Title

Early-Life Exposure to Green Space and Mid-Childhood Cognition in the Project Viva Cohort, Massachusetts.

Journal
American Journal of Epidemiology, 191(1)

Authors
Jimenez, Marcia
Shoaff, Jessica
Kioumourtzoglou, Marianthi-Anna
et al.

Publication Date
2022

DOI
10.1093/aje/kwab209

Peer reviewed

American Journal of Epidemiology

Vol. 191, No. 1
https://doi.org/10.1093/aje/kwab209
Advance Access publication:
July 23, 2021

Original Contribution

Early-Life Exposure to Green Space and Mid-Childhood Cognition in the Project Viva Cohort, Massachusetts

Marcia P. Jimenez*, **Jessica Shoaff, Marianthi-Anna Kioumourtzoglou, Susan Korrick, Sheryl L. Rifas-Shiman, Marie-France Hivert, Emily Oken, and Peter James**

* Correspondence to Dr. Marcia P. Jimenez, Department of Epidemiology, Harvard T. H. Chan School of Public Health, Landmark Center 401 Park Drive, Boston, MA 02215 (e-mail: mpjimenez@hsph.harvard.edu).

Initially submitted August 21, 2020; accepted for publication July 19, 2021.

The association between early-life greenness and child cognition is not well understood. Using prospective data from Project Viva ($n = 857$) from 1999–2010, we examined associations of early-life greenness exposure with mid-childhood cognition. We estimated residential greenness at birth, early childhood (median age 3.1 years), and mid-childhood (7.8 years) using 30-m resolution Landsat satellite imagery (normalized difference vegetation index). In early childhood and mid-childhood, we administered standardized assessments of verbal and nonverbal intelligence, visual-motor abilities, and visual memory. We used natural splines to examine associations of early life-course greenness with mid-childhood cognition, adjusting for age, sex, race, income, neighborhood socioeconomic status, maternal intelligence, and parental education. At lower levels of greenness (greenness <0.6), greenness exposure at early childhood was associated with a 0.48% increase in nonverbal intelligence and 2.64% increase in visual memory in mid-childhood. The association between early-childhood greenness and mid-childhood visual memory was observed after further adjusting for early childhood cognition and across different methodologies, while the association with nonverbal intelligence was not. No other associations between early life-course greenness and mid-childhood cognition were found. Early childhood greenness was nonlinearly associated with higher mid-childhood visual memory. Our findings highlight the importance of nonlinear associations between greenness and cognition.

cognition; green space; longitudinal study; neurodevelopment; sensitive periods

Abbreviations: BC, black carbon; CI, confidence interval; IQ, intelligence quotient; KBIT-2, Kaufman Brief Intelligence Test; NDVI, normalized difference vegetation index; NSES, neighborhood socioeconomic status; SD, standard deviation; WRAML2, Wide Range Assessment of Memory and Learning; WRAVMA, Wide Range Assessment of Visual-Motor Abilities.

Increasing empirical evidence suggests that exposure to natural vegetation—also referred to as green space or greenness—may influence health, including cognition (1). While the exact mechanisms are not well understood, literature suggests that exposure to greenness may benefit cognition by mitigating exposures to air pollution, relieving mental stress, and promoting physical activity and social interaction (2). The attention restoration theory posits that natural environments enable us to overcome the mental fatigue associated with modern life by evoking a type of attention that does not require cognitive effort, thus restoring the brain's capacity to direct attention (3). Exposure to greenness may be especially pertinent during early-life periods as they are times of rapid brain growth and development (4).

Studies have reported associations between exposure to greenness and better cognitive function in adults (5) and a wide range of diagnosed neurobehavioral outcomes in children, including attention deficit hyperactivity disorder (6, 7) and autism spectrum disorder (8). While several studies have reported associations between greenness and cognition in children (1), there are few that are longitudinal (9–13) and that have evaluated sensitive periods of greenness exposure (7, 14, 15). To address this gap in the literature, we assessed greenness exposure during early life course (birth, early childhood, and mid-childhood) and its association with mid-childhood cognitive function. We used longitudinal data from the Project Viva cohort to examine the extent to which associations between early life-course greenness and cognition at early and mid-childhood varied by sensitive periods. We also evaluated whether associations were mediated by reduction in air pollution or increase in physical activity.

METHODS

Study population

Project Viva is a prebirth cohort that enrolled pregnant women during 1999–2002 at Atrius Harvard Vanguard Medical Associates in eastern Massachusetts (16). Demographic, health, and behavioral information were collected via in-person interviews or mailed questionnaires. We assessed neurodevelopment at early childhood (median age = 3.1 (standard deviation (SD), 0.3) years) and mid-childhood (median age = 7.8 (SD, 0.8) years). Of the 2,128 mother-child pairs enrolled in the cohort, 1,089 had complete information on cognitive outcomes, 1,047 on residential greenness exposure, and 857 on all covariates for this analysis. Study protocols were approved by the Harvard Pilgrim Health Care review board. Mothers provided written informed consent, and children provided verbal assent at the mid-childhood visit.

Exposure assessment

To ascertain participant's exposure to greenness at each geocoded residential address at birth and in early and mid-childhood, we used the normalized difference vegetation index (NDVI). NDVI is a satellite-based objective indicator of the quantity of ground green vegetation (range, −1 to 1). Negative values represent water, values around zero correspond to barren areas of sand, and values approaching 1 indicate tropical rainforests. NDVI has been widely used in previous studies of greenness and health (17–19). Since NDVI reaches its maximum and highest level of geographic variation during the height of the summer, we used Landsat satellite data at 30-m resolution from July 1999 to 2010. Average greenness at 90-m and 270-m buffers were estimated using the focal function in the R raster package (https://cran.r-project.org/web/packages/raster/). We used continuous NDVI at the 90-m buffer for the main results, and NDVI interquartile range and the continuous 270-m buffer for sensitivity analyses.

