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Exposure to Fine Particulate Matter During Pregnancy Is Associated With Hippocampal Development in Offspring

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ABSTRACT

BACKGROUND: As the global climate crisis persists, it becomes increasingly important to understand how exposure to environmental toxins can affect the developing brain. Although researchers are beginning to document links between prenatal exposure to air pollution and brain structure, it is not clear when these associations emerge.

METHODS: We leveraged data from the GUSTO (Growing Up Toward Healthy Outcomes in Singapore) longitudinal birth cohort study to examine prenatal exposure to air pollution and brain development during childhood. Spatiotemporally interpolated prenatal exposure to particulate matter <2.5 μm was averaged across each prenatal week. Structural magnetic resonance imaging data were obtained when children were ages 4.5, 6.0, 7.5, and 10.5 years (N = 325, 47.7% female) and segmented with FreeSurfer 7.1. A subset of parents completed the Child Behavior Checklist at the final assessment (n = 195, 46.7% female). We used latent growth modeling to estimate a slope of hippocampal volume growth in each hemisphere from ages 4.5 to 10.5 years, adjusted for intracranial volume.

RESULTS: Distributed lag models indicated that late gestational exposure (during weeks 36–40) was associated with slower hippocampal growth in both hemispheres. Importantly, we also found that faster hippocampal volume growth in the right hemisphere was associated with more externalizing and attention problems at 10.5 years.

CONCLUSIONS: Future research should examine mechanisms that may underlie or contribute to these associations. These findings underscore the importance of efforts to reduce pollution, particularly for pregnant people and their children.

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Gestation is a critical period for offspring neurodevelopment (1,2). Difficulties in maternal mental and physical health during the prenatal period have been found to have significant negative consequences for offspring, including alterations in neural structure and function, behavioral and emotional problems, and psychopathology (2,3). The developmental origins of health and disease (DOHaD) hypothesis posits that by altering biological pathways, early maternal experiences can have long-lasting consequences for offspring (1). In this context, researchers have begun to examine associations between maternal exposure to outdoor air pollutants during gestation and subsequent child development.

Investigators have now identified a range of child psychological difficulties related to prenatal exposure to air pollutants. For example, Wang *et al.* (4) found that maternal prenatal exposure to particulate matter <2.5 μm ($PM_{2.5}$), particularly during mid- to late gestation, was associated with poorer motor skills, communication, problem solving, and personal-social skills in early childhood. Similarly, prenatal exposure to $PM_{2.5}$ was associated with autism symptoms (5) and prenatal exposure to PM_{10} was associated with lower scores on a mental development index in early childhood (6), but see Gong *et al.* (7) and Jorcano *et al.* (8) for reports of null effects of exposure on psychopathology symptoms in later childhood.

Researchers have also examined the association between prenatal exposure to air pollutants and brain development in offspring. For example, higher levels of PM_{10} and lower levels of nitrogen dioxide during pregnancy have been shown to be related to a range of alterations in brain structure in infants, including smaller cortical gray matter, amygdala, and hippocampus and larger brainstem and ventricular volume (9). Similarly, Lubczyńska *et al.* (10) found that maternal exposure to air pollutants during pregnancy was associated with smaller hippocampus, corpus callosum, and nucleus accumbens volume but larger amygdala volume in 9- to 12-year-old children. Importantly, some investigators have reported that neural alterations in children whose mothers were exposed to prenatal air pollutants underlie difficulties in the children's psychological functioning. For example, Guxens *et al.* (11) found that thinner cortex in frontal regions of the brain partially mediated the association between prenatal air pollution and impaired inhibition in 6- to 10-year-old children. Similarly, Mortamais *et al.*

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(12) found that prenatal exposure to air pollution was associated with smaller corpus callosum volume, which in turn predicted more hyperactivity in 8- to 12-year-old children.

