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Adult Neuropsychological Performance Following Prenatal and Early Postnatal Exposure to Tetrachloroethylene (PCE)-contaminated Drinking Water

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Abstract

This population-based retrospective cohort study examined adult performance on a battery of neuropsychological tests 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 a Geographic Information System (GIS). Results of crude and multivariate analyses among 35 exposed and 28 unexposed subjects showed no association between prenatal and early postnatal exposure and decrements on tests that assess abilities in the domains of omnibus intelligence, academic achievement or language. The results were suggestive of an association between prenatal and early postnatal PCE exposure and diminished performance on tests that assessed abilities in the domains of visuospatial functioning, learning and memory, motor, attention and mood. Because the sample size was small, most findings were not statistically significant. Future studies with larger sample sizes should be conducted to further define the neuropsychological consequences of early developmental PCE exposure.

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Conflict of Interest

Three year ago, Dr. Aschengrau served as a consultant in a personal injury case involving chlorinated solvent contamination. None of the parties in this litigation supported, reviewed or had knowledge of this paper.

All other authors (Patricia Janulewicz, Roberta White, Brett Martin, Michael Winter, Janice Weinberg, Veronica Vieira) attest to having no conflict of interest.

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Indexing Terms

Tetrachloroethylene; PCE; development; neuropsychological assessment

1. Introduction

Tetrachloroethylene (PCE, Perc or perchloroethylene) is a manufactured colorless liquid most commonly used for fabric dry cleaning and metal degreasing. PCE 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 (TOXICS, 1994; TOXICS, 1994; Stevens et al., 1997; Feldman, 1999; Klaassen, 2001, Brown Dzubow et al., 2010, Bale et al., 2011). These fat soluble substances have a high affinity for the lipophilic tissues of the central nervous system (Altmann et al., 1995, Brown Dzubow et al., 2010). PCE also readily crosses 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 sequelae among adults with occupational exposures to mixtures of organic solvents. Impairments in cognition and vision have been observed, as have mood changes (White et al., 1995; Grosch et al., 1996; Pauling et al., 1996; Morrow et al., 1997; Tsai et al., 1997; Daniell et al., 1999; Condray et al., 2000; Morrow et al., 2000; Bowler et al., 2001; Klaassen, 2001; Bockelmann et al., 2002; Kilburn, 2002; Morrow et al., 2002; Rosenberg et al., 2002; Fiedler et al., 2003; Reif et al., 2003; Ichihara et al., 2004; Wood et al., 2005). The cognitive sequelae observed following mixed organic solvent exposures included diminished performance on measures of memory, 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 (TOXICS, 1994; Grosch et al., 1996), while other studies have not found any adverse neurological effects (Grosch et al., 1996; Daniell et al., 1999). All studies that examined visuospatial abilities have found a diminished performance associated with PCE exposure (TOXICS, 1994; Echeverria et al., 1995; Daniell et al., 1999).

Three prior studies have examined effects of maternal occupational mixed solvent exposure during the prenatal period on neurodevelopment. A study by Eskenezi et al. (Eskenezi et al., 1988) showed no significant impact on general mental abilities assessed by the McCarthy Scales of Children's Abilities among children at ages 3-4 years. Domain-specific functions such as memory and language tests were not examined.

In contrast, Till et al 2001 (Till et al., 2001) found that prenatal maternal exposure to organic solvent mixtures was associated with worse performance on measures of expressive and receptive language and reduced graphomotor skills using NEPSY tests among children at ages 3-7 years. Study parents also rated exposed children as having more behavioral problems on a child behavior checklist than unexposed children. Laslo-Baker et al. (Laslo-Baker et al., 2004) also found that children exposed to organic solvent mixtures during the prenatal period scored lower on neurobehavioral tests of general intelligence, language and motor abilities at ages 3-7 years.

One study examined postnatal exposure to PCE and subsequent neurobehavioral function among children who attended a day care facility adjacent to a dry cleaning establishment using PCE. Behavioral assessment took place when children were between the ages of 4-5 years (NYSDOH, 2005b) and 4-5 years later (NYSDOH, 2005a; NYSDOH, 2005c). No behavioral effects were found at either assessment.

The present study examined environmental PCE exposure in an unusual scenario. 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 (Larson et al., 1983). These towns were Barnstable, Brewster, Bourne, Chatham, Falmouth, Mashpee, Provincetown, and Sandwich. 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 decided to flush and bleed the VL/AC pipes in order to reduce the PCE concentrations to 40 µg/L, the action level determined to be safe at the time (Commonwealth of Massachusetts, Department of Environmental Quality Engineering Report, 1982). The current United States Environmental Protection Agency (USEPA) maximum contaminant level (MCL) is 5 µg/L (TOXICS, 1994).

These unique circumstances presented a valuable setting for examining the neurodevelopmental impact of prenatal and early postnatal exposure to PCE because thousands of pregnant Cape Cod residents were exposed to a large range of levels, and other water contaminants were rare (Aschengrau and Ozonoff, 1991). Furthermore, the VL/AC pipes were irregularly distributed according to the replacement and expansion needs of the towns, leading to little confounding by environmental and population characteristics. The irregular distribution of VL/AC pipes also meant that specific subjects could be identified as having water supplied through VL/AC pipes while others could be identified as unexposed. The current paper describes an evaluation of the associations between early PCE exposure and neurobehavioral function in this population. We predicted that young adults with prenatal and early childhood PCE exposure would show decrements in performance on neuropsychological outcomes measures relative to unexposed controls, particularly in the domains of visuospatial abilities, attention and executive function, short-term memory and mood.

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. Over 13,000 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. 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.

Based on the initial exposure assessment, two groups of children were selected, those tentatively labeled as exposed and those tentatively labeled unexposed. The initial exposed group included 1,910 individuals. A total of 1,928 “unexposed” children 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 which included residential histories as well as information on the drinking water source. For a more detailed explanation see Janulewicz et al., 2008 (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 the 24A/B/11B Review Committee at the Massachusetts Department of Public Health.