Outcome assessment

At early childhood and mid-childhood in-person visits, trained Project Viva staff administered standardized and well-validated assessments of cognitive development (16, 20–22). At the early childhood visit, staff administered the Peabody Picture Vocabulary Test (PPVT-III) to assess vocabulary comprehension (20) and the Visual Motor subtest of the Wide Range Assessment of Visual Motor Abilities (WRAVMA) (21) to assess visual-motor, fine-motor, and visuospatial skills. At the mid-childhood visit, staff administered the Kaufman Brief Intelligence Test (KBIT-2) (22), the Visual Motor subtest of the WRAVMA (21), and the Visual Memory Index of the Wide Range Assessment of Memory and Learning (WRAML2) (23). The verbal intelligence quotient (IQ) subscore of the KBIT-2 test measures crystalized intelligence (i.e., vocabulary), while the nonverbal IQ subscore measures fluid intelligence (i.e., ability to perceive relationships). The Visual Motor subtest is a specific component of the WRAVMA that involves drawing/copying increasingly complex figures (21). Visual Memory was derived as the sum of standardized picture and design memory subtests (23). KBIT-2 IQ and WRAVMA Visual Motor scores are standardized to a mean of 100 (SD, 15); WRAML2 design memory and picture memory subtests are each standardized to a mean of 10 (SD, 3) using published reference data (21). Neurobehavioral functional domains measured by each of the cognitive assessments are outlined in Web Table 1 (available at https://doi.org/10.1093/aje/kwab209).

Covariates

Covariates included characteristics of the child (sex, race (White vs. non-White), and age at cognitive testing), mother's intelligence, parents' education (high-school degree, some college, or at least a college graduate), annual household income at enrollment (in $, <40,000, 40,000–70,000, >70,000), and neighborhood median annual income (at Census-tract level at birth). Neighborhood population density, used as a proxy for urbanicity, was assessed from residential address at birth using nationwide land-use data derived from satellite images with approximately 30-m resolution (24). Mothers' intelligence was assessed using the KBIT-2 (22) (at the mid-childhood visit), which is a valid and reliable measure for ages 4–90, standardized using a representative US sample.

We analyzed air pollution and physical activity measured at early childhood as mediators. For traffic-related air pollution, we averaged daily black carbon (BC) residential exposure over 365 days prior to the child's cognitive assessment with a land-use regression model (25). Physical activity was reported by the mother as a response to the question: "In the past month, on average, how many hours a day is your child involved in active play (e.g. running)?" (16).

Statistical analysis

We assessed correlations among exposures, outcomes, and covariates with Pearson correlation. Statistical significance was assessed at $\alpha = 0.05$. We examined prospective associations of greenness at birth with early childhood cognition (Web Figure 1, line L1) and greenness at birth and early childhood with mid-childhood cognition assessments (Web Figure 1, lines L2–L3). We also assessed cross-sectional associations of greenness at early childhood with early childhood cognition (Web Figure 1, line C1) and greenness at mid-childhood with mid-childhood cognitive assessments (Web Figure 1, line C2). To assess the shape of exposure-outcome associations, we fitted generalized additive models for continuous exposures. Penalized splines suggested deviations from linearity (degrees of freedom > 1) for associations with all cognition measurements. Thus, we used natural splines with 3–4 knots based on Akaike's information criterion. Unless otherwise indicated, all variables were evaluated as continuous. To ease interpretation of the splines, we evaluated change in cognition scores for a percentile increase in exposure.

All models adjusted for potential confounders based on prior evidence (9, 15, 26), directed acyclic graphs (27), and greenness exposure in all preceding age periods but not in subsequent age periods (28). Thus, models assessing exposure at birth adjusted for confounders, models assessing exposure at early childhood adjusted for confounders and birth exposure, and so on. Plotted splines were assessed visually. Sensitivity analyses were conducted excluding outliers for cognitive scores (>3 SD) to explore their influence. Further, in order to contribute to meta-analytical work, we estimated change in outcome scores associated with 1 interquartile-range increase in average NDVI, adjusting for a minimal set of confounders, matching prior work (9, 15, 26, 29), as well as additional confounders available in Project Viva.

In addition, we assessed effect measure modification of associations of greenness with cognition by child's sex, parental education (both parents with college education vs. none or only 1 parent with college education), neighborhood socioeconomic status (NSES; tertiles), and neighborhood population density (tertiles) using stratified analyses.

Greenness has been associated with decreased levels of air pollution (19, 30) and increased levels of physical activity in children (31); we used a causal mediation framework (32–34) to determine whether the effect of greenness (at early childhood) on mid-childhood cognitive measures was mediated through pathways represented by air pollution and physical activity (both measured at early childhood). We used BC as a marker of traffic pollution following previous studies on the association between air pollution and cognition in children (35, 36). We used the "mediation" package in R (R Core Team, R Foundation for Statistical Computing, Vienna, Austria), which combines estimates from the mediator and outcome models to estimate natural direct and indirect effects (37). Mediation analysis requires the assumptions that there are no unmeasured exposure-outcome, mediator-outcome, or exposure-mediator confounders and no mediator-outcome confounders affected by exposure. While these assumptions are not verifiable, we believe ours are reasonable since we have included major confounders in our mediation analyses. We used 1,000 Monte Carlo draws for nonparametric bootstrap confidence intervals (CIs). Natural direct and indirect effects are reported in our results. Statistical analyses were performed in R, version 3.4.0 (R Core Team) (38). Code to run all analyses and reproduce our results is available on GitHub (GitHub Inc., San Francisco, California) (39).

RESULTS

A total of 857 participants provided data for this analysis. The mean age at mid-childhood cognitive assessment was 7.85 (SD, 0.77) years (Table 1). Overall, 71% of participants were White, but this percentage increased among the higher quartiles of greenness, as did the percentage of parents who had at least a college education. Less than half (44.72%) of the households in the lowest greenness quartile reported having a household income over $70,000/year at enrollment, compared with 85.96% in the highest quartile. Median neighborhood household income at birth varied across greenness quartiles from $46,557 to $69,697 (Table 1). In the lowest greenness quartile, the maternal intelligence score was 104.8 (SD, 16.4), slightly above the standardized mean of 100, while in the highest quartile, it was 113.0 (SD, 11.6), about 1 standard deviation higher than the reference population average. In mid-childhood, the average score for verbal IQ was 114 (SD, 14), nonverbal IQ 107 (SD, 17), visual-motor 93 (SD, 17), and visual memory 17 (SD, 4) (Table 1). All mid-childhood cognition scores were on average higher than the reference population mean, except for visual-motor abilities, which were below the reference population average.

