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Exposure to green space and leukocyte mitochondrial DNA copy number in children and adolescents

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ABSTRACT

Mitochondrial DNA (mtDNA) is vulnerable to environmental exposure and is related to various diseases. However, the relationship of green space exposure with mtDNA copy number (mtDNAcn) is not yet well clarified. In this study, we sought to explore how green space exposure influences mtDNAcn in children and adolescents. This cross-sectional study involved 1151 participants aged 6–18 years from Liuzhou, China. Green space exposure was quantified using the normalized difference vegetation index (NDVI) within several circular buffers (250–2000 m). Leukocyte mtDNAcn was measured using the qPCR method. Multiple linear regression was employed to estimate the relationship of green space exposure with mtDNAcn. Per interquartile range increment in $NDVI_{250m}$, $NDVI_{500m}$, $NDVI_{1000m}$, and $NDVI_{2000m}$ were related to 3.33% (95% confidence interval [CI]: 1.00%, 5.72%), 3.37% (95% CI: 1.02%, 5.78%), 3.34% (95% CI: 0.93%, 5.81%), and 3.25% (95% CI: 0.49%, 6.08%) increase in mtDNAcn, respectively. Subgroup analyses showed that the positive relationship of green space exposure with mtDNAcn was more evident in children, females, participants with normal weight, and those not exposed to passive smoking. Our findings indicate a positive relationship of green space exposure with mtDNAcn in children and adolescents. Given the significance of mtDNAcn during childhood and adolescence, it is essential to implement strategies that enhance green environments to support the health and development of children and adolescents.

1. Introduction

Mitochondria are the primary sources and targets of reactive oxygen species at the intracellular level (Yakes and Van Houten, 1997). Due to the absence of protective histones and the limited capacity for DNA repair, mitochondrial DNA (mtDNA) is vulnerable to oxidative stress (Hagberg et al., 2014). To cope with oxidative damage, mitochondria can alter mtDNA copy number (mtDNAcn), making it a useful marker for quantifying mtDNA damage (Malik and Czajka, 2013). Research has reported that mtDNAcn is associated with various health conditions, such as biological aging (Foote et al., 2018), all-cause mortality (Ashar et al., 2015), cardiovascular disease (Ashar et al., 2017), and neurodegenerative diseases (Cerantonio et al., 2024).

Beyond genetic factors, mtDNAcn is susceptible to various environmental stressors, such as air pollution (Qiao et al., 2024), metals (Smith et al., 2021; Kupsco et al., 2019; Song et al., 2020), and polycyclic aromatic hydrocarbons (Duan et al., 2020; Cao et al., 2020). However, studies on mtDNAcn alterations in relation to environmental stressors

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have primarily focused on newborns or adults and have yielded inconclusive results. Childhood and adolescence are critical periods marked by dynamic physiological and metabolic changes, making them significant vulnerable windows for various environmental exposures (Wright, 2017). Moreover, reduced mtDNAcn in children and adolescents has been related to health issues such as obesity (Bordoni et al., 2019) and impaired cognitive function (Bijnens et al., 2019), which are important indicators of later-life health. Therefore, understanding environmental factors related to mtDNAcn during childhood and adolescence is crucial for uncovering potential long-term health implications.

Green space is a widely recognized environmental factor in promoting human health (Twohig-Bennett and Jones, 2018). The beneficial effects of green space may be partially explained by its ability to reduce psychological stress (Bloemsma et al., 2022; Towe-Goodman et al., 2024), promote physical activity (McCormack et al., 2010), and mitigate environmental stressors like air pollution (Nowak et al., 2006), all of which have been linked to mtDNAcn alterations (Wang et al., 2020; Hong et al., 2023; Brunst et al., 2017; Chang et al., 2016). However, research about the association of green space exposure with mtDNAcn is still sparse, particularly during childhood and adolescence. To date, only one research from Belgium has explored the association of residential green space with mtDNAcn in primary school children, reporting a positive association (Hautekiet et al., 2022), with no other studies available on this impact in adolescents. The findings from this study in a developed country may not generalize to developing countries because of discrepancies in cultural, sociodemographic, and environmental factors.

Therefore, we aimed to examine the relationship of green space exposure with mtDNAcn in Chinese children and adolescents through a cross-sectional study. We hypothesized that green space exposure would be positively related to mtDNAcn in this study.

2. Methods

2.1. Study population

We conducted a cross-sectional study, recruiting participants from eight schools that were randomly selected (three primary schools, three middle schools, and two high schools) in Liuzhou, China, from February to May 2018. The enrollment criteria were as follows: (a) residing in Liuzhou city, (b) aged 6–18 years, and (c) free from significant health issues like neurological or congenital heart diseases. A total of 1388 children and adolescents were initially enrolled. After excluding 173 individuals with missing blood samples or ineligible DNA quality and 64 individuals with missing information about home and school addresses, we ultimately included 1151 participants in this study.

