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# Residential greenness and pollen exposure across gestational trimesters in relation to preschool wheezing: Results for the PIPO birth cohort

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## ABSTRACT

**Introduction:** Previous studies on prenatal green space exposure and early respiratory health show inconsistent results. This may reflect stage-specific in utero effects and pollen influence. We examine associations of surrounding greenness and pollen exposure during pregnancy (overall and by trimester) with preschool wheezing, and assess potential mediation by pollen.

**Methods:** We used data from the PIPO birth cohort (n = 860). Wheezing was reported biannually between 18 and 48 months of age. Residential greenness was measured with Normalized Difference Vegetation Index (NDVI) in 100 and 250 m buffer. Cumulative grass and birch pollen was estimated using modelled airborne pollen counts and categorized per trimester into no, low and high. All exposures were assessed for the overall pregnancy and per trimester. We used Generalized Estimated Equations to obtain odds ratios (OR) and 95% confidence intervals (CI). To assess mediation by pollen we used a data duplication algorithm with a generalized estimation approach.

**Results:** Approximately 10% of participants wheezed. During pregnancy, greenness (OR = 1.07, CI: 1.05–1.08) and grass pollen exposure (OR = 1.09, CI: 1.03–1.15) increased the odds of wheezing, while birch pollen decreased it (OR = 0.86, CI:0.87–1.00). Per trimester, more greenness during the 2nd trimester increased the odds (OR = 1.21, CI: 1.16–1.26), whereas third-trimester greenness decreased it (OR = 0.87, CI: 0.84–0.91). Grass pollen exposure in the 1st and 3rd trimesters increased the odds of wheezing (OR = 1.23, CI: 1.12–1.34 and OR = 1.13, CI: 1.00–1.27, respectively), while birch pollen exposure in the 1st and 2nd trimesters decreased the odds (OR = 0.88, CI: 0.77–1.00 and OR = 0.83, CI: 0.73–0.95, respectively). No significant associations were found for greenness in the 1st trimester, grass pollen in the 2nd trimester, and birch pollen in the 1st and 3rd trimester. Mediation analysis showed large uncertainty.

**Discussion:** Surrounding greenness and pollen exposure during pregnancy may impact the likelihood of preschool wheezing differently depending on the timing of exposure and the pollen type.

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## 1. Introduction

Wheezing is a symptom commonly experienced during childhood (Alvarez-Alvarez et al., 2018). It can have an important impact on the child's quality of life (Braig et al., 2014) and is associated with asthma and lung trajectories in later life (Belgrave et al., 2018). In Europe, an estimated 30 percent of the children experience wheezing during childhood (Alvarez-Alvarez et al., 2018). Several risk factors such as viral infections, environmental tobacco smoke and air pollution have been identified (Alvarez-Alvarez et al., 2016; Bercedo-Sanz et al., 2015). In a systematic review, Mueller et al. (2022) investigated the effect of green spaces on respiratory health. They showed that in most studies, the effect of green space during childhood on wheezing in children was protective, although most of the associations found were non-significant. More generally, studies investigating the effect of postnatal exposure to residential green on respiratory health remain inconclusive (Mueller et al., 2022). Especially for asthma, some studies show a protective association of residential green space (Sbihi et al., 2015), while others show a detrimental association (Aerts et al., 2020; Andrusaityte et al., 2016).

To date, only a few studies have investigated the effect of prenatal exposure to green spaces on respiratory health. Yet the prenatal period is known to be a critical period for child development and health (Darling et al., 2020) and the effect of environmental factors on respiratory health have been shown to be different depending on the gestational trimesters (Aguilera et al., 2013; Guilbert et al., 2023). Especially for allergies, the first thousands days after conception are an important time window for gene-environment interaction that could initiate allergies (Darling et al., 2020). Results of the few studies available on prenatal green space and respiratory health suggest that prenatal exposure to green spaces may impact the development of asthma (Sbihi et al., 2015; Lovasi et al., 2013; Lowe et al., 2012) and other atopic diseases (Lee et al., 2018). However, the results of these studies are conflicting. Sbihi et al. (2015) found a decrease in the odds of asthma at school age with increased surrounding greenness around the prenatal address. Similarly, Lee et al. (2018) showed a small-size inverse association between the percentage of green space around the prenatal address and atopic dermatitis. In contrast, Lovasi et al. (2013) found a direct association between tree canopy cover around the prenatal address and wheezing, allergic sensitization and asthma in childhood. However, the association found for wheezing did not reach statistical significance. Similarly, Rantala et al. (2024) found a higher rate of asthma before the age of 6 with increasing greenness prenatally. Moreover, they found that the effect size changed for exposure in the different gestational trimesters with the largest effect for exposure in the third trimester.

A possible explanation for the inconsistent findings is that the used green space indicators are nonspecific and static. This makes it difficult to disentangle the true effect and exploring critical time windows of exposure and specific pathways may help to explain the observed inconsistencies (Mueller et al., 2022). One hypothesized pathway in the systematic review by Mueller et al. (2022) is pollen exposure. Previous studies have shown that pollen exposure during pregnancy and early life is associated with respiratory health (Lowe et al., 2012; Lambert et al., 2021). For example, Lowe et al. (2012) found an increased risk of asthma hospitalization with increasing total ambient pollen exposure during the last 12 weeks of pregnancy. In addition, pollen exposure has been linked to surrounding landscape characteristics (Stas et al., 2021).

