Varying effects of greenness in the spring and summer on the development of allergic rhinitis up to 27 years of age: The Espoo Cohort Study

Jouni Jaakkola[1], Inês Paciência[1], Aino K. Rantala[1], Harri Antikainen[1], Timo Hugg[1], and Maritta S. Jaakkola[1]

[1]Oulun yliopisto

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Abstract

Background: Previous inconsistent evidence on effects of green space on the development of allergic rhinitis could be explained by the season of exposure. We explored whether the season and timing of exposure to green space play a role in the development of allergic rhinitis during the first 27 years of life. **Methods:** In a longitudinal study of 2568 participants from the Espoo Cohort Study, green space was assessed using the mean Normalized Difference Vegetation Index (NDVI) within 300 m of the participant's residence during pregnancy and the first two years after birth during spring and summer seasons. We applied Cox proportional hazards regression to estimate adjusted hazard ratios (aHRs) and 95% confidence intervals (95% CI) for the associations between cumulative exposure to NDVI (1-unit increase) and allergic rhinitis. **Results:** Early-life exposure to abundant vegetation during the spring was associated with an increased risk of allergic rhinitis at 12 years of age [aHR (95% CI) = 1.726 (1.078; 2.765)] and 27 years of age [1.703 (1.139; 2.545)]. However, abundant vegetation during the summer was associated with a decreased risk of allergic rhinitis at 12 years of age [0.754 (0.585; 0.972)] and 27 years of age [0.801 (0.649; 0.989)]. Perinatal exposure to green spaces had no effect on allergic rhinitis. **Conclusions:** Green space has opposite effects on the development of allergic rhinitis in the spring and summer: early-life exposure to green spaces during the spring increases the risk of developing allergic rhinitis, whereas exposure to greenness in the summer decreases this risk.

Introduction

The world has experienced considerable growth of urban areas in recent decades, with approximately 54% of the world population living in cities.[1] While this development provides some benefits, such as better health care, education and social services, unplanned, uncontrolled and rapid urbanization has also been associated with environmental degradation, land changes, as well as loss of green areas.[2] There is increasing evidence that exposure to greenness may improve human health. A recent review suggested that exposure to green spaces can substantially improve physical and mental health and wellbeing, and reduce the risk of adverse birth outcomes.[3] Moreover, green spaces may reduce the adverse effects of environmental exposures to air pollution, noise, extreme temperatures, and loss of biodiversity, while providing benefits for citizens and producing economic value by increasing the quality of landscapes.[4] At the same time, there has been an increase in the incidence of chronic inflammatory diseases, including allergy,[5] which cannot be explained by genetic reasons.

Epidemiological studies on the association between urban green spaces and development of allergic diseases have reported inconsistent results.[6,7] This heterogeneity of results may be related to different definitions of green spaces (i.e., exposure), seasonal qualitative and quantitative variation in greenness, features, proximity

and accessibility of green spaces, timing and duration of exposure, exposure to other environmental factors, such as air pollution, as well as differences in the study design and outcome definitions used.[6] Several studies have reported pregnancy and early-life being important critical time periods of exposure.[8,9] A recent review suggested that a variety of environmental factors acting on the mother during pregnancy may have long-term effects on the immune system of their children, which will affect their susceptibility to develop inflammatory diseases, including allergic diseases.[8] Garcia-Serna et al.[9] also emphasized the first two years of life as the critical time period for the development of immune system, reporting that both prenatal and postnatal environmental factors can induce an unbalanced Th1/Th2 response, thus increasing the risk of inflammatory diseases later in life. Furthermore, exposure to ambient air pollutants during pregnancy and early-life have been reported to increase the risk for development of asthma and allergic diseases[10,11], but green spaces may mitigate such effects.[12,13] However, potential association between exposure to green spaces during pregnancy and early-life and occurrence of allergic diseases has been explored less.[14]Furthermore, greenness has spatio-temporal variation, which depends on the climatic conditions. The season of exposure is particularly important due to increased pollen exposure in green spaces in certain seasons, as increased pollen has been associated with an increased specific IgE sensitisation and allergic responses, which have been shown to play a role in the development of allergic diseases.[15]

We hypothesised that prenatal and early-life exposure to residential green spaces reduce the risk of allergic rhinitis in childhood and young adulthood. We tested this hypothesis in the longitudinal Espoo Cohort Study by estimating the associations between exposure to green spaces during pregnancy and early-life, in both spring and summer seasons, and development of allergic rhinitis up to 27 years of age. We also elaborated the role of exposure to air pollution as a modifier for the studied associations.

