Environment International 141 (2020) 105793

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

The associations of residential greenness with fetal growth in utero and birth weight: A birth cohort study in Beijing, China

Lizi Lin[a,h,1], Qin Li[a,b,1], Jie Yang[c], Na Han[c], Gongbo Chen[d], Chuyao Jin[a], Xiangrong Xu[a], Zheng Liu[a], Jue Liu[e], Shusheng Luo[a], Hein Raat[f], Yuming Guo[g], Haijun Wang[a,h,*]

[a] *Department of Maternal and Child Health, School of Public Health, Peking University, Beijing, People's Republic of China*
[b] *Reproductive Medical Centre, Department of Obstetrics and Gynaecology, Peking University Third Hospital, Beijing 100191, People's Republic of China*
[c] *Tongzhou Maternal and Child Health Hospital, Beijing 101101, People's Republic of China*
[d] *Department of Global Health, School of Health Sciences, Wuhan University, Wuhan 430071, People's Republic of China*
[e] *Department of Epidemiology and Biostatistics, School of Public Health, Peking University, Beijing 100191, People's Republic of China*
[f] *Department of Public Health, Erasmus University Medical Centre, Rotterdam, the Netherlands*
[g] *Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia*
[h] *National Health Commission Key Laboratory of Reproductive Health, Beijing, People's Republic of China*

ARTICLE INFO

Keywords:
Residential greenness
Environmental factors
Fetal growth
Birth weight

ABSTRACT

Background: Although studies have examined the association between residential greenness and birth weight, there is no evidence regarding the association between residential greenness and fetal growth in utero. We aimed to investigate the associations of residential greenness with both fetal growth in utero and birth weight.

Methods: A birth cohort (2014–2017) with 18,665 singleton pregnancies was established in Tongzhou Maternal and Child hospital of Beijing, China. Residential greenness was matched with maternal residential address and estimated from remote satellite data using normalized difference vegetation index with 200 m and 500 m buffers (NDVI-200 and NDVI-500). Fetal parameters including estimated fetal weight (EFW), abdominal circumference (AC), head circumference (HC) and femur length (FL) were assessed by ultrasound measurements during pregnancy. Fetal parameters were standardized as gestational-age- and gender-adjusted Z-score and undergrowth was defined as Z-score < -1.88. Birth weight Z-score, low birth weight (LBW) and small for gestational age (SGA) were assessed as birth outcomes. Generalized estimating equations with the autoregressive working correlation structure and generalized linear regression were used to examine the associations of residential greenness with quantitative and categorized outcomes.

Results: We found an increase Z-score of EFW [0.054, 95% confidence interval (CI): 0.020–0.087], AC (0.045, 95%CI: 0.011–0.080) and HC (0.054, 95%CI: 0.020–0.089) associated with residential greenness above NDVI-500 median compared to less than and equal to NDVI-500 median. Stratified analyses indicated that the associations might be stronger in women exposed to lower levels of particles with aerodynamic diameters ≤ 2.5 μm. No associations were found in the analyses of NDVI-250 with fetal growth in utero. We didn't observe significant associations of NDVI with birth weight Z-score, LBW and SGA.

Conclusions: This study identified a positive association of NDVI-500 and fetal growth in utero, but we didn't observe its association with birth weight measures. Our results suggest that building sufficient green infrastructure might potentially promote early life health.

1. Introduction

The urban population of the world has grown rapidly to 4.2 billion in 2018, and Asia, despite its relatively lower level of urbanization, is home to 54% of the world's urban population (Revision of World Urbanization Prospects, 2018). Urban areas are characterized by a network of man-made infrastructures with increased ambient air pollution and less greenspace (Dadvand et al., 2012a). In recent years, more and more studies have focused on the ability of residential greenness to promote the development of fetal growth and mitigate

---

[*] Corresponding author at: Department of Maternal and Child Health, School of Public Health, Peking University, No. 38 Xueyuan Rd, Haidian District, Beijing 100191, People's Republic of China.

E-mail address: whjun@pku.edu.cn (H. Wang).

[1] These authors contributed equally as first authors.

https://doi.org/10.1016/j.envint.2020.105793
Received 15 December 2019; Received in revised form 17 April 2020; Accepted 2 May 2020

adverse health effects of urban-related environmental hazards (Biodiversity and Health in the Face of Climate Change, 2019).

Residential greenness is thought to improve health through reducing exposure to air pollution or extreme temperatures, restoring mental health, enhancing social contacts and increasing physical activities (Markevych et al., 2017). In this context, residential greenness could improve maternal health with a healthier fetal environment during pregnancy. As a result, a growing body of studies has linked residential greenness with fetal growth using birth weight as an outcome, but there were inconsistent results in the previous studies (Dzhambov et al., 2014). Several studies indicated the positive association between residential greenness and birth weight (Agay-Shay et al., 2014, 2019, Cusack et al., 2017, 2018, Dadvand et al., 2012a, 2014; Ebisu et al., 2016; Fong et al., 2018; Hystad et al., 2014; Laurent et al., 2013, 2019; Markevych et al., 2014; Nieuwenhuijsen et al., 2019) while other studies indicated null associations (Cusack et al., 2018; Cusack et al., 2017; Dadvand et al., 2012b; Casey et al., 2016; Eriksson et al., 2019; Glazer et al., 2018; Abelt and McLafferty, 2017; Grazuleviciene et al., 2015). However, they were mostly conducted in western countries, and the associations between residential greenness and birth weight remained unclear in Asian countries where both rapid urbanization and high air pollutions were found.

Moreover, there is another gap in understanding the associations between residential greenness and fetal growth. Classifying newborns as growth-restricted at birth may lead to biased estimates because birth weight cannot adequately reflect dynamic growth patterns in utero during the whole pregnancy (Valero De Bernabe et al., 2004). Ultrasound measurement is one of the promising approaches to capture the fetal growth pattern in utero, which could be a better indicator than assessments at birth for explaining growth restriction related to environmental exposures during pregnancy (Smarr et al., 2013). However, to the best of our knowledge, there is no available epidemiological evidence regarding the association between residential greenness and fetal growth in utero using ultrasound measurement.