The aim of this study is to investigate whether the timing of exposure during pregnancy influences the risk of preschool wheezing, focusing on surrounding greenness and cumulative pollen exposure. We hypothesize that surrounding greenness and pollen exposure are directly associated with preschool wheezing, with the strength of this association varying based on the timing of exposure, becoming stronger as pregnancy progresses through the trimesters. Additionally, we hypothesize that pollen acts as a mediator in the association between surrounding greenness and preschool wheezing. To test these hypotheses, we examine the associations of surrounding greenness and cumulative airborne birch and grass pollen exposure during the total pregnancy and for each trimester of pregnancy with the occurrence of preschool wheezing between 18 and 48 months of age. Additionally, we assess potential mediation effects of pollen in the associations between greenness and wheezing.

## 2. Methods

### 2.1. Study population and design

We used data from a Belgian ongoing birth cohort, the Prospective project on the Influence of Perinatal factors on the Occurrence of asthma and allergies (PIPO) (Hagendorens et al., 2005). In brief, between 1997 and 2001, 2006 women were recruited by obstetricians during pregnancy in the area of Antwerp (Belgium) and 1128 mother–child pairs accepted to participate. Inclusion criteria were residing in the (sub)urban area of Antwerp and having sufficient comprehension of the Dutch language. Pregnant women and their partners provided written consent covering all parts of the study. The study was approved by the Ethics committee of the University of Antwerp. During pregnancy (around week 20) and at the child's age of 3 months, questionnaires were administered by nurses on home visits. Clinical information of the participant at birth was obtained during the second home visits. In addition, parents were asked to fill in questionnaires including health (family history, pregnancy, and child), and other relevant information (e.g. socio-economic position, housing conditions, other health risk factors and residential address) regularly, starting from pregnancy. Furthermore, participants were invited to participate in periodic clinical examinations where blood samples were collected and lung function was measured.

For this study, we used information collected through questionnaires during pregnancy, at the age of 3 months, and bi-annually between 18 and the 48 months of age. We included all participants with at least one follow-up questionnaire, and excluded twins (n=34) due to their differing asthma risk (Wang et al., 2023). Additionally, we excluded participants with a gestational age of more than 42 weeks of pregnancy (n=16), due to the high likelihood of errors in gestational age and thus uncertainty about the timing of the different trimesters. In total, we included 860 participants in the present study. A flow diagram can be found in supplementary material (Figure S1).

### 2.2. Outcome assessment

Preschool wheezing between 18 and 48 months of age was the primary outcome and was derived from the question 'Did your child wheeze in the past 6 months?' (yes/no) on the bi-annual questionnaires. We selected the questionnaires of these age groups, to have an even spacing between the timing of different questionnaires. For the sensitivity analysis, we additionally estimated the frequency of wheezing based on the question 'How often has this [wheezing] occurred in the last 6 months?' in the questionnaires. We categorized the parental reports of frequency into three groups: never, once, and frequent (i.e. wheezing more than once in the last 6 months). Based on those two questions, we categorized the participants into two groups: those who wheezed only once (i.e. at one follow-up moment and at that time reported wheezing only once in the last 6 months) and those who either never wheezed or wheezed more than once.

### 2.3. Residential greenness

Perinatal exposure to surrounding greenness was assessed for the total pregnancy, by trimester of pregnancy and in the first year of life using the remotely-sensed Normalized Difference Vegetation Index (NDVI). NDVI is a metric that measures greenness at area level and it has been validated for use in epidemiological studies as a measure of neighbourhood greenness (Rhew et al., 2011). It is derived from remote sensing data on spectral reflectance values and can be computed as the difference between the reflectance of near-infrared and red light bands. NDVI values range between −1 and 1, with high values representing dense green vegetation.

Landsat 5 thematic mapper (TM) satellite imagery products from 1997 to 2001 were used to calculate NDVI based on the geocoded residential address during pregnancy. First, NDVI values were derived per pixel (30 × 30 m) on each image from the timeframe of interest. Next, a composite image was produced by selecting per pixel the maximum NDVI. From this NDVI composite image a mean value was calculated in buffer zones surrounding the participants' residences. Two buffer sizes were used with different radii: 100 m and 250 m. We used only small buffer sizes to better capture the child's immediate surrounding, as children spend most of their time indoors, primarily at home (Farrow et al., 1997; Matz et al., 2014). As a sensitivity analysis, we also used a larger buffer size (1000 m). Each women's gestational trimester periods were approximated using the most overlapping season by date in the pregnancy year. Each composite image was based on twelve images of the respective season and a maximum NDVI per pixel function. The images were directly acquired from the 8-day NDVI available Landsat 5 product (Landsat 5 TM 8-day NDVI Composite courtesy of the U.S. Geological Survey). This closely captured greenness around the pregnant women's residential address and allowed us to investigate differences in the associations with the exposure to green during pregnancy while accounting for the changing patterns in greenness. For the total pregnancy, we calculated the maximum NDVI of the different trimesters. In this way, we tried to capture the maximum greenness a participant could have experienced during pregnancy. In the sensitivity analysis, we used NDVI during the first year of life. For this, Landsat 5 TM surface reflectance (SR) products were used (Landsat 5 Level 2, Collection 2, Tier 1 courtesy of the U.S. Geological Survey). A composite image was created from four summer images in the year 1998 which had the least cloud cover of all years in the recruitment period (1997–2001). The final composite image was created based on a maximum NDVI value per pixel function in Google Earth Engine. This image of maximum greenness values approximates the surrounding maximum greenness that children could have experienced after birth around their home addresses.

