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Pollen effects in a changing climate: Ragweed pollen exposure and sleepiness in immunotherapy patients of a Southeastern Michigan allergy clinic

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Abstract

Allergic rhino-conjunctivitis (AR) is a globally relevant health disorder characterized by sneezing, rhinorrhea and sleep disturbance. Ragweed (*Ambrosia artemisiifolia*) is a plant common to North America and an important allergen. Coarse methods of measuring airborne pollen counts are used to predict seasonal allergy symptoms. This research used a longitudinal study design with a novel, model-based raster of predicted pollen counts to test associations with self-reported symptoms of AR collected from patients receiving immunotherapy for pollen allergies at an allergy clinic. Researchers visited a clinic six times over three weeks. Immunotherapy patients were asked to fill out a brief intake survey on allergic and symptomatic profiles, daytime sleepiness, housing quality, and demographics. Participants responded to a daily, emailed survey on sleepiness and asthma symptoms for 21 days. Using the date and location of responses, ragweed pollen counts were extracted from a prognostic, model based raster (25km pixels). Lag associations of pollen counts with sleepiness were tested using a logistic regression model , adjusted for housing and demographic characteristics, in a distributed lag non-linear model (DLNM) framework. 49 people participated in the study. 26 (52%) were female. The mean age was 37.9 years. Asthma/allergy symptoms were not associated with ragweed pollen but sleepiness was highest two days after exposure (Estimate: 0.33 [0.04,0.62]). Subjects traveled widely during the study period. Intense exposures to ragweed pollen may be associated with daytime sleepiness within small exposure windows. Model-based predicted pollen counts could be used to study health impacts of pollen

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in people with disease severe enough to receive immunotherapy. Daytime sleepiness can affect productivity and injury risk, and pollen season length and allergenicity may be increasing with climate change. Thus our results may have important implications for population health.

Keywords

Allergy; Pollen; Allergic rhinitis; Climate change

Introduction

Ragweed and ragweed allergies are of increasing concern as climate change modifies the plant's range, seasonal length, and intensity of pollination (Smith et al. 2013; Beggs 2004; Agnew et al. 2018; Schmidt 2017; Zhang et al. 2015; Stach et al. 2001). Increased ragweed concentrations were associated with emergency visits by children for conjunctivitis and rhinitis in a Canadian study (Cakmak et al. 2002).

Allergic rhino-conjunctivitis (AR) is a global health disorder of the nose and eyes associated with sneezing, rhinorrhea, pruritus, and discomfort (Eguiluz-Gracia et al. 2020; Asher et al. 2006). AR is associated with a wide variety of debilitating physical health conditions such as asthma and coronary heart disease (Kim et al. 2010) but also behavioral outcomes such as depression, social avoidance, and suicide (Postolache et al. 2007; Qin et al. 2013; Manalai et al. 2012; Woo et al. 2011; Guzman et al. 2007; Han and Chung 2018; Jeon-Slaughter et al. 2016; Muzalyova et al. 2019a; Richardson et al. 2006)-along with cognitive outcomes (Papapostolou et al. 2021). AR symptoms such as nasal obstruction and coughing have been associated with poor sleep quality and a number of resulting negative physical and mental health outcomes (Juniper et al. 2005; Muñoz-Cano et al. 2018). AR has also been associated with daytime sleepiness which has been shown to worsen for AR sufferers independent of typical night time AR related sleep disturbances (Stuck et al. 2004).

Determinants of AR include air pollutants and molds (Bush et al. 2006; Bornehag et al. 2005; Wang et al. 2019,-but many kinds of pollens are known to also be important causal agents (D'Amato et al. 2007; Illi et al. 2006; Plaschke et al. 2000). Temporal patterns of pollen seasons have been shown to coincide with patterns of AR symptoms (Pfaar et al. 2017). Exposure-response effects have been noted for exposure to some types of pollens and allergic rhinitis and asthma symptoms (Erbas et al. 2012; Jones et al. 2019). Studies suggest that there has been an increasing effect of aeroallergens on patients, and those with AR might experience even more intense symptoms (Cecchi et al. 2010).

Among the aeroallergens, common ragweed (*Ambrosia artemisiifolia*) is a determinant of late summer and early fall seasonal allergies in the Northern hemisphere. Ragweed is a short day species, which indicates that its flowering and pollen release is triggered by day length. Pollen counts tend to peak in the late summer and early fall (Stach et al. 2001). Over 26% of people in the United States are sensitive to ragweed pollen, and the prevalence of ragweed sensitivity in Europe is thought to be increasing (Schmidt 2017; Burbach et al. 2009).

