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Prenatal greenspace exposure and cord blood cortisol levels: A cross-sectional study in a middle-income country

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ABSTRACT

Exposure to greenspace has been associated with reduced stress; however, the available evidence on such an association for the fetus is still very scarce. We, for the first time, investigated the association between maternal greenspace exposure and the level of cortisol, a stress hormone, in the cord blood. Our study was based on a cohort of 150 pregnant women in Sabzevar, Iran (2018). We comprehensively assessed greenspace exposure for each participant through (i) residential surrounding greenspace (using two satellite-derived vegetation indices), (ii) residential proximity to green spaces, (iii) maternal visual access to greenspace, (iv) use of public and private green spaces, (v) having a private garden, and (vi) the number of plant pots at home. Linear regression models were developed to assess the association of each indicator of greenspace exposure with cord blood cortisol levels, controlled for the relevant covariates. We observed that a higher residential surrounding greenspace (100 m buffer), having a window with greenspace view, window greenspace coverage of more than 50%, frequently looking at greenspace through window, residential proximity to large green spaces, and more time spent in green spaces were associated with lower cortisol levels in the cord blood. The findings for residential surrounding greenspace at 300 m and 500 m buffers, residential proximity to any green space regardless of its size, having a private garden, and number of plant pots at home were not conclusive. While about one-third of the association between residential surrounding greenspace (100 m buffer) could be mediated through reduction in exposure to air pollution, we did not observe any strong evidence for such a mediatory role for the visual access to greenspace. The findings stratified for parental education and housing type showed mixed patterns. Our findings suggest that more greenspace exposure might reduce cortisol level in the cord blood.

1. Introduction

The ongoing urbanization is projected to lead about two-third of the world population living in urban areas by 2050 (United Nations, 2018). Urban living is often associated with more stressful and sedentary lifestyle and higher exposure to urban-related environmental hazards such as air pollution (Carlsten and Rider, 2017), noise (McMahon et al., 2017), and heat (Shahmohamadi et al., 2011), which could detrimentally influence physical and mental health and wellbeing (Shahmohamadi et al., 2011; Montes-González et al., 2018). In contrast, urban greenspace has been associated with improved physical and mental health and wellbeing (Dadvand et al., 2016; Lachowycz and Jones, 2011; Amoly et al., 2015), partly by reducing exposure to air pollution (Janhäll, 2015), heat (Aram et al., 2019), and noise

Abbreviations: LMIC, low- and middle-income countries; BMI, body mass index; ELISA, enzyme-linked immunosorbent assay; ESPA, earth resources observation and science (EROS) center science processing architecture; NDVI, normalized difference vegetation index; $MSAVI_2$, modified soil-adjusted vegetation index 2; SES, socioeconomic status

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perception (Dzhambov and Dimitrova, 2015), increasing physical activity (Coombes et al., 2010), enhancing social contacts (Dadvand et al., 2016; Jennings and Bamkole, 2019), and reducing stress (Gong et al., 2016). A substantial body of experimental evidence has shown that short exposure to greenspace (either real greenspace or its pictures or videos) could have beneficial short-term effects on the stress level (Kim et al., 2010; Lee et al., 2011; Tsunetsugu et al., 2013). Moreover, a limited body of epidemiological evidence is suggestive for a long-term beneficial association between greenspace exposure and stress (Triguero-Mas et al., 2017). However, the available evidence on the association between prenatal exposure to greenspace and stress level in the developing fetus is still very scarce.

The corticoid hormone cortisol is essential for our stress response and is produced by the adrenal cortex as an end product of the hypothalamic-pituitaryadrenal axis. It regulates the insulin production, activates the catabolic metabolism, and suppresses the immune system to reduce inflammation. However, a long-term overexposure to cortisol can disturb the hormone balance. For the fetus, a sustained excessive level of cortisol could be associated with higher risk of adverse pregnancy outcomes such as lower head circumference and birth weight (Cherak et al., 2019; Su et al., 2015), altered brain structure, and postnatal behavioral disorders (Reynolds, 2013). We hypothesized that exposure to greenspace during pregnancy could be inversely associated with cortisol level in the cord blood, an indicator of the level of this hormone in the fetal circulation. To our knowledge, there is no study reporting on such an association.

To date, much of the available studies on health benefits of greenspace exposure have been conducted in high-income countries. As differences in climate, native vegetation types, and cultures constitute different types of green space between high-income and low- and middle-income countries (LMICs), the transfer of evidence from high-income countries to LMICs could be challenging. Apart from the design aspects and vegetation types that could vary among different countries, maintenance of these spaces could differ between high-income countries and LMICs due to variations in available resources. Up to the present, little is known on the health effect of green spaces in LMICs where much of the urbanization is predicted to happen. This study aimed to investigate the association between a comprehensive array of different indicators of greenspace exposure on the level of the cortisol in the cord blood of newborns in Iran, a LMIC.

2. Methods and Material

2.1. Study setting

This study was conducted in Sabzevar, a city of around 240 000 inhabitants (Census 2016 (Iran, 2016)) in the north-east of Iran (coordinates: 36°12′ N 57°35′, elevation: 977 m). It has an arid climate (Kottek et al., 2006) with an annual precipitation of 180 mm (mostly occurring in winter) and an annual humidity of 43% (Center, 2020). The annual average temperature is 18 °C, with average monthly minimum and maximum temperatures ranging between −2 and 45 °C (Center, 2020). Sabzevar has four distinct seasons with maximum vegetation occurring during the spring months. Fig. S1 in the supplementary materials presents the location of the study area.

2.2. Study population

This cross-sectional study was based on a sample of pregnant women recruited at their delivery time at the Shahidan Mobini university hospital (the only tertiary hospital in the Sabzevar) during June and August 2018. We included women who: (i) were non-smokers and did not smoke during pregnancy, (ii) had a normal term pregnancy (37–42 weeks), (iii) had a normal vaginal delivery, (iv) had no history of diabetes or hypertension, (v) had no pregnancy complications (i.e. gestational diabetes, pregnancy-induced hypertensive disorders), (vi) did not work outside home (i.e. housewives), (vii) spent their entire pregnancy in Sabzevar and (viii) did not change their home address during their current pregnancy. Of the women who were approached, 150 mothers met these criteria and agreed to participate in the study after being informed about the research aims and steps. Data on demographic characteristics, socioeconomic status, and lifestyle were obtained through questionnaires by face-to-face interviews. The participants were enrolled in the study after signing the consent form that was approved by the Clinical Research Ethical Committee (IR.MEDSAB.REC.1395.82) of the Sabzevar University of Medical Science, Sabzevar, Iran.

2.3. Exposure measurement

We comprehensively characterized six different aspects of exposure to greenspace including: (1) residential surrounding greenspace, (2) visual access to greenspace, (3) the time spent in green spaces, (4) residential access to green space, (5) having a private garden, and (6) the number of plant pots at home.

2.3.1. Residential surrounding greenspace

To measure the residential surrounding greenspace, we used the Normalized Difference Vegetation Index (NDVI). It quantifies the density of photosynthetically active greenspace by measuring the proportion of near-infrared light (strongly reflected by vegetation) and visible light. Its values range from −1 to 1 with higher values indicating more vegetation. To achieve maximum exposure contrast, we looked for available cloud-free Landsat 8 images during the spring months (i.e. the maximum vegetation period of the year for our study region) of 2018 (our study year) from the earth resources observation and science (EROS) center science processing architecture (ESPA) (ESPA, 2017). Based on this search, we obtained NDVI data for our study region using the image captured by Landsat 8 on June 14th 2018 at 30 m × 30 m resolution. For each participant, the residential surrounding greenspace was abstracted as the average NDVI within a buffer of 100 m, 300 m and 500 m (Dadvand et al., 2017) around her geocoded residential address.

2.3.2. Visual access

We obtained data on visual access to greenspace through three questions: (i) Can you see plants, trees, grass, flowers, etc. from any window of your home? with possible answers being yes/no; (ii) How often do you see the vegetation through the window (s)? with possible answers being rarely, sometimes, and always. Due to a small number of answers in some categories, we dichotomized the answers to this question by having “rarely” together with those who answered “no” to the previous question as the baseline category and “sometimes” and “always“ as the other category; and (iii) If yes, what proportion of the window surface is covered by vegetation (If there are multiple windows, please describe the window most used)? with answers being 25%, 50% and 100%. To achieve enough number of participants in each category, we dichotomized the answer by considering those who did not have a window with green view together with those who answered 25% as baseline category, and those who answered 50% and 100% as the other category.