Meanwhile, the associations between residential greenness and health outcomes also depend on other influencing factors, such as socioeconomic status, gender, ethnicity or air pollution (Markevych et al., 2017). Therefore, assessment of effect modification is also necessary to better understand the relationships between residential greenness and fetal growth.

In this study, we investigated the associations of residential greenness with both fetal growth in utero and birth weight using a birth cohort in Tongzhou District, Beijing, China. We used normalized difference vegetation index (NDVI), a proxy of residential greenness, to investigate the association of residential greenness with fetal growth in utero and understand whether the associations persisted from pregnancy to birth. We also explored potential effect modification by other influencing factors.

2. Methods

2.1. Study design and participants

From January 1st, 2014 to December 31st, 2017, a birth cohort was established in Tongzhou Maternal and Child hospital in Beijing, China. We recruited all the pregnant women during their first prenatal visit to the hospital after their early pregnancy confirmation. Pregnant women were interviewed face-to-face by trained nurses in the first prenatal visit, and we collected their demographic information, socioeconomic characteristics, gynecological history and last menstrual period (LMP). If the woman had an irregular menstrual cycle, the obstetricians would re-check the LMP based on the report of the first ultrasound measurement, which was done for the confirmation of early pregnancy. The pregnant women were kept tracking for obstetric complications (gestational diabetes, gestational hypertension, etc.) and routine ultrasound measurements during the routine follow-up prenatal visits (20–24, 29–32 and 37–41 week). At the time of birth, birth information was collected including the date of birth, neonatal gender, and birth weight. Pregnant women were selected if: (1) LMP ranged from January 1st, 2014 to December 31st, 2017; (2) offering full information of residential address; (3) the current pregnancy was first pregnancy during the study period; (4) not diagnosed as diabetes, chronic hepatitis, hypertension, heart diseases or kidney diseases before pregnancy; (5) age ranged from 18 to 45 years. A total of 20,867 women were selected from the birth cohort. Women were excluded if: (1) the pregnancy ended in stillbirth or birth defects; (2) the gestational age (GA) $\geq$ 43 weeks; (3) no available ultrasound measurements at all the follow-up visits; (4) having unreasonable outlier of birth weight (absolute values of Z-score greater than 3.5) (Lunde et al., 2007)and (5) missing exposure of NDVI (described in exposure assessment). Finally, a total of 18,665 women were included in the study (Fig. S1). The study was approved by the Institutional Review Board of Peking University Health Science Center (No. IRB00001052-18008).

2.2. Outcome measurements

Abdominal circumference (AC), head circumference (HC) and femur length (FL) were obtained from routine ultrasound measurements. There were 13,243 (70.95%) participants with three scans, while 4812 (25.78%) and 610 (3.27%) participants had two scans and one scan during the pregnancy. These fetal parameters were used to calculate estimated fetal weight (EFW) based on the Hadlock's formula: $\log_{10}(\text{EFW}) = 1.326–0.00326*\text{AC}*\text{FL} + 0.0107*\text{HC} + 0.0438*\text{AC} + 0.158*\text{FL}$ (Hadlock et al., 1985). GA at the ultrasound measurement was calculated as the date of a measurement minus the date of LMP. The fetal parameters were measured at different GA. The use of GA- and gender-adjusted Z-score enabled comparison of effect estimates throughout different GA. The Generalized Additive Models for Location, Scale and Shape (GAMLSS) was used to generate Z-score for all the fetal parameters, which has been well applied in previous environmental studies (Hu et al., 2018a, 2018b; Peng et al., 2018). Assuming the distribution of each parameter depends on GA for different fetal gender, each parameter was modeled by a penalized spline of GA after the normalization of the parameters by using Box-Cox power exponential transformations. Z-score for all the fetal parameters at each GA was generated based on the best fitting models. We defined undergrowth of fetal parameters as Z-score < -1.88 ($<$ 3rd centile) (Zhao et al., 2018) based on the clinical consensus (Gordijn et al., 2016).

GA at birth was calculated as the date of birth minus the date of LMP. We calculated the GA- and gender-adjusted birth weight Z-score based on the same method described above. We defined low birth weight (LBW) as a birth weight of less than 2500 g. We defined small for gestational age (SGA) as birth weight below the 10th percentile for the GA based on the Chinese birth weight reference percentiles (Dai et al., 2014).

2.3. Residential greenness assessments

We used the NDVI as a proxy of residential greenness. The NDVI is estimated based on the 16-day composite images derived from the Terra Moderate Resolution Imaging Spectroradiometer (MODIS) satellite, which ranges from -1 to 1 with the higher numbers indicating more greenness. The datasets offer composite images of 250 m and 500 m buffer (NDVI-250 and NDVI-500) as the spatial resolution, which allows us to compare the results with the previous publications (Dadvand et al., 2012a; Laurent et al., 2019). We used the method described by Cusack et al. (2017) to estimate NDVI over the time interval of interest for each participant based on their resident address (Fig. S2). Estimates of NDVI were based on averaging composite images over the time interval of interest, with each image weighted based on the number of estimated pregnancy days covered by the image. We found that four participants (with seven scans) had more than two missing images (e.g., more than one month) during the time interval of interest, and they were excluded in the final analyses. The calculation of NDVI was shown in Appendix A.

2.4. Covariate assessments

We selected a range of covariates as potential confounders using directed acyclic graph method (Fig. S3) based on prior literatures (Dadvand et al., 2012a; Cusack et al., 2017; Dadvand et al., 2012b; Casey et al., 2016; Hystad et al., 2014; Fong et al., 2018; Laurent et al., 2019), including maternal age (< 35 years/≥ 35 years), ethnicity (Han/Minority), current employment (no/yes), maternal educational levels (low for uneducated participants, primary, secondary, and high school, middle for vocational college, and high for university and above), particles with aerodynamic diameters ≤ 2.5 μm ($PM_{2.5}$) and ambient temperature. We further included GA at birth and gender only in the analyses of LBW.