### 2.4. Pollen exposure

The cumulative prenatal exposure to airborne grass and birch pollen was assessed for each trimester, the total pregnancy period, and the first year of life. Daily airborne birch and grass pollen concentrations near the surface for Belgium were estimated using the SILAM (System for Integrated modeLling of Atmospheric coMposition) pollen transport model (Sofiev et al., 2015) on a native 0.1 × 0.1-degree grid. SILAM is a large-scale dispersion model that simulates and forecasts the spatio-temporal distribution of airborne pollen levels based on maps with pollen emission sources. The model is driven by meteorological data from the European Centre for Medium-Range Weather Forecasts (ECMWF). For Belgium, these emission maps were generated by combining satellite data with areal fractions of birch tree and grass maps from inventory data (for details, see Verstraeten et al., 2022, 2019, 2021). Pollen seasons were defined for birch (March 1–July 1) and grass pollen (May 1–September 1) assuming zero pollen concentrations outside of these pollen seasons. The model performance for generating these daily airborne pollen concentration distributions was thoroughly evaluated for Belgium using daily observations from the Belgian aerobiological surveillance network for the period 1982-2019 (Verstraeten et al., 2022, 2019, 2021). Daily pollen concentrations during each participant's pregnancy were extracted from the model output based on gridcells that co-locate with their municipality and then summed for each trimester, the total pregnancy, and the first year of life. Cumulative exposure during each trimester was categorized as no, low, or high, with the median as the cut-off between low and high exposure to address potential non-linear effects. This categorization was also applied to birch pollen for the total pregnancy period, but not for grass pollen, as all participants had some level of exposure during pregnancy. In a sensitivity analysis, we also categorized cumulative exposure based on the critical thresholds (50 grains/$m^3$ for grass, 80 grains/$m^3$ for birch), categorizing exposure as either none, exposure only below the threshold, and exposure above the threshold.

### 2.5. Potential confounders

Potential confounders and effect modifiers were identified upfront based on scientific evidence and using a Directed Acyclic Graph (DAG). The DAG for the associations can be found in supplementary material (See Figure S2 in supplementary material).

Potential confounders included parental education, parental allergy and season of birth. For parental education, both parents were asked up to what age they had been in full-time education. The highest educational age of both parents was calculated and categorized into low (lower or equal to 21 years of age) and high (higher than 21 years of age). Parental allergy was considered as the parental report of asthma or allergic rhinitis for either one or both parents. Additionally, we considered prematurity as potential effect modifier. Prematurity was a binary variable calculated from the gestational age, with 37 weeks of pregnancy as the cut-off value.

### 2.6. Statistical analysis

To analyse the associations between prenatal greenness/ pollen and wheezing longitudinally, we used a Generalized Estimating Equation (GEE) with wheezing as a binary outcome. First, we assessed the linearity of the associations with wheezing at 18 months of age. Next, the Correlation Information Criteria (CIC) was applied to determine the optimal correlation structure, using the most complex model as a basis. Finally, we compared various models to account for uncertainties regarding the best parameterization of potential confounders and potential non-linearity in the association with wheezing at 18 months, using Quasi Information Criteria (QIC) to identify the best-fitting model. For the association between surrounding greenness and preschool wheezing, all models included greenness measurements for the first and second trimesters, parental education, and family history of allergies. Models were then compared based on different specifications for NDVI in the third trimester (using a quadratic term, excluding the third trimester, or interacting greenness in the third trimester with prematurity) due to observed non-linearity at 18 months. We also evaluated models with different adjustments for season and follow-up month. The model with the lowest QIC included an interaction term for NDVI in the third trimester with prematurity, season of birth, and follow-up month. For the association between cumulative pollen exposure and preschool wheezing, we also tested multiple models. Specifically, we compared models where prematurity was included either as an interaction term with exposure in the third trimester or as an independent covariate. Additionally, we evaluated models with and without adjustments for follow-up months and NDVI (for either the first trimester or the first year of life). For grass pollen, the best model included an interaction term between exposure in the third trimester and prematurity, without NDVI adjustment but with follow-up month adjustment. For birch pollen, the optimal model was similar but included prematurity as a separate variable. However, to maintain comparability across exposures, we used the model where prematurity interacted with third-trimester exposure for both pollen types".

Multicollinearity of the models was checked with the adjusted generalized standard error inflation factor (aGSIF) and we used a square of aGSIF below four to decide on multicollinearity. We used three separate GEE models for surrounding greenness, pollen of grass- and birch.

Multiple imputation of chained equations was used to deal with missing data (Buuren and Groothuis-Oudshoorn, 2011) with 30 imputations. Performance was checked by visual inspection of the proportions (categorical variables) and distributions (continuous variables) of observed and imputed data.