2.3.3. Residential access to green space

The residential access to green space was measured as the Euclidean distance of the participant’s geocoded residential address to (i) the nearest green space of any area and (ii) the nearest green space with an area of at least a 5000 m^2. The land use map of Sabzevar (2016) provided by the municipality of Sabzevar was used to calculate these variables for each participant’s home address.

2.3.4. Having a private garden

We asked participants whether they have a private garden with

possible answers being yes/no.

2.3.5. Use of green spaces

Questionnaires already applied in previous studies (Amoly et al., 2015; Dadvand et al., 2018) were used to obtain data on the total time that each participant spent in green spaces during her pregnancy. We asked participants about the average time (hours per week) spent separately in public green spaces (e.g. parks, forest) and in private green spaces in a normal week during their pregnancy.

2.3.6. Number of indoor plant pots at home

The participants were asked to report the number of indoor plant pots at home during the pregnancy period.

2.4. Cortisol level in the umbilical cord blood

To determine cortisol level, 4 mL blood was drawn from the umbilical cord after delivery. The sample was allowed to clot in a serum-separating tube with clot activator at room temperature for 30 min, before being separated from the serum by centrifugation at 3000 rpm for 15 min. Afterwards, the serum samples were stored at −80 °C till the time of analysis. The level of cortisol in the blood samples was then analysed by an enzyme-linked immunosorbent assay (ELISA) using the Cortisol Kit (LDN, Nordhorn, Germany). Laboratory assays followed manufactorýs instructions. All samples were measured in duplicate and all measured values were in linear range (0.2–800 ng/mL). The coefficient of variation (CV) for intra- and inter-assay variability for the average cortisol level in our analyses (43.9 ng/mL) were 7.9% and 5.8%, respectively, which agree with the available recommendations (EMA, 2012; Food and Drug Administration, 2018).

2.5. Main analysis

We developed linear regression models to estimate the change in the cord blood cortisol levels associated with a one-interquartile range (IQR) increase in each of the continuous indicators of greenspace exposure (one at a time). We did not include all the indicators of greenspace exposure in one model to prevent collinearity. Given that the first and third quartiles of the time spent in private green spaces were both zero, it was not possible to scale this exposure and hence we conducted the analyses only for the total time spent in green spaces (hour per week) as the sum of the time spent in public and private green spaces. For the visual access to greenspace, the indicators were included as a binary categorical variable in the models with baseline category indicating less visual access to greenspace.

Based on the available literature, we identified common predictors of greenness exposure and cord blood cortisol levels as presented in a direct acyclic graph (DAG) in the supplementary materials (Fig. S2). As such, we adjusted all models for the maternal age (years, continuous) and body mass index (BMI, kg/m^2, continuous), the fetal sex (girls/boys), parity (continuous), gestational age at delivery (days, continuous), being exposed to tobacco at home (yes/no), three indicators of household socioeconomic status (SES) and two indicators of neighborhood SES. We used income (≥15 million Rials per month/15 to 30 million Rials per month/30 ≤ million Rials per month), paternal education (elementary school/high school/university) and maternal education (elementary school/high school/university) as indicators of the household SES and the percentage of people with no completed degree and the percentage of unemployment per census tract (based on 2016 census) as indicators of the neighborhood SES. All statistical analyses were performed using STATA software version 15, considering a significance level of 0.05 (StataCorp, 2017).

2.6. Mediation analysis

We hypothesized that the association of the immediate residential surrounding greenspace (100 m buffer) and the cord blood cortisol level could be partly explained through the visual access to greenspace. We also hypothesized that reduction in the ambient air pollution levels at the participant's residence could partly explain the aforementioned association. The level of air pollution was assessed as the level of particular matter pollutant with aerodynamic diameter of 1 μm (PM_1), 2.5 μm ($PM_{2.5}$) and 10 μm (PM_{10}) at the participants' residential addresses estimated using a land use regression (LUR) models developed for Sabzevar and described elsewhere (Miri et al., 2019). Briefly, these models were developed based on data from 26 monitoring stations that measured PM_1, $PM_{2.5}$, and PM_{10} levels during four campaigns/seasons from April 2017 till March 2018. Five categories of potential predictor variables were applied to develop these LUR models: urban morphology, traffic, population density, geographic location of monitoring station and land use. The final models were able to explain 68%, 71% and 75% of the variation of the annual average of PM_1, $PM_{2.5}$ and PM_{10} in the study area. Following the approach of Baron and Kenny (Baron and Kenny, 1986), we fitted separately a model for the outcome given the mediator and the exposure, and a model for the mediator given the exposure to compute the percentage of the association between residential surrounding greenspace and cortisol level that could be mediated through each indicator of visual access to greenspace and the air pollutant $PM_{2.5}$ (one at a time). Bootstrap was used to obtain percentile-based 95% confidence intervals for the different estimates.

2.7. Further analysis

2.7.1. Potential effect modifiers

We evaluated the statistical significance of the multiplicative interaction term between each indicator of greenspace exposure and housing type (apartment vs. single-family house) as well as parental education (one at a time) and fetal sex (girls/boys), using likelihood ratio test, comparing fully adjusted models with and without multiplicative interaction term between each indicator of greenspace exposure and each of the aforementioned potential effect modifiers. We then stratified the analyses based on these two factors. For the parental education, a new variable was created containing the education status from the parent with the higher educational degree (elementary school/high school/university).

2.7.2. Soil-adjusted residential surrounding greenspace

We applied Modified Soil Adjusted Vegetation Index 2 ($MSAVI_2$) (Qi et al., 1994) to abstract an alternative set of estimates for the residential surrounding greenspace. $MSAVI_2$, compared to NDVI, has the advantage of controlling for background soil reflectance and has been shown to be a proper measure for characterizing sparse vegetation in arid areas of Iran (Barati et al., 2011). We applied the same Landsat image from ESPA (ESPA, 2017) used for calculating NDVI to abstract $MSAVI_2$ and then characterized residential surrounding greenspace as the average of $MSAVI_2$ across buffers of 100 m, 300 m and 500 m. We repeated our analyses for residential surrounding greenspace using this alternative set of exposure.

2.7.3. Residential surrounding tree cover

In order to disentangle the association of different types of greenspace, we used Vegetation Continuous Fields (VCF) as a measure of tree coverage. The VCF is an estimate of the percentage of land in each image pixel covered by woody vegetation (i.e. trees) (Sexton et al., 2013). We abstracted the VCF data for our study region from Landsat images from 2015 provided by the Land Processes Distributed Active Archive Center (LP DAAC) at 30 m resolution (LP DAAC, 2017). For each participant we calculated the average percent of tree coverage across buffers of 100 m, 300 m and 500 m around her residential address. We repeated our analyses using this alternative exposure. Given that the first and third quartiles of VCF at a buffer of 100 m were both zero, it was not possible to scale this exposure. Therefore, we reported

Table 1
Descriptive statistics of the study participants (n = 150).[a]

Variable	Description
Age of the mother (years)	27 (8)
BMI of the mother (kg/m^2)	23.6 (5.8)
Number of pregnancies	2 (1)
Gestational age (days)	278 (13)
Fetal Sex (girls)	78 (52%)
Census tract illiteracy (%)	24.5 (15.2)
Census tract unemployment (%)	7.0 (4.3)
Exposure to the environmental tobacco smoke at home (Yes)	29 (19.3%)
Parental education	
Low	63 (42%)
Middle	56 (37.3%)
High	31 (20.7%)
Maternal education	
Low	43 (28.7%)
Middle	65 (43.3%)
High	42 (28.0%)
Income	
Low	104 (69.3%)
Middle	36 (24.0%)
High	10 (6.7%)
Cortisol (ng/ml)	43.90 (19.00)
Residential surrounding greenspace (NDVI)	
100 m buffer	0.066 (0.016)
300 m buffer	0.070 (0.014)
500 m buffer	0.073 (0.017)
Soil-adjusted residential surrounding greenspace (MSAVI$_2$)	
100 m buffer	0.06 (0.01)
300 m buffer	0.07 (0.01)
500 m buffer	0.07 (0.01)
Residential surrounding tree cover (VCF)	
300 m buffer	0.009 (0.025)
500 m buffer	0.017 (0.034)
Distance to the nearest green space (m)	
of any size	92.3 (112.5)
of at least 5.000 m^2	190.1 (245.2)
Time spent in total (h/week)	4 (2.5)
Number of pots at home	2 (2)
Having a window with greenspace view (Yes)	85 (56.7%)
Frequently looking at greenspace (Sometimes/always)	48 (32.0%)
50% or more of window covered by greenspace (Yes)	35 (23.3%)
Having a private garden (Yes)	64 (42.7%)
PM_1 (μg/m^3)	39.2 (7.9)
$PM_{2.5}$ (μg/m^3)	44.4 (9.8)
PM_{10} (μg/m^3)	49.0 (12.0)

[a] Categorical variables are presented as count (%) and continuous variables as median (interquartile range).

the associations only for buffers of 300 m and 500 m.