Prediction of allergic symptoms with pollen exposures has relied on spatially sparse and expensive methods of measuring airborne pollen counts. The most common method of forecasting uses past records of pollen counts through rotorod and Hirst-type monitors, with the former being the most prevalent type of monitor in the United States (Hirst 1952; Buters et al. 2018; Oteros et al. 2015; Frenz 2000; Nunez et al. 2017). In some studies, results from nearby monitors are used to test associations of changes in airborne pollen counts of various plant species with pollen related AR symptoms (Durham et al. 2014), however this monitor network in the US is sparse. Monitor based pollen counts have been combined with climatic and environmental data to generate more precise spatial and temporal estimates to test associations with pollen related AR outcomes (Eguiluz-Gracia et al. 2020). This research, however, used a novel model based raster of predicted pollen counts that provides a spatially consistent dataset to test associations with self-reported symptoms of AR collected from patients receiving immunotherapy for pollen allergies. This research used these data within a longitudinal study to test lag effects of pollen exposure on of allergy symptoms and sleep quality. This study will provide insights into the extent and temporal patterns of pollen exposure and health in at-risk populations in the context of the changing climate.

This research will test three major hypotheses. First, we hypothesize that same day exposure to increased levels of ambient pollen will result in worse sleep quality and greater reporting of allergy symptoms. Second, we anticipate that there will be lag effects of exposure on sleep quality and allergy symptoms; exposure to intense levels of pollen one day will result in worse sleep quality and allergy symptoms days later. Finally, we suspect that the impacts of pollen on health will be cumulative; repeated exposures will lead to even worse sleep quality and allergy symptoms over time.

Methods

Participants

Participants were enrolled from the Allergy and Immunology Clinic of the University of Michigan. Adults over the age of 18 receiving immunotherapy for AR were considered for inclusion in the study during August 2019. Researchers visited the clinic six times over three weeks. Per clinic protocol, patients are required to wait for 30 minutes after receiving injections to monitor for severe reactions. During this time, patients were offered participation in the study. The goals, risks and benefits to the study were explained by the researchers and written informed consent was obtained. Participants were provided with paper versions of the consent form to take home. Data was deidentified at the time of data collection so that authors could not identify individual participants during or after data collection. To reduce possible bias in subjects from overrepresentation of people with specific allergy profiles, researchers did not inquire into the specific reasons for visiting the clinic before administering the surveys. The survey size was capped at 50 people, as this was all that the research budget allowed. This research was conducted with the approval of the Institutional Review Board of the University of Michigan (HUM #HUM00166964.) All methods were performed in accordance with the relevant guidelines and regulations.

Survey

The allergy survey comprised two parts. First, to assess baseline allergy and health status and demographics, participants were given a short intake survey while in the clinic receiving immunotherapy. The survey instrument included several questions related to allergy profiles, symptoms, use of pharmaceuticals, and housing conditions.

The second part of the data collection phase was a daily survey administered by sending participants a link to a data collection form over email. Participants were sent a reminder email for each of 21 days containing a link to a short survey of daily sleepiness and activity patterns.

The daily survey included questions based on the Epworth Sleepiness Scale (ESS), a widely used composite measure of sleepiness based on responses to eight situational questions (Johns 1991). These eight questions were included in each of the daily surveys to allow us to assess changes in sleep quality and daytime sleepiness. We also included questions on symptoms associated with AR, use of medications, and basic quality of life measures. All data were collected using Qualtrics software (Qualtrics, Provo, UT). Latitude and longitude locations of responses are automatically included in the survey responses by the software.

Environmental data

A prognostic pollen emissions model was used to associate allergic events and sleepiness with atmospheric concentrations of speciated aeroallergens (i.e. deciduous trees, evergreen trees, grass, and ragweed) (Wozniak and Steiner 2017). The pollen emissions model provides daily estimates of counts for each speciated aeroallergen at a 25-km grid scale, and accounts for geography, vegetation type, and meteorological parameters. Based on the time of the survey in August 2019, the dominant pollen type in the region was estimated to be ragweed by the model.

