J Autism Dev Disord (2012) 42:2323–2334
DOI 10.1007/s10803-012-1468-1

ORIGINAL PAPER

Parental Occupational Exposures and Autism Spectrum Disorder

Erin C. McCanlies · Desta Fekedulegn · Anna Mnatsakanova · Cecil M. Burchfiel · Wayne T. Sanderson · Luenda E. Charles · Irva Hertz-Picciotto

Published online: 8 March 2012

Abstract Both self-report and industrial hygienist (IH) assessed parental occupational information were used in this pilot study in which 174 families (93 children with ASD and 81 unaffected children) enrolled in the Childhood Autism Risks from Genetics and Environment study participated. IH results indicated exposures to lacquer, varnish, and xylene occurred more often in the parents of children with ASD compared to the parents of unaffected children. Parents of children with ASD were more likely to report exposures to asphalt and solvents compared to parents of unaffected children. This study was limited by the small sample size, but results suggest that workplace exposures to some chemicals may be important in the etiology of ASD and deserve further investigation.

Keywords Autism · Autism spectrum disorder · Parental exposures · Parent · Occupation · Exposure

The findings and conclusions in this report are those of the author(s) and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

E. C. McCanlies (✉) · D. Fekedulegn · A. Mnatsakanova · C. M. Burchfiel · L. E. Charles
National Institute for Occupational Safety and Health, MS: L4050, 1095 Willowdale Rd., Morgantown, WV 26505, USA
e-mail: Eim4@cdc.gov

W. T. Sanderson
College of Public Health, The University of Kentucky, 121 Washington Avenue, Room 213B, Lexington, KY 40536, USA

I. Hertz-Picciotto
University of California, Davis, One Shields Ave, MS 1C, Davis, CA 95616, USA

Introduction

Autism spectrum disorder (ASD) is a group of developmental conditions of neuropathologic origin that include full syndrome autism, Asperger's syndrome, and pervasive developmental disorder—not otherwise specified (PDD-NOS) (Klin et al. 2002; Szatmari 2003). In the last few decades, clinical characterization has greatly expanded our understanding of ASDs; however, the etiology is still elusive.

Research into the neuropathology of ASD has found a number of brain abnormalities. These include abnormal brain growth as measured by unusually large head circumference as well as neuroanatomical abnormalities such as a reduced number of Purkinje neurons, the presence of molecular defects, and abnormal gray and white matter volume (Courchesne 2004; Courchesne et al. 2004; Pardo and Eberhart 2007). While some neuropathology may be a consequence of germline genetic mutations, they may also be the result of environmental or parental occupational exposures, which have been shown to be associated with adverse pregnancy outcomes and other neurodevelopmental conditions in children (Grandjean and Landrigan 2006; Laslo-Baker et al. 2004; Logman et al. 2005; Perera et al. 1999).

Human and animal research demonstrates that, due to the size and speed with which cellular structures are growing and forming during development, the fetus and neonate are exquisitely more sensitive to toxicants compared to an adult (Grandjean and Landrigan 2006; Perera et al. 1999). It is this sensitivity that may put the fetus or neonate at risk of aberrant developmental conditions, some of which are lifelong, as a result of toxicant exposure. Spontaneous abortion, neurologic and physical malformation, and central nervous system disturbances have all been reported to be associated with occupational exposures

(Bove et al. 1995; Hooiveld et al. 2006; Irgens et al. 1998; Laslo-Baker et al. 2004; Logman et al. 2005; McMartin et al. 1998; Roman et al. 1996; Xu et al. 1998). Environmental, chemical, and physical agents may influence the processes of immune, endocrine, or neuro-development, thereby increasing risk of chronic, metabolic, immunologic, or other diseases (Dietert and Dietert 2008; Hertz-Picciotto et al. 2008; Pessah et al. 2008; Doumouchtsis et al. 2009). Notably, recent research on ASDs suggests immunologic and metabolic perturbations in autism (Dietert and Dietert 2008; Hertz-Picciotto et al. 2008; Wiest et al. 2009), although etiologic significance remains to be clarified.

Evidence has already accumulated that some non-inherited factors, encompassing obstetric conditions, environmental pollutants, and exposure to neurotoxins are associated with ASD (Glasson et al. 2004; Larsson et al. 2005; Moore et al. 2000; Newschaffer et al. 2007; Roberts et al. 2007; Stromland et al. 1994; Windham et al. 2006; Volk et al. 2011). Earlier studies also suggested that parental occupational exposure to chemicals may be associated with autism (Wiedel and Coleman 1976; Felicetti 1981; Gillberg and Coleman 2000; Allred and Wilbur 2002).

