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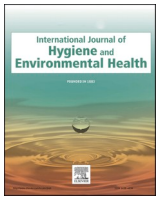

Is local air pollution concentration a moderator or mediator of the association between residential greenspace and pediatric asthma exacerbations? A longitudinal study of pediatric patients in Philadelphia, Pennsylvania

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ABSTRACT

Background: Despite mixed evidence supporting the link between greenspace and asthma exacerbations, several studies suggest a negative association. The mechanisms underlying this relationship are unclear, with air pollution concentrations potentially playing a key role. This study investigated whether air pollution concentrations modify or mediate the relationship between residential greenspace and pediatric asthma exacerbations.
Methods: Data were drawn from a pediatric asthma cohort at Children's Hospital of Philadelphia (2011–2016), including children aged <18 years. Participants were followed from their initial visit until their first asthma exacerbation. Greenspace (tree canopy, grass/shrub cover) near homes was assessed. Daily air pollution data, including $PM_{2.5}$, ozone, NO_2, and SO_2, were obtained from the US Environmental Protection Agency. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated, adjusting for individual and neighborhood characteristics. Effect modification by air pollution concentrations was tested, and causal mediation analyses were conducted.
Results: On days with high SO_2 concentrations, children living near the highest quartile of tree canopy coverage had a 14% lower incidence of asthma exacerbations compared to those in the lowest quartile (HR = 0.86, 95% CI = 0.74, 0.98). Conversely, on days with low SO_2 concentrations, tree canopy coverage was associated with a nonsignificant 12% higher incidence (HR = 1.12, 95% CI = 0.97, 1.28). Similar patterns were observed for NO_2, but no interactions were found for $PM_{2.5}$ or ozone. Mediation analyses indicated no significant mediation by air pollution.
Conclusion: In urban areas with high SO_2 or NO_2 levels, greenspace near homes may support children with asthma by mitigating air pollution's impact, suggesting greenspace-based urban strategies.

1. Introduction

Pediatric asthma exacerbations are a leading cause of hospitalizations, emergency room visits, and school absences, representing a significant public health burden(Guttmann et al., 2007; Ismaila et al., 2013; Zahran et al., 2018). Addressing these adverse outcomes and actively seeking strategies are top priorities for public health officials. Epidemiological studies have consistently linked ambient air pollutants

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—such as fine particulates ($PM_{2.5}$), ozone (O_3), nitrogen dioxide (NO_2), and sulfur dioxide (SO_2) to the onset and severity of asthma exacerbations(Delfino et al., 2014; Eisenman et al., 2019a; Mar and Koenig, 2009; Patel et al., 2010; Sabrin et al., 2021). Local strategies to mitigate air pollution exposure, including increasing greenery and vegetation with air-purifying capabilities, have emerged as promising approaches to asthma management. Additionally, stress reduction has been shown to alleviate inflammation, which is a key contributor to asthma flare-ups (Chen and Miller, 2007). Given the well-documented stress-reducing benefits of greenspace exposure(Zhang et al., 2020), enhancing access to greenspace presents a dual opportunity to promote respiratory health: decreasing exposure to harmful air pollutants and improving stress management. This dual mechanism positions greenspace as a potentially effective public health intervention for pediatric asthma control.

Several studies have found residential greenspace to be associated with reductions in asthma exacerbations and hospitalizations(Alcock et al., 2017; Chen et al., 2017; De Roos et al., 2022; Dzhambov et al., 2021), including evidence from studies conducted in Philadelphia(De Roos et al., 2022). For instance, De Roos et al. (2022) found that increased access to residential greenspace in Philadelphia was linked to a lower risk of asthma morbidity among children(De Roos et al., 2022). Similarly, Alcock et al. (2017) reported fewer asthma-related hospitalizations in neighborhoods with higher tree density, private gardens, or public green spaces(Alcock et al., 2017). Kim and Ahn (2021) further reinforced these findings by demonstrating an inverse relationship between neighborhood greenspaces and emergency department visits for asthma-related issues(Kim and Ahn, 2021). Collectively, these studies underscore the potential of greenspace within residential areas to improve asthma outcomes, likely through mechanisms that involve environmental and psychological benefits. These findings highlight the importance of considering greenspace as a public health intervention to address asthma-related morbidity, particularly in urban environments

Despite the observed negative associations with asthma exacerbation, the underlying mechanism of this protection remains unclear. Air pollution has been proposed as a potential factor influencing this relationship, yet few epidemiological studies have directly investigated this hypothesis(Eisenman et al., 2019b). Considering the well-documented detrimental impacts of air pollution on respiratory health and the potential of greenspace to buffer against these adverse impacts, further research is warranted to elucidate the role of air pollution in mediating or modifying the association between greenspace and asthma exacerbations. Such investigations could provide critical insights into the pathways through which greenspace influences respiratory health and inform targeted public health interventions.

The relationship between greenspace and health outcomes may be mediated or modified by air pollution under specific conditions. Regarding mediation, experimental and modeling studies have shown that particulate and gaseous pollutants can be deposited on or absorbed by leaf surfaces, or, conversely, air pollution concentrations may increase as a result of dispersion by tree surfaces near emission sources (Eisenman et al., 2019a). These observations suggests that greenspace can effectively reduce air pollution concentrations – i.e. greenspace might be mediated by air pollution – which, itself, is known to cause asthma exacerbations.

From the perspective of effect modification, greenspace is hypothesized to create a calming environment that promotes relaxation, alleviates stress, and reduces airway inflammation and constriction, thereby mitigates asthma exacerbations. Conversely, children living in areas with high air pollution levels face an elevated risk of inflammatory biological processes(Altman et al., 2023), which can worsen asthma symptoms. Consequently, air pollution may modify the relationship between greenspace and asthma exacerbations by influencing stress and inflammation pathways. An epidemiological study conducted in England showed that higher urban tree density was linked to a decrease in asthma-related hospitalizations in regions with elevated average ambient air pollution levels(Alcock et al., 2017). This result suggests that the negative association of greenspace and asthma exacerbation may be particularly pronounced in highly polluted regions, offering greater benefits for asthma control. Investigating effect modification is crucial for identifying areas where greening interventions could have the greatest impact, enabling targeted urban planning strategies to optimize respiratory health outcomes.