We estimated $PM_{2.5}$ over the time interval of interest for each participant using the random forest model with machine learning algorithms. The detail of the models was shown in Appendix B. In the analyses of fetal parameters, time-varying mean concentrations were calculated and averaged from the date of conception to the date of ultrasound measurement for each follow-up of participants. In the analyses of birth weight, mean concentrations over the whole pregnancy were calculated and averaged from the date of conception to the date of delivery for each participant. We obtained daily temperature during the study period from the National Oceanic and Atmospheric Administration (https://www.ncdc.noaa.gov/cdo-web/). The same approach as we did for $PM_{2.5}$ was used to assign average ambient temperature over the time interval of interest for each participant. Other individual covariates were obtained from the interviews at the first prenatal visit.

2.5. Statistical analyses

In the analyses of fetal parameters, we fitted generalized estimating equation (GEE) (Zeger and Liang, 1986) to handle repeated measurements within a subject using a first-order autoregressive correlation structure (AR1) to investigate the associations of NDVI and Z-score (using an identity link function), or the events of undergrowth (using a logit link function). In the analyses of birth weight, we analyzed continuous birth weight Z-score using linear regression and LBW/SGA using logistic regression. We built a crude model without adjusting for any covariate, while in the adjusted model, we adjusted for all the covariates. We used a spline function for ambient temperature to estimate the potential non-linear relationship between ambient temperature and fetal growth. We used Akaike's Information Criterion (AIC) to choose the degree of freedom for the spline (Li et al., 2016; Li et al., 2016). A smaller AIC value indicates the better model. Eventually, we used a spline with 4 degrees of freedom to control for temperature. The associations are presented corresponding as a continuous variable per 0.1 increase in NDVI or as a dichotomous variable with a cut-off at the median value ($\leq$median vs $>$ median). Analyses were performed with the data set restricted to complete cases of covariates (only 2.6% missing) while missing values in final models were not imputed.

Stratified analyses were performed to assess effect modification considering maternal education level, gender, ethnicity or $PM_{2.5}$ (dichotomized at the median and the 25th percentile of $PM_{2.5}$ level: 68.06 and 60.78 μg/m^3). We performed the Wald test for the interaction term between NDVI and these factors. Two sensitivity analyses were performed by re-running the models (a) on the sample of mothers without gestational diabetes ($n = 14,013$) and (b) on the sample of mothers without gestational hypertension ($n = 17,687$).

All statistical analyses were conducted with the statistical software R 3.6.1 (R Core Team 2019). A P value < 0.05 for a two-sided test was considered statistically significant.

Table 1
General characteristics of the birth cohort (N = 18,665).

	N (%)/Mean (SD)
Maternal Characteristics	
Year of conception	
2014	3952 (21.2%)
2015	5132 (27.5%)
2016	5818 (31.2%)
2017	3763 (20.2%)
Maternal age	
< 35 years	16,717 (89.6%)
≥35 years	1948 (10.4%)
Ethnicity	
Han	17,507 (93.8%)
Minority	1156 (6.2%)
Maternal education levels	
Low (primary, secondary, high school and uneducated)	4655 (25.2%)
Middle (junior college)	5686 (30.8%)
High (university and above)	8103 (43.9%)
Current employment	
No	2569 (14.0%)
Yes	15,831 (86.0%)
Parity	
Primapara	12,123 (65.0%)
Multipara	6542 (35.0%)
Birth Characteristics	
Gestational age (week)	39.23 (1.45)
Birth weight (gram)	3390.38 (450.64)
Proportion of boys	9544 (51.1%)
Prevalence of LBW	467 (2.5%)
Prevalence of SGA	1045 (5.6%)

Abbreviation: SD, Standard deviation; LBW, Low birth weight; SGA, small for gestational age.

3. Results

There were 18.665 women and their children in this birth cohort (Table 1). Most of the pregnant women were < 35 years (89.6%), Han ethnicity (93.8%), and had employment (86.0%). There were 43.9% of pregnant women with a high education level and 65.0% of them being primiparous. The mean GA and birth weight of the newborns were 39.23 ± 1.45 weeks and 3390.38 ± 450.64 g, and 51.1% of the newborns were boys. The prevalence of LBW and SGA were 2.5% and 5.6%.

The fetal parameters were measured by ultrasound at the mean GA of 23.22 ± 0.49, 30.12 ± 0.89 and 37.87 ± 1.10 weeks, respectively. Among the three measurements, the mean EFW were 612.94 ± 62.88, 1576.03 ± 192.87 and 3079.87 ± 358.15 with the Z-score of 0.06 ± 1.03, 0.04 ± 1.05 and 0.10 ± 1.07, respectively. The prevalence of EFW undergrowth among the three measurements were 2.6%, 3.2% and 3.2%, respectively. More details of the other fetal parameters were shown in Table 2.

The characteristics of residential greenness were presented (Table 3). The average NDVI-250 during the whole pregnancy ranged from 0.12 to 0.50 with mean of 0.26 ± 0.05 and IQR of 0.06. The average NDVI-500 during the whole pregnancy ranged from 0.10 to 0.57 with mean of 0.26 ± 0.06 and IQR of 0.08. The correlation between $PM_{2.5}$ (66.23 ± 7.54 μg/m^3) and NDVI-250 and NDVI-500 were -0.12 and -0.12 while the correlations between temperature (13.21 ± 3.16 °C) and NDVI-250 and NDVI-500 were 0.46 and 0.47.

The NDVI-500 was associated with fetal parameters (Table 4). We found an increase Z-score of EFW [0.054, 95% Confidence Interval (CI): 0.020–0.087], AC (0.045, 95%CI: 0.011–0.080) and HC (0.054, 95%CI: 0.020–0.089) associated with residential greenness above NDVI-500 median compared to less than and equal to NDVI-500 median. We didn't observe significant associations in the analyses of NDVI-250 Results were similar in all the sensitivity analyses of fetal parameters (Table S1).

The associations between NDVI and birth weight outcomes were less

Table 2
Characteristics of fetal growth in utero during pregnancy.