2.2. Follow-up and Enrollment

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. Two percent of the selected population were deceased, 6.8% were not located, 45.8% were located but never responded to any contact attempts (4 attempts were made by mail and telephone), and 3.9% refused to participate (Table 1). In addition, the Massachusetts Department of Public Health did not allow us to contact 9.0% of the subjects whose mothers refused to participate in our prior cohort study of reproductive and developmental outcomes (Janulewicz et al., 2008). These percentages were similar for both the exposed and unexposed groups. In all, 619 exposed and 626 unexposed subjects returned the study questionnaire. Of those who returned the survey, 2.5% were deemed ineligible due to inadequate exposure information, thus leaving 585 exposed and 562 unexposed subjects who were considered for neuropsychological testing.

As shown in Table 1, 30.2% percent of these subjects resided outside of our testing area, 17% were missing key data from maternal questionnaires, and 6.8% had only postnatal exposure and thus were excluded from neuropsychological testing. Based on information collected from the self-administered questionnaires, another 24.8% 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 minutes, used three or more illicit drugs, or drank excessive amounts of alcoholic beverages (average daily volume>3 drinks). An additional 2.0% of the subjects were excluded because they were a twin or triplet. The latter exclusions were made because of the known associations between these characteristics and the outcomes under investigation. These exclusion percentages were similar for both the exposed and unexposed groups

Following these exclusions, a total of 219 subjects were available for neuropsychological testing. As shown in Table 1, 11.9% refused to participate and 58.4% of subjects were located but never responded to any contact attempts, which included three letters and multiple telephone calls, leaving 65 subjects who underwent testing.

There were no meaningful differences in the characteristics of eligible subjects who participated in the neuropsychological 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% of unexposed vs. 22.6% unexposed non-participants had self-reported learning problems, and 10.4% of exposed and 8.9% of unexposed non-participants ever used self-service dry cleaners.

2.3. Data Collection

Birth certificate review 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, lead poisoning, received a diagnosis of Attention Deficit Disorder (ADD) or Hyperactivity Disorder (HD), had an Individual Education Plan (IEP) from their school system, 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 subject in 2005-2008, were used to gather additional demographic information and developmental, educational, occupational, medical and residential histories. Demographic information collected included race, marital status, occupational titles and parental education. The questionnaire also determined the subject's educational history, including highest level of education and presence of any learning problems. Other questionnaire information included the subject's history of neurological disease (e.g., epilepsy); mental illness (e.g., depression); 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 study participation options. Option 1 included a battery of neuropsychological and vision tests, Option 2 included the battery of neuropsychological and vision tests along with structural Magnetic Resonance Imaging and Magnetic Resonance Spectroscopy, and Option 3 included the battery of neuropsychological and vision tests along with structural and functional Magnetic Resonance Imaging and Magnetic Resonance Spectroscopy. Only results from the neuropsychological testing are reported in this paper.

All neuropsychological tests were conducted by a trained examiner masked to exposure status of the subject. Descriptions of the tests are summarized in Table 3. Tests were administered in a fixed order, alternating tasks with different kinds of demands to limit boredom and maintain an effortful performance. For each of the tests, sensitivity to focal brain lesions and to several types of neurological and developmental disorders is well established. Because low-level PCE effects may not result in diagnosable disorders of attention or learning, but nonetheless affect CNS function, the battery was designed to allow investigation of dose-effect relationships that reveal preclinical effects of exposure (Echeverria et al., 1995; White et al., 2001). Tasks included measures from all commonly assessed neuropsychological domains – attention and executive function, manual motor speed, verbal/language abilities, visuospatial skills, short-term memory, mood and motivation. In addition, tasks assessing omnibus intelligence (IQ) and basic academic skills were included. The tasks included in the battery have been applied widely in both research and clinical situations, and the psychometric properties and validity of the tasks are well established (Strauss, 2006).

2.4. PCE Exposure Assessment

Using a visual assessment of the water pipe distribution maps, children were assigned tentative exposure designations based on the presence of VL/AC pipes in the immediate vicinity of their birth address. Each child'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 (Webler, 1993; Aschengrau et al., 2003) 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. EPANet software, which was developed by the U.S. Environmental Protection Agency, has been used in multiple epidemiologic studies (Rossman, 1994; Aral et al., 1996; Maslia et al., 2000; Reif et al., 2003; Aschengrau et al., 2009).

Study subjects may have been exposed to PCE in drinking water through ingestion, dermal absorption and 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. For example, the modeled cumulative mass of PCE was diluted before entering the home in an estimated 90,000 gallons of water used by an average household in a year. We assumed that all users on the water distribution network drew the same amount of water because the study area consisted mostly of residences. We also assumed that water sources did not change over the study period. The distribution systems that were in place by the 1960s and early 1970s remained generally unchanged until population growth during the 1980s required some systems to expand and add water sources. Our model was applied to the water distribution system conditions in 1980, near the end of the prenatal exposure period.

PCE exposure levels were calculated for the study children who had completely geocoded residential histories and information on their mother's last menstrual period (LMP). The LMP was based on birth certificate information on date of birth and gestational duration. Cumulative exposure to PCE (in grams) during the prenatal and early postnatal period was calculated by summing the amount of PCE delivered to each subject's residence from the month and year of the LMP through the month and year of his/her fifth birthday. Most subjects with prenatal exposure also had postnatal exposure and so it was not possible to examine these developmental stages separately.

