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Association between neighbourhood green space and biological markers in school-aged children. Findings from the Generation XXI birth cohort

Ana Isabel Ribeiro[a,b,*], Carla Tavares[c], Alexandra Guttentag[d], Henrique Barros[a,b]

[a] EPIUnit – Instituto de Saúde Pública, Universidade do Porto, 4050-600 Porto, Portugal
[b] Department of Public Health, Forensic Sciences and Medical Education University of Porto Medical School, 4200-319 Porto, Portugal
[c] Unidade de Saúde Pública do ACeS Entre Douro e Vouga I – Feira/Arouca, 4520-244 Santa Maria da Feira, Portugal
[d] College of Global Public Health, New York University, New York, NY 10012, United States of America

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ABSTRACT

Background: There is considerable literature on the psychological and behavioural benefits of green space. However, less is known about its health-promoting effects, as expressed on biological markers. Additionally, incorporating biomarkers into pediatric research may help elucidate the links between exposures to environmental stressors and lifelong health.

Objective: To measure the association between geographical accessibility to green spaces and allostatic load (AL), a measure of biological multi-system dysregulation.

Methods: We used data from 3108 7-year old children enrolled in Generation XXI, a population-based birth cohort from the Porto Metropolitan Area (Portugal). We computed an AL index based on seven biomarkers representing four regulatory systems: immune/inflammatory system (high sensitivity C-reactive protein); metabolic system (high density lipoprotein; total cholesterol; glycated hemoglobin; waist-hip ratio) and cardiovascular system (systolic and diastolic blood pressure). Accessibility to green spaces was calculated using a Geographic Information System and crude and adjusted associations were estimated using mixed-effects regression models.

Results: Among the 3108 children (51.7% male; mean age 87.3 months), the mean AL index was 0.00 (standard deviation 2.94). Adjusted models showed that having a green space within 400 m and 800 m from the child's school was inversely associated with AL (400 m: beta −0.29 95% CI −0.54 to −0.02; 800 m: −0.29 95% CI −0.51 to −0.07). Also, there was a 12% (0%; 23%) increase in the AL index for every 1 km increase in distance to the nearest green space. No significant associations with AL were observed with residential accessibility to green space or with the presence of a garden at home.

Conclusion: We found a cross-sectional negative association between accessibility to green space near schools and AL in children, suggesting that the provision of green space may contribute to improvements in population health beginning early in life.

1. Introduction

Exposure to green space has been associated with better health, including improved levels of mental health (Cox et al., 2017; Gascon et al., 2015), physical fitness (Marselle et al., 2013), cognitive (Gidlow et al., 2016) and immune function (Kuo, 2015), and lower mortality (Gascon et al., 2016). A growing body of research suggests that exposure to green space and natural environments is particularly beneficial in childhood, a critical and sensitive period during which time the foundations for good health are laid (Richardson et al., 2017; Seltenrich, 2015).

The effects of green space on children's health may involve numerous pathways (Markevych et al., 2017). Proximity to green space encourages physical activity and exercise, which in turn promote cardiorespiratory fitness, bone health, and weight control (McCurdy et al., 2010). Contact with green spaces has also been related to improved cognition (Dadvand et al., 2015) and concentration (Faber Taylor and Kuo, 2009), reduced behavioural problems among school-aged children (Kuo and Faber Taylor, 2004), improved immune function, and lower risk of allergic and respiratory diseases (Ruokolainen et al., 2015). Moreover, green spaces can alleviate social and physical environmental stressors. The presence of green space improves air and water quality

* Corresponding author at: EPIUnit - Instituto de Saúde Pública, Universidade do Porto, Rua das Taipas, n° 135, 4050-600 Porto, Portugal.
E-mail address: ana.isabel.ribeiro@ispup.up.pt (A.I. Ribeiro).

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(Calfapietra et al., 2016), reduces noise pollution (Van Renterghem et al., 2015), and mitigates the impact of extreme weather events (Govindarajulu, 2014), thereby reducing some of the environmental risks associated with urban life. Additionally, neighbourhood green space may minimize socioeconomic inequalities in health (Mitchell and Popham, 2008), alleviate symptoms of chronic stress and anxiety, and promote relaxation (van den Berg et al., 2010; Berto, 2014).

Proximity to green spaces is likely to affect multiple physiological systems. Whilst the literature on the psychological and behavioural benefits of green space is considerable, less is known about the health-promoting effects of green space on biological markers (Haluza et al., 2014). Incorporating biomarkers into pediatric research studies may help elucidate the links between exposure to environmental stressors and lifelong health (Condon, 2018). Biomarkers can be used to directly determine children's exposure to certain environmental factors, the effects of the exposures, and individual susceptibility to the exposures, including genetics (Lanphear and Bearer, 2005). Further, biomarkers may predict future disease risk, allowing researchers to better comprehend how physiological damage develops across bodily systems.

The concept of allostatic load (AL) (McEwen and Stellar, 1993) offers an integrative model for understanding how exposure to chronic environmental and social stressors during development can lead to a state of multisystem dysregulation and predisposition to disease (Haluza et al., 2014). AL is operationalized as a combination of biomarkers including primary mediators (stress-related hormones that help maintain homeostasis after exposure to stressful stimuli, e.g. cortisol) and secondary outcomes (sub-clinical disturbances in markers of cardiovascular, metabolic, and immune functioning, e.g. blood lipids); AL ultimately provides a measure of the cumulative toll of the aforementioned on biological systems (Bird et al., 2010; Gruenewald et al., 2006).

