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Does the home environment and the sex of the child modify the adverse effects of prenatal exposure to chlorpyrifos on child working memory?

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ABSTRACT

Prenatal exposure to chlorpyrifos (CPF), an organophosphorus insecticide, has long been associated with delayed neurocognitive development and most recently with decrements in working memory at age 7. In the current paper, we expanded the previous work on CPF to investigate how additional biological and social environmental factors might create or explain differential neurodevelopmental susceptibility, focusing on main and moderating effects of the quality of the home environment (HOME) and child sex. We evaluate how the quality of the home environment (specifically, parental nurturance and environmental stimulation) and child sex interact with the adverse effects of prenatal CPF exposure on working memory at child age 7 years. We did not observe a remediating effect of a high quality home environment (either parental nurturance or environmental stimulation) on the adverse effects of prenatal CPF exposure on working memory. However, we detected a borderline significant interaction between prenatal exposure to CPF and child sex (B (95% CI) for interaction term = −1.714 (−3.753 to 0.326)) suggesting males experience a greater decrement in working memory than females following prenatal CPF exposure. In addition, we detected a borderline interaction between parental nurturance and child sex (B (95% CI) for interaction term = 1.490 (−0.518 to 3.499)) suggesting that, in terms of working memory, males benefit more from a nurturing environment than females. To our knowledge, this is the first investigation into factors that may inform an intervention strategy to reduce or reverse the cognitive deficits resulting from prenatal CPF exposure.

1. Introduction

1.1. Background

Chlorpyrifos (CPF) is an organophosphorus (OP) insecticide widely recognized for its neurotoxic properties and effectiveness at eliminating household pests including cockroaches. Once the leading insecticide used throughout the Unites States in residential and agricultural settings, widespread use resulted in ubiquitous exposure (Landrigan et al., 1999; Whitemore et al., 1994) until the US EPA curtailed its residential use in 2001 (U.S. EPA, 2000). Previous studies have reported that prenatal and early childhood exposure to OP insecticides, including CPF, is associated with indicators of delayed neurodevelopment (Berkowitz et al., 2004; Engel et al., 2007; Eskenazi et al., 2007; Guillette et al., 1998; Lizardi et al., 2008; Young et al., 2005). Most recently, results from three separate longitudinal birth cohort studies demonstrate that prenatal exposure to OP insecticides is negatively associated with cognitive development at 7-years of age (Bouchard et al., 2011; Engel et al., 2011; Rauh et al., 2011). Rauh et al. (2011) reported evidence of deficits in 7-year working memory and full scale IQ scores as a function of prenatal CPF exposure (Rauh et al., 2011). Working memory is one of the core processes of executive function. It encompasses the ability to memorize new information, hold it in short-term memory, concentrate, and manipulate information to produce results (Baddeley and Logie, 1999; Smith and Jonides, 1997). Insufficient development of executive functioning during early childhood has been associated with an array of adverse outcomes including psychopathology (Pennington and Ozonoff, 1996), increased physical aggression (Tremblay et al., 2005), cortisol reactivity (Blair et al., 2005), and lack of school readiness (Blair, 2002).

It is recognized that biologic and social factors interact to affect neurologic development in children (Escanola, 1982), including the development of executive functions such as working memory (Diamond, 2009). The quality of the home environment is a particularly important social factor that predicts child neurodevelopment. Numerous prior studies demonstrate associations between the home environment and child cognition, including assessment among groups that differed by ethnicity, socioeconomic status, child weight, child disabilities, maltreatment and/or exposures to neurotoxicants (Bradley, 1993). Intervention studies suggest that improving the quality of the home environment can improve child cognitive performance (Wasik et al., 1990). The Home Observation for the Measurement of the Environment (HOME) (Caldwell and Bradley,

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1984) is a well-validated instrument for assessing the quality of the home environment. It was designed to assess a child's physical, intellectual, and emotional milieu through both direct observation and unstructured interview with the child's primary caregiver. Notably, the HOME scale includes subscales measuring specific aspects of the child's home life such as parental nurturance and environmental stimulation. Farah et al. (2008) used the HOME scale to demonstrate that these different aspects of the home environment affect different components of cognitive development in humans (Farah et al., 2008). Parental nurturing was associated with improved working memory while environmental stimulation facilitated improved language development. In the current study, we evaluate whether specific aspects of the home environment can remediate the adverse effects of environmental toxicants on children's cognitive development.