To analyse the potential mediation effect of pollen in the third trimester in the association between surrounding greenness in the third trimester and wheezing, we used a data duplication algorithm together with a generalized estimation equations approach (Nevo et al., 2017). Surrounding greenness in the third trimester was used as exposure variable. Pollen exposure in the third trimester was the potential mediator, defined as a binary variable (exposure vs no exposure). In this way, natural direct effect (NDE), natural indirect effect (NIE) and the mediation proportion were estimated in a counterfactual framework. The natural direct effect is defined as the effect on the outcome of one unit increase in the exposure while holding the mediator at a fixed level and the natural indirect effect as the effect of one unit increase in the mediator when the exposure is held fixed. Lastly, the mediation proportion is defined as the change in the effect of the exposure due to mediation and this relative to the total effect (the sum of NDE and NIE).

We conducted several sensitivity analysis. First, we excluded participants who reported wheezing only once. Second, we investigated the association between the first year of life exposure and wheezing. Third, we explored alternative exposure metrics: for greenness, we used a larger buffer (1000 m), and for pollen, we used the critical threshold as the cut-off for high versus low exposure, instead of the median above zero.

R statistical software (R Core Team, 2022) was used for analysis (package 'geepack', 'mice', 'GEEmediate').

## 3. Results

### 3.1. Study population

The characteristics of the study population are summarized in Table 1. Among the 860 participants in our study, 434 participants (50.5%) were male and almost three quarters (72.8%) had parents with a high level of education. Seasonal distribution of birth showed a generally even spread, but with a slightly higher percentage (30.6%) born during the summer months. About half (57.5%) of the participants had at least one parent with a history of asthma or allergic rhinitis.

The prevalence of wheezing decreased over time, starting from 17% at the age of 18 months and then stabilizing to around 10% between 24 and 48 months of age (Table 1).

**Table 1**
Characteristics of the study population (n = 860)

| | | N(%) |
|---|---|---|
| **Parental education** | | |
| | Low | 229 (27.2) |
| | High | 614 (72.8) |
| **Birth year** | | |
| | 1997 | 10 (1.2) |
| | 1998 | 199 (23.1) |
| | 1999 | 230 (26.7) |
| | 2000 | 250 (29.1) |
| | 2001 | 171 (19.9) |
| **Season of birth** | | |
| | Autumn | 206 (24.0) |
| | Spring | 210 (24.4) |
| | Summer | 263 (30.6) |
| | Winter | 181 (21.1) |
| **Sex** | | |
| | Boys | 434 (50.5) |
| | Girls | 426 (49.5) |
| **Familial allergy** | | 473 (57.5) |
| **Wheezing** | | |
| | 18 m (n = 703) | 122 (17.4) |
| | 24 m (n = 551) | 61 (11.1) |
| | 30 m (n = 611) | 65 (10.6) |
| | 36 m (n = 598) | 56 (9.4) |
| | 42 m (n = 592) | 50 (8.4) |
| | 48 m (n = 643) | 65 (10.1) |

### 3.2. Missing data

Data on surrounding greenness were missing for 6% of the participants, while data on pollen exposure were complete. As for wheezing data, missing values ranged from 0.3 to 1.1% across the different follow-ups. Less than half of the participants had data for all follow-up moments (n = 359, 42%). Missingness in covariates varied, with the highest proportion of missing values in family history of allergy (4.3%). We assumed missingness at random. Data were not missing completely at random, because missingness was associated with certain characteristics of the study population, such as parental education.

### 3.3. Exposure to greenness and pollen

A description of the exposure to greenness and pollen throughout the entire pregnancy and by trimester is provided in Table 2. Median values of surrounding greenness indicated sparse vegetation (NDVI range 0.1–0.5) for both the total pregnancy and across the different trimesters. On average, surrounding greenness was consistent throughout the trimesters, with a slight increase observed in the third trimester.

Regarding cumulative exposure to grass pollen, all participants were exposed to some extent to grass pollen during pregnancy. For each individual gestational trimester, approximately one-third of participants were not exposed. For birch pollen, about one-tenth of the participants were not exposed during the total pregnancy, while in each trimester, about two-thirds were not exposed. The median pollen concentrations per trimesters used as cut-off for low vs. high exposure can be found in supplementary material (Table S1). The description of the exposure to pollen using an alternative definition can be found in Table S9.

Information on residential greenness and cumulative pollen exposure by season of birth is provided in supplementary material (Table S2 and S3). NDVI values during each gestational trimester ranged from 0.20 to 0.36 for the different seasons of birth. Grass pollen exposure clearly varied across different birth seasons and trimesters. For example, only one child born in winter was exposed to grass pollen during the third trimester. A similar pattern was observed for birch pollen, with no child born in winter being exposed to birch pollen in the second or third trimester.

