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High ambient levels of grass, weed and other pollens are associated with asthma admissions in children and adolescents: A large 5-year case-crossover study

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ABSTRACT

Background: Pollen is an important aeroallergen that triggers asthma exacerbations in children, but we know little about the impact of different pollen types in cities with varying climatic conditions and pollen seasons.

Objectives: We aimed to assess the role of ambient level of different types of pollen on a large time series of child and adolescent asthma hospitalizations in Sydney, Australia.

Methods: Childhood asthma hospitalization and the daily ambient pollen concentrations of different species were collected in South-West Sydney. With a bi-directional case-crossover design, we fitted conditional logistic regression models to measure the associations between instantaneous and up to 3 days lagged effects of pollen concentrations on asthma hospitalizations after controlling for potential confounders and testing for interactions. **Results:** A total of 2098 children, more boys (59.7%) and 2 to 5 years old (62.6%), were hospitalized due to asthma. The geometric mean concentration of *Cupressus*, 7.88 [5.02] grains/m³, was the highest during the study period. The increase from 75th to 90th percentile of grass (OR=1.037, 95%CI 1.005-1.070), weed other than *Plantago* species (OR=1.053, 95%CI 1.009-1.098) and unclassified pollens (OR=1.034, 95%CI 1.010-1.058) were significantly associated with the odds of asthma hospitalizations. Boys were at greater risk of asthma exacerbations associated with grass (OR=1.046, 95%CI 1.003-1.090) and unclassified pollens (OR=1.041, 95%CI 1.010-1.073). There was evidence of effect modification by age groups for *Cupressus*, conifer, total tree and total pollens. **Conclusions:** Although boys are more vulnerable to grass pollen, weed, and other pollens are also important triggers of asthma exacerbations in all children and adolescents. These findings are important for urban green space planning and the development of pollen monitoring systems for families with children at risk of asthma exacerbations during peak pollen seasons.

Key words: Asthma, hospitalization, pollen, children, case-crossover

Abbreviations:

CI	Confidence Interval
ED	Emergency Department
HRV	Human rhinovirus
NO ₂	Nitrogen dioxide
O ₃	Ozone
OR	Odds ratios
PM _{2.5}	Particulate matter up to 2.5µm median diameter

PM₁₀ Particulate matter up to 10µm median diameter
ppb parts per billion (by volume)

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1 1. INTRODUCTION

2 Asthma remains a significant global chronic public health problem¹ and the burden of disease
3 is greatest in children.^{2, 3} Although childhood asthma prevalence varies significantly ranging
4 from 1 to 18% across different countries,² it is highest among high income countries
5 including Australia.⁴ Asthma admissions are a huge burden on children, families and the
6 health care system with short term triggers occurring during peak seasonal periods such as
7 winter associated with respiratory viral infections and spring as a marker of pollen load.^{5, 6}
8 Understanding the role of these environmental triggers would allow better management of
9 those at risk enabling them to take additional precautions for limiting exposures.

10

11 Pollen is an important aeroallergen, especially grass due to its significant allergy producing
12 capabilities.⁷ High pollen grain allergen release during peak pollen seasons trigger asthma
13 exacerbations.⁸ The effects can be fatal in combination with changing extreme weather
14 patterns as was observed in Melbourne, Australia in November 2016 during the outbreak of
15 thunderstorm asthma where ten people died and nearly 10,000 presented to emergency
16 department (ED).⁹ Studies evaluating associations in large cities with urban demographics
17 and different magnitude and timing of the pollen seasons are still lacking. As pollen seasons
18 vary both spatially and temporally, the effect of pollen on respiratory health could also differ
19 in various geographical and climatic conditions. With climate change, including changing
20 extreme weather patterns, the allergenic effect of pollen is projected to increase,¹⁰ especially
21 in urban areas.¹¹

22

23 Although studies including our own have strengthened our understanding of the link between
24 ambient pollen levels and childhood asthma hospitalizations,¹²⁻¹⁴ no study has examined
25 different pollen types and their impacts over a long period only focusing on children and
26 adolescents who have been admitted to hospital for asthma. Our earlier studies found
27 significant associations between grass pollen in Melbourne and asthma admissions but over
28 short period,^{12,13} Im et al assessed effects of only weed and ragweed pollen during the fall
29 season on asthma admissions in children 0 to 14 years of age. They found increases in 13
30 counts of weed pollen (per cubic metre) 3 days prior increased daily hospital admissions in
31 this age group.¹⁴ Chen et al conducted a comprehensive analysis of environmental variables
32 including total pollen and admissions for all age groups in Adelaide, Australia. Among
33 children, total pollen was a significant predictor of asthma admissions in multipollutant
34 distributed lag models (IRR=1.01 95% CI 1.010, 1.034).¹⁵