2.5. Statistical Analysis

Of the 65 subjects tested, two were excluded from the analyses because they failed the Test of Memory Malingering (TOMM) (Tombaugh, 1996) and their data were deemed unreliable. The following measures of neuropsychological performance were assessed (Table 3): Omnibus Intelligence using the Wechsler Abbreviated Scales of Intelligence (WASI) (Wechsler, 1999); academic achievement using two subtests of the Wide Range Achievement Test 3 (WRAT-Reading and Arithmetic) (Wilkinson, 1993); language using the Boston Naming Test (BNT) (Kaplan et al., 1983); visuospatial skills using the Hooper Visual Organization Test (HVOT) (Hooper, 1983) and the copy condition of the Rey-Osterrieth Complex Figure (ROCF) (Osterrieth, 1944); learning and memory using the recall conditions of the ROCF and Wechsler Memory Scale–Visual Reproduction (Wechsler, 1945) and the California Verbal Learning Test (CVLT) (Delis et al., 2000); attention and executive function using the Trail-making Test (TMT) (Reitan, 1992) parts A and B and the

Conners Adult ADHD Rating Scale (Conners et al., 1999); motor skills using the continuous performance and finger tapping subtests of the Neurobehavioral Evaluation System-3 (NES) (Baker et al., 1985), and current mood using the Profile of Mood States (POMS) (McNair et al., 1992).

Regression models were used to assess the relationship between PCE exposure and the test scores. All analyses compared subjects with prenatal and early postnatal PCE exposure combined to subjects with no exposure during both periods. Mean differences (for continuous scores) and relative risks (for dichotomous scores) were used to assess the strength of the association between the exposure and a particular outcome. Ninety-five percent confidence intervals were used to assess the precision of the associations.

Review of the PCE exposure distribution did not identify any natural cut points for a dose-response assessment. Therefore, a logical cut point of 76.7 g was derived to delineate “low” and “high” exposure which corresponded to being exposed to an average drinking water concentration of 40 ug/L, the suggested action level when the contamination was discovered in 1980, for the entire prenatal and postnatal exposure period.

First, crude analyses were conducted for each neuropsychological outcome without adjusting for any potential confounders. Next, multivariate analyses were conducted to control for confounding variables. For all continuous outcomes and categorical outcomes with sufficient numbers, the confounder assessment began with a multivariate model that included subject’s education and gender because of their known association with the outcomes. The remaining possible confounders (see Table 2) were entered into the education- and gender-adjusted model one at a time to determine which additional variables to control (Aschengrau et al., 2003). Variables that changed an outcome measure by more than 30% were included in the final multivariate model. Confounder assessment for categorical outcomes with small numbers also followed this process but began with a crude model with only the exposure variable.

To assess group differences by neuropsychological domain, individual test scores within a domain were converted to a t-score based on the entire sample. T-scores for each domain were averaged and mean differences were used to assess the strength of the association between the exposure and an outcome. Ninety-five percent confidence intervals were used to assess the precision of the differences.

3. Results

A total of 63 subjects was available for the final analysis. Two neuropsychological tests had fewer subjects available for analysis because of lost data due to computer failure (computer-based NES = 56 and Conners Adult ADHD Rating Scale = 58). According to the initial exposure designation, there were 31 exposed and 32 unexposed children. Following the in-depth exposure assessment, there were 35 exposed and 28 unexposed children because four unexposed children switched to the exposed group (Table 1). The primary reason for switching 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, 29-30 years old at testing. Subjects also gave similar self-reports of ADD/HD, learning problems, mental illness (mainly depression), and solvent exposure. Mothers in both groups were, on average, 28-29 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. There were some differences in mother's breastfeeding practices and maternal solvent exposure.

3.1. Neuropsychological Test Results

The crude and adjusted neuropsychological test results are presented in Table 4 (continuous outcomes) and Table 5 (dichotomous outcomes). There were no meaningful differences between the exposed and unexposed groups in the domains of omnibus intelligence, academic achievement and language. Results in the omnibus intelligence domain were not statistically significant and were also inconsistent, with exposed subjects performing better on some measures (Table 4, VIQ β 4.8, 95% CI -1.1, 10.8, $p=0.11$; FSIQ β 1.6, 95% CI -4.0, 7.3, $p=.56$) and worse on others (Table 4, PIQ β -2.8, 95% CI -9.1, 3.4, $p=0.37$). The academic achievement domain had similar non-significant and inconsistent results with exposed subjects performing better on WRAT3 reading (Table 4, β 1.2, 95% CI -9.9, 12.3, $p=0.83$) and worse on WRAT3 spelling (Table 4, β -6.8, 95% CI -17.1, 3.5, $p=0.19$). Exposed subjects had, on average, less than a one word reduction on the Boston Naming Test (Table 4, β -0.2, 95% CI -2.1, 1.7, $p=0.83$) that was not statistically significant. In the visuospatial domain, exposed subjects performed worse on the Hooper Visual Organization Test (HVOT) (Table 5, RR 5.6 for total score ≤ 24 , 95% CI 0.7-42.9, $p=0.07$) and showed a slight decrement in scores on the ROCF copy condition (Table 4, β -0.5, 95% CI -1.4, 0.3, $p=0.21$), but none of these differences results were statistically significant.

Exposed subjects also performed consistently worse than unexposed subjects on the neuropsychological tests in the learning and memory domain. Scores among exposed subjects were significantly worse than among unexposed subjects on the WMS-VR delayed recall condition (Table 4, β -1.5, 95% CI -2.9, -0.1, $p=0.04$). Performance of exposed subjects was slightly worse than that of unexposed subjects on the WMS-VR immediate recall condition (Table 4, β -0.5, 95% CI -1.8, 0.7, $p=0.42$); the CVLT short delay recall (Table 4, β -0.9, 95% CI -2.5, 0.8, $p=0.31$) and long delay recall (Table 4, β -0.6, 95% CI -1.9, 0.8, $p=0.43$), but these results were not statistically significant. Compared to the unexposed subjects, the exposed subjects also showed a slight increase in CVLT long delay recognition false positives (Table 4, β 0.6, 95% CI -0.7, 1.9, $p=0.36$) and in the number of free recall repetitions (perseverations) (Table 4, β 1.6, 95% CI -0.5, 3.7, $p=0.13$), but these findings were not statistically significant. Exposed subjects also performed slightly worse than controls on the ROCF immediate recall condition (Table 4, β -0.5, 95% CI -3.6, 2.6, $p=0.74$) and delayed recall condition (Table 4, β -1.1, 95% CI -4.1, 2.0, $p=0.49$), but again these results were not statistically significant.