Methods

Study design and population

The study comprised data collected in the Espoo Cohort Study (ECS), which included 2568 children delivered between 1 January 1984 and 31 March 1990 and living in 1990 in the city of Espoo in Southern Finland, and who had been followed regularly since the birth. Espoo is an urban–suburban municipality with a population of 289,731 (1/2020,*https://www.espoo.fi/en*) and it is located across the western border of Helsinki, the capital of Finland. A random sample of children, who were living in Espoo in 1991, was taken from the roster of Statistics Finland. The baseline data collection was conducted in 1991 (response rate, 80·3%) and the 6- and 20-year follow-ups were conducted in 1997 and 2010-11 (follow-up rates 77·3% and 63·2%, respectively).[16-19] Ethical approval for the study was obtained from the Ethics Committee of the Northern Ostrobothnia Hospital District and signed informed consent was obtained from all participants or their caregivers. The study was conducted in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

The life-time home coordinates of the participating mothers and children were retrieved from the Population Register Centre of Finland, processed and georeferenced using ArcGIS Online World Geocoding Service, allowing matching of participants to places and allowing tracking of cumulative and spatially varying environmental exposures. The present study included all the cohort members (n=2568).

Data collection

Health outcome

The outcome of interest was the development of allergic rhinitis during the follow-up time – assessed in early childhood (up to six years of age), later childhood (up to 12 years of age), and young adulthood (up to 27 years of age). Information on allergic rhinitis was collected at baseline and in the follow-up surveys by applying questions from the 1978 American Thoracic Society Division of Lung Disease questionnaire for

children. These had been modified and translated into Finnish and Swedish.[16] Allergic rhinitis ever was defined as a parent- or self-reported answer 'yes' to "*Has/have the child/you ever had doctor diagnosed allergic rhinitis?* ". The age of the onset of allergic rhinitis was asked in the 20-year follow-up questionnaire.

Exposure assessment

Green spaces

The exposure of interest was the amount of greenness in the residential environment. Green space was assessed using the mean Normalized Difference Vegetation Index (NDVI) within 100 m, 300 m, 500 m, and 1000 m of the participant's residence during pregnancy and the first two years of life in both spring and summer seasons. These area sizes were selected to cover immediate areas of exposure, containing accessible green spaces in accordance with the World Health Organization (WHO) recommendations and within five to ten minute walking distances.[20-23] We selected the 300 m buffer for NDVI for the main analyses, in accordance with the WHO and UNICEF recommendations.[23,24] The calculation of the NDVI was based on land surface reflectance of visible red (VISR) and near-infrared (NIR) wavelengths,[25] applying the following equation (Eq. (1)):

$$NDVI = \frac{NIR-VISR}{NIR+VISR} \quad (1)$$

The values range between -1 (water) through zero (rock, sand and snow) to 1, with higher positive values indicating denser green vegetation (i.e., photosynthetically active and healthy vegetation).[25] Only cloud-free images from Landsat 5 (spatial resolution: 30 m) during the spring (April–May) and summer (June–August) periods were used from conception (1983-90) to the first two years of life (1984-92) to capture maximum spatial contrasts in greenness (Appendix). In Finland, spring begins in April and summer usually begins in late May in southern Finland (*https://en.ilmatieteenlaitos.fi/seasons-in-finland*). Negative NDVI values were not included in the calculation. ArcMap 10.5 was used to process satellite images, and QGIS 3.8 was used to extract the average NDVI within each buffer size.

Covariates

Any determinant of allergic rhinitis was considered a potential confounder of the studied associations between green spaces and occurrence of allergic rhinitis.[18,26-32] We were able to adjust for the following confounders: age, sex, socioeconomic status measured by parental education level and occupation, maternal smoking during pregnancy and environmental tobacco smoke exposure (Appendix). Data on the covariates was obtained from the baseline questionnaire.

