Air pollution, residential greenspace, and the risk of incident immune thrombocytopenic purpura: a prospective cohort study of 356,482 participants

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Abstract

This study investigated the associations of air pollution and residential greenspace with immune thrombocytopenic purpura (ITP) risk, along with their combined effects, in a cohort of 356,482 UK Biobank participants free of ITP at baseline. Ambient nitrogen dioxide (NO_2), nitrogen oxides (No_x), fine particulate matter ($PM_{2.5}$), coarse particulate matter with aerodynamic diameters ranging between 2.5 and 10 μm (Pm_{coarse}) and particulate matter with diameters of less than 10 μm (PM_{10}) exposures were estimated by land-use regression models and residential greenspace was calculated using land-use data, defined as the percentage of outdoor greenspace surrounding each participant's home location. The hazard ratios (HR) and 95% confidence intervals (CI) were estimated by using Cox proportional hazard models, and non-linear relationships were assessed using restricted cubic spline (RCS) curves. A total of 500 incident ITP cases were diagnosed during a median follow-up of 13.54 years. Long-term exposure to high ambient concentrations of $PM_{2.5}$ (HR=1.15, 95% CI: 1.04-1.28; *P*=0.007), NO_2 (HR=1.23, 95% CI: 1.10-1.37; $P=1.83\times10^{-4}$), and NO_x (HR=1.12, 95% CI: 1.03-1.21; *P*=0.011), as well as low residential greenspace (HR=0.77, 95% CI: 0.67-0.87; $P=7.96\times10^{-5}$), were associated with an increased risk of ITP. RCS curve revealed a non-linear relationship of PM_{10} and NO_x with ITP risk (*P* for non-linearity=0.003 for PM_{10} and =0.030 for NO_x). Participants with high air pollution and low residential greenspace had the highest risk of ITP, though no evidence of mediation or interaction effects were observed. In conclusion, long-term exposure to ambient $PM_{2.5}$, PM_{10}, NO_2 and NO_x may increase ITP risk, whereas residential greenspace may decrease this risk.

Introduction

Immune thrombocytopenic purpura (ITP), also described as idiopathic thrombocytopenic purpura, is an acquired autoimmune disease characterized by a decrease in platelet count due to excessive platelet destruction and/or impaired platelet production.[1] From 1966 to 2009, the global incidence of ITP in children ranged from 0.5 to 10.5 cases per 100,000 person-years, and in adults it ranged from 1.6 to 3.9 cases per 100,000 person-years, respectively.[2] Although the incidence of ITP was relatively low, it substantially impaired patients' quality of life and negatively affected their emotional well-being, social activities, work, and productivity.[3] Moreover, severe ITP can also lead to substantial bleeding, such as intracranial and gastrointestinal bleeding, increasing the risk of infection, thrombosis, and death.[4-6] Given the absence of a cure, current treatment strategies for ITP primarily focus on controlling the condition. Therefore, identifying modifiable risk factors is crucial for preventing this disease.

Emerging epidemiological studies have indicated that long-term exposure to ambient air pollution facilitated the occur-

rence of various autoimmune diseases such as rheumatoid arthritis, chronic obstructive pulmonary disease, multiple sclerosis, and inflammatory bowel disease.[7-10] *In vivo* and *in vitro* studies have also demonstrated that prolonged exposure to air pollution could trigger oxidative stress, induce inflammation, and disrupt immune regulatory pathways, thereby leading to the onset of autoimmune diseases.[11] However, studies on the relationship between air pollution and ITP have remained extremely limited. To date, only one matched case-control study from Taiwan reported that maternal exposure to particulate matter with diameters of less than 10 μM (PM_{10}) during pregnancy increased the risk of childhood ITP.[12] The association between air pollution and the risk of ITP in adults remains unknown.

Residential greenspace has been associated with various health outcomes by mitigating environmental hazards such as air pollution, noise and heat, as well as promoting physical activity and mental well-being.[13,14] Nevertheless, currently there is no evidence linking residential greenspace to the risk of incident ITP. Despite the spatial correlation between residential greenspace and air pollution, few studies have simultaneously considered residential greenspace and air pollution exposure and explored the potential mechanisms by which they influence outcomes.[15] In this study, we hypothesized that residential greenspace may influence ITP risk through multiple potential pathways: (i) as an independent protective factor; (ii) with air pollution acting as a mediator in the association between residential greenspace and ITP risk; or (iii) in synergy with air pollution to modify the overall ITP risk.