3. Results

3.1. Study population

The descriptive statistics of the sociodemographic characteristics of the study participants and their greenspace exposure and cord blood cortisol levels are presented in Table 1. The median (IQR) of the cord blood cortisol levels was 43.9 (19.0) ng/ml. As presented in Fig. S3 (see supplementary materials) there was a relatively small variation in residential surrounding greenspace based on NDVI. The correlations between the exposure variables are presented in Fig. 1. We found a very strong correlation between the two measurements of residential surrounding greenspace (NDVI and MSAVI$_2$) at each buffer size. Residential surrounding greenspace, proximity to green spaces (any size and those larger than 5.000 m^2) and having a private garden were moderately correlated with the use of green space. We further observed a moderate correlation between residential surrounding greenspace and visual access to greenspace.

3.2. Main analysis

We observed a significant, inverse association between residential surrounding greenspace (NDVI) at a 100 m buffer and cortisol levels (Table 2). A one-IQR increase in the residential surrounding greenspace was associated with a decrease of 3.18 ng/ml (95% confident intervals (CIs): −5.43; −0.93) in the cord blood cortisol level. Additionally, an IQR increase in distance to a green space larger than 5,000 m^2 was significantly associated with an increase of 3.56 ng/ml (95% CIs: 0.32; 6.80) in the cord blood cortisol level. Moreover, we observed an inverse association between an IQR increase of the time spent in green spaces and the cord blood cortisol levels by −2.27 ng/ml (95% CI: −3.88; −0.67). Table 2 further presents the associations between indicators of visual access to greenspace and cortisol level in the cord blood. Having a window with greenspace view was associated with a 3.67 ng/ml (95% CI: −7.83; 0.49) lower cortisol levels (p-value = 0.06). Having more than half of the window covered by greenspaces was significantly associated with lower cortisol levels in the cord blood (β = -7.11 ng/ml (95% CI: −11.90; −2.32). Looking at greenspace through a window at least sometimes, compared to never or rarely, was associated with a change of −4.69 ng/ml (95% CI: −9.09; −0.28) in blood cortisol level. Having a private garden, residential proximity to a green space of any size, and the residential surrounding greenspace (NDVI) over buffers of 300 m and 500 m were also inversely associated with cortisol levels in the cord blood; however, none of these associations attained statistical significance. Our observed association for the number of plant pots at home was null.

3.3. Mediation analysis

Table 3 presents the percentage of the association between the residential surrounding greenspace (NDVI) across a 100 m buffer and the cord blood cortisol levels that could be explained by each indicator of visual access as well as air pollution. $PM_{2.5}$ and PM_{10} could explain about one-third (28.6% (95% CIs: −1.6; 128.9) and 32.7 (95% CIs: −7.0 and 160.9, respectively)) of the aforementioned association, while PM_1 could only explain about 5.1% (95% Cis: −2.9; 18.8) of this association. Having a window with greenspace view, frequent viewing of greenspace, and more than half of the window(s) covered by greenspace could respectively explain only 5.3% (95% CIs: −23.9; 26.3), 8.3% (95% CIs: −63.2; 19.0), and 3.2% (95% CIs: −10.3; 21.1) of the aforementioned association.

3.4. Further analysis

3.4.1. Potential effect modifiers

We tested the statistical significance of the interaction term between each indicator of greenspace exposure and the parental education, housing type or fetal sex in association with the cord blood levels of the cortisol. As presented in supplementary Table S1, among our evaluated interaction terms between each indicator of greenspace exposure and parental education, housing type, and fetal sex, we only observed a statistically significant interaction between parental education and distance to a green space larger than 5,000 m^2 (p-value = 0.02). Other interaction terms were not statistically significant (p-value > 0.10).

Fig. 2 presents the associations between exposure to greenspace and cord blood cortisol levels stratified for parental education, the participants' housing type, and fetal sex. For having more than half of the window covered with a green view and having a private garden we observed some suggestions for a trend with potentially stronger associations for participants with lower parental education. In contrast, for the residential surrounding greenspace (NDVI) across buffers of 300 m and 500 m, time spent in a green space and residential proximity to green spaces larger than 5000 m^2, there were some indications for

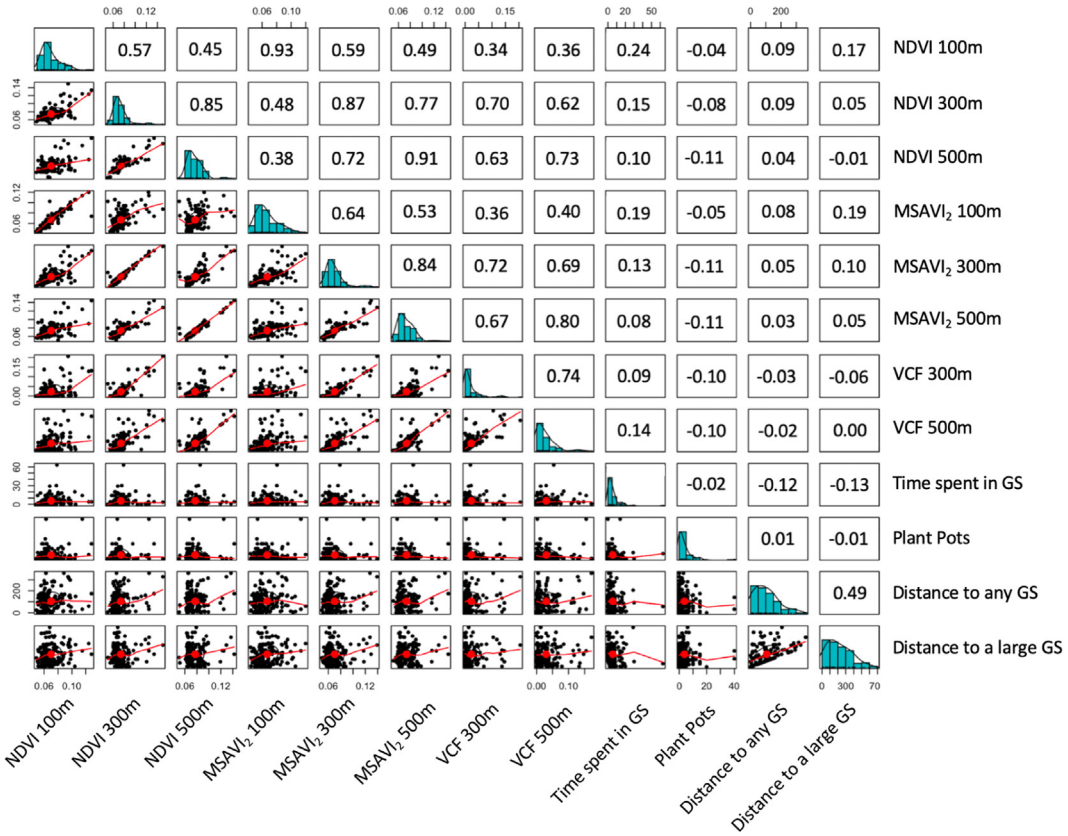

Fig. 1. Scatterplot matrix and histograms of the continuous Greenspace variables. Bivariate scatterplots of continuous variables below the diagonal; histograms of each variable on the diagonal; Spearman's correlation coefficient above the diagonal. Note: NDVI = normalized difference vegetation index within buffers of 100 m, 300 m and 500 m; MSAVI2 = modified soil-adjusted vegetation index within buffers of 100 m, 300 m and 500 m; VCF = Vegetation Continuous Fields within buffers of 300 m and 500 m; Time spent in GS = Total time spent in green spaces; Plant Pots = Number of Indoor Plant Pots; Distance to any GS = Distance to a green space of any size; Distance to a large GS = Distance to a green space $< 5000\ m^2$. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

potentially stronger associations for those participants with higher parental education. No clear trend was observed for other greenspace exposure indicators across strata of parental education.