In 1976, Wiedel and Coleman conducted a study in which they evaluated a number of demographic, biochemical and psychological factors in 78 children with autism compared to 78 control children from the National Society for Autistic Children. Although an occupational questionnaire was not administered, the preconception history questionnaire indicated that the parents of children with autism were exposed to more chemicals during the child's preconception period compared to the parents of the control children. In 20 families of children with autism, the parents reported some type of chemical exposure. In four, both the mother and father reported exposure while working as chemists. Only one of the control families reported exposure to chemicals. In this case, both the mother and father reported working as chemists. Further inquiry did not elicit a particular type of chemical to which the parents were exposed.

Felicetti (1981), following up on the work conducted by Wiedel and Coleman (1976), also found that occupational exposure to chemicals might be associated with autism. He evaluated occupational exposures in the parents of 20 children with autism, 20 children diagnosed as developmentally delayed, and 20 control children. Parents were asked to complete a questionnaire about their occupations. The children were then matched based on sex, age, and parental occupational class. The authors found that, of 37 respondent parents, eight of the parents who had a child with autism (21%) reported occupational exposure to chemicals compared to only 2.7% of the parents with a child who was developmentally delayed, and 10% of the parents of control children (Felicetti 1981). Five of the eight parents who reported chemical exposure were chemists and the remaining three were said to "work in related fields." Information on the specific types of chemicals was not obtained, however this early research suggests that occupational exposures could be relevant in the etiology of ASD. In the three decades since these earlier reports, little research has been conducted to confirm or extend these findings. The aim of this pilot study was to evaluate whether parental occupational exposures may be associated with ASD.

Methods

Participants

The study population from which our sample was selected has been previously described (Hertz-Picciotto et al. 2006). Our study sample consists of 249 children, born between 1998 and 2003, and their parents sampled from those enrolled in the Childhood Autism Risk from Genetics and the Environment (CHARGE) study. Briefly, CHARGE enrolls children with a previous designation of autism as well as children from the general population, selected from State Vital Statistics files on births in the relevant time period, regardless of their developmental status. To enhance efficiency for controlling confounders, CHARGE used frequency matching by strata based on the projected distributions of age, sex, and broad geographic region of the ASD children. Although the CHARGE study enrolled children with mental retardation/developmental delay, we did not include this group in these pilot analyses.

In all diagnostic groups, children were eligible for CHARGE if they met the following criteria: (a) between the ages of 24–60 months, (b) living with at least one biologic parent, (c) having a parent who speaks either English or Spanish, (d) born and living in California, and (e) living in the study's designated catchment area, within approximately 1.5 h drive to the study clinic. Participants were asked to complete several questionnaires as well as a telephone interview about exposures during 3 months prior to pregnancy, during the pregnancy, up through birth or up to either birth or weaning if the child was breastfed. Each child underwent cognitive, social, and medical evaluations at either the UC Davis MIND (Medical Investigation of Neurodevelopmental Disorders) Institute clinic in Sacramento, CA or the University of California, Los Angeles (UCLA) Neuropsychiatric Institute. All participants completed the same protocol, with the exception that only those children who entered the study with a prior diagnosis of autism, or who entered without such diagnosis but screened

positive on the Social Communication Questionnaire (SCQ), were assessed on the Autism Diagnostic Interview-Revised (ADI-R) and the Autism Diagnostic Observation Schedules (ADOS) (Lord et al. 1994, 2000). Both of these instruments have been established for research purposes as providing reliable and valid assessments for the diagnosis of ASD (American Psychiatric Association 2000).

Cognitive and adaptive development was assessed for all children using standardized instruments (Mullen 1995; Sparrow et al. 1984). Population (birth certificate) controls without ASD who scored no lower than 2 standard deviations below the mean for both cognitive development and adaptive function were considered to have typical development (TD) (Hertz-Picciotto et al. 2006). All instruments were administered by trained psychometric clinicians with established reliability.

A diagnosis of autism (AU) was defined as meeting criteria on the communication, social, and repetitive behavior domains of the ADI-R and scoring at or above the cutoff for autistic disorder on the ADOS (module 1, 2 or 3). Children classified with ASD were those who did not meet full criteria for AU on either or both of the ADI-R and ADOS, but did meet criteria on either the communication or the social interaction domain of the ADI-R prior to 36 months, were within two points of the cut-off on the other domain, and were above the social and communication cutoff for ASD on the ADOS module 1, 2, or 3. The AU and ASD groups are combined for analyses and are referred to as ASD in this manuscript.