Exposed subjects also had consistently lower scores than unexposed subjects on tests in the attention domain, although these differences were not statistically significant. Exposed subjects had a 60% increase in the number of errors on Part A of the Trail-making Test, (Table 5, RR 1.6, 95% CI 0.5, 4.8, $p=0.39$) and an increase in the time to its completion, with a corresponding decrease in percentile score (Table 4, β 2.9, 95% CI -0.1, 6.0, $p=0.06$ and percentile, β -11.8, 95% CI -23.9, 0.3, $p=0.05$). Though not statistically significant, the exposed subjects' reaction time was, on average, 11.9 seconds slower on the NES continuous performance test (reaction time β 11.9, 95% CI -8.2, 31.9, $p=0.24$) than unexposed subjects. There were mixed results on the Conners Adult ADHD Rating Scale. For example, exposed subjects were 50% more likely to endorse items of hyperactivity and

restlessness (Table 5, RR 1.5, 95% CI 0.6, 3.9, $p=0.37$) and 40-60% less likely to endorse items of inattention and ADHD symptomology (Table 5, Inattention RR 0.5, 95% CI 0.2, 1.2, $p=0.12$; DSM-IV inattentive symptoms RR 0.6, 95% CI 0.2, 1.4, $p=0.22$; DSM-IV ADHD symptoms RR 0.4, 95% CI 0.1, 1.0, $p=0.03$), with the DSM-IV ADHD symptom scale results reaching statistical significance.

Exposed subjects also had a slight but consistent decrease in motor speed (Table 4, NES finger tapping – non dominant hand β -1.8, 95% CI -5.7, 2.2, $p=0.37$; dominant hand β -0.8, 95% CI -5.1, 3.6, $p=0.72$). Lastly, exposed subjects were 30% more likely to report being irritable and 60% more likely to report being fatigued (Table 5, POMS Anger RR 1.3, 95% CI 0.6, 2.8, $p=0.57$, POMS Fatigue RR 1.6, 95% CI 0.9, 3.0, $p=0.14$). There were no differences on the other measures of mood function including the total mood score (Table 5, Total Mood Score RR 1.0, 95% CI 0.5, 1.8, $p=0.99$). Evaluation of the relationships between estimated exposure dose and test outcomes showed no statistically significant findings (results not presented).

3.2. Neuropsychological Tests by Domain Results

When domains with multiple tests were combined into single t-scores, a trend was identified for slightly worse performance in the visuospatial, learning and memory, attention and executive function domains, with a slight trend for mood alterations among exposed subjects. Beta estimates of mean differences were -0.3 for the visuospatial domain (95% CI -0.6, 0.1, $p=0.14$), -0.2 for learning and memory (95% CI -0.6, 0.1, $p=0.17$), -0.2 for attention and executive function (95% CI -0.5, 0.1, $p=0.16$), and -0.1 for mood alterations (95% CI -0.6, 0.1, $p=0.79$). These decrements were not statistically significant.

4. Discussion

The results of this study suggest that prenatal and early postnatal exposure to PCE does not cause major decrements in adult neuropsychological performance, although there was a suggestion of an association between exposure and diminished performance in specific domains of functioning on tests assessing cognitive performance. Exposed subjects performed worse on both measures in the visuospatial domain and both measures of motor functioning but none of the decrements were statistically significant. Examining the learning/memory domain as a whole, exposed subjects performed worse on all 10 scores in the domain, but only one decrement was statistically significant. Similarly, for the attention domain, exposed subjects performed worse on all 7 scores in the domain, but only one was statistically significant. Results of this study also suggest that prenatal and early postnatal exposure to PCE may be associated with a slight though not statistically significant increase in mood complaints, specifically fatigue and irritability. There was also a statistically significant reduction in the total ADHD symptom score in the exposed group, though the other results on the Conners Adult ADHD Rating Scale were mixed. No clear dose-response pattern was observed for these outcomes and no associations were observed with deficits in the omnibus intelligence, academic achievement or language domains. The domain-specific findings are similar to results from studies of workers with occupational exposures to PCE (Echeverria et al., 1995, Daniell et al., 1999), and are consistent with the idea that PCE exposure targets frontal-subcortical function in the brain, with limbic system involvement (Daniell et al., 1999).

The small size of this study limited its power to detect subtle yet statistically significant differences between exposed and unexposed subjects. However, the associations observed within specific domains suggest that PCE exposure may lead to subtle deficits in visuospatial, motor, learning and memory and attention.

Exposure misclassification also limited the study's ability to detect group differences. Historical exposures were calculated using a leaching and transport model and a 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 = 0.48, $p < 0.0001$) (Spence et al., 2008), some non-differential misclassification was likely due to errors in estimating the magnitude and direction of the water flow. While individual exposures may differ due to differences in water ingestion and bathing habits findings from recent studies suggest that taking these factors into account does not change the exposure ranking in a meaningful way (Vieira et al., 2005). When dichotomous exposures were examined, non-differential misclassification likely biased results towards the null. However, because three exposure groups were examined in the dose-response assessment, results for the low exposure group may have been biased either towards or away from the null, while results for the high exposure group were likely biased toward the null (Rothman et al., 1998). This phenomenon may explain why no consistent pattern was seen in the dose-response assessment.

