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The associations between residential greenness and allergic diseases in Chinese toddlers: A birth cohort study

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ABSTRACT

Background: Green space in the living environment has been linked to the development of allergic diseases. However, evidence regarding early-onset allergy in toddlers was limited, and the critical exposure window remained unclear. We aimed to investigate associations between residential greenness with allergic diseases in early life.
Methods: This prospective birth cohort study included 522 mother-child pairs in Guangzhou, China. We quantified prenatal, postnatal, and early-life (i.e., the first 1000 days of life) residential greenness, estimated from remote satellite data using normalized difference vegetation index (NDVI), enhanced vegetation index (EVI), and tree cover. We identified physician-diagnosed allergic diseases (eczema, atopic dermatitis, urticaria, allergic rhinitis, allergic conjunctivitis, food allergy, and asthma) based on medical records at age 2 years. Generalized linear regression was conducted to examine the associations of greenness with allergic outcomes.
Results: The ranges of residential NDVI and EVI values in 500-m buffer during early life were 0.06–0.70 and 0.03–0.46, respectively. We found a 0.1 unit increase of NDVI in 500-m buffer throughout early life was associated with higher odds of any allergic diseases (prenatal: OR [odds ratio], 1.25; 95%CI, 1.02–1.53; postnatal: OR, 1.24; 95%CI, 1.02–1.52; early-life: OR, 1.25, 95%CI: 1.02–1.53) and higher odds of eczema (prenatal: OR, 1.28; 95%CI, 1.04–1.59; postnatal: OR, 1.24; 95%CI, 1.01–1.54; early-life: OR, 1.26, 95%CI: 1.02–1.56). The results were consistent when using EVI as a proxy for greenness. We only observed that prenatal exposure to the highest tertile of NDVI-500 was adversely associated with any allergic diseases (OR, 1.63; 95%CI, 1.03–2.58) and eczema (OR, 1.70; 95%CI: 1.04–2.78) compared with the lowest tertile.
Conclusions: This study identified detrimental associations of residential greenness with allergic diseases especially eczema among toddlers, and pregnancy appears to be the critical exposure window. Our findings highlighted the importance of urban planning to develop friendly-green neighborhood to improve maternal and child health.

Author contributions

Lizi Lin: Conceptualization, Writing-original draft, Methodology, Formal analysis. **Yujing Chen**: Conceptualization, Writing-original draft, Investigation, Formal analysis. **Jing Wei**: Methodology, Writing-Reviewing and Editing. **Shengchi Wu**: Investigation, Writing- Reviewing and Editing. **Shu Wu**: Investigation, Writing- Reviewing and Editing. **Jin Jing**: Resources, Funding acquisition, Writing- Reviewing and Editing. **Guanghui Dong**: Supervision, Resources, Funding acquisition,

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Abbreviations

AR	allergic rhinitis
NDVI	normalized difference vegetation index
EVI	enhanced vegetation index
MODIS	Terra Moderate Resolution Imaging Spectroradiometer
VIIRS	NASA Visible Infrared Imaging Radiometer Suite.
LBW	low birth weight
PTB	preterm birth

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1. Introduction

The prevalence of childhood allergic diseases has been increasing globally (Yoo et al., 2015; Asher et al., 2006), which substantially contributed to disease burden among developing children and severely undermine their health-related quality of life (Ferrante and La Grutta, 2018; Hay et al., 2014; Montalbano et al., 2020). Despite strong genetic evidence for the spectrum of allergic diseases, notable exposures in the living environment have been linked to this allergy epidemic such as allergens, tobacco smoke, air pollution, and microbial diversity (Murrison et al., 2019; Pfefferle et al., 2021). Recently, green space in the living environment has attracted attention although the potential mechanisms between green space and allergic diseases remained controversial. Early-life contact with green space might protect children from allergies by improving the microbiome, inducing tolerance to allergens, and modulating Treg and Th2 cell-mediated immune response (Rook, 2013). Meanwhile, green vegetations are sources of allergenic pollens and fungi, and their interactions with air pollutants might exacerbate allergic reactions (Lam et al., 2021; Ghiani et al., 2012). The first 1000 days of life (i.e., from conception to 2 years of age) was thought to be the most critical window to initiate allergies (Darling et al., 2020), when the immune system is highly susceptible to gene-environment interactions (Martino and Prescott, 2011). Therefore, it's of importance to understand the associations between green space and allergic diseases during the first 1000 days of life.