Collectively, this study aimed to utilize the UK Biobank (UKB) to investigate the individual or combined associations of long-term exposure to ambient air pollutants and residential greenspace with the risk of incident ITP.

Methods

Study design and population

UKB is a cohort study that enrolled approximately 0.5 million participants from 2006 to 2010.[16] Participants completed touchscreen questionnaires, physical measurements and provided biological samples.[17] Ethical approval was obtained from the North West Multi-center Research Ethics Committee, and detailed information on study design and data collection is available in the *Online Supplementary Appendix*.

Assessment of air pollution and residential greenspace

The concentrations of fine particulate matter ($PM_{2.5}$), coarse particulate matter with aerodynamic diameters ranging between 2.5 and 10 μm (PM_{coarse}), PM_{10}, nitrogen dioxide (NO_2), and nitrogen oxide (NO_x) were estimated by the UK Small Area Health Statistics Unit using land use regression (LUR) models.[18,19] Residential greenspace exposure for each participant was determined by calculating the percentage of greenspace within 300 m and 1,000 m buffers around their homes using the 2005 Generalized Land Use Database (GLUD) for England. Following Natural England's guideline for greenspace access within 300 m, this study focused mainly on the 300 m buffer (field ID: 24503).[20] Further information on the LUR models and greenspace assessments is provided in *Online Supplementary Appendix*.

Ascertainment of immune thrombocytopenic purpura

Incident ITP was defined by the International Classification of Diseases 10th Revision (ICD-10) code D69.3. Participants were followed from their initial visit to the assessment centers until the time of diagnosis of ITP, loss to follow-up, death, or the end of the follow-up (Oct 31, 2022), whichever came first.

Statistical analysis

Baseline characteristics were summarized as numbers (percentages) for categorical variables and as mean ± standard deviation (SD) or median ± interquartile range (IQR) for continuous variables. Pearson correlation analysis was used to explore the correlations of air pollutants with greenspace. The associations of environmental factors with ITP were evaluated using multivariable Cox proportional hazard models. The assumption of proportional hazards was tested using Schoenfeld residuals (*Online Supplementary Figure S2*). Covariates were selected based on biological plausibility and prior studies,[21-23] with details provided in *Online Supplementary Table S1*. Model A was adjusted for age and sex, and Model B was additionally adjusted for ethnicity, body mass index (BMI), education, household income, alcohol consumption, smoking, and physical activity. Non-linear dose-response relationships were explored using restricted cubic spline (RCS) models with three knots, selected based on Akaike Information Criterion.[24] Interactions between air pollutants and greenspace were assessed using multiplicative and additive models, and additive interactions were evaluated by relative excess risk due to interaction (RERI) and the attributable proportion due to interaction (AP).[25,26] Mediation analysis examined air pollution's role in greenspace and ITP associations. Details of interaction and mediation analysis are provided in the *Online Supplementary Appendix*.

We also conducted stratification analyses and sensitivity analyses excluding participants who developed ITP within the first year, resided at the same location for <10 years, or had prior diagnoses of other purpura and hemorrhagic conditions (ICD10: D69.0-D69.2, D69.4-D69.9). Analyses also incorporated residential greenspace buffer at 1,000 m (field ID: 24500) to examine broader residential greenspace coverage and ITP risk.

Two-sided *P* values of <0.05 were considered statistically significant, and all analyses were performed in R (v4.3.1) using the survival, interactionR, and regmedint packages.

Results

As shown in *Online Supplementary Figure S1*, a total of 356,482 participants free of ITP at baseline were included in this study. Table 1 presents the baseline characteristics of study participants. The mean age was 56.21 years (SD 8.08), and 52.5% (N=187,218) were female. The majority of the participants reported being previous or current consumers of alcohol (96.3%) and engaging in regular physical activity (71.5%). Over a median follow-up time of 13.54 years (4,711,602 person-years), 500 new-onset cases of ITP were identified. The median concentrations of ambient $PM_{2.5}$, PM_{coarse}, PM_{10}, NO_2, and NO_x were 9.92 μg/m^3 (IQR, 9.28-10.55), 6.10 μg/m^3 (IQR, 5.84-6.62), 16.02 μg/m^3 (IQR, 15.23-16.98), 26.04 μg/m^3 (IQR, 21.28-31.20), and 42.07 μg/m^3 (IQR, 34.04-50.64), respectively. Additionally, residential greenspace values were higher within a larger buffer. Specifically, within the 300 m and 1,000 m buffer, the median residential greenspace was 29.81% (IQR, 17.32-48.86) and 42.05% (IQR, 27.61-60.43), respectively. Strong correlations were observed for NO_2 and NO_x with $PM_{2.5}$ (r=0.87 for NO_2, r=0.85 for NO_x, respectively), and moderate correlations were found with PM_{10} (r=0.51 for NO_2, r=0.52 for NO_x, respectively). Residential greenspace buffers at 300 m and 1,000 m were highly correlated (r=0.85). Meanwhile, moderately negative correlations were observed for ambient $PM_{2.5}$, NO_2, NO_x with residential greenspace in different buffer sizes (Table 2).