For both parents, basic demographic information was collected by interview or obtained from birth records, and included information on their age, level of education, race/ethnicity, as well as mother's birth place, regional center/geographic location of residence at child's birth, and payment method for the delivery of the child. Information collected about the children included the child's age, gender, date of birth, race/ethnicity, and duration of breastfeeding.

Occupational Exposure Data

Occupational exposures were estimated using two approaches. The first was through self-reported data collected during a structured interview. The second was estimated qualitatively by a panel of three experienced industrial hygienists based on a job history. Each will be described.

Self-reported Exposure

Occupational history and potential exposures for each parent were collected via phone interview. Parental occupational information and potential exposure data were collected for the time period that began 3 months prior to the pregnancy with the child and continued to either the birth of the child, or until weaning if the child was breast fed. Henceforth, this time period will be referred to as the index period. For most of the analyses, we focused on exposures reported to have occurred during this index period. For the sensitivity analyses we evaluated the pregnancy period which was measured from the 1st month of pregnancy to the 9th month of pregnancy. Occupational information included the place of employment, month and year each position started and ended, which month(s) of pregnancy the job was held, and hours per week worked at each job. Information about what the company made or did, the parents' job title, and his or her duties/responsibilities was also collected. Mothers were interviewed about their job histories, and whenever possible, the father was interviewed about his job history. Each parent was able to report information on all jobs during this period. The parents were also asked about exposures at their workplace or school during the index period from a list of specific substances and conditions (Table 3). For each item, there were four possible responses: yes, no, refused, and don't know.

Industrial-Hygienist Evaluation

The three industrial hygienists (IH) selected for this study have over 70 years of combined experience conducting occupational exposure evaluations for research studies, health hazard evaluations, and technical consulting. They have conducted exposure evaluations in a wide variety of industries; however, they supplemented their knowledge with literature searches on occupational exposures based on a list of 49 agents supplied by the principal investigator (Table 2). These agents were chosen to be evaluated based on literature indicating they are considered hazardous. All are suspected, or have been found, to be associated with adverse pregnancy outcomes, neurologic or physical malformation, or central nervous system disturbances (Bove et al. 1995; Hooiveld et al. 2006; Irgens et al. 1998; Laslo-Baker et al. 2004; Logman et al. 2005; McMartin et al. 1998; National Institute for Occupational Safety and Health (NIOSH) 2001; Roman et al. 1996; Xu et al. 1998). As few exposures have been examined in relation to ASDs, the list of agents is broad, comprising substances with toxic properties that were considered of potential relevance to the as-yet unknown mechanisms leading to ASD.

None of the IHs were provided with the parents' responses on exposures to specific agents. Instead they were provided an Excel database with the job history data collected during the phone interview, as described above, covering all jobs for both parents, and including the tasks, responsibilities, and industry for the index period. Using

this information, the three industrial hygienists independently assigned a qualitatively defined ordinal exposure level estimate to the selected chemical and physical agents for every job in the database. They were blinded to the children's case status (ASD or TD). They were also blinded to the codes entered by the other industrial hygienists.

In order to estimate the exposure levels of the jobs in the database, the IHs collected information from the literature on the uses of the selected agents in industry and the types of jobs that were likely to have those exposures. The principal sources for this information were provided by the Occupational Safety and Health Administration (OSHA), NIOSH, and the Agency for Toxic Substances and Disease Registry (ATSDR). This information was assembled into notebooks which were frequently referred to by the IHs. As they estimated the exposures of the parent's jobs, they also collected literature on the exposures associated with some specific jobs—particularly those jobs with which they were less familiar—and included this information in the notebooks.

Based on the information provided in the database on the industry and job title, a code of 0 (none), 1 (low), 2 (moderate), or 3 (high) was entered to estimate the level of exposure to each of the selected agents. These codes represented, in an ordinal scale from least to greatest, the relative concentration or amount of exposure to these agents, as well as the relative frequency with which workers in those jobs would encounter the agents.

After the IHs had independently estimated exposure levels for all the selected agents, they compared their estimates. The jobs for which one or more exposure estimates differed among the IHs were then compared. The IH team discussed the differences in exposure entries, and came to consensus on the estimated exposure levels and occupational groups. The consensus dataset was then sent back to NIOSH for data analyses.

Statistical Analysis

As described above, the IHs independently assessed likelihood of occupational exposure to 49 agents. Because the prevalence of parental exposures in the moderate and high exposure categories were so few, the levels of exposure reported by the IHs were dichotomized into yes/no groups (low, moderate, or high vs. no exposure) for all exposures. Similarly, the self-reported exposure data contained 14 agents that were categorized into exposed/not exposed groups. The frequency of each exposure was calculated for both self-reported and IH assessed exposures stratified by disease status.

