Prenatal Exposure to Air Pollution and Early Life Stress Effects on Hippocampal Subregional Volumes and Associations With Visual-Spatial Reasoning

SUPPLEMENTAL INFORMATION

Supplemental Methods

Participants

Beginning in 2008, pregnant women were recruited to the Sibling-Hermanos birth cohort, based on prior enrollment in the Columbia Center for Children's Environmental Health, Mothers and Newborns Study. The Mothers and Newborns Study created a prospective birth cohort starting in 1998 to measure effects of fetal exposure to indoor and ambient pollutants including maternal secondhand smoke, rather than active maternal smoking; all women were nonsmokers (by self-report and validated by maternal prenatal urinary cotinine levels; Rauh et al. 2004).

Air Pollution

Polycyclic aromatic hydrocarbon (PAH) exposure was measured by polyurethane foam filters in air monitoring backpacks, worn for 48 continuous hours. The concentration of eight carcinogenic PAH were assayed using gas chromatography - mass spectroscopy, and the concentrations were then summed, and the natural log, calculated. Figure S1 shows the distribution of PAH exposures. Groups split at the median served as our variable of interest.

Supplemental Results

Continuous PAH Exposure

In sensitivity analyses, log PAH exposure was tested as a continuous variable, instead of using a median-split. First, PAH exposure, maternal perceived stress and their interaction were entered into multiple linear regressions to separately predict right whole and subregional hippocampal volumes. Second, the natural log of exposure, maternal perceived stress and their interaction were entered into multiple linear regressions to separately predict PIQ and VIQ. The interaction between maternal perceived stress and continuous PAH exposure predicted neither hippocampal volumes nor PIQ and VIQ (Table S10-S11).

Outliers

One participant had right whole and subregional hippocampal volumes which sat more than three standard deviations from the mean. In sensitivity analyses, instead of Winsorizing those values, we trimmed them, leaving us with n = 39 brain volumes. We re-ran all main analyses which incorporated right hippocampal volumes and our findings were sustained (Table S12-S14).

Supplemental Figures

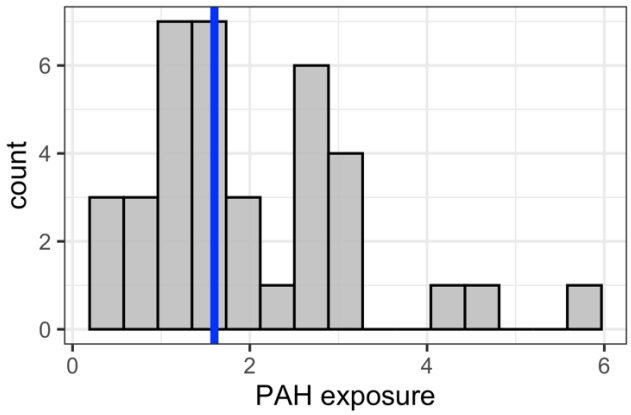

Figure S1. *Polycyclic Aromatic Hydrocarbon exposure distribution. Blue line marks median value for group split PAH exposure variable. Units: (ng/m^3)*

