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Structural Magnetic Resonance Imaging in an Adult Cohort Following Prenatal and Early Postnatal Exposure to Tetrachloroethylene (PCE)-contaminated Drinking Water

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Abstract

This population-based retrospective cohort study examined Structural Magnetic Resonance Imaging (MRI) of the brain in relation to prenatal and early postnatal exposure to tetrachloroethylene (PCE)-contaminated drinking water on Cape Cod, Massachusetts. Subjects were identified through birth records from 1969 through 1983. Exposure was modeled using pipe network information from town water departments, a PCE leaching and transport algorithm, EPANet water flow modeling software, and Geographic Information System (GIS) methodology. Brain imaging was performed on 26 exposed and 16 unexposed subjects. Scans were acquired on a Philips 3T whole body scanner using the ADNI T1-weighted MP-RAGE scan. The scans were processed by FreeSurfer version 4.3.1 software to obtain measurements of specific brain regions. There were no statistically significant differences between exposed and unexposed subjects on measures of white matter hypointensities (β : 127.5 mm³, 95% CI: -259.1, 1514.0), white matter volumes (e.g. total cerebral white matter: β : 21230.0 mm³, 95% CI: -4512.6, 46971.7) or gray matter volumes (e.g. total cerebral gray matter: β : 11976.0 mm³, 95% CI: -13657.2, 37609.3). The

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Conflict of Interest Four years ago, Ann Aschengrau served as a consultant on a personal injury case involving chlorinated solvent contamination. None of the parties of this case supported, reviewed, or had knowledge of this publication. Patricia Janulewicz, Ronald Killiany, Roberta White, Brett Martin, Michael Winter, Janice Weinberg, and Veronica Vieira have no conflict of interest.

results of this study suggest that exposure to PCE during gestation and early childhood, at the levels observed in this population, is not associated with alterations in the brain structures studied.

Keywords

Tetrachloroethylene; PCE; development; structural magnetic resonance imaging

1. Introduction

Tetrachloroethylene (PCE, Perc or perchloroethylene) is a manufactured colorless solvent commonly used for dry cleaning fabrics and degreasing metals. It is one of the most frequently detected solvents in groundwater (Moran, et al. 2007) and at United States Environmental Protection Agency (USEPA) Superfund sites (EPA 2008). PCE and its main metabolite dichloroacetylene (DCA) are recognized human and animal neurotoxicants (Feldman 1999, Klaassen 2001, Stevens and Eisenmann 1997, TOXICS 1994, TOXICS 1994). These fat soluble substances have a high affinity for the lipophilic tissues of the central nervous system (Altmann, et al. 1995) and readily cross both the placental and blood brain barriers (Klaassen 2001).

Most of the epidemiological literature on the neurotoxic effects of solvents such as PCE has focused on neurobehavioral sequelae among adults with occupational exposures to mixtures of organic solvents. Cognitive and visual dysfunction have been observed, as have mood changes (Bockelmann, et al. 2002, Bowler, et al. 2001, Condray, et al. 2000, Daniell, et al. 1999, Fiedler, et al. 2003, Grosch, et al. 1996, Ichihara, et al. 2004, Kilburn 2002, Klaassen 2001, Morrow, et al. 2000, Morrow and Scott 2002, Morrow, et al. 1997, Pauling and Ogden 1996, Reif, et al. 2003, Rosenberg, et al. 2002, Tsai, et al. 1997, White, et al. 1995, Wood and Liossi 2005). The cognitive sequelae associated with mixed organic solvent exposures have included diminished performance on measures of memory, visuospatial abilities, attention/executive function, and motor skills.

The few studies examining adult occupational exposures to PCE alone have produced mixed results. Some studies found diminished performance on measures of attention/executive function (Grosch, et al. 1996, TOXICS 1994), while others have not found any adverse neuropsychological effects (Daniell, et al. 1999, Grosch, et al. 1996). All studies focused on visuospatial abilities have reported diminished performance associated with PCE exposure (Daniell, et al. 1999, TOXICS 1994).

The published literature examining neurobehavioral effects among children with prenatal and childhood exposure is comparatively small, is also mixed. Three studies found no decrements in cognitive or behavioral function in disorders of attention and learning (Eskenazi, et al. 1988, Janulewicz, et al. 2008, NYSDOH 2005b), while two found lower test scores and more behavioral problems among children with prenatal or early childhood exposure to organic solvents, including PCE (Laslo-Baker, et al. 2004, Till, et al. 2001).

