Article

Effects of greenness on preterm birth: A national longitudinal study of 3.7 million singleton births

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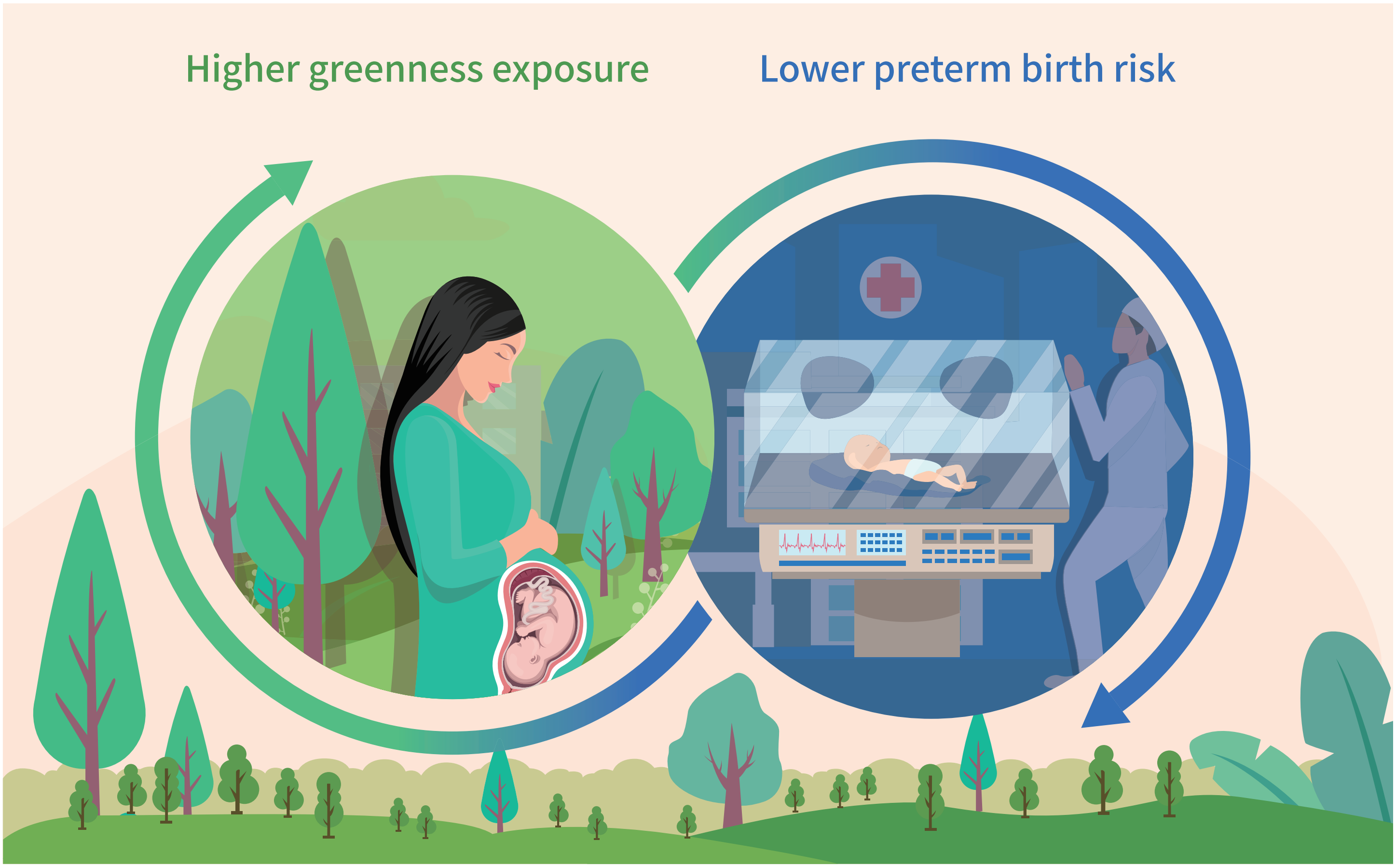
GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- A national study with 3.7 million births on greenness-PTB in China
- Higher greenness was associated with lower risks of PTB and its subcategories
- PTB of shorter gestational weeks may benefit more from greenness exposure

Effects of greenness on preterm birth: A national longitudinal study of 3.7 million singleton births

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Exposure to greenness may lead to a wide range of beneficial health outcomes. However, the effects of greenness on preterm birth (PTB) are inconsistent, and limited studies have focused on the subcategories of PTB. A total of 3,751,672 singleton births from a national birth cohort in mainland China were included in this study. Greenness was estimated using the satellite-based Normalized Difference Vegetation Index (NDVI) and Enhanced Vegetation Index with 500-m and 1,000-m buffers around participants' addresses. The subcategories of PTB (20–36 weeks) included extremely PTB (EPTB, 20–27 weeks), very PTB (VPTB, 28–31 week), and moderate-to-late PTB (MPTB, 32–36 weeks). Gestational age (GA) was included as another birth outcome. We used logistic regression models and multiple linear regression models to analyze these associations throughout the entire pregnancy. We found inverse associations between greenness and PTB and positive associations between greenness and GA. Specifically, an increase of 0.1 NDVI exposure within a 500-m buffer throughout the entire pregnancy was significantly associated with decreases in PTB (odds ratio [OR], 0.930; 95% confidence interval [CI], 0.927–0.932), EPTB (OR, 0.820; 95% CI, 0.801–0.839), VPTB (OR, 0.913; 95% CI, 0.908–0.919), MPTB (OR, 0.934; 95% CI, 0.931–0.936), and an increase in GA (β = 0.050; 95% CI, 0.049–0.051 weeks). These results suggest the potential protective effects of greenness on PTB and its subcategories: MPTB, VPTB, and EPTB in China.