Therefore, it appears that prenatal exposure to air pollution adversely affects offspring neurodevelopment, which can impair subsequent psychological functioning. The hippocampus, in particular, has been reported to be affected by exposure to air pollution (9,10) and to be related to a range of domains of psychological functioning, including emotion, memory, and learning (13,14). Hippocampal volume (HCV) growth is particularly dynamic early in life, with volume peaking in adolescence (15–17); however, we know little about the trajectory of HCV growth during early childhood and even less about the effects of prenatal exposure to air pollution on this trajectory and its effects on subsequent levels of symptoms of psychopathology. Elucidating these associations will inform both the risks to mental health posed by air pollution and public policy initiatives aimed at improving human health and well-being.

In the current study, we used data from the GUSTO (Growing Up in Singapore Toward Healthy Outcomes) (18) study to 1) characterize the trajectory of HCV in 4- to 10-year-old children, 2) examine the impact of maternal prenatal exposure to $PM_{2.5}$ on HCV development in their children, and 3) explore associations among $PM_{2.5}$ exposure, HCV trajectories, and symptoms of psychopathology at age 10 years. First, we hypothesized that HCV growth would be linear and positive, representing the initial portion of the inverted U–shaped trajectory that has been reported by other investigators (15–17). Second, we hypothesized that greater $PM_{2.5}$ exposure during pregnancy would be associated with slower HCV growth across childhood; furthermore, based on research that has shown that exposure to air pollution during late gestation is associated with poor child functioning (4), we hypothesized that exposure to $PM_{2.5}$ later rather than earlier in gestation would be associated more strongly with HCV. Finally, we hypothesized that slower HCV development would mediate the association between $PM_{2.5}$ exposure and symptoms of psychopathology. Finally, because previous findings concerning the link between $PM_{2.5}$ exposure and subcortical gray matter development volume have been inconsistent, we also conducted sensitivity analyses to examine whether pollution-related effects on HCV would also be found for amygdala volume.

METHODS AND MATERIALS

Participants

Mother-child dyads were part of the ongoing birth cohort study GUSTO (18). Mothers were recruited during pregnancy in 2009 and 2010. Demographic characteristics of the 325 (47.7% female) mother-child dyads that had complete data available for analysis in this study are presented in Table 1. The mothers were 42.0% Chinese, 17.3% Indian, 34.5% Malay, and 6.3% other race; 47.7% of the children in the 325 dyads were female. The National Healthcare Group Domain Specific Review Board and the SingHealth Centralized Institutional Review Board approved study activities. Mothers gave informed written consent, and children gave oral assent to participate.

Table 1. Sample Demographic Characteristics

	Values
Race	
Chinese	42.0%
Indian	17.3%
Malay	34.5%
Other	6.3%
Monthly Household Income	
S$0–S$999	3.0%
S$1000–S$1999	13.7%
S$2000–S$3999	31.0%
S$4000–S$5999	26.2%
S$6000+	26.2%
Gestational Age, Months	38.79 (1.31)
Hippocampal Volume, mm^3	
4.5 years old	*n* = 185
Left hemisphere	3605.53 (355.07)
Right hemisphere	3808.28 (371.05)
6.0 years old	*n* = 235
Left hemisphere	3767.47 (367.43)
Right hemisphere	3995.90 (364.00)
7.5 years old	*n* = 252
Left hemisphere	3894.03 (344.03)
Right hemisphere	4044.38 (380.59)
10.5 years old	*n* = 229
Left hemisphere	4040.47 (346.1)
Right hemisphere	4255.10 (376.52)
Participants With MRI Data at 1, 2, 3, and 4 Time Points	
1 Scan	65 (20.0%)
2 Scans	69 (21.2%)
3 Scans	95 (29.2%)
4 Scans	96 (29.5%)

Values are presented as %, *n* (%), or mean (SD). Household income is measured in Singapore dollars.

MRI, magnetic resonance imaging.

Measures

Demographic Characteristics. Mothers reported their monthly household income at recruitment (prenatal week 11) in the following increments of Singapore dollars: S$0 to S$999, S$1000 to S$1999, S$2000 to S$3999, S$4000 to S$5999, and S$6000 or more. The Department of Statistics Singapore reports that the median monthly household income in 2010 was S$5000. Child sex (1 = female, 0 = male) and gestational age at birth were recorded at delivery.