35

36 A better understanding of the role of different types of pollen as triggers for asthma
37 exacerbations requiring hospitalization in cities with complex pollen seasons is critical for the
38 management of asthma. Such knowledge may be used to better inform plant choices for
39 greening cities. Therefore, the aim of this study was to assess the role of ambient levels of
40 different types of pollen on asthma hospitalization over a 5 year period in children and
41 adolescents in Sydney, Australia.

42

43 **2. METHODS**

44 **2.1 Study design**

45 We used a case -crossover design over a 5-year period, between May 1, 2008 and May 31,
46 2013. The case-crossover study is suitable for measuring transient and acute health
47 outcomes,¹⁶ such as asthma hospitalization and exposure to daily environmental factors such
48 as ambient pollen concentrations. Case status was defined as the date of admission, while the
49 control status was defined as periods on the same day of week in the same month as the case
50 date. In this design, each case serves as his/her own control and eliminates the potential
51 confounding effects that result from individual differences due to selection of other controls.
52 Also, the bi-directional approach for selection of control dates from the same day of the week
53 and month also prevents any time trend biases resulting from the time series nature of the
54 data.¹⁶ We excluded cases readmitted within the period of one month (1-28 days) to avoid
55 confusion related to the definition of the case (index) and control dates.

56

57 **2.2 Study population and asthma hospitalization data**

58 The study sample included a total of 2,098 children and adolescents, aged between 2-18
59 years, admitted to hospital for asthma in three hospitals: Campbelltown, Camden and
60 Liverpool in Sydney. Due to variations in coding between different hospitals, three
61 classification systems for the diagnosis coding were included: 1. ICD10-AM¹⁷: Asthma
62 (J45), Status asthmaticus (J46); 2. SNOMED CT-AU¹⁸: Asthma (195967001), Asthma NOS
63 (266365004); 3. ICD-9¹⁹: Extrinsic asthma (493.0); Intrinsic asthma (493.1); Asthma
64 unspecified (493.9); Chronic obstructive asthma (493.2); Other forms of asthma (493.8) and
65 Cough variant asthma (493.82). Data on the age, sex, admission date, and re-admission cases
66 within 28 days were also available. Children below the age of 2 years were excluded because
67 diagnosis of asthma in this group is difficult.²⁰

68

69 **2.3 Pollen data**

70 Daily ambient concentrations of pollen, expressed as total pollen grains per cubic metre (m³)
71 of air, were collected using a 7-day Burkard volumetric spore trap. The trap was located on
72 the rooftop of Campbelltown hospital free from obstruction. The pollen was collected in the
73 trap by air drawn into the chamber, at a rate of 10L/min, through the 2 mm by 14 mm slit.
74 The constantly moving adhesive tape/slide captured the pollen over 1-7 day period. A trained
75 technician counted the pollen by family, since it is difficult to identify to taxa level by
76 microscopy. The pollen was classified into eight different categories: grass (Poaceae),
77 *Plantago* (weed), Other weeds (*Echium plantagineum* and *Parietaria pollen*) and pollen from
78 the tree *Cupressus*, *Casuarina*, *Eucalyptus*, conifer and *Platanus*. In addition, “Total tree”
79 and “Total pollen” categories were also created that included the sum of the tree and all
80 pollen counts respectively. The “unclassified” group included pollens that were not identified
81 into any of the categories specified above. Earlier studies in Sydney have shown two distinct
82 grass pollen peaks: the first smaller peak occurs between January to April and the second
83 major pollen peak between July to October^{21, 22} but we do acknowledge that other species
84 maybe present in the atmosphere throughout the year.

86 **2.4 Air quality and meteorological data**

87 Daily air quality data were obtained from the Environment Protection Authority in NSW with
88 fixed monitoring stations located in Liverpool and Campbelltown. Air pollutant data were
89 available including 24-hour average daily concentrations of particulate matter (µg/m³) PM_{2.5}
90 and PM₁₀ (<2.5 and <10µm diameter respectively). Daily maximum one hour average of
91 nitrogen dioxide (NO₂) in parts per billion (ppb) and daily maximum four hour average of
92 ozone (O₃) in ppb were also available. The data from Liverpool were used in the study as
93 they contained the most complete data for the time period. Daily maximum temperature,
94 daily total rainfall (mm) and average daily relative humidity (%) were also available from the
95 Bureau of Meteorology station in Liverpool.