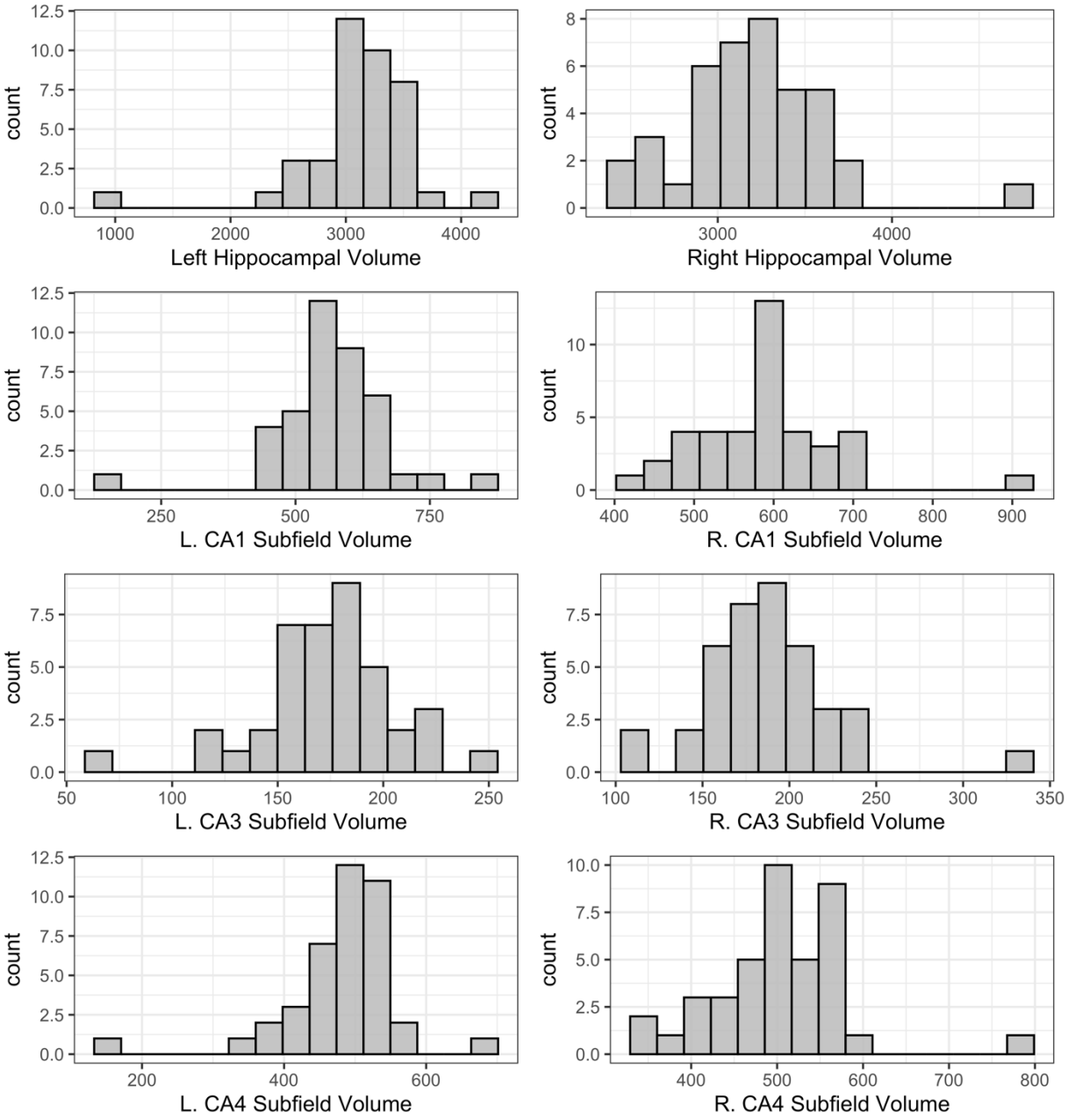

Figure S2. *Distribution of hippocampal volumes prior to being residualized and Winsorized (n = 40)*