Previous epidemiological studies used residential greenness to represent green space, examining its association with allergic outcomes and inconsistent findings were reported (Cavaleiro Rufo et al., 2021; Fuertes et al., 2016; Markevych et al., 2020; Sbihi et al., 2015; Lovasi et al., 2013; Zeng et al., 2020; Squillacioti et al., 2019; Eldeirawi et al., 2019; Li et al., 2019; Dadvand et al., 2014; Yu et al., 2021; Parmes et al., 2020; Shrestha et al., 2018). Cross-sectional studies have demonstrated either protective or detrimental associations regarding allergic respiratory symptoms and diseases (Zeng et al., 2020; Squillacioti et al., 2019; Eldeirawi et al., 2019; Li et al., 2019; Dadvand et al., 2014; Yu et al., 2021). Longitudinal studies also showed high heterogeneity, while few of them focused on early-life exposure. Two birth cohorts conducted in the US and Canada investigated the prenatal residential greenness in relation to asthma among preschool children, with one reporting a positive association (Sbihi et al., 2015) and the other finding the opposite (Lovasi et al., 2013). When assessing exposure at birth, one study using data of seven birth cohorts across several western countries (Sweden, Australia, Denmark, Canada, and Germany) documented that the cohort specific-associations between residential greenness and allergic rhinitis (AR) among children aged 6–12 years were mixed and the pooled effect was nonsignificant (Fuertes et al., 2016). Most previous studies focused on asthma or AR, but allergies often occur early in life, first manifested as atopic eczema or food allergy among infants and toddlers (Hill and Hosking, 2004; Yang et al., 2020). Studying the allergic diseases in early life might help us to capture the exposure windows of residential greenness on the so-called allergic march (i.e., the progression from eczema to later developing food allergies, AR, and asthma) (Yang et al., 2020). Meanwhile, previous studies seldom discussed the vulnerable exposure window of residential greenness by distinguishing between the early-life exposure during the prenatal and postnatal periods, and little was known about the associations in Asian populations who live in the countries with rapid urbanization. Detailed investigations are still needed to comprehensively review different types of allergic diseases in the early life and the critical exposure windows of residential greenness.

In this birth cohort study, we aimed to investigate the associations between early-life exposure to residential greenness and allergic outcomes in Chinese toddlers aged 2 years. We hypothesized that the associations between residential greenness and allergic outcomes might be different when considering different types of allergic diseases and the exposure timing of the first 1000 days of life.

2. Methods

2.1. Study design and population

The study utilized data from an ongoing prospective birth cohort study conducted in the central urban area of Guangzhou, China (Registration number: NCT03023293). At baseline (2017–2018), we recruited pregnant women at 20–28 weeks of gestation to whom a face-face interview has been conducted in Yuexiu district maternal and child health hospital. Women were eligible if: (1) aged 20–45 years; (2) without preexisting diabetes mellitus, cardiovascular disease, thyroid disease, hematopathy, polycystic ovary syndrome, pregnancy infection, mental disorder, or multiple pregnancies; (3) offering full information of residential address. The mother-infant pairs were invited for a series of clinical visits or interviews at postnatal 6 weeks, 6 months, 2 years, and 3 years. This study included 559 children who completed 2-year follow-ups. We further excluded children who changed residence ($n = 6$) after birth, had no information of greenness exposure ($n = 20$), or had missing data of allergic outcomes ($n = 11$). Finally, a total of 522 toddlers were included. The study protocol was approved by the ethics committee of the School of Public Health of Sun Yat-sen University, and written informed consent was obtained from all participants before inclusion.

2.2. Outcome measurements

Allergic diseases were diagnosed by physicians in the hospitals, and we identified the diagnoses from outpatient medical records offered by parents and assessed detailed allergic conditions with the standardized questions adapted from the International Studies on Asthma and Allergies in Childhood questionnaire (Asher et al., 1995). We determined whether the child has been diagnosed by a physician as having different types of allergic diseases from birth to age 2 years, including eczema, atopic dermatitis, urticaria, allergic rhinitis (AR), allergic conjunctivitis, food allergy, and asthma. Different allergic diseases were binary variables encoded as 0 for no and 1 for yes, respectively. We defined any allergic disease as having one or more aforementioned allergic diseases, which may be helpful to provide clues on the overall association between greenness and allergy.