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 (Aschengrau and Ozonoff, 1991). Information from birth certificates and questionnaires was also available for a large number of important confounding variables. 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. While 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 and so selection bias was unlikely. Recall bias was also unlikely. While there were newspaper articles in the 1980s reporting the streets where the VL/AC pipes were located, most participants did not accurately report their exposure status on the questionnaire. When asked whether they believed their water was contaminated, 11.4% of exposed subjects believed their water was contaminated while 34.3% did not believe it was contaminated and 54.3% did not know. Furthermore, 32.1% of the unexposed group believed their water was not contaminated while 7.1% believed it was contaminated and 60.7% did not know.

Two prior epidemiologic studies of pregnant women occupationally exposed to solvents found that the offspring showed decrements in neuropsychological function relative to controls when tested at ages 3-9 years (Till et al., 2001; Laslo-Baker et al., 2004). These studies used sensitive measures to assess brain function and found that exposed children performed worse on measures of general intelligence, expressive and receptive language abilities and motor tasks than unexposed children. In contrast, one previous epidemiologic study of the offspring of pregnant women occupationally exposed to solvents found no association between exposure and general intelligence among children at ages 3-4 years (Eskenazi et al., 1988). The test measure used in this is less sensitive than those used by Till et al. (Till et al., 2001) and Laslo-Baker et al. (Laslo-Baker et al., 2004). Other differences in study design also make it difficult to compare the results of the occupational studies to ours. For example, the occupational studies assessed the impact of early life exposure to mixed solvents on a limited number of domains of neuropsychological functioning among children. In contrast, the current study examined the impact of early life exposure to a single solvent on a wide range of neuropsychological outcomes among adults.

Only one prior study, the Pumpkin Patch Day Care Center Follow-up Evaluation, has examined exposure to PCE alone in an environmental setting and subsequent neuropsychological performance. In this study, postnatal exposure to contaminated air occurred while children attended a day care facility adjacent to a dry cleaning establishment

using PCE. Behavioral assessments took place when children were between the ages of 4-5 years (NYSDOH, 2005b) and again 4-5 years later (NYSDOH, 2005a; NYSDOH, 2005c). No behavioral decrements were found in these children at either assessment. However, this study's ability to detect subclinical neuropsychological deficits was limited due to its small sample size (exposed N = 13, unexposed N = 13). The null findings may also stem from examining only postnatal exposure.

In summary, the results of this study suggest that prenatal and early postnatal exposure to PCE may lead to decreased performance on neuropsychological tests, specifically in the visuospatial, fine manual motor, learning and memory, and attention domains. In addition, no associations were found between prenatal and early postnatal exposure to PCE and decrements in performance on tests assessing omnibus intelligence, academic achievement, or language. 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. Future studies with a larger sample size among populations with prenatal and early postnatal PCE exposure should include tests of visuospatial, motor, learning and memory and attention domains to further understand and define the deficits in neuropsychological performance following early developmental PCE exposure and to further determine whether there is an adverse neurobehavioral effect following exposure.

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Table 1

Selection, Enrollment, Exposure Status and Exclusions of Study Population

	Initial exposure status		
	Exposed	Unexposed	Total
Selected for Neuropsychological Testing	619^a	626^a	1245^a
Excluded from Neuropsychological Testing ^a			
Outside geographic area	167	179	346
No maternal questionnaire data	126	157	283
Only postnatal exposure	44	34	78
Multiple birth	7	16	23
Other ^c	153	132	285
Eligible for Neuropsychological Testing	112^a	107^a	219^a
Unable to contact	63	65	128
Refused	17	9	26
Underwent Neuropsychological Testing			
Final exposure status ^b			
Exposed during pre and postnatal period	31	4	35^b
Unexposed	0	28	28^b

^abased on initial exposure assessment.^bbased on questionnaire data and in depth exposure assessment.^cReported 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	Exposed Mean(SD)	Unexposed n	Unexposed Mean(SD)
Age when tested (years)	35	29.8 (3.6)	28	30.2 (3.2)
Birth weight (grams)	35	3511 (447)	28	3474 (509)
Gestational age (weeks)	35	40.8 (1.7)	28	39.8 (1.7)
	Exposed n	Exposed %	Unexposed n	Unexposed %
Year of birth				
1969-1974	4	11.4	6	21.4
1975-1980	19	54.3	17	60.7
1981-1983	12	34.3	5	17.9
Multiple pregnancy				
No	35	100.0	28	100.0
Sex				
Male	13	37.1	7	25.0
Female	22	62.9	21	75.0
White race				
Yes	34	97.1	28	100.0
Hispanic/Latino origin or descent				
No	35	100.0	28	100.0
Education				
HS Grad or Less	2	5.7	3	10.7
Some College	5	14.3	4	14.3
4 yr college grad or higher	28	80.0	21	75.0
Breastfed				
Missing	1	2.9	0	0.0
Yes	19	54.3	22	78.6
No	15	42.9	6	21.4
History of mental illness				
Yes	4	11.4	3	10.7
Self reported diagnosis of ADD/HD				
Yes	1	2.9	0	0.0
Self reported learning problems				
Yes	4	11.4	2	7.1
Characteristic	Exposed n	Exposed Mean(SD)	Unexposed n	Unexposed Mean(SD)
Maternal age at birth of subject	35	29.4 (4.9)	28	27.2 (4.2)
Paternal age at birth of subject	35	32.0 (5.9)	28	30.1 (5.9)
	Exposed n	Exposed %	Unexposed n	Unexposed %
Maternal educational level at subject's birth				
HS Grad or Less	11	31.4	11	39.3