The correlation between greenness exposures within individuals across time ranged between 0.50 and 0.74 (Web Figure 2). We did not find significant associations between greenness exposure at any time point with early childhood cognition (Web Figure 3), but we did with mid-childhood cognitive measures. We observed positive nonlinear relationships between greenness at early childhood and mid-childhood nonverbal IQ as well as mid-childhood visual memory, accounting for confounders (Figure 1). In early childhood, at greenness levels below the median of 0.6, higher greenness was associated with higher levels of mid-childhood nonverbal IQ; specifically, an increase from the 25th to the 50th NDVI percentile was associated with a 0.48% increase in mid-childhood nonverbal IQ. Above an NDVI of 0.6, there was no clear evidence of additional improvement in mid-childhood nonverbal IQ (Figure 1E). Similarly, increasing greenness at early childhood was associated with higher mid-childhood visual memory, where an increase from the 25th to the 50th NDVI percentile was associated with a 2.64% increase in mid-childhood visual memory (Figure 1H). No evidence of consistent improvement was observed at levels of greenness above 0.8. The association between early childhood greenness and mid-childhood visual memory was also observed in the fully adjusted linear regression analysis (Web Table 2), with a minimal set of confounders (Web Table 3), and further adjusting for early childhood cognition (Web Figure 4), while the association with mid-childhood nonverbal IQ was not. We observed a U-shaped association between greenness at early childhood and mid-childhood visual-motor abilities (Figure 1K). However, this association was not observed in the linear regression analysis (Web Table 2). Further, we did not find significant associations of greenness at any time point with mid-childhood verbal IQ, and there was no clear evidence of a beneficial association of NDVI at birth or mid-childhood with any of the mid-childhood cognitive measures.

Sensitivity analyses showed that the relationships between greenness and mid-childhood cognition excluding outliers (Web Figure 5) and at a 270-m buffer (Web Figure 6) were similar but attenuated. A comparison between the final (n = 857) and the full sample (n = 2,128) showed

Table 1. Characteristics of 857 Children With Information on Greenness Exposures and Mid-Childhood Cognitive Outcomes, Project Viva, Massachusetts, 1999–2010

Variable	NDVI Early Childhood									
	Quartile 1		Quartile 2		Quartile 3		Quartile 4		Overall	
	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)
Female sex	43.22		58.42		49.32		54.04		51.34	
White race	56.78		61.88		78.73		84.68		71.30	
Mother's education level										
Some college	29.15		23.76		19.46		11.06		20.42	
College degree or more	60.80		71.78		77.38		86.38		74.68	
Father's education level										
Some college	26.63		26.24		19.46		11.91		20.65	
College degree or more	54.77		61.39		73.30		82.55		68.73	
Household income at enrollment, $										
40,000–70,000	29.15		25.25		22.62		10.64		21.47	
>70,000	44.72		59.9		71.95		85.96		66.63	
Age, years		7.87 (0.84)		7.83 (0.72)		7.87 (0.77)		7.83 (0.73)		7.85 (0.77)
Neighborhood median household income, $		46,557.59 (17,005.33)		54,033.61 (17,757.75)		64,709.90 (18,974.18)		69,697.94 (21,489.68)		59,355.23 (21,004.38)
Maternal intelligence score		104.79 (16.44)		106.08 (14.63)		109.5 (13.52)		112.97 (11.56)		108.55 (14.37)
Exposure to greenness at birth		0.4 (0.12)		0.52 (0.09)		0.59 (0.12)		0.62 (0.16)		0.54 (0.15)
Exposure to greenness at early childhood		0.38 (0.08)		0.53 (0.03)		0.63 (0.02)		0.72 (0.04)		0.57 (0.14)
Exposure to greenness at mid-childhood		0.46 (0.14)		0.57 (0.08)		0.64 (0.07)		0.72 (0.07)		0.6 (0.13)
Mediators										
Air pollution (black carbon) exposure		0.72 (0.16)		0.57 (0.14)		0.49 (0.11)		0.43 (0.12)		0.55 (0.17)
Physical activity, hours per day		2.8 (1.64)		2.72 (1.55)		3.05 (1.62)		2.95 (1.61)		2.89 (1.61)
Cognition measures at early childhood										
Vocabulary		101.81 (14.93)		104.26 (13.87)		105.16 (13.2)		107.4 (13.04)		104.88 (13.81)
Motor abilities		101.8 (11.33)		103.03 (11.08)		102.57 (10.15)		103.43 (11.04)		102.77 (10.88)
Cognition measures at mid-childhood										
Verbal intelligence score		109.87 (16.4)		113.66 (13.28)		114.36 (12.98)		116.97 (12.16)		113.87 (13.92)
Nonverbal intelligence score		104.85 (17.59)		108.23 (15.67)		106.85 (16.25)		109.59 (16.43)		107.46 (16.55)
Visual-motor abilities		93.62 (17.86)		90.2 (15.04)		92.86 (17.52)		95.28 (16.79)		93.07 (16.92)
Visual memory		16.09 (4.64)		17.34 (4.22)		17.06 (4.41)		17.78 (4.21)		17.1 (4.4)

Abbreviations: NDVI, normalized difference vegetation index; SD, standard deviation.