The recorded daily latitude and longitude of the survey participants was used to extract data from the pollen raster and for the climatic and environmental measures. All exposures along 21 lag days were merged with the daily responses. Same day and lagged exposures accounted for geographic movement so that if, for example, a participant were at another location (n) days previous, the lag(n) exposure would correspond to that location. The pollen emissions model is focused on the continental United States (with some data in Mexico and Canada); however locations outside the continental U.S. were excluded from the analysis.

Statistical methods

Participant demographics were analyzed using standard descriptive methods. To test for associations of sleep and pollen counts, linear mixed effects regression was used for models with a continuous measure of sleep quality including a random effect for subject and time as a predictor. Plots of sleepiness were produced using the percentage of responses in each category.

Raster based predictions were extracted using the GPS coordinate from which the participant responded to the daily survey. For comparison, we also checked models using the GPS coordinate of the reported residence-unless the participant was out of state the previous day, in which case the response was associated with the location of report. Regression models using sleep and asthma related health events as predicted by pollen counts were created.

Distributed lag non-linear models (DLNMs) are a modeling framework used to describe associations showing potentially non-linear and lag exposure effects in time series data (Gasparrini 2011). DLNMs have seen increased application in health related research, investigating associations between environmental exposures and mortality (Entezari and Mayvaneh 2019; Guo et al. 2021; Qiu et al. 2021, incidence of scrub typhus (Bhopdhornangkul et al. 2021, hand, foot and mouth disease (Qi et al. 2018, and temporal trends of malaria (Matsushita et al. 2019), suicide (Luan et al. 2019), hospital admissions (Gronlund et al. 2014) and cognitive decline (Khan et al. 2021). Very few studies have applied the method to investigations of environmental exposures and AR (Gao et al. 2021). We could find no study which used DLNM for research on daily sleep quality or sleepiness. The essence of DLNM is in the definition of a crossbasis, a bi-dimensional functional space created through the combination of two sets of basis functions. These basis functions specify relationships in the dimensions of predictor and lags. We used the lag exposure data to create a cross basis which we used in a logistic regression model. Crossbases for exposure and lag spaces were parameterized at 4 and 3 degrees of freedom, respectively.

Results

Demographics of study participants are presented in Table 1). Out of those approached in the clinic, only two refused participation. No reason was given for refusal. In total, 49 people consented to participate in the study. 26 (53%) participants were female. Out of 48 respondents who reported it, the mean age was 38.4 years (sd 13.4 years). Most (96%) people had resided in their reported home location for a year or more before the survey. More than 94% of respondents reported that this was not the first time they received treatment for allergy related issues. More than half of respondents reported receiving immunotherapy for ragweed (28), which was more than any other type of immunotherapy. Some people reported receiving injections for multiple types of aeroallergens.

Most participants (30 (61%)) lived in suburban or rural locations. 38 (78%) reported living in a house (as opposed to an apartment). Most respondents reported having forced air heating and central air conditioning in their homes and living in homes with carpeting in both the main living areas and the bedroom. Approximately half of respondents reported having pets of some kind.

Surveys were sent out for each of the 21 days of the survey period following enrollment to all participants. The median number of responses per participant was 19. One person responded only once. 10 participants sent responses for the entire 21 day study period. There were a total of 722 responses.

Distance travelled

Locations of responses in the Continental U.S. are shown in Fig. 1). While most responses were from locations within 20 miles of the clinic, some responses came from areas far from the initial survey location within the US. Within the U.S., responses came from locations as far as California. Outside the U.S., responses came from as far as London, England (not shown). Using the latitude/longitude locations of responses, we calculated the straight line distance between subsequent daily responses in kilometers. Subjects were stationary from day to day for approximately 59% of daily responses. The mean distance travelled between the remaining 41% of response days was 57.3 km.

Patterns and determinants of daily sleepiness

Most subjects did not experience daytime sleepiness for most of the days surveyed. The fraction of survey results that indicated that the fraction of responses indicating moderate to severe sleepiness increased over time (See Fig. 2). Since many respondents reported little or no sleepiness, we recategorized the sleep scale into a binary measure. All responses that indicated any level of sleepiness above “normal” on the Epworth scale were considered “sleepy” for the purposes of all the following analyses. Approximately 10% (78 out of a total 722 responses) of daily responses indicated sleepiness.

We tested bivariate relationships between daily sleepiness and individual and household factors. Men had a higher odds (1.65 95% CI [1.02;2.66]) of being sleepy on any given day than women. None of the types of immunotherapy were significantly associated with sleepiness. We found that wood or laminate floors in living areas were significantly protective against sleepiness. We also found that having pets (dogs and cats) was protective against daily sleepiness. See Table 2 for full results.