Characteristic	Exposed n	Exposed Mean(SD)	Unexposed n	Unexposed Mean(SD)
Some College	10	28.6	9	32.1
4 yr college grad or higher	14	40.0	8	28.6
Paternal occupation at subject's birth				
White collar	20	57.1	12	42.9
Blue collar	12	34.3	8	28.6
Other	3	8.6	8	28.6
Maternal diabetes at subject's birth				
Missing	1	2.9	0	0.0
Yes	2	5.7	1	3.6
No	32	91.4	27	96.4
Maternal prenatal cigarette smoking				
Missing	1	2.9	0	0.0
Didn't smoke	26	74.3	20	71.4
1-10 cigarettes/day	2	5.7	6	21.4
11+ cigarettes/day	6	17.1	2	7.1
Maternal prenatal alcohol consumption				
Missing	1	2.9	0	0.0
Didn't drink	13	37.1	11	39.3
1-3 drinks/month	15	42.9	11	39.3
1+ drinks/week	6	17.1	6	21.4
Maternal prenatal marijuana use				
Missing	1	2.9	0	0.0
Yes	1	2.9	2	7.1
No	33	94.3	26	92.9
Maternal prenatal multivitamin use				
Missing	1	2.9	0	0.0
Yes	32	91.4	25	89.3
No	2	5.7	3	10.7
Maternal occupational exposure to solvents before or during pregnancy				
Missing	1	2.9	0	0.0
Yes	7	20.0	3	10.7
No	27	77.1	25	89.3
Maternal use of solvent-based spot removers				
Missing	1	2.9	0	0.0
Yes	29	82.9	17	60.7
No	5	14.3	11	39.3
Maternal use of professional dry cleaning: >= once/month				
Missing	3	8.6	2	7.1

Characteristic	Exposed n	Exposed Mean(SD)	Unexposed n	Unexposed Mean(SD)
Yes	10	28.6	9	32.1
No	22	62.9	17	60.7
Subject ever had solvent-exposed job				
Missing	1	2.9	0	0.0
Yes	2	5.7	0	0.0
No	32	91.4	28	100.0
Subject ever had solvent-exposed hobby				
Yes	33	94.3	25	89.3
Subject ever lived near professional dry cleaners				
Yes	5	14.3	1	3.6
Subject ever used solvent-based spot remover				
Missing	2	5.7	2	7.1
Yes	5	14.3	2	7.1
No	28	80.0	24	85.7
Subject used dry cleaners once/month or more				
Missing	0	0.0	1	3.6
Yes	5	14.3	5	17.9
No	30	85.7	22	78.6
Subject ever used self-service dry cleaners				
No	35	100.0	28	100.0
Any alcohol consumption in the 24 hours before testing				
No	31	88.6	26	92.9
Any illicit drug use in the 24 hours before testing				
No	35	100.0	28	100.0

Table 3

Neuropsychological Test Description by Domain

Domain	Test	Description
Omnibus Intelligence		
	Wechsler Abbreviated Scale of Intelligence (WASI)	Short test of omnibus intelligence with four subtests
Academic Achievement		
	Wide Range Achievement Test - (WRAT)	Screening test of academic knowledge
Language		
	Boston Naming Test (BNT)	Line drawings of common objects must be named
Visuospatial		
	Hooper Visual Organization Test (HVOT)	Drawings of common objects presented in cut-up form. Requires identification of the object.
	Rey-Osterreith Complex Figure (ROCF) – copy condition	A complex design is presented. Examinee must draw a copy of figure.
Learning and Memory		
	California Verbal Learning Test II (CVLT II)	List learning task requiring examinee to learn list over 5 trials with delayed recall conditions.
	Wechsler Memory Scale (WMS) – Visual Reproduction	Four visual designs are presented individually. Examinee must draw each design immediately after stimulus is withdrawn and after a delay.
	Rey- Osterreith Complex Figure (ROCF)	A complex design is presented. Examinee must draw immediately after stimulus is withdrawn and after a delay.
Attention and Executive Function		
	Trail-making Test – Part A and B	Circles containing numbers must be connected by a drawn line (A condition) and circles containing numbers and letters must be connected by alternating between numbers and letters (B condition).
	Conners Adult ADHD Rating Scale	Self-report inventory of symptoms of attention deficit hyperactivity disorder.
	Neurobehavioral Evaluation System-3 (NES 3) – continuous performance test	Computer-assisted task in which animal profiles are presented. Key press required following presentation of target item.
Motor		
	Neurobehavioral Evaluation System 3 (NES 3) – finger tapping test	Computer-assisted task requiring tapping of a key separately with index finger of each hand.
Mood		
	Profile of Mood States (POMS)	60 single-item descriptors of emotional reactions on 6 dimensions are presented. Examinee indicates the intensity of response to each affective descriptor on a likert scale
Motivation		
	Test of Memory Malingering (TOMM)	Drawings of objects are presented followed by multiple choice recognition paradigm.