Statistical analysis

The statistical inference was based on estimation of the time of onset of allergic rhinitis in relation to the green space in residential surroundings during pregnancy and the first two years of life. Hazard ratio (HR) was used as the measure of effect. We applied Cox proportional hazards regression models to estimate crude and adjusted hazard ratios for the association between green space, measured as the cumulative exposure to NDVI (during pregnancy and during the first two years of life), and the risk of allergic rhinitis, measured as the time of onset of allergic rhinitis up to six, 12 and 27 years of age. Both crude and adjusted models were fitted, and the effect estimates were expressed for a 1 NDVI-month change in exposure. The final model was adjusted for participants' sex and age, parental socioeconomic status, maternal smoking, and environmental tobacco smoke exposure, and NDVI during pregnancy (spring and summer) or early-life NDVI exposure (spring and summer). We hypothesized that air pollution ($PM_{2.5}$, PM_{10}, O_3, NO_2 and SO_2) modifies the association between NDVI and allergic rhinitis through several potential underlying mechanisms (see Discussion).[32] The CAUSALMED procedure in SAS was used to calculate the proportions of the mediated effect based on theoretical assumptions proposed by Valeri et al. [33]. Based on exploratory analyses, we used the cut-off based on the highest quartile of air pollutant level during pregnancy and early-life to define lower (air

pollutants level <4thquartile) or higher air pollution (air pollutant level [?]4th quartile) levels. We stratified the associations between NDVI and allergic rhinitis by air pollution levels. Sensitivity analysis using different buffer sizes (100 m, 500 m, and 1000 m) and quartiles of exposure to NDVI (Table S1) were performed to evaluate the robustness of our findings. Statistical analyses were performed using SAS software version 9.4 TS Level 1M5.

Results

Characteristics of the study population are presented in Table 1. Among the 2568 participants included, 1257 (48.9%) were female. Fourteen percent of children were exposed to maternal smoking during pregnancy, and about 5% of mothers had been exposed to secondhand smoke during pregnancy. The percentage of cohort members who had developed allergic rhinitis during the follow-ups increased from 6.4% (up to six years of age) to 26.0% (up to 27 years of age).

Distribution of the mean values of cumulative exposure to NDVI and air pollution levels are presented in Tables E2 (Figure S1) and E3, respectively. The mean cumulative NDVI (SD) values within 300 m during pregnancy in spring were significantly lower among children with allergic rhinitis up to six years of age compared to children without allergic rhinitis [0.200 (0.158) *vs.* 0.244 (0.201), p =0.046]. Similarly, lower mean cumulative NDVI (SD) values within 300 m during pregnancy in summer were also observed among children with allergic rhinitis up to 27 years of age compared to children without allergic rhinitis [0.794 (0.428)*vs.* 0.834 (0.436), p =0.037] (Table S4). Although no statistically significant differences were found, the mean NDVI values during pregnancy and early-life for both seasons were lower among children with allergic rhinitis up to 12 years of age compared to children without allergic rhinitis (Table S4).

Figure 1 shows the adjusted associations between residential exposure to NDVI at specific time points and allergic rhinitis. There was no clear evidence of association between the cumulative exposure to NDVI during pregnancy and allergic rhinitis (Figure 1, Table S5). However, an increase in cumulative exposure to NDVI during spring season in early-life was associated with an increased risk of allergic rhinitis up to 12 years of age [HR (95% CI) = 1.726 (1.078; 2.765)] and up to 27 years of age [HR (95% CI) = 1.703 (1.139; 2.545)]. During the summer, an increase in the cumulative exposure to NDVI was associated with a decrease in the risk of allergic rhinitis up to 12 years of age [HR (95% CI) = 0.754 (0.585; 0.972)] and up to 27 years of age [HR (95% CI) = 0.801 (0.649; 0.989)]. Similar results were observed when considering the 500 m and 1000 m buffer sizes (Table S5).

Air pollution levels modified the association between early-life cumulative exposure to NDVI and allergic rhinitis. In children exposed to high levels of primary air pollutants (PM_{10}, $PM_{2.5}$, SO_2, and NO_2), an increase in NDVI during early-life in summer decreased the risk of allergic rhinitis (Table 2). In children exposed to low levels of primary air pollutants, an increase in NDVI values in early-life in spring increased the risk of allergic rhinitis up to 12 and 27 years of age. Similar results were observed between early-life cumulative exposure to NDVI during spring and summer within larger buffer sizes (500 m and 1000 m) and allergic rhinitis among children exposed to different levels of air pollution (Table S6). No significant associations were observed between the cumulative exposure to NDVI during pregnancy in both seasons and allergic rhinitis in children exposed to different levels of air pollution (Table 2). Additionally, the mediation analysis revealed that associations between NDVI and allergic rhinitis do not appear to be mediated by ambient air pollution (Table S7).