When we stratified the analyses based on the participants' housing type, we observed some suggestions for potentially stronger associations between the residential proximity to green spaces (any size and those larger than 5.000 m^2), having a private garden, and cord blood cortisol level for participants living in an apartment compared to a single-family house. In contrast, for the indicators of the visual access to greenspace, we generally observed some indications for a potentially stronger association with cord blood cortisol levels for the participants living in a single-family house than those living in an apartment. The results for the residential surrounding greenspace were mixed with some suggestions for a stronger association for the residential surrounding greenspace at 100 m buffer for those participants living in a single-family house and a stronger association for the residential surrounding greenspace at 500 m buffer for those living in an apartment. For other measures of greenspace exposure, we did not observe any clear pattern.

After stratifying the analyses based on the fetal sex, we observed some suggestions for a potentially stronger association for the visual access to greenspace (window area covered by greenspace and looking at greenspace frequently) and for residential proximity to large green spaces among girls. We did not observe any notable sex difference in our evaluated associations for other indicators of greenspace exposure.

3.4.2. Soil-adjusted residential surrounding greenspace

The results of the analyses for the residential surrounding greenspace based on $MSAVI_2$ were consistent with those of the main analysis based on NDVI. We observed an inverse association between average $MSAVI_2$ across a 100 m buffer around the participant's residential address and the cord blood cortisol level (Table 2). An increase in average $MSAVI_2$ in this buffer by one IQR was associated with a decrease in the cord blood cortisol level by 3.66 ng/ml (95% CIs: −6.04; −1.29). Similarly, for the $MSAVI_2$ averages over buffers of 300 m and 500 m, we observed inverse associations with the cord blood cortisol levels; however, these associations were not statistically significant.

3.4.3. Residential surrounding tree cover

Similar to our findings for NDVI and $MSAVI_2$, we observed inverse associations between residential surrounding tree cover (i.e. VCF averages across 300 m and 500 m buffers around the participant's residential address) and cord blood cortisol levels; however, none of these associations attained statistically significance.

4. Discussion

To our knowledge, this cross-sectional study is the first to evaluate the association of maternal exposure to greenspace during pregnancy and cortisol level in the cord blood. Furthermore, this study is the first to evaluate the association of having access to a private garden and the number of plant pots at home on an indicator of stress. This study also adds to the very scarce available epidemiological evidence on health benefits of visual access to greenspace. Moreover, this is the first study to investigate the relationship between pregnancy exposure to greenspace and cortisol levels in a LMIC. The findings of this study also adds to the limited number of available reports on health benefits of the greenspace exposure in LMICs where much of the urbanization is

Table 2
Adjusted[a] associations between prenatal exposure to greenspace and cord blood cortisol level.

	Estimate (95%)	p
Residential surrounding greenspace (NDVI)[b]		
100 m buffer	−3.18 (−5.43; −0.93)	0.01
300 m buffer	−0.91 (−2.79; 0.98)	0.34
500 m buffer	−1.05 (−3.44; 1.35)	0.39
Soil-adjusted residential surrounding greenspace ($MSAVI_2$)[b]		
100 m buffer	−3.66 (−6.04; −1.29)	< 0.01
300 m buffer	−1.54 (−3.39; 0.31)	0.10
500 m buffer	−1.84 (−4.45; 0.76)	0.16
Residential surrounding tree cover (VCF)[b]		
300 m buffer	−0.08 (−1.54; 1.38)	0.91
500 m buffer	−0.45 (−2.81; 1.31)	0.48
Distance to green space[b]		
of any size	1.54 (−1.32; 4.39)	0.29
of at least 5,000 m^2	3.56 (0.32; 6.80)	0.03
Total time spend in green space [b]	−2.27 (−3.88; −0.67)	0.01
Number of plant pots at home [b]	0.14 (−1.70; 1.98)	0.88
Have a window with greenspace view	−3.67 (−7.83; 0.49)	0.08
Frequently looking at greenspace	−4.69 (−9.09; −0.28)	0.04
50% or more of window covered by greenspace	−7.11 (−11.90; −2.32)	< 0.01
Having a private garden	−0.99 (−5.37; 3.38)	0.65

[a] Adjusted for the maternal age, body mass index, number of pregnancies, gestational age in days, exposure to tobacco at home, percentage of illiterates and unemployed per census, paternal and maternal education and household income. Effect estimates in cortisol (ng/ml) are reported with their 95% confidence interval (95% CI).

[b] Effect estimates are reported as increase in cortisol (ng/ml) per one-interquartile range increase with their 95% confidence interval (95% CI).

Table 3
Percentage (%) of the association between residential surrounding greenspace (100 m buffer) and cord blood cortisol level mediated by visual access and air pollution.[a.]

Mediator	Percentage mediated (%, 95% confidence intervals)
Visual access:	
Having a window with greenspace view	5.3 (−23.9; 26.3)
Frequently looking at greenspace	8.3 (−63.2; 19.0)
50% or more of window covered by greenspace	3.18 (−109.3; 21.1)
Air pollution:	
PM_1	5.1 (−2.9; 18.8)
$PM_{2.5}$	28.6 (−1.6; 128.9)
PM_{10}	32.7 (−7.0; 160.9)

[a] Adjusted for the maternal age, body mass index, number of pregnancies, gestational age in days, exposure to tobacco at home, percentage of illiterates and unemployed per census, paternal and maternal education and household income.

projected to occur (United Nations, 2018). We used data obtained through questionnaires, land cover maps, and satellite imagery to comprehensively characterize exposure to greenspace. We observed inverse associations between higher residential surrounding greenspace (NDVI and $MSVAI_2$) across a 100 m buffer, residential proximity to a large green space, more visual access to greenspace, and more time spent in green spaces and the cord blood cortisol levels. We also observed an inverse association between residential surrounding greenspace (NDVI and $MSVAI_2$) and tree cover (VCF) in larger buffers of 300 m and 500 m and residential proximity to a green space with any size and cortisol levels in the cord blood; however, these associations did not attain statistical significance. The finding for the number of plant pots at home was not conclusive. While about one-third of the association between residential surrounding greenspace (100 m buffer) could be mediated through reduction in exposure to $PM_{2.5}$ and PM_{10}, we did not observe any strong evidence for such a mediatory role for the exposure to PM_1 and the visual access to greenspace. We observed mixed patterns of associations across the strata of parental education, housing type, and fetal sex.

4.1. Available evidence

Given that this is the first study looking at the association between greenspace exposure and cortisol level in cord blood, no previous studies can be used as comparison. However, our findings line up with past studies finding an association between greenspace exposure and reduced stress level in adults. Several experimental studies have examined the inverse associations between short-term exposure to greenspace and physiological indicators of stress. Tyrväinen *et al.*, for example, found an accelerated reduction in perceived stress in adults walking in natural areas compared to the city center (Tyrväinen et al., 2014). Ulrich et al. (1991) observed an association between short-term exposure to greenspace sceenery and physiological stress indicators, which has been replicated by several other studies in recent years (Kim et al., 2010; Tsunetsugu et al., 2013; Jiang et al., 2014). These observations are in line with the findings of other experimental studies showing amelioration of the physiological markers of stress such as blood pressure and heart rate as a result of short-term exposure to green environment (Lee et al., 2011; Tsunetsugu et al., 2013). More recently, a limited but emerging body of epidemiological evidence has documented the positive influence of the long-term exposure to greenspace on stress (Triguero-Mas et al., 2017). A study on mental health with over 10,000 participants in UK found an association between the distance to green space and stress (White et al., 2013), which is consistent with findings of a Danish study of more than 11,000 participants that observed lower levels of perceived stress among people living less than one kilometer from a green space (Stigsdotter et al., 2010). Studies further suggest a greater impact of greenspace exposure on stress levels among people with lower SES (Gov.uk, 2019; Allen and Balfour, 2012). Since people with a low SES are more likely to have poorer health status and more stressful lifestyle and live in areas with poorer environmental conditions, exposure to greenspace could have a stronger effect on them compared to people from high SES groups. Our observed findings for the stratified analyses based on parental education were partly supporting this hypothesis, showing a stronger association for the participants with lower parental education for some of the greenspace exposure indicators, but not others. Similarly, we observed a mixed pattern of associations across the strata of housing type, which we cannot compare with those of the previous study, given lack of available evidence on such an effect modification. The available evidence on a potential sex difference in the cord blood level of cortisol is not consistent. While some studies support such a difference (Giesbrecht et al., 2016; Wynne-Edwards et al., 2019), others did not find any differences between the sexes (Bagnoli et al., 2013; Travers et al., 2018). The stratification of our analyses by sex suggested a potentially stronger association for maternal visual access and residential proximity to large green spaces among girls. However, the pattern was mix for most of our other evaluated exposure variables. Such an effect modification of the health effects of greenspace exposure remains as an open question for future studies.