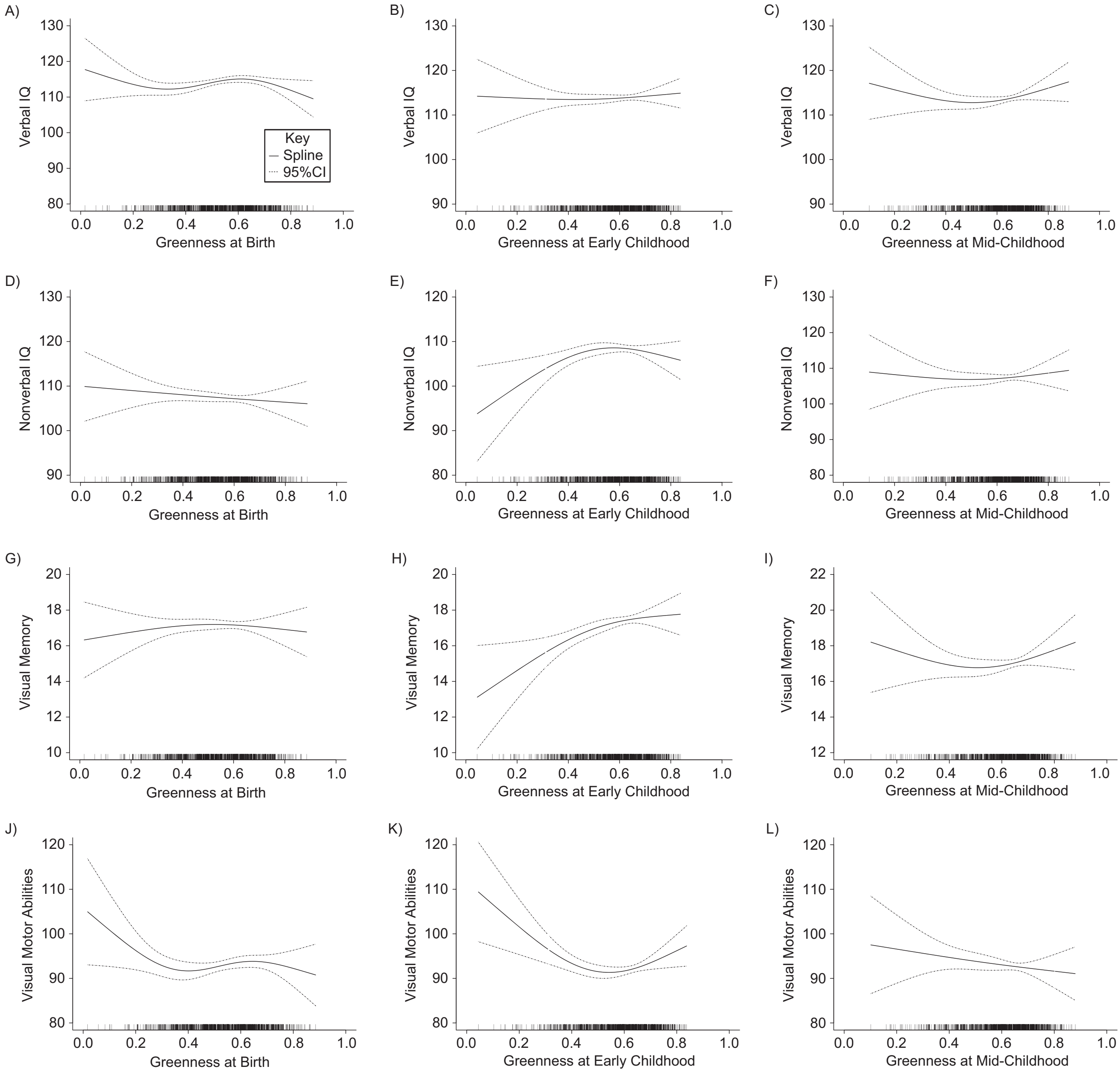

Figure 1. Nonlinear relationship between greenness and cognitive assessments at mid-childhood, Project Viva, Massachusetts, 1999–2010. A–C) Verbal intelligence quotient; D–F) nonverbal intelligence quotient; G–I) visual memory; J–L) visual-motor abilities. First column, greenness at birth; second column, greenness in early childhood; third column, greenness in mid-childhood. Adjusted for sex, age, maternal characteristics (intelligence quotient, education, race), paternal education, household annual income at enrollment in early pregnancy, neighborhood median annual income at birth, and greenness exposure in all preceding age periods but not in subsequent age periods. *P* values correspond to spline terms for greenness exposure at each time point: A) $P = 0.09$; B) $P = 0.82$; C) $P = 0.27$; D) $P = 0.61$; E) $P = 0.04$; F) $P = 0.80$; G) $P = 0.74$; H) $P < 0.01$; I) $P = 0.36$; J) $P = 0.23$; K) $P = 0.01$; L) $P = 0.48$.

that participants in the final sample were more likely to be White, have mothers with higher than college education, and live in a household with an income greater than $70,000/year. Greenness exposure at all time points and cognition measures at mid-childhood were similar between the full and final sample (Web Table 4).

Stratified analysis

In general, the highest cognitive scores were observed among girls, children of parents with high education, and those with high NSES (Web Table 5). We did not observe effect measure modification by sex, consistent with previous

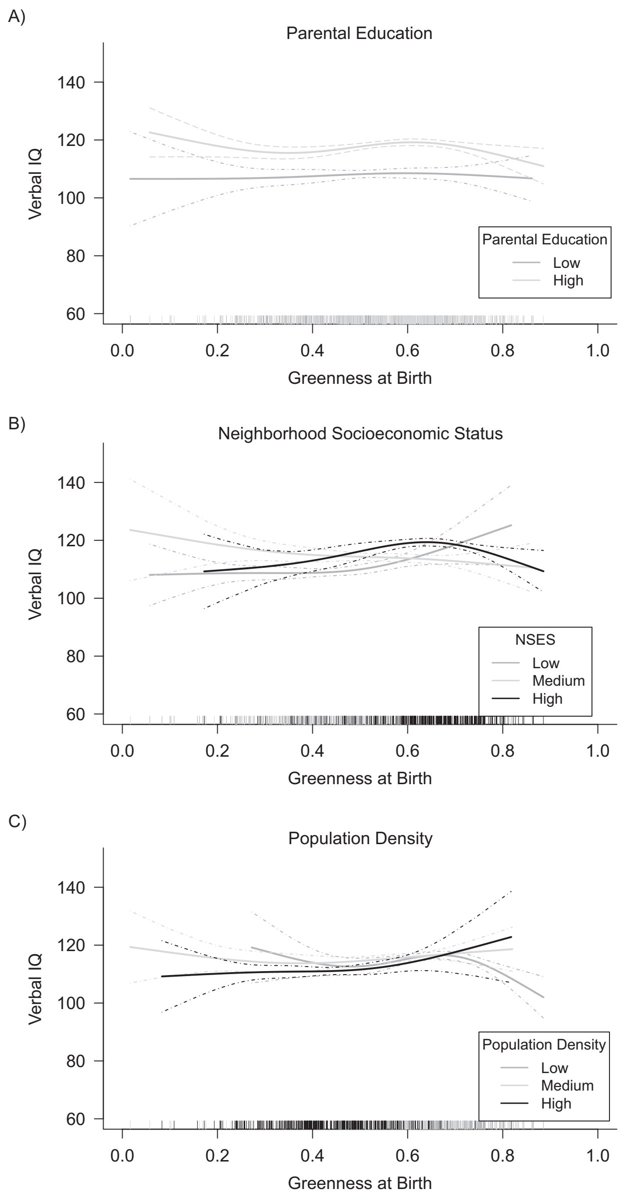

Figure 2. Stratified analysis of verbal intelligence quotient (IQ), Project Viva, Massachusetts, 1999–2010. A) Parental education; B) neighborhood socioeconomic status (NSES); C) population density. Bold line indicates estimated spline, and dotted lines indicate 95% confidence intervals.