There is growing evidence that child sex is also an important determinant of behavior and cognition. Research has shown that developing males and females respond differently to the effects of chemical stressors (e.g. polychlorinated biphenyls) and nonchemical stressors (e.g. poverty) on child behaviors (Weiss, 2002; Werner and Ruth, 1992). In the guinea pig, prenatal social stress resulted in elevated cortisol levels in male offspring with no effect in female offspring (Kaiser and Sachser, 1998, 2001). While clinical evidence suggests males are generally more susceptible to infectious disease, hypertension (cardiovascular disease), and aggressive behaviors (Wang et al., 2007), it is less clear how sex may influence the impact of toxicant exposure on developmental outcomes. In a recent epidemiologic study examining the impact of prenatal exposure to phthalates, common plasticizers, on reproductive development, adverse effects were only observed in male children (Swan et al., 2005). Conversely, in a study examining the impact of bisphenol A (BPA) exposure on behavior in children, effects were observed especially among female children (Braun et al., 2011). Notably, many studies of the adverse effects of endocrine disrupting compounds on cognition and behavior do not investigate differential effects in males vs. females (Engel et al., 2009; Whyatt et al., 2012). In general, the evaluation of child sex as a potential effect modifier of the effects of environmental toxicants on child development has received little attention in epidemiologic studies to date (Schwartz, 2003; Vahter et al., 2007a,b).

In the current study, we built on our prior investigation of prenatal CPF exposure (Rauh et al., 2011) to evaluate how the quality of the home environment (specifically, parental nurturance and environmental stimulation) and child sex interact with the adverse effects of prenatal CPF exposure on working memory at child age 7 years. We hypothesize that a nurturing home environment may moderate the adverse effects of prenatal CPF exposure on children's working memory at age 7. Further, we hypothesize that the moderation effect may be stronger in males than in females.

2. Methods

2.1. Participants

The sample consisted of 335 mother–child pairs selected from an ongoing prospective cohort study (Columbia Center for Children's Environmental Health) of inner-city mothers and their children (Perera et al., 2002). The larger parent cohort (N = 725), enrolled between 1998–2006, comprised pregnant women age 18–35 years who self-identified as either African-American or Dominican, did not smoke, were low-risk pregnancies (classified as free of diabetes, hypertension, and known HIV infection), lived in the designated neighborhoods for at least one year, and had registered at the Obstetrics and Gynecology prenatal clinics at New York Presbyterian Medical Center or Harlem Hospital by the 20th week of pregnancy. All participants gave informed consent and the Institutional Review Board of Columbia University approved the study.

For the current study, we selected all offspring from this cohort who had reached age 7 at the time of this analysis and had complete data in the following areas: maternal prenatal and 7-year interview; biomarkers of prenatal CPF exposure, HOME assessment completed at 3 years of age; and WISC-IV administered at 7 years of age. The characteristics of this subsample are presented in Table 1. In general, the 335 subjects selected for the current study did not differ from the full parent cohort with respect to demographic characteristics.

2.2. Maternal interview and HOME assessment

Mothers were interviewed in the 3rd trimester of pregnancy and annually thereafter by a trained bilingual interviewer. Interviews included questions about demographics; residential history; living conditions; maternal education; maternal income and employment; illness, alcohol and drug use during pregnancy; and chemical exposures, including pesticides, polycyclic aromatic hydrocarbons (PAHs), lead and environmental tobacco smoke (ETS).

Children's home environments were evaluated at 3 years of age (mean = 3.6 years; range = 1.1–6.3 years) using the HOME Inventory (Bradley, 1993; Caldwell and Bradley, 1984). The HOME Inventory is an unstructured 1-hour observational interview administered by a trained researcher and widely used as a predictor of child intelligence and achievement (Bradely et al., 1989). The 55-item checklist is divided into eight subscales. Based on previous literature employing the HOME inventory to examine the association between childhood experience and cognitive development (Farah et al., 2008), we divided the 8 subscales into two composite scales, Environmental Stimulation and Parental Nurturance. The Environmental Stimulation variable was created by summing the z-scores of the Learning Materials, Language Stimulation, Academic Stimulation, and Variety subscales, which measure the availability of intellectually stimulating materials in the home and the mother's encouragement of learning. The Parental Nurturance variable was created by summing the z-scores of the Responsivity, Modeling, and Acceptance subscales, which measure such maternal behaviors as attentiveness, displays of physical affection, encouragement of delayed gratification, limit setting, and the ability of the mother to control her negative reactions.

In addition to the primary predictors included in the final models described below, we examined other maternal toxicant exposures with the potential to impact children's cognitive development including prenatal exposure to PAHs (Perera et al., 2006), ETS (Eskenazi and Castorina, 1999), and lead (Lanphear et al., 2005). PAHs were measured in personal

Table 1
Demographic characteristics of the study population, New York City, 2009–2010 (N = 335).

