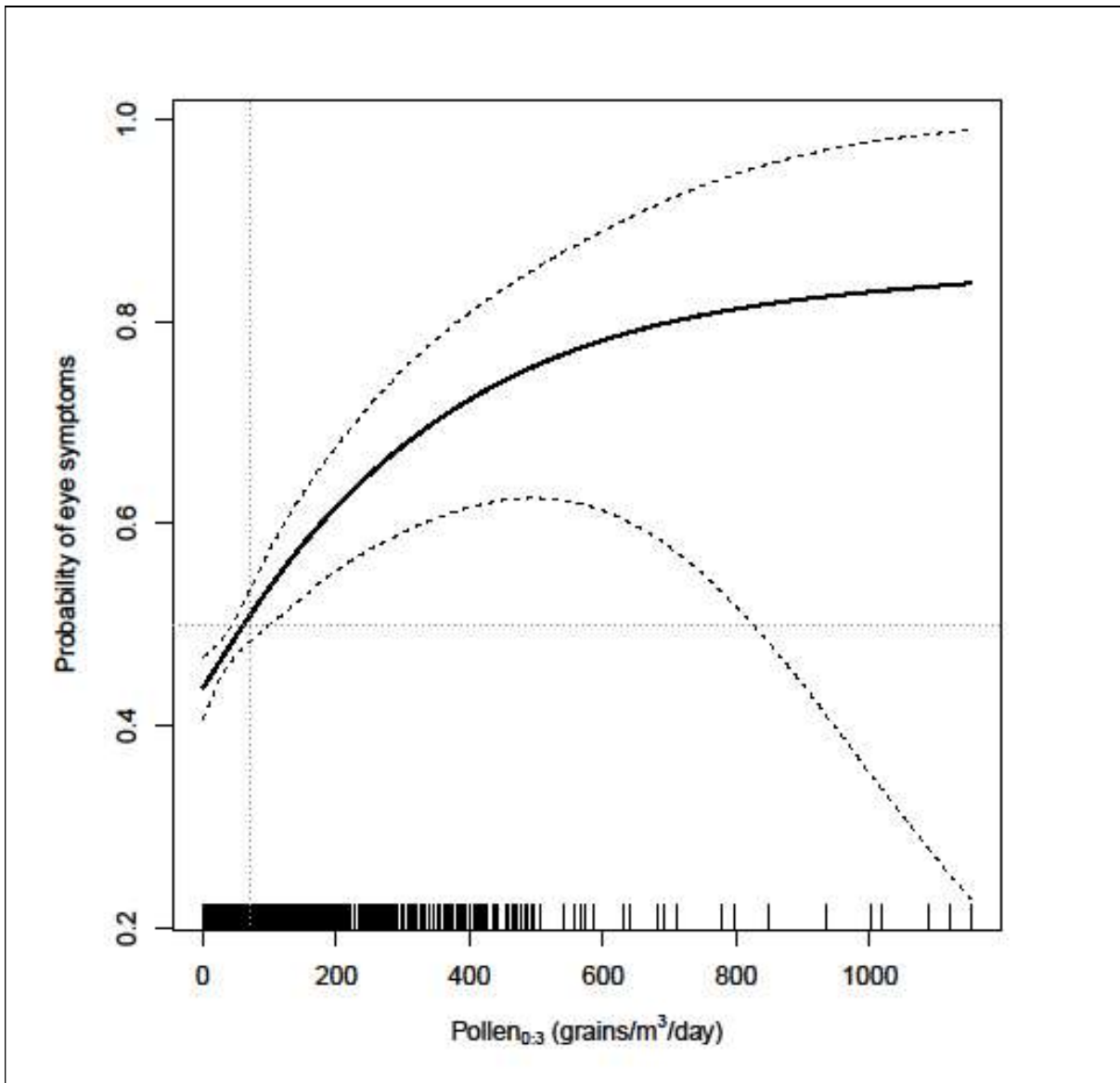
Figure 2: Relationship between mean daily pollen concentration lagged 0 to 3 days (Pollen03) and reported eye symptoms from a Generalised Additive Mixed Model. The X axis represents increasing pollen concentration. The rug (lines) at the bottom indicates the density of observations at each level of pollen. The Y axis represents the probability of reported eye symptoms. The smooth line indicates the maximum likelihood estimates for the probability of symptoms, and the dashed lines represent the 95% confidence intervals. The dotted lines indicate the threshold at which 50% of children reported symptoms.