We also collected information regarding allergic symptoms, which have been described in our previous study (Chen et al., 2022). For example, wheeze was defined based on an affirmative answer to the question, "Has your child ever had wheezing or whistling in the chest, but not noisy breathing from the nose?"

2.3. Residential greenness assessments

We used the normalized difference vegetation index (NDVI) as the primary proxy of residential greenness. The NDVI estimates the density of green vegetation using the difference in the intensities of reflected light in the red and near-infrared range, which ranged from −1 to +1, with the higher values indicating more greenness (Rhew et al., 2011). In this study, NDVI value was derived from the Terra Moderate Resolution Imaging Spectroradiometer (MODIS) and NASA Visible Infrared Imaging Radiometer Suite (VIIRS) which offered the best available pixel value of NDVI every 16 days. For each participant, the NDVI value within buffer radiuses of 250 m and 500 m (i.e., NDVI-250 and NDVI-500) around the geocoded residence address was extracted at 250-m and 500-m spatial resolution, respectively. We calculated mean value of NDVI during the time interval of interest using the method described by Cusack et al. (2017). According to information on the last menstrual period and the date of delivery obtained from the hospital medical records, NDVI in pregnancy, postnatal 2 years, and the first 1000 days of life was obtained. We further excluded the negative NDVI value to avoid confounding effects of blue space (n = 2). We also used another two indicators of greenness to provide more comprehensive information in secondary analyses, including the enhanced vegetation index (EVI) and tree cover percentage. Details of the calculation for all indexes of residential greenness were described in Appendix A.

2.4. Covariate assessments

At baseline interview, we collected maternal socio-demographic characteristics and lifestyle factors, including maternal age, maternal highest education level (high school or below, junior college, university and above), current employment (yes or no), monthly household income (≤6000 RMB, 6000–12000 RMB, and >12,000 RMB), maternal smoking (yes or no), and the intensity of physical activity [expressed in metabolic equivalents (METs) per week]. Birth information including child's sex, the season of birth (spring-summer, or autumn-winter), low birth weight (LBW, <2.5 kg), and preterm birth (PTB, <37 weeks of gestation) were obtained from the hospital birth registry system. We also collected postnatal factors via parent-reported questionnaires. Exclusive breastfeeding duration was collected at 6 months of age. Family history of allergy and postnatal exposure to secondhand smoke, family pet, and indoor dampness and mold were investigated at 2 years old.

We used $PM_{2.5}$ as a proxy of air pollution, collected from the CHAP dataset, which was estimated from remote sensing observations at a 1-km spatial resolution using a well-developed space-time extra-trees model described by Wei et al., 2020, 2021. We derived the daily average concentration of $PM_{2.5}$ and aggregated them into average exposures for the entire pregnancy based on the residence address of each participant.

2.5. Statistical analysis

Characteristics of the study population were described as means and standard deviations (SD) for continuous variables and frequencies and percentages for categorical variables. Differences across groups with or without any allergic diseases were tested using *t*-tests or χ^2 tests.

We analyzed the association between residential NDVI and allergic outcomes by fitting generalized linear models with a logit link function. We considered any allergic diseases and several allergic diseases (i.e., eczema, urticaria, AR, and food allergy) as primary outcomes, and the others (i.e., atopic dermatitis, allergic conjunctivitis, and asthma) were not separately analyzed due to their limited numbers in the preliminary analysis. The exposure of NDVI was examined as a continuous variable or categorized into tertiles to assess whether the outcomes were more sensitive to the higher level of residential greenness. We first built a crude model without adjusting for any covariates and then fitted the main model which was adjusted for the potential confounding factors *a priori* identified based on the directed acyclic graph, including maternal age, maternal employment status, maternal education level, monthly household income, child's sex, birth season, physical activity in pregnancy, and $PM_{2.5}$ during pregnancy (Fig. S1).

Several sensitivity analyses were conducted to confirm our findings: (1) we additionally adjusted for several important risk factors for allergy (maternal smoking during pregnancy, LBW, PTB, postnatal secondhand smoke exposure, exclusive breastfeeding, and family history of allergy) based on the main model (Murrison et al., 2019); (2) we re-analyzed the data by excluding children who were exposed to indoor dampness and mold (n = 58) or kept a family pet (n = 80) during the early life, respectively; (3) we used wheeze as early sign for asthma and re-analyzed the associations; and (4) we re-analyzed the data by using other proxies for residential greenness including EVI and tree cover.