Studies using structural MRI in populations of adults with solvent encephalopathy have reported diffuse atrophy in the frontal and parietal cortices, cerebellum and brainstem regions (Keski-Santti, et al. 2009, Thuomas, et al. 1996). To date, there have been no published MRI studies of individuals with subtle toxicant-induced brain changes due to solvent exposure during adulthood or early life.

The present study examined an unusual scenario involving environmental exposure to PCE. In early 1980, elevated levels of PCE were discovered in the drinking water supplies of

many New England towns. Investigations revealed that the public water distribution systems in these towns had installed vinyl-lined asbestos-cement (VL/AC) pipes to address alkalinity problems. Approximately 660 miles of VL/AC pipes were installed in Massachusetts from 1968 through early 1980; a large proportion was installed in eight towns in the Cape Cod region (Barnstable, Bourne, Falmouth, Mashpee, Sandwich, Brewster, Chatham, and Provincetown) (Larson, et al. 1983). The pipe manufacturing process involved spraying a mixture of vinyl toluene resin and PCE onto the interior of the pipe. It was believed that the PCE would volatilize before the pipes were installed; however, substantial quantities remained. PCE measurements taken in 1980 from Cape Cod public drinking water supplies ranged from 1.5 µg/L to 7,750 µg/L (Demond 1982). State officials began a program of flushing and bleeding the affected pipes in order to reduce the PCE concentrations to 40 µg/L, the action level at the time. The current United States Environmental Protection Agency (USEPA) maximum contaminant level (MCL) is 5 µg/L (TOXICS 1994).

Before remediation efforts were completed, tens of thousands of Cape Cod residents, including pregnant women and their children, were exposed to PCE-contaminated drinking water. The present population-based retrospective cohort study was undertaken to examine the long-term neurotoxic effects of prenatal and early childhood exposure to this water. The parent study that generated these data was undertaken to examine a wide range of neurotoxic effects following prenatal and early postnatal exposure to PCE contaminated drinking water. Outcomes that were examined included risky behaviors (Aschengrau, et al. 2011); mental illness (Aschengrau, et al. 2012); clinical and behavioral problems and learning disabilities based on questionnaire data (Janulewicz, et al. 2008); and subtle functional changes assessed with neuropsychological (Janulewicz, et al. 2012) and vision tests (Getz, et al. 2012); overt structural brain changes using MRIs. The current paper focuses only on the structural MRI results.

Currently, very little is known about the relationship between PCE exposure and structural changes that can be detected using brain imaging methodology. While not the most sensitive measure of neurotoxicant effects, structural MRI findings are important to understanding the full range of exposure-related brain damage. PCE is a well-known lipophilic solvent that is thought to act mechanistically through action on the myelin sheaths of white matter (Feldman 1999, Kyrklund et al., 1990). For this reason, we hypothesized that early life exposure would be associated with increases in white matter hypointensities and decreases in total white matter measures on structural MRI. White matter hypointensities reflect an abnormal pallor of the white matter as visualized using T1 weighted sequences with MRI. The hypointensities are often interpreted as disruption to the structure of the white matter as a consequence of disease, inflammation, infection, or toxic exposure.

2. Material and Methods

2.1. Study Population Selection

Subjects were eligible if they were born between 1969 and 1983 to mothers who lived in one of eight Cape Cod towns with VL/AC water distribution pipes. These towns were Barnstable, Brewster, Bourne, Chatham, Falmouth, Mashpee, Provincetown, and Sandwich. Birth certificates were manually reviewed and the maternal addresses on the certificate were cross-matched with a database of all street locations with VL/AC pipes in order to tentatively designate subjects as “exposed” or “unexposed”. The database also contained information on the installation year and diameter of the pipes. This tentative designation was based on visual inspection of the maps of water pipes in the immediate vicinity of the birth residence (Janulewicz, et al. 2008).

The study was approved by the Institutional Review Boards (IRB) of the Massachusetts Department of Public Health and Boston University Medical Center, and by the 24A/B/11B Review Committee at the Massachusetts Department of Public Health.

2.2. Follow up and Enrollment

Based on initial exposure assessment, two groups of children were selected: 1) children who were tentatively designated as “exposed” to PCE, and 2) children who were tentatively designated as “unexposed” to PCE. Children designated as “unexposed” were randomly selected and frequency matched to exposed children on the month and year of birth. More extensive exposure assessments were conducted following the return of self-administered questionnaires that included residential histories as well as information on drinking water sources.