Fetal parameters	First time (n = 15081)	Second time (n = 16369)	Third time (n = 13596)
Gestational age at measurements, week	23.22 (0.49)	30.12 (0.89)	37.87 (1.10)
EFW$^{\alpha}$			
Original scale, g	612.94 (62.88)	1576.04 (192.90)	3079.79 (358.10)
Z-score$^{\beta}$	0.06 (1.03)	0.04 (1.05)	0.10 (1.07)
Undergrowth of EFW, % $^{\sigma}$	395 (2.6%)	523 (3.2%)	438 (3.2%)
AC			
Original scale, mm	190.80 (8.86)	264.00 (13.09)	336.29 (17.02)
Z-score$^{\beta}$	0.05 (1.03)	0.03 (1.04)	0.08 (1.05)
Undergrowth of AC, % $^{\sigma}$	402 (2.7%)	504 (3.1%)	435 (3.2%)
HC			
Original scale, mm	213.99 (8.03)	282.31 (10.37)	327.63 (11.04)
Z-score$^{\beta}$	0.06 (1.02)	0.02 (1.05)	0.07 (1.05)
Undergrowth of HC, % $^{\sigma}$	393 (2.6%)	488 (3.0%)	430 (3.2%)
FL			
Original scale, mm	41.20 (1.82)	57.07 (2.37)	69.62 (2.35)
Z-score$^{\beta}$	0.05 (1.02)	0.04 (1.05)	0.08 (1.05)
Undergrowth of FL, % $^{\sigma}$	323 (2.1%)	482 (2.9%)	425 (3.1%)

Abbreviation: AC, Abdominal circumference; EFW, Estimated fetal weight; FL, Femur length; HC, Head circumference.

$^{\alpha}$: EFW were calculated by the Hadlock's formula using AC, HC and FL: $\log_{10}(EFW) = 1.326–0.00326*AC*FL + 0.0107*HC + 0.0438*AC + 0.158*FL$.

$^{\beta}$: All fetal parameters were quantified as gestational-age- and gender-adjusted Z-score using the Generalized Additive Models for Location, Scale and Shape (GAMLSS).

$^{\sigma}$: Undergrowth was defined as Z-score < -1.88 ($<$ 3rd centile).

pronounced (Table 5). We didn't find significant results in the analyses in birth weight Z-score, LBW or SGA. Results were similar in all the sensitivity analyses of birth weight outcomes (Table S2).

We also explored the possible effect modification between NDVI-500 and fetal parameters (Table 6). We found a significant interaction between NDVI-500 and different levels of $PM_{2.5}$ exposure in the Z-score of EFW, AC and HC ($P_{\text{interaction}}$ = 0.003, 0.003 and 0.002). In women exposed to lower levels of $PM_{2.5}$ exposure ($<$ 68.06 μg/m^3), we found an increase Z-score of EFW (0.064, 95% CI: 0.026–0.101), AC (0.059, 95%CI: 0.021–0.097) and HC (0.064, 95%CI: 0.025–0.102) associated with residential greenness above NDVI-500 median compared to less than and equal to NDVI-500 median. In contrast, we didn't observe significant associations in the women exposed to higher levels of $PM_{2.5}$ exposure ($\geq$68.06 μg/m^3). We found a similar result when using the 25th percentiles of $PM_{2.5}$ (60.78 μg/m^3) as a cut-off (Table S3). We didn't find a significant interaction between NDVI and maternal education level, gender or ethnicity.

4. Discussion

To our knowledge, the study was the first in China to examine the associations between residential greenness and fetal growth in utero based on a birth cohort. The results showed that maternal exposure to a higher level of NDVI-500 was associated with increased Z-score of EFW, AC and HC, and the associations were stronger in women exposed to lower levels of $PM_{2.5}$. Moreover, we didn't observe consistent associations in the analyses of birth outcomes.

The NDVI was commonly used in epidemiology studies, which is easy to retrieve across different study areas and has been shown to be a valid and practical index to study associations between residential greenness and birth weight measures (Dadvand et al., 2012a; Cusack et al., 2017; Dadvand et al., 2012b; Casey et al., 2016; Hystad et al., 2014; Fong et al., 2018; Laurent et al., 2019). We are not able to compare our findings with others because there is no previous study on the associations of residential greenness and fetal growth in utero. The observed positive associations of NDIV-500 with fetal parameters in our study were in line with previous findings showing that the benefits of residential greenness in improving birth weight and head circumference at birth (Dadvand et al., 2012a; Hystad et al., 2014; Fong et al., 2018; Laurent et al., 2019). However, we only found significant results in NDVI with 500 m buffers but not 250 m buffers. A previous systematic review (Dzhambov et al., 2014)summarized that larger buffers (e.g., 500 m) had more pronounced results of improving birth weight (Dadvand et al., 2012a; Laurent et al., 2019), while smaller buffers (e.g., 250 m or 100 m) had inconsistent results (Hystad et al., 2014; Fong et al., 2018; Cusack et al., 2017; Dadvand et al., 2012b; Casey et al., 2016). There were several possible explanations for this observation. First, close-range exposure of residential greenness (e.g., window views) could reflect the benefits of psychological restoration and stress reduction, which might not be captured by using NDVI with smaller buffers in current resolution (Markevych et al., 2017). The use of better resolutions would allow better capturing the high variability and reducing the potential underestimation of residential greenness that occurred at small buffers (Gascon et al., 2016). Second, wider buffers reflected the potential social function of greenspace on recreational physical activity (Dzhambov et al., 2014). A previous study suggested that higher physical activity was associated with lower birth weight, but optimal physical activity during pregnancy might be beneficial to reduce the risk of having a large newborn without a change in the risk of having a small newborn (Wiebe et al., 2015). Therefore, further studies are needed to confirm the associations between residential greenness with wider buffers and the underlying pathology for growth restriction in utero.