We also explored the mediation and the modification of air pollution and physical activity on the associations between residential greenness and the outcomes, as existing evidence suggested (Dzhambov et al., 2021; Kim et al., 2020; Donovan et al., 2021). We used R package of "mediation" to calculate the proportions of the mediated effect, with bias-corrected confidence intervals.

All analyses were performed in the statistical software R 4.1.1 (R Core Team, 2021). A P value < 0.05 for a two-sided test was considered statistically significant.

3. Results

3.1. Characterization of study population and allergic outcomes

A total of 522 toddlers aged 2 years were included in this study, and 50.88% of them were boys (Table 1). Among all toddlers, the proportion of having physician-diagnosed allergic diseases ranged from 31.99% (167/522) for eczema and 0.57% (3/522) for asthma and allergic conjunctivitis. There were 219 (41.59%) children with any allergic diseases, who were less likely to have exclusive breastfeeding during the first 6 months of life, compared to those without any allergic diseases.

3.2. Distribution of residential greenness among the study population

Table 2 summarized the characteristics of residential NDVI in the different buffers during the first 1000 days of life. The average NDVI-250 and NDVI-500 during the pregnancy were 0.25 ± 0.07 and 0.34 ± 0.09 with medians [IQR] of 0.23 [0.06] and 0.34 [0.11]. The average NDVI-250 and NDVI-500 during the postnatal 2 years were 0.24 ± 0.07 and 0.32 ± 0.09 with medians [IQR] of 0.23 [0.06] and 0.34 [0.11]. The correlation of NDVI with EVI and tree cover has been shown in Table S1.

3.3. Association of greenness and allergic diseases during the first 1000 days of life

In the main models (Table 3), NDVI-500 in the first 1000 days of life was associated with higher odds of having any allergic diseases (OR [odds ratio], 1.25; 95%CI, 1.02–1.53) and eczema (OR, 1.26; 95%CI, 1.02–1.56) among toddlers. In pregnancy, a 0.1 unit increase in NDVI-500 was associated with 25% (95%CI, 2%–53%) higher odds for any allergic diseases and 28% (95%CI, 4%–59%) higher odds for eczema. In 0–2 years of age, a 0.1 unit increase in NDVI-500 was associated with 24% (95%CI, 2%–52%) higher odds for any allergic diseases and 24% (95%CI, 1%–54%) higher odds for eczema. When we used categorical NDVI-500 in tertiles, the associations were more pronounced in pregnancy (any allergic diseases: OR, 1.63; 95%CI, 1.03–2.58; eczema: OR, 1.70; 95%CI: 1.04–2.78) than those in other periods (Table 4). We did not observe any significant associations in the analyses of NDVI-250.

Results of the sensitivity analyses were presented in Tables S2–S6. The observed associations remained similar when we additionally adjusted for other risk factors for allergic diseases (Table S2) and re-ran the analyses in the subsample of children who were not exposed to several indoor allergens (Tables S3 and S4). We also observed stronger associations in the highest tertile of NDVI compared to the lowest tertile in the analyses of wheeze in overall early life (Table S5). When using other indicators of residential greenness, we found similar associations

Table 1
Characteristics of study population.