Follow-up and enrollment of subjects took place between 2006 and 2010. Subjects were traced to obtain their current addresses and telephone numbers using Massachusetts residence lists; death, marriage, divorce, credit bureau and alumni records, and telephone books, directory assistance, and the Internet White Pages. Recruitment letters explaining the purpose of the study and accompanying self-administered questionnaires were sent to all traced subjects. In all, 619 exposed and 626 unexposed subjects returned the study questionnaire.

As shown in Table 1, 27.9% percent of the subjects resided outside of our testing area, 23.5% were missing key data from maternal questionnaires, and 6.3% had only postnatal exposure and thus were excluded from brain imaging. Based on information collected from the self-administered questionnaires, another 22.7% of subjects were excluded for one or more of the following reasons: had a neurological condition, experienced lead or carbon monoxide poisoning, suffered a head injury with a loss of consciousness >5 mins, used 3 or more illicit drugs, or drank excessive amounts of alcoholic beverages (average daily volume>3 drinks). An additional 1.8% of the subjects were excluded because they were a twin or triplet. The exclusion percentages were similar for both the exposed and unexposed groups.

Following the exclusions, a total of 219 subjects were available for brain imaging. As shown in Table 1, 22.4% refused to participate and 58.4% of subjects were located but never responded to any contact attempts, which included 3 letters and multiple telephone calls, leaving 42 subjects who underwent structural MRI.

There were no meaningful differences in the characteristics of eligible subjects who participated in structural MRI testing and those who did not. Participants and non-participants were similar with regard to birth year, gender, race, education and the prevalence of low birth weight and prematurity. However, non-participants were more likely than participants to have self-reported learning problems (22.5% vs. 10.8%) and to have used self-service dry cleaners (9.8% vs. 0%). These differences held true for both exposed and unexposed non-participants. For example, 21.6% vs. 22.6% of exposed and unexposed non-participants had self-reported learning problems, and 10.4% and 8.9% of exposed and unexposed non-participants ever used self-service dry cleaners.

2.3. Data Collection

Birth certificates provided information on subject’s date of birth, gestational duration and birth weight, and parents’ ages, occupations and educational level. Self-administered questionnaires filled out by the mother (or father, if the mother was deceased) in 2002-2003 gathered additional demographic information on the subjects and parents; developmental, educational and medical information on the subject, and medical information and solvent

exposures among the mothers (Janulewicz, et al. 2008). In particular, the questionnaire determined if the subject had any birth defects, severe mental retardation, cerebral palsy, fetal alcohol syndrome or lead poisoning; received a diagnosis of Attention Deficit Disorder (ADD) or Hyperactive Disorder (HD); had an Individual Education Plan (IEP) during school, or repeated a school grade. The questionnaire also determined information on maternal diseases before and during pregnancy, including diabetes and high blood pressure; pregnancy complications, including gestational diabetes and pre-eclampsia, and use of legal drugs, marijuana, vitamins, and iron supplements during pregnancy. Questions about the use of professional dry cleaners, spot removers, and occupations provided information on other potential sources of maternal solvent exposure.

Self-administered questionnaires filled out by the subjects in 2005-2008 were used to gather additional demographic information; developmental, educational, occupation and medical histories, and residential histories. Demographic information collected included race, marital status, occupational histories and parental education. The questionnaire also determined the subject's educational history including highest level of education; history of neurological disease (e.g., epilepsy), mental illness (e.g., depression) and lead or carbon monoxide poisoning, and smoking, alcohol and drug use. Questions about the use of professional dry cleaners, spot removers, and occupations provided information on other potential sources of solvent exposure.

Subjects were given three testing options. Option 1 included a battery of neuropsychological and vision tests, Option 2 included the battery of neuropsychological and vision tests along with structural MRIs, and Option 3 included the battery of neuropsychological and vision tests along with structural and functional MRI. Only results from the structural MRI are reported in this paper.