This study received approval from Tongji Medical College, Huazhong University of Science and Technology, and all procedures were conducted in accordance with the Declaration of Helsinki. Written informed consents were obtained from the parents or legal guardians of all participants. Furthermore, all personal data underwent rigorous anonymization and de-identification to protect participant confidentiality and privacy.

2.2. Green space exposure assessment

Green space was characterized by the normalized difference vegetation index (NDVI). The NDVI data was extracted at 250 m and 16-day spatiotemporal resolutions from the Terra Moderate Resolution Imaging Spectroradiometer (MODIS) Vegetation Indices (MOD13Q1) (Didan, 2015) based on the geocode of residential and school addresses in this study. The NDVI captures vegetation density, varying from −1 to 1, with higher values signifying denser green vegetation. The average annual NDVI values for the year preceding participant enrollment were evaluated at four radial buffers of 250 m ($NDVI_{250m}$), 500 m ($NDVI_{500m}$), 1000 m ($NDVI_{1000m}$), and 2000 m ($NDVI_{2000m}$). Total green space exposure was weighted by time participants spent at home (18 h) and at school (6 h) during the day.

2.3. Mitochondrial DNA copy number measurement

The genomic DNA extraction of blood leukocytes was performed using the Wizard® Genomic DNA Purification Kit (Promega Corporation, USA). The purity and concentration of DNA templates were measured using the NanoDrop™ One Spectrophotometer (Thermo Fisher Scientific, USA). DNA samples with A260/280 in the range of 1.8–2.0 were considered eligible. Relative mtDNAcn was determined using the ratio of mitochondrial gene copy numbers (ND1) to a single-copy nuclear control gene [human β-globulin (hbg)] using quantitative polymerase chain reaction on the QuantStudio™ 7 Flex Real-Time PCR System (Applied Biosystems, USA). Details on mtDNAcn measurement were described in the **Supplementary methods**. Briefly, each sample was run in triplicate. The coefficients of variation for inter-run mitochondrial and single-copy gene were 1.24% and 1.06%, respectively.

2.4. Covariate assessment

We collected demographic and lifestyle data, including age, sex, maternal education, and passive smoking, through a questionnaire. Children were defined as 6–11 years old, and adolescents as 12–18 years old. Maternal education was classified into three groups: junior school or below, high school, and college or above. Height and weight measurements followed standardized protocols, and body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Age- and sex-standardized BMI z-scores were determined based on the World Health Organization (WHO) Child Growth Standards (WHO). Participants with BMI z-score >1 were considered overweight/obese (WHO).

2.5. Statistical analysis

A correlation heatmap was utilized to present Spearman correlations among indicators of green space exposure. Missing values for passive smoking were addressed using the multiple imputation method based on the "mice" package in R. All available data were used to generate 5 imputed data sets, and the pooled results were used. Multiple linear regression model was employed to assess the relationship of green space exposure with mtDNAcn, with mtDNAcn log-transformed due to its skewed distribution. To enhance the interpretation of regression models, we expressed all coefficients and 95% confidence intervals (CIs) as percent change (95% CIs) in mtDNAcn for per interquartile range (IQR) increase or quartile of green space exposure. We calculated the percent change in mtDNAcn as $\left(e^{\beta}-1\right)\times 100\%$ with 95% CI calculated as $\left(e^{(\beta\pm 1.96\times \mathrm{SE})}-1\right)\times 100\%$, where SE and β are the estimated standard error and regression coefficient, respectively. The analyses utilized two models: Model 1 was adjusted for age (continuous) and sex (male, female); Model 2 was further accounted for BMI z-score (continuous), passive smoking (yes, no), and maternal education (junior school or below, high school, college or above). Moreover, the restricted cubic spline regression model was used to examine the dose-response relationship of green space exposure with mtDNAcn. The models incorporated three knots placed at the 10th, 50th, and 90th percentiles of green space exposure, with the 10th percentile serving as the reference.

Subgroup analyses were conducted to evaluate potential modifications by demographic and lifestyle factors, including age (children, adolescents), sex (males, females), maternal education (junior school or below, high school, college or above), overweight/obesity (yes, no), and passive smoking (yes, no). The interaction effects of green space exposure with these factors were assessed by introducing multiplicative terms into the models, considering a P value < 0.1 as statistically significant. To explore the potential impact of rapid developmental phases,

we analyzed age- and sex-related differences in the association between green space exposure and mtDNAcn. Based on developmental stages (Ren et al., 2003), participants were divided into three groups for each sex: females (6–9 years, 10–14 years, 15–18 years) and males (6–11 years, 12–16 years, 17–18 years).

Furthermore, some sensitivity analyses were performed. First, we excluded first-year students, including those in grades 1, 7, and 10, due to their relatively short admission period in schools. Besides, we conducted the analyses after further adjustment for $PM_{2.5}$, PM_{10}, and NO_2, respectively. Daily concentrations of $PM_{2.5}$, PM_{10}, and NO_2 were estimated as described previously (Wei et al., 2021a, 2021b, 2023). We then calculated the average annual concentrations of $PM_{2.5}$, PM_{10}, and NO_2 at participants' residential and school addresses. Total exposure to $PM_{2.5}$, PM_{10}, and NO_2 was weighted by the time spent at home (18 h) and school (6 h) during the day.