Characteristics	Total (N = 522)	Any allergic diseases		
		No (n = 303)	Yes (n = 219)	P value
Maternal characteristics during pregnancy				
Maternal age at enrollment, n (%), year				0.375
>35	95 (18.20)	59 (19.47)	36 (16.44)	
≤35	427 (82.80)	244 (80.53)	183 (84.56)	
Current employment (yes), n (%)	358 (72.03)	209 (71.98)	147 (72.03)	0.983
Education level, n (%)				0.187
High school and below	170 (33.46)	107 (36.15)	63 (29.72)	
Junior college	158 (31.10)	93 (31.42)	65 (30.66)	
University and above	180 (35.43)	96 (32.43)	84 (39.62)	
Monthly household income, n (%), RMB				0.866
<6000	216 (42.77)	128 (43.69)	88 (41.51)	
6000-12000	168 (33.27)	95 (32.42)	73 (34.43)	
≥12,000	121 (23.96)	70 (23.89)	51 (23.06)	
Physical activity, mean (SD), METs·h/w	31.72 (27.38)	32.25 (27.74)	32.28 (26.99)	0.696
$PM_{2.5}$, mean (SD), μg/m^3	37.70 (4.28)	37.92 (4.20)	37.70 (4.38)	0.161
$PM_{2.5}$, n (%), μg/m^3				0.242
≤35	211 (40.42)	116 (38.28)	95 (43.38)	
>35	311 (59.58)	187 (61.72)	125 (56.62)	
Maternal smoking (yes), n (%)	154 (30.02)	79 (26.78)	75 (34.40)	0.063
Child's characteristics				
Child's sex (boys), n (%)	261 (50.88)	149 (50.34)	112 (51.61)	0.775
Birth season, n (%)				0.184
Spring-summer	213 (40.80)	131 (43.23)	82 (37.44)	
Autumn-winter	309 (59.20)	172 (56.77)	137 (62.56)	
Breastfeeding, n (%)				**0.026**
<6 months	**304 (61.79)**	**163 (57.60)**	**141 (67.46)**	
≥6 months	**188 (38.21)**	**120 (42.40)**	**68 (32.54)**	
Family history of allergy (yes), n (%)	150 (28.74)	78 (25.74)	72 (32.88)	0.075
Low birth weight (yes), n (%)	10 (2.09)	8 (2.99)	2 (0.95)	0.122
Preterm birth (yes), n (%)	19 (3.97)	13 (4.85)	6 (2.84)	0.264
Passive smoking (yes), n (%)	72 (13.87)	43 (14.24)	29 (13.36)	0.776

Abbreviation: METs, metabolic equivalents.
P values from t-test or χ^2 test.
Any allergic diseases: any diseases of eczema, atopic dermatitis, urticaria, allergic rhinitis, allergic conjunctivitis, food allergy, or asthma.

between EVI and allergic outcomes, but no associations regarding tree covers (Table S6).

We did not find significant modification or mediation regarding $PM_{2.5}$ or physical activity in the association between residential greenness and eczema (Tables S7 and S8).

4. Discussion

To our knowledge, this was the first birth cohort in China investigating associations between early-life residential greenness and allergic diseases among young toddlers. We found that early-life exposure to NDVI-500 was associated with a higher risk of having allergic diseases especially eczema in 2-year-old toddlers. The associations attenuated to null with the similar direction when considering a 250-m buffer of residential greenness.

One birth cohort in Portugal has evaluated the overall allergic diseases, which suggested the non-significant association between residential NDVI at birth and allergy at 4 and 7 years of age (Cavaleiro Rufo et al., 2021). However, this study only examined the NDVI exposure at birth without considering the confounding influence of indoor and ambient exposure (e.g., certain allergens, secondhand smoke, air pollution). Our study estimated the time-varying NDVI exposure in the early-life and considered a rich covariate set, demonstrating an adverse association between residential greenness and any allergic diseases. When examining specific diseases, previous studies on eczema observed null associations among school-aged children (Cavaleiro Rufo et al., 2021; Li et al., 2019; Parmes et al., 2020; Dzhambov et al., 2021), while results regarding allergic respiratory outcomes were inconsistent, and many of them indicated that greenness might be a risk factor for developing wheeze, AR, or asthma (Fuertes et al., 2014, 2016; Markevych et al., 2020; Parmes et al., 2020; Shrestha et al., 2018). Specifically, we found that the association was stronger for eczema, and the sensitivity analyses of wheeze outcomes also highlight the potential connection to asthma. Our results, in combination with previous findings, might be partially interpreted by the temporal progression of allergy. Eczema in infancy is generally considered as the onset of "allergy march", which may subsequently develop into wheeze and diagnosed AR and asthma in later childhood (Yang et al., 2020). We speculated that early-life exposure to greenness might trigger infantile eczema and early respiratory symptoms, marching into asthma and AR subsequently, and further studies are needed to track the developmental trajectories of allergies from early life when investigating the health impact of greenness.

Although the underlying mechanism remained unclear, one possible explanation was that neighborhood green space is the source of pollens, fungal spores, endotoxins, and mycotoxins, all of which have been shown to initiate inflammation reaction and trigger allergic diseases (Cecchi et al., 2018; Tham et al., 2019; Idrose et al., 2020). Since toddlers in our studies spent an average time of 1.5 h per day on outdoor activities, they might contact with allergens emitted by green spaces. Particularly, the pollens released by grassland were considered as one of the most important allergens due to their significant allergy-producing

Table 2
Distribution of Residential greenness (NDVI) in the first 1000 days of life among 522 toddlers.