Sleepiness and pollen exposures

We tested for associations of cumulative environmental exposures and sleepiness using the binary measure of sleepiness based on responses to the ESS questions. Associations were tested using mixed effects logistic regression models, including a random intercept for individual and the DNLM crossbasis which modelled the lag structure of the exposure variables. We initially included covariates for other climatic variables (precipitation and temperature) but their inclusion did not change the estimates for ragweed exposure on sleep by more than 10 percent. Our final model, thus, only included a term for ragweed concentration. Figure 3 shows a three-dimensional plots of sleepiness vs. the range of ragweed exposure at different lags up to lag day 7. The odds of being sleepy was highest for around lag days 3 and 4 for ragweed at the highest levels of pollen exposure, reaching a peak OR of approximately two times that of those unexposed. Figure 3 also shows lag associations of sleepiness with ragweed exposure at the 90th percentile level. Exposure to the 90th percentile compared to none for ragweed was associated with worse sleepiness at lag day 3.

Discussion

With climate change and associated increasing levels of pollen, a better understanding of the effects of pollen on health is crucial. Using a clinic based survey of patients receiving immunotherapy for allergic rhinoconjunctivis, we tested associations between aeroallergens and sleepiness using a method common to studies of sleep and sleepiness. We have shown evidence that suggests that the risk of daytime sleepiness is increased given intense exposures to ragweed pollen at the third lag day.

The control of exposure to pollens in Artimesia sensitive patients has been shown to improve sleep quality as measured by the Epworth Sleep Scale (Li et al. 2020). Some research, however, has suggested that allergic symptomatic severity has greater impacts to sleep quality than possible seasonal exposures to pollens (Muñoz-Cano et al. 2018). One factor that may have influenced our results was the use of antihistamines to control allergy symptoms, which have been shown to have negative impacts on sleep quality (Ozdemir et al. 2014). We asked participants whether they used allergy medications the previous day and initially attempted to include it in our models, but found no effect.

Future research might seek to discover better methods of assessing specific allergic rhinitis symptoms on a daily basis. Further, research characterizing the health impacts of pollen exposure, might consider how features of the home environment may modify the effect of outdoor pollen exposure on health. Additionally, effect modification by urbanicity and daily meteorological factors may exist, although our sample size was too small to test for effect modification by these characteristics in this study.

Geolocating the participants allowed us to better assess locations of exposure. Many studies of exposures to pollens and air pollutants assume that participants are static, and in many cases this could be correct-in this study, however, we found that this was not at all the case. Participants were highly mobile, and thus the nature and levels of exposures to aeroallergens varied throughout the study period. We did not ask participants their reasons for travelling, but it is possible that people who have severe allergies-to ragweed for example-might seek to travel to other regions to mitigate the risk of symptoms during the ragweed season. We found no research exploring the topic of travel as a means of avoiding pollen exposures though we did find research exploring the potential for specific destinations to be possible retreats for those suffering from pollen allergies (Camacho et al. 2016).

This study had several limitations. While we set out to test for temporal patterns of association of lagged exposure days and sleepiness, we were unable to conduct tests for effect modification by immunotherapy status. It is possible that immunotherapy mitigated the strongest impacts of ragweed exposure on sleepiness, so that association of exposure with outcomes were missed. Future studies might attempt to apply a similar design to people not receiving treatment for allergy related health conditions. Next, the length of data collection might have been insufficient to capture temporal patterns of exposures and outcome. We noticed that sleepiness declined for the patients surveyed in the final weeks of data collection after weeks of low variability in daily changes in sleepiness for other participants. Extending the window of data collection might have allowed us to better test associations of exposures and outcomes. For this research we also collected data on allergic rhinitis symptoms and use of inhalers, but there was not enough within person variation to draw valid conclusions using the methods here.

Our results were possibly biased by the location of participant selection, which included people who are aware of their own sensitization to pollens. Some research has suggested that many people are either unaware of being allergic to some types of pollens or do not seek treatment for AR symptoms (Muzalyova et al. 2019b). A study that included people unaware of their sensitization to pollens, or who had not sought treatment for allergic symptoms, might have provided additional insights into the relationship of pollen exposures and daytime sleepiness. Future studies, then, might also test associations within non-clinical samples. Another source of bias might have been associated with the pollen model. While the models are validated against observations from pollen monitors, the sparse locations measured might impact the validity of the results at locations without monitors. Further, the 25km grid might be too large to sufficiently capture the actual levels of pollen people are exposed to; many people might be exposed through plants in the vicinity of the home and might not be as common throughout the 25km space.