Scans were acquired on a Philips 3T whole body scanner using the ADNI T1-weighted MP-RAGE scan. The details of this scan have been described in detail previously (Jack, et al. 2008). The scans were processed through FreeSurfer version 4.3.1 software, which is freely available at surfer.nmr.mgh.harvard.edu/, to obtain measurements of various regions of the brain. The details of this postprocessing program have been described elsewhere (Dale, et al. 1999, Fischl and Dale 2000, Fischl, et al. 2001, Fischl, et al. 2002, Fischl, et al. 1999, Han, et al. 2006, Jovicich, et al. 2006, Segonne, et al. 2004, Segonne, et al. 2007). Briefly, images were motion-corrected; intensity normalized using nonparametric, nonuniform (N3) correction (Sled, et al. 1998), and stripped of nonbrain tissue (Segonne, et al. 2004). Images underwent a subcortical segmentation (Fischl, et al. 2002, Segonne, et al. 2004), identification of the gray/white matter boundary, automated topography correction (Fischl, et al. 2001, Segonne, et al. 2005), and surface deformation (Dale, et al. 1999, Fischl and Dale 2000). Surface representations were reviewed by an anatomically trained operator (RJK), and edits to ensure accurate surfaces were completed where necessary. Once reviewed, further processing was completed, including surface inflation (Fischl, et al. 1999), registration to a neuroanatomical atlas based on cortical folding patterns (Desikan, et al. 2006, Fischl, et al. 1999, Segonne, et al. 2004), and maps of curvature and sulcal depth. The boundaries of each region of interest within the neuroanatomical atlas were visually inspected by the same neuroanatomically trained operator (RJK), and edits to these boundaries were completed where needed. All image processing, edits and reviews of boundaries were conducted while the operator (RJK) was blinded to the subject exposure status.

2.4. PCE Exposure Assessment

Subjects were assigned tentative exposure designations using a visual assessment of VL/AC pipes in the immediate vicinity of their birth address. Each subject's final exposure

designation was determined by integrating information from several additional sources. Along with information from town water departments on the location of vinyl-lined pipes, other sources incorporated into the exposure assessment included 1) a Geographic Information System (GIS, ArcGIS 8.1) to spatially locate the vinyl-lined pipes and residences, 2) EPANet water distribution system software to model water flow and direction, and 3) a leaching and transport model to estimate the amount (grams) of PCE that was delivered to each reported residence during the exposure period. The leaching and transport model was developed by Webler and Brown (Aschengrau, et al. 2003, Webler 1993) and the leaching rate was estimated from experiments by Demond (Demond 1982). The Webler and Brown model estimates the amount of PCE entering the drinking water using information on the initial PCE stock in the pipe liner, the pipe's age, and the leaching rate of PCE from Demond's experiments. The pipe's initial stock of PCE was based on the size of the pipe (i.e., diameter and length) and information from the pipe manufacturer on the application of the liner. For a more detailed explanation see Janulewicz et al., 2008. EPANet software, which was developed by the U.S. Environmental Protection Agency, has been used in multiple epidemiologic studies (Aral, et al. 1996, Aschengrau, et al. 2009, Maslia, et al. 2000, Reif, et al. 2003, Rossman 1994).

Study subjects may have been exposed to PCE in drinking water through ingestion, dermal absorption or inhalation, particularly during bathing (Vieira, et al. 2005). However, questionnaire data on water consumption and bathing habits occurring decades earlier were not considered to be reliable enough to further refine the exposure measure. Instead, exposures values represent the modeled cumulative mass of PCE entering the homes of study participants, rather than a direct measure of PCE intake by the subjects.

We estimated PCE exposure during the prenatal period by multiplying the annual mass of PCE that entered the subject's residence during their birth year by 9/12. We estimated cumulative exposure during early childhood by summing the estimated mass of PCE that entered their residences from the month and year after birth through the month and year of the fifth birthday. Simple percentages were used to account for partial years. Since most subjects with prenatal exposure also had postnatal exposure, it was not possible to examine these periods separately.

2.5. Statistical Analysis

The following brain measurements were assessed in the 42 subjects who underwent structural MRI: white matter hyperintensities and volumetric measures of total cerebral white matter, total cerebellar white matter, total cerebral gray matter, total cerebellar gray matter, cingulate, parahippocampal gyrus, entorhinal cortex, thalamus proper, caudate, putamen, pallidum, hippocampus, amygdala, and acumbens.

Regression models were used to assess the relationship between PCE exposure and brain measurements. All analyses compared subjects with prenatal and early postnatal exposure combined to subjects with no exposure during both periods. Mean differences were used to assess the strength of the association between the exposure and a particular brain measurement. Ninety-five percent confidence intervals were used to assess the precision of the associations and the $p < 0.05$ level was used for statistical significance.