findings (10). The relationship between greenness at birth and mid-childhood verbal intelligence differed by parental education, NSES, and neighborhood population density (Figure 2). The analysis by parental education suggested that the positive association between greenness at birth and mid-childhood verbal intelligence was mostly driven by parental high education. Stratified analysis by NSES suggested that at greenness levels of >0.5, there was a positive association with mid-childhood verbal IQ for low NSES. For high NSES, the positive association with mid-childhood verbal IQ seemed to decrease after 0.6 NDVI. These results are in contrast to a recent study reporting no significant effect modification by maternal education or NSES (9). The analysis by population density suggested a positive association between greenness at birth and verbal IQ at mid-childhood for areas with high population density. This was similar to a study that reported stronger associations between greenness and psychiatric disorder in the highest urbanized areas (14). There was no effect measure modification by any strata for early or mid-childhood greenness.

Mediation

The estimate of the indirect effect of the association between early childhood greenness and mid-childhood nonverbal IQ mediated by BC (assuming that underlying assumptions of the mediation analyses hold) was statistically significant ($P < 0.001$, Table 2). The indirect effect estimate was negative since the estimated association between early childhood greenness and early childhood BC was −0.13 (95% CI: –0.15, –0.12), while the estimated association between early childhood BC and mid-childhood nonverbal IQ was 14.72 (95% CI: 5.59, 23.83), and thus the estimated indirect effect of early childhood greenness on mid-childhood cognition via early childhood BC was −1.94 (i.e., -0.132×14.72, 95% CI: –3.13, −0.78). The total effect was 1.66 (95% CI: −0.59, 3.79), resulting in a negative ratio of the natural indirect effect to the total effect ("proportion" mediated, i.e., −1.94/1.66); however, the confidence interval for the ratio included the null (−1.17, 95% CI: −9.54, 6.67) (Table 2). No other estimates of mediation by BC or physical activity were significant. Further, interaction terms between exposure and mediator were not significant in any of the models.

DISCUSSION

We observed nonlinear relationships of exposure to greenness at early childhood with cognition at mid-childhood among Project Viva participants, with findings varying across NDVI values. Our results suggested that greenness exposure at early childhood was associated with better visual memory in mid-childhood. The observed association with visual memory was consistent after adjustment for child age, sex, and race and with mother's IQ, mother's education, father's education, household annual income, and NSES. The results with visual memory were also observed after further adjusting for early childhood cognitive assessment, strengthening the evidence of an association. Sensitivity analyses excluding outliers had little influence on the relationship between exposure to greenness across childhood and mid-childhood cognition.

There was some evidence that the association between greenness exposure at birth and mid-childhood verbal intelligence differed by parental education, NSES, and neighborhood population density. We observed that greenness did not benefit participants with low parental education. Participants with low parental education had lower cognitive scores at baseline and were not benefited by greenness exposure (perhaps due to limited access), while participants with higher parental education started off with higher cognitive scores

Table 2. Mediation Analysis[a] Estimating the Proportion of the Association Between Greenness at Early Childhood and Mid-Childhood Cognition Explained by Air Pollution Exposure, and Physical Activity, Both Measured at Early Childhood (n = 733[b]), Project Viva, Massachusetts, 1999–2010

Mediators at Early Childhood	Verbal IQ		Nonverbal IQ		Visual-Motor Abilities		Visual Memory	
	Proportion	95% CI	Proportion	95% CI	Proportion	95% CI	Proportion	95% CI
Air pollution								
Indirect effect	−0.70	−1.58, 0.18	−1.94	−3.13, −0.78	0.2	−1.05, 1.61	−0.07	−0.42, 0.24
Direct effect	1.07	−0.92, 3.07	3.61	1.06, 6.02	−0.17	−3.28, 2.33	0.84	0.17, 1.46
Total effect	0.37	−1.28, 2.10	1.66	−0.59, 3.80	0.03	−2.43, 2.18	0.76	0.21, 1.32
Proportion of association explained by mediator	−1.87	−12.7, 11.91	−1.17	−9.54, 6.67	6.06	−7.52, 6.72	−0.10	−0.8, 0.47
Physical activity								
Indirect effect	−0.03	−0.17, 0.06	−0.04	−0.2, 0.08	0.01	−0.08, 0.15	0	−0.03, 0.04
Direct effect	0.40	−1.27, 2.11	1.71	−0.62, 3.83	0.02	−2.18, 2.32	0.76	0.22, 1.30
Total effect	0.37	−1.28, 2.10	1.66	−0.51, 3.90	0.03	−2.15, 2.33	0.76	0.22, 1.30
Proportion of association explained by mediator	−0.09	−0.62, 0.81	−0.03	−0.44, 0.20	0.25	−0.68, 0.67	0	−0.05, 0.06

Abbreviations: CI, confidence interval; IQ, intelligence quotient.
[a] Mediation analyses assume that there is no unmeasured exposure-outcome confounding, no unmeasured mediator-outcome confounding, no unmeasured exposure-mediator confounding, and no mediator-outcome confounder affected by exposure.
[b] Analytical sample for mediation analysis excluded participants with missing data on any of the mediators of interest.

and seemed to benefit from greenness. It is possible that parents with lower levels of education had occupations that kept them and their children from enjoying outdoor space. On the other hand, for participants with low NSES, we observed cognitive benefits of greenness at levels above 0.5, reaching verbal IQ scores comparable to participants with high NSES. This finding is in line with the theory of equigenic environments, which suggests that greenness disrupts the usual conversion of socioeconomic adversity to greater risk of poor health and might be important to reduce socioeconomic health inequalities (40). The observed positive association between greenness at birth and mid-childhood verbal intelligence in areas with high population density, that may be more urbanized, suggests that policies to increase urban greenness may have sustainable public health benefits. In areas of lower population density, we observed a plateau/drop-off of benefit at higher NDVI values which may suggest that more greenness in suburban areas may have different associations with cognition.