We utilized electronic health records from Children's Hospital of Philadelphia to investigate whether air pollution, specifically $PM_{2.5}$ and ozone, mediates or modifies the relationship between residential greenspace and the incidence of childhood asthma exacerbations. Urban populations are disproportionately exposed to higher levels of air pollution compared to suburban and rural areas(Clark et al., 2014), making urban environments a primary focus of our research. Our first hypothesis posited that dense tree canopy and grass/shrub coverage may directly reduce $PM_{2.5}$ and ozone concentrations in the ambient environment, thereby leading to lower incidence of asthma exacerbations in densely vegetated neighborhoods. To test this, we conducted causal mediation analyses to evaluate whether air pollution serves as a mediator in the relationship between greenspace and asthma exacerbations. Our second hypothesis suggested that greenspace may provide greater reductions in asthma exacerbations when pollutant levels ($PM_{2.5}$, ozone, NO_2, SO_2) in children's neighborhoods are high – possibly given greenspace's role in stress regulation. We tested this hypothesis by examining the effect modification of air pollution on the greenspace-asthma exacerbations, hypothesizing that children living in neighborhoods with higher air pollution and more greenspaces would experience more substantial reductions in asthma exacerbations. These analyses aim to elucidate the mechanisms by which greenspace influences respiratory health outcomes in urban settings.

2. Material and methods

2.1. Background

This study was conducted in Philadelphia, Pennsylvania, a large and diverse urban area with a mix of residential, commercial, and industrial zones. Covering 142.7 square miles (369.62 km^2), the city is situated on a coastal plain with flat terrain that gradually transitions to rolling hills in the northwest. Philadelphia's urban environment includes dense neighborhoods, extensive transportation networks, and industrial areas, which contribute to localized air pollution challenges(Adams et al., 1993).

Greenspace is unevenly distributed across the city, with an estimated 21% tree cover and 18% grass cover. Northern and western neighborhoods have the highest tree canopy coverage, while central and southern areas have less greenspace availability. Parkland makes up about 9.3% of the city's total area (90,990 acres) and features various tree species such as spicebush, black cherry, ash, tree-of-heaven, boxelder, and American beech(Nowak et al., 2016).

Air quality in Philadelphia presents challenges typical of urban environments, influenced by vehicular emissions, industrial activity, and regional pollutant transport. The annual mean concentration of $PM_{2.5}$ is 12 $\mu g/m^3$, meeting but approaching the threshold of the National Ambient Air Quality Standards (NAAQS). The three-year average of the fourth-highest 8-h daily average ozone (O_3) concentrations is less than or equal to 0.07 ppm, generally aligning with the NAAQS standard. Nitrogen dioxide (NO_2) and sulfur dioxide (SO_2) levels are within acceptable ranges, with 99th percentile maximum 1-h average concentrations of 100 ppb and 75 ppb, respectively(USEPA, 2024). Despite these values being within regulatory limits, localized pollution hotspots, particularly near industrial zones and major roadways, remain a concern (Cummings et al., 2021). The city's climate, characterized by hot, humid summers and cold winters, further influences air pollution dynamics, with higher ozone levels typically occurring in summer. This combination of urban characteristics, air quality concerns, and greenspace variability underscores the importance of examining the interplay

between greenspace and respiratory health outcomes in this setting.

2.2. Ascertainment of study population and outcome

The study population was identified using electronic health record (EHR) data from patients of the Children's Hospital of Philadelphia (CHOP) as children (<18 years of age) living in Philadelphia who were diagnosed with asthma during a face-to-face clinical visit at CHOP from 2011 to 2016. Asthma diagnoses were identified using the Systematized Nomenclature of Medicine (SNOMED) diagnostic codes, which are consistent with ICD-9/ICD-10 classifications (CM493.XX/CMJ45) (Kenyon et al., 2020; Schinasi et al., 2022).

The asthma patient clinical visit database was analyzed as a longitudinal cohort spanning the study period from 2011 to 2016. Children were followed from their first asthma-related clinical visit within this timeframe until the occurrence of their first asthma exacerbation. Residential addresses were geocoded to obtain latitude and longitude coordinates, which were and subsequently linked to 2010 census tracts for integration with environmental data.

To ensure the inclusion of children consistently seeking asthma care within the CHOP system, the study population was restricted to those who attended one of the four CHOP primary care clinics for non-exacerbation asthma appointments during the study period. For children whose sequence of CHOP visits included a gap of over 18 months, we implemented a random selection process to include either the pre-gap or post-gap sequence of visits. This approach helped mitigate the impact of missing data due to large gaps in care at CHOP, which might reflect care-seeking elsewhere.

We defined asthma exacerbation as meeting two criteria: (1) a face-to-face clinical visit with a confirmed asthma diagnosis, and (2) the prescription of a systemic steroid during the encounter(Fuhlbrigge et al., 2012). To distinguish separate exacerbation events within the same child, we applied a seven-day window, counting only one event during this period and prioritizing the most severe case based on the treatment setting. Specifically, inpatient visits were classified as the most severe, followed by emergency department visits, and then outpatient visits. For multiple visits occurring on the same date, we retained the visit associated with the most severe level of care. Finally, we excluded children with only a single visit after applying all other exclusion criteria, as a single visit did not provide sufficient information to capture the time leading to an exacerbation event. This study was approved by the Institutional Review Boards (IRBs) of both the Children's Hospital of Philadelphia (CHOP) and Drexel University.

2.3. Measuring greenspace

In this study, we measured greenspace, specifically tree canopy and grass/shrub coverage, in proximity to the residential locations of children at the time of their clinical visits, accounting for potential residential relocations during the study period. To evaluate greenspace, circular buffer zones with radii of 250m, 500m, 1000m, and 2000m were generated around each child's home to quantify tree canopy and grass/shrub coverage. The selection of buffer sizes for greenspace measures was guided by identifying the best-fitting buffer size for each measure's association with asthma exacerbation incidence, determined by Akaike Information Criterion (AIC) statistics derived from primary association analyses (see Supplementary Table A1). Additionally, greenspace metrics, including tree canopy and grass/shrub coverage, were assessed at the census tract level to provide a broader contextual measure of greenspace availability in the children's residential environments.