INTRODUCTION

The World Health Organization (WHO) has stated that approximately 15 million preterm infants (20–36 weeks) are born worldwide every year.[1] Across 107 countries, China had the second highest number of preterm births (PTBs), behind India in 2014.[2] Among children under 5 years of age, the leading causes of death were complications from PTB, which led to nearly 1 million deaths (18% of all deaths) globally in 2015.[3] The incidence of PTB has been increasing over the past 30 years in China, which may be due to the assisted reproductive technology and the recent two-child policy launched in 2015.[4–6] Moreover, PTB is the leading risk factor for infectious or chronic diseases in early childhood as well as throughout the life course. Therefore, exploring effective interventions to reduce PTB risk could gain health benefits for public health.[2,3]

Recently, an increasing number of studies have indicated that greenness may lead to a wide range of beneficial health outcomes, such as those related to cardiovascular disease, mental health and birth weight.[7–14] Although some studies have reported a protective effect of greenness on birth weight, conclusions for the associations between greenness and PTB were inconsistent.[15–19] Some investigators have attempted to determine the association between greenness and PTB.[20–27] Most of the studies found no associations between greenness and PTB[15–19] and a few studies indicated an inverse association.[26,27] Currently, it remains unclear how greenness may benefit human health. Potential mechanisms include restoring the physiological or psychological health of mothers, based on the biophilia hypothesis; increasing the possibility of physical activity or social interaction; and decreasing exposure to concentrations of air pollutants in the environments.[28,29] Owing to the large burden of PTB and the current inconsistent conclusions between greenness and PTB, it is essential to understand whether there is a protective effect of greenness on PTB.

Previous studies mainly involved PTB, while limited studies focused on its subcategories.[15–19] The subcategories of PTB (20–36 weeks) are categorized as extremely PTB (EPTB, 20–27 weeks), very PTB (VPTB, 28–31 weeks), and moderate to late PTB (MPTB, 32–36 weeks).[1,30] There is a large gap in the survival rates of these subcategories, and EPTB and VPTB are more vulnerable than MPTB.[31] To our knowledge, only two studies, which were conducted in America[27] and Canada,[26] further explored the associations of the subcategories with exposure to greenness. However, their conclusions were inconsistent. Specifically, greenness was inversely associated with MPTB (<35 weeks) and VPTB (<30 weeks) in America, whereas it had no association with VPTB (<30 weeks) in Canada. Second, the majority of studies were conducted in developed countries, such as the United States, Canada, and several countries in Europe.[21,23,24,26,32–34] In Asia, a few studies were conducted in Israel[20,35] and Taiwan, China.[36] To date, little evidence exists on the associations between greenness and PTB in mainland China.[15–19] It is essential to evaluate such associations in China, as China had the second largest number of preterm infants worldwide, accounting for 7.8% of all global PTBs.[2] Third, few studies have been conducted on a national scale, and the aforementioned studies in Western countries were mostly conducted at a regional or city scale, such as the case of four Spanish birth cohorts.[22] Implementing national studies with uniform study designs may contribute more valid and certain results to the field.

Therefore, to explore whether higher exposure of greenness is associated with a decreased risk of PTB in mainland China, we conducted a national longitudinal study with 3.7 million singleton births. Moreover, we examined the associations between greenness and the subcategories of PTB (EPTB, VPTB, and MPTB).

METHODS

The birth cohort

The National Free Preconception Health Examination Project (NFPHEP) is a nationwide birth cohort throughout mainland China that started in 2010. It aims to provide free preconception health examinations and follow-up of participants' pregnancy outcomes. Participants of the NFPHEP cohort come from 31 provinces in China. Detailed information on this cohort has been provided elsewhere.[37] A total of 5,061,751 participants with singleton births from January 2010 to December 2015 were recruited into the NFPHEP. Informed consent was obtained from all participants. Mothers' examinations and follow-ups were conducted before, during, and after pregnancy. Participants who lacked information on maternal demographic characteristics, maternal socioeconomic status (SES), maternal lifestyles, fetal data and exposure data were excluded from our study (Figure S1). A total of 3,751,672 participants were included in the final analysis, and their locations are shown in Figure 1.

Greenness assessments

We used two satellite-derived vegetation indices, the Normalized Difference Vegetation Index (NDVI) and the Enhanced Vegetation Index (EVI), to evaluate participants' exposure levels to greenness by indicating the density of vegetation. These two vegetation indices (NDVI and EVI) were both extracted from Moderate Resolution Imaging Spectroradiometer (MODIS) aboard NASA's Terra satellite. The NDVI is a commonly used indicator in previous