Child Emotional and Behavioral Problems. Mothers completed the Child Behavior Checklist (19) when their child was age 10.5 years (*n* = 195, 46.7% female). This measure has 120 items to which mothers responded on a 3-point Likert scale that comprises 8 subscales: anxious/depressed, withdrawn/depressed, somatic complaints, rule-breaking, aggression, thought problems, social problems, and attention problems. An internalizing problems score is computed from the anxious/depressed, somatization, and withdrawn

subscales, and an externalizing problems score is computed from the rule-breaking and aggression subscales. We also included the attention problems subscale in our analyses.

Fine Particulate Matter. As reported by Sum *et al.* (20), the National Environment Agency of Singapore provided data reflecting the daily 24-hour average $PM_{2.5}$ concentration in μg/m^3 collected from 8 stations in urban, suburban, roadside, and industrial areas of Singapore between January 1, 2009, and December 31, 2013. $PM_{2.5}$ was spatiotemporally interpolated to produce individual-level daily averages by inverse distance squared weighting of stations within 20 km of the centroid of each participant's residential subzone and validated using the leave-one-out approach. Subzones, or small geographic areas used by the Singapore Urban Redevelopment Authority to define land use and regulation, were matched to participant postal code using QGIS software (version 3.10.1). Mothers' dates of conception were estimated based on date of delivery, and ultrasound was used to estimate the gestational age of the child. Then, we operationalized and calculated early and late gestational $PM_{2.5}$ as the average $PM_{2.5}$ values from day 1 (conception) through day 139, or the median, of the pregnancy (early in gestation) and from day 140 through day 278 of the pregnancy (late in gestation). Finally, we calculated average $PM_{2.5}$ during the first postnatal year of the child's life.

Neuroimaging. Children participated in magnetic resonance imaging (MRI) scans when they were ages 4.5, 6.0, 7.5, and 10.5 years. MRI scans were acquired with a 3T Magnetom scanner (at ages 4.5 and 6.0 years: Skyra, Siemens; 7.5 and 10.5 years: Prisma, Siemens). The same 3-dimensional T1-weighted magnetization prepared rapid-acquisition gradient echo (MPRAGE) sequence was used on both scanners. The scan parameters were number of slices = 192, slice thickness = 1 mm, in-plane resolution = 1 × 1 mm, FOV = 192 × 192 mm, TR = 2000 ms, TE = 2.08 ms, inversion time = 877 ms, flip angle = 9°, sagittal acquisition, and scanning time = 3.5 minutes. The T1 images were processed using the recon-all pipeline in FreeSurfer version 7.1.1 (21). The hippocampus and amygdala were segmented using a probabilistic atlas (22) as part of the recon-all pipeline, and the resultant mask was used to extract volumetric measurements. We regressed out the effect of total intracranial volume on hippocampal and amygdala volume at each time point.

Analysis

All analyses were conducted in R. Descriptive statistics for relevant study variables are presented in Table 2.

Latent Growth Modeling. We used the lavaan package (23) to model HCV growth from ages 4.5 to 10.5 years using latent basis growth modeling. This approach makes no assumptions about the shape of the trajectory being modeled, estimates individual intercepts and slopes, and allows for intercepts and slopes to be correlated. We also considered linear and quadratic models. The following models were estimated separately for left and right hemispheric growth: model 1, intercept only; model 2, linear growth; model 3, quadratic growth; and model 4, latent basis with no covariates. We evaluated model fit using the lowest relative sample-adjusted Bayesian information criterion, nonsignificant χ^2 values, comparative fit index >0.95, root-mean-square error of approximation <0.06, and standardized root-mean-square residual <0.05. Models were estimated with full information maximum likelihood and with maximum likelihood estimation with robust standard errors.