Characteristics	N	%
Family income		
<$20,000	172	51.3
≥$20,000	163	48.7
Maternal education (years)		
<12 years	230	68.7
≥12 years	105	31.3
Race/ethnicity		
Dominican	132	39.4
African American	203	60.6
	Median	Range
Prenatal CPF (ng/g)	0.36	0.25–32.1
	Mean	SE
HOME score (total score)	39.8	0.34
WISC_IV*		
Full Scale IQ	99.3	0.70
Working memory	98.3	0.77
Perceptual reasoning	100.5	0.75
Verbal comprehension	96.97	0.65
Processing speed	102.0	0.87

* Wechsler Intelligence Scale for Children, 4th edition, composite scores of We.

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air during the 3rd trimester using a previously described method (Perera et al., 2003). We computed a composite log-transformed PAH variable from eight correlated PAH air concentration measures (r values ranging from 0.34–0.94; all p-values<0.001 by Spearman's rank) (Perera et al., 2003). The ETS variable was generated using maternal report of smoking and/or smokers in the home during pregnancy. The variable has been previously validated against maternal cotinine values and shown to accurately represent exposure to ETS (Rauh et al., 2004). In this subset selected for analysis in the current paper, PAH was not an independent predictor of working memory (B (95% CI) = 0.10 (−0.31 to 0.52), p = 0.62). ETS weakly, though non-significantly, predicted working memory in unadjusted models (−2.72 (−0.59 to 0.51), p = 0.09), though it was not a significant predictor in models adjusted for income, maternal education and prenatal CPF (−1.956 (−5.203 to 1.290), p = 0.24). As inclusion of PAH or ETS did not change the effect size or the significance of the relationship between chlorpyrifos and working memory, or between the HOME inventory and working memory at 7 years of age, they were not included in the final models.

Blood lead was measured in only 91 blood samples collected when subjects were 7 years of age. Although in this small subset of 91, lead appeared to have an inverse relationship with working memory in models controlling for income, education, and HOME inventory (B (95% CI) = −3.62 (−5.98 to −1.26), CPF levels were below the limit of detection in all 91 blood samples thus we are unable to test the potential confounding effect of lead on the relationship between prenatal CPF and working memory.

2.3. Biological samples and pesticide exposure

Trained hospital staff collected a 30–60 ml sample of umbilical cord blood at delivery and a 30–35 ml sample of maternal blood within two days of delivery. Collection, processing, and storage of blood samples has been described elsewhere (Perera et al., 2002; Whyatt et al., 2003). Aliquots of blood samples were sent to the Centers for Disease Control and Prevention (Atlanta, Georgia) for analysis of levels of CPF, cotinine, and metals (Barr et al., 2002). For 12% of the subjects included in the current analysis, the umbilical cord blood sample was unavailable and mother's values were substituted using a standardized algorithm (Whyatt et al., 2005). Within this subset, 40% of samples had CPF measurements less than the limit of detection (LOD). For these subjects, values below the limits of detection (0.5-1 pg/g) were assigned a value of one half the detection limit concentration.

2.4. Measures of neurodevelopment

To assess neurodevelopment at 7 years of age, trained research workers administered the Wechsler Scales of Infant Intelligence (WISC-IV) (Wechsler, 1991). The instrument consists of 4 indices designed to measure 4 different areas of mental functioning that are associated with, but distinct from, overall IQ, and is sensitive to cognitive deficits related to learning and working memory. The 4 indices include Verbal Comprehension, Perceptual Reasoning, Working Memory, and Processing Speed. The full scale IQ is a summary of the 4 separate indices. We examined the influence of the HOME inventory on all 4 indices of the WISC-IV as well as the full-scale score. However, due to the inverse relationship between CPF and working memory previously published in this cohort (Rauh et al., 2011), we focused primarily on this index.

Conforming to the demographics of the study populations, subjects were offered the choice of completing the WISC-IV in English or Spanish. The Spanish version of the WISC-IV was designed to test the same constructs as the WISC-IV and results are compared to all U.S. children of the same age (Wechsler, 2005). 28/315 (8.4%) of the subjects in this cohort selected to test in Spanish. The scores for the working memory were not significantly different between subjects tested in English or Spanish (mean working memory score ± SE; English = 98.55 ± 0.81, Spanish = 95.54 ± 2.648, p = 0.279). Addition of language of administration (0 = Spanish, 1 = English) to the linear regression models did not alter the association between prenatal CPF exposure and working memory, nor the relationship between parental nurturance and working memory we therefore did not include this variable in the presented analyses.