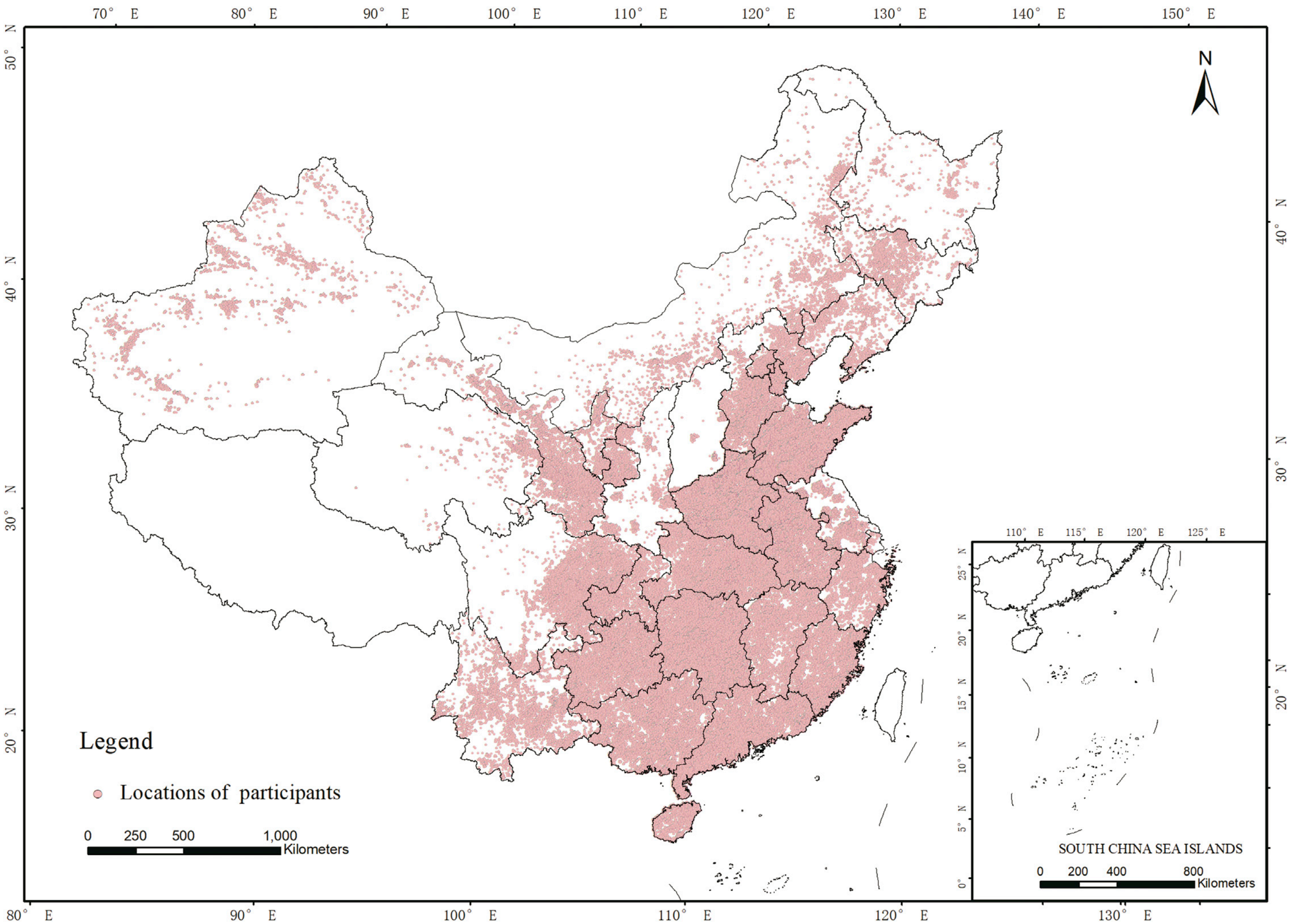

Figure 1. Geographic locations of participants in NFPHEP included in this study in China

studies, while EVI is recommended as an improved vegetation indicator based on the NDVI, which may better interpret the high density of vegetation and may eliminate part of the influence of residual aerosols in the atmosphere.[38] Therefore, we used both the EVI and the NDVI in this study so that we could compare our results with other studies and validate the robustness of our findings with different exposure metrics. The original NDVI and EVI data of MOD13Q1 at 250 × 250 m and 16-day spatiotemporal resolutions were downloaded from https://ladsweb.modaps.eosdis.nasa. These indices range from −1 to 1, which represent a high-density cover of vegetation with high positive values, bare land or water bodies with 0 or negative values. Negative values for water or snow cover were omitted. The maximum value composite method was used to reconstruct the maximum vegetation index during the entire pregnancy for each participant. One reason is that the max greenness indices are less influenced by the seasonal variation of vegetation and could better reflect the spatial distribution of green space,[39] so that the exposure levels to greenness are more comparable in different biogeographic regions. Another reason is that though Vegetation Index (including the NDVI and the EVI) data from MODIS (MOD13Q1) adjust to the effect of cloud cover to some extent, some pixels of the retrievals are still affected on the cloudiest days. Therefore, following the method to achieve the greenness exposure for the largest vegetation cover in previous studies,[22,39,40] we structured the max greenness indices during the entire pregnancy in this study.

In this study, we used the NDVI and the EVI within 500-m and 1,000-m buffers around participants' addresses during their pregnancy according to the dates of last menstruation and birth to estimate greenness exposure levels. This represented the average exposure of greenness surrounding the participant's home and a 10–15 min walking distance from their home, respectively.[9,12] We calculated the mean EVI and NDVI values for each participant every 16 days throughout their entire pregnancy within the 500-m and 1,000-m buffers respectively, to obtain the maximum NDVI ($NDVI_{max}$) and EVI (EVI_{max}) values for each participant.

PTB outcomes

According to the definition of the WHO, PTB is defined as gestational age (GA) from 20 and before 37 weeks. EPTB, VPTB, and MPTB are defined as GA from 20 through 27 weeks, 28 through 31 week, and 32 through 36 weeks, respectively.[1,30] The GA was typically calculated by weeks from the first day of the last menses to the birth date.

Covariate data

We selected priori confounders based on previous studies on the NFPHEP,[30] associations of greenness and PTB,[22,26] and associations of greenness and other health outcomes[40,41] in the fully-adjusted model. The directed acyclic graph was shown in Figure S2. The NFPHEP cohort provided a wide range of covariates of maternal and fetal information, including maternal demographic characteristics, maternal SES, maternal lifestyles during pregnancy, and fetal information. Maternal demographic characteristics included age (years, 5-year intervals from 16 to 50 years), body mass index (BMI, ≤18.5, 18.6–23.9, or ≥24, calculated as weight divided by height squared [kg/m^2]) before pregnancy, season of conception (spring, summer, autumn or winter) and parity (0, ≥1). Maternal SES included educational level (junior high school or below, senior high school or college/higher), occupation (workers, farmers or others), household registration (urban, rural), provincial gross domestic product (GDP, Yuan); maternal lifestyles included smoking (no/quit, yes), partner smoking (no/quit, yes), drinking (no/quit, yes), meat and eggs intake (no, yes), folacin intake (regular, no/unregular); and fetal information included the neonate's sex (male, female). We also assessed fine particulate matter ($PM_{2.5}$) and O_3 as potential influencing environmental factors for further sensitivity analyses.[26,29] We evaluated $PM_{2.5}$ concentrations throughout the entire pregnancy using a random forest model at 1 × 1 km and daily resolutions by incorporating $PM_{2.5}$ measurements, aerosol optical depth, and other predictors following a previously described methodology.[42] We evaluated O_3 concentrations using a similar approach.