Distributed Lag Models. We conducted 5 distributed lag models of average weekly $PM_{2.5}$ levels during the 40 weeks of gestation predicting the left and right slopes of HCV growth and internalizing, externalizing, and attention problems. We used an inverse weighting approach to calculate the cumulative effect of exposure, allowing for weeks closer together in time to make a greater contribution to exposure during a given week than exposure at weeks farther away in time, following Sheridan *et al.* (24). We estimated the models using the geepack package for R (25–27), accounting for within-subjects effects across gestation and with an independent correlation structure. Models were adjusted for participants' sex, gestational age (centered), and household income (centered).

Table 2. Fit Criteria for Growth Models

	χ^2, p	Log Likelihood	CFI	SABIC	RMSEA	SRMR
Left Hemisphere						
Model 1	χ^2_{11} = 274.94, p < .001	−1056.53	0.465	2121.11	0.391	0.227
Model 2	χ^2_{10} = 15.62, p = .111	−896.30	0.991	1803.33	0.052	0.046
Model 3	χ^2_{8} = 11.68, p = .166	−894.09	0.996	1804.23	0.042	0.039
Model 4	χ^2_{8} = 7.92, p = .441	−891.83	1.000	1799.76	0.000	0.036
Right Hemisphere						
Model 1	χ^2_{11} = 187.33, p < .001	−1052.50	0.574	2113.06	0.337	0.194
Model 2	χ^2_{10} = 25.27, p = .005	−935.60	0.971	1881.92	0.092	0.050
Model 3	χ^2_{8} = 12.42, p = .133	−927.45	0.991	1871.00	0.059	0.032
Model 4	χ^2_{8} = 13.84, p = .086	−928.57	0.988	1873.23	0.067	0.036

Model 1, intercept only/no growth; model 2, linear growth; model 3, quadratic growth; and model 4, latent basis growth model.

CFI, comparative fit index; RMSEA, root-mean-square error of approximation; SABIC, sample-adjusted Bayesian information criteria; SRMR, standardized root-mean-square residual.

Predicting Emotional and Behavioral Problems. We tested whether left and right HCV growth slopes were associated with internalizing, externalizing, and attention problems reported when children were age 10.5 years. We conducted one multiple regression in lavaan with internalizing, externalizing, and attention problem as dependent variables; left and right HCV growth slopes as independent variables; and sex, age, and household income as covariates.

Sensitivity Analysis. To examine whether findings were specific to HCV, we repeated the analyses outlined above with left and right hemisphere amygdala volume growth.

RESULTS

Participant Characteristics

Participant characteristics for the sample are summarized in Table 1. HCV data were collected at ages 4.5 (n = 178), 6.0 (n = 229), 7.5 (n = 243), and 10.5 years (n = 222), and 325 participants had HCV data from at least 1 time point available for analysis. There were no significant differences as a function of the number of usable time points of data on child sex (p = .620), gestational age (p = .723), ethnicity (p = .899), or monthly household income (p = .715). There were also no differences between participants who had any usable HCV data and participants who had none on sex (p = .780), gestational age (p = .885), ethnicity (p = .327), or monthly household income (p = .818). Little's missing completely at random test was not significant (χ^2_{70} = 80.74, p = .179).

Correlations among relevant study variables are presented in Table S1. HCV was highly intercorrelated across time points, as were the $PM_{2.5}$ averages and psychopathology symptoms at year 10. Household income was associated with larger bilateral HCV at years 4 and 7 and with larger left HCV at year 10. Right HCV at year 4 was negatively correlated with attention problems at year 10.

Latent Growth Modeling

We estimated 4 different models of HCV growth in each hemisphere. Fit criteria for each model are reported in Table 2. Model 4, which used latent growth, was the best fit to the data in the left hemisphere, although it was saturated. In the right hemisphere, the quadratic model (model 3) slightly outperformed the latent basis model. We could not perform likelihood ratio tests to compare the fit of the quadratic and latent models because they had the same number of degrees of freedom. Because the fit criteria were similar for the latent and quadratic models, we chose to use the slopes of HCV growth from the latent models for both the left and right hemisphere to be consistent.