Table 4
Neuropsychological Test Results - Crude and Adjusted Continuous Outcomes

Outcome	Crude Results				Adjusted Results ^c	
	Exposed Mean (SD)	Unexposed Mean (SD)	Beta Estimate of Mean Difference (95% CI)	p value	Exposed Adj. Mean (SE)	Unexposed Adj. Mean (SE)
Academic Achievement						
Wildie Range Achievement Test 3 ^f						
Spelling Percentile ^a	54.4 (23.8)	61.1 (22.2)	-6.8 (-18.5, 5.0)	0.25	39.4 (4.6)	46.2 (4.8)
Reading Percentile ^a	61.4 (20.1)	59.3 (24.9)	2.1 (-9.4, 13.5)	0.72	51.2 (5.0)	49.9 (5.2)
Omnibus IQ						
Wechsler Abbreviated Scale of Intelligence ^f						
Verbal IQ ^a	107.3 (11.5)	105.7 (9.3)	1.6 (-3.7, 7.0)	0.55	104.7 (3.3)	99.9 (3.1)
Performance IQ ^a	110.0 (13.2)	113.6 (11.7)	-3.5 (-9.9, 2.8)	0.27	108.6 (3.0)	111.4 (2.8)
Full Scale IQ ^a	109.5 (10.8)	110.5 (10.0)	-1.0 (-6.4, 4.3)	0.70	108.5 (3.1)	106.9 (2.7)
Language						
Boston Naming Test ^f						
Total Raw Score (total possible = 60)	55.0 (3.6)	55.6 (3.2)	-0.5 (-2.3, 1.2)	0.55	54.5 (0.9)	54.7 (0.9)
# stimulus cues given ^b	5.3 (3.8)	4.8 (3.1)	0.6 (-1.2, 2.4)	0.51	6.4 (0.8)	5.6 (0.8)
# phonemic cues given ^b	5.0 (3.5)	4.4 (3.0)	0.6 (-1.0, 2.3)	0.45	5.9 (0.8)	5.1 (0.8)
Visuospatial						
Rey-Osterreith Complex Figure ^f						
Copy condition raw score (total possible = 36) ^a	34.8 (2.1)	35.3 (1.0)	-0.5 (-1.4, 0.3)	0.19	34.7 (0.4)	35.2 (0.4)
Learning and Memory						
Wechsler Memory Scale ^f						
Immediate recall raw score (total possible = 14) ^a	8.3 (2.7)	8.6 (2.3)	-0.4 (-1.7, 0.9)	0.55	7.1 (0.6)	7.6 (0.6)
Delayed recall raw score (total possible = 14) ^a	6.5 (2.8)	7.9 (2.8)	-1.4 (-2.8, 0.03)	0.05	5.7 (0.7)	7.2 (0.7)

Outcome	Crude Results				Adjusted Results ^c			
	Exposed Mean (SD)	Unexposed Mean (SD)	Beta Estimate of Mean Difference (95% CI)	p value	Exposed Adj. Mean (SE)	Unexposed Adj. Mean (SE)	Beta Estimate of Mean Difference (95% CI)	p value
California Verbal Learning Test II ^j								
Trials 1-5 free recall T-score ^a	58.4 (9.6)	59.8 (8.6)	-1.4 (-6.0, 3.3)	0.56	56.2 (3.0)	56.3 (2.9)	-0.1 (-5.6, 5.3) ^{d,e,h}	0.96
Short delay free recall raw score (total possible = 16) ^a	12.5 (2.9)	13.6 (1.9)	-1.0 (-2.4, 0.4)	0.17	12.4 (0.8)	13.2 (0.6)	-0.9 (-2.5, 0.8) ^{h,i}	0.31
Long delay free recall raw score (total possible = 16) ^a	12.5 (3.1)	13.3 (2.6)	-0.8 (-2.3, 0.6)	0.26	11.9 (0.6)	12.5 (0.7)	-0.6 (-1.9, 0.8)	0.43
Long delay recognition – false positive raw score ^b	1.7 (2.9)	0.9 (1.6)	0.8 (-0.4, 2.0)	0.17	1.8 (0.7)	1.2 (0.7)	0.6 (-0.7, 1.9)	0.36
Total number of Intrusions raw score ^b	2.2 (3.2)	1.9 (2.4)	0.3 (-1.2, 1.7)	0.70	2.2 (0.9)	2.5 (0.9)	-0.3 (-2.0, 1.3) ^{d,e,g,h,i}	0.15
Total number of Repetitions raw score ^b	5.8 (4.6)	3.9 (3.3)	1.9 (-0.2, 3.9)	0.07	5.9 (1.0)	4.2 (1.0)	1.6 (-0.5, 3.7)	0.13
Rey-Osterreith Complex Figure ^j								
Immediate recall raw score (total possible = 36) ^a	23.0 (5.4)	23.8 (5.1)	-0.8 (-3.5, 1.9)	0.56	23.0 (1.7)	23.5 (1.5)	-0.5 (-3.6, 2.6) ^{g,h,i}	0.74
Delayed recall raw score (total possible = 36) ^a	22.3 (5.6)	23.2 (5.5)	-0.9 (-3.8, 1.9)	0.50	20.8 (1.5)	21.8 (1.4)	-1.1 (-4.1, 2.0) ^{h,i}	0.49
Attention and Executive Function								
Trail Making Test ^j								
Part A – time to completion (seconds) ^b	21.9 (6.9)	18.7 (4.5)	3.2 (0.2, 6.2)	0.03	23.1 (1.4)	20.2 (1.4)	2.9 (-0.1, 6.0)	0.06
Part A – Percentile ^a	57.9 (26.8)	70.5 (18.8)	-12.7 (-24.6, -0.7)	0.03	53.3 (5.4)	65.1 (5.7)	-11.8 (-23.9, 0.3)	0.05
Part B – time to completion (seconds) ^b	54.1 (17.4)	52.9 (19.7)	1.3 (-8.1, 10.6)	0.79	62.0 (5.8)	61.2 (5.4)	0.8 (-9.5, 11.0) ^{d,i}	0.88
Part B – Percentile ^a	48.4 (30.7)	52.0 (32.5)	-3.5 (-19.5, 12.5)	0.66	28.8 (9.0)	32.9 (7.8)	-4.1 (-20.3, 12.1) ^{g,i}	0.61
Neurobehavioral Evaluation System 3 ^k								
Continuous Performance Test reaction time (milliseconds) ^b	468 (34.2)	452 (33.5)	15.2 (-3.0, 33.4)	0.10	459.0 (10.9)	447.1 (10.4)	11.9 (-8.2, 31.9) ^g	0.24
Motor								
Neurobehavioral Evaluation System 3 ^k								
Finger Tapping	53.5 (6.0)	53.6 (7.5)	-0.1 (-3.7, 3.5)	0.96	51.4 (2.5)	52.2 (2.1)	-0.8 (-5.1, 3.6) ^{d,g,h,i}	0.72
Mean # taps, Dominant hand ^a								