4.2. Potential mechanisms

One potential mechanism on how prenatal exposure to greenspace may influence the cortisol level in the cord blood is the reduction of maternal stress. Former studies found a positive correlation between maternal and fetal cortisol concentrations (Keshavarzi et al., 2014); suggesting a linear relation due to placental exchange of cortisol. Although the placenta enzyme 11β-hydroxysteroid-dehydrogenase (11β-HSD-2) partly protects the human fetus from high cortisol levels by

A

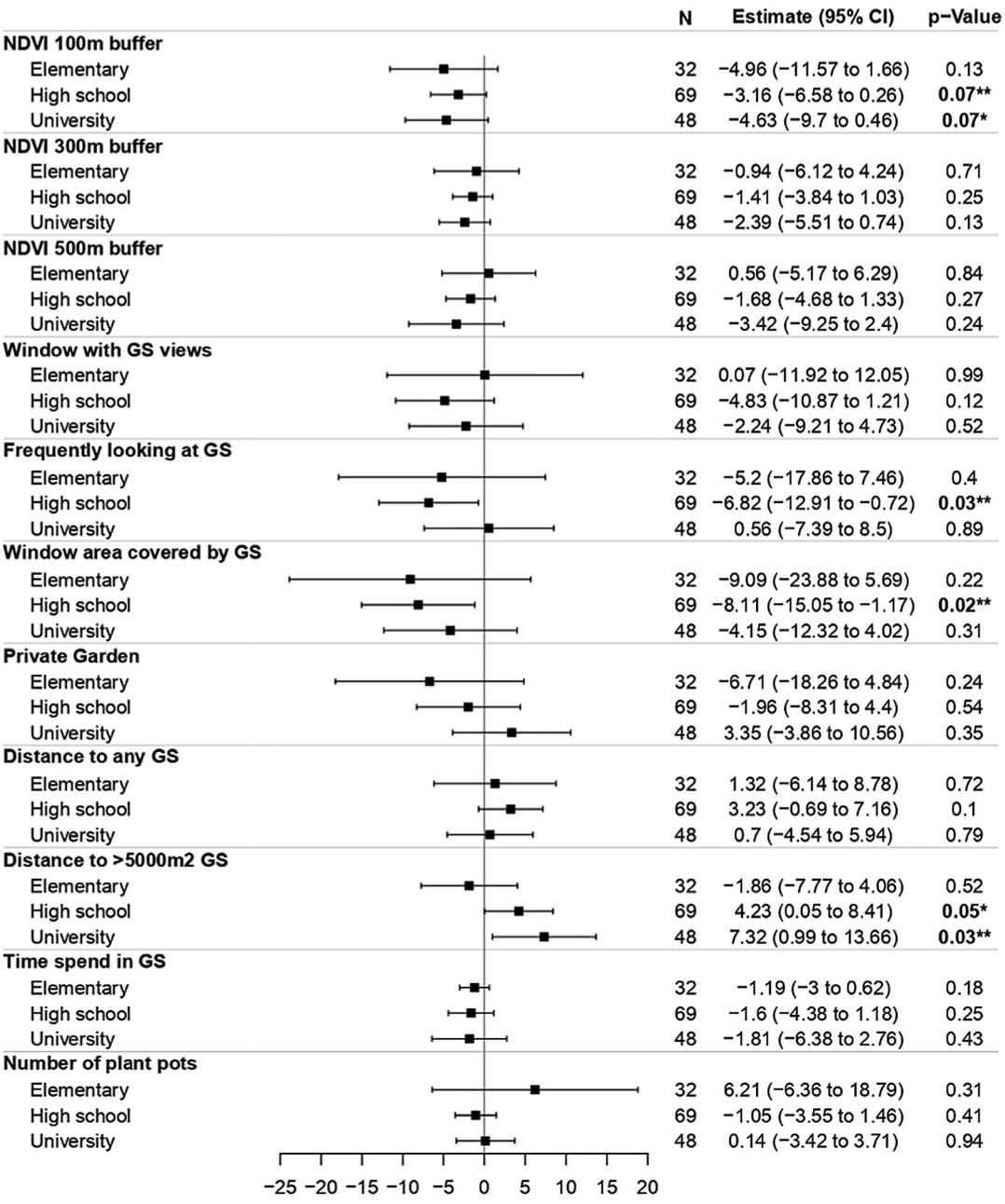

Fig. 2. Adjusted[a] associations between prenatal exposure to different indicators of greenspace with cord blood cortisol level stratified for parental education status (A), housing type (B) and fetal sex (C). [a] Adjusted for the maternal age, body mass index, number of pregnancies, gestational age in days, exposure to tobacco at home, percentage of illiterates and unemployed per census, paternal and maternal education and household income. Effect estimates in cortisol (ng/ml) are reported per one-interquartile range increase with their 95% confidence interval (95% CI). *Note*: NDVI = normalized difference vegetation index with a buffer of 100 m, 300 m and 500 m; GS = green space.

converting 80–90% of it into the biologically inactive cortisone (Duthie and Reynolds, 2013), some cortisol still passes the placenta barrier. The fetal cord blood cortisol level was found to be much lower than the maternal, thus a small increase in maternal cortisol could have a substantial effect on fetal cortisol levels (Mulder et al., 2002). Assuming that the cord blood cortisol level could be associated with maternal stress, we can assume direct and indirect pathways through which exposure to greenspace could reduce maternal stress, and hence cortisol levels.

Stress reduction theory offers an explanation for a direct pathway. Ulrich et al. (1991) proposed that a greener surrounding could result in physiological recovery in the form of less muscle tension and skin conductance and lower pulse rate and blood pressure, while invoking an emotional response in terms of increased positive feelings and reduced negative thoughts and emotions such as fear and anger. In this context, a study using functional magnetic resonance imaging (fMRI) of brain demonstrated the activation of the areas in the human brain normally responsive to positive emotions (basal ganglia) when participants were shown pictures of natural environments, while looking at pictures of urban setting activated the amygdala, which is responsible

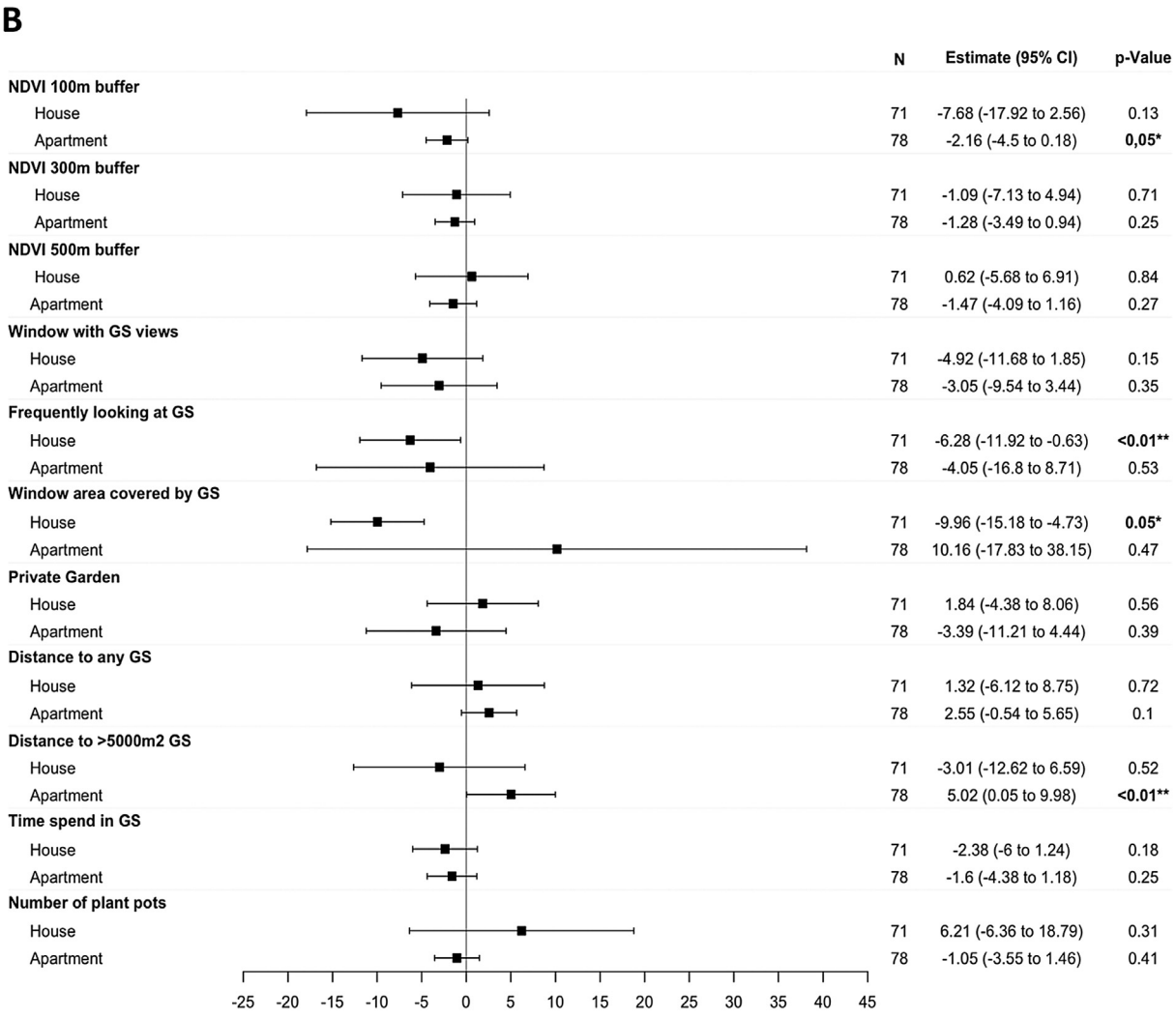

Fig. 2. (*continued*)