97 **2.5 Statistical methods**

98 Conditional logistic regression models were used to assess the association between different
99 pollen taxa and the asthma hospitalizations outcome using daily pollen concentration as a
100 continuous exposure variable. In most studies of environmental exposures and hospital
101 related outcomes where the unit of analysis is per day, Poisson regression or General
102 Additive Models that assume a Poisson distribution for the outcome have been commonly

103 used. The conditional logistic model we used was based on a bi-directional approach to a
104 case crossover design with reduced bias. Although our choice of method has potentially
105 reduced efficiency,²³ our result may be somewhat conservative (less precise CI) but the
106 estimates are accurate. Furthermore, the assumption of a Poisson process was not justified by
107 our data based on a deviance goodness of fit and a Pearson goodness of fit test ($p < 0.001$).
108 Therefore, our choice of the use of a conditional logistic regression is appropriate in this
109 instance. We modelled instantaneous (L0) and up to 3 days lagged (L1, L2 and L3) effects of
110 various pollen types. Results are presented as the odds ratio of asthma hospitalization for the
111 75th to 90th percentile increase in pollen concentrations (grains/m³) with 95% confidence
112 intervals (CI). Possible confounding variables such as rainfall, relative humidity, temperature
113 and pollutants such as O₃, NO₂, PM_{2.5} were included in the models if they changed the
114 associations between pollen and asthma hospitalization by 10% or more or were statistically
115 significant at the 5% level of significance.

116

117 We conducted stratified analyses for sex and age group (categorised into three groups: 2-5
118 years, 6-12 years and 13-18 years) for assessing the effect modification by these variables on
119 pollen and asthma association. The stratum specific odds ratio of pollen effect on asthma
120 hospitalization and the p-value of the interaction terms were calculated. For the age
121 categories, the 13-18 years age group was taken as the reference group for calculating p-value
122 of interaction for other two categories. We constructed smooth time series plots of daily
123 asthma hospitalization count smoothed using the LOWESS-locally Scatterplot Smoothing
124 over the daily pollen counts. All analyses were conducted using statistical analysis package
125 Stata SE 14.1 (StataCorp, College Station, Texas).

126 **2.6 Ethics**

127 Ethics approvals for the study were obtained from South West Sydney Local Health District
128 Human Research Ethics Committee (HREC Number: LNR/13/LPOOL/189) and La Trobe
129 University.

130

131 **3. RESULTS**

132 A total of 2,098 children were admitted for asthma between 25th May 2008 and 3rd May 2013.
133 Among them, 44.3% (n=929) children were admitted during the first pollen peak, 21.5%
134 (n=450) in the second peak and 34.3% (n=719) during other months. More boys than girls
135 were admitted during the study period, but no significant association was observed between
136 age group and asthma hospitalization during pollen and non-pollen peaks (Table 1).

137 Smoothed graphs of daily asthma hospitalization cases and pollen counts were plotted for
138 grass (Figure 1), *Cupressus* (Fig 2), conifer (Fig 3) and total tree pollen (Fig 4). The plots
139 suggest variations in asthma and distribution patterns for different pollen taxa across different
140 time points. Table 2 shows the summary statistics of the daily pollen grain concentrations
141 from 1st May 2008 to 31st May 2013. Most pollen counts remained relatively low for the most
142 part of the year (50th percentile=0), while very high pollen counts of *Cupressus* (over 500
143 grains/m³) were recorded for a total of 8 days in the entire period. The high pollen counts
144 occurred mainly during the second pollen period that peaked during September to November
145 reaching over 1000 grains/m³. The distribution of the grass species was distributed more
146 consistently over the years, reaching the peak concentration (142 grains/m³) during October
147 to January. Conifer and total tree pollen peaked during the second peak season between July
148 and October. *Eucalyptus* pollen reached peak concentration during the October to January,
149 while other weeds were predominant during October to December.

150

151 Due to the large positive skewness of the pollen data, we present the geometric means (GM)
152 and geometric standard deviation of daily pollen concentrations. *Cupressus*, 7.9 [5.0]
153 grains/m³, had the highest geometric mean, followed by grass, 4.8 [3.2] grains/m³ (Table 2).