	Mean	SD	IQR	NDVI distribution				
				Min	P_{25}	Median	P_{75}	Max
NDVI-250 m								
Pregnancy	0.25	0.07	0.07	0.06	0.21	0.23	0.28	0.63
0–2 years	0.24	0.07	0.07	0.09	0.20	0.23	0.27	0.55
The first 1000 days	0.24	0.07	0.07	0.09	0.20	0.23	0.27	0.57
NDVI-500 m								
Pregnancy	0.33	0.09	0.11	0.07	0.27	0.34	0.38	0.73
0–2 years	0.32	0.09	0.11	0.06	0.26	0.33	0.37	0.69
The first 1000 days	0.33	0.09	0.11	0.06	0.26	0.33	0.38	0.70

Abbreviation: NDVI, normalized difference vegetation index; SD, Standard deviation; IQR, Interquartile range; P_{25}, First quartile; P_{75}, Third quartile.

Table 3
Association between residential greenness (per 0.1 units increase in NDVI) and allergic diseases in the first 1000 days of life among 522 toddlers.

	Any allergic diseases[a] [*OR (95% CI)*]	Specific allergic diseases [*OR (95% CI)*]			
		Eczema ($n = 167$)	Urticaria ($n = 34$)	Food Allergy ($n = 57$)	Allergic Rhinitis ($n = 27$)
Crude model					
NDVI-250 m					
Pregnancy	1.13 (0.87–1.47)	1.19 (0.91–1.56)	0.78 (0.43–1.32)	1.04 (0.56–1.76)	1.15 (0.76–1.67)
0–2 years	1.12 (0.86–1.45)	1.21 (0.92–1.58)	0.77 (0.42–1.31)	1.17 (0.65–1.95)	1.03 (0.68–1.53)
The first 1000 days	1.13 (0.87–1.46)	1.21 (0.92–1.59)	0.77 (0.41–1.32)	1.14 (0.62–1.91)	1.07 (0.70–1.58)
NDVI-500 m					
Pregnancy	**1.24 (1.03–1.50)**	**1.28 (1.05–1.56)**	1.01 (0.69–1.45)	1.01 (0.67–1.51)	1.12 (0.84–1.48)
0–2 years	**1.22 (1.01–1.47)**	**1.22 (1.00–1.49)**	0.97 (0.66–1.40)	1.04 (0.68–1.55)	1.09 (0.81–1.45)
The first 1000 days	**1.23 (1.02–1.49)**	**1.24 (1.02–1.52)**	0.98 (0.67–1.42)	1.03 (0.67–1.55)	1.10 (0.82–1.47)
Main model					
NDVI-250 m					
Pregnancy	1.13 (0.86–1.47)	1.20 (0.91–1.60)	0.70 (0.36–1.26)	0.78 (0.41–1.42)	1.15 (0.75–1.70)
0–2 years	1.19 (0.91–1.56)	1.30 (0.97–1.73)	0.76 (0.41–1.33)	1.01 (0.55–1.74)	1.08 (0.69–1.62)
The first 1000 days	1.01 (0.83–1.20)	1.04 (0.86–1.25)	0.73 (0.38–1.23)	0.93 (0.50–1.29)	1.01 (0.69–1.25)
NDVI-500 m					
Pregnancy	**1.25 (1.02–1.53)**	**1.28 (1.04–1.59)**	1.01 (0.66–1.49)	0.94 (0.60–1.45)	1.09 (0.80–1.47)
0–2 years	**1.24 (1.02–1.52)**	**1.24 (1.01–1.54)**	0.94 (0.62–1.41)	0.93 (0.58–1.44)	1.08 (0.79–1.47)
The first 1000 days	**1.25 (1.02–1.53)**	**1.26 (1.02–1.56)**	0.96 (0.63–1.43)	0.93 (0.58–1.45)	1.09 (0.79–1.48)

Crude model was adjusted for nothing; The main model was adjusted for maternal age, maternal employment status, maternal education level, monthly household income, child's sex, birth season, physical activity in pregnancy, and PM2.5 during pregnancy.
Statistically significant results are in bold ($P < 0.05$).
Abbreviation: NDVI, normalized difference vegetation index.
[a] There were 41.95% (219/522) children having any of the allergic diseases, including eczema, atopic dermatitis, urticaria, allergic rhinitis, allergic conjunctivitis, food allergy, and asthma.