### 3.4. Association between greenness/pollen and wheezing

The adjusted associations of surrounding greenness and pollen with wheezing are presented in Fig. 1 and the exact values of the OR and 95% CI are provided in the supplementary material (Table S4). More greenness during the total pregnancy was associated with a higher odds of wheezing (e.g., OR = 1.07, 95%CI: 1.05–1.08 for an IQR increase in NDVI within a 100 m buffer around the residential address). When examining trimester-specific associations, greenness in the second trimester was associated with a higher odds of wheezing (e.g. OR = 1.21, 95% CI: 1.16–1.26 for an IQR increase in NDVI within a 100 m buffer around the residential address). Conversely, in the third trimester an increase in surrounding greenness was associated with lower odds of wheezing (e.g. for 100 m buffer OR = 0.87, 95% CI: 0.84–0.91). We did not observe an association for surrounding greenness in the first pregnancy trimester. Regarding cumulative grass pollen exposure, a direct association for exposure during the total pregnancy was observed (OR = 1.09, 95%CI: 1.03–1.15 for an IQR increase in cumulative grass pollen levels). This direct association was also present for the first trimester exposure (e.g. OR = 1.23, 95%CI: 1.12–1.34 and OR =

 

**Table 2**
Description of residential surrounding greenness and pollen exposure during the total pregnancy and the different pregnancy trimesters.

| Variable | Description |
|---|---|
| **Total pregnancy** | |
| Surrounding greenness, median (IQR) | |
| 100 m buffer | 0.38 (0.16) |
| 250 m buffer | 0.40 (0.17) |
| Grass pollen total, median (IQR) | 2508 (1364) |
| Grass pollen category, n (%) | |
| No | 0 (0) |
| Low[a] | 430 (50) |
| High[b] | 430 (50) |
| Birch pollen total, median (IQR) | 6122 (4166) |
| Birch pollen category, n (%) | |
| No | 103 (12) |
| Low[a] | 377 (44) |
| High[b] | 380 (44) |
| **First pregnancy trimester** | |
| Surrounding greenness, median (IQR) | |
| 100 m buffer | 0.29 (0.21) |
| 250 m buffer | 0.31 (0.23) |
| Grass pollen category, n (%) | |
| No | 384 (44.7) |
| Low[a] | 285 (27.7) |
| High[b] | 285 (27.7) |
| Birch pollen category, n (%) | |
| No | 583 (67.8) |
| Low[a] | 141 (16.4) |
| High[b] | 136 (15.8) |
| **Second pregnancy trimester** | |
| Surrounding greenness, median (IQR) | |
| 100 m buffer | 0.29 (0.21) |
| 250 m buffer | 0.31 (0.23) |
| Grass pollen category, n (%) | |
| No | 290 (33.7) |
| Low[a] | 273 (33.1) |
| High[b] | 273 (33.1) |
| Birch pollen category, n (%) | |
| No | 460 (53.5) |
| Low[a] | 204 (23.7) |
| High[b] | 196 (22.8) |
| **Third pregnancy trimester** | |
| Surrounding greenness, median (IQR) | |
| 100 m buffer | 0.31 (0.21) |
| 250 m buffer | 0.33 (0.21) |
| Grass pollen category, n (%) | |
| No | 297 (34.5) |
| Low[a] | 282 (32.8) |
| High[b] | 281 (32.7) |
| Birch pollen category, n (%) | |
| No | 576 (67.0) |
| Low[a] | 142 (16.5) |
| High[b] | 142 (16.5) |

Grass and birch pollen expressed as grains/$m^3$
IQR = Interquartile Range.
[a] Cumulative exposure equal or below the median of the pregnancy trimester.
[b] Cumulative exposure higher than median

1.37, 95% CI: 1.17–1.61 for low and high grass pollen concentrations, respectively) and third trimester exposure, but only when comparing low with no exposure. No significant associations were observed when the exposure occured during the second trimester. Last, higher exposure to birch pollen during the total pregnancy was inversely associated with the odds of wheezing (OR = 0.86, 95%CI:0.84–0.88 for an IQR increase in cumulative birch pollen levels). Similarly, exposure to high levels of birch pollen during the first and second trimester decreased the odds of wheezing (e.g. OR = 0.83, 95%CI: 0.73–0.95 for the exposure during the second trimester when comparing high with no exposure). No clear associations were observed for the exposure in the third trimester, or for low vs. no exposure in all trimesters.

The complete case analysis showed similar results, although all associations found were statistically non-significant (Table S7).

Regarding the mediation analyses, we observed that grass pollen mediated 52.9% of the association, however the confidence intervals were wide, and the mediation estimate was not statistically significant (95% CI: −488% to 594%). After multiple imputation, there was inconsistent mediation in several imputations (i.e. natural direct effects (NDE) and natural indirect effects (NIE) were in opposite directions) (data not shown). For birch pollen, this inconsistent mediation was the case both with and without multiple imputation. The estimated NDE, NIE and mediation proportion without multiple imputation can be found in supplementary material (Table S5).

The sensitivity analyses, excluding participants that reported wheezing only once, resulted in similar results (Table S6). When considering surrounding greenness in the first year of life on wheezing, instead of by trimester, we observed a small (but statistically significant) direct association with wheezing (Table S8). Grass- and birch pollen exposure during the first year of life was also associated with a higher odds of wheezing, with the strongest effect for birch pollen exposure (Table S8). In addition, for our pollen exposures, we have conducted sensitivity analyses using an alternative definition. When we calculated the cumulative exposure based on levels exceeding the critical threshold, we found a direct association between grass pollen exposure and wheezing in the first trimester and the total pregnancy and an inverse association in the second trimester (Table S10). For birch pollen, a direct association was observed with exposure in the third trimester and an inverse association for the total pregnancy.

## 4. Discussion

In our cohort study, we found that surrounding greenness and pollen exposure during pregnancy are associated with the odds of preschool wheezing. The strength and the direction of these associations varied between pregnancy trimesters. For pollen, results were also different depending on the type of exposure (grass or birch).