Statistical analyses

First, generalized additive models were used to examine the associations between greenness and the risk of PTB and GA. The risk of preterm outcomes had an approximately linear relationship with $NDVI_{max}$ (Figure S3). Therefore, the main analyses were conducted using multiple linear regression and logistic regression analysis for the associations between greenness exposure and GA and PTB, respectively. The variance inflation factor values for the covariates used in the fully-adjusted models were all less than 2.

Sensitivity analyses were conducted to further examine the robustness of the results: (1) the fully adjusted model was further adjusted for $PM_{2.5}$ and O_3 to examine the robustness; (2) the model was adjusted for provincial GDP to test the stability considering the possible impact of economic levels on PTB; (3) the model was conducted by excluding multiparas and adverse pregnancy outcomes (including stillbirths, spontaneous and induced abortions) of mothers, respectively; (4) according to the definition of the subcategories of PTB in a Chinese national study,[5] the model followed a revised definition of preterm subcategories as very preterm (28–31 week), moderate preterm (32–33 weeks) and late preterm (34–36 weeks); (5) the model was also conducted within 250-m and 1,500-m buffers to examine the robustness; and (6) the model was conducted for the effect estimates on the associations between the $NDVI_{mean}$/EVI_{mean} and PTB, as well as GA within 500-m and 1,000-m buffers throughout the entire pregnancy in the sensitivity analysis.

Stratified analyses were conducted by maternal age, education, occupation, BMI before pregnancy, and household registration to explore the effect modifications between $NDVI_{max}$ and preterm outcomes within a 500-m buffer. These variables were stratified as maternal age (16–24 years, 25–29 years, and 30–50 years), educational levels (low, junior high school or below; middle, senior high school; and high, college/higher), occupation (farmer, worker, and others), BMI ($\leq$18.5, 18.6–23.9, and $\geq$24 kg/m^2), and household registration (rural and urban). Multiplicative interaction was assessed between greenness and the variables mentioned above. Moreover, we examined significant differences among the subgroups of the modifiers.[43,44]

RESULTS

Descriptive analyses

In this study, 3,751,672 singleton live births with GA between 20 and 45 weeks in mainland China were included in the analysis. Participants' descriptive characteristics are summarized in Table 1. A total of 290,361 newborns (7.7%) were PTB, and among them 2,370 (0.06%), 40,843 (1.1%), and 247,148 (6.6%) newborns were EPTB, VPTB, and MPTB, respectively. Among all participants who underwent preterm labor for all PTB subgroups, subjects were younger at conception (<20 years old [11.74%]), had a low educational level (junior high school or below [8.17%]), lived in rural areas (7.77%), were farmers (8.00%), were overweight before conception (8.40%), smoked (9.35%), had a partner who smoked (7.86%) and drank (9.17%) after conception, delivered a boy (8.11%), had at least one baby before conception (9.54%), did not eat meat or eggs (9.00%), and did not take or irregularly took folacin (8.13%). The spatial distribution of $NDVI_{max}$ for the participants included in this study during the entire pregnancy within a 500-m buffer around their addresses was shown in Figure S4. Throughout the entire pregnancy, subjects with preterm deliveries were exposed to lower greenness levels ($NDVI_{max\text{-}500m}$, 0.644) compared with those with full-term births ($NDVI_{max\text{-}500m}$, 0.657). The correlations for these exposure metrics, such as $NDVI_{max}$ and EVI_{max}, are presented in Table S1. The correlation was 0.94 between the $NDVI_{max}$ and the EVI_{max} throughout the entire pregnancy.

Main analyses

Table 2 presents the associations between $NDVI_{max}$ and EVI_{max} and preterm outcomes throughout the entire pregnancy within the 500-m and 1,000-m buffers, which were all statistically significant. Within the 500-m buffer, with a 0.1 increase in $NDVI_{max}$, the odds ratio (OR) and increment were 0.930 (95% confidence interval [CI], 0.927–0.932) and 0.050 weeks (95% CI, 0.049–0.051 weeks) in PTB and GA throughout the entire pregnancy, respectively. Specifically, the ORs were 0.820 (95% CI, 0.801–0.839), 0.913 (95% CI, 0.908–0.919), and 0.934 (95% CI, 0.931–0.936) for EPTB, VPTB, and MPTB per 0.1 increase in $NDVI_{max}$, respectively. In the 1,000-m buffer, the associations were still robust among PTB, EPTB, VPTB, MPTB, and GA throughout the entire pregnancy (Table 2).

With the assessments of EVI_{max} in the 500-m and 1,000-m buffers, the results also suggested inverse associations between PTB and its subcategories with greenness, which were slightly stronger than those of $NDVI_{max}$-PTB (Table 2). The trend of protective effects of greenness on the subcategories of PTB (EPTB, VPTB, and MPTB) was still robust.