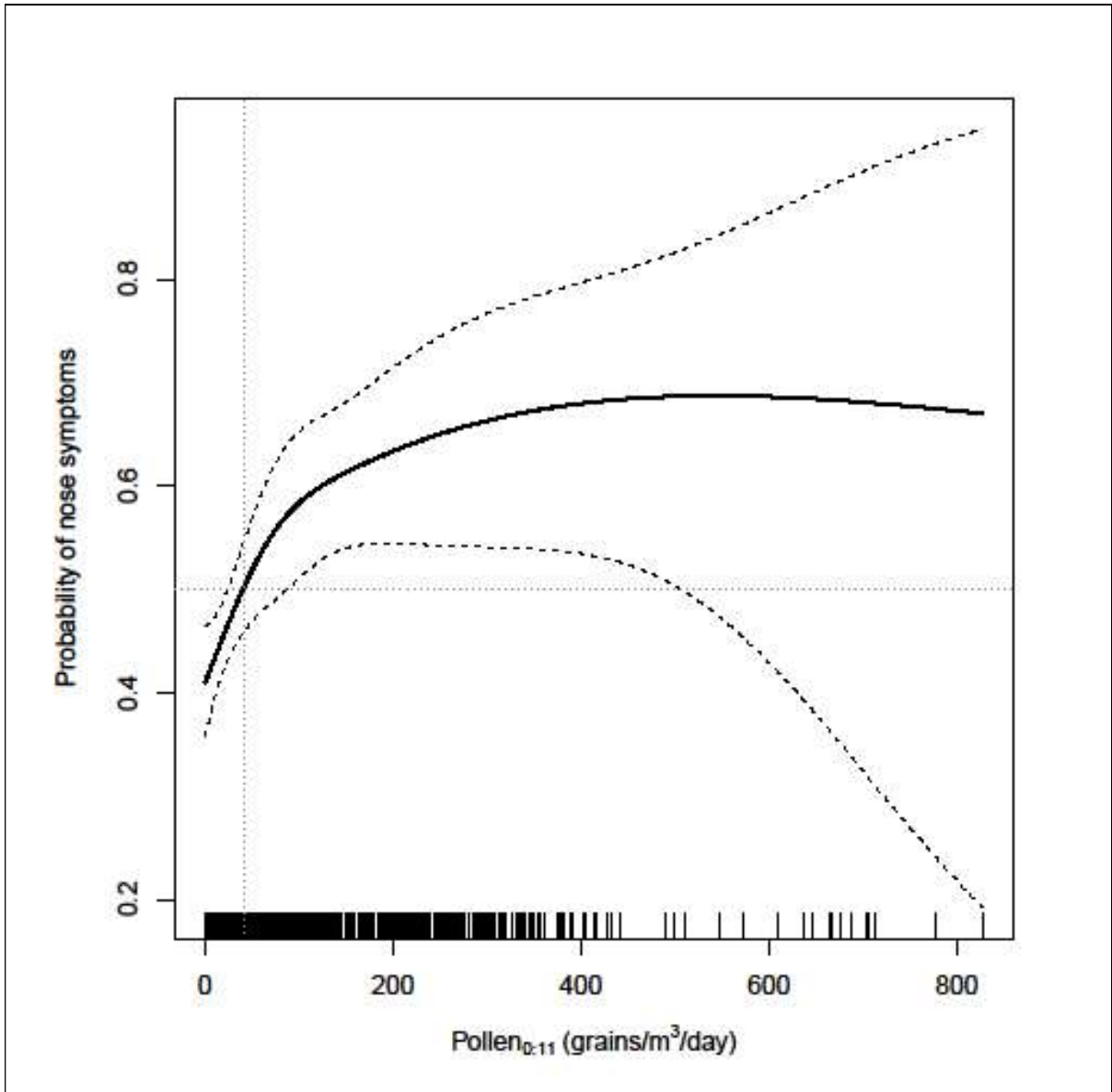
Figure 3: Relationship between mean daily pollen concentration lagged 0 to 11 days (Pollen011) and reported nasal symptoms from a Generalised Additive Mixed Model. The X axis represents increasing pollen concentration. The rug (lines) at the bottom indicates the density of observations at each level of pollen. The Y axis represents the probability of reported eye symptoms. The smooth line indicates the maximum likelihood estimates for the probability of symptoms, and the dashed lines represent the 95% confidence intervals. The dotted lines indicate the threshold at which 50% of children reported symptoms.