Regarding surrounding greenness, we observed that the exposure during pregnancy was directly associated with wheezing. A similar direct association was found for the second trimester, while exposure during the third trimester was inversely associated with wheezing. To date, few studies have investigated the effect of exposure to greenness or green spaces during pregnancy on respiratory or allergic symptoms during childhood (Lovasi et al., 2013; Abellan et al., 2024; Sbihi et al., 2015), and only one study made a distinction between different trimesters (Rantala et al., 2024). Results of the few studies available are inconclusive. Lovasi et al. (2013) found an increase in the risk of wheezing during childhood with increasing residential tree canopy cover prenatally, but results were not significant. Conversely, a study investigating the effect of the prenatal urban environment on childhood wheezing (Abellan et al., 2024) showed that a cluster with less surrounding greenness was associated with a higher odds of preschool wheezing. Recently, Fernandes et al. (2024) could not find a clear association between surrounding greenness during pregnancy and childhood wheezing in a large birth cohort. The results of our study indicate that the effect of surrounding greenness on wheezing might be different depending on the prenatal timing of exposure (i.e. the trimesters). This may partly explain inconsistencies observed in the aforementioned studies that considered the entire pregnancy period as the time window of exposure. Similar to our study, Rantala et al. (2024) considered the exposure to greenness per trimester of pregnancy. Our results for the entire pregnancy were consistent to those reported by them, but our trimester-specific effects were different. We observed a direct association in the second trimester and an inverse association in the third trimester, while Rantala et al. observed direct associations for all pregnancy trimesters. However, there are important differences between our study and the one of Rantala et al. We used one NDVI value per trimester, while they calculated a cumulative value. We assumed that the effect of greenness during pregnancy is not simply captured by summing up NDVI values. Furthermore, we investigated the effect on preschool wheezing and not on asthma.

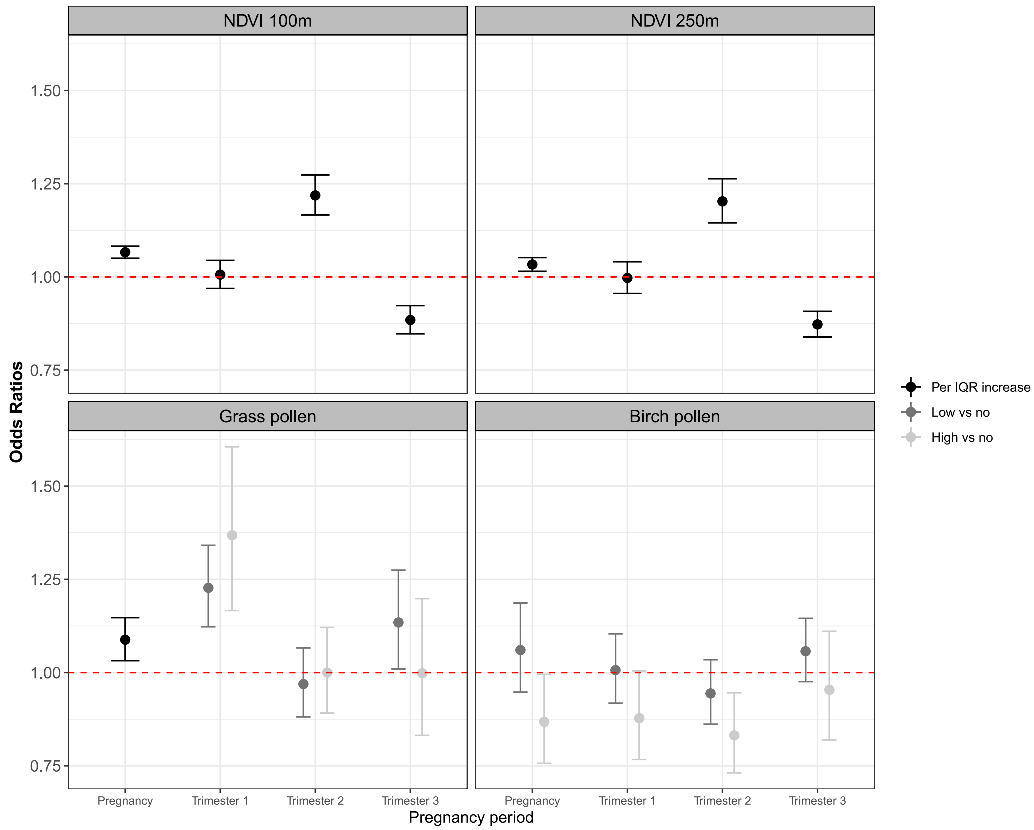


**Fig. 1.** Adjusted associations (Odds Ratios and 95% Confidence Intervals) between prenatal surrounding greenness/pollen and preschool wheezing. The association estimates were adjusted for family history of allergy, parental education, season of birth and follow-up time. An interaction term with prematurity was added for exposure in the 3rd trimester.