154

155 The adjusted odds ratios for asthma hospitalization, per unit increase in the same day and 4-
156 day (Lag0, Lag1, Lag2 and Lag3) cumulative lagged pollen concentrations along with 95%
157 confidence intervals are presented in table 3. The same day grass (OR=1.037, 95%CI: 1.005,
158 1.070), other weeds (OR=1.053, 95% CI: 1.009, 1.098), and unclassified pollen (OR=1.034,
159 95% CI: 1.010, 1.058) were significantly associated with increased likelihood of asthma
160 hospitalization. The cumulative lagged concentrations of unclassified pollen (OR=1.008,
161 95%CI: 1.001, 1.015) and *Platanus* (OR=0.996, 95%CI: 0.991, 0.999) were also associated
162 with asthma hospitalizations (Table 3). Few associations were observed for Lag1 and Lag3
163 pollen concentrations. *Plantago* (OR=0.948, 95%CI: 0.907, 0.992) and unclassified pollen
164 (OR=1.016, 95%CI: 1.000, 1.032) were significant at Lag3 and *Platanus* (OR=0.981, 95%CI:
165 0.965, 0.996) was significant at Lag1 (result not shown).

166

167 Sex stratified analysis was also conducted and p-values of the interaction terms between the
168 sex and pollen estimated. There was a trend for grass (OR=1.046, 95%CI: 1.003, 1.090) and
169 other unidentified pollens (OR=1.041, 95%CI: 1.010, 1.073) to increase odds of asthma

170 hospitalizations in boys when stratified, but the p-value for the interaction term in the main
171 effects model was not statistically significant (Online supplementary table 1).

172

173 Age stratification showed that grass (OR=1.047 95%CI: 1.005-1.091), other weeds
174 (OR=1.075, 95% CI: 1.024-1.129), *Platanus* (OR=1.017, 95% CI: 1.003-1.032) and
175 unclassified pollens (OR=1.059, 95% CI: 1.027-1.091) were associated with asthma hospital
176 admissions among 2 to 5 year old children. However, the p-value for the interaction term was
177 only significant for conifer (p=0.008), total tree (p=0.004) and total pollen (p=0.004). Conifer
178 was significant among 6 to 12 year olds (OR=1.051, 95% CI: 1.011-1.092, p=0.003 for the
179 interaction term) (Online supplementary table 2).

180

181 4. DISCUSSION

182 Our study suggests that grass, weeds (*Echium plantaginium* & *Parietaria*) and unclassified
183 pollens were significantly associated with childhood asthma hospitalizations in South-West
184 Sydney, a city with two peak pollen seasons. Boys and children aged 2-5 years were more
185 vulnerable than girls or older children to grass and unclassified pollens. This is the first study
186 to assess the role of different types of pollen concurrently on a large time series of asthma
187 admissions in children and adolescents.

188

189 Our findings on grass pollen are consistent with others including a case-crossover study by
190 our group that showed an increase in grass pollen concentration of 50 grains/m³ was
191 significantly associated with the risk of asthma hospital admissions (OR=1.11, 95%CI 1.00-
192 1.22) in children.¹² A large study in Adelaide reported significant associations between total
193 pollen counts and childhood asthma hospitalizations in a multipollutant moving average
194 model (OR=1.013 95% CI 1.001, 1.025) but not in a multi-pollutant distributed lag model¹⁵.
195 They also reported stronger effects in the cooler seasons. It is uncertain why the effects were
196 observed in cooler seasons, but the effect may be modified by respiratory viral infections
197 during winter, which were not accounted for. It was also unclear if grasses were the
198 prominent trigger of child admissions as they only used total pollen counts as their exposure.
199 In addition to grass, we found other species were important too in this region including weed
200 pollens, such as *Echium plantaginium* and *Parietaria species*. This finding confirms a much
201 earlier study by Bass et al²⁴ that indicated a possible association between weed species,
202 *Parietaria Judaica* and IgE-mediated rhinitis and asthma in Sydney. Weed pollens seems to
203 be important in the USA too especially on severity of asthma symptoms in asthmatic

204 children.^{14, 25} Im et al's study of asthma hospital admissions in children age 0 to 14 years
205 focused only on weed including ragweed as these were the prominent pollens during the fall
206 season. In regression models, they found 3-day lag of elevated weed pollen was significantly
207 associated with admissions.¹⁴ We cannot directly compare our findings with theirs as they
208 only presented beta coefficients from a linear regression model. As overall weed taxa
209 constitute a significant proportion of total pollen counts in Sydney,²⁶ urban vegetation
210 planning needs to be carefully monitored and these factors need to be taken into
211 consideration. In contrast to studies that have focused on tree pollens and childhood asthma
212 exacerbation^{5, 8, 27} we found no associations.