All statistical analyses were conducted using R software (version 4.3.2). A two-tailed P value < 0.05 was considered statistically significant.

3. Results

Table 1 presents participants' characteristics. The average age of the 1151 participants was 11.7 ± 3.3 years. Among them, 47.2% were children, and 46.0% were males. A total of 226 participants (19.6%) were overweight/obese, and 255 participants (22.6%) reported passive smoking exposure. Maternal education level at college or above accounted for 23.7% of participants. The median (IQR) of mtDNAcn was 1.1 (0.8, 1.3). Table S1 displays the distribution of green space exposure. The median (25th–75th percentile) values for $NDVI_{250m}$, $NDVI_{500m}$, $NDVI_{1000m}$, and $NDVI_{2000m}$ were 0.27 (0.25, 0.32), 0.28 (0.25, 0.32), 0.28 (0.25, 0.31), and 0.30 (0.27, 0.34), respectively. Spearman correlation analysis showed strong positive correlations among indicators of green space, with coefficients ranging from 0.79 to 0.96 (Fig. S1).

Table 2 illustrates the relationship of green space exposure with mtDNAcn in children and adolescents. Per IQR increment in $NDVI_{250m}$, $NDVI_{500m}$, $NDVI_{1000m}$, and $NDVI_{2000m}$ were related to 3.33% (95% CI: 1.00%, 5.72%), 3.37% (95% CI: 1.02%, 5.78%), 3.34% (95% CI: 0.93%, 5.81%), and 3.25% (95% CI: 0.49%, 6.08%) increase in mtDNAcn, respectively. Compared to the lowest quartiles, the highest quartiles of $NDVI_{250m}$, $NDVI_{500m}$, $NDVI_{1000m}$, and $NDVI_{2000m}$ were related to an 8.46% (95% CI: 2.53%, 14.74%), 9.34% (95% CI: 3.44%, 15.58%), 7.67% (95% CI: 1.83%, 13.84%), and 6.56% (95% CI: 0.73%, 12.73%) increase in mtDNAcn, respectively (all $P_{trend} < 0.05$) (Table S2). The restricted cubic spline regression models indicated linear relationships of $NDVI_{250m}$, $NDVI_{500m}$, $NDVI_{1000m}$, and $NDVI_{2000m}$ with mtDNAcn (Fig. 1, all $P_{nonlinear} > 0.05$).

Table 1
Characteristics of participants (n = 1151).

Variables	mean ± SD, median (25th-75th percentile)/n (%)
Age (years)	11.7 ± 3.3
Children (6–11 years)	543 (47.2)
Adolescents (12–18 years)	608 (52.8)
Sex	
Males	529 (46.0)
Females	622 (54.0)
BMI z-score	0.03 ± 1.2
Overweight/obesity	
Yes	226 (19.6)
No	925 (80.4)
Passive smoking	
Yes	255 (22.6)
No	502 (77.4)
Maternal education	
Junior school or below	592 (51.4)
High school	286 (24.9)
College or above	273 (23.7)
$NDVI_{250m}$	0.27 (0.25, 0.32)
$NDVI_{500m}$	0.28 (0.25, 0.32)
$NDVI_{1000m}$	0.28 (0.25, 0.31)
$NDVI_{2000m}$	0.30 (0.27, 0.34)
$PM_{2.5}$ (μg/m^3)	42.2 (41.3, 43.0)
PM_{10} (μg/m^3)	67.8 (66.3, 69.8)
NO_2 (μg/m^3)	27.4 (23.2, 28.8)
Mitochondrial DNA copy number	1.1 (0.8, 1.3)

Table 2
Association between per IQR increase in green space and mitochondrial DNA copy number in children and adolescents (n = 1151).

Green space	Model 1		Model 2	
	Percent change (95% CI)	P value	Percent change (95% CI)	P value
$NDVI_{250m}$	2.84 (0.55, 5.19)	0.02	3.33 (1.00, 5.72)	0.01
$NDVI_{500m}$	2.94 (0.62, 5.32)	0.01	3.37 (1.02, 5.78)	0.01
$NDVI_{1000m}$	2.90 (0.52, 5.34)	0.02	3.34 (0.93, 5.81)	0.01
$NDVI_{2000m}$	2.58 (−0.13, 5.37)	0.06	3.25 (0.49, 6.08)	0.02

Model 1: adjusted for age and sex.
Model 2: adjusted for age, sex, maternal education, BMI z-score, and passive smoking.
IQR: $NDVI_{250m}$, 0.072; $NDVI_{500m}$, 0.071; $NDVI_{1000m}$, 0.070; $NDVI_{2000m}$, 0.077.