First, crude analyses were conducted for each brain measurement without adjusting for any potential confounders. Next, multivariate analyses were conducted to control for confounding variables. For all outcomes the confounder assessment began with a model that included intracranial volume. The remaining possible confounders (see variables in Table 2) were entered into the intracranial volume-adjusted model one at a time to determine which additional variables needed to be controlled. This was done in a sequential manner; the

confounder of greatest impact was added to the model first, and then other potential confounders were evaluated in an updated model. This process was repeated until no additional potential confounders impacted the exposure-outcome relationship.

3. Results

A total of 42 subjects were available for the final analysis, including 22 exposed and 20 unexposed subjects according to the initial exposure designation. Following the in-depth exposure assessment, four unexposed subjects were classified as exposed, resulting in 26 exposed and 16 unexposed subjects in the final analytic groups (Table 1). The primary reason for switching exposure categories was having a residence down gradient from a VL/AC pipe that was originally considered unexposed by visual inspection. This information was not available when the original exposure designations were made.

There was a wide distribution of estimated exposures during the prenatal and postnatal periods. Among exposed individuals, levels ranged from 0.4 grams to 1255 grams during the prenatal exposure period and from 0.7 grams to 3413 grams during the postnatal exposure period. These values represent the modeled cumulative mass of PCE entering the homes of study participants and were not a direct measure of PCE intake by the subjects.

The characteristics of the exposed and unexposed groups were, for the most part, very similar (Table 2). The subjects were predominately white, educated beyond high school, and, on average, 30 years old at testing. Subjects also gave similar self reports of ADD/HD, learning problems, and mental illness (mainly depression). Mothers in both groups were, on average, 28 years old at the subject's birth and mostly educated beyond high school. Maternal histories of prenatal cigarette smoking, alcohol consumption, marijuana use and multivitamin supplementation were also similar across groups. In contrast, exposed subjects were less likely to be breast fed and more likely to have mothers who used solvent-based spot removers. The total number of covariates added to any model did not exceed three and so our models were not overfit.

3.1. Structural Magnetic Resonance Imaging Results

The crude and adjusted structural MRI results are presented in Table 3. There were no statistically significant differences between the exposed and unexposed groups on measures of white matter hypointensities, total cerebral white matter volume, total cerebellum white matter volume, total cerebral gray matter volume or total cerebellum gray matter volume. There were also no statistically significant differences between the exposed and unexposed on measures of cingulate, entorhinal cortex, thalamus proper, caudate, putamen, pallidum, hippocampal, amygdala or acumbens volumes. However, the parahippocampal gyrus was larger, on average, in exposed subjects. Evaluation of the relationships between estimated exposure dose and test outcomes showed no statistically significant findings (results presented in supplemental materials).

4. Discussion

The present study did not confirm our hypotheses that exposed subjects would have more white matter hypointensities and less total white matter. It should be pointed out that the subjects in this study were in the young to middle-aged range and that white matter hypointensities are typically associated with aging and small vessel disease. It is plausible that while the white matter appears normal at this age in exposed subjects, it may be more susceptible to alterations with the aging process than that found in unexposed subjects. Further studies will be needed to determine the impact of aging and disease risk in this population.

The gray matter volume of the parahippocampal gyrus was found to be *larger* in the exposed subjects than in the unexposed subjects, a finding that was unexpected and unintuitive. The parahippocampal gyrus is responsible for memory encoding and retrieval, and when the current study population was examined with a battery of neuropsychological tests, we found suggestive associations between prenatal and early postnatal PCE exposure and decrements in test scores on tasks of learning and memory (Janulewicz et al., 2012). Decrements in function in this domain would be expected with smaller hippocampal volumes, not larger ones. Also, many analyses were conducted and this result could be statistically significant by chance alone. Therefore, these structural imaging results should be confirmed by other studies focusing on this area of the brain before it is considered a reasonable outcome measure.

The results should be considered in light of the study's limitations. First, the study was likely affected by exposure misclassification. Historical exposures were calculated using a leaching and transport and computer model that estimated the mass of PCE delivered to each residence. While results from a validation study suggest reasonable agreement between the modeled exposure estimates and historical PCE water samples (Spearman correlation coefficient = 0.65, $p < 0.0001$) (Spence, et al. 2008), some non-differential misclassification was likely due to errors. While individual exposures may differ due to differences in water ingestion and bathing habits, previous work suggests that taking these factors into account does not change the exposure ranking in a meaningful way (Vieira, et al. 2005). Another limitation is the small number of participants. It is possible that a subtle effect could be detected in a larger sample. Because our population was highly educated, predominately white, and had good access to prenatal care, the present results may not be generalizable to more ethnically diverse and disadvantaged populations.