2.3.1. Tree canopy and grass/shrub coverage

To quantify tree canopy and grass/shrub coverage, we used high-resolution data with a 1-m resolution developed by the Spatial Analysis Laboratory at the University of Vermont in 2013(UVM, 2016b). This dataset was derived from Light Detection and Ranging (LiDAR) data using an Object-Based Image Analysis (OBIA) technique. OBIA involved extracting land cover information from the best available remotely sensed and vector GIS data, grouping pixels into coherent objects based on their spatial characteristics(UVM, 2016b). Each 1-m pixel was classified into one of twelve land cover classes. We grouped the greenspace land cover classes into two categories: tree canopy (including tree canopy, tree canopy over structures, tree canopy over impervious surfaces, and tree canopy over roads), and grass/shrub vegetation (including emergent wetlands, low vegetation, and shrub/scrub)(UVM, 2016a). For the Philadelphia metropolitan area, we generated 30-m resolution surfaces representing the percentage of tree canopy and grass/shrub vegetation within four buffer distances. These percentage were extracted from the generated surfaces to represent tree canopy and of grass/shrub vegetation at varying spatial scales to the children's residential locations. Analyses were conducted using ArcGISPro 2.0.

2.4. Ambient air pollutants

We obtained modeled daily average $PM_{2.5}$ and daily 8-h maximum ozone concentrations at the census-tract level from the Fused Air Quality Surface using Downscaling (FAQSD) datasets available from USEPA (USEPA, 2010b). These pollutant estimates were generated using a Bayesian space-time downscaling model that integrated daily average fine particulate and daily 8-h maximum ozone data collected from the National Air Monitoring Stations/State and Local Air Monitoring Stations with 12-km gridded output from the Models-3/Community Multiscale Air Quality (CMAQ) model(Berrocal et al., 2012). These resulting downscaled data provide daily air quality estimates for the geographic centroids of census tracts across the United States. For nitrogen dioxide (NO_2) and sulfur dioxide (SO_2), we obtained maximum daily concentrations from the EPA's Air Quality System (AQS). Daily means or maximum air pollution concentrations were assigned to each child on the day of their clinical visit. This assignment used data from the nearest AQS monitoring station to the child's residential location.

2.5. The covariates

We selected covariates hypothesized to be associated with both our exposure and outcome variables. For each clinical visit, we recorded individual-level variables including the child's age, sex, payment source (Medicaid/sCHIP vs. other), race/ethnicity (White non-Hispanic, Black non-Hispanic, Hispanic or Latinx, other, or multiple or unknown), calendar month, day of the week, and residential address. In addition, we incorporated census-tract-level socio-demographic data from the American Community Survey (ACS). These data enabled the estimation of population density (per square kilometer), racial segregation (percentage of non-Hispanic Black residents), and the socioeconomic status (SES) index for each census tract. The SES index included multiple components: the logarithmically transformed median value of occupied housing units, the proportion of residents aged 25 and older with a high school education, the proportion of residents aged 25 and older with a bachelor's degree, the percentage of civilians aged 16 and older employed in managerial or professional occupations, the logarithmically transformed median household income, and the proportion of households with income derived from interest, dividends, and net rentals (Roux et al., 2001). We also included a measure estimating the likelihood of Philadelphia residents utilizing the CHOP main campus in University City, Philadelphia, based on their proximity to the campus (Mudd et al., 2020), quantified as a continuous term, with higher value indicating closer proximity to CHOP. Finally, we adjusted for local meteorology variables, including average dry-bulb temperature (in Fahrenheit), and total precipitation (in inches), sourced from the National Centers for Environmental Information, National Oceanic and Atmospheric Administration (NOAA).

2.6. Statistical analyses

2.6.1. Overarching modeling approach

We employed Cox proportional hazards models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). The estimates quantify associations between greenspace measures, air pollution and/or their joint effects on the incidence of asthma exacerbations. Our time-to-event analysis focused on monitoring children from their initial study visit until the occurrence of their first exacerbation event, measured in days. Once a child experienced their first event, they were no longer subject to further follow-up. For children who did not experience an exacerbation, follow-up continued until their last clinical visit during the study period (except for excluded visits; see above). The decision to focus on the first exacerbation was guided by methodological and clinical considerations. From a methodological perspective, analyzing the first event avoids complexities associated with recurrent event modeling during mediation analyses. Clinically, the first exacerbation is a critical marker, as it often signals an acute health burden and the initiation of more intensive asthma management. Identifying predictors of the first event is particularly relevant for preventative strategies aimed at reducing the recurrence of exacerbations. Separate models were developed to evaluate associations with each specific greenspace metric. All models were adjusted for various factors, including calendar month (categorized into 12 months), day of the week (categorized into 7 days), child's age (categorized in 2-year intervals), sex (female or male), race/ethnicity (Hispanic, non-Hispanic Black, non-Hispanic White, other), Medicaid/sCHIP coverage (yes or no), and residential proximity to the CHOP main campus emergency department and hospital (categorized by cut points at the tenth decimal place, with low-frequency categories combined: 0 to $<$ 0.3, 0.3 to $<$ 0.4, 0.4 to $<$ 0.6, 0.6 to $<$ 0.7, 0.7 to $<$ 0.8, 0.8 to $<$ 1.0), census tract population density (categorized into quintiles), socioeconomic status index (categorized into quintiles), and racial segregation (percent non-Hispanic black population categorized into quintiles). Local meteorology variables, including average dry-bulb temperature (in Fahrenheit) for the day, and total precipitation for the day (inches), were also included. These covariates were selected for adjustment based on *a priori* hypotheses concerning their potential to confound the associations between greenspace and asthma exacerbations. Our modeling was conducted using the *coxph* package in R version 4.1.2(Therneau and Lumley, 2015).

2.6.2. Analyses of the modification of effect

We examined whether the relationship between greenspace measures and the incidence of childhood asthma exacerbations was modified by the daily levels of $PM_{2.5}$, ozone, NO_2, or SO_2, categorized into tertiles to observe associations in the high, medium, and low levels of air pollution (on the same day as the asthma exacerbation event). This examination involved the incorporation of interaction terms between air pollutant levels and greenspace measures into separate regression models.

We constructed models that included interactions between tertiles of air pollutants and quartiles of greenspace measures. Based on the model outcomes, we aggregated the relevant coefficients to determine the associations between greenspace quartiles and asthma exacerbations within each air pollution tertile. Pairwise comparisons of coefficients were conducted using Wald tests to assess effect modification, comparing the coefficients for greenspace quartiles in the second or third tertile of air pollutants with those in the first tertile. Statistical significance was defined as $p < 0.05$, indicating meaningful differences in regression coefficients across categories of air pollution levels.