Figure 4: Relationship between mean daily pollen concentration lagged 0 to 18 days (Pollen018) and reported lung symptoms from a Generalised Additive Mixed Model. The X axis represents increasing pollen concentration. The rug (lines) at the bottom indicates the density of observations at each level of pollen. The Y axis represents the probability of reported eye symptoms. The smooth line indicates the maximum likelihood estimates for the probability of symptoms, and the dashed lines represent the 95% confidence intervals. The dotted lines indicate the threshold at which 50% of children reported symptoms.
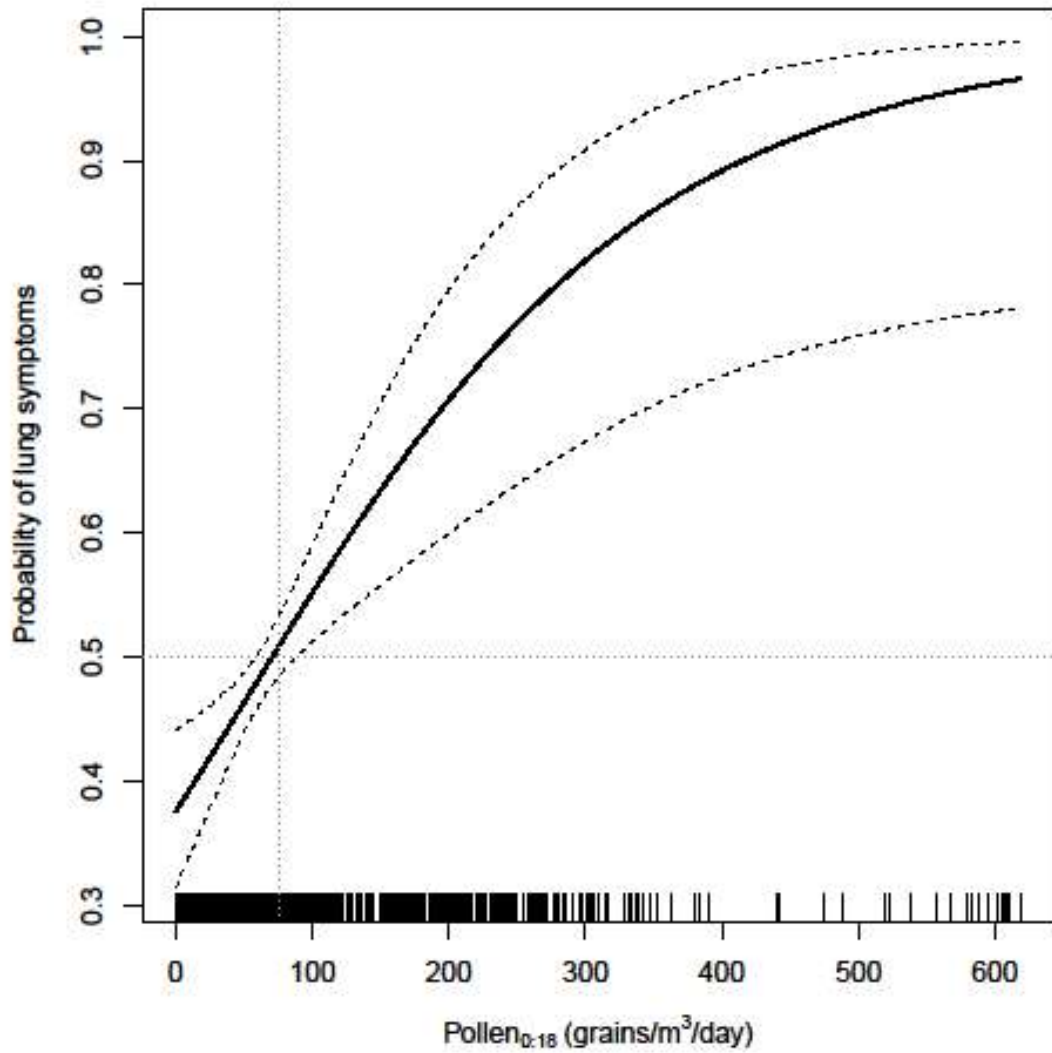
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Table S1: Significance of daily pollen lags for eye, nose and lung symptoms