2.5. Data analyses

These following analyses included observations from children with complete data on prenatal CPF exposure, HOME inventory administered at 3 years of age, and 7-year WISC-IV (n = 335). We conducted all analyses using SPSS (PAWS 18). CPF values were log transformed to an approximate normal distribution. We treated CPF (log pg/g), WISC-IV working memory scores, and HOME inventory variables including the total HOME score and the 2 composite scores as continuous variables.

Unadjusted analyses were used to explore the associations between prenatal CPF exposure, the quality of the home environment (Total HOME, as well as Parental Nurturance and Environmental Stimulation subscales), childhood IQ (WISC-IV) and demographic characteristics (Table 1).

Multivariable linear regression models examined the association between predictor variables and working memory scores at 7 years of age. Interaction terms were created to represent 1) prenatal CPF * Total HOME score 2) prenatal CPF * child sex and 3) Parental Nurturance * child sex.

Effect estimates, 95%CIs, and p-values were calculated for all analytic procedures. Results were considered significant at p<0.05.

3. Results

3.1. Sample characteristics

Demographic characteristics of the families included in this study are presented in Table 1. Families were of low economic standing. Over half of the mothers enrolled in the cohort (51.3%) reported an annual family income<$20,000. Mothers also reported low educational status. 31% had not completed high school at the time of the child's 7-year evaluation. Chlorpyrifos was detected in 60% of blood samples (cord or maternal), concentrations ranged from 0.25 to 32.14 pg/g. The mean WISC-IV Full Scale Composite IQ score for children at age 7 was 99.25 (range 48–133). The working memory composite score was 98.4 (range 54–135). The mean HOME Total score was 39.8 ± 0.34 (out of a maximum of 55).

3.2. Unadjusted relationships between CPF concentrations and working memory

Table 2 shows the unadjusted associations between family income, and maternal education and child sex with prenatal CPF levels, Total HOME scores and WISC-IV Working Memory scores. Although predictive analyses (presented later) considered the Parental Nurturance and Environmental Stimulation subscales of the HOME, in Table 1 we present the more familiar Total HOME score (Wasserman et al., 2001). Family income and maternal years of education were positively associated with Total HOME score and WISC-IV working memory score. CPF levels and Total HOME scores did not differ significantly by child sex; however, WISC-IV working memory scores were higher among females (p = 0.034).

Univariate regression analyses examining prenatal CPF and WISC-IV working memory score confirmed the inverse relationship between CPF exposure and working memory (B (95%CI) = −1.479 (−2.52 to −0.44)) (Rauh et al., 2011). Total HOME score was positively associated with WISC-IV working memory (B (95% CI) = 0.427 (0.18 to 0.67)). Of the two HOME subscales, Parental Nurturance was more strongly associated with working memory than Environmental Stimulation (B (95% CI) = 1.68 (0.68 to 2.69) vs. 0.52 (0.06 to 0.98), respectively).

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Table 2
Unadjusted associations[a] between prenatal chlorpyrifos measured in maternal blood samples collected during pregnancy (log pg/g), Total HOME score and WISC-IV working memory scores at age 7 (n = 335).

Characteristics	All		Prenatal CPF (log pg/g)	Total HOME	WISC-IV Working Memory
	N	%	Mean ± SE	Mean ± SE	Mean ± SE
Family Income					
<$20,000	172	51.3	−0.068 ± 0.12	38.21 ± 0.45	96.5 ± 1.17
≥$20,000	163	48.7	0.031 ± 0.11	41.37 ± 0.46	100.2 ± 0.97
			$p = 0.389$	$\mathbf{p < 0.001}$	$\mathbf{p = 0.014}$
Maternal education (years)[b]					
<12 years	105	31.3	0.0002 ± 0.15	37.52 ± 0.59	95.9 ± 1.30
≥12 years	230	68.7	−0.029 ± 0.09	40.76 ± 0.38	14.27 ± 0.94
			$p = 0.866$	$\mathbf{p < 0.001}$	$\mathbf{p = 0.017}$
Child sex					
Female	184	54.9	−0.07 ± 0.11	40.2 ± 0.44	99.8 ± 1.00
Male	151	45.1	0.04 ± 0.12	39.3 ± 0.51	96.5 ± 1.20
			$p = 0.519$	$p = 0.162$	$\mathbf{p = 0.034}$

[a] Students t-test, p value.
[b] Maternal education was categorized for the table only, it was used as a continuous value in the regression analyses.