To the best of our knowledge, only one study has addressed the relationship between exposure to green space and AL (Egorov et al., 2017), using a relatively small sample of adults, two-thirds of whom were women. In the present study, we estimated the association between geographical accessibility to green spaces and AL at the age of 7 years.

2. Material and methods

2.1. Study design and participants

This cross-sectional investigation uses data from Generation XXI (G21), a population-based birth cohort of 8647 newborns recruited in 2005/06 (wave 1) in the Porto Metropolitan Area, Northern Portugal (Fig. 1). Recruitment occurred in five public maternity units, where 95% of the region's births occur. During the hospital stay, women delivering live births were invited to participate in the G21 study, and 92% of mothers agreed. All participants were invited for a re-evaluation when the child was four (2009/11; wave 2) and seven (2012/14; wave 3) years of age. We used data from the 7-year evaluation of the cohort, which took place between April 2012 and March 2014. At 7 years, 6889 (80% of the initial cohort) children participated. More details about the cohort have been published elsewhere (Larsen et al., 2013).

All phases of the study complied with the Ethical Principles for Medical Research Involving Human Subjects expressed in the Declaration of Helsinki. The study was approved by the University of Porto Medical School/S. João Hospital Centre ethics committee and a signed informed consent was obtained from all participants.

In this study, we only included participants residing in and attending schools in areas for which the cartography of the green areas was available. Participants were also excluded if their AL biomarkers data, obtained via study staff, was incomplete. The final sample size was 3108 children. Supplementary material 1 describes the participant selection process.

We performed a comparative analysis between the group of children included in the study and those excluded. Data indicated that the included children belonged to families with lower incomes ($p < 0.001$; monthly household income > 1500 euros 41.5% among included vs. 47.0% among excluded) and lower education levels, as measured by maternal education ($p = 0.003$; tertiary education 27.9% included vs. 31.3% excluded), but the two groups shared similar demographic characteristics (age and sex).

2.2. Biomarkers and allostatic load index

During the evaluation, participants completed structured questionnaires and received a physical examination by trained personnel. Anthropometric measurements were taken, with children in underwear and bare feet. Weight was measured to the nearest one-tenth of a kilogram with the use of a digital scale (Tanita® UM-018), and standing height was measured to the nearest one-tenth of a centimeter with the use of a wall stadiometer (Seca® 208). Waist circumference was measured at umbilical level (Gibson, 2005), with abdomen relaxed and hip circumference was measured at the level of large femoral protuberances using a SECA 201 tape. All anthropometric measurements were rounded to the nearest 0.1 kg or cm. Body mass index (BMI) (kg/m^2) and waist-hip ratio were calculated afterwards. BMI was transformed into age and sex-specific z-scores using the World Health Organization (WHO) standards as reference (WHO, 2006). Children with BMI z-score < -2 were classified as underweight, those between ≥ -2 and $\leq +1$ were classified as normal weight; those with z-score between $> +1$ and $\leq +2$ were classified as overweight; and those with z-score $> +2$ were classified as obese. Blood pressure was measured with an electronic sphygmomanometer (Medel Elite) with the child comfortably sitting in a chair, with the cuff on the non-dominant arm, 2–3 cm above the elbow (without clothes compressing the arm). Research staff took two measurements of systolic (SBP) and diastolic (DPB) blood pressure, separated by at least 5 min, after 10-minute resting period. If the difference between the two measurements was < 5 mmHg for SBP or DBP, the mean was calculated. If the difference was larger than 5 mmHg, a third measurement was taken and the mean of the two closest values was used. After an overnight fast, research personnel collected a venous blood sample, according to standard procedures, after applying a topical analgesic cream (EMLA cream). The Clinical Pathology Department of Centro Hospitalar São João (Porto) performed measurements of the different blood markers on fresh blood samples.

In this study, we based the AL index on seven biomarkers representing four regulatory systems: immune and inflammatory systems (high sensitivity C-reactive protein, hsCRP); metabolic system (high density lipoprotein HDL; total cholesterol, glycated hemoglobin, HbA1C; and waist-to-hip ratio) and cardiovascular system (SBP and DBP). Our index differs from the original one proposed by Seeman, because ours did not include primary mediators (these were unavailable in the G21 study) but did include hsCRP. The AL index we used was defined as the sum of the sex-specific z-scores of the seven biomarkers that make up the index, so that a larger index number indicates a higher allostatic load. The z-score for HDL cholesterol was multiplied by -1 to account for its protective effect.