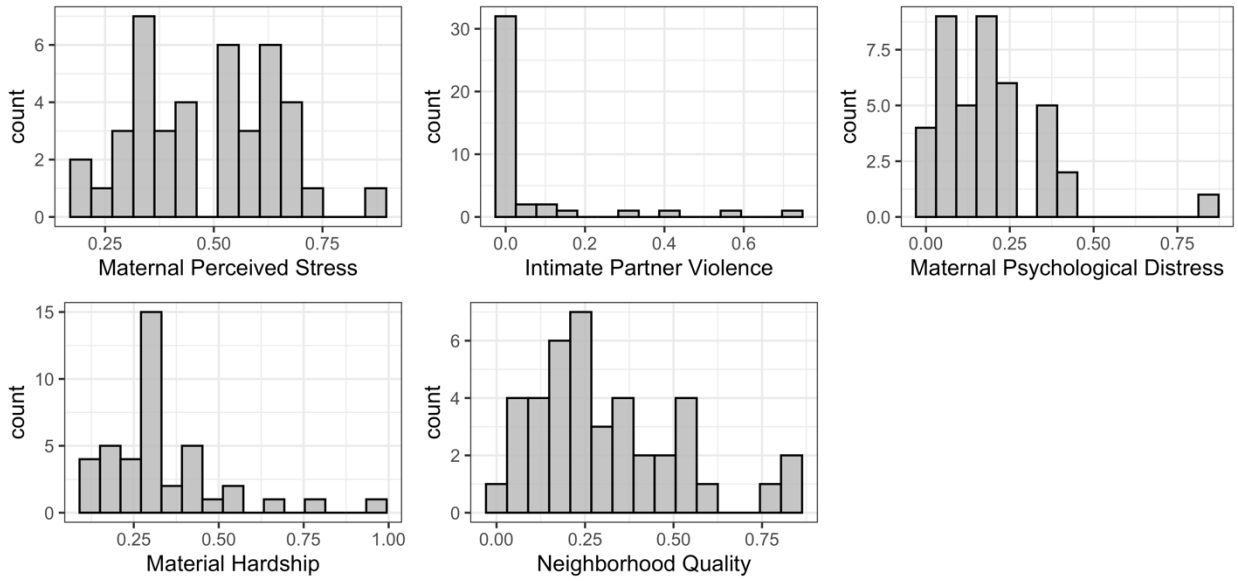

Figure S3. *Distribution of early life stress measured across five domains (n = 41)*

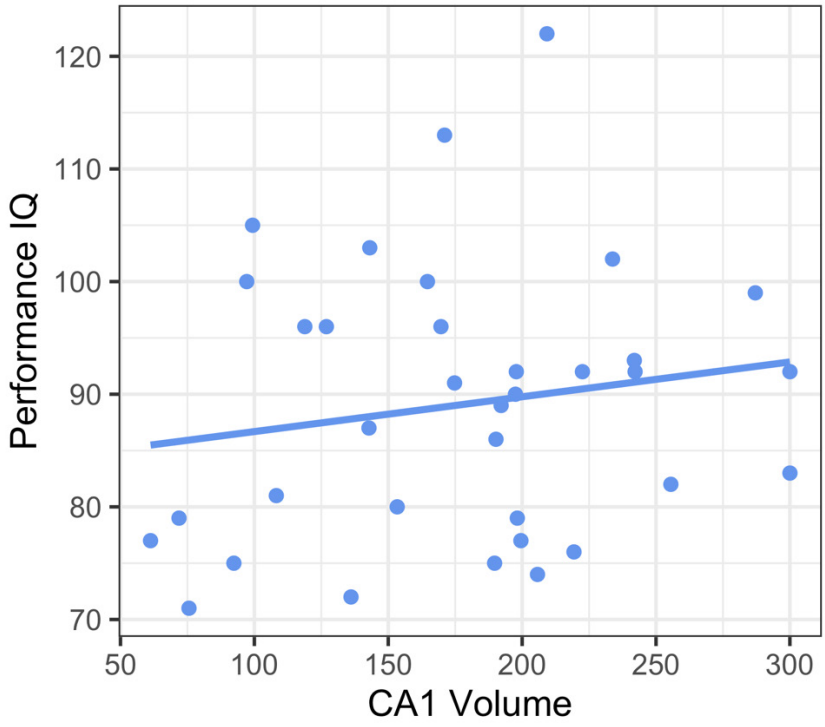

Figure S4. *Hippocampal subfield volume CA1, Winsorized and residualized for age, sex and ICV, does not significantly predict visual-spatial reasoning (PIQ).*