As expected, the slope of HCV growth, relative to intracranial volume, was positive over time, although not linear. According to the latent basis model, in the left hemisphere, 15.5% of total growth (relative to intracranial volume) occurred between years 4.5 and 6.0, 55.0% between 6.0 and 7.5 years, and 29.5% between 7.5 and 10.5 years. In the right hemisphere, 20.1% of total growth (relative to intracranial volume) occurred between 4.5 and 6.0 years, 31.2% between 6.0 and 7.5 years, and 48.7% between 7.5 and 10.5 years.

Distributed Lag Models Predicting HCV Growth

In the distributed lag model predicting left HCV growth, while adjusting for participant sex, age, and household income, we found that $PM_{2.5}$ exposure during the first and 25th weeks of gestation was associated with faster growth, whereas exposure during weeks 36 and 38 to 40 was associated with slower growth. Full model details are provided in Table 3, and these effects are illustrated in Figure 1A. Participant sex and household income were also associated with HCV growth.

In the model predicting right HCV growth, we found that $PM_{2.5}$ exposure during the first and 13th weeks of gestation was associated with faster growth, whereas exposure during weeks 36 to 40 was associated with slower growth. Full model details are presented in Table 3, and these effects are illustrated in Figure 1B. Participant sex and gestational age were also associated with HCV growth.

Distributed Lag Models Predicting Emotional and Behavioral Problems

We conducted an additional 3 distributed lag models to predict internalizing, externalizing, and attention problems from gestational $PM_{2.5}$ while adjusting for child sex, age, and household income. There were no significant direct effects of $PM_{2.5}$ on any of these measures (see Table S2 for full model details).

Predicting Emotional and Behavioral Problems From HCV

Next, we predicted internalizing, externalizing, and attention problems simultaneously from left and right HCV growth and

Table 3. Distributed Lag Models Predicting Hippocampal Volume Growth

	Left Hippocampal Volume Growth			Right Hippocampal Volume Growth		
	B	95% CI	p	B	95% CI	p
Sex	−0.0245	−0.0385 to −0.0105	<.001	0.0916	0.0718 to 0.1115	<.001
Gestational Age	−0.0031	−0.0088 to 0.0027	.297	0.0152	0.0085 to 0.0220	<.001
Household Income	−0.0031	−0.0490 to −0.0361	<.001	0.0011	−0.0082 to 0.0103	.821
Weekly $PM_{2.5}$	−0.0024	−0.0042 to −0.0005	.012	−0.0042	−0.0069 to −0.00015	.003
Cumulative $PM_{2.5}$	0.0008	−0.0039 to 0.0023	.607	−0.0013	−0.0059 to 0.0033	.570
Weekly $PM_{2.5}$ × Cumulative $PM_{2.5}$	0.0001	0.0000 to 0.0002	.033	0.0002	0.0000 to 0.0003	.009

Sex assigned at birth was coded as 1 for female and 0 for male.
$PM_{2.5}$, particulate matter <2.5 μm.