2.3. Address geocoding

Interviewers collected each child's residential addresses during routine telephone calls with the caregiver. At the time of evaluation (in our study, the 7 year evaluation), caregivers were asked to confirm the child's residential address once again. Following, residential addresses were processed and georeferenced using ArcGIS Online World Geocoding Service and Google Earth, due to their superior positional accuracy (Ribeiro et al., 2014). School location information came from the G21 study questionnaire, which included a question that asked for the name of the school that the child attended at the time of the

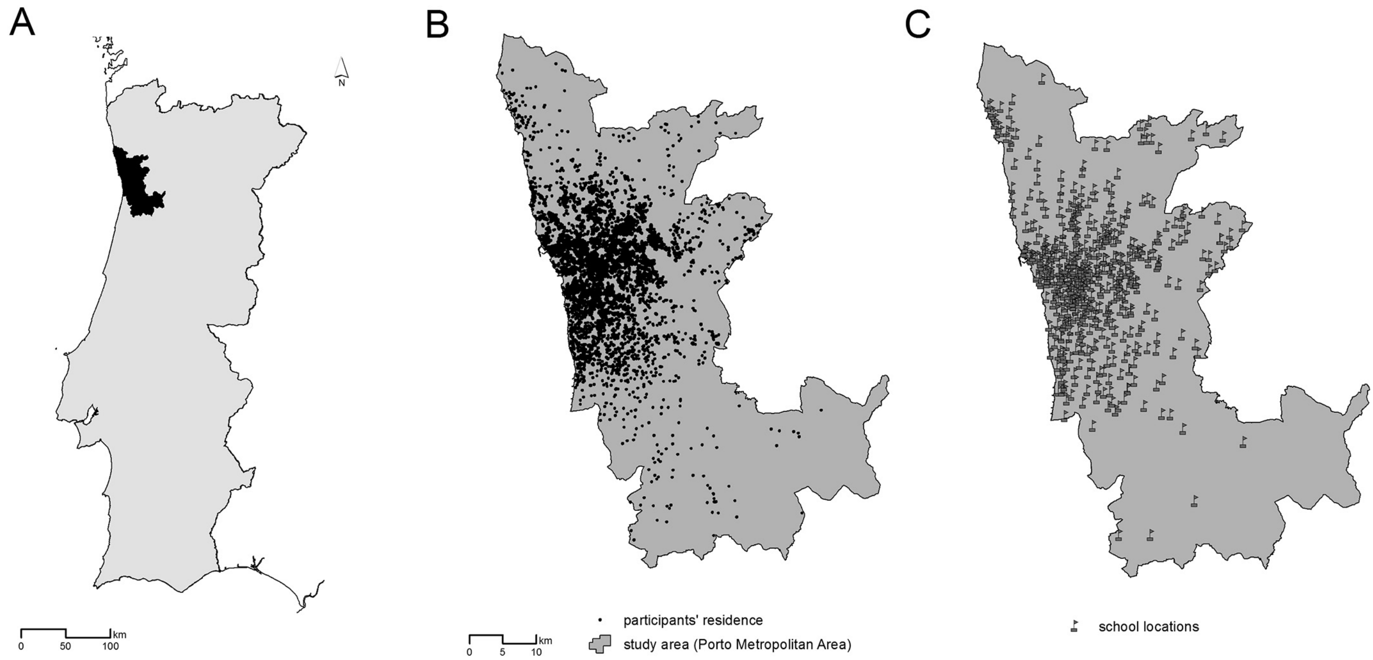

Fig. 1. Location of the study area in the country of Portugal (A) and spatial distribution of participants' residence (B) and school locations (C) across the study area.

evaluation. The school location was then identified in the DGEST (Direção-Geral dos Estabelecimentos Escolares, in English, General Direction of School Establishments) database (https://www.dgeste.mec.pt/index.php/pesquisa-de-agrupamentos/), which provides the X and Y coordinates of every private/public school in the country.

2.4. Geographical accessibility to urban green spaces

We considered a total of 226 public green spaces available in 2012–14, without restrictions on size, location, or characteristics, to cover the universe of public green spaces available in the study area that could be freely (at no cost) used by the population. Green space polygons and entrance locations were obtained from the city council's digital maps, described in previous studies (Hoffimann et al., 2017).

Using the point location of each child's residence and school as a starting point, the following network-based measures of geographical accessibility to green spaces were calculated: (i) availability of green spaces within 400 and 800 m from the residence and school (yes/no); (ii) number of green spaces available within 400 and 800 m from the residence and school (count); (iii) shortest distance to the nearest green space (km). When green spaces were bounded (i.e. with fencing) we used the distance to the entrance; otherwise, the distance to the boundary was used.

For calculations, we used ArcGIS version 10.5 software and the Network Analyst extension, using an updated street network dataset provided by the Environmental Systems Research Institute.

2.5. Covariates

The following variables were considered: child's sex, BMI, socioeconomic conditions of the household (measured by the mother's education level and household disposable income), quintiles of neighbourhood socioeconomic deprivation (fully described elsewhere (Guillaume et al., 2016; Ribeiro et al., 2017)), neighbourhood population density, urbanity level, physical activity (minutes/day spent in sports and active leisure activities) and self-reported medical diagnosis of asthma, rhinitis, and/or allergy. Maternal educational attainment was measured by years of schooling, which was then categorized into three classes: primary (≤9 years of education, ISCED-International Standard Classification of Education 2011 classes 0–2), which corresponds to the compulsory education in Portugal in the age-cohort of the G21 mothers; secondary (10–12 years, ISCED = 3) and tertiary (13 years or more, ISCED = 4–6). Household monthly disposable income was grouped into three ordinal categories to generate a more uniform distribution of the participants across the classes: < 1001, 1001–1500, > 1500 euros. The first class includes the situation wherein both parents receive the minimum national wage (475 euros in 2010, ~559 US dollars).