Subgroup analyses revealed a positive association between green space exposure and mtDNAcn in children and participants with normal weight, with a significant interaction effect observed for age and BMI z-score (Fig. 2 and Table S3, $P_{interaction} < 0.1$). Besides, the positive relationships of green space exposure with mtDNAcn were more pronounced among females, and those not exposed to passive smoking, despite the lack of a significant interaction effect (Fig. 2 and Table S3, $P_{interaction} > 0.1$). The sex- and age-specific analyses revealed a significant association in females aged 6–9 years and 10–14 years, while no such association was observed in males (Table S4). In the sensitivity analyses, the positive relationship of green space with mtDNAcn was still robust after excluding first-year students (Table S5) or after additional adjustment for $PM_{2.5}$, PM_{10}, and NO_2, respectively (Table S6).

4. Discussion

In this Chinese cross-sectional study, we observed that green space exposure was positively related to mtDNAcn in children and adolescents. Moreover, we found stronger relationships of green space exposure with mtDNAcn in children, females, individuals with normal weight, and those not exposed to passive smoking.

Research regarding the relationship of green space exposure with mtDNAcn is still limited, with only two studies assessing this association. A cross-sectional study in China reported that green space exposure was related to a higher mtDNAcn in adults (Li et al., 2022). Childhood and adolescence are critical stages of growth, representing susceptible windows to various exposures (Wright, 2017). To date, only one study involving 246 Belgian primary school children reported a similar positive relationship of green space exposure with buccal mtDNAcn (Hautekiet et al., 2022). We confirmed these findings in Chinese children and expanded upon them in adolescents. It is noteworthy that this previous study of children (Hautekiet et al., 2022) assessed mtDNAcn using buccal swabs, whereas our study measured mtDNAcn from leukocytes, ensuring higher-quality DNA and greater concentrations of DNA (Wolf et al., 2024). Belgium, being a developed country, typically has more abundant green spaces compared to our study context (Rodriguez-Loureiro et al., 2022a, 2022b). Therefore, exploring the relationship of green space exposure with mtDNAcn among Chinese children and adolescents is particularly significant.

Green space exposure may influence mtDNAcn through several mechanisms, although the precise pathways remain unclear. One plausible factor is oxidative stress, as mtDNAcn serves as a marker reflecting

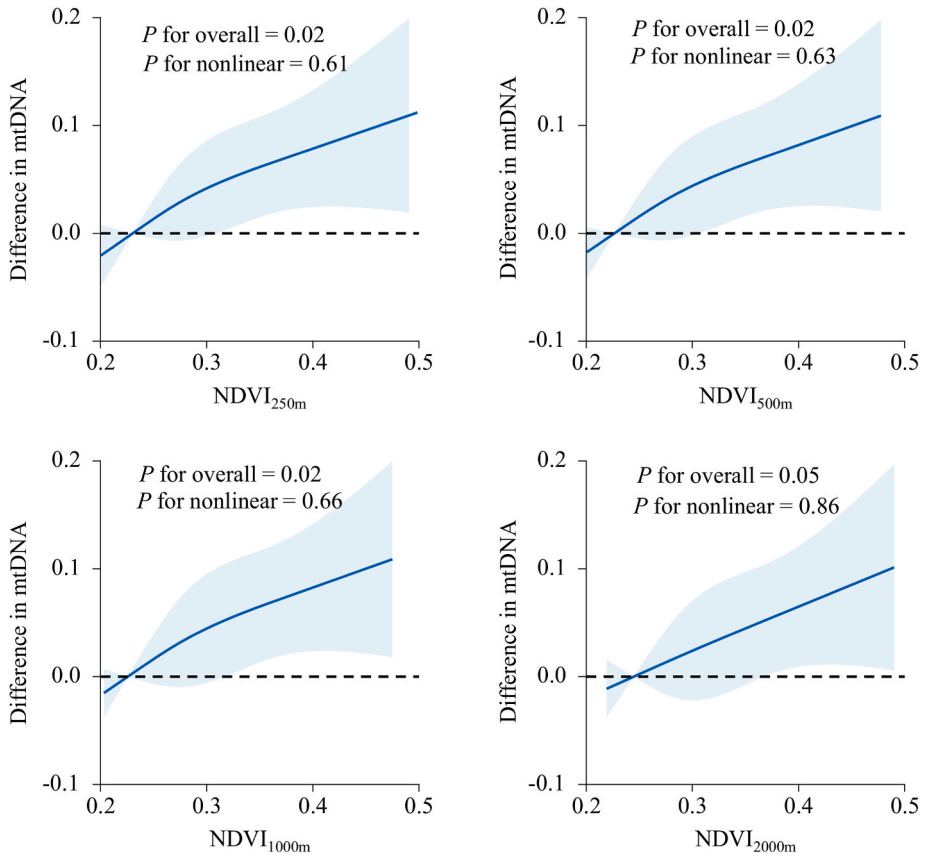

Fig. 1. Dose-response relationship between green space exposure and mitochondrial DNA copy number in children and adolescents using the restricted cubic spline regression models (n = 1151). The solid line represents the point estimates, and the shaded area represents 95% confidence intervals. Models were adjusted for age, sex, maternal education, BMI z-score, and passive smoking. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