Meanwhile, we found little evidence regarding the associations between NDVI and birth weight in different buffers. Several studies indicated similar null associations in the less green areas with lower values of NDVI (Cusack et al., 2018; Cusack et al., 2017; Dadvand et al., 2012b; Casey et al., 2016; Eriksson et al., 2019; Glazer et al., 2018; Abelt and McLafferty, 2017; Grazuleviciene et al., 2015). Moreover, a systematic review also indicated limited evidence regarding the associations between NDVI and birth weight (Dzhambov et al., 2014). The inconsistent results might be due to the variation in populations and design settings within different areas and countries. Another explanation for our findings was that the differential ecological environment and different vegetation patterns of the Tongzhou District compared to

Table 3
Distribution of the NDVI, $PM_{2.5}$ and temperature for the birth cohort.

Whole pregnancy	Mean (SD)	IQR	Distribution					Correlations			
			Min	25th	50th	75th	Max	NDVI-250	NDVI-500	$PM_{2.5}$	Temperature
NDVI-250	0.26 (0.05)	0.06	0.12	0.22	0.25	0.28	0.50	1	0.79	−0.12	0.46
NDVI-500	0.26 (0.06)	0.08	0.10	0.21	0.25	0.30	0.57	–	1	−0.12	0.47
$PM_{2.5}$ (μg/m^3)	66.23 (7.54)	21.58	48.23	60.78	68.06	71.89	89.87	–	–	1	−0.04
Temperature (°C)	13.21 (3.16)	5.96	3.87	10.34	12.73	16.29	21.21	–	–	–	1

Abbreviation: SD, Standard deviation; IQR, Interquartile range; NDVI, Normalized Difference Vegetation Index; $PM_{2.5}$: Particles with aerodynamic diameters $\leq$2.5 μm.

Table 4
Associations between residential greenness and fetal growth in utero.[α]

	NDVI with buffer of 250 m				NDVI with buffer of 500 m			
	Crude Model		Adjusted Model		Crude Model		Adjusted Model	
	Estimates/Odd ratios	*P*	Estimates/Odd ratios	*P*	Estimates/Odd ratios	*P*	Estimates/Odd ratios	*P*
EFW[β]								
Z-score								
Continuous variable	0.015 (−0.003, 0.033)	0.106	0.009 (−0.022, 0.040)	0.579	0.007 (−0.007, 0.021)	0.355	−0.003 (−0.028, 0.022)	0.798
NDVI > median	0.015 (−0.006, 0.036)	0.167	0.020 (−0.013, 0.052)	0.230	**0.026 (0.005, 0.048)**	**0.014**	**0.054 (0.020, 0.087)**	**0.002**
Undergrowth[σ]								
Continuous variable	0.988 (0.903, 1.081)	0.794	1.007 (0.864, 1.174)	0.924	1.003 (0.935, 1.076)	0.926	0.990 (0.873, 1.122)	0.873
NDVI > median	0.948 (0.845, 1.063)	0.360	0.983 (0.810, 1.194)	0.867	0.980 (0.873, 1.099)	0.726	0.872 (0.718, 1.058)	0.165
AC								
Z-score								
Continuous variable	**0.023 (0.005, 0.041)**	**0.014**	−0.001 (−0.032, 0.030)	0.964	0.013 (−0.001, 0.027)	0.059	−0.012 (−0.037, 0.013)	0.346
NDVI > median	**0.028 (0.007, 0.049)**	**0.010**	0.019 (−0.014, 0.053)	0.254	**0.033 (0.012, 0.054)**	**0.002**	**0.045 (0.011, 0.080)**	**0.009**
Undergrowth[σ]								
Continuous variable	0.980 (0.895, 1.074)	0.671	1.017 (0.864, 1.197)	0.840	0.985 (0.916, 1.059)	0.678	1.012 (0.889, 1.153)	0.852
NDVI > median	0.973 (0.867, 1.093)	0.648	0.989 (0.809, 1.208)	0.911	0.959 (0.855, 1.077)	0.484	0.937 (0.766, 1.147)	0.528
HC								
Z-score								
Continuous variable	0.016 (−0.002, 0.033)	0.084	0.019 (−0.011, 0.050)	0.206	0.001 (−0.012, 0.015)	0.857	−0.003 (−0.027, 0.022)	0.834
NDVI > median	0.010 (−0.011, 0.031)	0.355	0.016 (−0.016, 0.049)	0.328	0.018 (−0.003, 0.039)	0.098	**0.054 (0.020, 0.089)**	**0.002**
Undergrowth [σ]								
Continuous variable	1.001 (0.911, 1.100)	0.983	0.955 (0.804, 1.134)	0.600	1.027 (0.957, 1.103)	0.457	0.973 (0.849, 1.114)	0.688
NDVI ≥ median	1.018 (0.906, 1.143)	0.770	0.885 (0.726, 1.077)	0.223	1.034 (0.921, 1.162)	0.568	0.836 (0.681, 1.026)	0.087
FL								
Z-score								
Continuous variable	−0.013 (−0.030, 0.005)	0.161	0.011 (−0.018, 0.041)	0.448	−0.011 (−0.025, 0.002)	0.104	0.007 (−0.016, 0.031)	0.541
NDVI > median	**−0.021 (−0.042, −0.000)**	**0.045**	0.001 (−0.032, 0.034)	0.938	−0.003 (−0.024, 0.018)	0.774	0.024 (−0.010, 0.059)	0.168
Undergrowth [σ]								
Continuous variable	1.022 (0.936, 1.115)	0.635	0.951 (0.816, 1.108)	0.518	1.017 (0.949, 1.089)	0.632	0.909 (0.802, 1.031)	0.138
NDVI > median	1.058 (0.939, 1.192)	0.353	1.034 (0.848, 1.261)	0.743	1.036 (0.920, 1.166)	0.558	0.941 (0.770, 1.149)	0.548

Abbreviation: AC, Abdominal circumference; EFW, Estimated fetal weight; FL, Femur length; HC, Head circumference; NDVI, Normalized Difference Vegetation Index; Particles with aerodynamic diameters ≤2.5 μm.

[α] : The crude model adjusted for no covariates. The adjusted model adjusted for all the covariates including maternal age (< 35 years/≥35 years), ethnicity (Han/Minority), current employment (no/yes), maternal educational levels (low for primary, secondary, high school and uneducated participants, middle for junior college, and high for university and above), $PM_{2.5}$ and ambient temperature (a natural spline with 4 degrees of freedom).