3.3. Adjusted relationships between CPF concentrations and working memory

Based on Farah (2008), we next sought to determine the specific aspects of the HOME environment that influenced working memory in the presence of prenatal CPF exposure. We applied linear regression models to predict the adjusted relationship between prenatal CPF exposure and WISC-IV working memory, controlling for family income, maternal education, child sex and the three different HOME scale scores (total HOME, Parental Nurturance and Environmental Stimulation). The three adjusted models are presented in Table 3. Chlorpyrifos is significantly predictive of working memory in all three models. Parental Nurturance more strongly predicts working memory than the Total HOME score or the Environmental Stimulation subscale: (B (95% CI)) Total HOME score = 0.283 (−0.02 to 0.55), p = 0.037; Parental Nurturance = 1.265 (0.27 to 2.28), p = 0.013; Environmental Stimulation 0.292 (−0.19 to 0.77), p = 0.230). Although the Total HOME Score did not differ by child sex, Parental Nurturance was significantly higher among females than males (Students T-test, p = 0.02).

To determine the role of child sex on the relationship between prenatal CPF exposure and working memory, we stratified subjects based on child sex. In unadjusted stratified models, the impact of CPF on working memory was only observed in males (B (95% CI) males = −2.382 (−3.88 to −0.88) p = 0.002; B (95%CI) females = −0.524 (−1.90 to 0.85) p = 0.453). Figs. 1 and 2 and Table 4 demonstrate the unadjusted and adjusted interactions between child sex, prenatal CPF, and Parental Nurturance on working memory at age 7. We detected a borderline significant interaction between prenatal exposure to CPF and child sex (B (95% CI) for interaction term = −1.714 (−3.753 to 0.326), p = 0.099) suggesting that males experience a greater decrement in working memory score following prenatal CPF exposure (Fig. 1). In addition, we detected a borderline interaction between Parental Nurturance and child sex (B (95% CI) for interaction term = 1.490 (−0.518 to 3.499), p = 0.145) suggesting that, in terms of working memory, males benefit more from a nurturing environment than females (Fig. 2). We did not detect an interaction between prenatal exposure to CPF and the quality of the home environment using either Total HOME score as a covariate (B (95% CI) for interaction term = −0.069 (−0.240 to 0.101), p = 0.424) or Parental Nurturance (B (95% CI) for interaction term = 0.024 (−0.069 to 0.738), p = 0.947), suggesting that the quality of the home environment does not modify the relationship between prenatal CPF exposure and working memory (Table 4).

4. Discussion

This study presents results from analyses exploring the influence of social and biological factors on the inverse association between prenatal CPF exposure and working memory at child age 7. In 2011, Rauh et al reported a deficit in working memory and full scale IQ among 7 years olds following prenatal exposure to CPF using the WISC-IV instrument (Rauh et al., 2011). We replicated the inverse association previously reported by Rauh (2011) between prenatal CPF exposure and neurodevelopment, focusing on the working memory component of IQ. We extended the previous model to determine how additional biological and social environmental factors might create or explain differential neurodevelopmental susceptibility, focusing on the main and moderating effects of the quality of the home environment (HOME) and child sex. Contrary to our hypothesis, we did not observe a buffering or remediating effect of a high quality home environment on the adverse effects of prenatal CPF exposure on working memory. To our knowledge, this is the first investigation into a potential intervention strategy to reduce or reverse the cognitive deficits resulting from prenatal CPF exposure.

Biologic and social factors may exacerbate the negative affects of toxic exposures, as is the case of stressful or impoverished conditions (Rauh et

Table 3
Adjusted linear regression models predicting WISC-IV working memory at age 7 adjusting for Total HOME score, Parental Nurturance (z-score) or Environmental Stimulation (z-score).

N = 335	WISC-IV working memory		
	B	95% CI	p
Total HOME score			
CPF	−1.451	−2.265 to −0.438	0.005
Family income	2.459	−0.611 to 5.528	0.116
Maternal education	0.475	−0.137 to 1.088	0.128
Child sex	−3.032	−6.003 to −0.062	0.072
Total HOME score	0.283	−0.017 to 0.548	0.037
Parental nurturance			
CPF	−1.355	−2.368 to −0.341	0.009
Family income	2.870	−0.136 to 5.875	0.061
Maternal education	0.617	0.036 to 1.199	0.037
Child sex	−2.863	−5.835 to 0.109	0.059
Parental Nurturance	1.275	0.273 to 2.278	0.013
Environmental stimulation			
CPF	−1.478	−2.496 to −0.459	0.005
Family income	2.817	−0.243 to 5.876	0.071
Maternal education	0.581	−0.025 to 1.188	0.060
Child sex	−3.231	−6.207 to −0.256	0.033
Environmental Stimulation	0.292	−0.186 to 0.770	0.230

Variable/covariate definitions: CPF = log transformed prenatal chlorpyrifos exposure (log pg/g); family income 0 (<$20,000), 1 (≥$20,000); maternal education = years of maternal education at child age 7; child sex 0 (female), 1 (male).