The outcome was a binary variable with two categories, ASD and TD. Due to a small number of exposed subjects for each group, exposure data for mothers and fathers were combined for each agent (i.e. 'exposed' if either mom or dad, or both were exposed; 'not exposed' if neither mom nor dad were exposed). To assess the associations of each of the exposures with ASD, odds ratios and 95% confidence intervals were calculated using logistic regression models. Analyses were done separately for the self-report data and the IH data. All p values were corrected using the false discovery rate (FDR) method and adjusted (corrected) p values are denoted in the results section as p_c.

Eleven covariates were initially considered (Table 1). Some were eliminated because they were not independently associated with the outcome, or because multicollinearity with other covariates was observed. Logistic regression models were then used to evaluate if ASD was associated with parental occupational exposures controlling for covariates not eliminated in earlier steps. Based on a series of models, beginning with an unadjusted model, we found that the addition of duration of breast-feeding, mother's age, mother's education, regional center, child's gender, child's age, and payment method appreciably altered some ORs. Final results were based on adjustment for those factors, as the remaining covariates (fathers' age, education, race, and child's race) did not appreciably alter the ORs.

Because we evaluated jobs through the end of breast-feeding, those children who were breastfed had a potentially longer period during which their parents might have held a job with exposures of interest. We therefore conducted analysis of variance to determine if the duration of breast-feeding differed for children with ASD compared to the children with TD. We also conducted a sensitivity analysis limited to only those exposures occurring during the pregnancy. This could only be done for the self-report data not the IH data, because the IHs did not have months of pregnancy information. They only had work history information for the index period.

All statistical analyses were performed using SAS/STAT software, version 9.2 for Windows.

Results

Of the 249 children for whom we received data, diagnosis was unavailable for 21 children and 54 children received a diagnosis other than ASD or TD. Therefore, these 75 children were excluded from further analyses, leaving 174 children of whom 93 met the criteria for a diagnosis of ASD and 81 met the criteria for TD controls.

Comparison of duration of breastfeeding found that on average, the children with TD were breast fed for 9.9 months and the children with ASD on average 8.8 months. This difference was not statistically significant ($p = 0.43$), indicating similar follow-up periods during

Table 1 Demographic characteristics of the CHARGE participants stratified by ASD and TD

Characteristics	ASD		TD	
	N	Mean ± SD (%)	N	Mean ± SD (%)
Mother's age at time of child's birth (years)	93	31.8 ± 5.6	81	31.2 ± 5.6
Father's age at time of child's birth(years)	89	34.7 ± 6.7	80	33.8 ± 7.0
Duration of breast-feeding (months)	83	8.8 ± 7.3	76	9.9 ± 9.9
Child's age at assessment (years)	93	3.2 ± 0.8	81	3.0 ± 0.7*
Mother's education				
Less than high school	4	4.30	3	3.70
High school/GED	11	11.83	13	16.05
Some college	42	45.16	24	29.63
Bachelor degree	17	18.28	29	35.80
Graduate degree	19	20.43	12	14.81
Father's education				
Less than high school	10	10.75	6	7.41
High school/GED	15	16.13	16	19.75
Some college	28	30.11	28	34.57
Bachelor degree	26	27.96	21	25.93
Graduate degree	14	15.05	10	12.35
Mother's race/ethnicity				
White	56	60.22	47	58.02
Black	5	5.38	3	3.70
Asian	5	5.38	2	2.47
White Hispanic	22	23.66	23	28.40
Other[a]	5	5.4	6	7.4
Father's race/ethnicity				
White	56	60.22	47	58.02
Black	6	6.45	3	3.70
Asian	6	6.45	2	2.47
White hispanic	20	21.51	24	29.63
Other[a]	5	5.4	5	6.2
Payment method				
Government program	13	13.98	10	12.35
Insurance	80	86.02	71	87.65
Race/ethnicity—child				
White	50	53.76	35	43.21
Asian and Asian/White	29	31.18	34	41.98
Black and Black/White	6	6.45	4	4.94
Hispanic any race	7	7.53	5	6.17
Mixed and other[a]	1	1.08	3	3.70
Sex of child				
Male	82	88.17	61	75.31*
Female	11	11.83	20	24.69

* $p < 0.05$

[a] Other is composed of American Indian, Non-white Hispanic, and Multi-racial

which exposure may have been relevant. However, because this difference of 1 month could be biologically relevant, particularly in infants, we controlled for length of breast-feeding in the analyses.