[β] : EFW were calculated by the Hadlock's formula using AC, HC and FL: $\log_{10}(EFW) = 1.326–0.00326*AC*FL + 0.0107*HC + 0.0438*AC + 0.158*FL$.

[σ] : Undergrowth was defined as Z-score < -1.88 (< 3rd centile).

Table 5
Associations between residential greenness and birth weight outcomes.[α]

	NDVI with buffer of 250 m				NDVI with buffer of 500 m			
	Crude Model		Adjusted Model		Crude Model		Adjusted Model	
	Estimates/Odd ratios	*P*	Estimates/Odd ratios	*P*	Estimates/Odd ratios	*P*	Estimates/Odd ratios	*P*
Birth weight Z-score								
Continuous variable	0.022 (-0.008, 0.051)	0.146	−0.003 (-0.036, 0.031)	0.878	0.008 (-0.014, 0.030)	0.493	−0.011 (-0.037, 0.014)	0.383
NDVI > median	**0.040 (0.011, 0.069)**	**0.006**	0.023 (-0.009, 0.055)	0.164	0.021 (-0.007, 0.050)	0.145	−0.000 (-0.033, 0.033)	0.999
LBW								
Continuous variable	0.822 (0.649, 1.035)	0.099	0.792 (0.595, 1.047)	0.106	0.964 (0.807, 1.146)	0.678	0.964 (0.777, 1.188)	0.735
NDVI > median	0.873 (0.689, 1.105)	0.258	0.877 (0.665, 1.156)	0.351	0.978 (0.773, 1.238)	0.854	0.997 (0.754, 1.317)	0.982
SGA								
Continuous variable	1.020 (0.874, 1.186)	0.802	1.081 (0.907, 1.283)	0.381	1.076 (0.960, 1.204)	0.203	1.120 (0.983, 1.272)	0.086
NDVI > median	0.872 (0.751, 1.013)	0.073	0.877 (0.740, 1.039)	0.129	0.997 (0.859, 1.157)	0.967	1.015 (0.855, 1.203)	0.867

Abbreviation: LBW, low birth weight; NDVI, Normalized Difference Vegetation Index; $PM_{2.5}$, Particles with aerodynamic diameters ≤2.5 μm; SGA, small for gestational age.

[α] : The crude model adjusted for no covariates. The adjusted model adjusted for all the covariates including maternal age (< 35 years/≥35 years), ethnicity (Han/Minority), current employment (no/yes), maternal educational levels (low for primary, secondary, high school and uneducated participants, middle for junior college, and high for university and above), $PM_{2.5}$ and ambient temperature (a natural spline with 4 degrees of freedom). The adjusted model of LBW further adjusted for gestational age at birth and gender.

other study areas. For example, the range of NDVI values in our study indicated that there might be more shrubs and grassland in the study areas with less high trees (Gascon et al., 2016). The Tongzhou district is a new urban development zone, where woodlands were located in the southeastern area of the district (Dong et al., 2017) and most of the participants lived in the northwestern and intermediate areas of the district (shown in Fig. S2). The effect of residential greenness on birth weight might be more pronounced in high trees but not shrubs or grassland. Further studies are needed in different areas within different ecological zones in China to determine whether the associations

Table 6
The effect modification of different levels of PM$_{2.5}$ exposure on the associations between residential greenness and fetal growth in utero[α].

NDVI with buffer of 500 m	Different levels of PM$_{2.5}$ exposure				P interaction
	PM$_{2.5}$ ≤ median Estimates	P	PM$_{2.5}$ > median Estimates	P	
EFW Z-score[β]					
NDVI > median	**0.064 (0.026, 0.101)**	**0.001**	−0.020 (−0.056, 0.017)	0.287	**0.003**
AC Z-score					
NDVI > median	**0.059 (0.021, 0.097)**	**0.002**	−0.029 (−0.065, 0.006)	0.106	**0.003**
HC Z-score					
NDVI > median	**0.064 (0.025, 0.102)**	**0.001**	−0.018 (−0.054, 0.017)	0.318	**0.002**

Abbreviation: AC, Abdominal circumference; EFW, Estimated fetal weight; HC, Head circumference; NDVI, Normalized Difference Vegetation Index; Particles with aerodynamic diameters ≤ 2.5 μm.

[α] : The adjusted model adjusted for all the covariates including maternal age (< 35 years/≥35 years), ethnicity (Han/Minority), current employment (no/yes), maternal educational levels (low for primary, secondary, high school and uneducated participants, middle for junior college, and high for university and above), PM$_{2.5}$ and ambient temperature (a natural spline with 4 degrees of freedom).

[β] : EFW were calculated by the Hadlock's formula using AC, HC and FL: $\log_{10}(EFW) = 1.326–0.00326*AC*FL + 0.0107*HC + 0.0438*AC + 0.158*FL$.

between residential greenness and birth weight could be extrapolated.

The associations between NDVI-500 and the fetal parameters were robust in our study. Although the clinical interpretation of Z-score is not straightforward, we can still interpret our findings using absolute values. For example, the mean EFW of a 30-week male fetus is 1577.19 g with a Z-score of 0 and 1585.55 g with a Z-score of 0.054. Therefore, the increase of the Z-score of 0.054 was equal to a change of 8.36 g for this fetus, which was associated with residential greenness above NDVI-500 median compared to less than and equal to NDVI-500 median. However, the associations attenuated to null at birth, indicating that a catch-up growth of EFW might occur from late pregnancy to birth to compensate for the impairment during pregnancy. Restricted growth during pregnancy could still affect the children's long-term outcomes independent of birth weight (Henrichs et al., 2010; Jaddoe et al., 2014). More studies are needed to validate the greenness effect on fetal growth in utero in addition to birth weight.