Table 3 summarizes the associations between air pollutant concentrations, residential greensapce and the risk of incident ITP in multivariable-adjusted models. Per IQR increase in the concentrations of ambient $PM_{2.5}$ (HR=1.15,

Table 1. Baseline characteristics of participants from UK Biobank at baseline.

Characteristics	Total population
Sample, N	356,482
Age in years, mean ± SD	56.21±8.08
Sex, N (%)	
Male	169,264 (47.5)
Female	187,218 (52.5)
Alcohol drinking status, N (%)	
Never	13,250 (3.7)
Current/previous	343,232 (96.3)
Smoking status, N (%)	
Never	194,168 (54.5)
Current/previous	162,314 (45.5)
Physical activity, N (%)	
Irregular	101,556 (28.5)
Regular	254,926 (71.5)
BMI kg/m^2, mean ± SD	27.35±4.74
BMI kg/m^2, N (%)	
<30	271,965 (76.3)
>=30	84,517 (23.7)
Household income £, N (%)	
<31,000	170,344 (47.8)
>=31,000	186,138 (52.2)
Ethnicity, N (%)	
White	339,133 (95.1)
Others	17,349 (4.9)
Education level, N (%)	
Lower vocational qualifications or less	190,661 (53.5)
Higher vocational qualifications or more	165,821 (46.5)

BMI: body mass index; SD: standard deviation.

Table 2. Descriptive statistics and Pearson correlation matrix for pollutants and residential greenspace.

Exposure	Mean ± SD	Minimum	Maximum	Median	P25	P75	Pearson correlation coefficient						
							$PM_{2.5}$	PM_{coarse}	PM_{10}	NO_2	NO_x	Residential greenspace buffer at 300 m	Residential greenspace buffer at 1,000 m
$PM_{2.5}$ μg/m^3	9.98±1.05	8.17	21.31	9.92	9.28	10.55	1	0.22	0.54	0.87	0.85	-0.63	-0.64
PM_{coarse} μg/m^3	6.41±0.89	5.57	12.82	6.10	5.84	6.62	-	1	0.81	0.20	0.24	0.02	-0.01
PM_{10} μg/m^3	16.20±1.88	11.78	31.39	16.02	15.23	16.98	-	-	1	0.51	0.52	-0.41	-0.38
NO_2 μg/m^3	26.57±7.62	12.93	108.49	26.04	21.28	31.20	-	-	-	1	0.92	-0.64	-0.74
NO_x μg/m^3	43.82±15.48	19.74	265.94	42.07	34.04	50.64	-	-	-	-	1	-0.54	-0.57
Residential greenspace buffer at 300 m, %	35.51±23.31	0.28	99.18	29.81	17.32	48.86	-	-	-	-	-	1	0.85
Residential greenspace buffer at 1,000 m, %	45.32±21.68	4.49	99.19	42.05	27.61	60.43	-	-	-	-	-	-	1

P25 and P75 are 25th and 75th percentiles. IQR: interquartile range; NO_2: nitrogen dioxide; NO_x: nitrogen oxides; $PM_{2.5}$: fine particulate matter; PM_{coarse}: coarse particulate matter with aerodynamic diameters ranging between 2.5 and 10 μm; PM_{10}: particulate matter with diameters of less than 10 μm; SD: standard deviation.

Table 3. The associations between five air pollutants and residential greenspace buffer at 300 m with per interquartile range increase and the risk of immune thrombocytopenic purpura.