Level of urbanity was determined according to Statistics Portugal's 2014 classification of urban areas. This classification groups the Portuguese civil parishes into three classes: predominantly urban areas, moderately urban areas, and predominantly rural areas (INE, 2014). Population density (inhabitants per km^2) in 2011 (the most recent census) at the neighbourhood-level was also obtained from Statistics Portugal (INE, 2011).

2.6. Statistical analysis

We computed absolute frequencies and percentages or means and standard deviations (SD) for categorical and continuous variables, respectively. *t*-Tests or Mann-Whitney tests were used for two-group comparisons, as appropriate. A significance level of $p < 0.05$ was adopted for these analyses.

To estimate associations between the AL index and the measures of geographical accessibility to green spaces, we used mixed-effects linear regression models that take into account the hierarchical data structure (several individuals living in the same neighbourhood and attending the same school) by adding random effects at school level and neighbourhood-level. The associations were estimated by including a fixed effect slope for the determinants of interest and were expressed using regression coefficients ("beta") along with corresponding 95% confidence intervals ("95% CI"). Both crude and adjusted models were fitted. In the adjusted models, we considered the following confounding variables: child's sex, mother's education level, quintiles of neighbourhood socioeconomic deprivation, urbanity level and neighbourhood population density.

We hypothesized that physical activity, BMI and allergic and respiratory diseases could be potential mechanisms underlying the association between green space and AL. Thus, following Preacher and Kelley (2011) and, more recently, Dadvand et al. (2015), to quantify these mediation effects, we calculated the percent of the associations between green space and AL explained by physical activity, BMI, and allergic and respiratory disease as $[1 - (\beta_{gm}/\beta_g)] \times 100$, where β_{gm} was the regression coefficient for the green space exposure in a fully adjusted model including the mediators (i.e., physical activity, BMI, or allergic/respiratory diseases) and β_g was the regression coefficient in the fully adjusted model without including the mediator. Additionally, the presence of interaction effects was evaluated by including interaction terms between school and residential greenness and between greenness and sex and socioeconomic variables. As Supplementary material, we have presented the adjusted associations between green space and each individual biomarker composing the AL index.

To confirm that the chosen distance thresholds did not affect the study results, we performed sensitivity analyses to compare the results obtained using two distinct and commonly-used buffer sizes (400 and 800 m).

Additionally, to guarantee that we were not violating the independence assumption of linear regression, we investigated whether spatial autocorrelation was present in the model. Moran's I global spatial autocorrelation, obtained using ArcMap 10.5, was 0.014 ($p = 0.441$) indicating very low levels of global autocorrelation.

Statistical analysis was performed using R software version 3.3.3 and the statistical package 'lme4' (Bates et al., 2014).

3. Results

Table 1 depicts the sample characteristics. Among the 3108 included participants, 51.7% were male. Participants were, on average, 85.3 months old (SD 2.3). Forty-two percent of the mothers had a primary education level, and 30.1% and 27.9% had secondary and tertiary levels, respectively. Twenty percent of the children resided in the most deprived neighbourhoods and 30.3% resided in households with a monthly disposable income of 1000 euros or fewer. Twenty-one percent of the participants were overweight and 10.5% were obese. Regarding the residential exposure to green space, 13.7% of the children lived within 400 m from a green space and 35.3% lived within 800 m from a green space. Availability of green space around schools was slightly higher: 20.1% and 40.2% of the children attended a school with green spaces within 400 m and 800 m, respectively. Only 5.4% and 24.3% of the children were simultaneously exposed to green spaces around school and home within a distance of 400 m and 800 m, respectively. Among the 616 children who had a green space within 400 m from school, 26.8% also had a green space in the home surroundings. This percentage increased to 60.4% when adopting the 800 m distance threshold.

Table 1 also shows the mean values of the biomarkers that were used to calculate the AL index, with a mean of 0.00 (SD 2.94, range: −8.76 to 21.23). As shown in Table 2, the mean AL index was lower among children residing in areas within 400 m and 800 m from a green space versus those who did not have any accessible green space in the home surroundings (400 m: −0.21 vs. 0.03, $p = 0.10$; 800 m: −0.07 vs. 0.04, $p = 0.35$). Larger differences were observed when comparing those with and without accessible green spaces in the school surroundings: the mean AL was significantly lower among children attending schools with green spaces within 400 m and 800 m (400 m: −0.27 vs. 0.06, $p = 0.01$; 800 m: −0.22 vs. 0.13, $p = 0.001$). Similar trends were observed for the individual biomarkers that compose the AL index.

Table 3 shows the results from the mixed-effects regression models. No significant association between the different measures of geographical accessibility to green space around residence and AL were observed, despite the fact there was a trend of decreasing AL with increasing availability of green space around the home and a trend of increasing AL with increasing distance to the nearest green space.

Table 1
Sample sociodemographic, clinical, and environmental characteristics ($n = 3108$).