213

214 Our study suggests that pollen is a contributing trigger for asthma exacerbations mostly in
215 young children. Grass, certain weed and other unclassified pollen were significant risk factors
216 for asthma hospitalization in 2 to 5 year old children. However other studies have observed
217 the pollen sensitisation peaks in the second decade of life.^{28,29} We observed an effect
218 modification by age group for *Cupressus*, conifer, total tree and total pollen. Similar to other
219 studies, we also observed a trend toward a greater pollen effect in boys,¹² but it did not reach
220 statistical significance when we included an interaction term in the main effects analysis.

221

222 This study has several strengths. It was based on a robust design extended over a period of 5
223 years with a large sample size. This study is unique in that it has also assessed the association
224 of a wide range of pollen species with asthma. This has not been examined in the Australian
225 context before and has been addressed in few studies only elsewhere. The case-crossover
226 design increased the power of this study and controlled for confounding factors that result
227 from individual differences.

228

229 However, this study also had some limitations. The potential for exposure misclassification
230 cannot be excluded, since it was not possible to confirm that the population were exposed to
231 the same levels of pollen as recorded in our study. Although pollen counts might vary across
232 larger distances,³⁰ the three hospitals included in the study were located within 30 km
233 distance of pollen trap station to minimize the exposure differences across distances. We did
234 not have information on respiratory viruses or pollen sensitisation, which may be important
235 on the pollen trigger pathways to asthma admissions. However, our Melbourne study showed
236 consistent effects of grass as significant predictors of asthma exacerbation, even after
237 adjusting for human rhinovirus and taking pollen sensitisation into account.¹² Therefore, at

238 least for grass, we are reasonably confident that our result is close to a true estimate of
239 asthma hospitalization risk in children. We also acknowledge the differences in coding
240 between hospitals as a potential limitation.

241

242 In summary, grass and weed pollens were associated with asthma hospitalizations in children.
243 Boys and 2 to 5 year old children were more vulnerable than girls or older children to the
244 adverse effects of pollen. These findings further contribute to the evidence that different
245 species of pollen are important triggers of asthma exacerbations. These factors are important
246 for urban planning and greening cities. In countries with varying climatic conditions and
247 different pollen species, standardized national pollen monitoring with advanced warning
248 systems could assist patients at risk of pollen induced asthma exacerbations.

249 **Conflict of interest**

250 MJA holds investigator initiated grants from Pfizer and Boehringer-Ingelheim for unrelated
251 research. The other authors have no potential conflicts of interest to declare.

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Table 1. Descriptive statistics of asthma hospitalization segregated by pollen peaks periods in Sydney.

	All	First pollen peak January-April	Second pollen peak July- October	Other months	<i>p-value</i>
N (% of All)	2098	929 (44.3)	450 (21.5)	719 (34.3)	
Sex					
Boys	1253	564 (45.0)	263 (21.0)	426 (34.0)	0.69 ^a
Girl	845	365 (43.2)	187 (22.1)	293 (34.7)	
Age group					
2-5 years	1314	597 (45.4)	276 (21.0)	441 (33.6)	0.63 ^b
6-12 years	644	272 (42.3)	140 (21.7)	232 (36.0)	
13-18 years	140	60 (42.9)	34 (24.3)	46 (32.9)	

^aX² test for association between sex and pollen seasons
^bX² test for association between age groups and pollen seasons

361 Table 2. Descriptive statistics and percentile distribution of pollens from 1st May
 362 2008 to 31st May 2013.

Pollen Types	Geometric Mean (SD)	Min	Percentiles				Max
			25th	50th	75th	90 th	
Grass	4.8 (3.2)	0	0	1	5	14	142
<i>Plantago</i>	3.6 (2.9)	0	0	0	3	8	83
Other weeds ¹	2.9 (2.6)	0	0	0	1	5	51
<i>Cupressus</i>	7.9 (5.0)	0	0	0	5	29	1266
<i>Casuarina</i>	3.3 (2.9)	0	0	0	3	7	358
<i>Eucalyptus</i>	3.8 (2.9)	0	0	1	5	10	146
Conifer	4.7 (3.5)	0	0	0	0	7	135
<i>Platanus</i>	4 (3.6)	0	0	0	1	5	203
Unclassified pollen	4.4 (2.8)	0	0	3	7	12	264
Total Tree	15.1 (4.0)	0	2	11	29	75	1401
Total Pollen	20.8 (3.9)	0	4	15	42	106	1426