The clinic from which our participants were recruited generally serves patients of higher socioeconomic status. We did not inquire as to why the participants were traveling, but we hypothesize that some of the motivation for travel during ragweed season is to decrease exposure. With the potential for increasing effects of pollen with climate change, and the decreased ability of individuals of lower socioeconomic status to afford travel to areas with less pollen, socioeconomic disparities in these health impacts may be exacerbated. Given the projected increased intensity and range of exposures to various pollens due to climate change, more work should be done to assess how pollen seasonality impacts severe AR symptoms. We also hope that our work will inform efforts to provide advanced warning of pollen exposure by incorporating pollen level predictions and alerts into, e.g., heat health warning systems.

Conclusions

Our research suggests that exposure to intense levels of seasonal ragweed pollen can worsen sleepiness at short exposures lags. We also concluded that assessing the relationship of exposure and sleep quality was complicated by travel behaviors of patients suggesting that studies on aeroallergen exposures and symptomatic outcomes should take care to account for travel. This research contributes to our understanding of the health effects of climate change to better prepare for and adapt to climate change.

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Data Availability

Code and fully deidentified data will be available through the GitHub respository: https://github.com/kambanane/Allergy-Clinic-Survey

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Fig. 1.
GPS locations of responses to the daily sleep survey

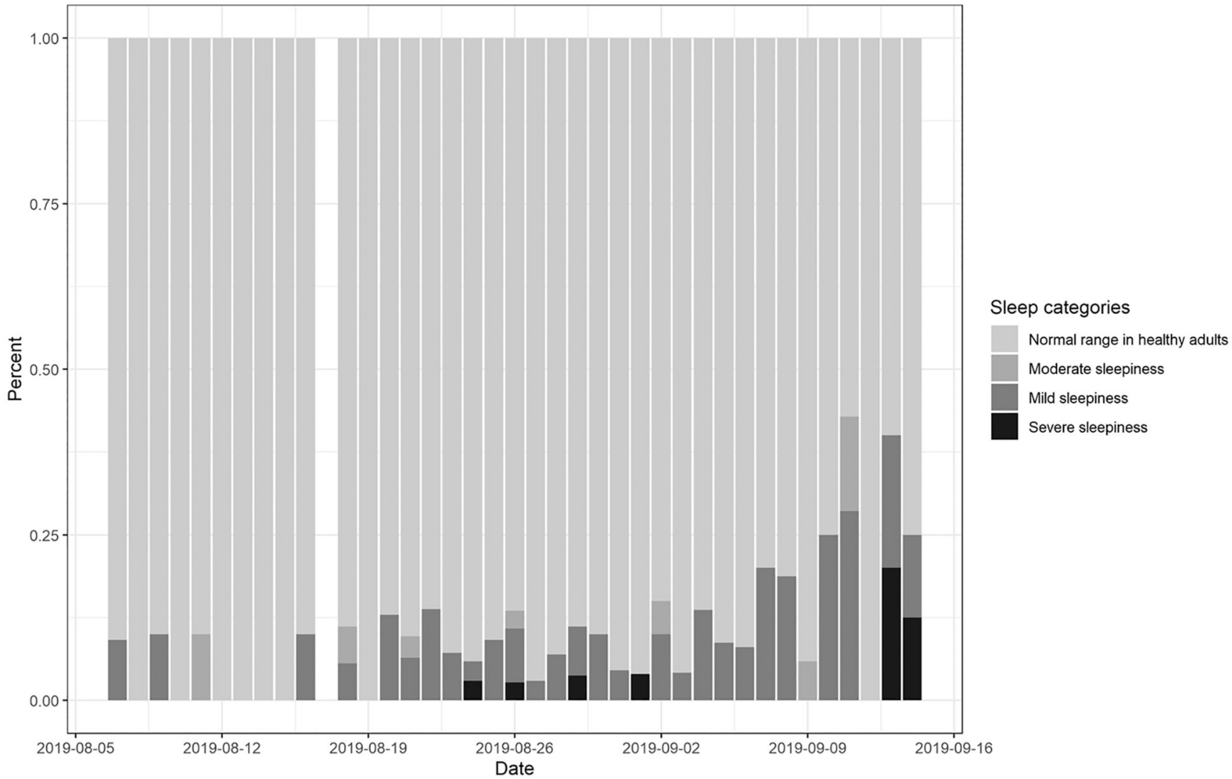

Fig. 2.
Daily distribution of responses to daily sleepiness survey

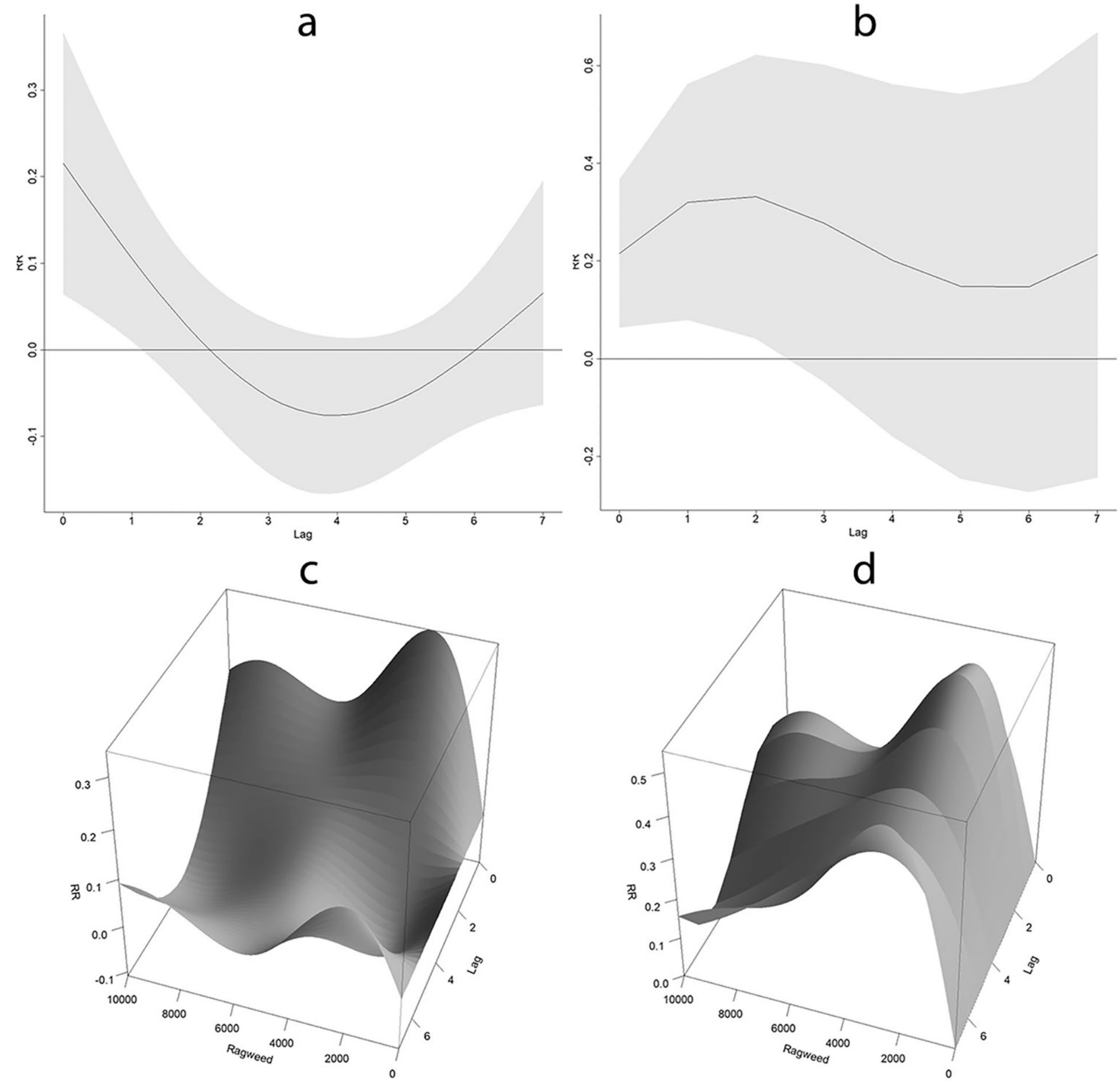

Fig. 3.