The stratified analyses indicated that the associations of residential greenness with fetal parameters might be stronger in women who were exposed to lower levels of PM$_{2.5}$. A retrospective cohort in California didn't find a significant interaction between PM$_{2.5}$ and residential greenness on birth weight (Laurent et al., 2019). We did not find any study investigating the interaction between PM$_{2.5}$ and greenness on fetal growth in utero. Urban areas with high traffic density may interact with greenness to induce higher levels of air pollutants. For example, trees in urban street canyons can obstruct the wind flow, thereby simultaneously increasing on-road concentrations of air pollutants and overweighing the benefits of residential greenness (Vos et al., 2013). Given that limited evidence is available, further studies are needed to elucidate the effect modification of air pollution on the association between residential greenness and fetal growth.

There are some strengths of this study. This was the first study in China that both fetal growth in utero and birth weight measures were used. It is a true longitudinal study with several ultrasound measurements and a large sample size for clarifying the associations between residential greenness and fetal growth. However, the potential limitations of our study should be considered. First, we couldn't preclude the possibility of measurement errors due to the different measurement techniques between individual ultrasound technicians in the hospital. However, the hospital provides strict internal quality control and the technicians were required to follow the Chinese guideline to minimize the errors (Chinese Association of Ultrasound in Medicine and Engineering, 2012). Second, MODIS NDVI provides medium spatial resolution, but the good temporal resolution allowed us to estimate the time-varying residential greenness during the pregnancy. Third, we relied on addresses extracted from discharge records after delivery to generate residential greenness measures but did not have information on moving home during pregnancy. We couldn't preclude the possibility of exposure misclassification. However, the percentage of pregnant women who moved during pregnancy was very small in the view of the obstetricians in this hospital. Finally, we didn't collect detailed information on residential greenness, such as the specific types of vegetation or land cover, or the efficiency of the use of residential greenness.

5. Conclusions

In conclusion, the present birth cohort study in Beijing identified the positive association of NDVI-500 with fetal growth in utero, but we didn't observe its association with birth weight measures. The results support that residential greenness may have a beneficial impact on fetal growth in utero, and building sufficient green infrastructure might potentially promote early life health.

CRediT authorship contribution statement

Lizi Lin: Conceptualization, Methodology, Writing - original draft, Formal analysis. **Qin Li:** Conceptualization, Validation, Writing - original draft, Formal analysis. **Jie Yang:** Investigation, Resources, Writing - review & editing. **Na Han:** Investigation, Resources, Writing - review & editing. **Gongbo Chen:** Methodology, Software. **Chuyao Jin:** Investigation, Resources, Writing - review & editing. **Xiangrong Xu:** Investigation, Resources, Writing - review & editing. **Zheng Liu:** Investigation, Resources, Writing - review & editing. **Jue Liu:** Investigation, Resources, Writing - review & editing. **Shusheng Luo:** Investigation, Resources, Writing - review & editing. **Hein Raat:** Writing - review & editing. **Yuming Guo:** Methodology, Software. **Haijun Wang:** Supervision, Conceptualization, Project administration, Funding acquisition, Writing - review & editing.

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.

Acknowledgements

The present study was supported by the National Natural Science Foundation of China (Grant No. 81973053 and 81703240). Lizi Lin was supported by the China Scholarship Council for a one-year study at the Erasmus University Medical Centre, Rotterdam, The Netherlands.

Appendix. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2020.105793.

References

Abelt, K., McLafferty, S., 2017. Green streets: urban green and birth outcomes. Int. J. Environ. Res. Public Health [Electronic Resource] 14 (7), 13.

Agay-Shay, K., Peled, A., Crespo, A.V., et al., 2014. Green spaces and adverse pregnancy outcomes. Occup. Environ. Med. 71 (8), 562–569.

Agay-Shay, K., Michael, Y., Basagana, X., et al., 2019. Mean and variance of greenness and pregnancy outcomes in Tel Aviv during 2000–14: longitudinal and cross-sectional approaches. Int. J. Epidemiol. 48 (4), 1054–1072.

Biodiversity and Health in the Face of Climate Change. Springer Nature Switzerland AG, Switzerland, 2019.

Casey, J.A., James, P., Rudolph, K.E., Wu, C.D., Schwartz, B.S., 2016. Greenness and birth outcomes in a range of Pennsylvania communities. Int. J. Environ. Res. Public Health. 13 (3).

Chinese Association of Ultrasound in Medicine and Engineering, 2012. Guidelines of fetal ultrasound scan (Chinese association of ultrasound in medicine and engineering). Chin. J. Med. Ultrasound (Electronic Edition) 9 (7), 574–580.

Cusack, L., Larkin, A., Carozza, S., Hystad, P., 2017. Associations between residential greenness and birth outcomes across Texas. Environ. Res. 152, 88–95.

Cusack, L., Sbihi, H., Larkin, A., et al., 2018. Residential green space and pathways to term birth weight in the Canadian Healthy Infant Longitudinal Development (CHILD) Study. Int. J. Health Geographics 17 (1), 43.

Dadvand, P., Sunyer, J., Basagana, X., et al., 2012a. Surrounding greenness and pregnancy outcomes in four Spanish birth cohorts. Environ. Health Perspect. 120 (10), 1481–1487.

Dadvand, P., de Nazelle, A., Figueras, F., et al., 2012b. Green space, health inequality and pregnancy. Environ. Int. 40, 110–115.

Dadvand, P., Wright, J., Martinez, D., et al., 2014. Inequality, green spaces, and pregnant women: roles of ethnicity and individual and neighbourhood socioeconomic status. Environ. Int. 71, 101–108.

Dai, L., Deng, C., Li, Y., et al., 2014. Birth weight reference percentiles for Chinese. PLoS ONE 9 (8), e104779.

Dong, S.W., Li, H., Sun, D.F., 2017. Fractal Feature analysis and information extraction of woodlands based on MODIS NDVI time series. Sustainability-Basel 9 (7).

Dzhambov, A.M., Dimitrova, D.D., Dimitrakova, E.D., 2014. Association between residential greenness and birth weight: Systematic review and meta-analysis. Urban for Urban Gree. 13 (4), 621–629.

Ebisu, K., Holford, T.R., Bell, M.L., 2016. Association between greenness, urbanicity, and birth weight. Sci. Total Environ. 542 (Pt A), 750–756.