Discussion

This is the first population-based cohort study to assess longitudinally the effects of exposure to green spaces on the development of allergic rhinitis up to 27 years of age. Unlike previous studies, we applied individual-

level exposure based on information on prenatal and life-time residential addresses. Our results based on a strong study design provide novel evidence that early-life cumulative exposure to green spaces, measured as mean NDVI, during the spring increases the risk of developing allergic rhinitis up to young adulthood, whereas green space exposure in the summer decreases this risk. In addition, the results suggest that air pollution levels may modify the associations between green space and allergic rhinitis, so that the beneficial effects of green space are stronger at high levels of air pollution.

Validity of results

This population-based cohort study was based on a random sample of children identified from the roster of Statistics Finland. Additionally, the relatively high rates of participation (80.3% at baseline and 63.2% at follow-ups) and the similar participant characteristics at baseline and follow-ups,[18] suggest that any major selection bias was unlikely. We assessed exposure to green spaces at individual level, independently from the assessment of allergic rhinitis. We were able to use both the prenatal and life-time residential addresses in the exposure assessment, thus minimizing the likelihood of misclassification of exposure. Furthermore, we evaluated the effects of cumulative exposure to green spaces separately for spring and summer seasons. Season-specific exposures to allergenic pollen may affect the risk of allergic rhinitis differently from each other,[15] which can explain the heterogeneity in associations between green spaces and allergic rhinitis at least partly. The outcome assessment was based on parental and self-administered questionnaire information on the presence and age of onset of allergic rhinitis up to 27 years and thus, this study captured the effect of prenatal and early-life exposure to green spaces across life course. Any misclassification of the outcome was independent from exposure assessment and could introduce non-differential error, potentially leading to underestimation of the studied effects. We were able to adjust for several potential confounders, including individual characteristics, socioeconomic status, and environmental exposures. This is also one of the few studies assessing the mediation and modification effects of air pollution on the association between green spaces and allergic rhinitis.[34-36] Finally, sensitivity analyses were conducted to assess the impact of the selected distance buffers (100 m, 500 m, and 1000 m) and quartiles for exposure to NDVI, and their consistent results demonstrate the robustness of the study findings.

The current study had some limitations. NDVI is an objective measure used to assess green vegetation cover and density, but it does not provide qualitative information on vegetation characteristics (e.g., plant species), feature, nor on quality or accessibility to green spaces. We did not measure the pollen counts/concentrations or their quality, nor specific weather characteristics that could affect pollen and air pollutant concentrations and NDVI exposures. These may limit the assessment of potential mechanistic pathways. However, considering that the season may affect the type and the conditions of greenness/vegetation as well as the levels of pollens,[37] the season-specific effect estimates indirectly provide information on the role of the quality of vegetation or on changes in the abundance of vegetation on the association between exposure to green spaces and allergic rhinitis. Additionally, similarly with other studies on neighborhood health effects, our study may not capture an individual's true geographic context (Uncertain Geographic Context Problem), since some of mothers' and children's activities may take place outside of their residential environment.[38]

Synthesis with previous knowledge

There are some previous studies which suggested that exposure to green spaces may be protective against allergic rhinitis, although the evidence has been inconsistent.[15,34] A study including 1251 school children from Italian and Austrian alpine valleys showed an inverse association between NDVI within 100 m around schools and the prevalence of allergic rhinitis.[39] The results from a study that included seven birth cohorts suggested that the effect of NDVI differed by geographic location; green spaces within 500 m were inversely associated with allergic rhinitis in GINI/LISA North and PIAMA cohorts, but positively associated in BAMSE and GINI/LISA South.[34] In addition, the modifying effect of outdoor levels of NO_2 was also heterogenous across those cohorts. A protective effect of green spaces was observed in PIAMA cohort among those who were exposed to middle levels of NO_2, but an increased risk was observed in BAMSE cohort among those exposed to higher levels of NO_2.[34] Ruokolainen et al.[40] and Paciencia et al. [41] also found previously a protective effect of exposure to green spaces on allergic sensitization in children, although this has previously been