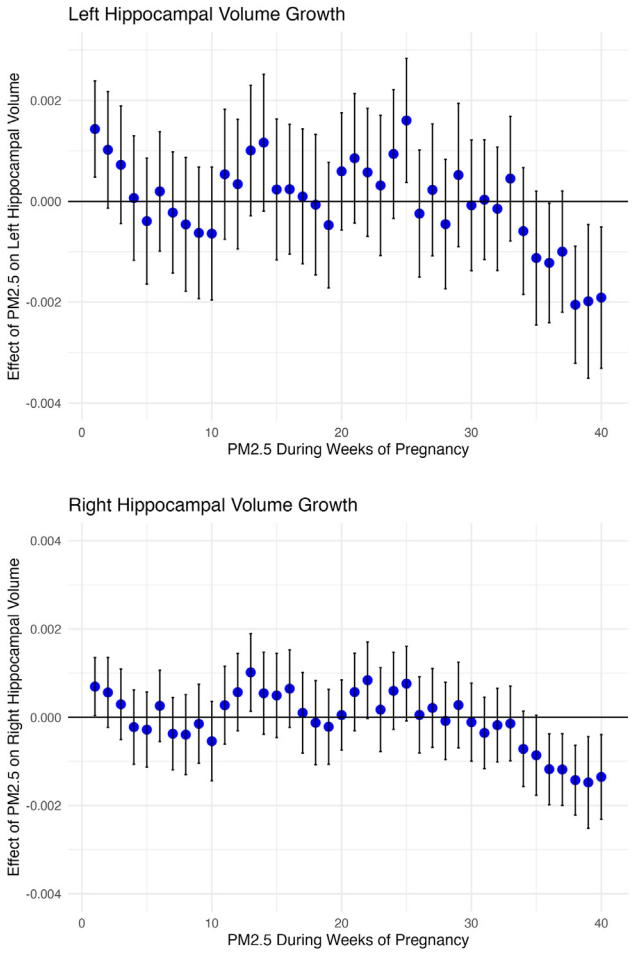

Figure 1. Predicting hippocampal volume growth from prenatal exposure to particulate matter <2.5 μm ($PM_{2.5}$). Dots represent standardized regression coefficients representing the association between $PM_{2.5}$ exposure at a given gestational week (x-axis) on the slope of hippocampal volume growth in the left (above) and right (below) hemispheres. Error bars represent 95% CIs.

participant sex, age, and household income. More attention problems were significantly predicted by right (B = 3.677), but not left (B = −1.362), HCV growth such that faster growth was associated with more problems. Female sex (B = 0.450) and household income (B = 0.196) were also associated with more attention problems. Internalizing problems were not significantly associated with either right (B = 3.231) or left (B = −0.858) HCV growth, but both were positively associated with household income (B = 0.197). Finally, more externalizing problems were predicted by faster right (B = 5.072), but not left (B = −1.552), HCV growth and by household income (B = 0.314). See Table 4 for model details.

Sensitivity Analysis

Latent basis models (model 4) provided the best fit to the amygdala volume growth data in the left and the right hemispheres (see Table S2). In the left hemisphere, 43.3% of amygdala growth occurred between 4.5 and 6.0 years, 18.3% occurred between 6.0 and 7.5 years, and 38.4% occurred between 7.5 and 10.5 years. In the right hemisphere, 67.4% of amygdala growth occurred between 4.5 and 6.0 years, 10.8% occurred between 6.0 and 7.5 years, and 21.8% occurred between 7.5 and 10.5 years. Distributed lag models conducted to predict amygdala volume growth in the left and right hemispheres did not yield significant effects of gestational $PM_{2.5}$ exposure (see Table S3). Finally, faster right amygdala volume growth was associated with more attention problems (B = 5.670), more internalizing problems (B = 4.768), and more externalizing problems (B = 5.567); conversely, faster left amygdala growth was associated with fewer attention problems (B = −9.786), fewer internalizing problems (B = −8.303), and fewer externalizing problems (B = −9.202) (see Table S4 for full model details).

Table 4. Predicting Emotional and Behavioral Problems From Hippocampal Growth

	B	*p*	95% CI
Attention Problems			
Sex	0.450	.015	0.087 to 0.814
Household Income	0.196	.032	0.017 to 0.376
Age	0.004	.997	−1.711 to 1.718
Right HCV Slope	3.677	.019	0.607 to 6.747
Left HCV Slope	−1.362	.209	−3.488 to 0.763
Internalizing Problems			
Sex	0.351	.074	−0.035 to 0.736
Household Income	0.197	.042	0.007 to 0.387
Age	0.856	.356	−0.961 to 2.673
Right HCV Slope	3.231	.052	−0.022 to 6.484
Left HCV Slope	−0.858	.455	−3.110 to 1.394
Externalizing Problems			
Sex	0.360	.078	−0.040 to 0.760
Household Income	0.314	.002	0.117 to 0.511
Age	−0.763	.428	−2.648 to 1.122
Right HCV Slope	5.072	.003	1.697 to 8.448
Left HCV Slope	−1.552	.193	−3.889 to 0.785

HCV, hippocampal volume.