Day	Eye symptoms	p Nose symptoms	Lung symptoms
0	<0.001	<0.001	<0.001
1	<0.001	<0.001	<0.001
2	<0.001	0.001	<0.001
3	<0.001	<0.001	<0.001
4	0.010	<0.001	0.002
5	0.016	0.003	<0.001
6	0.028	<0.001	<0.001
7	0.024	<0.001	<0.001
8	0.114	0.001	<0.001
9	0.035	<0.001	<0.001
10	0.074	0.001	<0.001
11	0.009	0.001	<0.001
12	0.210	0.035	<0.001
13	0.847	0.081	<0.001
14	0.761	0.117	0.001
15	0.807	0.006	0.001
16	0.737	0.043	<0.001
17	0.555	0.028	<0.001
18	0.370	0.049	0.007
19	0.076	0.498	0.019
20	0.223	0.961	0.049

Table S2: Explanatory variables used in analysis

		Variable
Time series		Mean Pollen concentration lagged over days zero to three (Pollen 0:3)
		Mean Pollen concentration lagged over days zero to eleven (Pollen 0:11)
		Mean Pollen concentration lagged over days zero to eighteen (Pollen 0:18)
		Day of the week
		Weekend
		Year (2012; 2013; 2014)
		Season (Early or late pollen season)
		Location of child in Day (At home or Away from home)
		Reported eye symptoms on previous day
		Reported nasal symptoms on previous day
		Reported lung symptoms on previous day
		Self (or parental)-reported allergic rhinitis symptoms in child
		Self (or parental)-reported allergic asthma symptoms in child
		Taking nasal spray or nose drops on day of symptoms
		Taking nasal spray or nose drops on previous day
		Taking anti-allergy tablets on day of symptoms
		Taking anti-allergy tablets on previous day
		Taking asthma medication on day of symptoms
		Taking asthma medication on previous day
		Time spent being active
		Time spent being active outside
		Mean daily temperature (^{o}C)
		Maximum daily temperature (^{o}C)
		Minimum daily temperature (^{o}C)
		Daily rainfall (mm)
		Mean SO_2 ($\mu g/m^3$) over previous 4/12/19 days
		Mean PM10 ($\mu g/m^3$) over previous 4/12/19 days
		Mean NO_2 ($\mu g/m^3$) over previous 4/12/19 days
		Mean O_3 ($\mu g/m^3$) over previous 4/12/19 days
Individual		Age at entry into study
		Gender
		Sensitisation to other allergens
		Atopic parent
		Child order
		Use of antibiotics in first year of life
		Maternal smoking in pregnancy
		Child has been treated by doctor for worms
		Respiratory infection in childhood
		Does child sleep on feather pillow
		Asthmatic parent
		Has atopic family member
		Number of bedrooms in home
		Number of adults in household
		Education of father (Higher than secondary level; High school diploma or lower)
		Education of Mother (Higher than secondary level; High school diploma or lower)

	Monthly Household Income (<€660; €660-€1320; >€1320)
	Lives in Urban or Rural area

Table S3: Change in AIC over each model addition

Additions to model	AIC
Eye model	
Core model	2358.19
Monthly household Income	1955.25
Mean O_3 ($\mu g/m^3$) over previous 4 days	1750.75
Location (at home or away from home)	1640.88
Taking anti-allergy tablets on day of symptoms	1564.37
Taking nasal spray or nose drops on day of symptoms	1502.76
Self (or parental)-reported allergic rhinitis symptoms in child	1446.85
Self (or parental)-reported asthma symptoms in child	1399.50
Mean PM10 ($\mu g/m^3$) over previous 4 days	1373.26
Mean SO_2 ($\mu g/m^3$) over previous 4 days	1363.46
Taking nasal spray or nose drops on previous day	1354.90
Time spent being active outside	1349.82
Nose model	
Core model	2369.80
Monthly household Income	1815.58
Mean O_3 ($\mu g/m^3$) over previous 12 days	1536.82
Location (at home or away from home)	1447.77
Taking nasal spray or nose drops on day of symptoms	1385.68
Child has been treated by doctor for worms	1330.46
Mean PM10 ($\mu g/m^3$) over previous 12 days	1283.12
Self (or parental)-reported allergic rhinitis symptoms in child	1261.51
Mean SO_2 ($\mu g/m^3$) over previous 12 days	1241.56
Self (or parental)-reported asthma symptoms in child	1230.32
Lung model	
Core model	1381.89
Mean O_3 ($\mu g/m^3$) over previous 19 days	1063.19
Monthly household Income	855.82
Mean PM10 ($\mu g/m^3$) over previous 19 days	772.61
Location (at home or away from home)	724.38
Mean SO_2 ($\mu g/m^3$) over previous 19 days	697.24
Child has asthmatic parent	673.04
Taking asthma medication on day of symptoms	654.89
Self (or parental)-reported allergic rhinitis symptoms in child	646.52
Time spent being active	642.51
Self (or parental)-reported asthma symptoms in child	639.52
Type of area child lives in (Rural or Urban)	636.66

Core model: Child (random effect), Area (random effect), average pollen (over 4/12/19 days), reported eye/nose/lung symptoms on previous day, gender, age, year, mean daily temperature (^{o}C), daily rainfall (mm)