2.6.3. Evaluations of mediation

We conducted causal mediation analyses to estimate the proportion of the association between census-tract-level greenspace and childhood asthma exacerbations that could be explained by daily concentrations of $PM_{2.5}$ and ozone. Using census-tract-level data allows us to evaluate air pollution and greenspace at the same spatial scale, facilitating the investigation of potential mediating pathways. NO_2 and SO_2 were not included as mediators due to their limited spatial resolution and the scarcity of point monitors.

For mediation analyses, greenspace measures were treated as continuous variables to accommodate the modeling process. We incorporated interactions between greenspace measures and the assessed mediators, which allowed for fewer assumptions compared to models without interaction terms(Therneau and Lumley, 2015). Mediation effects were estimated using the *CMAverse* R package, which facilitate the calculation of the total effect (TE), pure natural direct effect (PNDE), total natural indirect effect (TNIE), and the proportion mediated (PM) through a regression-based approach(Shi et al., 2021). This methodology was specifically chosen to accommodate survival outcomes, linear mediators, and linear exposure variables. The natural direct effect (PNDE) reflects the effect of greenspace on asthma exacerbation independent of air pollution mediation (pathway A-Y) (Figure A.2), while the natural indirect effect (TNIE) represents the portion of the greenspace effect mediated through air pollution (pathway A-M-Y). To quantify mediation, we calculated the proportion mediated by dividing TNIE by total effect (TNIE/[PNDE + TNIE]). We used bootstrapping with multiple imputations to generate 95% confidence intervals (CIs) for these estimates to ensure robust statistical inference.

3. Results

The study followed a cohort of 17,259 children from their initial visit until the occurrence of their first exacerbation, resulting in a total of 17,259 visits and a complete case of 17,198 visits for modeling. Time was measured in days. Table 1 summarizes the characteristics of all visits for children diagnosed with asthma. Most visits were made by male (57%), non-Hispanic Black (80%), and children covered by Medicaid/sCHIP (69%). Asthma-related visits were most frequently recorded during the months of October through December, with weekdays being the most common days for such visits. Exacerbation visits were more prevalent among younger children, with a median age of 5 years, compared to a median age of 10 years for non-exacerbation visits. A higher proportion of exacerbation visits occurred among children residing in low-SES census tracts (below the 75^{th} percentile) or in racially segregated census tracts (where the proportion of non-Hispanic Black residents exceed the 75^{th} percentile). Additionally, exacerbation visits were more likely during the winter months (December to February) and the spring months (March to May).

Table 2 and Supplementary Figure A1 present the distributions and pairwise correlations between greenspace metrics and air pollutants. Near children's homes, the average tree canopy coverage within a 1000m buffer was 19%, while grass/shrub coverage within a 2000m buffer averaged 13% (Table 2). At the census-tract level, greenspace coverage was slightly lower, with an average of 17% for tree canopy and 12% for grass/shrub coverage. Tree canopy coverage exhibited greater variability compared to grass/shrub coverage at both the buffer census-tract levels. Moderate correlations were observed between different buffer-level greenspace measures, with a correlation coefficient of 0.46 between grass/shrubs and tree canopy. Similarly, at the census tract level, greenspace measures showed moderate correlations, with a coefficient of 0.37 for grass/shrubs and tree canopy. Census tract SES was weakly correlated with grass/shrub coverage (−0.06) but moderately correlated with tree canopy coverage (0.44). The proportion of non-Hispanic Black residents in a census tract exhibited a modest positive correlation with grass/shrubs (0.20) and a weak negative correlation with tree canopy (−0.09). Regarding air pollutants, moderate correlations were identified between $PM_{2.5}$ and NO_2 (0.49), $PM_{2.5}$ and SO_2 (0.30), and NO_2 and SO_2 (0.34). In contrast, ozone demonstrated low negative correlations with other air pollutants, with correlation coefficients ranging from −0.17 to −0.04 (Supplementary Fig. A1).

Key findings on the main effects of greenspace on asthma

Table 1
Characteristics of asthma patient visits [a] in Philadelphia by asthma exacerbation status.

Children's characteristics [b]	Asthma exacerbation and non-exacerbation visits [e] (N = 17,198 visits)		Non-exacerbation visits [e] (N = 9538 visits)		Exacerbation visits [e] (N = 7660 visits)	
	(N or Median)	(% or IQR range)	(N or Median)	(% or IQR range)	(N or Median)	(% or IQR range)
Age (years) [c]	7.9	4.2-12.6	10.2	6.1–14.4	5.4	2.8-9.3
Sex						
Male	9787	56.9	5305	55.6	4482	58.5
Female	7411	43.1	4233	44.4	3178	41.5
Race/ethnicity						
White non-Hispanic	1551	9.0	925	9.7	626	8.2
Black non-Hispanic	13683	79.6	7571	79.4	6112	79.8
Hispanic/Latinx	967	5.6	498	5.2	469	6.1
Other/multiple/unknown	997	5.8	544	5.7	453	5.9
Medicaid/sCHIP coverage						
No	5298	30.8	3123	32.7	2175	28.4
Yes	11900	69.2	6415	67.3	5485	71.6
Probability of using CHOP main campus [c]	0.7	0.4-0.8	0.7	0.4-0.8	0.7	0.4-0.8
Census-tract characteristics [d]						
Census-tract population density (per km^2)						
$\leq 25^{th}$ percentile	4531	26.4	2549	26.7	1982	25.9
$>25^{th}$ to 50^{th} percentile	4322	25.1	2416	25.3	1906	24.9
$>50^{th}$ to 75^{th} percentile	4203	24.4	2301	24.1	1902	24.8
$>75^{th}$ to 90^{th} percentile	2457	14.3	1328	13.9	1129	14.7
$>90^{th}$ percentile	1685	9.8	944	9.9	741	9.7
Census-tract SES index						
$\leq 25^{th}$ percentile	4234	24.6	2301	24.1	1933	25.2
$>25^{th}$ to 50^{th} percentile	4188	24.4	2296	24.1	1892	24.7
$>50^{th}$ to 75^{th} percentile	4194	24.4	2316	24.3	1878	24.5
$>75^{th}$ to 90^{th} percentile	2638	15.3	1473	15.4	1165	15.2
$>90^{th}$ percentile	1944	11.3	1152	12.1	792	10.3
Census-tract % non-Hispanic Black population						
$\leq 25^{th}$ percentile	4446	25.9	2543	26.7	1903	24.8
$>25^{th}$ to 50^{th} percentile	4309	25.1	2404	25.2	1905	24.9
$>50^{th}$ to 75^{th} percentile	4296	25.0	2445	25.6	1851	24.2
$>75^{th}$ to 90^{th} percentile	2524	14.7	1296	13.6	1228	16.0
$>90^{th}$ percentile	1623	9.4	850	8.9	773	10.1
Visit timing						
Month						
January	1208	7.0	601	6.3	607	7.9
February	1204	7.0	645	6.8	559	7.3
March	1386	8.1	623	6.5	763	10.0
April	1461	8.5	724	7.6	737	9.6
May	1412	8.2	679	7.1	733	9.6
June	1024	6.0	612	6.4	412	5.4
July	943	5.5	633	6.6	310	4.1
August	1223	7.1	854	9.0	369	4.8
September	1554	9.0	894	9.4	660	8.6
October	1741	10.1	1009	10.6	732	9.6
November	2003	11.7	1162	12.2	841	11.0
December	2039	11.9	1102	11.6	937	12.2
Day-of-week						
Sunday	701	4.1	112	1.2	589	7.7
Monday	3281	19.1	1880	19.7	1401	18.3
Tuesday	3310	19.3	1923	20.2	1387	18.1
Wednesday	3071	17.9	1789	18.8	1282	16.7
Thursday	2969	17.3	1822	19.1	1147	15.0
Friday	2603	15.1	1537	16.1	1066	13.9
Saturday	1263	7.3	475	5.0	788	10.3