Previous experimental studies have found that, compared with urban experience, nature experience leads to cognitive benefits such as improved attention among school-aged children (41–47). However, prior cohort studies assessing greenness surrounding schools and residences have reported inconsistent associations with brain development in children (1, 9, 12, 13), and few studies have examined sensitive periods of greenness exposure (7, 14, 15). The life-course associations found in our study suggest that early childhood is potentially a sensitive period for greenness exposure and visual memory development. Early childhood (approximately 3 years of age) has been considered a major window of developmental vulnerability (48), particularly for brain maturation, during which environmental exposures may be particularly relevant (4, 49). Research has shown that high levels of green space during childhood are associated with lower risk of psychiatric disorders later in life (14). Our findings were not consistent with those from a birth cohort study that found that higher residential greenness at birth was associated with better neurodevelopmental assessments at 24 months (10) and a longitudinal study that found that lifelong exposure to residential surrounding greenness since birth was positively associated with working memory and reduced inattentiveness in 7-year-old children (50). However, our finding on early childhood as a sensitive period for visual memory is in line with a meta-analysis that found an association between exposure to toxic substances throughout early childhood and childhood cognition (51). Contrary to our hypotheses, our results suggested that higher greenness exposure at early childhood might also be related to lower visual-motor abilities in mid-childhood. A recent analysis of the same population also found unexpected associations between polyfluoroalkyl substances and visual-motor abilities, where visual-motor abilities were higher among children born to mothers in the highest quartile of perfluorooctanoate plasma concentrations (vs. lowest) (52). Another study, assessing the association between greenness and visual-motor delays in children living in Berlin, reported no significant findings (13).

Assuming that the assumptions of the mediation analysis hold, our estimates suggest that air pollution did not explain the association between green space exposure in early life and mid-childhood cognition. This is inconsistent with a study by Dadvand et al. (9) and another by Liao et al. (10), which found that indoor levels of elemental carbon explained 20% to 65% and traffic-related air pollution explained 13.6% to 28.0%, respectively, of the association between green space exposure and early childhood neurodevelopment. The difference might be explained by the use of BC as traffic-related air pollution as opposed to indoor levels of elemental carbon or fine particular matter (having an aerodynamic diameter $\leq$2.5 μm). Moreover, the positive association found between early childhood BC and mid-childhood nonverbal IQ was unexpected but also found in a previous study of Project Viva. The authors found that BC exposure in the first 6 years of life was associated with higher nonverbal IQ in mid-childhood (1.7 points per interquartile-range increase, 95% CI: 0.1, 3.4) (53). The difference in our estimate on the association between BC and nonverbal IQ compared with Harris et al. (53) might be due to using BC as a continuous variable (vs. interquartile range) or due to different covariates in the model. This unexpected association could be due to participants living in more urbanized areas with higher access to education but also greater traffic-related air pollution exposure. Further, our estimates suggested that the observed association between greenness and mid-childhood cognitive function was not explained through physical activity, similar to 2 previous studies (54, 55). However, another study reported evidence that physical activity mediates the association between residential surrounding green space and mental health among young adults (56). These differences may be due to distinct outcome and mediator measurements, participants' ages (children vs. older adults), and covariate adjustment.

This study had a few limitations. First, residential greenness may reflect socioeconomic disparities. Although we adjusted for parental education and NSES, we cannot rule out residual confounding by unmeasured socioeconomic factors. Residual confounding of the mediator-outcome association may also explain the unexpected association between early childhood BC and mid-childhood cognition. We used sensitivity analysis further adjusting for potential mediator-outcome confounders; however, our results remained similar (results not shown). Second, use of NDVI did not allow us to identify specific types of vegetation (e.g., grass vs. trees) that may drive the association with cognition. Third, our study population had on average high socioeconomic status, so generalizability to less-advantaged populations may be limited. However, based on 2010 Census data (57), regional Boston characteristics such as median household income, percentage of households with income over $70,000, and percentage of White individuals were comparable to those of Project Viva, suggesting that the Project Viva cohort is generalizable to the Boston population. Further, Project Viva participants did very well on the outcome measures, with mean scores well above the standardization population, which is consistent with their generally being a sociodemographically/economically advantaged cohort. However, this also suggests that their lower (relative to the standardization population) performance on visual-motor testing is notable and could play a role in the paradoxical findings for that outcome. Fourth, missing data may result in selection bias. Although it is reassuring that early-life exposure to greenness and mid-childhood cognition measures of included participants were similar to those of the excluded participants, there were small differences in some factors correlated with both exposures and outcomes (mother's education and household income), suggesting potential selection bias (Web Table 4). Selection bias could also be possible due to parental socioeconomic status and their ability to decide where to live, which would also be related to child cognition. Fifth, we tested multiple time periods for several outcomes and evaluated effect modifiers and mediators, which could potentially lead to multiple testing problems and finding statistically significant results purely by chance. Finally, statistical power may be limited for mediation or stratified analysis.

This study has several notable strengths. The use of the longitudinal data from the Project Viva cohort allowed us to examine prospective associations between residential exposure to greenness and validated cognitive measures. To our knowledge, this study is the first to examine multiple windows of greenness exposure (birth, early childhood, and mid-childhood) in relation to cognitive development (early childhood and mid-childhood). The study was conducted in a relatively large, prospective cohort with rich data on maternal and child health, which enabled adjustment for important potential confounders, including maternal IQ and sociodemographic factors. The temporal ordering of the exposure, mediator, and outcome measurements facilitated interpretation of the mediation results.