Variables	Count (%) or Mean (standard deviation)
Gender (male)	1606 (51.7%)
Age (months)	85.3 (2.3)
Maternal education	
Primary (≤9 years)	1304 (42.0%)
Secondary (10–12 years)	937 (30.1%)
Tertiary (> 12 years)	867 (27.9%)
Household monthly income	
≤1000 euros	941 (30.3%)
1001–1500 euros	876 (28.2%)
> 1500 euros	1291 (41.5%)
Body mass index	
Underweight	4 (0.1%)
Normal	2091 (67.3%)
Overweight	686 (22.1%)
Obese	327 (10.5%)
Neighbourhood socioeconomic deprivation quintiles	
Q1-least deprived	629 (20.2%)
Q2	609 (19.6%)
Q3	627 (20.2%)
Q4	621 (20.0%)
Q5-most deprived	622 (20.0%)
Home garden (yes)	1263 (40.6%)
Time spent in sports and active leisure activities (min/day)	93.0 (56.0)
Medical diagnosis of asthma at 7 years	194 (6.3%)
Medical diagnosis of allergy at 7 years	527 (17.2%)
Medical diagnosis of rhinitis at 7 years	238 (7.7%)
Green space at 400 m from school (yes)	616 (20.1%)
Green space at 800 m from school (yes)	1230 (40.2%)
No. of green spaces at 400 m from school	0 (0–3)[a]
No. of green spaces at 800 m from school	0 (0–7)[a]
Distance from school to the nearest green space (km)	1.2 (1.1)
Population density of the school location (inhab/sq meter)	393.4 (390.4)
Urbanity level of the school location	
Predominantly urban	2948 (97.4)
Moderately urban	72 (2.4)
Predominantly rural	8 (0.3)
Green space at 400 m from residence (yes)	425 (13.7%)
Green space at 800 m from residence (yes)	1098 (35.3%)
No. of green spaces at 400 m from residence	0 (0–3)[a]
No. of green spaces at 800 m from residence	0 (0–8)[a]
Distance from residence to the nearest green space (km)	1.4 (1.1)
Population density of the residence location (inhab/sq meter)	975.8 (938.7)
Urbanity level of the residence location	
Predominantly urban	3021 (97.2)
Moderately urban	75 (2.4)
Predominantly rural	12 (0.4)
Systolic blood pressure (mmHg)	105.6 (7.4)
Diastolic blood pressure (mmHg)	70.2 (6.3)
Waist-to-hip-ratio	0.9 (0.04)
High density lipoprotein cholesterol (mg/dl)	55.8 (10.7)
Total cholesterol (mg/dl)	169.3 (28.4)
Glycated hemoglobin (%)	5.2 (0.4)
High sensitivity C-reactive protein (mg/L)	1.3 (3.9)
Allostatic load index	0.0 (2.9)

[a] Mean (maximum and minimum).

Similarly, no significant associations between AL and the presence of a garden at home were observed.

On the other hand, the availability of green spaces within 400 and 800 m from the school was negatively and significantly associated with AL. Further, the greater the distance from the school to the nearest green space, the higher the AL index. Contrastingly, the number of accessible green spaces around schools did not seem to be associated with AL, particularly when using the 400 m distance threshold.

To account for the confounding effect of several variables, models

Table 2
Allostatic load index and individual biomarkers according to the availability of accessible green space in the home and school surroundings (n = 3108).

Variables	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	Waist-to-hip-ratio	High density lipoprotein cholesterol (mg/dl)	Total cholesterol (mg/dl)	Glycated hemoglobin (%)	High sensitivity C-reactive protein (mg/L)	Allostatic load index
Green space at 400 m from school (yes)	105.12	69.66	0.89	55.98	170.15	5.22	1.18	−0.27
Green space at 400 m from school (no)	105.68	70.36	0.89	55.71	169.08	5.23	1.39	0.06
p-Value[a]	0.09	0.01	0.20	0.58	0.41	0.44	0.91	0.01
Green space at 400 m from residence (yes)	105.05	69.75	0.89	56.75	172.75	5.22	1.16	−0.21
Green space at 400 m from residence (no)	105.71	70.30	0.89	55.61	168.71	5.23	1.37	0.03
p-Value	0.10	0.20	0.42	0.04	0.01	0.80	0.99	0.10
Green space at 800 m from school (yes)	105.09	69.86	0.89	56.21	170.26	5.22	1.12	−0.22
Green space at 800 m from school (no)	105.89	70.46	0.89	55.47	168.65	5.23	1.50	0.13
p-Value	0.003	0.01	0.74	0.06	0.13	0.54	0.28	0.001
Green space at 800 m from residence (yes)	105.46	70.03	0.89	56.18	170.41	5.23	1.19	−0.07
Green space at 800 m from residence (no)	105.71	70.33	0.89	55.53	168.64	5.22	1.43	0.04
p-Value	0.37	0.20	0.77	0.11	0.10	0.39	0.73	0.35
Home garden (yes)	105.50	70.01	0.89	56.35	170.13	5.23	1.22	−0.07
Home garden (no)	105.71	70.38	0.89	55.39	168.71	5.22	1.42	0.05
p-Value	0.43	0.10	0.38	0.02	0.17	0.39	0.25	0.26

[a] Comparisons based on the *t*-test or Mann-Whitney (the latter used for high sensitivity C-reactive protein).

Table 3
Crude and adjusted associations between allostatic load index and accessibility to green spaces around the residence and school (n = 3108).