Exposure	Increment per IQR	Total	Events/person years	Model A		Model B	
				HR (95% CI)	*P*	HR (95%CI)	*P*
$PM_{2.5}$ μg/m³	1.27	356,482	500/4711,602	1.20 (1.09-1.33)	2.78×10^{-4}	1.15 (1.04-1.28)	0.007
PM_{coarse} μg/m³	0.78	356,482	500/4711,602	0.99 (0.92-1.07)	0.832	0.98 (0.91-1.06)	0.679
PM_{10} μg/m³	1.75	356,482	500/4711,602	1.06 (0.98-1.15)	0.124	1.04 (0.96-1.13)	0.300
NO_2 μg/m³	9.92	356,482	500/4711,602	1.27 (1.15-1.41)	5.37×10^{-6}	1.23 (1.10-1.37)	1.83×10^{-4}
NO_X μg/m³	16.60	356,482	500/4711,602	1.15 (1.06-1.25)	5.42×10^{-4}	1.12 (1.03-1.21)	0.011
Residential greenspace buffer at 300 m, %	31.54	356,482	500/4711,602	0.75 (0.66-0.85)	1.26×10^{-5}	0.77 (0.67-0.87)	7.96×10^{-5}

Model A: age and sex. Model B: age, sex, ethnicity, body mass index (BMI), education level, household income, smoking status, alcohol drinking status, and physical activity. CI: confidence intervals; HR: hazard ratio; IQR: interquartile range; NO_2: nitrogen dioxide; NO_x: nitrogen oxides; $PM_{2.5}$: fine particulate matter; PM_{coarse}: coarse particulate matter with aerodynamic diameters ranging between 2.5 and 10 μm; PM_{10}: particulate matter with diameters of less than 10 μm.

95% CI: 1.04-1.28; *P*= 0.007), NO_2 (HR=1.23, 95% CI: 1.10-1.37; $P=1.83\times10^{-4}$), and NO_x (HR=1.12, 95% CI: 1.03-1.21; *P*=0.011) were associated with an increased risk of incident ITP, while no statistically significant associations were observed for PM_{coarse} (HR=0.98, 95% CI: 0.91-1.06; *P*=0.679) and PM_{10} (HR=1.04, 95% CI: 0.96-1.13; *P*=0.300). Long-term exposure to residential greenspace buffer at 300 m was associated with a reduced risk of incident ITP, with each IQR increase in residential greenspace linked to a 23% (95% CI: 13-33; $P=7.96\times10^{-5}$) decrease in the risk of ITP. Similarly, using a wide-area residential greenspace buffer at 1,000 m showed a 24% (95% CI: 12-34; $P=2.54\times10^{-4}$) reduction in the risk of incident ITP (*Online Supplementary Table S2*). Consistent associations were also observed in the analysis of per 10 μg/m³ increase in air pollutant concentrations or per 10% increase in residential greenspace buffer at 300 m (*Online Supplementary Table S3*). Stratified analyses by age, sex, BMI, household income, alcohol drinking status and physical activity showed that none of the baseline characteristics significantly modified the associations of ambient air pollutants or residential greenspace buffer at 300 m with the risk of incident ITP (all *P* for heterogeneity >0.05) (*Online Supplementary Figure S3*). Additionally, a series of sensitivity analyses further supported the primary findings, reinforcing the robustness of the study (*Online Supplementary Tables S4-S6*).

Restricted cubic spline models were used to evaluate potential non-linear associations between these environmental factors and ITP risk (Figure 1). Statistically significant dose-response associations were found for $PM_{2.5}$, PM_{10}, NO_2, NO_x, and residential greenspace with ITP risk (all *P* for overall <0.05). Notably, PM_{10} and NO_x demonstrated non-linear associations with ITP risk (*P* for non-linearity=0.003 for PM_{10} and =0.030 for NO_x), with PM_{10} showing an inverted U-shaped curve and NO_x displaying a L-shaped curve, indicating potential differences in risk across different concentration levels.

To further investigate these non-linear associations, we categorized participants into quartiles based on their baseline PM_{10} and NO_x exposure levels. As shown in *Online Supplementary Table S7*, compared with participants in the lowest quartile of PM_{10} exposure group (Q1), those in the second (Q2), the third (Q3) and the highest exposure group (Q4) showed 1.46, 1.38 and 1.32-fold increased risk of ITP, respectively. Although the trend test did not reach statistical significance (*P* for trend =0.098), these quartile-based results suggest a concentration-specific risk pattern for PM_{10}. Similarly, for NO_x, participants in the third quartile (42.10-50.60 μg/m³) showed the strongest association with ITP risk (HR=1.54, 95% CI: 1.20-1.98; $P=7.29\times10^{-4}$) (*P* for trend =0.003).