Lag and risk response for ragweed exposure and sleepiness. a) Cumulative risk for a one unit increase in sleepiness given exposure to the 90th percentile of ragweed concentration over the study period compared with no exposure. b) Cumulative risk for a unit increase in sleepiness given exposure to the 90th percentile of ragweed concentration over the study period compared with no exposure. c) Surface plot of risk for a unit change in sleepiness given exposure to the range of ragweed exposures over 7 days of lags. d) The same plot, but for cumulative exposures up to 7 lag days

Table 1

Number (and percent) of respondents by age, gender, residential tenure, prior clinic visit, current tobacco use, and immunotherapy type

	[ALL] N=49	**N**
Age	38.4 (sd = 13.4)	48
Gender:		49
Female	26 (53.1%)	
Male	22 (44.9%)	
Prefer not to answer	1 (2.04%)	
Length lived at current address:		49
All my life	8 (16.3%)	
Between one and six months	1 (2.04%)	
Between six months and one year	1 (2.04%)	
More than a year but not all my life	39 (79.6%)	
First time at clinic:		49
No	46 (93.9%)	
Yes	3 (6.12%)	
Do you currently use tobacco:		49
No	45 (91.8%)	
Yes	4 (8.16%)	
Ragweed immunotherapy:		49
No	21 (42.9%)	
Yes	28 (57.1%)	
Birch immunotherapy:		49
No	38 (77.6%)	
Yes	11 (22.4%)	
Oak immunotherapy:		49
No	38 (77.6%)	
Yes	11 (22.4%)	
Grass immunotherapy:		49
No	15 (30.6%)	
Yes	34 (69.4%)	
Other type of pollen immunotherapy:		49
No	35 (71.4%)	
Yes	14 (28.6%)	

Table 2

Descripitive statistics and unadjusted odds of sleepiness among those with the characteristic vs. those with the reference value (OR) for bivariate logistic regression models by sleep

	Not sleepy N=705	Sleepy N=78	OR [95% CI]	p
Age	40.5 (13.1)	42.2 (13.1)	1.01 [0.99;1.03]	0.322
Gender:				
Female	419 (59.4%)	37 (47.4%)	Ref.	Ref.
Male	268 (38.0%)	39 (50.0%)	1.65 [1.02;2.66]	0.041
Prefer not to answer	18 (2.55%)	2 (2.56%)	1.34 [0.19;4.94]	0.720
Birch immunotherapy:				
No	507 (71.9%)	55 (70.5%)	Ref.	Ref.
Yes	198 (28.1%)	23 (29.5%)	1.07 [0.63;1.78]	0.785
Oak immunotherapy:				
No	507 (71.9%)	55 (70.5%)	Ref.	Ref.
Yes	198 (28.1%)	23 (29.5%)	1.07 [0.63;1.78]	0.785
Grass immunotherapy:				
No	218 (30.9%)	17 (21.8%)	Ref.	Ref.
Yes	487 (69.1%)	61 (78.2%)	1.60 [0.93;2.88]	0.092
Ragweed immunotherapy:				
No	276 (39.1%)	31 (39.7%)	Ref.	Ref.
Yes	429 (60.9%)	47 (60.3%)	0.97 [0.61;1.59]	0.914
Region of residence:				
Rural/country	124 (17.6%)	19 (24.4%)	Ref.	Ref.
Suburb	453 (64.3%)	33 (42.3%)	0.47 [0.26;0.88]	0.019
Urban	128 (18.2%)	26 (33.3%)	1.32 [0.70;2.55]	0.394
Type of AC				
Central	631 (89.5%)	74 (94.9%)	Ref.	Ref.
Window units	74 (10.5%)	4 (5.13%)	0.48 [0.14;1.20]	0.124
Type of bedroom floor				
Carpeting	473 (67.1%)	76 (97.4%)	Ref.	Ref.
Wood/laminate	232 (32.9%)	2 (2.56%)	0.06 [0.01;0.19]	<0.001
Type of floor family room				
Carpeting	404 (57.3%)	62 (79.5%)	Ref.	Ref.
Wood/laminate	301 (42.7%)	16 (20.5%)	0.35 [0.19;0.60]	<0.001
Pets:				
None	349 (49.5%)	61 (78.2%)	Ref.	Ref.
Cats	80 (11.3%)	6 (7.69%)	0.44 [0.16;0.98]	0.044
Dogs	197 (27.9%)	6 (7.69%)	0.18 [0.07;0.39]	<0.001
Dogs and cats	79 (11.2%)	5 (6.41%)	0.37 [0.13;0.88]	0.022