for processing of fear and stressful emotions (Kim et al., 2010). These findings could suggest that the effect of greenspace exposure on the neuronal system is not only through direct immersion in a green environment but also could be through visual access to greenspace. Our analysis of the mediatory role of visual access to greenspace in the association of residential surrounding greenspace and cord blood cortisol level, however, did not support such a mediation.

Physical activity has been suggested as a pathway through which green spaces exert their health benefits (Nichani et al., 2016). Physical activity could be a relevant mechanism underlying our finding, given that it has been shown to decrease stress through increasing endorphin levels, inhibiting the activation of the hypothalamic-pituitaryadrenal axis (Dishman and O'Connor, 2009) and directly decreasing cortisol levels (Beserra et al., 2018). Another potential mechanism of greenspace restoring capacity could be by increasing social cohesion (De Vries et al., 2013). Increased interpersonal interactions could promote mutual respect, meaningful connections and trust, thus positively influence the emotional state and decrease levels of stress hormones such as cortisol (Kawachi and Berkman, 2015). Furthermore, urban green spaces are shown to mitigate exposure to heat, noise and air pollution in urban areas (Bowler et al., 2010; Hartig et al., 2014), which, in turn, have been associated to an increased stress response (Niu et al., 2018; Lederbogen et al., 2011). By reducing these environmental risk factors, greenspace could therefore have the potential to decrease stress, which can be reflected by lower cortisol levels. Consistently, our mediation analysis of air pollution showed that up to one-third of the association between the residential surrounding greenspace and the cord blood cortisol levels could be explained by lower exposure to $PM_{2.5}$ or PM_{10}.

4.3. Limitations

This study faced some limitations. Our relatively small sample size of 150 participants could have limited our statistical power, especially for the stratified analyses. We are further aware that our participants represented a specific population, thus generalization of our findings to other areas with different climate, vegetation types, and cultures should be done with caution. Like any observational study, there was a possibility of the residual SES confounding in our study. To minimize this possibility, we controlled our analyses for five SES indicators including three household and two neighborhood-level indicators of SES. We tested the mediatory role of PM_1, $PM_{2.5}$, and PM_{10} in our evaluated association between maternal exposure to greenspace and cord blood level of cortisol. However, we could not evaluate mediatory roles of other air pollutants such as ozone (Miller et al., 2016) and NO_2 (Dadvand et al., 2012) because of unavailability of data on these pollutants. Exposure to ozone could have been particularly relevant, given the warm climate of our study region. However, our previous study of the association of residential surrounding greenspace with personal exposure of pregnant women to $PM_{2.5}$ and NO_2 based on personal monitoring of these pollutants showed that while higher residential surrounding greenspace was associated with lower personal exposure to $PM_{2.5}$, it was not associated with personal exposure to NO_2 (Dadvand

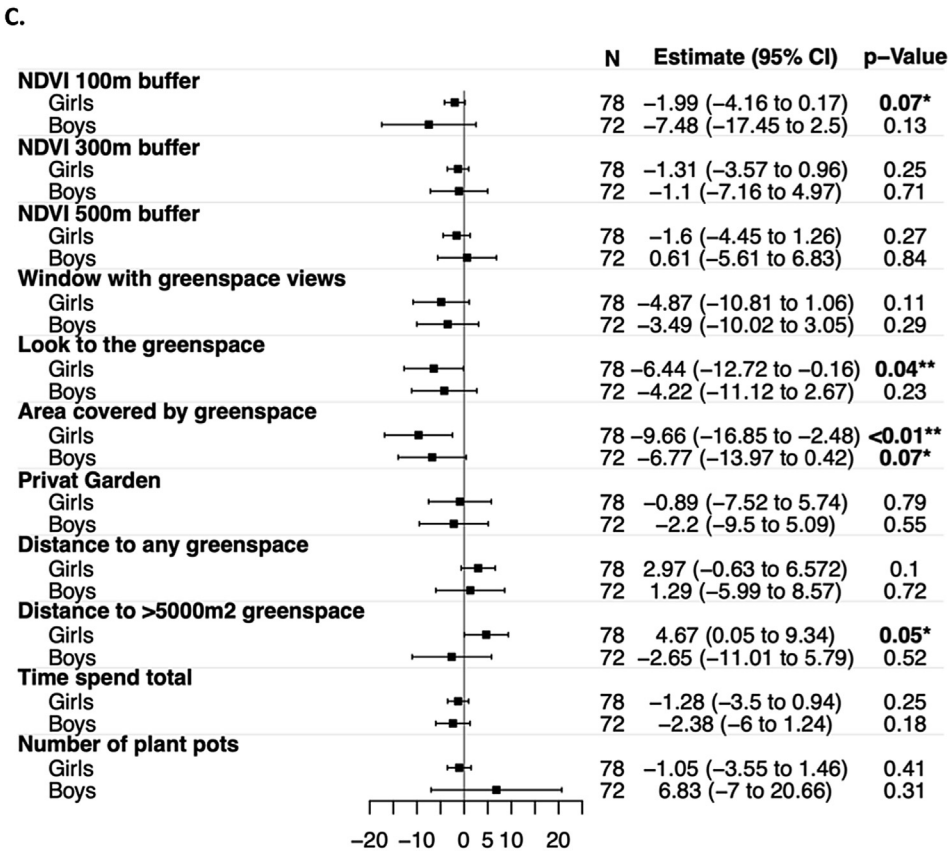

Fig. 2. (*continued*)

et al., 2012). The use of the cortisol level in the cord blood as a surrogate marker of stress could be influenced by delivery circumstances, such us labor duration or fetal distress; however, we obtained samples from women with a normal, term vaginal delivery without complications at delivery that could have minimized such an influence in our analyses. Moreover, we used ELISA to measure the level of cortisol in the cord blood, while High-Performance Liquid Chromatography (HPLC) could provide more accurate measures. Furthermore, our assessment of the residential surrounding greenspace and proximity to green spaces did not address the quality of these spaces, which could have influenced the use of these spaces by our participants. Unsafe or unattractive green spaces, for example, could discourage pregnant women to visit these spaces. Moreover, our characterization of time spent in greenspace and visual access to greenspace was based on questionnaires, which were not validated using objective measures and could have been prone to subjectivity and recall bias. Given the relatively small contrast in VCF levels across our study area and the resulting limited statistical power, our non-statistically significant results for VCF should be interpreted with caution.

5. Conclusion

We observed that higher residential surrounding greenspace, residential proximity to green spaces larger than 5,000 m^2, more time spent in green spaces, having a window with greenspace view, having a window covered at by at least 50% of greenspace view, and frequently looking at greenspace through window during pregnancy were associated with lower cortisol levels in the cord blood. Our findings for the association between indoor plants and cortisol levels were not conclusive. Similarly, we observed some indications for the mediation of the association between the residential surrounding greenspace and cord blood cortisol levels by air pollution but not by visual access to greenspace. Given that fetal exposure to sustained high cortisol levels during pregnancy have been associated with adverse pregnancy outcomes and postnatal growth and development, our findings, if replicated by future studies, could offer evidence base for policymakers to implement interventions targeted at improving pregnancy outcomes and child health and development in our rapidly urbanizing world. More studies are needed to evaluate effects on perinatal outcomes using larger sample sizes in other settings and climates, while considering the quality of green spaces in their exposure assessment and relying on objective measures of visual access to greenspace.