We also observed that the risk of incident ITP exhibited a dose-response pattern in relation to the joint effects of air pollutants and the residential greenspace buffer at 300 m. As illustrated in Figure 2, the trend of increased risk of incident ITP persisted with higher air pollution levels or decreased residential greenspace (all *P* for trend <0.05). Compared to the reference group characterized by low air pollution concentrations and high residential greenspace buffer at 300 m, the group with high air pollution concentrations and low residential greenspace buffer at 300 m had an increased risk of incident ITP. Specifically, the risk of incident ITP increased by 44% (HR=1.44, 95% CI: 1.17-1.78; *P*=0.001), 36% (HR=1.36, 95% CI: 1.09-1.70; *P*=0.006), 56% (HR=1.56, 95% CI: 1.26-1.92; $P=3.01\times10^{-5}$), and 58% (HR=1.58, 95% CI: 1.28-1.95; $P=2.25\times10^{-5}$) in the groups with high concentrations of $PM_{2.5}$, PM_{10}, NO_2, and NO_x and low residential greenspace buffer at 300 m, respectively. However, we did not observe any statistically significant interaction between air pollution or residential greenspace and the risk of ITP (Table 4). The mediation analysis indicated that $PM_{2.5}$, PM_{10}, NO_2, and NO_x mediated 13.30%, -1.49%, 18.53%, and -0.18% of the association between residential greenspace and incident ITP, respectively. However, the natural indirect effects (NIE) were not statistically significant (Figure 3).

Discussion

In this study, we observed that long-term exposure to high ambient concentrations of $PM_{2.5}$, PM_{10}, NO_2, and NO_x, as well as lower residential greenspace, was associated with an increased risk of incident ITP. Furthermore, individuals with high air pollution concentrations and low residential greenspace coverage experienced the highest relative increase in ITP risk.

Scarce studies have explored the associations between air pollution and the risk of incident ITP. A case-control study involving 917,359 children from Taiwan revealed positive