[a] Clinical visit that resulted in an asthma diagnosis.
[b] Reported as N (%) unless otherwise specified.
[c] Reported as median and interquartile range.
[d] Census tract of child's residence, recorded at the time of the clinical visit.
[e] Complete case sample included in the modeling of vegetation measures, excluding observations with missing values for census-tract SES index and census-tract % non-Hispanic Black population.

exacerbations in Philadelphia are detailed in Supplementary Table A1. These findings indicate that grass/shrub coverage at larger buffer distances (2000m) was associated with a 10–12% reduction in asthma exacerbation incidence. However, tree canopy coverage was not consistently associated with lower asthma exacerbation incidence among children residing in Philadelphia.

Effect modification analyses (Fig. 1) revealed associations between greenspace measures (comparing the highest quartile to the lowest quartile) and asthma exacerbation incidence within strata of each studied air pollutant concentrations. Notably, daily maximum concentrations of NO_2 and SO_2 significantly modified the association between tree canopy coverage and asthma exacerbations (p for pairwise comparisons < 0.05). On days with high NO_2 concentrations (highest tertile), the highest quartile (vs. the lowest) of residential tree canopy coverage was associated with an 11% lower asthma exacerbation incidence (HR = 0.89, 95% CI = 0.77, 1.02; p for pairwise comparisons $<$ 0.01). Conversely, on days with low NO_2 concentrations, the highest quartile of tree canopy coverage was associated with an 15% higher

Table 2
Distribution of residential greenspace and air pollutants in Philadelphia.

	Mean (S.D.)	Range						
		Min	10p [a]	25p	50p	75p	95p	Max
Buffer-level residential greenspace								
Tree canopy coverage in 1000m buffer (%)	19.34 (11.67)	3.52	7.27	11.91	16.16	23.58	43.77	83.87
Grass/shrub coverage in 2000m buffer (%)	13.46 (3.51)	4.48	8.46	11.56	13.54	15.51	19.02	32.98
Census-tract residential greenspace								
Census-tract tree canopy coverage (%)	17.3 (11.56)	1.24	6.68	9.35	14.34	20.71	38.30	87.00
Census-tract grass/shrub coverage (%)	12.27 (5.78)	0.15	5.81	8.79	11.26	14.69	23.52	45.38
Ambient air pollutant concentrations								
Census-tract daily average PM2.5 ($\mu g/m^3$)	10.54 (5.45)	1.93	5.10	6.67	9.23	13.19	20.35	43.16
Census-tract daily 8-h maximum ozone ($\mu g/m^3$)	68.47 (28.53)	2.85	35.65	48.04	64.53	85.98	120.76	170.05
Nearest-monitor daily maximum NO_2 ($\mu g/m^3$)	54.9 (22.01)	3.01	28.2	38.73	52.64	69.00	92.9	164.69
Nearest-monitor daily maximum SO_2 ($\mu g/m^3$)	8.34 (8.23)	0	2.36	3.93	6.55	10.74	19.91	437.54

[a] p denotes percentile.