DISCUSSION

In this study, we examined the relationship between prenatal exposure to $PM_{2.5}$ and trajectories of HCV growth from ages 4 to 10 years in the offspring. We found that exposure to $PM_{2.5}$ in late gestation (weeks 36–40) was associated with slower HCV growth bilaterally. Gestational $PM_{2.5}$ was not directly associated with internalizing, externalizing, or attention problems. However, faster HCV growth in the right hemisphere was related to more externalizing and attention problems when children were age 10 years. Sensitivity analyses indicated that amygdala development was unrelated to prenatal exposure to $PM_{2.5}$; thus, these effects appear to be specific to HCV. These findings support the idea that pregnancy is a period of susceptibility for the development of HCV through at least age 10 years.

We hypothesized that HCV growth from ages 4 to 10 years would be linear and positive. While the trajectory of HCV throughout childhood and adolescence has been found to follow an inverted U–shaped curve that peaks in adolescence, we know little about the trajectory of HCV in children under age

10 years. We found that although positive (i.e., increasing over time), a linear slope was not the best fit to the data; rather, a latent curve that did not assume a constant rate of change was the best fit in the left hemisphere, and a quadratic curve was the best fit in the right hemisphere. Replication is needed to verify the shape of the trajectory of HCV growth in each hemisphere, and future work should examine the growth of individual hippocampal subfields as well.

We also hypothesized that prenatal exposure to $PM_{2.5}$ would be associated with a slower rate of HCV growth from 4 to 10 years. We found that $PM_{2.5}$ exposure during weeks 36 to 40 was associated with slower growth in both hemispheres. This is consistent with reports that greater prenatal exposure to air pollution predicts smaller HCV (9,10). Given that previous findings concerning the effects of prenatal exposure to air pollution on amygdala volume have been equivocal (9,10), we did not expect to find associations between gestational $PM_{2.5}$ and amygdala growth. DOHaD (1) and fetal programming (28) hypotheses provide a framework from which we may begin to advance our knowledge of how epigenetic, endocrine, and immune alterations can contribute to these associations. We are limited in our ability to generalize to human findings from studies of the prenatal development of the hippocampus in rodents; rodent studies show that hippocampal neurogenesis occurs during the final 8 days of gestation (29); in contrast, this appears to begin at 9 weeks gestation and peak at 22 weeks in humans (30). However, Arnold and Trojanowski (31) found that the dentate gyrus of the hippocampus develops later than other areas of this structure, becoming mature in the last 6 weeks of gestation, when myelination of hippocampal cells also begins. Either of these processes may be disrupted by exposure to chemicals in $PM_{2.5}$ that are able to cross the placental barrier or by maternal inflammation induced by $PM_{2.5}$. Future work that examines both gray and white matter may help clarify these processes. To determine the mechanisms that underlie these associations, future analyses should also consider both the chemical composition of $PM_{2.5}$ and the differential growth hippocampal subfields. Research with nonhuman animals has implicated alterations in microglia activity (32,33), higher levels of iron (32,33), altered methylation of genes involved in neurogenesis and neural differentiation (34), and other molecular changes related to maternal inflammation induced by air pollution exposure (33) as mechanisms that may underlie smaller HCV in offspring. Gaining a more comprehensive understanding of the ways in which the chemical compounds in $PM_{2.5}$ can disrupt neurodevelopmental processes and the consequences of the timing of these disruptions will help elucidate mechanisms that underlie the associations observed here.

Our finding that exposure to $PM_{2.5}$ during the first week of gestation was associated with faster growth has not been reported elsewhere. Because the neural tube, which develops into the brain, begins to form during the third to fourth gestational weeks, it is not clear exactly how disruption at this stage may affect the development of subsequent structures. These findings require replication, but they may indicate that epigenetic programming of fetal development occurs this early in gestation and has enduring effects throughout childhood. Future work should explore compensatory and protective mechanisms, which may include maternal mental and physical health, paternal characteristics, and the postnatal environment.