Despite these limitations, this study has many strengths. The study population was exposed to a wide range of PCE levels from an environmental source with little confounding by other water contaminants. Information was also available for a large number of important confounding variables from birth certificates and questionnaires. Small differences between the crude and adjusted results indicates that there was little confounding by the measured covariates and suggest that there is minimal residual confounding from unmeasured covariates. Although non-participants tended to have more self-reported learning problems and more use of self-service dry cleaners than participants, this was true for both exposed and unexposed non-participants making selection bias was unlikely.

In summary, the results of this study suggest that prenatal and early postnatal exposure to PCE, at the levels experienced in this population is not associated with increased white matter hypointensities or decreased total white or gray matter volumes assessed using structural MRI. The gray matter volume of the parahippocampal gyrus was, on average, larger among exposed than unexposed subjects, but this finding was unexpected and should be confirmed by other studies. Additional studies with this population and others with prenatal and early postnatal exposure should be conducted using more sensitive MR technology. Diffuse Tensor Imaging (DTI) would be an ideal MR technology to use. Animal studies have shown that solvents readily cross the blood brain and placental barriers (Ghantous and Danielsson 1986, Ghantous, et al. 1986) and that these lipophilic substances permanently affect the matter of the brain (Brown Dzubow, et al. 2010). DTI is the best MR method for detecting alterations in white matter and would be an ideal tool for future studies to examine whether prenatal and early postnatal PCE exposure alters the white matter of the brain.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

Our population was exposed to PCE through contaminated drinking water in the Cape Cod region of Massachusetts.

A total of 42 subjects were available for the final analysis. There were no meaningful differences between exposed and unexposed subjects on measures of white matter hypointensities (β : 127.5 mm³, 95% CI: -259.1, 1514.0), white matter volumes (e.g. total cerebral white matter: β : 21230.0 mm³, 95% CI: -4512.6, 46971.7) or gray matter volumes (e.g. total cerebral gray matter: β : 11976.0 mm³, 95% CI: -13657.2, 37609.3).

The results of this study suggest that exposure to PCE during gestation and early childhood, at the levels observed in this population, is not associated alterations in the brain structures studied.

This paper will add to the small amount of literature on the neurodevelopmental effects following prenatal solvent exposure.

Table 1

Selection, enrollment, and exposure status of study subjects

	Initial exposure status ^a		
	Exposed	Unexposed	Total
Selected for Imaging	619	626	1245
Excluded from Imaging			
Outside geographic area	167	179	347
Exposure data not available	126	157	283
Only postnatal exposure	44	34	78
Multiple birth	7	16	23
Other ^c	153	132	285
Eligible for Imaging	112	107	219
Unable to contact	63	65	128
Refused	27	22	49
Underwent Imaging	22	20	42
Final exposure status ^b			
Exposed prenatally and postnatally	22	4	26
Unexposed	0	16	16

^a based on initial visual exposure assessment.^b based on questionnaire data and in depth exposure assessment.^c Reported use of 2 or more illicit drugs, N=168; Reported excessive alcohol use (e.g. Average Daily Volume >3 drinks), N = 162; History of neurological disease, N = 123; Possible occupational exposure to solvents, N = 121; Severe hearing or vision problems, N = 20; Other environmental exposure to solvents, N = 14; Other, N = 4). Exclusions do not add up to the total number excluded because some subjects are counted in multiple categories.

Table 2

Population Characteristics by Exposure Group

Characteristic	Exposed (N=26) Mean (SD)	Unexposed (N = 16) Mean (SD)	P value
Age when tested (years)	30.0 (3.9)	30.1 (3.5)	0.88
Birth weight (grams)	3558 (428)	3411 (486)	0.31
Gestational age (weeks)	40.7 (1.9)	39.7 (1.9)	0.10
	Exposed n (%)	Unexposed n (%)	
Year of birth			
1969-1974	5 (19.2)	4 (25.0)	0.91
1975-1980	14 (53.8)	8 (50.0)	
1981-1983	7 (26.9)	4 (25.0)	
Sex			
Male	13 (50.0)	6 (37.5)	0.43
Female	13 (50.0)	10 (62.5)	
White race			
Yes	25 (96.2)	16 (100.0)	1.00
Hispanic/Latino origin or descent			
Yes	0 (0.0)	0 (0.0)	
Education			
HS Grad or Less	1 (3.8)	4 (25.0)	0.12
Some College	2 (7.7)	0 (0.0)	
4 yr college grad or higher	23 (88.5)	12 (75.0)	
Breastfed			
Missing	1 (3.8)	1 (6.3)	0.67
Yes	13 (50.0)	10 (62.5)	
No	12 (46.2)	5 (31.3)	
History of mental illness			
Yes	2 (7.7)	1 (6.3)	1.00
Self reported diagnosis of ADD/HD			
Yes	1 (3.8)	0 (0.0)	1.00
Self reported learning problems			
Yes	4 (15.4)	2 (12.5)	1.00
	Exposed (N=26) Mean (SD)	Unexposed (N = 16) Mean (SD)	
Maternal age at birth of subject	28.8 (4.1)	28.1 (5.7)	0.64
	Exposed n (%)	Unexposed n (%)	
Maternal educational level at subject's birth			