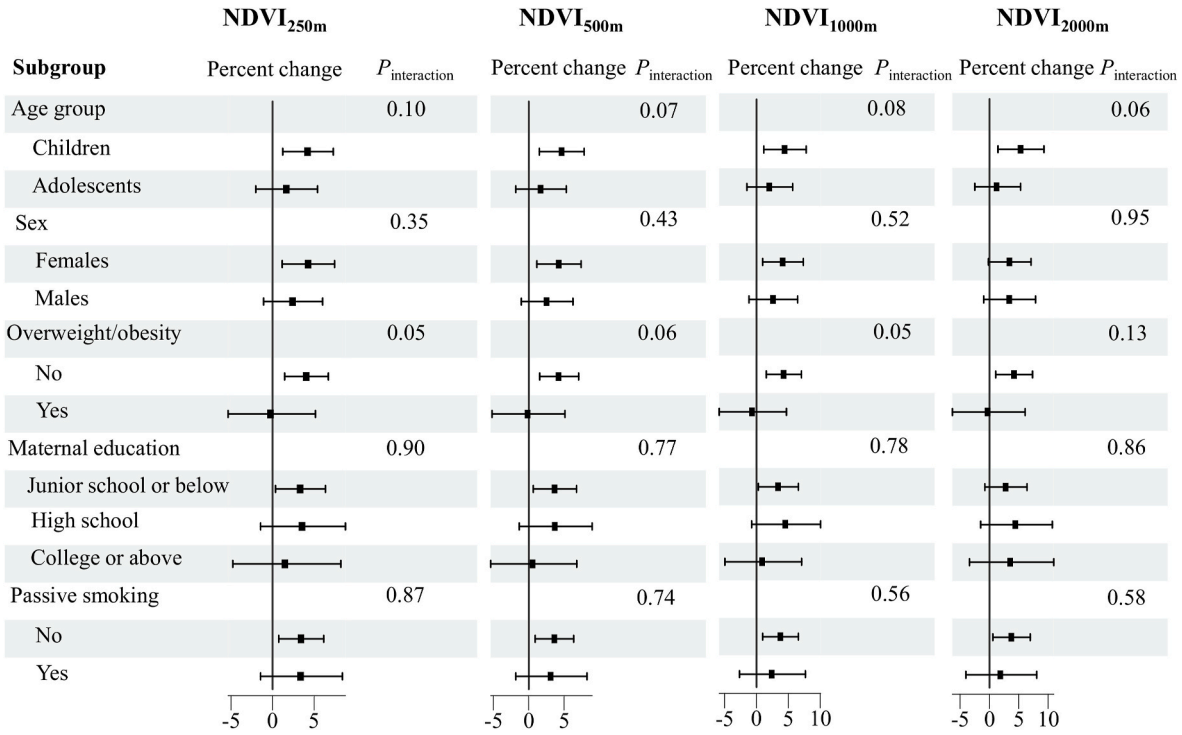

Fig. 2. Subgroup analyses of the association between per IQR increase in green space exposure and mitochondrial DNA copy number in children and adolescents (n = 1151). IQR: $NDVI_{250m}$, 0.072; $NDVI_{500m}$, 0.071; $NDVI_{1000m}$, 0.070; $NDVI_{2000m}$, 0.077.

mitochondrial damage and dysfunction in response to oxidative stress (Malik and Czajka, 2013). Research indicates that green space exposure can directly reduce oxidative stress (Squillacioti et al., 2022), potentially mitigating its impact on mtDNAcn levels. Additionally, green spaces contribute to a reduction in oxidative stress through various indirect mechanisms (de Oliveira et al., 2020; El et al., 2022; Schiavone et al., 2013), including stress reduction (Bloemsma et al., 2022; Towe-Goodman et al., 2024), air pollution mitigation (Nowak et al., 2006), and promotion of physical activity (McCormack et al., 2010). Specifically, exposure to green space helps alleviate psychological stress, thereby protecting mitochondrial DNA and maintaining mtDNAcn levels (van den Berg et al., 2010). Moreover, green spaces act as natural filters, improving air quality by reducing pollutants that contribute to oxidative stress and mitochondrial DNA damage (Steffens et al., 2012). Furthermore, green spaces encourage physical activity, which decreases oxidative stress and enhances mtDNAcn levels (Almanza et al., 2012). These factors provide insights into how green space exposure may influence mtDNAcn levels, though further studies are needed to clarify the exact mechanisms.