Supplemental Tables

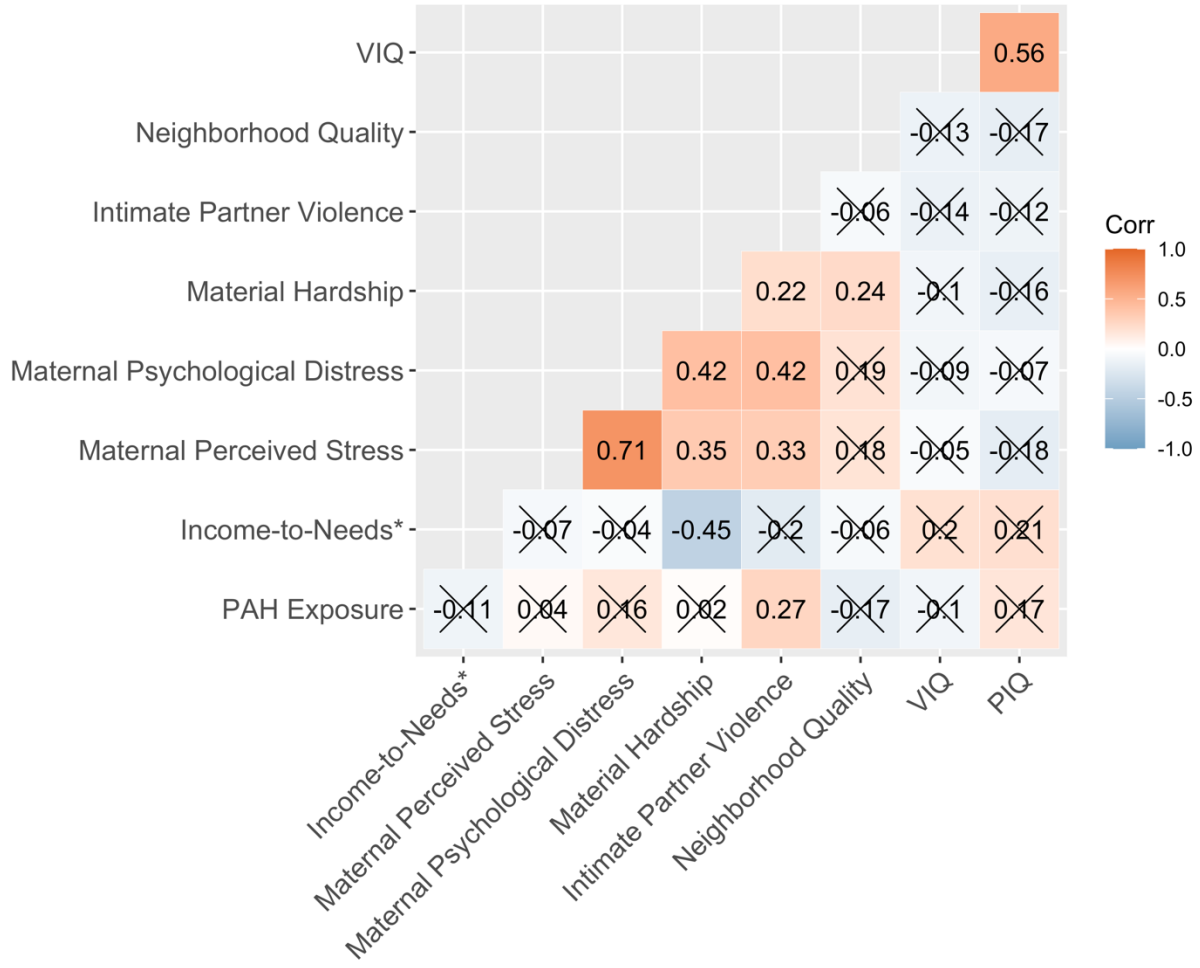

Table S1. *Correlations between measures of ELS and income-to-needs ratio at age 5, as well as WASI-II VIQ and PIQ at age 7. Pearson correlation coefficients (r) are displayed for each pair of variables with an "X" over those which were not significant ($\alpha = 0.05$). Correlations were based on varying sample sizes (n = 66 – 98; exact sample sizes for each pair can be found in Table S2).*
**Income-to-needs was calculated by dividing mother-reported household income by the federal poverty threshold for each participant's household size.*

Table S2. *Sample sizes per correlation.*

	INR	Maternal Perceived Stress	Maternal Psychological Distress	Material Hardship	Intimate Partner Violence	Neighborhood Quality	VIQ	PIQ
PAH	86	87	84	87	86	88	66	66
INR		94	93	96	96	97	67	67
Maternal Perceived Stress			92	95	95	95	67	67
Maternal Psychological Distress				93	94	94	68	68
Material Hardship					96	98	67	67
Intimate Partner Violence						97	68	68
Neighborhood Quality							68	68
VIQ								69

Table S3. *Predicting right and left whole hippocampal volumes with five domains of early life stress (n = 40).*

Dependent	Independent Variables	Beta	SE	t	2.5%	97.5 %	p	p-adjusted *
Right Whole Hippocampus	Intercept	< 0.01	0.14	0.00	-0.29	0.29	1.00	
	Maternal Perceived Stress	-0.57	0.19	-3.05	-0.95	-0.19	< 0.01	0.04
	Maternal Psychological Distress	0.38	0.19	1.94	-0.02	0.77	0.06	0.15
	Material Hardship	-0.11	0.16	-0.68	-0.44	0.22	0.50	0.63
	Intimate Partner Violence	-0.22	0.15	-1.45	-0.54	0.09	0.16	0.31
	Neighborhood Quality	-0.12	0.15	-0.81	-0.43	0.18	0.42	0.60
Left Whole Hippocampus	Intercept	< 0.01	0.15	0.00	-0.31	0.31	1.00	
	Maternal Perceived Stress	-0.39	0.20	-2.00	-0.79	0.01	0.05	0.15
	Maternal Psychological Distress	0.17	0.20	0.82	-0.25	0.58	0.42	0.60
	Material Hardship	0.03	0.17	0.19	-0.32	0.38	0.85	0.85
	Intimate Partner Violence	-0.33	0.16	-2.02	-0.66	0.00	0.05	0.15
	Neighborhood Quality	-0.04	0.16	-0.28	-0.37	0.28	0.78	0.85