capabilities (D'Amato et al., 2007). In our study, the moderate values of NDVI (0.24–0.33) cooperated with a low percentage of tree cover might indicate a higher proportion of shrubs and grassland in the study area (Gascon et al., 2016). One local vegetation survey (Zhuang et al., 2020) has demonstrated that the *Zoysia matrella* and *Cynodon dactylon* were dominant species of herbs that can release allergenic pollens recognized by the WHO/IUIS Allergen Nomenclature Sub-Committee (www.allergen.org). Moreover, the common tree species in Guangzhou are non-allergenic evergreen broadleaf (Jim and Chen, 2009), which were in line with our null associations regarding the sensitivity analyses of tree cover. A case-crossover study (Shrestha et al., 2018) also found that Australian children exposed to grass and weed pollens, instead of tree pollens, had a higher risk of asthma admissions, lending support to our results. Other pathways include modification and/or mediation of air pollutants and physical activity. Air pollutants were thought to modify allergenic potential of plant pollens and fungal spores (Lam et al., 2021), and physical activity could increase contact with green space. However, we did not observe these modified or mediated effects in the current study, and future studies are warranted to confirm our findings.

This study extended previous efforts to understand the susceptibility windows of greenness exposure. We found that residential greenness during prenatal and early postnatal periods contributed to the development of allergic diseases, and we identified the critical exposure window of pregnancy when the developmental programming is the most susceptible to the green space (Martino and Prescott, 2011). Early-life environmental exposure might modulate and program the development of the immune system (Strachan, 1989), and epigenetic mechanisms may be at play across generations (Martino and Prescott, 2011). The latest epigenome-wide association study found that residential NDVI-related DNA methylation profiles showed enrichments in allergic sensitization, suggesting greenness may impact allergic predisposition (Jeong et al., 2021). More evidences are still needed to look into the gene-environment interaction and elucidate the epigenetic changes related to early-life greenness.

Our study also suggested that residential greenness in 500-m buffer has a significant association with allergic diseases instead of 250-m buffer, and we found similar results when using EVI to improve the sensitivity to detect vegetation (Qiu et al., 2018). Previous study suggested that the wider buffer is less prone to underestimation of residential greenness (Gascon et al., 2016), which was also supported by the distributions of the average value of the NDVI-500 m and NDVI-250 m in our study. Moreover, the wider buffer might better reflect the potential exposure to aeroallergens (e.g., pollen and fungal spores) which can be transmitted over long distances and circulate into house through ventilation (Lovasi et al., 2013). Previous studies commonly used 500-m buffer when quantifying greenness exposure (Fuertes et al., 2016; Parmes et al., 2020; Lambert et al., 2017), but the optimal buffers remained unclear. Future studies should derive individual-level measures of exposure to greenness-related allergens and other emissions regarding different buffer sizes to confirm our findings.

Our findings have important implications for policy and clinical practice. Although greenness in urban areas might bring health benefits (e.g., mitigating mental stress, enhancing social interaction, and increasing physical activities) (Markevych et al., 2017), urban planners should take the potential negative influence on maternal and child health into account when planning green space in the living environment. In addition, health care professionals and expectant parents must be educated about the influence of neighborhood greenness, and health promotion should be developed to promote the awareness of unfavorable environmental exposure and early-onset allergic diseases.

Our study had several limitations. First, we could not confirm toddlers' allergic sensitization pattern and allergic diseases with clinic tests (e.g., allergen-specific IgE test). Nevertheless, allergic diseases diagnoses were identified based on medical records, and detailed information regarding allergic manifestations was collected. Second, MODIS and VIIRS products provide NDVI at medium spatial resolution, but the good temporal resolution allowed us to estimate the time-varying exposure of early life. Third, we didn't collect detailed information of the built environment and natural environment related to residential greenness, such as proximity to green space, the allergenic vegetation species, or the richness of biodiversity. Fourth, due to the limited case numbers in a small population, we could not separately analyze and provide specific evidence on associations between greenness and atopic dermatitis, allergic conjunctivitis, and asthma in 2-year toddlers, which should be further examined in studies with large sample size. Fifth, we used $PM_{2.5}$ data whose spatial resolution was inconsistent with NDVI, and the predictive models of $PM_{2.5}$ in this study have the best spatial resolutions and accuracy that we can access (Wei et al., 2021). Finally,

Table 4
Association between residential greenness (category of NDVI) and allergic diseases in the first 1000 days of life among 522 toddlers.