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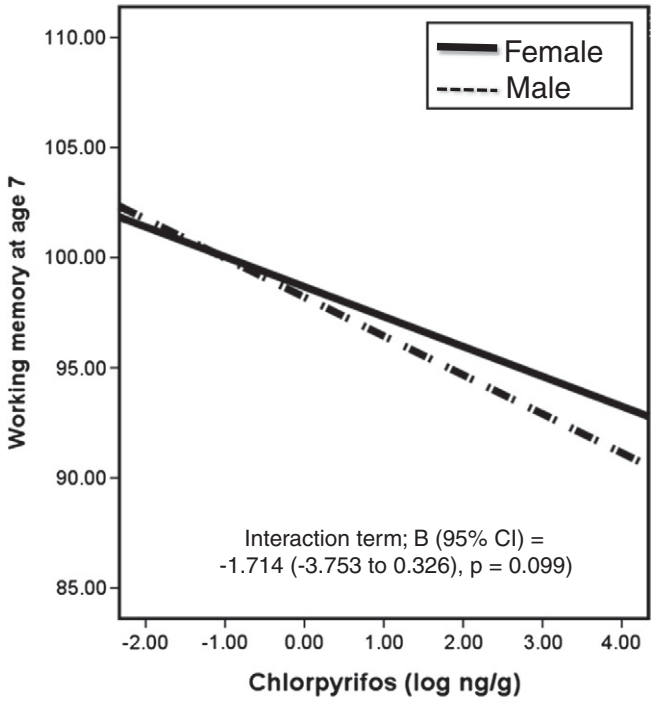

Fig. 1. Interaction between prenatal CPF (log ng/g) and child sex on working memory at age 7. This figure depicts the interaction between prenatal CPF exposure and child sex as they effect working memory at child age 7. The solid line represents females, dashed line males. Males exposures to CPF seem to experience greater decrements in working memory scores than females exposed to CPF.

al., 2008; Wright, 2009). Recently, the first population-based study demonstrated an association between a community level stressor (violence) and outdoor air pollution (NO_2) with increasing risk for childhood asthma in an urban sample (Clougherty et al., 2007). In this study, researchers observed an association between NO_2 and risk for childhood asthma only among children who were also exposed to social stress. A similar epidemiologic study demonstrated that chronic traffic-related air pollution exposure and stress interacted in predicting increased asthma symptoms and heightened inflammatory profiles in adolescents with asthma (Chen et al., 2008). However, biologic and social factors may also serve to buffer or remediate adverse cognitive effects, as has been demonstrated in the rodent literature. Over 30 years ago, it was suggested that environmental enrichment of rodent cages (i.e., addition of tunnels, ladders and toys as well as reduction of overcrowding) was shown to remediate the adverse effects of experimental cretinism induced in rats. Compared to rats living in impoverished conditions, enrichment remediated the adverse effects of hypothyroid-induced cretinism in rats; hypothyroid rats raised in enriched environments demonstrated reduced deficits in maze learning, maze retention, and resistance to extinction of bar-pressing (Davenport et al., 1976). More recently, environmental enrichment has been shown to reverse the cognitive and molecular deficits induced by developmental lead exposure (Guilarte et al., 2003). Maternal nurturing behavior (i.e. licking and grooming) following a brief stressor regulated pups' later responses to stress and predicted better subsequent learning ability (Bredy et al., 2003; Weaver et al., 2005). In contrast to animal brain development, much less is known about the effect of childhood experience on the developing human brain (Rao et al., 2010). In assessing the direct effects of the social environment, we know that children raised in "impoverished environments" exhibit impairments in cognitive and behavioral functioning whereas children raised in highly stimulating or enriched environments exhibit enhanced behavioral and cognitive outcomes (Joseph, 1999; Kaler and Freeman, 1994). Studies using the HOME Inventory suggest that children raised in environments with more cognitive stimulation and less socioeconomic adversity demonstrate better outcomes on global cognitive measures such as IQ and school achievement (Bradley et al., 2001).