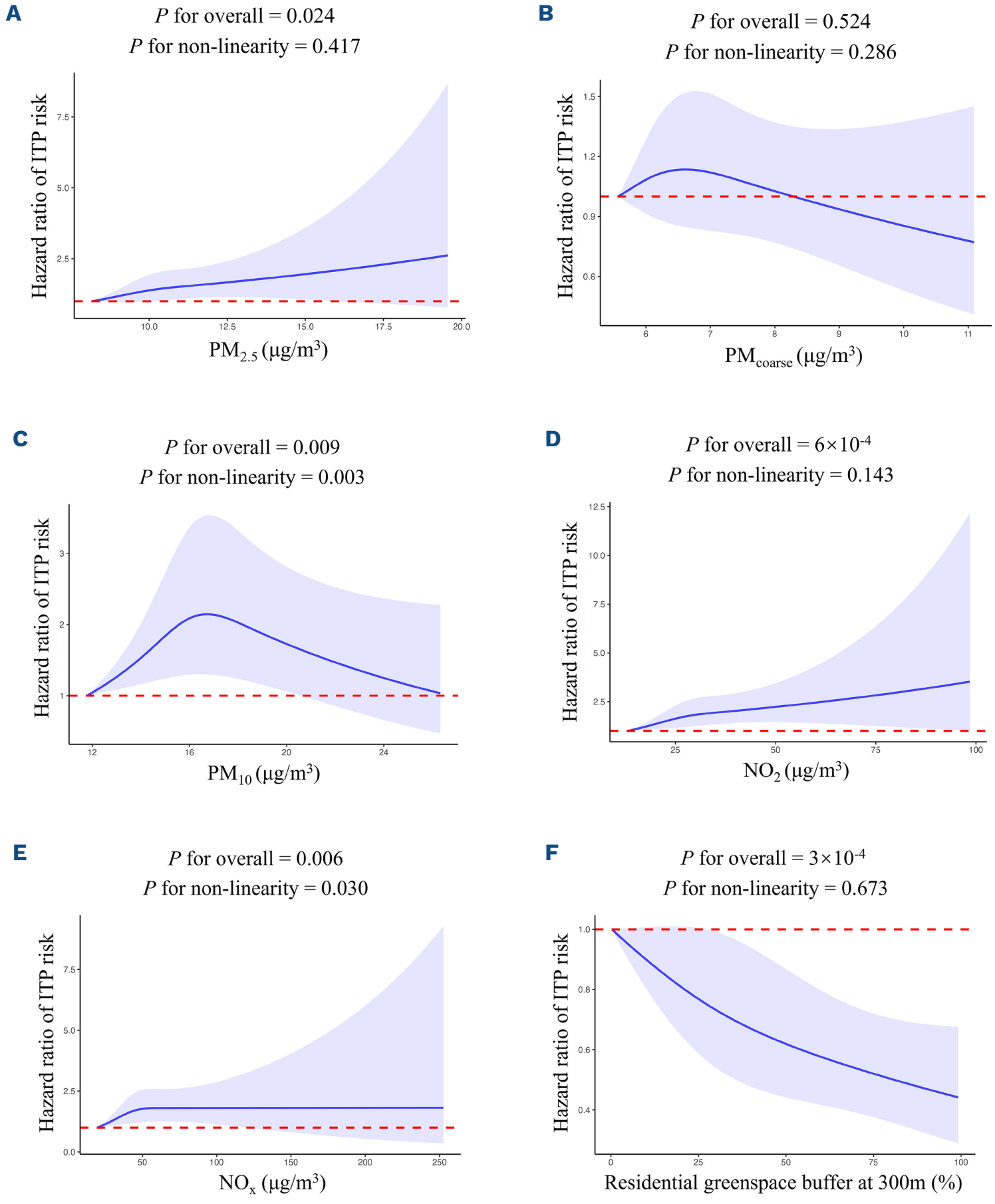

Figure 1. Dose response curves of associations between air pollutants and residential greenspace using restrict cubic splines. (A-F) The model adjusted for age, sex, ethnicity, body mass index, education level, household income, smoking status, alcohol drinking status, and physical activity. NO_2: nitrogen dioxide; NO_x: nitrogen oxides; $PM_{2.5}$: fine particulate matter; PM_{coarse}: coarse particulate matter with aerodynamic diameters ranging between 2.5 and 10 μm; PM_{10}: particulate matter with diameters of less than 10 μm.