Regarding the exposure to grass pollen, we observed a direct association with wheezing for the total pregnancy and for the first and third trimesters. To our knowledge, no prior studies have specifically investigated the effect of prenatal exposure to airborne grass pollen on wheezing or overall respiratory health. However, Susanto et al. (2018) found that cumulative exposure to outdoor grass pollen counts during the entire pregnancy was associated with lower odds of cord blood IgE levels above 0.5 kU/L, a known risk factor for wheezing later in life (Ferguson et al., 2009). This findings are not in line with our results. For birch pollen, we observed an inverse association for the total pregnancy and for exposure before the third trimester. Previous studies (Kihlström et al., 2003; Lowe et al., 2012),however, showed an increased risk of atopic diseases and asthma hospitalization with higher exposure to birch pollen during pregnancy. Similar to greenness, potential plausible explanations for inconsistencies between our results and those of previous studies are the different timing of exposure and the different outcome definitions. It is important to note that when using an alternative exposure definition based on the critical threshold, the results for grass pollen were robust across all pregnancy trimesters. For birch pollen, the effects during the second trimester were less pronounced, and the findings for the third trimester were not robust. This suggests that daily levels exceeding the critical threshold might be particularly relevant for exposure during the third trimester. However, results for birch pollen should be interpreted with caution due to the high proportion of cases with no exposure.

Our findings suggest differences in the association between grass and birch pollen, both for the gestational trimesters and the entire pregnancy. Previous studies on prenatal priming with birch and timothy grass pollen suggest that grass pollen has higher prenatal antigenicity (Van Duren-Schmidt et al., 1997; Szépfalusi et al., 2000). Moreover, Van Duren-Schmidt et al. (1997) reported that priming for grass pollen occurs earlier in pregnancy compared to birch pollen. These factors may help explaining the differences observed in our study.

The mediation analysis for the third pregnancy trimester showed inconsistent mediation (i.e. natural direct and indirect effects in opposite directions). In this case, the mediation proportion does not have a meaningful interpretation (Rijnhart et al., 2021). It is possible that the strong assumptions of mediation analysis are not met (i.e. no unmeasured confounding in the exposure-outcome, mediator-outcome and exposure-mediator effect and temporal sequence of the exposure, mediator, and outcome) and resulted in this inconsistent mediation. As exposure variable, we used NDVI in several buffers around the residential address. NDVI is a measure of greenness often used in epidemiological studies. However, it does not take into account the quality of green, nor the vegetation type (Markevych et al., 2017). Both pollen and NDVI may be related to different vegetation types and thus there may be unobserved exposure-mediator confounding, which is in conflict with the stringent assumptions to identify natural direct and indirect effects (Schuler et al., 2024). It is possible that considering the type of vegetation rather than land cover greenness (NDVI) would have led to more accurate results and allow for the mediation analyses. NDVI is a good predictor of biomass and plant health but is less suitable to discriminate different vegetation types, such as high green vs. low green or grasslands vs. forests. Vegetation types often show stronger associations with health indicators. Additionally, we were unable to measure surrounding greenness at a finer temporal scale and we were therefore constrained to characterize both surrounding greenness and pollen exposure within the same time window (i.e. per gestational trimester). Notwithstanding this limitation, we still used NDVI in this analysis as it is the only indicator for which a reliable time series for our study period could be reconstructed from the available remote sensing images. It is also important to note that the spatial scales of exposure to surrounding greenness and to pollen concentrations are different. This might result in a potential mismatch of the location exposed to allergenic pollen compared to surrounding greenness. As mediator in this analysis, we used a binary variable for airborne pollen, i.e. presence or absence of pollen exposure. The decision to use this classification was made to address non-linearity in the data, as a significant proportion of participants had no pollen exposure during at least one trimester of gestation. This variable, however, provides no information about the intensity or duration of exposure. From a clinical perspective it might be more relevant to use other variables, such as the number of days above the minimal threshold or the number of days with high pollen concentrations. Similarly, we used cumulative pollen exposure in the main analysis. This approach, in which daily pollen counts are summed for a given time period, is consistent with prior studies (Susanto et al., 2018; Lambert et al., 2021). To deal with non-linearity, we categorized the variable into three categories (no, low, high) using the median as a cut-off for low versus high and this to address non-linearity and to maintain sufficient statistical power. Nevertheless, alternative exposure variables might offer more meaningful insights. This is particularly underscored by the recent findings of Fuertes et al. (2024), which suggest that grass allergen (Phl p 5) levels could be more important for respiratory health than grass pollen counts.

The variation in our findings across different exposure time windows, may be explained by distinct underlying mechanisms. Various factors could contribute to an association between green exposure and wheezing, potentially operating within specific time windows prenatally. One potential explanation is that exposure to green during the last trimester of pregnancy influences the maternal microbiome, which could subsequently be transferred to the child during delivery (Xiao and Zhao, 2023). This, in turn, might affect the child's susceptibility to allergic diseases. Hoskinson et al. (2023) recently found an association between early life microbiome features and allergic diseases. Nevertheless, ongoing debates persist regarding the possibility of transfer of the maternal microbiome before delivery (Xiao and Zhao, 2023). On the other hand, it has been shown that antibodies, inflammatory mediators and antigens are transferred to the child during pregnancy (Jennewein et al., 2017). This transfer starts as early as the first trimester of pregnancy and increases towards the end of the pregnancy. This can have an impact on the immunoregulation of the child making it more vulnerable for allergic diseases (Krusche et al., 2019).