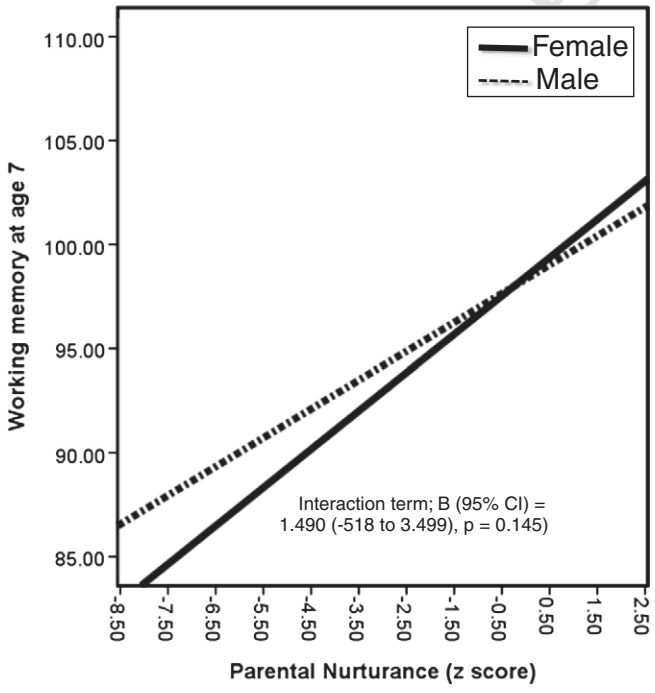

Fig. 2. Interaction between Parental nurturance subset score of the HOME assessment (z-score) and child sex on working memory at age 7. The solid line represents females, dashed line males. In terms of working memory, males appear to benefit more from a nurturing home environment than females.

Historically, children's environmental health studies have focused separately on how social, biological or environmental factors affect children's development. In the past decade, recognition has grown that adverse outcomes of exposure to environmental pollutants are not simply due to the inherent properties of the chemical but derive from the joint action of psychosocial and biologic conditions that may exacerbate or alleviate the effects of toxic exposures (Weiss and Bellinger, 2006). Because of covariance across exposures and evidence that environmental and social stressors may influence common physiologic pathways, understanding the potentially synergistic effects promises to more completely inform children's environmental health risk. This is all the more important because exposures to environmental hazards tend to co-occur with other forms of chronic psychosocial adversity, giving rise to environmental inequities whereby the most vulnerable members of society bear the greatest toxic burden (Krieger et al., 1993; Zapata et al., 1992) altering individual level and population level risk in systematic ways (Bellinger, 2000; Collins and Hammond, 1996; O'Campo et al., 1997).

In our study, we detected a borderline significant interaction between prenatal exposure to CPF and child sex, suggesting that males experience a greater decrement in working memory score following prenatal CPF exposure. This is consistent with the literature suggesting sex selectivity of the neurotoxic effects of CPF (Garcia et al., 2003; Levin et al., 2002). Several factors may contribute to the differential vulnerability to CPF by sex. One potential explanation is CPF's role as an endocrine disrupter. CPF has been shown to have anti-androgenic effects reducing serum testosterone levels in rats (Kang et al., 2004). Male rats have a higher rate of hepatic activation of the CPF oxon, the metabolite that inhibits acetylcholinesterase AcTH, as well as more rapid detoxification of the CPF oxon. Inhibition of AcTH is noted as the mechanism of systemic toxicity for chlorpyrifos (Smegal, 2000). However, sexual differences in the activities of these enzymes that carry out the functions generally do not emerge until puberty. Further, the effects observed occur at levels well below those required to inhibit AcTH. Males have a slower rate of cortical

Table 4
Unadjusted and adjusted linear regression relationships between prenatal CPF exposure and WISC-IV working memory at 7 years of age, including interactions between predictor variables.