Of the 174 eligible children, 172 had at least one parent who was employed during the index period. Of the 172, 79.7% of the mothers and 95.4% of the fathers reported working during the index period. Of the mothers, 68.6% reported working one job during the index period, 7.6% reported working two different jobs, and 3.5% reported working 3 jobs. Of the fathers, 74.4% reported working one job during the index period, 15.7% reported working two jobs, 3.5% worked three jobs, and 0.6% worked four jobs during the index period. For those parents working more

than one job, they were not necessarily simultaneous; rather, most were in series during the index period.

With the exception of the child's age at assessment and child's gender, there were no significant differences in demographic characteristics between the families with a child with ASD compared to the families with a child with TD (Table 1). Most of the parents attended at least some college (84.0% ASD; 80.2% TD). The majority of the participating families were either White non-Hispanic (60.2% ASD; 58.0% TD) or White-Hispanic (21.5% ASD; 29.6% TD). Insurance was the most common method of payment (86.0% ASD; 87.7% TD).

The three most common exposures the IHs reported in parents of ASD cases were toluene (30.4%), metal (30.4%), and nickel (30.4%) (Table 2). These were followed closely by exposure to chromium (29.4%), iron (28.3%), and aluminum (27.2%). Many of the IH assessed exposures were reported to occur in approximately 10–25% of the parents with a child with ASD. These included exposures such as paints (19.6%), disinfectants (12.0%), auto fluids (12.0%), and kerosene (9.8%). The least common exposures were carbon disulfide (1.1%) and perchlorate (1.1%). These percents differed for the parents of children with TD.

Among parents of children with TD, the top two most common IH assessed exposures were metals (32.5%) and aluminum (30.0%) (Table 2). The frequency of the metals iron, nickel, and chromium were the third most common exposures (28.8%). These were followed closely by manganese (26.3%), lead (25.0%), and toluene (23.8%). Neither carbon tetrachloride nor perchlorate was present in the parents of children with TD.

Table 3 presents the prevalence rates of exposure to the 14 agents assessed by the CHARGE questionnaire for both the index and pregnancy only periods. Parents of children with ASD most commonly reported being exposed to disinfectants (42.5%). Between 25 and 30% of parents reported exposure to cutting, cooling, or lubricating oil, solvents, and paint. Exposure to anesthetic gases and ethylene oxide were the least likely to be reported (~5%). These rates were similar to those observed during the pregnancy only period as well.

For parents of children with TD, during the index period disinfectants (37.2%), metal dust or fumes (25.6%), and heat (23.1%) were the three most commonly reported exposures (Table 3). Paint, lacquer, or varnish exposure (21.8%) and cutting, cooling, or lubricating oils (15.4%) were the next most commonly self-reported among parents with a child with TD. The least common exposures were ethylene oxide (1.3%)nd PCBs (3.9%). When we restricted to the pregnancy only, prevalence rates of self-reported exposures were very similar for most exposures, though often lower in both cases and controls.

Table 2 Prevalence of IH reported exposures in the parents of children with and without ASD

Agent	ASD (N = 92)		TD(N = 80)	
	N	%	N	%
1. Disinfectants	11	12.0	15	18.8
2. Paints	18	19.6	11	13.8
3. Lacquers	15	16.3	4	5.0
4. Varnish	12	13.0	4	5.0
5. Paint thinner	14	15.2	9	11.3
Solvents[a]				
6. Auto fluids	11	12.0	8	10.0
7. Freon	12	13.0	14	17.5
8. Antifreeze	12	13.0	11	13.8
9. Gasoline	13	14.1	9	11.3
10. Kerosene	9	9.8	7	8.8
11. Degreasers	16	17.4	15	18.8
12. Brake fluid	10	10.9	9	11.3
13. Lubricating oils	17	18.5	12	15.0
14. Cutting oils	7	7.6	8	10.0
15. Toluene	28	30.4	19	23.8
16. Carbon disulfide	1	1.1	2	2.5
17. Xylene	25	27.2	13	16.3
18. Benzene	18	19.6	15	18.8
19. Phenol	5	5.4	2	2.5
20. Styrene	6	6.5	2	2.5
21. Perchlorate	1	1.1	0	0.0
22. Trichlorethylene	22	23.9	18	22.5
23. Glycolethers	21	22.8	18	22.5
24. Phthlates	15	16.3	9	11.3
25. Plastics	4	4.4	5	6.3
26. PCBs	2	2.2	3	3.8
27. Carbontetrachloride	3	3.3	0	0.0
28. **Metals**[b]	28	30.4	26	32.5
29. Aluminum	25	27.2	24	30.0
30. Lead	21	22.8	20	25.0
31. Iron	26	28.3	23	28.8
32. Nickel	28	30.4	23	28.8
33. Chromium	27	29.4	23	28.8
34. Mercury	11	12.0	11	13.8
35. Manganese	24	26.1	21	26.3
36. Arsenic	3	3.3	3	3.8
37. Cadmium	15	16.3	16	20.0
38. Metal Fume	22	23.9	19	23.8
39. **Pesticides**[b]	4	4.4	5	6.3
40. Herbicides	3	3.3	5	6.3
41. Insecticides	5	5.4	5	6.3
42. Fungicides	4	4.4	4	5.0
43. Rodenticides	2	2.2	3	3.8
44. X-rays	9	9.8	9	11.3
45. Radiation	9	9.8	10	12.5