Notes: Hippocampal volumes were Winsorized and residualized for age, sex and ICV. Whole hippocampal volume and each measure of stress was mean-centered and scaled by its standard deviation. As maternal perceived stress and psychological distress were highly correlated (r = 0.59, t = 4.49, 95% CI: 0.34, 0.76, p < 0.001, n = 40), we entered each into a separate simple linear regression, predicting whole hippocampal volume on the left and right side, as an additional check for collinearity. Maternal perceived stress was associated with right whole hippocampal volume (B = -0.40, t = -2.66, 95% CI:-0.70, -0.10, p = 0.01) but not left whole hippocampal volume (B = -0.29, t = -1.87, 95% CI: -0.61, 0.02, p = 0.07). Maternal psychological distress was not associated with right whole hippocampal volume (B = -0.06, t = -0.38, 95% CI: -0.39, 0.27, p = 0.70) nor left whole hippocampal volume (B = -0.13, t = -0.81, 95% CI: -0.46, 0.20, p = 0.42). The relatively large but non-significant beta values for maternal perceived stress and intimate partner violence on left hippocampal volume and intimate partner violence and maternal psychological distress on right hippocampal volume likely reflect the reduced power due to limited sample size." FDR correction applied.*

Table S4. *Variance inflation factors for terms in main regression models, predicting right and left whole hippocampal volumes with five domains of early life stress.*

	model	
term	right	left
Maternal Perceived Stress	1.61	1.61
Maternal Psychological Distress	1.75	1.75
Material Hardship	1.24	1.24
Intimate Partner Violence	1.11	1.11
Neighborhood Quality	1.05	1.05

Table S5. *Mixed effects model to test the hemispheric specificity for the association between maternal perceived stress and whole hippocampal volume (n = 40)*

term	B	SE	t	2.5%	97.5%	p
Intercept	0.02	0.15	0.14	-0.28	0.32	0.89
Maternal Perceived Stress	-0.30	0.15	-1.98	-0.60	<0.01	0.05
Hemisphere	-0.04	0.21	-0.20	-0.47	0.38	0.84
Maternal Perceived Stress x Hemisphere	-0.08	0.22	-0.38	-0.51	0.35	0.71

Hippocampal volumes were Winsorized and residualized for age, sex and ICV. Whole hippocampal volumes and maternal perceived stress were mean-centered and scaled by their standard deviations.

Table S6. *Interactions between Maternal Perceived Stress and median-split PAH exposure predicting right hippocampal volumes (n = 37).*

Dependent	Independent Variable	Beta	SE	t	2.50 %	97.50 %	p	p-adjusted *
Whole Hippocampus	Intercept	-0.21	0.21	-0.99	-0.63	0.22	0.33	
	Maternal Perceived Stress	-0.66	0.25	-2.64	-1.17	-0.15	0.01	
	PAH exposure	0.48	0.30	1.62	-0.12	1.09	0.11	
	Maternal Perceived Stress*PAH exposure	0.49	0.31	1.57	-0.15	1.13	0.13	0.126
CA1	Intercept	-0.16	0.20	-0.79	-0.57	0.25	0.44	
	Maternal Perceived Stress	-0.81	0.24	-3.34	-1.30	-0.32	< 0.01	
	PAH exposure	0.41	0.29	1.42	-0.18	0.99	0.16	
	Maternal Perceived Stress*PAH exposure	0.68	0.30	2.24	0.06	1.29	0.03	0.049
CA3	Intercept	-0.13	0.19	-0.69	-0.52	0.26	0.50	
	Maternal Perceived Stress	-0.94	0.23	-4.12	-1.40	-0.47	< 0.01	
	PAH exposure	0.37	0.27	1.36	-0.18	0.92	0.18	
	Maternal Perceived Stress*PAH exposure	0.82	0.29	2.86	0.23	1.40	0.01	0.029
CA4	Intercept	-0.10	0.21	-0.47	-0.52	0.33	0.64	
	Maternal Perceived Stress	-0.78	0.25	-3.13	-1.29	-0.27	< 0.01	
	PAH exposure	0.28	0.30	0.96	-0.32	0.89	0.35	
	Maternal Perceived Stress*PAH exposure	0.68	0.31	2.17	0.04	1.32	0.04	0.049

Hippocampal volumes were Winsorized and residualized for age, sex and ICV. Hippocampal volumes and maternal perceived stress were mean-centered and scaled by their standard deviations.