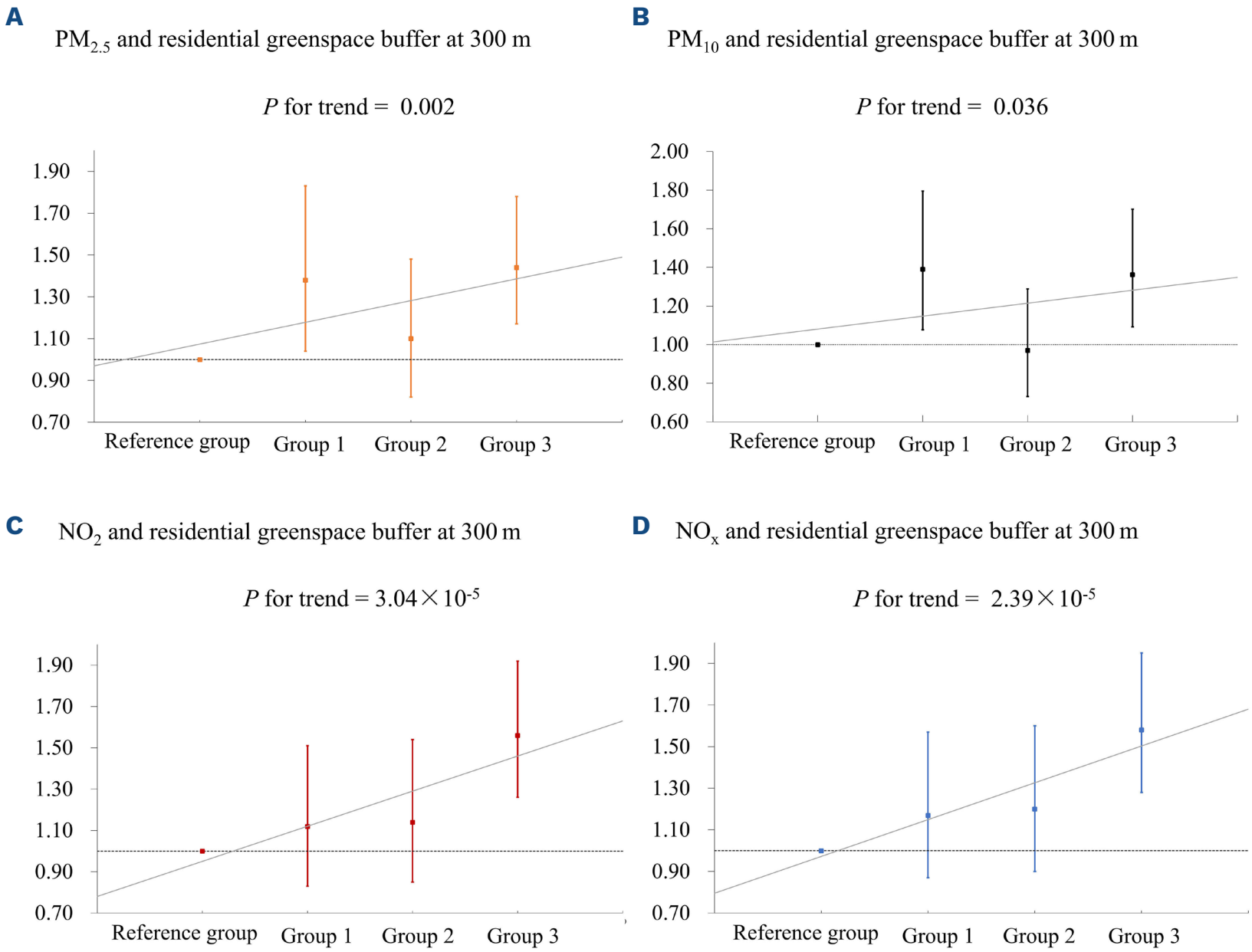

Figure 2. The joint effects between air pollution and residential greenspace buffer at 300 m on incident immune thrombocytopenic purpura. (A) $PM_{2.5}$ and residential greenspace buffer al 300 m. (B) PM_{10} and residential greenspace buffer at 300 m. (C) NO_2 and residential greenspace buffer at 300 m. (D) NO_x and residential greenspace buffer at 300 m. *Reference group: high residential greenspace buffer at 300 m and low air pollution; group 1: low residential greenspace buffer at 300 m and low air pollution; group 2: high residential greenspace buffer at 300 m and high air pollution; group 3: low residential greenspace buffer at 300 m and high air pollution. NO : nitrogen dioxide; NO_x: nitrogen oxides; $PM_{2.5}$: fine particulate matter; PM_{10}: particulate matter with diameters of less than 10 μm.

associations of prenatal exposure to PM_{10} (odds ratio [OR] =1.001, 95% CI: 1.000-1.002; *P*=0.039 per 10 μg/m^3) and the Pollution Standard Index (PSI) (OR= 1.016, 95% CI: 1.001-1.031; *P*=0.032) with the risk of childhood incident ITP.[12] Our study demonstrated that for per IQR increment, $PM_{2.5}$, NO_2, and NO_x were associated with a 15%, 23%, and 12% increased risk of incident ITP, respectively. For PM_{10}, we observed an inverted U-shaped relationship with ITP, with the most prominent effect observed in the second quartile (15.20-16.00 μg/m^3), where the risk of ITP increased by 46%. The second quartile appeared to be a critical concentration range where PM_{10} exerted its most significant impact on adult ITP risk. This nuanced relationship between PM_{10} and ITP might suggest that different biological mechanisms are triggered at varying levels of exposure. Notably, this critical concentration range falls below the World Health Organization guideline value for PM_{10} (20 μg/m^3), suggesting that PM_{10} may pose a considerable risk for ITP even at relatively low levels.[27] These findings underscore the importance of maintaining stringent air quality standards to mitigate potential health risks.

Previous studies have proposed potential mechanisms by which air pollution can trigger autoimmune diseases. Given the multiple immune dysregulations involved in ITP, such as abnormalities in various immune-related factors and effector cells, air pollution may induce ITP by stimulating chronic systemic inflammation and inducing oxidative stress through direct oxidation of proteins and lipids or activation of oxidative cell pathways.[28,29] Additionally, it might regulate the function and phenotype of dendritic cells, leading to an imbalance between dendritic cells and T cells. These mechanisms aligned with the observed abnormalities in precursor helper T cells, HLA-DR$^+$ T cells, and the elevated levels of soluble interleukin-2 receptors in ITP patients.[30,31]

Table 4. The interaction effects between air pollutants and the residential greenspace buffer at 300 m.