Table 2 continued

Agent	ASD (N = 92)		TD(N = 80)	
	N	%	N	%
46. Anesthetic gas	5	5.4	8	10.0
47. Ethylene oxide	8	8.7	10	12.5
48. Pharmaceuticals	8	8.7	9	11.3
49. Hormones	4	4.4	4	5.0

[a] Solvents is a group composed of all the indented chemicals

[b] The agents in bold represent general classes of agents—metals and pesticides—and are used to reflect potential exposures to any other metals and agrichemicals not specifically listed

Figures one and two are the plots of the odds ratios and 95% confidence intervals for each exposure from the logistic regression models. Virtually none of the IH-reported agents or self-reported exposures were significantly associated with ASD. However, there are a few findings worth mentioning. Among the IH reported agents, the OR associated with lacquer exposure was 7.3 (95% CI = 1.6, 33.5; $p = 0.01$; $p_c = 0.47$) for ASD compared to TD. For varnish, these figures were OR = 4.7 (95% CI = 1.0, 22.0; $p = 0.05$; $p_c = 0.76$) for ASD compared to TD; and for xylene, OR = 2.7 (95% CI = 1.1, 6.7; $p = 0.03$; $p_c = 0.62$) (Fig. 1). These agents are most similar to the self-report agents of paint and solvents. The OR associated with self-reported paint exposure was 2.0 (95% CI = 0.8, 5.1; $p = 0.12$; $p_c = 0.58$) for ASD compared to TD and for solvents, the OR was 3.1 (95% CI = 1.3, 7.7; $p = 0.01$; $p_c = 0.1$) for the ASD compared to TD (Fig. 2).

Similar to the IH assessed exposures, there were few self-reported exposures that were associated with ASD (Fig. 2). Besides solvents, described above, the parents of the children with ASD were more likely to self-report asphalt exposure (OR = 6.9; 95% CI = 1.5, 32.4; $p = 0.01$; $p_c = 0.1$) than the parents of TD children. There are no IH assessed agents comparable to asphalt. Both solvents and asphalt remained significant when the pregnancy period was evaluated. Similar to the index period there were no other exposures that occurred more often in the parents of children with ASD compared to the parents of children with TD. In fact, the odds ratios for the pregnancy only period were not significantly different than the odds ratios for the index period, therefore only the odds ratios for the IH and self-report data during the index period are shown.

Notably, although the OR's for these compounds are all equal to or greater than 2.0, the confidence intervals are quite wide, indicating inherent uncertainty related to our relatively small sample size and low prevalence rates for some of the exposures. Furthermore, after correcting the p values (p_c), none of the associations remained significant.

Discussion

The objective of this study was to conduct exploratory analyses of parental occupational exposures in relation to ASD, and thereby generate hypotheses worth pursuing in larger samples. The results indicate that for several

Table 3 Prevalence of self-reported exposures in parents of children with and without ASD during the index and pregnancy only periods