Among children in Project Viva, higher exposure to residential greenness at early childhood was associated with higher visual memory scores in mid-childhood. In a neurotypical population, subtle alterations in continuous measures of cognition have important implications for clinical impact at the population level (58). These findings suggest that exposure to greenness in early childhood might have a greater influence on cognitive development than later in childhood.

ACKNOWLEDGMENTS

Author affiliations: Department of Epidemiology, Harvard T. H. Chan School of Public Health, Boston, Massachusetts, United States (Marcia P. Jimenez, Jessica Shoaff); Division of Chronic Disease Research Across the Lifecourse, Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, Massachusetts, United States (Marcia P. Jimenez, Sheryl L. Rifas-Shiman, Marie-France Hivert, Emily Oken, Peter James); Channing Division of Network Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, United States (Jessica Shoaff, Susan Korrick); Department of Environmental Health Sciences, Mailman School of Public Health, Columbia University, New York, New York, United States (Marianthi-Anna Kioumourtzoglou); Department of Environmental Health, Harvard T. H. Chan School of Public Health, Boston, Massachusetts, United States (Susan Korrick, Peter James); Diabetes Unit, Massachusetts General Hospital, Boston, Massachusetts, United States (Marie-France Hivert); and Department of Nutrition, Harvard T. H. Chan School of Public Health, Boston, Massachusetts, United States (Emily Oken).

This work was funded by the National Institutes of Health (grants T32-HL098048, 1K99AG066949-01, and R00CA201542).

We thank the participants and staff of Project Viva and Dr. Maria Glymour for her fruitful feedback.

Conflict of interest: none declared.

REFERENCES

1. de Keijzer C, Gascon M, Nieuwenhuijsen MJ, et al. Long-term green space exposure and cognition across the life course: a systematic review. *Curr Environ Health Rep*. 2016; 3(4):468–477.
2. Nieuwenhuijsen MJ, Khreis H, Triguero-Mas M, et al. Fifty shades of green: pathway to healthy urban living. *Epidemiology*. 2017;28(1):63–71.
3. Kaplan S. The restorative benefits of nature: toward an integrative framework. *J Environ Psychol*. 1995;15(3): 169–182.
4. Miguel PM, Pereira LO, Silveira PP, et al. Early environmental influences on the development of children's brain structure and function. *Dev Med Child Neurol*. 2019; 61(10):1127–1133.
5. Hystad P, Payette Y, Noisel N, et al. Green space associations with mental health and cognitive function: results from the Quebec CARTaGENE cohort. *Environ Epidemiol*. 2019; 3(1):e040.
6. Yang B-Y, Zeng X-W, Markevych I, et al. Association between greenness surrounding schools and kindergartens and attention-deficit/hyperactivity disorder in children in China. *JAMA Netw Open*. 2019;2(12):e1917862.
7. Donovan GH, Michael YL, Gatziolis D, et al. Association between exposure to the natural environment, rurality, and attention-deficit hyperactivity disorder in children in New Zealand: a linkage study. *Lancet Planet Health*. 2019; 3(5):e226–e234.
8. Wu J, Jackson L. Inverse relationship between urban green space and childhood autism in California elementary school districts. *Environ Int*. 2017;107:140–146.
9. Dadvand P, Nieuwenhuijsen MJ, Esnaola M, et al. Green spaces and cognitive development in primary schoolchildren. *Proc Natl Acad Sci U S A*. 2015;112(26):7937–7942.
10. Liao J, Zhang B, Xia W, et al. Residential exposure to green space and early childhood neurodevelopment. *Environ Int*. 2019;128:70–76.
11. Reuben A, Arseneault L, Belsky DW, et al. Residential neighborhood greenery and children's cognitive development. *Soc Sci Med*. 2019;230:271–279.
12. Flouri E, Papachristou E, Midouhas E. The role of neighbourhood greenspace in children's spatial working memory. *Br J Educ Psychol*. 2019;89(2):359–373.
13. Kabisch N, Alonso L, Dadvand P, et al. Urban natural environments and motor development in early life. *Environ Res*. 2019;179(A):108774.
14. Engemann K, Pedersen CB, Arge L, et al. Residential green space in childhood is associated with lower risk of psychiatric