Eriksson, C., Lind, T., Ekstrom, S., et al., 2019. Neighbourhood greenness and birth outcomes in a Swedish birth cohort - A short communication. Health Place. 57, 200–203.

Fong, K.C., Kloog, I., Coull, B.A., et al., 2018. Residential greenness and birthweight in the state of Massachusetts, USA. Int. J. Environ. Res. Public Health. 15 (6).

Gascon, M., Cirach, M., Martinez, D., et al., 2016. Normalized difference vegetation index (NDVI) as a marker of surrounding greenness in epidemiological studies: the case of Barcelona city. Urban Urban Gree. 19, 88–94.

Glazer, K.B., Eliot, M.N., Danilack, V.A., et al., 2018. Residential green space and birth outcomes in a coastal setting. Environ. Res. 163, 97–107.

Gordijn, S.J., Beune, I.M., Thilaganathan, B., et al., 2016. Consensus definition of fetal growth restriction: a Delphi procedure. Ultrasound Obstet. Gynecol. 48 (3), 333–339.

Grazuleviciene, R., Danileviciute, A., Dedele, A., et al., 2015. Surrounding greenness, proximity to city parks and pregnancy outcomes in Kaunas cohort study. Int. J. Hyg. Environ. Health 218 (3), 358–365.

Hadlock, F.P., Harrist, R.B., Sharman, R.S., Deter, R.L., Park, S.K., 1985. Estimation of fetal weight with the use of head, body, and femur measurements - a prospective-study. Am. J. Obstet. Gynecol. 151 (3), 333–337.

Henrichs, J., Schenk, J.J., Barendregt, C.S., et al., 2010. Fetal growth from mid- to late pregnancy is associated with infant development: the Generation R Study. Dev. Med. Child Neurol. 52 (7), 644–651.

Hu, J., Wu, C., Zheng, T., et al., 2018a. Critical windows for associations between manganese exposure during pregnancy and size at birth: a longitudinal cohort study in Wuhan, China. Environ. Health Perspect. 126 (12), 127006.

Hu, J., Peng, Y., Zheng, T., et al., 2018b. Effects of trimester-specific exposure to vanadium on ultrasound measures of fetal growth and birth size: a longitudinal prospective prenatal cohort study. Lancet Planet Health. 2 (10), e427–e437.

Hystad, P., Davies, H.W., Frank, L., et al., 2014. Residential greenness and birth outcomes: evaluating the influence of spatially correlated built-environment factors. Environ. Health Perspect. 122 (10), 1095–1102.

Jaddoe, V.W.V., de Jonge, L.L., Hofman, A., Franco, O.H., Steegers, E.A.P., Gaillard, R., 2014. First trimester fetal growth restriction and cardiovascular risk factors in school age children: population based cohort study. Bmj-Brit Med J. 348.

Laurent, O., Wu, J., Li, L., Milesi, C., 2013. Green spaces and pregnancy outcomes in Southern California. Health Place. 24, 190–195.

Laurent, O., Benmarhnia, T., Milesi, C., et al., 2019. Relationships between greenness and low birth weight: investigating the interaction and mediation effects of air pollution. Environ Res. 175, 124–132.

Li, Q., Wang, H.-J., Song, Y., Ma, J., Song, J.-Y., Guo, Y., 2016. Association between children's forced vital capacity and long-term exposure to local ambient temperature in China: a national cross-sectional survey. Sci. Total Environ. 557–558, 880–887.

Li, Q., Guo, Y., Wei, D.-M., et al., 2016. Does local ambient temperature impact children's blood pressure? A Chinese National Survey. Environ. Health: Global Access Sci. Source 15, 21.

Lunde, A., Melve, K.K., Gjessing, H.K., Skjaerven, R., Irgens, L.M., 2007. Genetic and environmental influences on birth weight, birth length, head circumference, and gestational age by use of population-based parent-offspring data. Am. J. Epidemiol. 165 (7), 734–741.

Markevych, I., Fuertes, E., Tiesler, C.M.T., et al., 2014. Surrounding greenness and birth weight: results from the GINIplus and LISAplus birth cohorts in Munich. Health and Place. 26, 39–46.

Markevych, I., Schoierer, J., Hartig, T., et al., 2017. Exploring pathways linking greenspace to health: theoretical and methodological guidance. Environ. Res. 158, 301–317.

Nieuwenhuijsen, M.J., Agier, L., Basagana, X., et al., 2019. Influence of the urban exposome on birth weight. Environ. Health Perspect. 127 (4), 47007.

Peng, Y., Hu, J., Li, Y., et al., 2018. Exposure to chromium during pregnancy and longitudinally assessed fetal growth: findings from a prospective cohort. Environ Int. 121 (Pt 1), 375–382.

Revision of World Urbanization Prospects 2018. 2018. Accessed June 25, 2018.

Smarr, M.M., Vadillo-Ortega, F., Castillo-Castrejon, M., O'Neill, M.S., 2013. The use of ultrasound measurements in environmental epidemiological studies of air pollution and fetal growth. Curr. Opin. Pediatr. 25 (2), 240–246.

Valero De Bernabe, J., Soriano, T., Albaladejo, R., et al., 2004. Risk factors for low birth weight: a review. Eur. J. Obstet. Gynecol. Reprod. Biol. 116 (1), 3–15.

Vos, P.E., Maiheu, B., Vankerkom, J., Janssen, S., 2013. Improving local air quality in cities: to tree or not to tree? Environ. Pollut. 183, 113–122.

Wiebe, H.W., Boule, N.G., Chari, R., Davenport, M.H., 2015. The effect of supervised prenatal exercise on fetal growth: a meta-analysis. Obstet Gynecol. 125 (5), 1185–1194.

Zeger, S.L., Liang, K.Y., 1986. Longitudinal data analysis for discrete and continuous outcomes. Biometrics 42 (1), 121–130.

Zhao, N., Qiu, J., Ma, S., et al., 2018. Effects of prenatal exposure to ambient air pollutant PM10 on ultrasound-measured fetal growth. Int. J. Epidemiol. 47 (4), 1072–1081.