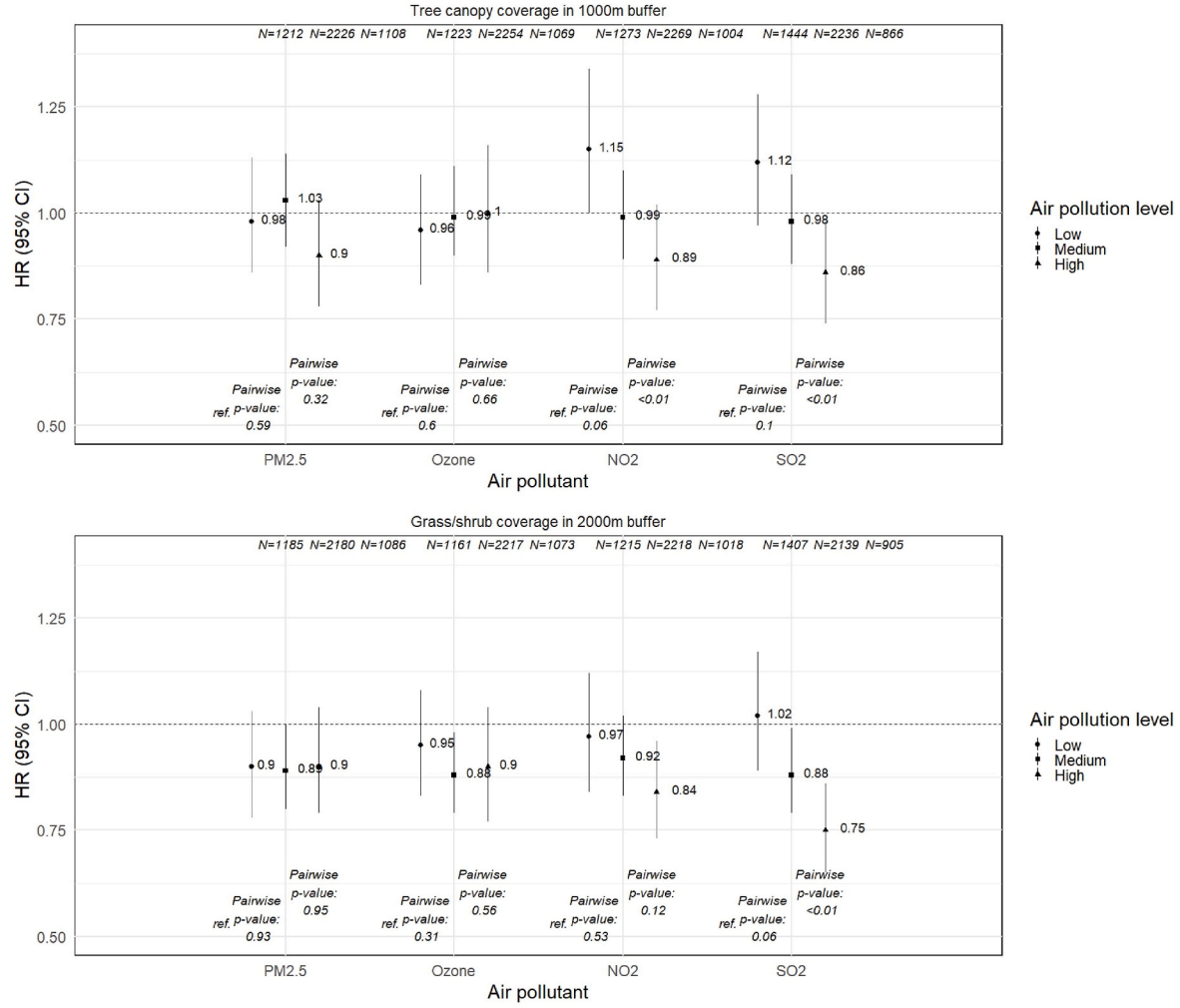

Fig. 1. Hazard ratio (HR) and 95% confidence interval (CI) [a] estimate of association of different greenspace measures with asthma exacerbation incidence (comparing greenspace levels in the highest-to lowest quartile category) stratified by air pollution concentrations among children living in Philadelphia.
[a] All associations adjusted for calendar month, day-of-week, child's age, sex, race/ethnicity, payment source for clinical visit, residential proximity to CHOP main campus, census-tract population density, census-tract SES index, census-tract non-Hispanic Black population, census-tract average dry-bulb temperature for the day (in whole degrees Fahrenheit), and total precipitation for the day (inches).
[b] N denotes numbers of events.
[c] p-value indicates the Wald test of the interaction term of greenspace measure and potential effect modifier.
[d] Based on AIC statistics, the most predictive buffer size for each greenspace measure concerning asthma exacerbation incidences were 1000m for tree canopy coverage and 2000m for grass/shrub coverage.

asthma exacerbation incidence (HR = 1.15, 95% CI = 1.00, 1.34). Similarly, on days with high SO_2 concentrations, children living in neighborhoods with the highest quartile of tree canopy coverage within 1000m of their homes had a 14% lower asthma exacerbation incidence compared to those in neighborhood with the lowest quartile of tree canopy coverage (HR = 0.86, 95% CI = 0.74, 0.98; p for pairwise comparisons < 0.01). In contrast, on days with low SO_2, higher tree canopy coverage was associated with higher asthma exacerbation incidence (HR = 1.12, 95% CI = 0.97, 1.28), Similar trends were observed for grass/shrub coverage in relation to the highest levels of NO_2 and SO_2, although statistically significant differences were only evident for SO_2 when comparing the interactions to the referent (p < 0.01).

Associations between asthma exacerbations and tree canopy or grass/shrub coverage did not appear to be significantly modified by $PM_{2.5}$ or ozone concentrations. However, an inverse relationship was observed between grass/shrub coverage and asthma exacerbation incidence at moderate ozone levels (HR = 0.88, 95% CI = 0.79, 0.98). Despite this observation, there was no statistical evidence of differences when comparing hazard ratio (HR) estimates for medium-pollutant days versus low-pollutant days (p > 0.05).

Table 3 summarizes the results of single-mediator and two-mediator analyses. Our findings provide no evidence that $PM_{2.5}$ or ozone mediates the association between greenspace and asthma exacerbations in either single- or two-mediator models. The indirect effects were not statistically significant, as indicated by confidence intervals that included one, suggesting the absence of statistically significant mediation effects.

4. Discussion

In our longitudinal study investigating the interplay between ambient air pollution and residential greenspace in relation to asthma exacerbation among children in Philadelphia, we made several noteworthy observations. First, we identified significant variations in the association between residential greenspace and the incidence of a child's first asthma exacerbation following diagnosis, depending on the ambient air pollution concentrations. Specifically, greenspace appeared to have a larger, or more significant negative association with asthma exacerbation in areas with higher concentrations of certain air pollutants, notably NO_2 and SO_2. Our study did not find evidence supporting mediation of the greenspace-asthma exacerbation relationship by ozone or $PM_{2.5}$ concentrations. This suggests that greenspace may have negative association with asthma exacerbation independently of its capacity to reduce air pollution concentrations or any potential mediation effects of air pollution on the association between greenspace and asthma exacerbations may be too subtle to detect in our analysis.

Our study demonstrated that higher levels of greenspace were associated with a lower incidence of first asthma exacerbation, particularly on days with elevated concentrations of NO_2 and SO_2. These findings align with a study by Alcock et al. in England, which reported the most substantial negative association between asthma hospitalizations and tree density in areas with elevated background concentrations of NO_2, SO_2, and $PM_{2.5}$ (Alcock et al., 2017). However, in our analysis, we did not observe the effect modification of greenspace associations by $PM_{2.5}$. This discrepancy may be attributed to the lower mean $PM_{2.5}$ concentrations in our study compared to those reported by Alcock et al., resulting in less pronounced effects of air pollution on the relationship between greenspace and asthma exacerbations. Our investigation generally found daily air pollutant concentrations below U.S. Environmental Protection Agency thresholds. For instance, the average daily $PM_{2.5}$ concentration in our study was 10.5 μg/m^3, below the EPA standard of 35 μg/m^3. Although ozone levels in Philadelphia frequently exceed regulatory limits, as noted by the Pennsylvania Department of Environmental Protection(DEP, 2015), the 95th percentile of daily 8-h maximum ozone concentrations in our study was 60.4 parts per billion (ppb) (120.8 μg/m^3), below the 70 ppb standard. Similarly, the average daily maximum concentrations of NO_2 (29.2 ppb, 54.9 μg/m^3) and SO_2 (3.2 ppb, 8.34 μg/m^3 were below their respective EPA threshold of 100 and 75 ppb(USEPA, 2006, 2010a, 2015, 2018) (Table 2). A key finding of our study was that NO_2 and SO_2 concentrations modified the associations between both grass/shrub and tree canopy coverage and asthma exacerbations. Specifically, on days with high SO_2 or NO_2 levels, grass/shrub and tree canopy coverage have negative association with asthma exacerbations. This expands upon the findings of Alcock et al., which primarily identified modifications related to trees. Our results suggest that various types of greenspaces, including grass and shrubs, may confer health benefits in the context of air pollution. These findings have implications for urban areas, where the availability of trees may be limited, and other types of greenspaces, such as grass and shrubs, are more prevalent. Recognizing the diverse contributions of different green space types may contribute to maximizing health benefits in urban environments.