**Note: FDR correction applied* across (4 volumes [whole, CA4/DG, CA3, and CA1] * number of domain-hemisphere associations identified in analysis 1)

Table S7. *Right hippocampal subfields volumes CA3 and CA4 predict PIQ, but not VIQ (n = 35).*

Dependent	Independent Variables	Beta	SE	t	2.50%	97.50%	p
PIQ	Intercept	0.00	0.17	0.00	-0.34	0.34	1.00
	CA1	0.16	0.17	0.95	-0.19	0.51	0.35
	Intercept	0.00	0.16	0.00	-0.32	0.32	1.00
	CA3	0.38	0.16	2.39	0.06	0.71	0.02
	Intercept	0.00	0.16	0.00	-0.33	0.33	1.00
	CA4	0.35	0.16	2.16	0.02	0.68	0.04
VIQ	Intercept	0.00	0.17	0.00	-0.35	0.35	1.00
	CA1	-0.15	0.17	-0.87	-0.50	0.20	0.39
	Intercept	0.00	0.17	0.00	-0.35	0.35	1.00
	CA3	-0.05	0.17	-0.29	-0.40	0.30	0.78
	Intercept	0.00	0.17	0.00	-0.35	0.35	1.00
	CA4	-0.03	0.17	-0.17	-0.38	0.32	0.86

CA1, CA3 and CA4 hippocampal volumes were separately entered into three simple linear regressions, predicting PIQ. Hippocampal subfield volumes were Winsorized and residualized for age, sex and ICV. Subfield volumes as well as PIQ and VIQ scores were mean-centered and scaled by their standard deviations.

Table S8. *Left hippocampal subfields predict neither PIQ nor VIQ (n = 35).*

Dependent	Independent Variables	Beta	SE	t	2.50%	97.50%	p
PIQ	Intercept	0.00	0.17	0.00	-0.34	0.34	1.00
	CA1	0.23	0.17	1.34	-0.12	0.57	0.19
	Intercept	0.00	0.17	0.00	-0.34	0.34	1.00
	CA3	0.25	0.17	1.46	-0.10	0.59	0.15
	Intercept	0.00	0.17	0.00	-0.34	0.34	1.00
	CA4	0.24	0.17	1.43	-0.10	0.59	0.16
VIQ	Intercept	0.00	0.17	0.00	-0.35	0.35	1.00
	CA1	-0.10	0.17	-0.56	-0.45	0.25	0.58
	Intercept	0.00	0.17	0.00	-0.35	0.35	1.00
	CA3	-0.02	0.17	-0.10	-0.37	0.34	0.92
	Intercept	0.00	0.17	0.00	-0.35	0.35	1.00
	CA4	-0.07	0.17	-0.43	-0.43	0.28	0.67

CA1, CA3 and CA4 left hippocampal volumes were separately entered into three simple linear regressions, predicting PIQ and separately VIQ. Hippocampal subfield volumes were Winsorized and residualized for age, sex and ICV. Subfield volumes as well as PIQ and VIQ scores were mean-centered and scaled by their standard deviations.

Table S9. *Interactions between Maternal Perceived Stress and median-split PAH exposure predicting WASI-II PIQ/VIQ (n = 64)*

Dependent	Independent Variable	Beta	SE	t	2.50 %	97.50 %	p
PIQ	Intercept	0.33	0.19	1.73	-0.05	0.72	0.09
	Sex	-0.24	0.26	-0.95	-0.76	0.27	0.35
	Maternal Perceived Stress	-0.33	0.17	-1.93	-0.67	0.01	0.06
	PAH exposure	-0.49	0.24	-2.00	-0.97	0.00	0.05
	Maternal Perceived Stress*PAH exposure	0.22	0.25	0.92	-0.27	0.72	0.36
VIQ	Intercept	0.04	0.20	0.22	-0.37	0.45	0.83
	Sex	-0.12	0.27	-0.44	-0.66	0.42	0.66
	Maternal Perceived Stress	-0.14	0.18	-0.78	-0.50	0.22	0.44
	PAH exposure	0.00	0.26	0.01	-0.51	0.52	0.99
	Maternal Perceived Stress*PAH exposure	0.17	0.26	0.64	-0.35	0.69	0.52

PIQ and VIQ are age adjusted. Hippocampal volumes, IQ scores, and maternal perceived stress were mean-centered and scaled by their standard deviations.