¹Sporadic and lower number weeds (*Echium plantagineum* & *Parietaria* pollen)

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372 Table 3. Adjusted odds ratios and 95% confidence intervals (CI) of childhood asthma
 373 hospitalizations associated with 75th to 90th percentile increase in same day (lag0) and
 374 cumulative lagged pollen concentrations.

Pollen Types	Lag 0 OR (95% CI)	Cumulative Lag OR (95% CI)
Grass	1.037 (1.005- 1.070)*	1.005 (0.995-1.015)
<i>Plantago</i>	1.003 (0.962-1.045)	0.994 (0.983-1.005)
Other weeds ¹	1.053 (1.009-1.098)	1.002 (0.990-1.015)
<i>Cupressus</i>	1.007 (0.986-1.027)	1.001 (0.994-1.008)

<i>Casuarina</i>	1.004 (0.992-1.015)	1.003 (0.997-1.009)
<i>Eucalyptus</i>	0.991 (0.962-1.022)	0.995 (0.986-1.005)
Conifer	1.015 (0.987-1.045)	1.004 (0.995-1.012)
<i>Platanus</i>	1.002 (0.987-1.017)	0.996 (0.991-0.999)*
Unclassified pollen	1.034 (1.010-1.058)*	1.008 (1.001-1.015)*
Total Tree	1.015 (0.988-1.042)	1.002 (0.993-1.010)
Total Pollen	1.026 (0.992-1.060)	1.002 (0.992-1.013)

375 (Adjusted for maximum temperature, mean humidity and average PM_{2.5})

376 ¹Sporadic and lower number weeds (*Echium plantagineum* & *Parietaria* pollen)

377 *p<0.05

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399 **Figure legends**

400 Figure 1: Daily smoothed asthma admissions counts and daily grass pollen count during the
401 study period

402 Figure 2: Daily smoothed asthma admissions counts and daily *Cypress* pollen count during
403 the study period

404 Figure 3: Daily smoothed asthma admissions counts and daily conifer pollen count during the
405 study period.

406 Figure 4: Daily smoothed asthma admissions counts and daily total tree pollen count during
407 the study period.

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Figure 1: Daily smoothed asthma admissions counts and daily grass pollen count during the study period