	Crude beta and 95% CI	Adjusted beta and 95% CI[a]
Around school		
Green space at 400 m from school (yes)	−0.11 (−0.20 to −0.02)	−0.29 (−0.55 to −0.02)
Green space at 800 m from school (yes)	−0.35 (−0.57 to −0.12)	−0.29 (−0.51 to −0.07)
No. of green spaces at 400 m from school	−0.19 (−0.39 to 0.01)	−0.15 (−0.34 to 0.04)
No. of green spaces at 800 m from school	−0.08 (−0.15 to −0.01)	−0.06 (−0.13 to 0.01)
Distance to the nearest green space (km)	0.13 (0.02–0.23)	0.12 (0.00–0.23)
Around residence		
Green space at 400 m from residence (yes)	−0.25 (−0.56 to 0.05)	−0.19 (−0.50 to 0.12)
Green space at 800 m from residence (yes)	−0.08 (−0.31 to 0.14)	−0.03 (−0.25 to 0.20)
No. of green spaces at 400 m from residence	−0.23 (−0.46 to 0.01)	−0.18 (−0.41 to 0.06)
No. of green spaces at 800 m from residence	−0.06 (−0.15 to 0.03)	−0.04 (−0.13 to 0.05)
Distance to the nearest green space (km)	0.09 (−0.01 to 0.19)	0.05 (−0.06 to 0.15)
At residence		
Home garden (yes)	0.13 (−0.08 to 0.34)	0.09 (−0.13 to 0.32)

95% CI: 95% confidence intervals.
[a] Adjusted for child's sex, maternal education, neighbourhood deprivation, urbanity and population density.

were adjusted for child's sex, maternal education, urbanity level, population density, and neighbourhood socioeconomic deprivation. Despite the slight attenuation of the effects, significant associations with the measures of accessibility to green space around school remained. Having a green space within 400 m and 800 m from the school was inversely associated with the AL index (400 m: beta −0.29 95% CI −0.55 to −0.02; 800 m: −0.29 95% CI −0.51 to −0.07). Moreover, for each 1 km increase in distance from the school to the nearest green space, the AL index increased 10% (95% CI 0–23%). Analyses of individual biomarkers also showed associations between presence of a green space near school (Yes/No) and cardiovascular biomarkers (SBP and DBP) and inflammation measured by hsCRP (see Supplementary material 2).

Analyses revealed no significant interaction effects between school and residential greenness and between greenness exposure and sex and socioeconomic variables. The mediation analysis, depicted in Table 4, revealed that associations between green space proximity and AL do not seem to be mediated by physical activity, BMI, or asthma, allergy and rhinitis.

4. Discussion

This study assessed, for the first time in a pediatric population, the relationship between proximity to green space and allostatic load (AL), a measure of biological multi-system dysregulation. Using data from a large population-based cohort from the Porto Metropolitan Area, we found a significant inverse association between greater accessibility to green space around schools and AL. The association remained after accounting for potential confounders at the individual- and neighbourhood-levels.

Our findings are in accordance with a previous investigation (Egorov et al., 2017) conducted in a relatively small sample of adults (mostly women) that showed that greater vegetated land cover was significantly associated with reduced adjusted odds of potentially unhealthy levels of several individual biomarkers and with reduced AL overall. We only identified one study that explicitly investigated the connection between green space and AL (Egorov et al., 2017). Nevertheless, there is a recent body of research demonstrating the short-term benefits of contact with green spaces on individual physiological biomarkers (Haluza et al., 2014; Lee et al., 2011; Roe et al., 2013; Park et al., 2007; Yamaguchi et al., 2006; Hartig et al., 2003; Twohig-Bennett and Jones, 2018). An experimental study showed that forest bathing (i.e., sitting still in a forest and observing the forest view) increases parasympathetic nervous activity and suppresses sympathetic activity (compared with the urban/built environment), resulting in lower cortisol levels and pulse rate (Lee et al., 2011). A study conducted in deprived communities in the United Kingdom demonstrated that residents in greener neighbourhoods had healthier diurnal salivary cortisol patterns, indicating reduced effects of chronic stress (Roe et al., 2013). Further, a recent meta-analysis on the health benefits of green space showed that green space exposure is significantly associated with reductions in diastolic blood pressure, salivary cortisol, and heart rate (Twohig-Bennett and Jones, 2018). Several studies have also assessed the impact of contact with nature/green space on biomarkers measured in youth/student populations; the majority of these studies reported significant positive effects, with exposure to green space associated with improved cortisol levels (Park et al., 2007), amylase activity (Yamaguchi et al., 2006), and blood pressure (Hartig et al., 2003). Such findings demonstrate that the effects of environmental exposures, such as a lack of green space in living environments, can manifest as early as childhood and adolescence.

Interestingly, we found that the association between green space exposure and AL only exists when considering school-based measures of accessibility to green space.