reported as a risk factor for allergic rhinitis.[42]Also other studies have provided evidence that exposure to green spaces may increase the risk of allergic rhinitis.[34,36] Our results showed how the season of exposure in early-life may be an important factor that influences the development of allergic rhinitis: our results suggested that NDVI exposure during spring, when pollen and air pollution exposure is at its highest (in the study area), is associated with a higher risk of allergic rhinitis. Seasonality of green space exposure is particularly important when considering the concentration of pollens. Green spaces may lead to a greater spread and higher concentrations of allergenic pollen, which has been associated with an increased prevalence of allergic diseases.[43]In Finland, pollen concentrations from birch trees, the most common cause of pollen sensitization rates [34.0% (26.8-41.2%)], are highest in April and May,[44-46] which could explain the observed results and the higher risk of allergic rhinitis during spring. Although there is increasing evidence showing the influence of prenatal and early-life exposures on the development of allergic diseases,[47] it remains unclear whether there is a specific time period (i.e., developmental window) within which individuals may be particularly sensitive to environmental exposures. Our study provides novel insights on time-specific critical periods in the life course – prenatal and early-life – during which exposures to green spaces may affect human health. Our results showed that early-life may be a critical period for exposure to environmental factors that affect development of allergic rhinitis during late childhood and early adulthood. Some previous studies have also suggested that early-life exposure to green spaces may enhance immune function so that it protects against inappropriate inflammatory responses and development of allergic diseases.[48-50]

Biological plausibility

Several mechanisms may be relevant for explaining the observed associations between green spaces and allergic rhinitis. The mediation analysis revealed that associations between NDVI and allergic rhinitis do not seem to be mediated by air pollution. However, our results suggest that this association may be modified by the levels of PM_{10}, $PM_{2.5}$, NO_2, and SO_2 exposures. Green spaces may remove pollutants from the atmosphere through deposition on the tree surfaces and/or by adsorption and absorption processes.[51,52] Moreover, the presence of healthy trees or vegetation could improve air quality by dispersing local pollutants or by limiting dispersion towards sidewalks.[53] During the summer, the highest NDVI levels, which indicate a higher density of vegetation, may reduce the levels of air pollutants,[51,52] as well as create a cooling effect through shade and evapotranspiration, and thus generate airflows and disperse the concentrations of pollutants more.[54] However, during the spring, the higher levels of air pollutants in Espoo during the study period (previously reported by Siddika et al. [55]) may induce changes into the chemical composition of pollens, intensifying their allergenic potential and thus, increasing allergen-induced inflammatory and cellular immune responses,[7,56] which consequently increase the risk of allergic rhinitis. There is some previous evidence that observed associations between exposure to green spaces and allergic diseases may be mediated or modified by air pollution levels.[35,36]Furthermore, the results observed during spring and summer may be related to changes in the type and abundance of vegetation,[51] which cannot be distinguished by using the NDVI value as an indicator of exposure.

Conclusions

Our findings provide new evidence that early-life exposure to green spaces, measured as NDVI, during the spring increases the risk of developing allergic rhinitis in childhood. In contrast, during the summer, similar exposure reduces the risk of allergic rhinitis. The important bi-directional role of the season in the effects of exposure to green spaces on allergic rhinitis is likely to be explained by qualitative and quantitative changes in vegetation over the seasons. This may also explain the previous inconsistent results on the association between the exposure to green spaces and the risk of allergic rhinitis. Our finding of effect modification of the relation between green spaces and allergic rhinitis by air pollution levels suggests that provision of green spaces in urban areas can be considered as a complementary preventive measure against adverse effects of air pollution.

Table 1 Characteristics of the baseline study population (n = 2568), The Espoo Cohort Study 1983-2011

Characteristics	n (%)$^{++}$
Sex [female] §	1257 (48.9)
Family socioeconomic status §	
Low or medium	1889 (73.9)
High	667 (26.1)
Maternal smoking during pregnancy §	
Yes	364 (14.2)
No	2199 (85.8)
Second-hand smoke exposure during pregnancy §	
Yes	101 (5.11)
No	1874 (94.9)
Allergic rhinitis up to 6 years of age	165 (6.4)
Mean age at the onset	5.7 (0.97)
Allergic rhinitis up to 12 years of age	473 (18.4)
Mean age at the onset	9.8 (3.1)
Allergic rhinitis up to 27 years of age	668 (26.0)
Mean age at the onset	14.7 (7.8)

$^{++}$missing values: family socioeconomic status, n=12; maternal smoking during pregnancy, n=5; secondhand smoke exposure, n=593; §characteristics of the baseline study population