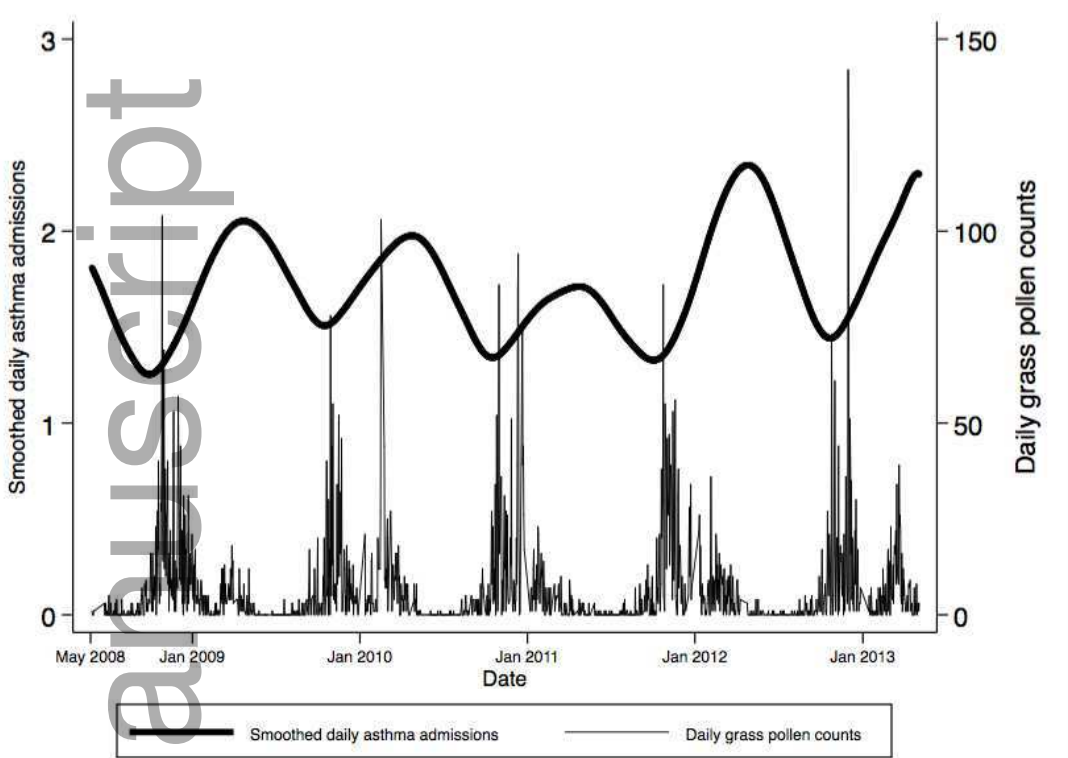


Figure 2: Daily smoothed asthma admissions counts and daily *Cypress* pollen count during the study period

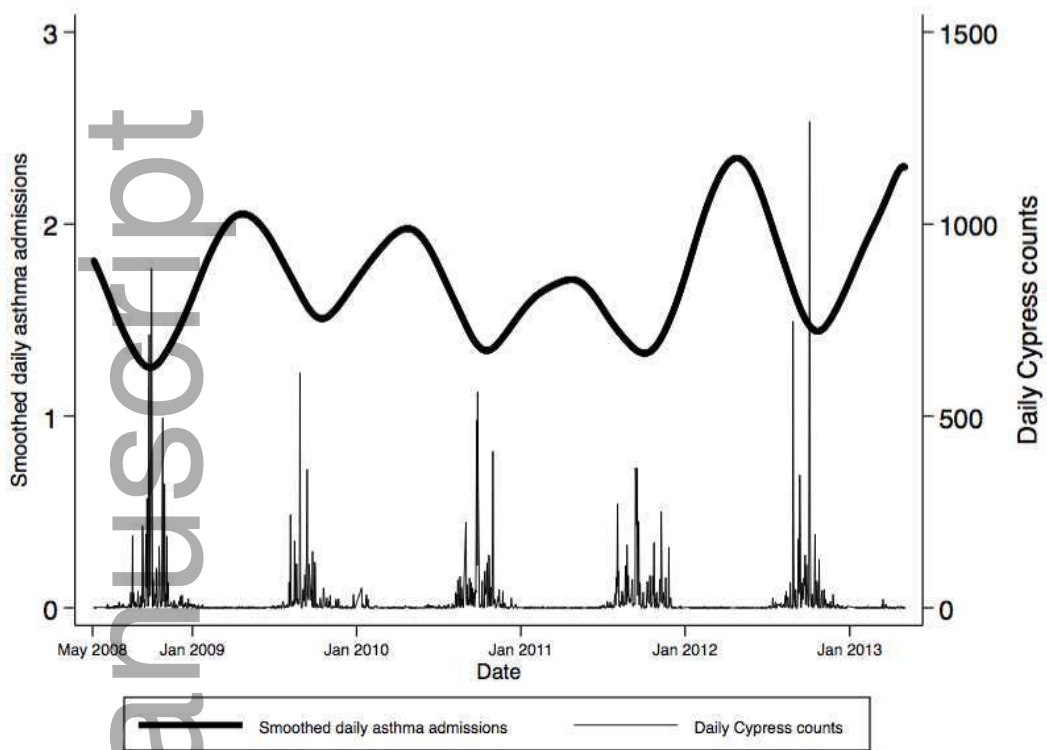


Figure 3: Daily smoothed asthma admissions counts and daily conifer pollen count during the study period.