Our results suggest an inverse relationship between greenspace and asthma exacerbations at moderate ozone levels, indicating a negative association between greenspace and asthma exacerbation under these conditions. This complexity may reflect the dual role of greenspace in influencing ozone dynamics: greenspace may reduce ozone levels by facilitating its deposition but can also contribute to ozone formation through the emission of biogenic volatile organic compounds(Eisenman et al., 2019a). This interplay highlights the multifaceted relationship between greenspace and ozone concentrations and underscores the importance of considering ozone's role as a potential modifier in the relationship between greenspace and children's respiratory health. The intricate mechanisms underlying this relationship warrant further investigation to better understand how greenspace may mitigate or exacerbate the impact of ozone on asthma outcomes.

Greenspace may improve asthma control through multiple

Table 3
Hazard ratio (HR) and 95% confidence interval (CI) [a] estimate of association of different greenspace measures with asthma exacerbation incidence (for interquartile-range increase in greenspace measure) mediated by air pollutants among children living in Philadelphia.

Mediators	Asthma exacerbation incidence	
	Census-tract tree canopy coverage (%)	Census-tract grass/shrub coverage (%)
Census-tract level daily average PM2.5 (μg/m^3)		
Total effect (Rte)	1.05 (0.78, 1.43)	0.71 (0.43, 1.23)
Pure natural direct effect (Rpnde)	1.05 (0.78, 1.43)	0.69 (0.42, 1.16)
Total natural indirect effect (Rtnie)	1.00 (0.97, 1.02)	1.03 (0.94, 1.19)
Proportion mediated (%) (pm)	−0.07	−0.07
Census-tract level daily 8-h maximum ozone (μg/m^3)		
Total effect (Rte)	1.05 (0.77, 1.41)	0.69 (0.41, 1.21)
Pure natural direct effect (Rpnde)	1.06 (0.78, 1.42)	0.69 (0.41, 1.19)
Total natural indirect effect (Rtnie)	0.99 (0.95, 1.02)	1.00 (0.95, 1.08)
Proportion mediated (%) (pm)	−0.30	−0.007
Census-tract level daily average PM2.5 and daily 8-h maximum ozone (μg/m^3)		
Total effect (Rte)	1.04 (0.78, 1.45)	0.71 (0.44, 1.23)
Pure natural direct effect (Rpnde)	1.06 (0.80, 1.48)	0.69 (0.42, 1.19)
Total natural indirect effect (Rtnie)	0.98 (0.94, 1.02)	1.03 (0.91, 1.20)
Proportion mediated (%) (pm)	−0.44	−0.07

[a] All associations adjusted for calendar month, day-of-week, child's age, sex, race/ethnicity, payment source for clinical visit, residential proximity to CHOP main campus, census-tract population density, census-tract SES index, and census-tract non-Hispanic Black population, census-tract average dry-bulb temperature for the day (in whole degrees Fahrenheit), and total precipitation for the day (inches).

mechanisms. The literature identifies three key domains of greenspace benefits—reducing harm, restoring capacities, and building capacities—which provide a framework for understanding its potential impact on respiratory health(Markevych et al., 2017; Triguero-Mas and Nieuwenhuijsen, 2021). These benefits are hypothesized to operate through reduced exposure to air pollution (reducing harm), stress alleviation (restoring capacities), and increased physical activity (building capacities). Additional pathways support these domains; for instance, improved sleep quality may restore capacities by reducing stress, while exposure to phytoncides may simultaneously reduce harm, restore capacities, and build capacities, contributing to overall health and well-being.

This study primarily focuses on examining the effects of air pollution reduction and stress alleviation on respiratory health, as well as their potential interplay. We propose that air pollution concentrations may modify the relationship between residential greenspace and asthma exacerbations by influencing the greenspace–airway inflammation pathway. While greenspace has been linked to stress reduction and inflammation alleviation(Zhang et al., 2020), air pollution exacerbates asthma through specific inflammatory mechanisms, including changes in gene expression, excessive mucus production, and heightened airway inflammation(Altman et al., 2023). Both air pollution and greenspace affect respiratory physiological responses through overlapping inflammatory pathways associated with asthma exacerbations. Consequently, greenspace may mitigate inflammation-induced exacerbations, particularly in areas with elevated air pollution levels. This mitigation is likely mediated through greenspace's aesthetic and recreational benefits, which help buffer the stress and inflammatory responses triggered by air pollution exposure.

Air pollution may interact with pollen(Ouyang et al., 2016) to modify the relationship between greenspace and asthma exacerbations, adding complexity to this association. Experimental evidence suggests that higher ambient air pollution concentrations enhance the uptake or deposition of pollutants by greenspace(Nowak et al., 2006), potentially reducing interactions between air pollution and pollen. This suggests that greenspace may mitigate asthma exacerbations by diminishing the harmful effects of pollen. However, at lower air pollution levels, the capacity of trees and grass to remove pollutants may be insufficient, and the adverse effects of pollen could outweigh the benefits of greenspace. Conversely, as air pollution levels increase, greenspace may play a more critical role in reducing exposure to airborne pollutants. Therefore, the ability of greenspace in reducing exposure to airborne pollutants and creating a safer environment for asthmatic children may become increasingly evident in studies. Additionally, variations in climate conditions can influence the dynamics of particulate matter ($PM_{2.5}$) and gaseous pollutants. For instance, pollutants can deposit on leaves and plant surfaces, with high humidity or wet conditions facilitating the dissolution of soluble pollutants and their absorption by leaves (Burkhardt, 2010). These suggest local climate conditions may play a role in the degree to which greenspace could influence respiratory health.