Table 2 Associations (adjusted hazard ratio, aHR, 95% confidence intervals, 95% CI) between cumulative exposure to Normalized Difference Vegetation Index (NDVI) within 300 m during pregnancy and early life and the risk of developing allergic rhinitis up to 27 years of age, stratified by air pollution exposure concentration, The Espoo Cohort Study 1983-2011

		Allergic rhinitis [aHR (95% CI) ++]	**Allergic rhinitis [aHR (95% CI) ++]**	**Allergic rhinitis [aHR (95% CI) ++]**	**Allergic rhinitis [aHR (95% CI) ++]**	**Allergic rhinitis [aHR (95% CI) ++]**	**Allergic rhinitis [aHR (95% CI) ++]**
		up to 6 years of age	**up to 6 years of age**	**up to 12 years of age**	**up to 12 years of age**	**up to 27 years of age**	**up to 27 years of age**
NDVI [300 m]	**NDVI [300 m]**	**Low exposure^{+}** *Pregnancy*	**High exposure^{+}** *Pregnancy*	**Low exposure^{+}** *Pregnancy*	**High exposure^{+}** *Pregnancy*	**Low exposure^{+}** *Pregnancy*	**High exposure^{+}** *Pregnancy*
Spring							
	PM_{10}	0.273 (0.061; 1.223)	7.808 (0.422; 144.339)	1.095 (0.494; 2.425)	0.679 (0.105; 4.417)	0.942 (0.482; 1.841)	0.987 (0.217; 4.481)
	$PM_{2.5}$	0.281 (0.063; 1.247)	10.120 (0.479; 213.712)	1.115 (0.505; 2.461)	0.626 (0.094; 4.147)	0.913 (0.470; 1.775)	1.127 (0.239; 5.308)
	O_3	0.378 (0.066; 2.152)	1.101 (0.055; 22.198)	0.977 (0.382; 2.498)	1.144 (0.235; 5.562)	0.679 (0.302; 1.528)	2.159 (0.572; 8.142)
	NO_2	0.297 (0.067; 1.312)	4.397 (0.233; 82.825)	0.893 (0.405; 1.969)	1.711 (0.276; 10.608)	0.803 (0.413; 1.559)	1.903 (0.421; 8.598)
	SO_2	0.258 (0.058; 1.138)	4.961 (0.269; 91.568)	0.883 (0.401; 1.943)	1.553 (0.247; 9.774)	0.839 (0.431; 1.632)	1.849 (0.418; 8.179)
Summer							