Subgroup analyses revealed that the relationship of green space exposure with mtDNAcn was more pronounced in children compared to adolescents. One possible interpretation for the age-specific associations may be that children are more sensitive to green space exposure than adolescents (Jimenez et al., 2021). During periods of rapid growth, this heightened sensitivity could further contribute to the observed effects (Ren et al., 2003). In addition, adolescents may spend more time indoors doing homework, thereby reducing their exposure to outdoor green spaces and potentially diminishing the benefits. Moreover, we found that the relationship between green space exposure and mtDNAcn was more evident in participants with normal weight. Previous research suggests that overweight and obesity are linked to lower mtDNAcn (Hang et al., 2018), potentially offsetting the benefits of green space exposure on mtDNAcn. Our analyses also indicated potentially stronger associations in females and participants who were not exposed to passive smoking, although the interaction effects were not statistically significant. The observed sex disparity may be attributed to the factors related to the duration of green space exposure, such as sex-specific physical activity patterns (Klinker et al., 2014). Additionally, females may be more responsive to the beneficial effects of green space (Sillman et al., 2022), warranting further investigation. Besides, previous research has shown that passive smoking is associated with lower mtDNAcn (Westbrook et al., 2010), which could counteract the positive effects of green space exposure on mtDNAcn. To further assess the robustness of our findings, we conducted sensitivity analyses to account for potential confounders. Excluding first-year students due to their relatively short admission period did not notably affect the results, suggesting that this factor has minimal influence on the observed associations. Additionally, we considered the potential impact of air pollutants, such as $PM_{2.5}$, PM_{10}, and NO_2, on the relationship between green space exposure and mtDNAcn. After adjusting for these pollutants, the results remained consistent, indicating that air pollution is unlikely to substantially affect the relationship observed. These findings strengthen the robustness of the associations we identified.

This study provides the first insights into how green space exposure correlates with mtDNAcn in a substantial sample of Chinese children and adolescents. Additionally, our study comprehensively considered the green space exposure in both residential and school environments for children and adolescents. Nevertheless, it is essential to note several limitations. First, the cross-sectional design inherently restricts the establishment of causal relationships between green space exposure and mtDNAcn. Second, although NDVI serves as a widely adopted measure of green space exposure, it does not offer detailed information on green space, like quality and type, limiting exploration into the varying effects of different green types in the association. Third, since the study participants were exclusively from one city in China, attention should be paid when applying the findings to broader populations. Fourth, despite efforts to control for various confounding variables, residual confounders may still exist.

In conclusion, our study demonstrated a positive relationship of green space exposure with mtDNAcn in children and adolescents, especially in children, females, participants with normal weight, and those who were not exposed to passive smoking. This finding underscores the potential health benefits of green spaces in supporting mitochondrial function during critical developmental stages. Efforts to enhance green environments may contribute to promoting the health effects related to mtDNAcn in children and adolescents.

CRediT authorship contribution statement

Gaojie Fan: Writing – original draft, Investigation, Formal analysis. **Xiaoning Lei:** Writing – original draft, Methodology, Data curation. **Qing Liu:** Validation, Investigation, Data curation. **Qing Fang:** Validation, Investigation. **Fei Luo:** Investigation. **Xiaofeng Huang:** Investigation. **Heng Li:** Investigation. **Wenwen Guo:** Investigation. **Binghai Liu:** Investigation. **Lianyan Yan:** Investigation. **Liqin Hu:** Investigation. **Jing Wei:** Methodology, Data curation. **Youjie Wang:** Writing – review & editing, Supervision, Funding acquisition. **Lulu Song:** Writing – review & editing, Funding acquisition, Data curation, Conceptualization.

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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.envres.2025.121352.

Data availability

Data will be made available on request.

References

Almanza, E., Jerrett, M., Dunton, G., Seto, E., Ann Pentz, M., 2012. A study of community design, greenness, and physical activity in children using satellite, GPS and accelerometer data. Health Place 18, 46–54.

Ashar, F.N., Moes, A., Moore, A.Z., Grove, M.L., Chaves, P., Coresh, J., et al., 2015. Association of mitochondrial DNA levels with frailty and all-cause mortality. J. Mol. Med. (Berl.) 93, 177–186.

Ashar, F.N., Zhang, Y., Longchamps, R.J., Lane, J., Moes, A., Grove, M.L., et al., 2017. Association of mitochondrial DNA copy number with cardiovascular disease. JAMA Cardiol 2, 1247–1255.

Bijnens, E.M., Derom, C., Weyers, S., Janssen, B.G., Thiery, E., Nawrot, T.S., 2019. Placental mitochondrial DNA content is associated with childhood intelligence. J. Transl. Med. 17, 361.

Bloemsma, L.D., Wijga, A.H., Klompmaker, J.O., Hoek, G., Janssen, N., Lebret, E., et al., 2022. Green space, air pollution, traffic noise and mental wellbeing throughout adolescence: findings from the PIAMA study. Environ. Int. 163, 107197.

Bordoni, L., Smerilli, V., Nasuti, C., Gabbianelli, R., 2019. Mitochondrial DNA methylation and copy number predict body composition in a young female population. J. Transl. Med. 17, 399.