Sensitivity analyses

The associations between greenness and PTB and GA were robust when further adjustments were made for air pollutants ($PM_{2.5}$ and O_3) and provincial GDP (Table 3). With the adjustments for air pollutants ($PM_{2.5}$ and O_3), the results showed little change. For example, after adjusting for $PM_{2.5}$ within the 500-m buffer, the OR and increment were 0.928 (95% CI, 0.926–0.931) and 0.053 weeks (95% CI, 0.052–0.054 weeks) in PTB and GA, respectively, corresponding with a 0.1 increase in $NDVI_{max}$ during the entire pregnancy. With the adjustment for GDP, the conclusion did not change. The results were still robust and slightly stronger when we excluded the multiparas (n = 1,040,120) and mothers with adverse pregnancy outcomes (n = 602,922, including stillbirths, spontaneous and induced abortions) in the fully adjusted models, respectively (Tables S2 and S3). When we redefined the subcategories of PTB, the effect estimates remained robust (Table S4). The results regarding greenness and PTB outcomes within 250-m and 1,500-m buffers were all statistically significant, and the comparison of effect estimates with different buffer sizes suggested that the effect estimates were slightly higher with larger buffers (Table S5). The relationship between effect estimates and buffer size may need to be further validated. The results on PTB and GA with the $NDVI_{mean}$/EVI_{mean} during the whole pregnancy were summarized in Table S6, which were still statistically significant.

Stratified analyses

The interactions of greenness with maternal age, education, occupation, BMI before pregnancy, and household registration were all statistically significant for the association between greenness and PTB and GA, respectively. The p values were all less than 0.001 for the interaction items of $NDVI_{max}$ and covariates when testing for interaction. The associations of greenness and PTB and GA among these subgroups of stratified analysis were all statistically significant (Figure 2). The protective effects of greenness on PTB tended to be stronger for mothers who had a lower educational level (junior high school or below, OR, 0.918; 95% CI, 0.915–0.921), were younger (16–24 years; OR, 0.920; 95% CI, 0.916–0.923) or older (30–50 years; OR, 0.929; 95% CI, 0.924–0.934), were farmers (OR, 0.918; 95% CI, 0.916–0.921), and who lived in rural areas (OR, 0.927; 95% CI, 0.925–0.929) (Figure 2). The trend was mostly consistent for GA.

DISCUSSION

In this nationwide birth cohort with 3,751,672 singleton births in China, we found protective effects of greenness exposure on PTB outcomes. These effects remained consistent for EPTB, VPTB, and MPTB. Moreover, the results suggested the possibility of increased protective effects of greenness on MPTB, VPTB, and EPTB in order of likelihood. Mothers of lower SES and older than 30 years or younger than 24 years were observed to benefit more from exposure to greenness.

When analyzing the entire pregnancy period, we observed a 7.0% decrease in risk of PTB and a 0.050-week increase in GA corresponding to a 0.1 increase in greenness ($NDVI_{max}$) within the 500-m buffer. Other studies also found protective effects of greenness on PTB,[26,27,32,36] but their effects were more modest in comparison with the findings from this study. For instance, a study with 3,753,799 singleton births reported a decrease of 2.3% in PTB per interquartile range (IQR; NDVI, 0.12) increase in greenness in a 500-m buffer during the entire pregnancy in California.[27] Other studies have shown no associations between greenness and PTB or GA.[21–23] One possible reason may be that most of the studies were conducted in the United States, Canada, and Europe, which are different from Asian countries in terms of geographical area and economic and cultural characteristics.[27] Other reasons might include different spatiotemporal resolutions of the original data for greenness assessments and different modeling approaches for estimates. Additionally, the greenness assessments in most of the aforementioned studies estimated greenness exposure by NDVI, whereas some suggested EVI was a better indicator of vegetation than the NDVI.[38] In our study, we also analyzed the associations between the EVI and PTB outcomes, which showed slightly stronger associations than did those with the NDVI. Moreover, the robust results of sensitive analyses, by excluding mothers of multiparas and mothers with adverse pregnancy outcomes, indicated the robust protection of greenness with PTB. Additional studies are still needed to further validate our conclusion.

Across the subcategories of PTB throughout the entire pregnancy, we found decreases of 18.0%, 8.7%, and 6.6% in the risks of EPTB, VPTB, and MPTB per

Table 1. Descriptive characteristics of participants in NFPHEP between term birth and PTB

Characteristic	No.(%) Term birth	PTB	P^a
No. of participants (N, %)	3,461,311 (92.26)	290,361 (7.74)	
GA (Mean ± SD)	39.38 ± 1.20	34.05 ± 2.39	<0.001
Age (years)			
16–19	21,181 (88.26)	2,818 (11.74)	<0.001
20–24	1,260,282 (91.98)	109,857 (8.02)	
25–29	1,588,218 (92.68)	125,450 (7.32)	
30–34	459,465 (91.90)	40,483 (8.10)	
35–39	109,100 (91.83)	9,712 (8.17)	
40–44	21,188 (91.73)	1,911 (8.27)	
45–50	1,877 (93.52)	130 (6.48)	
Household registration			
Rural	3,260,213 (92.23)	274,851 (7.77)	<0.001
Urban	201,093 (92.84)	15,510 (7.16)	
Education			
Junior high school or below	2,263,147 (91.83)	201,462 (8.17)	<0.001
Senior high school	708,001 (92.98)	53,422 (7.02)	
College or higher	490,138 (93.25)	35,477 (6.75)	
Occupation			
Farmer	2,619,301 (92.00)	227,814 (8.00)	<0.001
Worker	282,967 (92.83)	21,849 (7.17)	
Other	559,043 (93.21)	40,698 (6.79)	
Pre-pregnancy BMI (kg/m^2)			
≤18.5	492,899 (92.07)	42,428 (7.93)	<0.001
18.6–23.9	2,512,840 (92.42)	206,175 (7.58)	
≥24	455,572 (91.60)	41,758 (8.40)	
Maternal smoking after conception			
No or quit	3,450,778 (92.27)	289,275 (7.73)	<0.001
Yes	10,533 (90.65)	1,086 (9.35)	
Partner smoking after conception			
No or quit	2,898,223 (92.28)	242,305 (7.72)	<0.001
Yes	563,088 (92.14)	48,056 (7.86)	
Maternal drinking after conception			
No or quit	3,451,208 (92.26)	289,341 (7.74)	<0.001
Yes	10,103 (90.83)	1,020 (9.17)	
Meat and eggs			
No	37,490 (91.00)	3,706 (9.00)	<0.001
Yes	3,423,821 (92.27)	286,655 (7.73)	
Folacin			
Regular	1,237,576 (92.97)	93,547 (7.03)	<0.001
No or unregular	2,223,735 (91.87)	196,814 (8.13)	