		Allergic rhinitis [aHR (95% CI) ++]	**Allergic rhinitis [aHR (95% CI) ++]**	**Allergic rhinitis [aHR (95% CI) ++]**	**Allergic rhinitis [aHR (95% CI) ++]**	**Allergic rhinitis [aHR (95% CI) ++]**	**Allergic rhinitis [aHR (95% CI) ++]**
	PM_{10}	1.287 (0.722; 2.292)	0.721 (0.303; 1.715)	1.001 (0.716; 1.399)	0.851 (0.520; 1.392)	0.926 (0.702; 1.222)	0.849 (0.565; 1.277)
	$PM_{2.5}$	1.235 (0.696; 2.191)	0.744 (0.308; 1.800)	0.987 (0.706; 1.379)	0.882 (0.539; 1.445)	0.932 (0.706; 1.229)	0.844 (0.560; 1.270)
	O_3	0.885 (0.519; 1.511)	3.096 (0.949; 10.104)	0.938 (0.686; 1.283)	1.187 (0.476; 2.956)	0.869 (0.669; 1.128)	0.960 (0.448; 2.059)
	NO_2	0.995 (0.572; 1.363)	1.318 (0.518; 3.357)	0.955 (0.688; 1.325)	0.869 (0.522; 1.445)	0.876 (0.670; 1.145)	0.887 (0.576; 1.365)
	SO_2	1.250 (0.702; 2.228)	0.822 (0.350; 1.931)	0.980 (0.706; 1.361)	0.838 (0.505; 1.391)	0.889 (0.679; 1.164)	0.848 (0.552; 1.303)
		Early-life	*Early-life*	*Early-life*	*Early-life*	*Early-life*	*Early-life*
Spring							
	PM_{10}	1.823 (0.708; 4.696)	0.682 (0.080; 5.790)	**1.844 (1.088; 3.126)**	1.203 (0.351; 4.122)	**1.740 (1.107; 2.736)**	1.873 (0.654; 5.364)
	$PM_{2.5}$	1.777 (0.700; 4.516)	0.677 (0.069; 6.631)	**1.736 (1.030; 2.927)**	1.768 (0.492; 6.347)	**1.690 (1.080; 2.645)**	2.411 (0.813; 7.154)
	O_3	1.836 (0.646; 5.218)	1.184 (0.188; 7.451)	1.519 (0.840; 2.746)	2.512 (0.829; 7.613)	1.578 (0.958; 2.600)	2.572 (0.989; 6.689)
	NO_2	1.945 (0.745; 5.076)	0.766 (0.526; 3.758)	**1.996 (1.167; 3.414)**	0.910 (0.297; 2.791)	**1.814 (1.143; 2.878)**	1.512 (0.587; 3.892)
	SO_2	1.833 (0.692; 4.856)	0.865 (0.130; 5.753)	**1.838 (1.073; 3.149)**	1.326 (0.434; 4.054)	**1.727 (1.089; 2.740)**	1.932 (0.742; 5.032)
Summer							
	PM_{10}	1.018 (0.592; 1.751)	0.539 (0.230; 1.263)	0.869 (0.645; 1.169)	**0.525 (0.319; 0.866)**	0.878 (0.686; 1.125)	**0.602 (0.395; 0.917)**
	$PM_{2.5}$	0.918 (0.559; 1.505)	0.537 (0.231; 1.248)	0.872 (0.647; 1.175)	**0.514 (0.310; 0.851)**	0.867 (0.676; 1.113)	**0.616 (0.404; 0.938)**
	O_3	0.752 (0.462; 1.224)	0.951 (0.343; 2.640)	0.764 (0.570; 1.024)	0.682 (0.372; 1.249)	0.828 (0.650; 1.055)	0.671 (0.399; 1.129)
	NO_2	0.939 (0.573; 1.540)	0.460 (0.200; 1.056)	0.854 (0.633; 1.151)	**0.553 (0.342; 0.895)**	0.871 (0.679; 1.117)	**0.615 (0.411; 0.920)**
	SO_2	0.935 (0.563; 1.553)	0.497 (0.230; 1.074)	0.827 (0.611; 1.119)	**0.576 (0.358; 0.925)**	0.833 (0.647; 1.072)	0.684 (0.460; 1.019)

NDVI: normalized difference vegetation index; PM_{10}: particle with aerodynamic diameter [?] 10 μm; $PM_{2.5}$: particle with aerodynamic diameter [?] 2.5 μm; O_3: ozone; NO_2: nitrogen dioxide; SO_2: sulfur dioxide.

++Model adjusted for sex, age, socioeconomic status at baseline, maternal smoking and environmental

tobacco smoke exposure at baseline, NDVI during pregnancy (spring and summer) and early exposure (spring and summer) variables were mutually included in the model.

+ Lower exposure indicated the air pollution level < 4th quartile, higher exposure indicated the air pollution level [?] 4th quartile (during pregnancy: PM_{10}: 24.1 μg/m^3; $PM_{2.5}$: 22.1 μg/m^3; O_3: 54.9 μg/m^3; NO_2: 10.3 μg/m^3; SO_2: 13.3 μg/m^3; during early-life: PM_{10}: 22.5 μg/m^3; $PM_{2.5}$: 20.7 μg/m^3; O_3: 52.8 μg/m^3; NO_2: 9.78 μg/m^3; SO_2: 11.8 μg/m^3).

Bold denotes significant associations.

FIGURE 1 Associations (adjusted hazard ratio, aHR, 95% confidence intervals, 95% CI) between cumulative exposure to Normalized Difference Vegetation Index (NDVI) within 300 m during pregnancy and early life and the risk of developing allergic rhinitis up to 27 years of age, The Espoo Cohort Study 1983-2011. Model adjusted for sex, age, socioeconomic status at baseline, maternal smoking, and environmental tobacco smoke exposure at baseline, NDVI during pregnancy (spring and summer) and early exposure (spring and summer) variables were mutually included in the model.

Author Contributions

Inês Paciência: Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft, Writing - review & editing; Aino K. Rantala: Conceptualization, Methodology, Formal analysis; Writing - review & editing; Harri Antikainen: Methodology, Writing - review & editing; Timo Hugg: Conceptualization, Methodology, Writing - review & editing; Maritta S. Jaakkola: Writing - review & editing; Jouni J.K. Jaakkola: Conceptualization, Methodology, Writing - review & editing; Supervision.

Conflict of interest

The authors declare that they have no relevant conflicts of interest.

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