In Portugal, parents' decisions regarding where their children will attend school is commonly based on the (closest) distance from their residence or the parents' work; therefore, one would expect similar results between AL and green space when taking into account the school and residential setting. However, we found that the average distance from school to residence was 1885 m (median 948 m), indicating that these children attend schools located outside their immediate residential neighbourhood. A plausible explanation for the presence of a significant association between green space in the school environment (and not in the residential environment) and AL may be related to patterns of time utilization in youth and children. Portuguese children stay at school, in general, 9 h/day and, according to 2015 data on the countries belonging to the Organization for Economic Co-operation and Development (OECD), Portuguese children spend more time at school than the OECD average (UNESCO, 2015). Additionally, the ways children use and experience green space may be different between residential and school settings. Due to the presence of schoolmates and because daytime is spent in school (in general, classes start at 8 am and end at 5 pm), it is likely that children spend more time in leisure and social activities in their school surroundings, including green spaces, than in the home surroundings. Although we cannot infer this from our study, green areas in the vicinity of schools could be places of encounters among children during their leisure time, school breaks and/or commute. Further, even if the time spent in the spaces outside the school building is limited, studies have shown that the mere presence of 'naturalness' (e.g. trees) in views from windows have health benefits (Tranter and Malone, 2004). Finally, initiatives such as 'A natureza é a melhor sala de aula' (in English, 'Nature is the best classroom'), where teachers take students off-site to visit nearby parks, have been implemented in several schools in the Porto Metropolitan Area, with the goal of exposing children and young people to nature, in an educational context (Twohig-Bennett and Jones, 2018). Corroborating the stronger effects of school-based green space exposures that we found in this study, a 2017 study conducted in Porto found that green spaces in schools' surroundings were associated with increased physical activity among adolescents, but no effect was observed when considering green space around the residences (Magalhães et al., 2016).

Table 4
Associations (beta and 95% confidence intervals) between allostatic load index and accessibility to green spaces around the residence and school (n = 3108).

	Main analysis[a]	Further adjusted for mediators[b]	% explained by mediation
Around school			
Green space at 400 m from school (yes)	−0.29 (−0.55 to −0.02)	I) −0.35 (−0.63 to −0.07)	None
		II) −0.31 (−0.58 to −0.04)	None
		III) −0.30 (−0.54 to −0.06)	None
Green space at 800 m from school (yes)	−0.29 (−0.51 to −0.07)	I) −0.37 (−0.60 to −0.14)	None
		II) −0.31 (−0.53 to −0.09)	None
		III) −0.26 (−0.46 to −0.06)	3.8
No. of green spaces at 400 m from school	−0.15 (−0.34 to 0.04)	I) −0.19 (−0.39 to 0.02)	None
		II) −0.18 (−0.38 to 0.02)	None
		III) −0.18 (−0.36 to −0.01)	None
No. of green spaces at 800 m from school	−0.06 (−0.13 to 0.01)	I) −0.07 (−0.14 to 0.01)	None
		II) −0.07 (−0.14 to 0.00)	None
		III) −0.06 (−0.13 to 0.00)	None
Distance to the nearest green space (km)	0.12 (0.00–0.23)	I) 0.14 (0.02–0.26)	None
		II) 0.14 (0.01–0.23)	None
		III) 0.12 (0.02–0.22)	None
Around residence			
Green space at 400 m from residence (yes)	−0.19 (−0.50 to 0.12)	I) −0.16 (−0.49 to 0.16)	13.6
		II) −0.23 (−0.54 to 0.08)	None
		III) −0.11 (−0.39 to 0.18)	43.6
Green space at 800 m from residence (yes)	−0.03 (−0.25 to 0.20)	I) −0.08 (−0.32 to 0.16)	None
		II) −0.08 (−0.31 to 0.15)	None
		III) −0.03 (−0.23 to 0.18)	9.2
No. of green spaces at 400 m from residence	−0.18 (−0.41 to 0.06)	I) −0.16 (−0.41 to 0.09)	11.3
		II) −0.20 (−0.44 to 0.04)	None
		III) −0.13 (−0.35 to 0.09)	26.2
No. of green spaces at 800 m from residence	−0.04 (−0.13 to 0.05)	I) −0.05 (−0.14 to 0.05)	None
		II) −0.05 (−0.14 to 0.04)	None
		III) −0.04 (−0.12 to 0.04)	None
Distance to the nearest green space (km)	0.05 (−0.06 to 0.15)	I) 0.05 (−0.06 to 0.17)	None
		II) 0.06 (−0.05 to 0.17)	None
		III) 0.05 (−0.05 to 0.15)	None
At residence			
Home garden (yes)	0.09 (−0.13 to 0.32)	I) 0.11 (−0.13 to 0.35)	None
		II) 0.08 (−0.15 to 0.31)	14.6
		III) 0.04 (−0.17 to 0.25)	59.6

[a] Adjusted for child's sex, maternal education, neighbourhood deprivation, urbanity and population density.
[b] Adjusted for child's sex, maternal education, neighbourhood deprivation, urbanity, population density and potential mediators (I - physical activity; II - medical diagnosis of allergy, rhinitis and asthma, III-body mass index).

Looking at another endpoint, cognition, an investigation carried out in Barcelona found that the greener the school environment, the better the cognitive outcomes of school-age children, but no effect was observed when considering the residential environment (Dadvand et al., 2015). These findings, showing stronger beneficial effects of green space in the school surroundings, support the idea that local authorities and city planners must not neglect the school environment when developing legislation to improve the built environment and land-use distribution.