In addition to the potential mechanisms discussed, other factors should be considered when interpreting our results. These include other issues related to the timing of exposure, potential of residual confounding and the outcome assessment. Regarding the timing of exposure, issues related to seasonality, and the definition of the time windows must be considered. Firstly, the effect of pollen and greenness could partially be due to, or represent, seasonality. For instance, exposure to high NDVI or high birch pollen concentrations in the third trimester occurs only in children born in spring or early summer, whereas high exposure to NDVI and pollen in the first trimester occurs in children born in autumn and winter, when respiratory viruses circulate more intensively. Previous research has described an effect of season of birth on the development of asthma (Chang et al., 2013). Some respiratory infections like the Respiratory Syncytial Virus (RSV) infection are seasonal, and increase the risk of preschool wheezing and childhood asthma development (Rosas-Salazar et al., 2023). However, the effect of season of birth on the development of wheezing and asthma is only partly mediated by respiratory infections (Almqvist et al., 2019). In addition, in our study, we adjusted our models for season of birth and therefore, the impact of season on our results should be minimal. Secondly, one may argue that the prenatal exposure is associated to the exposure in early life and so that the effect shown could as well be an effect of postnatal exposure. Unfortunately, due to the strong correlations between pre- and postnatal exposure, we could not clearly separate these effects. However, when we examined the associations with the exposure to surrounding greenness and pollen in the first year of life, we observed a small size direct association for greenness and grass pollen. For birch pollen, the direction of the association was opposite as compared to the pregnancy results. Furthermore, although we adjusted our models for important potential confounders, some residual confounding remains possible. For instance, we adjusted our models for parental education as a proxy for socio-economic status, but we recognize that it does not fully capture the complex nature of socio-economic status. Nonetheless, parental education is an important risk factor associated with childhood allergies and wheezing (Dom et al., 2009). Moreover, studies have highlighted the relevance of educational level in the association between green spaces and health, while other aspects of socio-economic status may play a less prominent role (Ruijsbroek et al., 2017; Norbäck et al., 2018). Finally, it is important to mention that the distinction between the different trimesters of pregnancy is somewhat arbitrary. The classification into trimesters is primarily based on the mother's medical follow-up. However, the immune system development of the child prenatally happens throughout the whole pregnancy, with an increase towards the end of the pregnancy (Kuper et al., 2016; Krusche et al., 2019).

Regarding our outcome (wheezing), we should consider the fact that it is a rather common and not disease-specific symptom during preschool ages, and that it was self-reported by parents. First, the fact that preschool wheezing is not disease-specific makes it difficult to draw strong conclusions on the effect in the pathophysiological process. However, immunological and molecular influences are known to impact also the child's tendency to wheeze (El-Gamal and El-Sayed, 2011) and wheezing is associated with asthma and lung trajectories in later life (Belgrave et al., 2018). Second, previous studies showed that parents are not always able to correctly report wheezing of their child (Chisholm et al., 2024). Nevertheless, we believe the potential bias introduced by parental report in our study is non-differential, leading to a bias towards the null. In order to assess potential misclassification derived from parental report, we conducted sensitivity analyses excluding the children where only once wheezing was reported. We hypothesized that parents of children that frequently wheeze are better at identifying wheezing, and thus the probability of outcome misclassification among frequent wheezers is less. The results of these sensitivity analyses were similar to those presented for the full study population (main results), and generally showing stronger associations. This supports our hypothesis that the potential outcome misclassification in our study is non-differential, and has a minimal impact on our results. Third, in our outcome definition we did not include information on when wheezing occurred. However, previous studies have shown that the phenotype of wheezing can also affect respiratory health (Oostveen et al., 2009).

Our study also had some important strengths that should be acknowledged. We used longitudinal data, providing a more comprehensive understanding of the risk of preschool wheezing. Additionally, for surrounding greenness, we used multiple composite images to better approximate true green, further refining our analysis by dividing the exposure into different pregnancy trimesters. Last, we explored the potential of cumulative pollen exposure as one of the potential mechanism partly explaining the associations between greenness and preschool wheezing.

## 5. Conclusion

In conclusion, surrounding greenness and pollen exposure during pregnancy may impact the likelihood of preschool wheezing differently depending on the timing of exposure. These findings contribute to the ongoing debate about the effect of green space exposure on respiratory health, highlighting the complexities involved regarding the timing of exposure and the hypothesized mechanisms.

## CRediT authorship contribution statement

**Katrien De Troeyer:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Formal analysis, Conceptualization. **Alessandro Grosso:** Writing – review & editing, Methodology. **Seppe Heyvaert:** Writing – review & editing, Software, Data curation, Conceptualization. **Ben Somers:** Writing – review & editing. **Hilbert Mendoza:** Writing – review & editing, Validation. **Hayat Bentouhami:** Writing – review & editing, Validation. **Margo Hagendorens:** Writing – review & editing, Project administration, Funding acquisition, Data curation. **Kevin De Soomer:** Writing – review & editing, Project administration. **Ellie Oostveen:** Writing – review & editing, Project administration, Funding acquisition. **Willem W. Verstraeten:** Writing – review & editing, Data curation. **Andy Delcloo:** Writing – review & editing, Data curation. **Raf Aerts:** Writing – review & editing, Supervision, Methodology, Data curation, Conceptualization. **Lidia Casas:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization.

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## Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Katrien De Troeyer reports financial support was provided by Research Foundation Flanders and Hilbert Mendoza reports support by the University of Antwerp. Other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

Supplementary material related to this article can be found online at https://doi.org/10.1016/j.envres.2024.120646.

## Data availability

Data will be made available on request.

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