disorders from adolescence into adulthood. *Proc Natl Acad Sci U S A*. 2019;116(11):5188–5193.
15. Dadvand P, Tischer C, Estarlich M, et al. Lifelong residential exposure to green space and attention: a population-based prospective study. *Environ Health Perspect*. 2017;125(9): 097016.
16. Oken E, Baccarelli AA, Gold DR, et al. Cohort profile: Project Viva. *Int J Epidemiol*. 2015;44(1):37–48.
17. James P, Hart JE, Banay RF, et al. Exposure to greenness and mortality in a nationwide prospective cohort study of women. *Environ Health Perspect*. 2016;124(9):1344–1352.
18. Crouse DL, Pinault L, Balram A, et al. Urban greenness and mortality in Canada's largest cities: a national cohort study. *Lancet Planet Health*. 2017;1(7):e289–e297.
19. Fong K, Hart JE, James P. A review of epidemiologic studies on greenness and health: updated literature through 2017. *Curr Environ Health Rep*. 2018;5(1):77–87.
20. Dunn LM, Dunn LM, Bulheller S, et al. *Peabody Picture Vocabulary Test*. Circle Pines, MN: American Guidance Service; 1965.
21. Adams W, Sheslow D. *Wide Range Assessment of Visual Motor Abilities (WRAVMA)*. Wilmington, DE: Wide Range, Inc; 1995.
22. Kaufman AS. *Kaufman Brief Intelligence Test: KBIT*. Circle Pines, MN: American Guidance Service; 1990.
23. Sheslow DA, Adams W. *Wide Range Assessment of Memory and Learning (WRAML2): Administration and Technical Manual*. Lutz, FL: Psychological Assessment Resources, Inc.; 2003.
24. Bottino CJ, Rifas-Shiman SL, Kleinman KP, et al. The association of urbanicity with infant sleep duration. *Health Place*. 2012;18(5):1000–1005.
25. Fleisch AF, Luttmann-Gibson H, Perng W, et al. Prenatal and early life exposure to traffic pollution and cardiometabolic health in childhood: traffic pollution and childhood cardiometabolic health. *Pediatr Obes*. 2017;12(1):48–57.
26. Bijnens EM, Derom C, Thiery E, et al. Residential green space and child intelligence and behavior across urban, suburban, and rural areas in Belgium: a longitudinal birth cohort study of twins. *PLoS Med*. 2020;17(8):e1003213.
27. Hernan MA. Causal knowledge as a prerequisite for confounding evaluation: an application to birth defects epidemiology. *Am J Epidemiol*. 2002;155(2):176–184.
28. Jimenez MP, Wellenius GA, James P, et al. Associations of types of green space across the life-course with blood pressure and body mass index. *Environ Res*. 2020;185: 109411.
29. Amoly E, Dadvand P, Forns J, et al. Green and blue spaces and behavioral development in Barcelona schoolchildren: the BREATHE Project. *Environ Health Perspect*. 2014;122(12): 1351–1358.
30. James P, Banay RF, Hart JE, et al. Review of the health benefits of greenness. *Curr Epidemiol Rep*. 2015;2(2): 131–142.
31. Almanza E, Jerrett M, Dunton G, et al. A study of community design, greenness, and physical activity in children using satellite, GPS and accelerometer data. *Health Place*. 2012; 18(1):46–54.
32. Pearl J. Causal diagrams for empirical research. *Biometrika*. 1995;82(4):669–688.
33. Pearl J. Direct and indirect effects. *Proceedings of the Seventeenth Conference on Uncertainty in Artificial Intelligence.* 2001;411–420.
34. Robins JM, Greenland S. Identifiability and exchangeability for direct and indirect effects. *Epidemiology*. 1992;3(2): 143–155.
35. Chiu Y-HM, Bellinger DC, Coull BA, et al. Associations between traffic-related black carbon exposure and attention in a prospective birth cohort of urban children. *Environ Health Perspect*. 2013;121(7):859–864.
36. Suglia SF, Gryparis A, Wright RO, et al. Association of black carbon with cognition among children in a prospective birth cohort study. *Am J Epidemiol*. 2008;167(3):280–286.
37. Tingley D, Teppei Y, Hirose K et al. Mediation: R Package for Causal Mediation Analysis. R Statistical Software Package, 2019. https://cran.r-project.org/web/packages/mediation/. Accessed September 9, 2021.
38. R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing; 2020.
39. Jimenez MP. Code for paper entitled: early-life exposure to green space and mid-childhood cognition in the Project Viva Cohort, Massachusetts. Boston, MA. 2020. https://github.com/marciapjimenez/Early-Life-Exposure-to-Green-Space-and-Mid-childhood-Cognition. Accessed November 30, 2020.
40. Mitchell R, Popham F. Effect of exposure to natural environment on health inequalities: an observational population study. *The Lancet*. 2008;372(9650):1655–1660.
41. Berman MG, Jonides J, Kaplan S. The cognitive benefits of interacting with nature. *Psychol Sci*. 2008;19(12): 1207–1212.
42. Berto R. The role of nature in coping with psycho-physiological stress: a literature review on restorativeness. *Behav Sci (Basel)*. 2014;4(4):394–409.
43. Bourrier SC, Berman MG, Enns. Cognitive strategies and natural environments interact in influencing executive function. *Front Psychol*. 2018;9:1248.
44. Ohly H, White MP, Wheeler BW, et al. Attention restoration theory: a systematic review of the attention restoration potential of exposure to natural environments. *J Toxicol Environ Health B Crit Rev*. 2016;19(7):305–343.
45. Pasanen T, Johnson K, Lee K, et al. Can nature walks with psychological tasks improve mood, self-reported restoration, and sustained attention? Results from two experimental field studies. *Front Psychol*. 2018;9:2057.
46. Stevenson MP, Dewhurst R, Schilhab T, et al. Cognitive restoration in children following exposure to nature: evidence from the attention network task and mobile eye tracking. *Front Psychol*. 2019;10:42.
47. Amicone G, Petruccelli I, De Dominicis S, et al. Green breaks: the restorative effect of the school Environment's green areas on children's cognitive performance. *Front Psychol*. 2018;9:1579.
48. Rice D, Barone S. Critical periods of vulnerability for the developing nervous system: evidence from humans and animal models. *Environ Health Perspect*. 2000;108(suppl 3): 511–533.
49. Goldman LR, Shannon MW, American Academy of Pediatrics: Committee on Environmental Health. Technical report: mercury in the environment: implications for pediatricians. *Pediatrics*. 2001;108(1):197–205.
50. Dadvand P, Pujol J, Macià D, et al. The association between lifelong greenspace exposure and 3-dimensional brain magnetic resonance imaging in Barcelona schoolchildren. *Environ Health Perspect*. 2018;126(2):027012.
51. Nilsen FM, Ruiz JDC, Tulve NSA. Meta-analysis of stressors from the total environment associated with children's general cognitive ability. *Int J Environ Res Public Health*. 2020; 17(15):5451.
52. Harris MH, Oken E, Rifas-Shiman SL, et al. Prenatal and childhood exposure to per- and polyfluoroalkyl substances

(PFASs) and child cognition. *Environ Int*. 2018;115: 358–369.
53. Harris MH, Gold DR, Rifas-Shiman SL, et al. Prenatal and childhood traffic-related pollution exposure and childhood cognition in the Project Viva Cohort (Massachusetts, USA). *Environ Health Perspect*. 2015;123(10):1072–1078.
54. Zijlema WL, Triguero-Mas M, Smith G, et al. The relationship between natural outdoor environments and cognitive functioning and its mediators. *Environ Res*. 2017; 155:268–275.
55. Clarke PJ, Ailshire JA, House JS, et al. Cognitive function in the community setting: the neighbourhood as a source of 'cognitive reserve'? *J Epidemiol Community Health*. 2012; 66(8):730–736.
56. Dzhambov AM, Markevych I, Hartig T, et al. Multiple pathways link urban green- and bluespace to mental health in young adults. *Environ Res*. 2018;166:223–233.
57. Boston Region Metropolitan Planning Organization. Median household income for Massachusetts towns 1980–2015. https://www.ctps.org/node/3280. Accessed November 30, 2020.
58. Bellinger DCDC. What is an adverse effect? A possible resolution of clinical and epidemiological perspectives on neurobehavioral toxicity. *Environ Res*. 2004;95(3):394–405.