Brunst, K.J., Sanchez, G.M., Gennings, C., Hacker, M., Jara, C., Bosquet, E.M., et al., 2017. Maternal lifetime stress and prenatal psychological functioning and decreased placental mitochondrial DNA copy number in the PRISM study. Am. J. Epidemiol. 186, 1227–1236.
Cao, X., Li, J., Cheng, L., Deng, Y., Li, Y., Yan, Z., et al., 2020. The associations between prenatal exposure to polycyclic aromatic hydrocarbon metabolites, umbilical cord blood mitochondrial DNA copy number, and children's neurobehavioral development. Environ Pollut 265, 114594.
Cerantonio, A., Citrigno, L., Greco, B.M., De Benedittis, S., Passarino, G., Maletta, R., et al., 2024. The role of mitochondrial copy number in neurodegenerative diseases: present insights and future directions. Int. J. Mol. Sci. 25.
Chang, Y.K., Kim, D.E., Cho, S.H., Kim, J.H., 2016. Association between leukocyte mitochondrial DNA copy number and regular exercise in postmenopausal women. Korean J Fam Med 37, 334–339.
de Oliveira, A.N., Martins, P.G., Di Domenico, M., Costanzo, G., Benevenuto, S., de Oliveira, F.A., et al., 2020. Inflammation response, oxidative stress and DNA damage caused by urban air pollution exposure increase in the lack of DNA repair XPC protein. Environ. Int. 145, 106150.
Didan, K., 2015. Mod13q1 Modis/terra Vegetation Indices 16-day L3 Global 250m Sin Grid V006.
Duan, X., Yang, Y., Zhang, H., Liu, B., Wei, W., Wang, L., et al., 2020. Polycyclic aromatic hydrocarbon exposure, miRNA genetic variations, and associated leukocyte mitochondrial DNA copy number: a cross-sectional study in China. Chemosphere 246, 125773.
El, A.M., Álvarez-Bustos, A., Sosa, P., Angulo, J., Rodríguez-Mañas, L., 2022. Effect of physical activity/exercise on oxidative stress and inflammation in muscle and vascular aging. Int. J. Mol. Sci. 23.
Foote, K., Reinhold, J., Yu, E., Figg, N.L., Finigan, A., Murphy, M.P., et al., 2018. Restoring mitochondrial DNA copy number preserves mitochondrial function and delays vascular aging in mice. Aging Cell 17, e12773.
Hagberg, H., Mallard, C., Rousset, C.I., Thornton, C., 2014. Mitochondria: hub of injury responses in the developing brain. Lancet Neurol. 13, 217–232.
Hang, D., Nan, H., Kværner, A.S., De Vivo, I., Chan, A.T., Hu, Z., et al., 2018. Longitudinal associations of lifetime adiposity with leukocyte telomere length and mitochondrial DNA copy number. Eur. J. Epidemiol. 33, 485–495.
Hautekiet, P., Saenen, N.D., Aerts, R., Martens, D.S., Roels, H.A., Bijnens, E.M., et al., 2022. Higher buccal mtDNA content is associated with residential surrounding green in a panel study of primary school children. Environ. Res. 213, 113551.
Hong, Y.S., Battle, S.L., Puiu, D., Shi, W., Pankratz, N., Zhao, D., et al., 2023. Long-term air pollution exposure and mitochondrial DNA copy number: an analysis of UK biobank data. Environ. Health Perspect. 131, 57703.
Jimenez, M.P., Aris, I.M., Rifas-Shiman, S., Young, J., Tiemeier, H., Hivert, M.F., et al., 2021. Early life exposure to greenness and executive function and behavior: an application of inverse probability weighting of marginal structural models. Environ Pollut 291, 118208.
Klinker, C.D., Schipperijn, J., Christian, H., Kerr, J., Ersbøll, A.K., Troelsen, J., 2014. Using accelerometers and global positioning system devices to assess gender and age differences in children's school, transport, leisure and home based physical activity. Int J Behav Nutr Phys Act 11, 8.
Kupsco, A., Sanchez-Guerra, M., Amarasiriwardena, C., Brennan, K., Estrada-Gutierrez, G., Svensson, K., et al., 2019. Prenatal manganese and cord blood mitochondrial DNA copy number: effect modification by maternal anemic status. Environ. Int. 126, 484–493.
Li, R., Chen, G., Pan, M., Hou, X., Kang, N., Chen, R., et al., 2022. Adverse associations of long-term exposure to ambient ozone with molecular biomarkers of aging alleviated by residential greenness in rural Chinese adults. Environ. Int. 169, 107496.
Malik, A.N., Czajka, A., 2013. Is mitochondrial DNA content a potential biomarker of mitochondrial dysfunction? Mitochondrion 13, 481–492.
McCormack, G.R., Rock, M., Toohey, A.M., Hignell, D., 2010. Characteristics of urban parks associated with park use and physical activity: a review of qualitative research. Health Place 16, 712–726.
Nowak, D.J., Crane, D.E., Stevens, J.C., 2006. Air pollution removal by urban trees and shrubs in the United States. Urban For. Urban Green. 4, 115–123.