Agent	Total N	Index Period				Total N	Pregnancy Period			
		ASD		TD			ASD		TD	
		N	%	N	%		N	%	N	%
1. Anesthetic gases	164	4	4.7	7	9.0	164	4	4.7	7	9.0
2. Asphalt	163	13	15.1	3	3.9	161	9	10.7	2	2.6
3. Cutting, cooling or lubricating oils	165	22	25.3	12	15.4	165	22	25.3	12	15.4
4. Disinfectants	165	37	42.5	29	37.2	162	29	34.5	27	34.6
5. Ethylene oxide	161	4	4.8	1	1.3	160	3	3.6	1	1.3
6. Heat (>100°F or 38°C)	165	21	24.1	18	23.1	163	17	20.0	13	16.7
7. Cold (<32°F or 0°C)	165	5	5.8	5	6.4	164	4	4.7	5	6.4
8. Lead, mercury, nickel, chromium	162	12	14.3	8	10.3	162	12	14.3	7	9.0
9. Metal dust or fumes	165	20	23.0	20	25.6	165	19	21.8	17	21.8
10. Paint, lacquer, or varnishes	164	26	30.2	17	21.8	162	22	25.9	13	16.9
11. PCB's	163	5	5.8	3	3.9	163	4	4.7	3	3.90
12. Pesticides, herbicides, fungicides, insecticides, rat poison	164	12	13.8	7	9.1	162	9	10.6	5	6.5
13. X-ray or radioactive material	164	8	9.3	6	7.7	161	5	6.0	5	6.5
14. Solvents e.g. paint, thinners, auto fluid, toluene, carbon disulphide, carbon tetrachloride	166	26	29.6	13	16.7	166	26	29.6	12	15.4

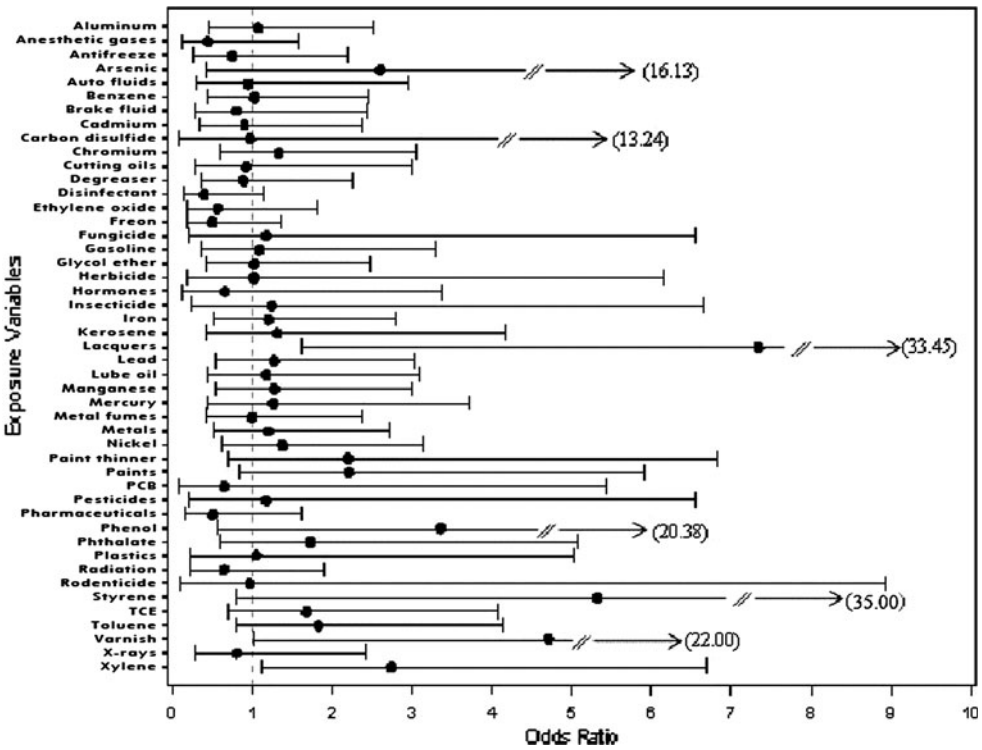

Fig. 1 Forest Plot of the adjusted odds ratios and corresponding 95% confidence intervals (CI) for the association between ASD and parental occupational exposure assessed by the IHs during the index period (*dot* shows the point estimate, the *solid line* extends from the lower limit to the upper limit of the CI). Odds ratios are adjusted for duration of breast-feeding, mother's age, mother's education, regional center, child's gender, child's age, and payment method

compounds or classes of exposures, further research may be warranted to investigate an etiologic role in ASD. IH assessment identified potential exposure to lacquers, varnish, and xylene as possible risk factors. Among parental self-reported exposures, asphalt and solvents stood out. Both the IH and self-report exposures fall into the broader category of solvents or solvent-containing products.