We conducted causal mediation analysis to evaluate whether the negative association of greenspace and asthma exacerbation operates primarily through the reduction of ambient air pollution via deposition. Initially, our analyses independently examined $PM_{2.5}$ and ozone. However, experimental evidence suggests that interactions between PM mixtures and ozone can produce significantly elevated levels of highly reactive hydroxyl radicals, which are potent respiratory irritants (Valavanidis et al., 2009). To account for this interaction, we extended our mediation analyses to jointly evaluate $PM_{2.5}$ and ozone. Despite this, we did not find evidence that either pollutant, individually or in combination, mediated the association between greenspace and asthma exacerbations. These findings suggest that the negative association between greenspace and asthma outcomes may not primarily operate through the reduction of $PM_{2.5}$ or ozone concentrations. The absence of observed mediation effects may be due to air pollutant levels not reaching a critical threshold necessary to detect such dynamics or to the mismatch in spatial resolution between air pollution and green space data. As shown in Fig. A1, the weak correlations between these variables suggest that the coarser spatial granularity of air pollution data could obscure potential relationships, thereby limiting the ability to identify mediation effects. While we acknowledge this limitation, it warrants further investigation to better understand its impact on the observed relationships, as the failure to observe mediation may stem from imprecise exposure data rather than the absence of a true relationship. However, previous research (Huang et al., 2021) has demonstrated an association between $PM_{2.5}$ variability at this census-tract level and asthma exacerbations, indicating that $PM_{2.5}$ may still serve as a potential mediator for greenspace. Future research should incorporate finer-scale air pollution data to improve the accuracy of exposure assessments and better capture these interactions. Additionally, investigating mediation pathways in regions with higher air pollution levels could provide a more comprehensive understanding of these mechanisms. Finally, an in-depth analysis of the dose-response relationship between air pollution levels and the effects of greenspace on respiratory health outcomes could help identify critical thresholds at which air pollution becomes a significant mediator in these associations.

These findings underscore the role of greenspace in urban planning and public health, particularly for mitigating asthma exacerbations. Greenspace may play a role in mitigating asthma exacerbations, not only by reducing ambient air pollution but also by alleviating stress and potentially disrupting inflammation pathways, especially in areas with elevated air pollution levels, providing support for children with pre-existing respiratory conditions. The statistical interaction that we found between air pollution and greenspace suggests that urban design strategies that emphasize public health benefits could be tested and may be further developed for specific contexts: in low-pollution areas, selecting vegetation species that minimize allergenic exposure may balance health benefits, while in high-pollution environments, increasing greenspace coverage may buffer stressors and improve air quality. However, experimental work would be required to assess whether these approaches have hypothesized effects. Additionally, local climate dynamics, such as humidity and precipitation, should be considered when implementing greenspace interventions to seek to optimize their effectiveness for pollution mitigation and respiratory health.

Our study possesses several notable strengths. A primary strength is the use of individual-level clinical visit data for pediatric asthma patients, which allowed for objective identification of asthma exacerbation episodes. This approach enabled precise assessment of residential greenspace for each patient and measurement of air pollution levels near their residence on the day of each clinical visit. Furthermore, the dataset allowed us to account for a wide range of independent predictors and potential confounding factors at both the individual and neighborhood levels. This is important because residential segregation patterns in Philadelphia influences the relationships between greenspace and individual characteristics (e.g., race and insurance status(De Roos et al., 2022) and other neighborhood factors (e.g., census-tract SES) among patients at the Children's Hospital of Philadelphia (CHOP). However, our study has limitations. By focusing on the time to the first exacerbation event as our outcome, we were unable to draw conclusions about how greenspace might influence the rate of asthma exacerbation over time within children. Additionally, we acknowledge the limitation of using air pollution data with coarser spatial resolution compared to the finer-scale greenspace data. This resolution mismatch may have led to an underestimation of the modification effect of air pollution. Moreover, the use of a study cohort based on patient visits to a healthcare system introduces the possibility of selection bias. This implies that the study participants may not be entirely representative of the general population, and the study might not encompass the full spectrum of outcomes. To mitigate potential biases, we restricted the study population to children seeking regular care, excluding those with significant gaps in

care or limited interactions with the healthcare system. Additionally, we adjusted for factors such as Medicaid/sCHIP coverage and residential proximity to the CHOP main campus to account for variations in clinical care utilization. While these measures likely reduced bias, we recognize that these limitations may impact the generalizability of our findings to other pediatric populations in Philadelphia or metropolitan areas with different demographic and environmental characteristics. Thus, caution should be exercised when extrapolating our results to other settings or populations.

5. Conclusions

This study reinforces existing evidence that ambient air pollutants can modify the relationship between greenspace and asthma exacerbations. It highlights a larger, or more significant negative association with asthma exacerbation among pediatric asthma patients in Philadelphia, particularly during periods of elevated air pollution levels. Increasing access to greenspaces, especially in areas with high concentrations of gaseous air pollution, could provide benefits for children with asthma. However, the precise mechanism underlying this negative association with asthma exacerbation remains unclear. Further research is needed to better understand how greenspace influences respiratory health in pediatric populations. Improved spatial resolution of air pollution measures could enhance the precision of future studies. Additionally, longitudinal and individual-level studies are warranted to explore the potential mediating roles of multiple air pollutants and other factors, such as mental restoration and pollen generation. The complexity of these interactions underscores the multifaceted nature of greenspace's negative association with asthma exacerbation. Air pollutants, stress reductions, and other potential mediators likely contribute collectively to the observed outcomes. Thorough examination of these dynamics could elucidate how these factors interact and inform targeted interventions to optimize the health benefits of greenspace for pediatric asthma patients.

CRediT authorship contribution statement

Yun-Ting Yen: Writing – review & editing, Writing – original draft, Visualization, Software, Methodology, Formal analysis, Data curation, Conceptualization. **Leah H. Schinasi:** Writing – review & editing, Methodology, Data curation. **Brisa N. Sánchez:** Writing – review & editing, Methodology. **Steven Melly:** Writing – review & editing, Data curation. **Kari Moore:** Writing – review & editing, Data curation. **Christopher B. Forrest:** Writing – review & editing. **Chén C. Kenyon:** Writing – review & editing. **Michelle C. Kondo:** Writing – review & editing. **Anneclaire J. De Roos:** Writing – review & editing, Supervision, Methodology, Data curation, Conceptualization.

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

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