Characteristic	Exposed (N=26) Mean (SD)	Unexposed (N = 16) Mean (SD)	P value
HS Grad or Less	8 (30.8)	6 (37.5)	0.90
Some College	7 (26.9)	4 (25.0)	
4 yr college grad or higher	11 (42.3)	6 (37.5)	
Paternal occupation at subject's birth			
White collar	17 (65.4)	5 (31.3)	0.05
Blue collar	7 (26.9)	6 (37.5)	
Other	2 (7.7)	5 (31.3)	
Maternal diabetes at subject's birth			
Missing	1 (3.8)	0 (0.0)	1.00
Yes	2 (7.7)	1 (6.3)	
No	23 (88.5)	15 (93.8)	
Maternal prenatal cigarette smoking			
Missing	1 (3.8)	0 (0.0)	0.64
Didn't smoke	19 (73.1)	12 (75.0)	
1-10 cigarettes/day	2 (7.7)	3 (18.8)	
11+ cigarettes/day	4 (15.4)	1 (6.3)	
Maternal prenatal alcohol consumption			
Missing	1 (3.8)	0 (0.0)	0.66
Didn't drink	8 (30.8)	7(43.8)	
1-3 drinks/month	14 (53.8)	6 (37.5)	
1+ drinks/week	3 (11.5)	3 (18.8)	
Maternal prenatal marijuana use			
Missing	1 (3.8)	1 (6.3)	1.00
No	25 (96.2)	15 (93.8)	
Maternal prenatal multivitamin use			
Missing	1 (3.8)	0 (0.0)	1.00
Yes	24 (92.3)	15 (93.8)	
No	1 (3.8)	1 (6.3)	
Maternal occupational exposure to solvents before or during pregnancy			
Missing	1 (3.8)	0 (0.0)	1.00
Yes	4 (15.4)	2 (12.5)	
No	21 (80.8)	14 (87.5)	
Maternal use of solvent-based spot removers			
Missing	1 (3.8)	0 (0.0)	0.02
Yes	23 (88.5)	9 (56.3)	
No	2 (7.7)	7(43.8)	
Maternal use of professional dry cleaning: >= once/month			

Characteristic	Exposed (N=26) Mean (SD)	Unexposed (N = 16) Mean (SD)	P value
Missing	3 (11.5)	1 (6.3)	0.80
Yes	6 (23.1)	5 (31.3)	
No	17 (65.4)	10 (62.5)	
Subject ever had solvent-exposed job			
Yes	2 (7.7)	0 (0.0)	0.52
Subject ever had solvent-exposed hobby			
Yes	26 (100.0)	13 (81.3)	0.05
Subject ever lived near professional dry cleaners			
Yes	5 (19.2)	1 (6.3)	0.38
Subject ever used solvent-based spot remover			
Missing	1 (3.8)	0 (0.0)	0.77
Yes	4 (15.4)	1 (6.3)	
No	21 (80.8)	15 (93.8)	
Subject used dry cleaners once/month or more			
Yes	3 (11.5)	2 (12.5)	1.00
Any alcohol consumption in the 24 hours before testing			
Yes	2 (7.7)	0 (0.0)	0.52
Any illicit drug use in the 24 hours before testing			
Yes	0 (0.0)	0 (0.0)	-