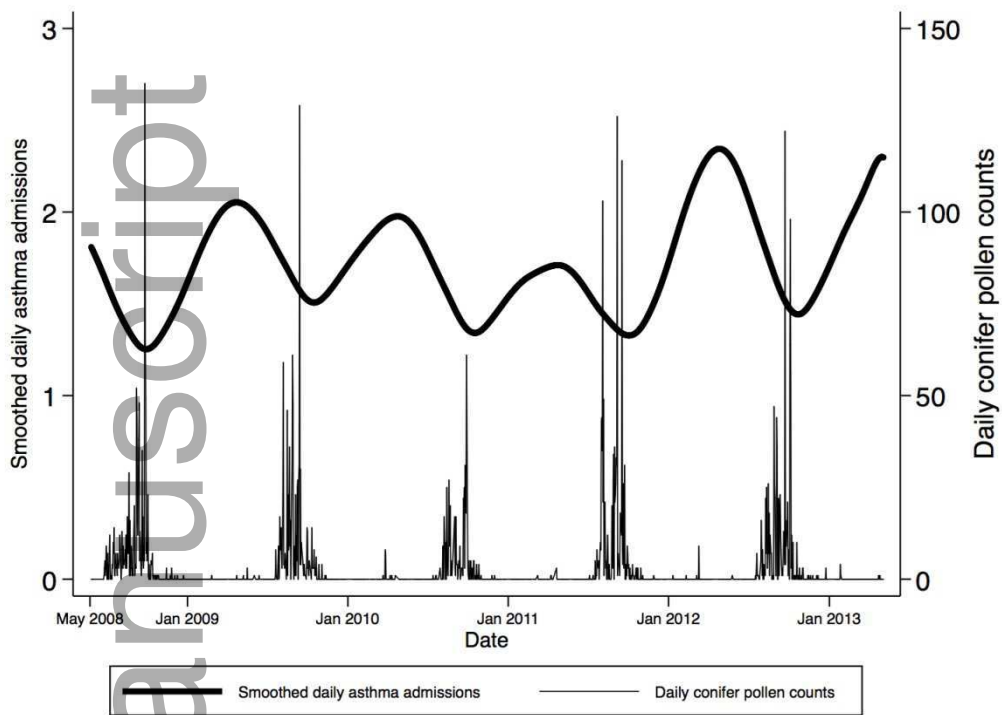
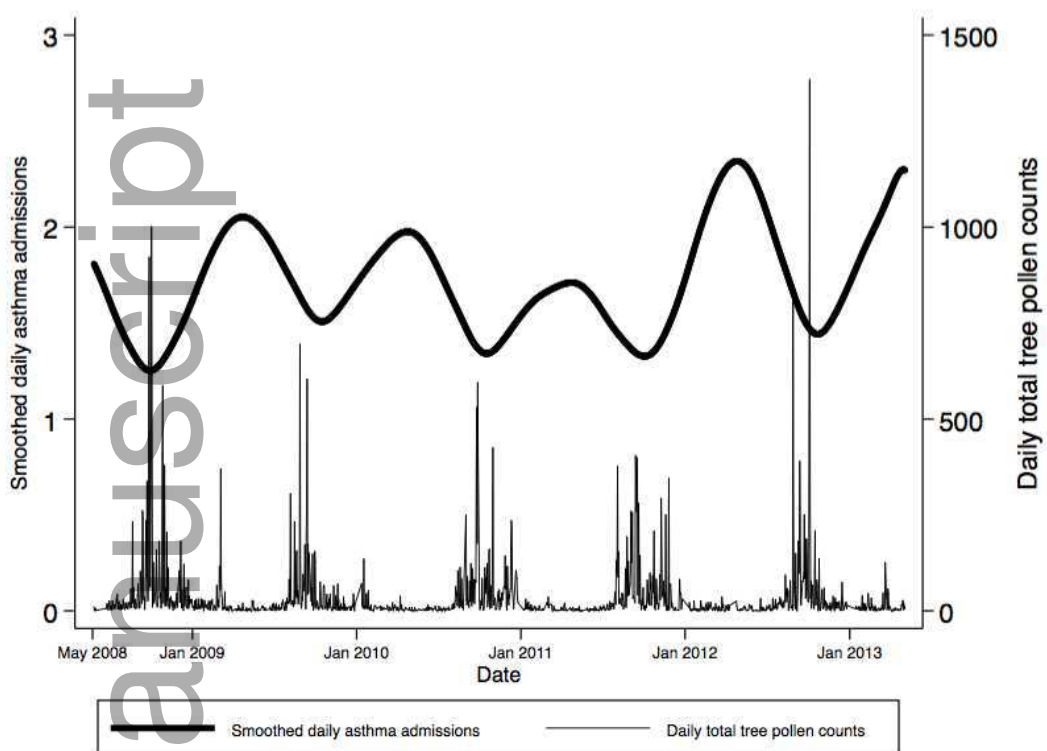


Figure 4: Daily smoothed asthma admissions counts and daily total tree pollen count during the study period.





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Title:

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