Air pollutant category#	Residential greenspace buffer at 300 m		
	Additive interaction		*Multiplicative interaction
	*RERI (95% CI)	*AP (95% CI)	
High $PM_{2.5}$ concentration	-0.04 (-0.53 to 0.46)	-0.03 (-0.37 to 0.32)	0.95 (0.64-1.42)
High PM_{10} concentration	0.002 (-0.43 to 0.44)	0.001 (-0.32 to 0.32)	1.01 (0.70-1.47)
High NO_2 concentration	0.30 (-0.17 to 0.76)	0.19 (-0.11 to 0.49)	1.22 (0.81-1.84)
High NO_x concentration	0.21 (-0.27 to 0.69)	0.13 (-0.17 to 0.43)	1.13 (0.75-1.69)

*The model adjusted for age, sex, ethnicity, body mass index (BMI), education level, household income, smoking status, alcohol drinking status, and physical activity. #Divided $PM_{2.5}$, PM_{10}, NO_2, and NO_x into low- and high-concentration groups based on their median values. AP: attributable proportion; CI: confidence interval; NO_2: nitrogen dioxide; NO_x: nitrogen oxides; $PM_{2.5}$: fine particulate matter; PM_{10}: particulate matter with diameters of less than 10 μm; RERI: relative excess risk due to interaction.

In addition to the negative association between residential greenspace buffer at 300 m and the risk of incident ITP, our analysis extended to a larger buffer at 1,000 m. As expected, we found a similar protective effect against incident ITP for both buffer sizes, suggesting that the extent of residential greenspace did not significantly impact its ability to mitigate the risk of incident ITP. Although previous studies have hinted at greenspace to potentially mediate the risk reduction related to reduced air pollution, our study did not find evidence supporting greenspace as a mediator in the associations between air pollution and the risk of ITP.[32,33] The mediation analysis in this study suggested that residential greenspace primarily reduced the risk of ITP through direct effects rather than through the mediating effects of air pollutants. This result underscored the value of increasing and maintaining greenspace in urban planning, particularly in densely populated areas with limited greenspace resources, providing a scientific foundation for enhancing residents' health. Furthermore, this study investigated the combined effects of air pollution and residential greenspace on incident ITP. The findings demonstrated an increased risk of incident ITP when air pollution levels were high and the residential greenspace was low, compared to the reference group. However, our study did not find any interaction between air pollution and residential greenspace.

To the best of our knowledge, our study is the inaugural large-scale prospective cohort investigation of the associations of air pollution and residential greenspace with the risk of ITP. However, several potential limitations warrant attention. Firstly, the measurements of certain air pollutant concentrations such as $PM_{2.5}$ and residential greenspace exposure were limited to a single baseline year, hindering the capture of dynamic changes before and after the baseline. We assumed that spatial patterns of air pollution exposure in the UK, a highly urbanized and industrialized country with slow-changing land use characteristics like greenspace, remained relatively stable over the years; however, exposure misclassification potential may still exist.[34,35] Secondly, the measurement data relied on participants' residential addresses, overlooking their activity patterns and residential mobility, which might not reflect their actual exposure levels. However, we performed a sensitivity analysis limited to participants who had resided in the same location for over 10 years, and the findings showed no substantial changes. Future cohort studies are encouraged to conduct multiple measurements of air pollution and residential greenspace across different times and locations to better understand their impact on the risk of incident ITP. Thirdly, the study was limited in its analysis of the associations between different types of greenspaces and the risk of incident ITP due to insufficient information about greenspace types, quality, and specific species from GLUD. Therefore, more advanced techniques and rigorous methods are needed for accurate measurement and characterization of greenspace. Fourthly, although stringent control of potential confounding factors in this study, the associations might be influenced by other unknown or unmeasured confounding factors. Lastly, our study's participant demographics were restricted to middle-aged and elderly individuals of European descent, which may introduce a bias in ITP prevalence estimates and limit generalizability to the broader UK population and other ethnicities and regions.

In this large-scale population-based cohort study, we observed positive associations between long-term exposure to high levels of air pollutants such as $PM_{2.5}$, PM_{10}, NO_2, and NO_x and an increased risk of incident ITP, while long-term exposure to high residential greenspace showed a negative association with ITP risk. Our research provided evidence for preventing ITP by improving environmental conditions, including increasing residential greenspace and mitigating air pollution. Further research is needed to delve deeper into the potential mechanisms between environmental factors and incident ITP.

Disclosures

No conflicts of interest to disclose.

Contributions

PL drafted the initial and subsequent versions of the manuscript. PL, FW and JY contributed to data verification and formal analysis. YM, KS and JT contributed to reviewing

and editing this study. All authors revised the manuscript for important intellectual content. PL, FW and YM had full access to the data and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript.

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Data-sharing statement

Data were accessed from https://www.ukbiobank.ac.uk. Data and code for this study are available from the correspondent authors upon reasonable request.

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