Table 3

Structural MRI Results - Crude and Adjusted Outcomes

Outcome (mm ³)	Exposed Mean (SE) (N=26)	Unexposed Mean (SE) (N=16)	Crude Beta Estimate (95% CI) ^a	P-value	Exposed Adj. Mean (SE) (N=26)	Unexposed Adj. Mean (SE) (N=16)	Adjusted Beta Estimate (95% CI)	P-value
White Matter Measures								
White Matter Hypointensities	2321.6 (110.4)	2182.4 (138.1)	139.3 (-219.1,497.6)	0.44	2424.9 (210.5)	2297.4 (181.5)	127.5 (-259.1,514.0) ^b	0.51
Total Cerebral White Matter	443932.5 (7777.6)	428314.4 (9915.6)	15618.1 (-9877.2,41113.4)	0.22	446070.2 (7686.6)	424840.6 (9878.4)	21230.0 (-4512.6,46971.7) ^c	0.10
Total Cerebellum White Matter	33281.9 (561.2)	33166.9 (715.5)	115.0 (-1724.6,1954.6)	0.90	33246.5 (574.9)	33224.5 (738.9)	22.0 (-1903.4,1947.4) ^c	0.98
Gray Matter Measures								
Total Cerebral Gray Matter	453568.6 (7389.5)	444712.0 (9420.8)	8856.7 (-15366.4,33079.8)	0.46	445969.5 (13807.9)	433993.5 (11425.9)	11976.0 (-13657.2,37609.3) ^d	0.35
Total Cerebellum Gray Matter	97510.8 (1567.4)	97763.4 (1998.3)	-252.63219 (-5390.7,4885.4)	0.92	96027.0 (3173.0)	97182.3 (2625.6)	-1155.3 (-7045.6,4735.1) ^d	0.69
Cingulate	20543.5 (456.7)	20170.3 (582.3)	373.2 (-1123.9,1870.4)	0.62	19913.7 (876.8)	19496.2 (725.5)	417.5 (-1210.1,2045.1) ^d	0.61
Parahippocampal gyrus	5092.7 (116.9)	4551.7 (149.0)	541.0 (157.8,924.1)	0.01	4899.7 (234.9)	4426.1 (194.4)	473.6 (37.5,909.7) ^d	0.03
Entorhinal Cortex	4117.0 (102.3)	4175.8 (130.4)	-58.9 (-394.2,276.5)	0.72	4102.4 (208.2)	4179.6 (172.3)	-77.2 (-463.7,309.3) ^d	0.69
Thalamus Proper	14736.6 (253.1)	13952.8 (322.7)	783.8 (-45.8,1613.4)	0.06	14863.6 (508.6)	13934.1 (420.8)	929.4 (-14.7,1873.5) ^d	0.05
Caudate	7779.0 (170.3)	7422.2 (217.1)	356.9 (-201.3,915.0)	0.20	7505.6 (342.1)	7294.8 (283.1)	210.8 (-424.3,846.0) ^d	0.51
Putamen	13075.1 (236.5)	12831.6 (301.5)	243.4 (-531.7,1018.5)	0.53	12791.5 (477.9)	12637.1 (395.4)	154.5 (-732.6,1041.6) ^d	0.73
Pallidum	3383.9 (103.2)	3258.1 (131.6)	125.7 (-212.5,464.0)	0.46	3428.3 (209.3)	3262.3 (173.2)	166.0 (-222.5,554.5) ^d	0.39

Outcome (mm ³)	Exposed Mean (SE) (N=26)	Unexposed Mean (SE) (N=16)	Crude Beta Estimate (95% CI) ^a	P-value	Exposed Adj. Mean (SE) (N=26)	Unexposed Adj. Mean (SE) (N=16)	Adjusted Beta Estimate (95% CI)	P-value
Hippocampus	8714.9 (143.5)	8565.1 (182.9)	149.8 (-320.5,620.0)	0.52	8767.7 (291.1)	8567.3 (240.9)	200.4 (-340.0,740.8) ^d	0.46
Amygdala	4310.3 (89.9)	4208.2 (114.6)	102.1 (-192.7,396.9)	0.49	4102.9 (178.6)	4078.6 (147.8)	24.3 (-307.3,355.9) ^d	0.88
Acuumbens	1607.4 (36.2)	1616.7 (46.1)	-9.3 (-127.9,109.3)	0.87	1568.1 (73.2)	1589.8 (60.6)	-21.6 (-157.5,114.2) ^d	0.75

^a = adjusted for intracranial volume

^b = adjusted for intracranial volume, maternal smoking and subjects solvent exposure

^c = adjusted for intracranial volume and gestational age (weeks)

^d = adjusted for intracranial volume, gestational age (weeks) and subjects solvent exposure