Finally, we examined associations of gestational $PM_{2.5}$ and HCV with internalizing, externalizing, and attention problems at age 10 years given the wide range of behaviors and types of psychopathology in which the hippocampus has been implicated (13,14). Gestational $PM_{2.5}$ levels were not related to these emotional and behavioral problems. The lack of association between $PM_{2.5}$ exposure and emotional and behavioral problems may be due to the young age of the participants in the current study, which is below the mean age of onset for many types of psychopathology. Although researchers have reported links between prenatal exposure to air pollution and mental development in young children (4,6), null associations with symptoms of psychopathology have also been reported (7,8). Further research with children who are older or who are exposed to higher levels of air pollution may help clarify the issue of whether prenatal pollutants are associated with emotional and behavioral problems.

However, we did find that right HCV growth was associated with more externalizing and attention problems; although in the same direction, the relationship with internalizing problems did not reach statistical significance. We did not hypothesize that our findings would be lateralized, although there is evidence in the literature to suggest that emotion, particularly negative emotion, is primarily processed in the right hemisphere of the brain (35,36); however, recent work emphasizes the role of integrated interhemispheric networks in emotion processing (37). We expected that slower HCV growth would be associated with more emotional and behavioral problems and would mediate an association with gestational $PM_{2.5}$. However, it is important to note that the finding that faster HCV growth was associated with more emotional problems is not without precedent. The literature on prenatal and early-life exposure to adverse conditions has been mixed. Whereas some investigators have found that faster neural development can be maladaptive and confer greater risk for psychopathology (38,39), others have reported that accelerated development can be adaptive and mitigate risk for psychopathology (40). In this context, our finding that faster right HCV growth was associated with more emotional and behavioral problems may represent accelerated development in response to adversity not measured in this study, given that gestational $PM_{2.5}$ was associated with slower growth (41). Additional research that simultaneously examines psychosocial stressors and exposure to environmental pollutants will help disentangle how developmental pace is affected by the confluence of these factors (42).

We should note 3 limitations of this study. First, $PM_{2.5}$ levels were measured using a spatiotemporal interpolation approach that captured exposure at the place of residence. However, it is almost certain that participants are exposed to $PM_{2.5}$ levels at other locations that we could not measure (43). Similarly, we lack data concerning the use of in-home air filtration systems. Furthermore, we encourage researchers to examine relationships between brain development and exposure to pollutants other than $PM_{2.5}$ to elucidate differential effects of pollutants on brain development and behavior. Second, we did not adjust our models for temperature; consequently, we cannot determine the role of extreme heat on fetal development of the

hippocampus, and future work should explore the interactive effects of air pollutants and extreme heat. It is also important to note that our findings do not rule out potentially confounding effects of maternal mental or physical health, delivery complications, parenting quality, or adverse childhood experience that could shape hippocampal development. Third, we did not examine hippocampal subfields, which have been shown to develop at different rates (16). Examining whether these subfields develop differentially as a function of prenatal exposure to air pollution will advance our knowledge of the ways in which behavior and well-being may be affected by pollution.

Conclusions

In this study, we found a link between exposure to $PM_{2.5}$ during pregnancy and the rate of growth of HCV through age 10 years. Late gestational exposure to $PM_{2.5}$ was associated with slower HCV growth in the left and right hemispheres. In addition, faster HCV growth in the right hemisphere was associated with more externalizing and attention problems at age 10 years. Future work should investigate the mechanisms by which prenatal exposure to $PM_{2.5}$ affects HCV development. For example, exposure to air pollution has been linked to increased oxidative stress and epigenetic alterations that may contribute to fetal programming of long-term brain development (44,45). Finally, additional research is needed that examines different pollutants and critical periods of susceptibility to inform clinicians and public policy makers about how to best protect vulnerable populations, including pregnant people and children, from the harmful effects of pollution.

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JLB conducted all analyses and prepared the article. PH, TB, JYH, and APT prepared and computed data. JYH and TB advised on the analytic approach. PDG, MVF, Y-SC, APT, and MJM conceived of and planned the study. Project administration and funding acquisition were provided by MVF and MJM. JYH, TB, JPU, JGM, and IHG reviewed, edited, and provided feedback on the article. All authors contributed to the final version of the article.

All deidentified data are available upon request at https://gustodatavault.sg/about/request-for-data following proposal approval.

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