Table 1. *Continued*

Characteristic	No.(%) Term birth	PTB	P^a
Season of conception			
Spring	909,796 (91.73)	81,974 (8.27)	<0.001
Summer	826,627 (92.84)	63,788 (7.16)	
Autumn	764,923 (93.10)	56,667 (6.90)	
Winter	959,965 (91.61)	87,932 (8.39)	
Neonate's sex			
Male	1806441 (91.89)	159,477 (8.11)	<0.001
Female	1654870 (92.67)	130,884 (7.33)	
Parity			
0	2,520,386 (92.95)	191,166 (7.05)	<0.001
≥1	940,925 (90.46)	99,195 (9.54)	
Exposures throughout the entire pregnancy (mean ± SD)			
$NDVI_{max\text{-}500m}$	0.657 ± 0.162	0.644 ± 0.167	<0.001
$NDVI_{max\text{-}1000m}$	0.663 ± 0.155	0.652 ± 0.160	<0.001
$EVI_{max\text{-}500m}$	0.473 ± 0.139	0.460 ± 0.141	<0.001
$EVI_{max\text{-}1000m}$	0.478 ± 0.133	0.466 ± 0.136	<0.001
$PM_{2.5}$ ($\mu g/m^3$)	54.725 ± 15.897	54.365 ± 17.504	<0.001
O_3 (ppb)	38.316 ± 4.571	38.692 ± 5.904	<0.001

Pre-pregnancy BMI, BMI in mothers before conception; $NDVI_{max\text{-}500m}$ ($EVI_{max\text{-}500m}$) and $NDVI_{max\text{-}1000m}$ ($EVI_{max\text{-}1000m}$) represented the max values of NDVI (EVI) throughout the entire pregnancy within 500-m and 1,000-m buffers, respectively.
[a]p values were calculated based on chi-squared test for categorical variables (age, household registration, education, occupation, pre-pregnancy BMI, maternal smoking after conception, partner smoking after conception, maternal drinking after conception, meat and eggs, folacin, season of conception, neonate's sex and parity) and t test for continuous variables (GA, $NDVI_{max\text{-}500m}$, $NDVI_{max\text{-}1000m}$, $EVI_{max\text{-}500m}$, $EVI_{max\text{-}1000m}$, $PM_{2.5}$, and O_3).

0.1 increase in greenness ($NDVI_{max}$) in China within the 500-m buffer, respectively. This finding suggests the possible highest effect estimate in EPTB (20–27 weeks), followed by VPTB (28–31 week), and MPTB (32–36 weeks). The study in California has suggested a similar trend throughout the entire pregnancy: decreases of 3.0% and 4.1% in MPTB (<35 weeks) and VPTB (<30 weeks) per IQR (NDVI, 0.11) increase in greenness in a 2,000-m buffer, respectively.[27] Not all studies showed the same trend. A cohort study with 64,705 singleton births has shown a decrease of 5% in MPTB (30–36 weeks) per IQR (NDVI, 0.1) increase in greenness in Vancouver, Canada, but this decrease was not significant for VPTB (<30 weeks) throughout the entire pregnancy.[26] EPTB and VPTB have a low incidence but are associated with greater challenges, whereas MPTB is more likely to occur (accounting for approximately 85% of total PTB), but is less dangerous.[2,31] A higher level of greenness might be an effective intervention for PTB, especially for VPTB and EPTB.

Our results suggest a stronger protective effect of greenness on PTB outcomes among mothers of lower SES and among older and younger mothers. In the stratified analyses, we found stronger associations between greenness and PTB outcomes among mothers who had a lower education level, were farmers, lived in rural areas, and were younger than 24 years of age. In China, most of these mothers were more likely to be of a lower SES. This finding suggests a stronger protective effect of greenness among the lower socioeconomic groups. Multiple studies on greenness-birth outcomes had a similar conclusion,[20–22] which also found higher protective effects of greenness in mothers among lower educational or income levels.[21,22] One potential explanation is that mothers with low socioeconomic levels may have less access to nutritional supplements or medical care sources during pregnancy.[45] Another possible explanation is that mothers with a lower SES may live in relatively polluted

Table 2. ORs and regression coefficients of PTB and GA for an increase of 0.1 $NDVI_{max}$/EVI_{max} within 500-m and 1,000-m buffers throughout the entire pregnancy

	Buffer 500-m		Buffer 1,000-m	
Outcome	**NDVI**	**EVI**	**NDVI**	**EVI**
PTB	0.930 (0.927– 0.932)	0.907 (0.905– 0.910)	0.926 (0.924– 0.928)	0.901 (0.898– 0.904)
EPTB	0.820 (0.801– 0.839)	0.745 (0.725– 0.766)	0.804 (0.785– 0.823)	0.722 (0.701– 0.743)
VPTB	0.913 (0.908– 0.919)	0.873 (0.867– 0.880)	0.908 (0.902– 0.913)	0.863 (0.857– 0.870)
MPTB	0.934 (0.931– 0.936)	0.915 (0.912– 0.918)	0.931 (0.928– 0.933)	0.910 (0.907– 0.913)
GA	0.050 (0.049– 0.051)	0.070 (0.068– 0.071)	0.055 (0.054– 0.056)	0.079 (0.077– 0.080)