Several mechanisms may be implicated in this association between green space and AL since behaviours and physical exposures commonly associated with green space proximity have an effect on biological systems. Increased levels of physical activity, for instance, may constitute an important pathway that links green space to improved biological markers of cardiovascular, metabolic and inflammation systems (Kim et al., 2016; Tamosiunas et al., 2014). In the Porto Metropolitan Area, physical activity was shown to be associated with the presence of green space in the home and school surroundings in adolescent and adult populations (Magalhães et al., 2016; Ribeiro et al., 2013; Ribeiro et al., 2015). Respiratory and allergic disease could also mediate the observed relation between green space and AL. Green space may have dual, and opposing, effects on allergic diseases and asthma, both beneficial and detrimental. Beneficial, as green spaces inherently provide greater numbers and diversity of microbes and improve air quality. Green spaces may also be detrimental in this regard, as they may cause an exacerbation of respiratory and allergic symptoms. Possibly due to these opposing effects, our mediation analysis revealed no association between asthma and allergy and green space. Future research on the topic should address additional, and possibly more important, pathways, namely exposure to air pollutants and noise, as well as relaxation effects, because these may help elucidate why green space exposure affects biological markers.

The current study has a number of limitations. First, the cross-sectional analysis precludes causal interpretation. Second, due to data unavailability, we did not include primary mediators (stress-related hormones that help maintain homeostasis after exposure to stressful stimuli, e.g. cortisol), which capture the acute response to environmental stressors. There is currently no consensus regarding the choice of the relevant markers to be included (Castagné et al., 2018) and a large share of the studies on AL have omitted primary mediators from AL index calculations (Ribeiro et al., 2018). This is primarily because these biomarkers are not commonly measured in population-based studies and because there are substantial day-to-day and circadian variations in neuroendocrine hormones (e.g. cortisol)(Chung et al., 2011) which make single-time measurements unreliable. Indeed, a recent study looking at the predictive power of the components of the AL index found that cortisol was the biomarker with the smallest association with mortality rates (Castagné et al., 2018). Third, our sample only includes about half of the participants evaluated at 7 years of age. Children who were included belonged to families with lower incomes ($p < 0.001$; monthly household income > 1500 euros was 41.5% among included vs. 47.0% among excluded) and lower education levels, as measured by maternal education ($p = 0.003$; tertiary education was 27.9% among included vs. 31.3% among excluded). Whilst the differences between included and excluded participants were relatively small, our sample does not fully represent the socioeconomic characteristics of the initial cohort. Fourth, no data on the time spent in school and home environments were collected and, therefore, we cannot accurately ascertain the burden of the exposures that occur in each of the home and school environments. Yet, because school timetables are very similar, it is unlikely that this omission introduces any kind of bias in our results. Fifth, our analysis did not take into account seasonal effects, which could potentially influence some biomarker levels (Liu and Taioli, 2015) and also green space utilization (Chen et al., 2015; Nikolopoulou and Lykoudis, 2006). Sixth, we used the traditional operationalization of AL, which assumes a linear and positive relationship between biomarker levels and poor health and, therefore, does not capture the potential detrimental effects of low biomarker values (e.g. low blood pressure). Finally, similarly to other studies on neighbourhood health effects, our work may be affected by the Uncertain Geographic Context Problem (UGCoP). The UGCoP happens whenever the method to delimitate a person's neighbourhood (e.g. the use of a certain buffer size/shape) does not capture that individual's true geographic context, because their activities take place outside of their local residential/school/work environment (Kwan, 2012).

The population-based approach used in this study is an important strength of this investigation, especially because previous research on the biological effects of the exposure to green spaces have focused mostly on small samples from experimental and observational studies. Additionally, we considered a comprehensive and large group of potential confounders. The AL index we defined was the result of summed sex-specific z-scores. This approach allowed us to use the whole spectrum of values and capture small deviations. It is known that summary measures based on continuous scale properties may be slightly better predictors of a wider range of health outcomes than other measures (Seplaki et al., 2005). Further, we included hsCRP in the AL index because studies comparing the predictive power of a wide range of biomarkers of AL found that hsCRP is a biomarker that is more strongly associated with health endpoints than others, namely with mortality (Castagné et al., 2018). We used strict geocoding methods that ensure good positional accuracy and accuracy in the exposure assessment (Ribeiro et al., 2014). Finally, sensitivity analyses were conducted to assess the impact of the chosen distance thresholds (400 and 800 m, the most commonly used thresholds in the literature (Hoffimann et al., 2017; Witten et al., 2011; Besenyi et al., 2014; Crawford et al., 2008)) on the study conclusions; our results remained mostly unchanged regardless of the chosen distance.

5. Conclusions

In conclusion, we found that accessibility to green space surrounding schools, but not residences, has beneficial effects on AL among a large sample of urban children. Our study extends previous findings on the benefits of green space by exploring and proposing a biological mechanism by which green space may affect health. From a public health perspective, our findings suggest that the provision of green space in urban settings may be an effective strategy to promote population health since early life.

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Declaration of competing interest

The authors declare they have no actual or potential competing financial interests.

Contributions

AIR conceptualized the study. AIR and CT managed the spatial data. AIR and AG conducted the statistical analysis. AIR, CT and AG wrote the first draft of the manuscript. HB conducted the cohort study, supervised the study, and reviewed and edited the final version of the manuscript. All authors revised the manuscript critically for important intellectual content. All authors approved the final version of the manuscript.

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