	Any allergic disease[a] [*OR (95% CI)*]	Specific allergic conditions [*OR (95% CI)*]			
		Eczema (*n* = 167)	Urticaria (*n* = 34)	Food Allergy (*n* = 57)	Allergic Rhinitis (*n* = 27)
NDVI-250 m					
Pregnancy (Reference: T1)					
T2	1.10 (0.70–1.73)	1.00 (0.61–1.63)	0.90 (0.37–2.19)	0.40 (0.13–1.12)	1.74 (0.87–3.58)
T3	1.15 (0.73–1.81)	1.16 (0.72–1.88)	0.70 (0.26–1.79)	0.63 (0.24–1.62)	0.99 (0.45–2.16)
0–2 years (Reference: T1)					
T2	1.13 (0.72–1.79)	1.08 (0.66–1.77)	0.88 (0.35–2.16)	0.54 (0.19–1.48)	0.58 (0.28–1.19)
T3	1.21 (0.77–1.91)	1.37 (0.85–2.22)	0.84 (0.33–2.08)	0.75 (0.28–1.96)	0.70 (0.34–1.39)
The first 1000 days (Reference: T1)					
T2	1.10 (0.70–1.74)	0.99 (0.60–1.61)	1.03 (0.41–2.59)	0.44 (0.15–1.17)	0.94 (0.47–1.88)
T3	1.11 (0.70–1.74)	1.21 (0.75–1.95)	1.01 (0.40–2.51)	0.54 (0.20–1.43)	0.72 (0.34–1.49)
NDVI-500 m					
Pregnancy (Reference: T1)					
T2	1.19 (0.75–1.89)	1.19 (0.72–1.97)	2.35 (0.94–6.46)	0.84 (0.30–2.33)	0.86 (0.41–1.79)
T3	**1.63 (1.03–2.58)**	**1.70 (1.04–2.78)**	1.50 (0.53–4.40)	1.15 (0.43–3.10)	1.10 (0.55–2.23)
0–2 years (Reference: T1)					
T2	1.04 (0.65–1.65)	0.97 (0.59–1.60)	1.96 (0.81–5.00)	0.87 (0.31–2.43)	1.25 (0.61–2.58)
T3	1.38 (0.88–2.18)	1.35 (0.84–2.20)	0.88 (0.30–2.47)	0.88 (0.32–2.43)	1.01 (0.48–2.11)
The first 1000 days (Reference: T1)					
T2	1.14 (0.72–1.81)	1.06 (0.64–1.74)	2.18 (0.90–5.66)	0.78 (0.27–2.21)	1.02 (0.49–2.13)
T3	1.54 (0.97–2.43)	1.59 (0.98–2.59)	0.99 (0.33–2.88)	1.05 (0.39–2.83)	1.19 (0.59–2.44)

NDVI was categorized into tertiles, and participants with the lowest tertile (T1) of NDVI value were the reference group.
The regression model (main model) was adjusted for maternal age, maternal employment status, maternal education level, monthly household income, child's sex, birth season, physical activity in pregnancy, and PM2.5 during pregnancy; Results of crude model were similar (data not shown).
Statistically significant results are in bold ($P < 0.05$).
Abbreviation: NDVI, normalized difference vegetation index.
[a] There were 41.95% (219/522) children having any of the allergic diseases, including eczema, atopic dermatitis, urticaria, allergic rhinitis, allergic conjunctivitis, food allergy, and asthma.

previous studies have suggested that the association between greenness and allergic outcomes varied by different levels of urbanization and geographical regions (Fuertes et al., 2014, 2016). Therefore, restriction to a central district of Guangzhou city may limit the generalizability of our findings to other populations or rural areas.

5. Conclusion

Our study demonstrated that residential greenness was adversely associated with allergic diseases especially eczema among 2-year-old toddlers, and pregnancy appears to be the critical exposure window. Our findings highlighted the importance of building a more friendly green neighborhood to improve maternal and child health.

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Ethical approval and trial registration statements

This study was approved by the Ethics Committee of the School of Public Health of Sun Yat-sen University. Written informed consent were provided by all the participants. The cohort study was registered at ClinicalTrials.gov (NCT03023293).

Declaration of competing interest

The 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 data to this article can be found online at https://doi.org/10.1016/j.envres.2022.114003.

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