CRediT authorship contribution statement

Lilian Marie Boll: Data curation, Formal analysis, Visualization, Writing - original draft. **Ramezanali Khamirchi:** Project administration, Writing - review & editing. **Lucia Alonso:** Data curation, Formal analysis, Writing - review & editing. **Elisa Llurba:** Conceptualization, Methodology, Writing - review & editing. **Óscar J Pozo:** Conceptualization, Methodology, Writing - review & editing. **Mohammad Miri:** Funding acquisition, Conceptualization, Methodology, Project administration, Writing - review & editing. **Payam Dadvand:** Conceptualization, Methodology, Supervision, Validation, 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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2020.106047.

References

Allen, J., Balfour, R., 2012. Natural solutions for tackling health inequalities: realising the opportunity. UCL Institute of Health Equity.

Amoly, E., Dadvand, P., Forns, J., López-Vicente, M., Basagaña, X., Julvez, J., et al., 2015. Green and blue spaces and behavioral development in barcelona schoolchildren: The BREATHE project. Environ. Health Perspect. 122 (12), 1351–1358.

Aram, F., Higueras García, E., Solgi, E., Mansournia, S., 2019. Urban green space cooling effect in cities [Internet]. Vol. 5, Heliyon, p. e01339 (cited 2020 Jan 24). Available from: https://linkinghub.elsevier.com/retrieve/pii/S2405844019300702.

Bagnoli, F., Mori, A., Fommei, C., Coriolani, G., Badii, S., Tomasini, B., 2013. ACTH and cortisol cord plasma concentrations in preterm and term infants. J. Perinatol. 33 (7), 520–524. https://doi.org/10.1038/jp.2012.165.

Barati, S., Rayegani, B., Saati, M., Sharifi, A., Nasri, M., 2011. Comparison the accuracies of different spectral indices for estimation of vegetation cover fraction in sparse vegetated areas. Egypt J. Remote Sens. Sp. Sci. 14 (1), 49–56.

Baron, R.M., Kenny, D.A., 2020. The moderator-mediator variable distinction in social psychological research. Conceptual, strategic, and statistical considerations. J. Pers. Soc. Psychol. [Internet] 51(6), 1173–1182 (cited 2020 Jan 24). Available from: http://doi.apa.org/getdoi.cfm? doi: 10.1037/0022-3514.51.6.1173.

Beserra, A.H.N., Kameda, P., Deslandes, A.C., Schuch, F.B., Laks, J., de Moraes, H.S., 2018. Can physical exercise modulate cortisol level in subjects with depression? A systematic review and meta-analysis. Vol. 40, Trends in Psychiatry and Psychotherapy. Sociedade de Psiquiatria do Rio Grande do Sul. p. 360–368.

Bowler, D.E., Buyung-Ali, L., Knight, T.M., Pullin, AS., 2010. Urban greening to cool towns and cities: A systematic review of the empirical evidence. Vol. 97, Landscape and Urban Planning. p. 147–155.

Carlsten, C., Rider, C.F., 2017. Traffic-related air pollution and allergic disease: An update in the context of global urbanization. Vol. 17, Current Opinion in Allergy and Clinical Immunology. Lippincott Williams and Wilkins, p. 86–89.

Center, K.R.W., 2020. پورتال اداره کل هواشناسی خراسان رضوی | اقلیم استان [Internet]. [cited 2020 Feb 11]. Available from: https://www.razavimet.ir/fa/node/38.

Cherak, S.J., Malebranche, M.E., Wynne-Edwards, K., Williamson, T., Giesbrecht, G.F., 2019 Aug. Quantitative meta-analysis of maternal prenatal salivary cortisol and newborn birthweight does not identify effect of fetal sex. Psychoneuroendocrinology. 1 (106), 117–121.

Coombes, E., Jones, A.P., Hillsdon, M., 2010 Mar. The relationship of physical activity and overweight to objectively measured green space accessibility and use. Soc. Sci. Med. 70 (6), 816–822.

Dadvand, P., Bartoll, X., Basagaña, X., Dalmau-Bueno, A., Martinez, D., Ambros, A., et al., 2016 May May. Green spaces and General Health: Roles of mental health status, social support, and physical activity. Environ Int. 1 (91), 161–167.

Dadvand, P., de Nazelle, A., Triguero-Mas, M., Schembari, A., Cirach, M., Amoly, E., et al., 2012. Surrounding greenness and exposure to air pollution during pregnancy: An analysis of personal monitoring data. Environ. Health Perspect. [Internet] 120(9), 1286–1290 (cited 2020 Jun 4). Available from: https://ehp.niehs.nih.gov/doi/10.1289/ehp.1104609.

Dadvand, P., Tischer, C., Estarlich, M., Llop, S., Dalmau-Bueno, A., López-Vicente, M., et al., 2017. Lifelong residential exposure to green space and attention: A population-based prospective study. Environ. Health Perspect. 125(9).

Dadvand, P., Poursafa, P., Heshmat, R., Motlagh, M.E., Qorbani, M., Basagaña, X., et al. Use of green spaces and blood glucose in children; a population-based CASPIAN-V study. Environ. Pollut. [Internet] 243, 1134–1140 (cited 2020 Jun 4). Available from: https://doi.org/10.1016/j.envpol.2018.09.094.

De Vries, S., van Dillen, S.M.E., Groenewegen, P.P., Spreeuwenberg, P., 2013 Oct Oct. Streetscape greenery and health: Stress, social cohesion and physical activity as mediators. Soc. Sci. Med. 94, 26–33.

Dishman, R.K., O'Connor, P.J., 2009 Jun. Lessons in exercise neurobiology: The case of endorphins. Ment. Health Phys. Act. 2 (1), 4–9.

Duthie, L., Reynolds, R.M., 2013. Changes in the Maternal Hypothalamic-Pituitary-Adrenal Axis in Pregnancy and Postpartum: Influences on Maternal and Fetal Outcomes. Neuroendocrinology 98 (2), 106–115. https://doi.org/10.1159/000354702.

Dzhambov, A.M., Dimitrova, D.D., 2015. Green spaces and environmental noise perception. Urban For Urban Green 14 (4), 1000–1008.

EMA, 2012. Committee for Medicinal Products for Human Use. Guideline on bioanalytical method validation. EMEA/CHMP/EWP/192217/2009 Rev 1 Corr 2** [Internet] 1–23 (cited 2020 Apr 30). Available from: www.ema.europa.eu/contact.

ESPA, 2017. ESPA - LSRD [Internet] (cited 2020 Jun 4). Available from: https://espa.cr.usgs.gov/.

Food and Drug Administration, 2018. Guidance for Industry Bioanalytical Method Validation Guidance for Industry Bioanalytical Method Validation. Biopharm. Fed. Regist. [Internet] (100) 66 (cited 2020 Apr 30). Available from: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htmand/orhttp://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/default.htm.

Giesbrecht, G.F., Rash, J.A., Edwards, H.E., Wynne-Edwards, K.E., 2016. Full-term deliveries without antecedent labor reveal sex differences in umbilical cord glucocorticoid concentrations. Psychoneuroendocrinology 74, 121–125. https://doi.org/10.1016/j.psyneuen.2016.08.030.

Gong, Y., Palmer, S., Gallacher, J., Marsden, T., Fone, D., 2016. A systematic review of the relationship between objective measurements of the urban environment and psychological distress. Environ. Int. [Internet] 96, 48–57 (cited 2020 Jan 24).

Gov.uk., 2019. Marmot Review report – 'Fair Society, Healthy Lives | Local Government Association [Internet]. https://www.local.gov.uk/marmot-review-report-fair-society-healthy-lives. (cited 2020 Jan 27). Available from: https://www.local.gov.uk/marmot-review-report-fair-society-healthy-lives.

Hartig, T., Mitchell, R., de Vries, S., Frumkin, H., 2014 Mar 18. Nature and Health. Annu. Rev. Public Health. 35 (1), 207–228.

Janhäll, S., 2015. Review on urban vegetation and particle air pollution - Deposition and dispersion. Vol. 105, Atmospheric Environment. Elsevier Ltd, pp. 130–137.

Jennings, V., Bamkole, O., 2019. The relationship between social cohesion and urban green space: An avenue for health promotion. Int. J. Environ. Res. Public Health [Internet] 16 (3) (cited 2020 Jan 24).

Jiang, B., Chang, C.Y., Sullivan, W.C., 2014 Dec Dec. A dose of nature: Tree cover, stress reduction, and gender differences. Landsc Urban Plan. 1 (132), 26–36.