The model was fully adjusted by $NDVI_{max}$/EVI_{max}, age, household registration, education, occupation, pre-pregnancy BMI, maternal smoking after conception, partner smoking after conception, maternal drinking after conception, meat and eggs, folacin, season of conception, neonate's sex, and parity.
Effect estimates are OR (95% CI) for PTB, EPTB, VPTB and MPTB, and β (95% CI) for GA.

environments.[29,46,47] Therefore, mothers with a lower SES might be more vulnerable and could gain more benefits from exposure to greenness.[22] A previous study including approximately 40.8 million population in England also indicated that greener environments might be a highly effective intervention strategy to address the inequality of mortality in deprived areas.[48] Additionally, our results indicate that not only younger mothers, but also mothers older than 30 years of age could benefit more from exposure to greenness. In China, maternal age has been increasing over the past years, which is an important risk factor for the increased rate of PTB.[4,49] Overall, our findings indicate that increasing accessible greenness around residential addresses might be an innovative and effective prevention to decrease the risk of PTB in China, especially for these susceptible groups of lower SES and higher ages.

One of the main causes of PTB in China was iatrogenic PTB.[6] This may be due to the potential risk of pregnancy complications among mothers of increasing childbearing age.[49] Other risk factors, such as the mental health of mothers and ambient air pollution, were also potential reasons for PTB.[4,5,50,51] Moreover, the policies for intervention in physical activity or diet also suggested effective protection on PTB in randomized trials.[49] Although the mechanisms of how the natural environment affects PTB remain unclear, there might be several possible pathways linking greenness to PTB.[28,29,52] First, the biophilia hypothesis indicates that humans are close to nature instinctively, which could enhance psychological or physiological restoration.[53,54] Increasing evidence suggests that poor maternal mental health during pregnancy may be related to an increased risk of PTB.[51,55] Previous studies indicated that pregnant women were more likely to have fewer depressive symptoms when exposed to greater greenness.[56,57] Therefore, greenness may be a protective environmental factor for maternal mental health, which may be indirectly associated with birth outcomes. Second, it is postulated that lower air pollution concentrations, more physical activity, and social interaction may be potentially pathways for greenness-human health.[28,29] Air pollution could induce inflammation and oxidative stress responses in mothers, which might increase the risk of PTB.[50,58,59] In this study, we further adjusted for air pollutants as potential confounders for the sensitivity analyses, which were consistent with results in other epidemiological studies.[26,29] Greenness could also provide an open green space, which could increase the possibility of physical activity or social interaction. These healthy lifestyles may be effective in preventing PTB.[49] Physical activity and social interaction were not measured in this study. Overall, these potential mechanisms are not yet well understood; hence, more studies are needed to further explore the mechanisms behind the association of greenness and PTB.

If the effects of this study hold, the potential gain in PTB with increasing greenness might be substantial globally. China has the second largest numbers of PTBs worldwide. Findings of this study might provide a new approach to

Table 3. The associations between $NDVI_{max}$/EVI_{max} and PTB and GA when further adjustments for $PM_{2.5}$, O_3 and GDP within 500-m and 1,000-m buffers throughout the entire pregnancy

		Buffer 500-m		Buffer 1,000-m	
Outcome	**Variables**	**NDVI**	**EVI**	**NDVI**	**EVI**
PTB	$PM_{2.5}$	0.928 (0.926– 0.931)	0.907 (0.904– 0.909)	0.925 (0.923– 0.927)	0.901 (0.898– 0.903)
	O_3	0.927 (0.925– 0.930)	0.902 (0.899– 0.904)	0.923 (0.921– 0.926)	0.894 (0.892– 0.897)
	GDP	0.929 (0.927– 0.931)	0.908 (0.905– 0.910)	0.925 (0.923– 0.928)	0.902 (0.899– 0.905)
EPTB	$PM_{2.5}$	0.812 (0.794– 0.831)	0.739 (0.719– 0.761)	0.797 (0.778– 0.816)	0.717 (0.696– 0.738)
	O_3	0.820 (0.801– 0.839)	0.744 (0.724– 0.766)	0.804 (0.785– 0.823)	0.720 (0.700– 0.742)
	GDP	0.820 (0.802– 0.839)	0.747 (0.726– 0.768)	0.804 (0.786– 0.823)	0.724 (0.703– 0.745)
VPTB	$PM_{2.5}$	0.910 (0.904– 0.915)	0.871 (0.865– 0.878)	0.904 (0.899– 0.910)	0.862 (0.856– 0.869)
	O_3	0.911 (0.906– 0.917)	0.868 (0.862– 0.874)	0.905 (0.899– 0.911)	0.857 (0.850– 0.863)
	GDP	0.916 (0.911– 0.922)	0.879 (0.873– 0.886)	0.911 (0.905– 0.917)	0.871 (0.865– 0.878)
MPTB	$PM_{2.5}$	0.933 (0.931– 0.936)	0.915 (0.912– 0.918)	0.930 (0.928– 0.933)	0.910 (0.907– 0.913)
	O_3	0.932 (0.929– 0.934)	0.910 (0.907– 0.912)	0.928 (0.926– 0.931)	0.903 (0.900– 0.906)
	GDP	0.933 (0.931– 0.936)	0.916 (0.913– 0.918)	0.930 (0.928– 0.933)	0.911 (0.908– 0.914)
GA	$PM_{2.5}$	0.053 (0.052– 0.054)	0.071 (0.069– 0.072)	0.058 (0.056– 0.059)	0.079 (0.077– 0.080)
	O_3	0.051 (0.049– 0.052)	0.072 (0.071– 0.074)	0.056 (0.055– 0.057)	0.082 (0.080– 0.084)
	GDP	0.051 (0.050– 0.052)	0.070 (0.068– 0.071)	0.056 (0.055– 0.058)	0.079 (0.077– 0.080)

Based on the main analyses, models were further adjusted by $PM_{2.5}$, O_3, and provincial GDP, respectively.
Effect estimates are OR (95% CI) for PTB, EPTB, VPTB and MPTB, and β (95% CI) for GA.