Table S10. *Interactions between Maternal Perceived Stress and continuous PAH exposure predicting right hippocampal volumes (n = 37).*

Independent	Dependent Variables	Beta	SE	t	2.50%	97.50%	p
Whole Hippocampus	Intercept	0.12	0.20	0.62	-0.28	0.52	0.54
	Maternal Perceived Stress	-0.31	0.20	-1.54	-0.73	0.10	0.13
	PAH continuous	-0.24	0.25	-0.99	-0.74	0.26	0.33
	Maternal Perceived Stress*PAH continuous	-0.14	0.29	-0.49	-0.74	0.46	0.63
CA1	Intercept	0.07	0.19	0.36	-0.32	0.46	0.72
	Maternal Perceived Stress	-0.24	0.20	-1.20	-0.64	0.17	0.24
	PAH continuous	-0.13	0.24	-0.55	-0.62	0.36	0.58
	Maternal Perceived Stress*PAH continuous	-0.37	0.29	-1.30	-0.96	0.21	0.20
CA3	Intercept	0.15	0.18	0.81	-0.22	0.52	0.42
	Maternal Perceived Stress	-0.22	0.19	-1.18	-0.60	0.16	0.25
	PAH continuous	-0.29	0.23	-1.27	-0.75	0.17	0.21
	Maternal Perceived Stress*PAH continuous	-0.51	0.27	-1.87	-1.06	0.04	0.07
CA4	Intercept	0.11	0.20	0.57	-0.29	0.51	0.57
	Maternal Perceived Stress	-0.21	0.20	-1.03	-0.62	0.20	0.31
	PAH continuous	-0.22	0.24	-0.90	-0.72	0.28	0.37
	Maternal Perceived Stress*PAH continuous	-0.36	0.29	-1.25	-0.96	0.23	0.22

Hippocampal volumes were Winsorized and residualized for age, sex and ICV. Hippocampal volumes and maternal perceived stress were mean-centered and scaled by their standard deviations.

Table S11. *Interactions between Maternal Perceived Stress and continuous PAH exposure predicting WASI-II PIQ and VIQ (n = 64).*

Independent	Dependent Variables	Beta	SE	t	2.50%	97.50%	p
PIQ	Intercept	0.10	0.15	0.63	-0.21	0.40	0.53
	Sex	-0.28	0.26	-1.07	-0.80	0.25	0.29
	Maternal Perceived Stress	-0.23	0.13	-1.75	-0.49	0.03	0.08
	PAH continuous	0.21	0.13	1.68	-0.04	0.46	0.10
	Maternal Perceived Stress*PAH continuous	<0.01	0.13	-0.01	-0.26	0.25	0.99
VIQ	Intercept	0.03	0.16	0.21	-0.29	0.35	0.83
	Sex	-0.09	0.27	-0.32	-0.63	0.46	0.75
	Maternal Perceived Stress	-0.04	0.14	-0.29	-0.31	0.23	0.77
	PAH continuous	-0.09	0.13	-0.67	-0.35	0.18	0.51
	Maternal Perceived Stress*PAH continuous	-0.04	0.13	-0.30	-0.31	0.23	0.77

Maternal perceived stress was mean mean-centered and scaled by its standard deviation. PAH continuous is natural log transformed.

Table S12. *Predicting right whole hippocampal volumes with five domains of early life stress (n = 39).*

Dependent	Independent Variables	Beta	SE	t	2.50%	97.50%	p
Right Whole Hippocampus	Intercept	0.00	0.14	-0.01	-0.30	0.29	1.00
	Maternal Perceived Stress	-0.56	0.18	-3.02	-0.93	-0.18	< 0.01
	Maternal Psychological Distress	0.36	0.19	1.88	-0.03	0.75	0.07
	Material Hardship	-0.09	0.16	-0.56	-0.42	0.24	0.58
	Intimate Partner Violence	-0.22	0.15	-1.44	-0.53	0.09	0.16
	Neighborhood Quality	-0.21	0.15	-1.37	-0.52	0.10	0.18