\$watermark-text

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Outcome	Crude Results				Adjusted Results ^c		
	Exposed Mean (SD)	Unexposed Mean (SD)	Beta Estimate of Mean Difference (95% CI)	p value	Exposed Adj. Mean (SE)	Unexposed Adj. Mean (SE)	Beta Estimate of Mean Difference (95% CI) p value
Mean # taps, Non Dominant hand ^a	49.2 (6.6)	49.5 (7.2)	-0.3 (-4.0, 3.4)	0.86	47.4 (1.8)	49.2 (1.8)	-1.8 (-5.7, 2.2) ^h 0.37

^a = higher score represents better performance

^b = lower score represents better performance

^c = adjusted for gender and education

^d = adjusted for breast feeding

^e = adjusted for maternal solvent use during pregnancy

^f = adjusted for maternal education

^g = adjusted for maternal smoking

^h = adjusted for use of spot removers

ⁱ = adjusted for paternal occupation

^j = exposed N=35; unexposed N = 28

^k = exposed N = 30; unexposed N = 26

Table 5
Neuropsychological Test Results - Crude and Adjusted Dichotomous Outcomes

Outcome	Group	% Yes (n/N)	Crude Relative Risk (95 % CI)	Adjusted Relative Risk (95% CI) [*]	p value
Visuospatial					
<i>Hooper Visual Organization Test</i>					
Total score ≤ 24 ^{a,e}	Exposed	20.0 (7/35)	5.6 (0.7, 42.9)	-----*	0.07
	Unexposed	3.6 (1/28)	1.0	-	-
Attention and Executive Function					
<i>Trail Making Test</i>					
Part A - errors >0 ^b	Exposed	22.9 (8/35)	1.6 (0.5, 4.8)	-----*	0.39
	Unexposed	14.3 (4/28)	1.0	-	-
Part B - errors >0 ^b	Exposed	25.7 (9/35)	1.0 (0.4, 2.4)	-----*	0.95
	Unexposed	25.0 (7/28)	1.0	-	-
<i>Conners Adult ADHD Rating Scale^f</i>					
Inattention/Memory Problems (T score >50 ^b)	Exposed	18.2 (6/33)	0.5 (0.2, 1.2)	-----*	0.12
	Unexposed	36.0 (9/25)	1.0	-	-
Hyperactivity/Restlessness (T score >50 ^b)	Exposed	30.3 (10/33)	1.5 (0.6, 3.9)	-----*	0.37
	Unexposed	20.0 (5/25)	1.0	-	-
Impulsivity/Emotional Lability (T score >50 ^b)	Exposed	18.2 (6/33)	1.1 (0.4, 3.6)	-----*	1.00
	Unexposed	16.0 (4/25)	1.0	-	-
Problems with Self-Concept (T score >50 ^b)	Exposed	21.2 (7/33)	1.1 (0.3, 3.0)	-----*	0.91
	Unexposed	20.0 (5/25)	1.0	-	-
DSM-IV Inattentive Symptoms (T score >50 ^b)	Exposed	18.2 (6/33)	0.6 (0.2, 1.4)	-----*	0.22
	Unexposed	32.0 (8/25)	1.0	-	-
DSM-IV Hyperactive-Impulsive Symptoms (T score >50 ^b)	Exposed	21.2 (7/33)	1.1 (0.4, 3.0)	-----*	0.91
	Unexposed	20.0 (5/25)	1.0	-	-
DSM-IV ADHD Symptoms Total (T score >50 ^b)	Exposed	15.1 (5/33)	0.4 (0.1, 1.0)	-----*	0.03
	Unexposed	40.0 (10/25)	1.0	-	-
ADHD Index (T score >50 ^b)	Exposed	9.1 (3/33)	0.5 (0.1, 1.7)	-----*	0.27

Outcome	Group	% Yes (n/N)	Crude Relative Risk (95 % CI)	p value	Adjusted Relative Risk (95% CI) [*]	p value
Mood	Unexposed	20.0 (5/25)	1.0	-	-	-
<i>Profile of Mood States^f</i>						
Tension (T score >50) ^b	Exposed	48.6 (17/35)	0.9 (0.6,1.5)	0.69	0.9 (0.5,1.6) ^d	0.77
	Unexposed	53.6 (15/28)	1.0	-	-	-
Depression (T score >50) ^b	Exposed	20.0 (7/35)	1.1 (0.4,3.2)	0.83	-----*	-----*
	Unexposed	17.9 (5/28)	1.0	-	-	-
Anger (T score >50) ^b	Exposed	31.4 (11/35)	1.3 (0.6,2.8)	0.57	-----*	-----*
	Unexposed	25.0 (7/28)	1.0	-	-	-
Fatigue (T score >50) ^b	Exposed	48.6 (17/35)	1.5 (0.8,2.9)	0.18	1.6 (0.9,3.0) ^c	0.14
	Unexposed	32.1 (9/28)	1.0	-	-	-
Confusion (T score >50) ^b	Exposed	37.1 (13/35)	1.2 (0.6,2.3)	0.68	1.1 (0.5,2.1) ^c	0.86
	Unexposed	32.1 (9/28)	1.0	-	-	-
Vigor (T score ≤/ <50) ^a	Exposed	31.4 (24/35)	1.0 (0.7,1.3)	0.81	1.0 (0.7,1.3) ^d	0.77
	Unexposed	71.4 (20/28)	1.0	-	-	-
Total Mood Disturbance (T score >50) ^b	Exposed	42.9 (15/35)	1.1 (0.6,2.0)	0.77	1.0 (0.5,1.8) ^c	0.99
	Unexposed	39.3 (11/28)	1.0	-	-	-

^a = higher score represents better performance^b = lower score represents better performance^c = adjusted for education^d = adjusted for education and gender^e = clinical cut off score = 24^f = clinical cut off score = 50^{*} = adjusted analyses were not performed