Kawachi, I., Berkman, L.F., 2015. Social capital, social cohesion, and health. In: Social Epidemiology [Internet]. Oxford University Press (cited 2020 Jan 24), pp. 290–319. Available from: http://oxfordmedicine.com/view/10.1093/med/9780195377903.001.0001/med-9780195377903-chapter-8.

Keshavarzi, F., Farnia, V., Yazdchi, K., Najafi, F., Brand, S., Bajoghli, H., et al., 2014 Dec 1. Effect of maternal anxiety on maternal serum and fetal cord blood cortisol. Asia-Pacific Psychiatry. 6 (4), 435–439.

Kim, T.H., Jeong, G.W., Baek, H.S., Kim, G.W., Sundaram, T., Kang, H.K., et al., 2010. Human brain activation in response to visual stimulation with rural and urban scenery pictures: A functional magnetic resonance imaging study. Sci. Total Environ. [Internet] 408(12), 2600–2607 (cited 2020 Jan 24). Available from: http://www.ncbi.nlm.nih.gov/pubmed/20299076.

Kottek, M., Grieser, J., Beck, C., Rudolf, B., Rubel, F., 2006. World map of the Köppen-Geiger climate classification updated. Meteorol. Zeitschrift [Internet] 15(3), 259–263 (cited 2020 Jan 24). Available from: http://gpcc.dwd.de.

Lachowycz, K., Jones, A.P., 2011 May May. Greenspace and obesity: A systematic review of the evidence. Obes Rev. 12 (501).

Lederbogen, F., Kirsch, P., Haddad, L., Streit, F., Tost, H., Schuch, P., et al., 2011 Jun 23. City living and urban upbringing affect neural social stress processing in humans. Nature. 474 (7352), 498–501.

Lee, J., Park, B.J., Tsunetsugu, Y., Ohira, T., Kagawa, T., Miyazaki, Y., 2011. Effect of forest bathing on physiological and psychological responses in young Japanese male subjects. Public Health. 125 (2), 93–100.

LP DAAC, 2017 (cited 2020 Aug 2); Available from: https://lpdaac.usgs.gov/products/gfcc30tcv003/.

McMahon, T.A., Rohr, J.R., Bernal, X.E., 2017. Light and noise pollution interact to disrupt interspecific interactions. Ecology [Internet] 98(5), 1290–1299 (cited 2020 Jan 27). Available from: http://www.ncbi.nlm.nih.gov/pubmed/28170099.

Miller, D.B., Ghio, A.J., Karoly, E.D., Bell, L.N., Snow, S.J., Madden, M.C., et al., 2016. Ozone exposure increases circulating stress hormones and lipid metabolites in humans. Am. J. Respir. Crit. Care Med. [Internet] 193(12), 1382–1391 (cited 2020 Jun 4). Available from: www.clinicaltrials.gov.

Miri, M., Ghassoun, Y., Dovlatabadi, A., Ebrahimnejad, A., Löwner, M.O., 2019. Estimate annual and seasonal PM 1, PM 2.5 and PM 10 concentrations using land use regression model. Ecotoxicol. Environ. Saf. [Internet] 174, 137–145 [cited 2020 Jan 27].

Montes-González, D., Vílchez-Gómez, R., Barrigón-Morillas, J.M., Atanasio-Moraga, P., Rey-Gozalo, G., Trujillo-Carmona, J., 2018 Oct 18. Noise and air pollution related to health in urban environments. Proceedings 2 (20), 1311.

Mulder, E.J.H, Robles de Medina, P.G, Huizink, A.C, Van den Bergh, B.R.H, Buitelaar, J.K, Visser, G.H.A, 2002. Prenatal maternal stress: effects on pregnancy and the (unborn) child. Early Human Develop. 70 (1-2), 3–14. https://doi.org/10.1016/S0378-3782(02)00075-0.

Nichani, V., Dirks, K., Burns, B., Bird, A., Morton, S., Grant, C., 2016. Green space and physical activity in pregnant women: Evidence from the growing up in new zealand study. J. Phys. Act Health [Internet] 13(12), 1341–1350 (cited 2020 Jan 27). Available from: http://www.ncbi.nlm.nih.gov/pubmed/27633620.

Niu, Y., Chen, R., Xia, Y., Cai, J., Ying, Z., Lin, Z., et al., 2018. Fine particulate matter constituents and stress hormones in the hypothalamus–pituitary–adrenal axis. Environ. Int. [Internet] 119, 186–192 (cited 2020 Jan 27).

Qi, J., Chehbouni, A., Huete, A.R., Kerr, Y.H., Sorooshian, S., 1994. A modified soil adjusted vegetation index. Remote Sens. Environ. 48 (2), 119–126.

Reynolds, R.M., 2013. Glucocorticoid excess and the developmental origins of disease: Two decades of testing the hypothesis – 2012 Curt Richter Award Winner. Psychoneuroendocrinology 38, 1–11.

Sexton, J.O., Song, X.P., Feng, M., Noojipady, P., Anand, A., Huang, C., et al., 2013. Global, 30-m resolution continuous fields of tree cover: Landsat-based rescaling of MODIS vegetation continuous fields with lidar-based estimates of error. Int. J. Digital Earth 6 (5), 427–448. https://doi.org/10.1080/17538947.2013.786146.

Shahmohamadi, P., Che-Ani, A.I., Etessam, I., Maulud, K.N.A., Tawil, N.M., 2011. Healthy environment: The need to mitigate urban heat island effects on human health. Procedia Eng. 61–70.

StataCorp, 2017. Stata Statistical Software: Release 15 MP [Internet]. College Station: TX:

Computer Software. Available from: http://www.jstor.org/stable/2234838?origin=crossref.
Stigsdotter, U.K., Randrup, T.B., Ekholm, O., Schipperijn, J., Toftager, M., Kamper-Jørgensen, F., 2010. Health promoting outdoor environments - Associations between green space, and health, health-related quality of life and stress based on a Danish national representative survey. Scand J Public Health. 38 (4), 411–417.
Su, Q., Zhang, H., Zhang, Y., Zhang, H., Ding, D., Zeng, J., et al., 2015. Maternal stress in gestation: birth outcomes and stress-related hormone response of the neonates. Pediatr. Neonatol. [Internet] 56(6), 376–381 (cited 2020 Jan 27). Available from: https://linkinghub.elsevier.com/retrieve/pii/S1875957215000492.
Travers, S., Martinerie, L., Boileau, P., Xue, Q.Y., Lombès, M., Pussard, E., 2018. Comparative profiling of adrenal steroids in maternal and umbilical cord blood. J. Steroid Biochem. Mol. Biol. 178, 127–134. https://doi.org/10.1016/j.jsbmb.2017.11.012.
Triguero-Mas, M., Donaire-Gonzalez, D., Seto, E., Valentín, A., Martínez, D., Smith, G., et al., 2017. Natural outdoor environments and mental health: Stress as a possible mechanism. Environ Res. 159, 629–638.
Tsunetsugu, Y., Lee, J., Park, B.J., Tyrväinen, L., Kagawa, T., Miyazaki, Y., 2013 May. Physiological and psychological effects of viewing urban forest landscapes assessed by multiple measurements. Landsc Urban Plan. 113, 90–93.
Tyrväinen, L., Ojala, A., Korpela, K., Lanki, T., Tsunetsugu, Y., Kagawa, T., 2014 Jun Jun. The influence of urban green environments on stress relief measures: A field experiment. J. Environ. Psychol. 38, 1–9.
Ulrich, R.S., Simons, R.F., Losito, B.D., Fiorito, E., Miles, M.A., Zelson, M., 1991. Stress recovery during exposure to natural and urban environments. J. Environ. Psychol. 11 (3), 201–230.
United Nations. 2018 Revision of World Urbanization Prospects | Multimedia Library - United Nations Department of Economic and Social Affairs [Internet]. 2018 Revision of World Urbanization Prospects | Multimedia Library - United Nations Department of Economic and Social Affairs. 2018 [cited 2020 Jan 27]. Available from: https://www.un.org/development/desa/publications/2018-revision-of-world-urbanization-prospects.html.
White, M.P., Alcock, I., Wheeler, B.W., Depledge, M.H., 2013. Would you be happier living in a greener urban area? A fixed-effects analysis of panel data. Psychol. Sci. 24 (6), 920–928.
Wynne-Edwards, K.E., Lee, K., Zhou, R., Edwards, H.E., 2019. Sex differences in substrates and clearance products of cortisol and corticosterone synthesis in full-term human umbilical circulation without labor: substrate depletion matches synthesis in males, but not females. Psychoneuroendocrinology 109. https://doi.org/10.1016/j.psyneuen.2019.104381.