Qiao, J.C., Sun, L.J., Zhang, M.Y., Gui, S.Y., Wang, X.C., Hu, C.Y., 2024. Association between ambient particulate matter exposure and mitochondrial DNA copy number: a systematic review and meta-analysis. Sci. Total Environ. 923, 171423.
Ren, H., Xu, G., Qi, G.Y., Jia, Z.Y., Zhou, D.M., 2003. The research on the peak age in adolescent growth. Journal of Beijing sports university 6, 762–763.
Rodriguez-Loureiro, L., Verdoodt, F., Lefebvre, W., Vanpoucke, C., Casas, L., Gadeyne, S., 2022a. Long-term exposure to residential green spaces and site-specific cancer mortality in urban Belgium: a 13-year follow-up cohort study. Environ. Int. 170, 107571.
Rodriguez-Loureiro, L., Gadeyne, S., Bauwelinck, M., Lefebvre, W., Vanpoucke, C., Casas, L., 2022b. Long-term exposure to residential greenness and neurodegenerative disease mortality among older adults: a 13-year follow-up cohort study. Environ. Health 21, 49.
Schiavone, S., Jaquet, V., Trabace, L., Krause, K.H., 2013. Severe life stress and oxidative stress in the brain: from animal models to human pathology. Antioxid Redox Signal 18, 1475–1490.
Sillman, D., Rigolon, A., Browning, M., Yoon, H.V., McAnirlin, O., 2022. Do sex and gender modify the association between green space and physical health? A systematic review. Environ. Res. 209, 112869.
Smith, A.R., Lin, P.D., Rifas-Shiman, S.L., Rahman, M.L., Gold, D.R., Baccarelli, A.A., et al., 2021. Prospective associations of early pregnancy metal mixtures with mitochondria DNA copy number and telomere length in maternal and cord blood. Environ. Health Perspect. 129, 117007.
Song, L., Liu, B., Wang, L., Wu, M., Zhang, L., Liu, Y., et al., 2020. Exposure to arsenic during pregnancy and newborn mitochondrial DNA copy number: a birth cohort study in Wuhan, China. Chemosphere 243, 125335.
Squillacioti, G., Carsin, A.E., Bellisario, V., Bono, R., Garcia-Aymerich, J., 2022. Multisite greenness exposure and oxidative stress in children. The potential mediating role of physical activity. Environ. Res. 209, 112857.
Steffens, J.T., Wang, Y.J., Zhang, K.M., 2012. Exploration of effects of a vegetation barrier on particle size distributions in a near-road environment. Atmos. Environ. 50, 120–128, 1994.
Towe-Goodman, N., McArthur, K.L., Willoughby, M., Swingler, M.M., Wychgram, C., Just, A.C., et al., 2024. Green space and internalizing or externalizing symptoms among children. JAMA Netw. Open 7, e245742.
Twohig-Bennett, C., Jones, A., 2018. The health benefits of the great outdoors: a systematic review and meta-analysis of greenspace exposure and health outcomes. Environ. Res. 166, 628–637.
van den Berg, A.E., Maas, J., Verheij, R.A., Groenewegen, P.P., 2010. Green space as a buffer between stressful life events and health. Soc. Sci. Med. 70, 1203–1210.
Wang, X., Hart, J.E., Liu, Q., Wu, S., Nan, H., Laden, F., 2020. Association of particulate matter air pollution with leukocyte mitochondrial DNA copy number. Environ. Int. 141, 105761.
Wei, J., Li, Z., Lyapustin, A., Sun, L., Peng, Y., Xue, W., et al., 2021a. Reconstructing 1-km-resolution high-quality PM2.5 data records from 2000 to 2018 in China: spatiotemporal variations and policy implications. Remote Sens. Environ. 252, 112136.
Wei, J., Li, Z., Xue, W., Sun, L., Fan, T., Liu, L., et al., 2021b. The ChinaHighPM(10) dataset: generation, validation, and spatiotemporal variations from 2015 to 2019 across China. Environ. Int. 146, 106290.
Wei, J., Li, Z., Wang, J., Li, C., Gupta, P., Cribb, M., 2023. Ground-level gaseous pollutants (NO2, SO2, and CO) in China: daily seamless mapping and spatiotemporal variations. Atmos. Chem. Phys. 23, 1511–1532.
Westbrook, D.G., Anderson, P.G., Pinkerton, K.E., Ballinger, S.W., 2010. Perinatal tobacco smoke exposure increases vascular oxidative stress and mitochondrial damage in non-human primates. Cardiovasc. Toxicol. 10, 216–226.
WHO. Child growth standards. Available at: https://www.who.int/tools/child-growth-standards/standards. Accessed.
Wolf, S.E., Hastings, W.J., Ye, Q., Etzel, L., Apsley, A.T., Chiaro, C., et al., 2024. Cross-tissue comparison of telomere length and quality metrics of DNA among individuals aged 8 to 70 years. PLoS One 19, e290918.
Wright, R.O., 2017. Environment, susceptibility windows, development, and child health. Curr. Opin. Pediatr. 29, 211–217.
Yakes, F.M., Van Houten, B., 1997. Mitochondrial DNA damage is more extensive and persists longer than nuclear DNA damage in human cells following oxidative stress. Proc. Natl. Acad. Sci. U. S. A. 94, 514–519.