Hippocampal volumes were residualized for age, sex and ICV, but NOT Winsorized. Hippocampal outliers (Z>3) w*ere dropped. Whole hippocampal volume and each measure of stress was mean-centered and scaled by its standard deviation.*

Table S13. *Interactions between Maternal Perceived Stress and median-split PAH exposure predicting right hippocampal volumes (n = 36)*

Dependent	Independent Variables	Beta	SE	t	2.50 %	97.50 %	p	p-adjusted*
Whole Hippocampus	Intercept	-0.16	0.21	-0.77	-0.59	0.27	0.45	
	Maternal Perceived Stress	-0.68	0.25	-2.73	-1.20	-0.17	0.01	
	PAH exposure	0.41	0.30	1.35	-0.21	1.03	0.19	
	Maternal Perceived Stress*PAH exposure	0.52	0.31	1.66	-0.12	1.16	0.11	0.11
CA1	Intercept	-0.11	0.20	-0.54	-0.51	0.30	0.59	
	Maternal Perceived Stress	-0.84	0.24	-3.51	-1.33	-0.35	0.00	
	PAH exposure	0.33	0.29	1.12	-0.27	0.92	0.27	
	Maternal Perceived Stress*PAH exposure	0.72	0.30	2.40	0.11	1.34	0.02	0.04
CA3	Intercept	-0.08	0.19	-0.41	-0.45	0.30	0.69	
	Maternal Perceived Stress	-0.99	0.22	-4.42	-1.44	-0.53	0.00	
	PAH exposure	0.28	0.27	1.03	-0.27	0.83	0.31	
	Maternal Perceived Stress*PAH exposure	0.88	0.28	3.12	0.30	1.45	< 0.01	0.02
CA4	Intercept	-0.05	0.21	-0.25	-0.47	0.37	0.81	
	Maternal Perceived Stress	-0.80	0.25	-3.23	-1.31	-0.30	< 0.01	
	PAH exposure	0.20	0.30	0.68	-0.41	0.82	0.50	
	Maternal Perceived Stress*PAH exposure	0.71	0.31	2.28	0.08	1.35	0.03	0.04

Hippocampal volumes were residualized for age, sex and ICV, but NOT Winsorized. Hippocampal outliers (Z>3) w*ere dropped. Hippocampal volumes and each measure of stress were mean-centered and scaled by its standard deviation.*
**Note: FDR correction applied.*

Table S14. *Right hippocampal subfields volumes CA3 and CA4 predict PIQ, but hippocampal subfield CA1 does not (n = 34).*

Dependent Variable	Independent Variables	Beta	SE	t	2.50%	97.50%	p
PIQ	Intercept	0.01	0.17	0.09	-0.34	0.37	0.93
	CA1	0.21	0.17	1.19	-0.15	0.56	0.24
	Intercept	0.01	0.16	0.09	-0.31	0.34	0.93
	CA3	0.45	0.16	2.81	0.12	0.78	0.01
	Intercept	0.01	0.16	0.09	-0.31	0.34	0.93
	CA4	0.40	0.16	2.44	0.07	0.73	0.02
VIQ	Intercept	0.05	0.17	0.30	-0.29	0.39	0.76
	CA1	-0.05	0.17	-0.31	-0.40	0.30	0.76
	Intercept	0.05	0.17	0.30	-0.29	0.39	0.76
	CA3	0.06	0.17	0.36	-0.29	0.41	0.72
	Intercept	0.05	0.17	0.30	-0.29	0.39	0.76
	CA4	0.06	0.17	0.36	-0.29	0.41	0.72

CA1, CA3 and CA4 hippocampal volumes were separately entered into three simple linear regressions, predicting PIQ and separately VIQ. Hippocampal subfield volumes were residualized for age, sex and ICV, but NOT Winsorized. Hippocampal outliers (Z>3) w*ere dropped. Subfield volumes as well as PIQ and VIQ scores were mean-centered and scaled by its standard deviation.*

Supplemental References

Rauh, V. A., R. M. Whyatt, R. Garfinkel, H. Andrews, L. Hoepner, A. Reyes, D. Diaz, D. Camann, and F. P. Perera. 2004. "Developmental Effects of Exposure to Environmental Tobacco Smoke and Material Hardship among Inner-City Children." *Neurotoxicology and Teratology* 26 (3): 373–85.