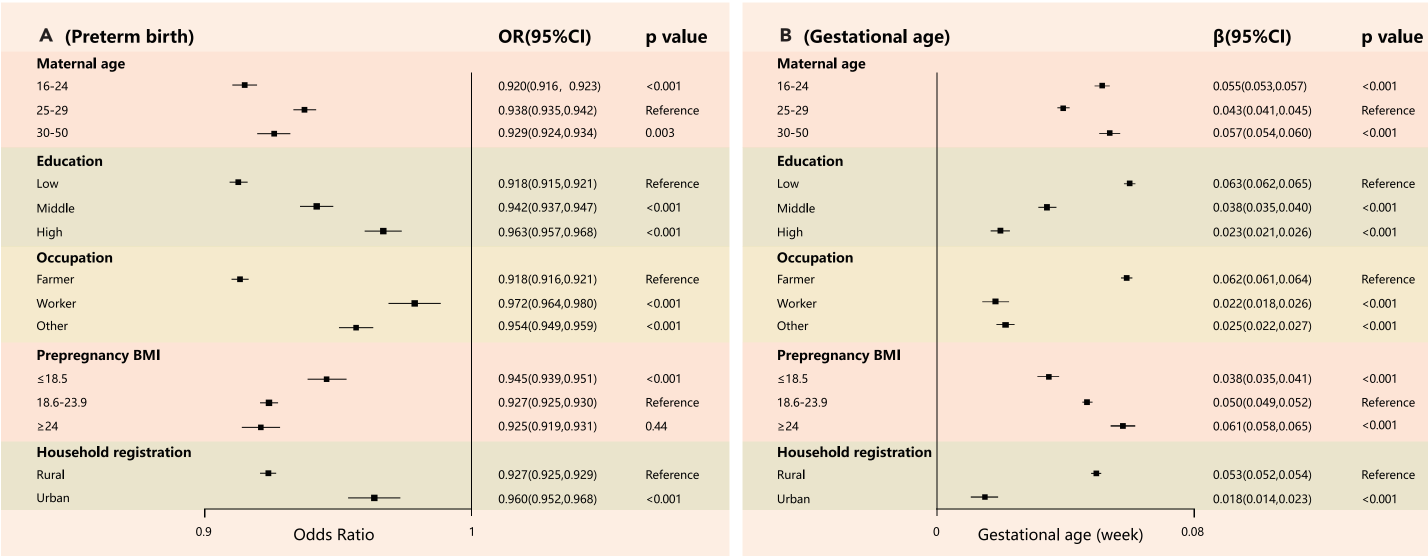

Figure 2. Stratified analyses for the associations of NDVImax within a 500-m buffer of addresses with PTB (A) and GA (B)

decrease the burden of PTB, particularly in low- and middle-income countries. Based on traditional medical efforts, such as improving the quality of pediatric care for mothers and neonates, an additional higher level of greenness exposure might further decrease the risk of PTB. This evidence-based strategy, planning for more greenness, might be a new actionable and cost-effective intervention to reduce PTB risk.

This study has some limitations. First, we assessed greenness according to participants' addresses, which may not reflect greenness exposure at their workplaces or other areas where they frequent. Second, we assumed that the mothers did not relocate throughout their pregnancy. Third, the NDVI was used to assess the greenness exposure, which may not reflect the details of greenness, such as the types (eg, forestland, grassland, farmland) or quality (eg, maintenance, safety, tidiness). Fourth, we did not adjust for other environmental confounders, such as noise or temperature. Fifth, participants in the NFPHEP cohort were not randomly selected; however, the proportion of PTB was 7.7% in the cohort, which was consistent with the national averaged incidence of PTB of 7%.[2,6,60] Moreover, our cohort of millions of participants, which was widely distributed across 31 provinces in China, should be representative of PTB in China. Sixth, although we conducted sensitivity analyses by excluding mothers with stillbirths, spontaneous abortions, and induced abortions and the results remained robust, we could not obtain other possible confounders of antepartum complications for mothers, such as gestational diabetes and pre-eclampsia. Therefore, more studies are in need to further validate our findings and explore the potential mechanisms behind the associations identified.

Conclusions

This national longitudinal study, including 3,751,672 singleton births, provides evidence of the protective effects of greenness on PTB in China. The protective effects varied in the subcategories of PTB, and the possible effect estimate was the highest for EPTB, followed by VPTB and MPTB. It suggested that PTB of fewer gestational weeks may benefit more from greenness exposure. Our results showed that mothers with a lower socioeconomic level and either older or younger were more susceptible to greenness exposure. Further studies are needed to validate our conclusions in different populations, cultures and settings. Our results might indicate an innovative and cost-effective strategy to reduce PTB risk, especially in developing countries.

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AUTHOR CONTRIBUTIONS

R.C., H.K., X.M., and Y.H. conceived this study. L.Z. and S.S. did formal analyses. Y.Y., J.X., S.W., and Y.Z. did investigations. C.L., W.W., Y.J., Y.Z., and S.S. provided analytical methods. Y.H., X.M., X.M., Q.W., H.S., Y.Z., D.Y., Z.P., R.C., and H.K. did supervision and project administration. L.Z. and S.S. wrote the draft manuscript, X.M., R.C., and Y.H. critically revised the manuscript. All authors reviewed and provided revisions for the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

SUPPLEMENTAL INFORMATION

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