N = 335	WISC-IV working memory								
	Unadjusted[a]			Adjusted[b]			Adjusted with interaction term[c]		
	B	95% CI	p	B	95% CI	p	B	95% CI	p
Prenatal CPF * Child sex									
Prenatal CPF	−1.479	−2.516 to −0.442	0.005	−1.355	−2.368 to −0.341	0.009	−0.553	−1.943 to 0.836	0.434
Family income				2.870	−0.136 to 1.199	0.061	2.862	−0.136 to 5.860	0.061
Maternal education				0.617	0.036 to 1.199	0.037	0.615	0.035 to 1.195	0.038
Parental Nurturance				1.275	0.273 to 2.278	0.013	1.150	0.139 to 2.161	0.026
Child sex				−2.863	−5.835 to 0.109	0.059	−2.930	−5.895 to 0.036	0.053
Prenatal CPF × child sex							−1.714	−3.753 to 0.326	0.099
Parental nurturance * child sex									
Prenatal CPF	−1.479	−2.516 to −0.442	0.005	−1.355	−2.368 to −0.341	0.009	−1.248	−2.270 to 0.227	0.017
Family income				2.870	−0.136 to 1.199	0.061	2.793	−2.09 to 5.795	0.068
Maternal education				0.617	0.036 to 1.199	0.037	0.621	0.040 to 1.201	0.036
Parental Nurturance				1.275	0.273 to 2.278	0.013	0.477	−0.992 to 1.947	0.523
Child sex				−2.863	−5.835 to 0.109	0.059	−2.969	−5.940 to 0.002	0.050
Parental nurturance × child sex							1.490	−0.518 to 3.499	0.145
Prenatal CPF * Parental nurturance									
Prenatal CPF	−1.479	−2.516 to −0.442	0.005	−1.355	−2.368 to −0.341	0.009	−1.354	−2.369 to −0.339	0.009
Family income				2.870	−0.136 to 1.199	0.061	2.864	−0.151 to 5.879	0.063
Maternal education				0.617	0.036 to 1.199	0.037	0.618	0.035 to 1.200	0.038
Parental Nurturance				1.275	0.273 to 2.278	0.013	1.280	0.267 to 2.293	0.013
Child sex				−2.863	−5.835 to 0.109	0.059	−2.846	−5.865 to 0.173	0.013
Prenatal CPF * Parental nurturance							0.024	−0.690 to 0.738	0.947

Variable/covariate definitions: CPF = log transformed prenatal chlorpyrifos exposure (log pg/g); family income 0 (<$20,000), 1 (≥$20,000); maternal education = years of maternal education at child age 7; child sex 0 (female), 1 (male).

[a] Unadjusted regression model.
[b] Adjusted models include family income, maternal education, parental nurturance, and child sex.
[c] Adjusted models include family income, maternal education, parental nurturance, child sex and interaction term.

development than females, making the male brain susceptible to insult for a longer period (Taylor, 1969).

We also observed a borderline interaction between Parental Nurturance and child sex suggesting that, in terms of working memory, males may benefit more from a nurturing environment than females. Our results support those of Farah et al. (2008) suggesting a causal relationship between parental nurturance on memory ability. Nurturance has been widely associated with cognitive development (Bergman et al., 2010; Farah et al., 2008), as well as long-term health (Chen et al., 2011). The effect of maternal nurturance appears to differ among males and females, with boys more strongly affected by the extremes at both ends of the spectrum. Attachment studies have shown that among children with an insecure or disorganized attachment style, boys are more likely than girls to manifest behavioral problems when they reach school age (Fearon et al., 2010; Pasco Fearon and Belsky, 2011; Rauh et al., 2008). In addition, a pregnancy cohort study demonstrated an association between breastfeeding duration and academic achievement at 10 years of age among boys, but not girls, suggesting that the mediator of this relationship could be increased mother bonding, attention, and interaction (Oddy et al., 2011).

Generalizability of our study is limited, as the cohort comprises exclusively low-income, urban, Dominican and African American children. The majority of households are headed by single mothers who, because of their role as sole caregivers, may nurture their children differently than partnered women. Certain covariates such as prenatal stress, a possible contributor to working memory in children (Entringer et al., 2010), were not included in the analysis. Further, because CPF exposure data were only collected at the time of delivery, it is impossible to draw any conclusions about the potentially differential effects of exposure at various stages of development. An additional limitation regarding the CPF measurements concerns the high frequency of subjects with levels of CPF below the limit of detection. A common practice in dealing with non-detects in to assign imputed values such as LOD/√2 (Arunajadai and Rauh, 2012), though it is possible that substitution of these values can lead to biased estimates (Lubin et al., 2004).

In conclusion, these results do not support our main hypothesis that a high quality home environment modifies the adverse effects of prenatal CPF exposure on working memory at age 7. However, similar to other studies examining environmental toxicants such as lead, social circumstances and childhood IQ, these results suggest that the effects of social circumstances (i.e. quality of the home environment) on childhood IQ scores are substantially greater than the effects of environmental exposure (Wasserman et al., 1997) and should be considered in studies examining the relationships between environmental exposures and child development. In addition to our main hypothesis examining the role of the home environment, we investigated the role of child sex in the relationship between prenatal CPF exposure and working memory. As child sex seems to interact with the relationship between the home environment and working memory, as well as between prenatal CPF exposure and working memory, we suggest that epidemiologic and laboratory based studies examining the relationship between prenatal and early childhood exposure to environmental toxicants and developmental outcomes include sex-specific analysis. Inclusion of both child sex and social circumstances in epidemiologic studies of environmental toxicants and neurodevelopment will greatly expand our understanding of these relationships and assist the development of studies to better identify vulnerable populations and perhaps direct interventions to protect them.

Conflict of interest statement

There are no competing interests.

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