Solvents are a diverse class of chemicals and can be found in a variety of products from asphalt and paint to petroleum products such as gas, lube oil and degreasers (Key et al. 1977). Furthermore, because of their diversity and usage patterns, an individual who works with solvents is often exposed to more than one type. Solvent exposure in non-ASD populations has been found to be associated independently and adversely with attention deficits, hyperactivity, behavioral and developmental abnormalities, and motor function abnormalities (Hooiveld et al. 2006; Laslo-Baker et al. 2004; Logman et al. 2005); these manifestations are also frequently observed in children with ASD (Gillberg and Coleman 2000). Consistent with these results, solvents were identified as a potential risk factor for ASD in two recent studies, one conducted by Windham et al. (2006) and another by Kalkbrenner et al. (2010). Windham et al. (2006) evaluated model-based estimated levels of hazardous air pollutants using the United States Environmental Protection Agencies hazardous air pollutants (HAPS) database in relation to ASD in 264 children with ASD and 657 children without ASD. She reported that although the relationship was attenuated when the presence of metals was taken into account, levels of chlorinated solvents estimated to be in the air near the maternal residence on the birth certificate about 2 years after the birth of the study child were associated with ASD (Windham et al. 2006).

Kalkbrenner et al. (2010) also evaluated if exposures to 35 HAPS from the 1996 National Air Toxics Assessment (NATA) program were associated with ASD in 383 children with ASD compared to 2,829 children with speech and language impairment. All the children were identified from the Autism and Developmental Disabilities Monitoring Network in North Carolina (born in 1994 and 1996) and West Virginia (born in 1992 and 1994) and had to reside in the surveillance region at their time of their birth. She reported that elevated levels of the solvents quinolone, styrene and methylene chloride were associated with higher odds of ASD.

In contrast to numerous publications using an ecologic analysis, the Windham et al. (2006) study was one of the first studies to link individual-level data on autism diagnoses with estimated ambient exposures to environmental toxicants. Our analysis also used individual-level data and focused on an earlier time period, namely pre-conception, prenatal, and postnatal periods ending, on average, at about 9–10 months of age.

Besides solvents, pesticides have also been evaluated in relation to ASD. Roberts et al. (2007) investigated the risk of ASD in the children of mothers who were exposed to agricultural pesticide application (Roberts et al. 2007). Children reported by the California Department of

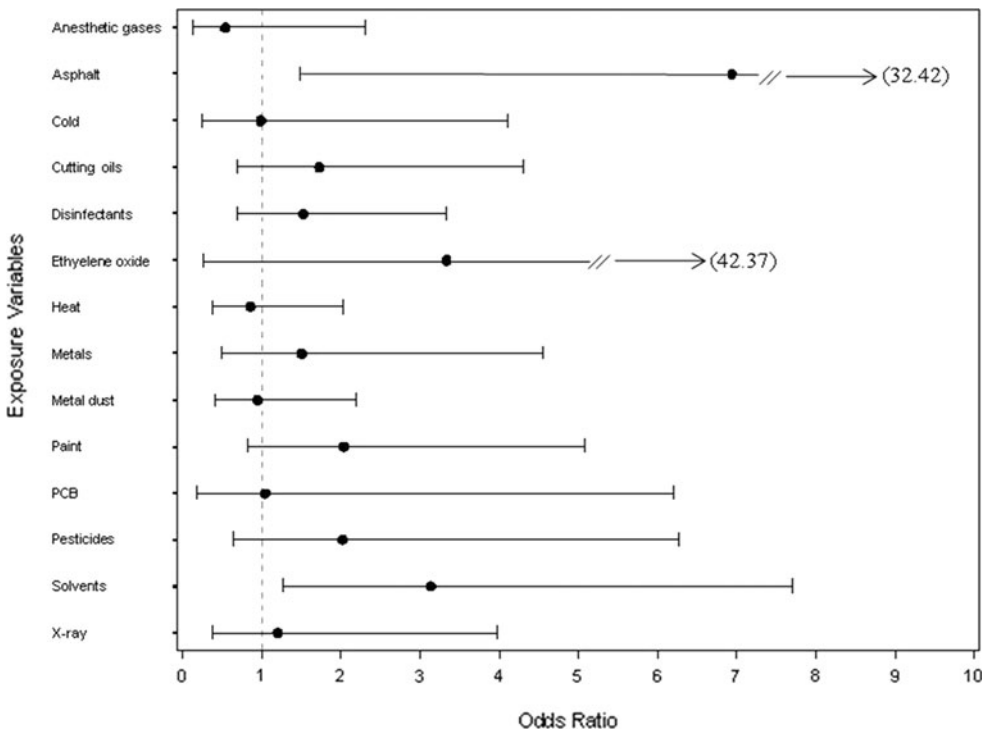

Fig. 2 Forest Plot of the adjusted odds ratios and corresponding 95% confidence intervals (CI) for the association between ASD and self-reported parental occupational exposure during the index period (*dot* shows the point estimate, the *solid line* extends from the lower limit to the upper limit of the CI). Odds ratios were adjusted for duration of breast-feeding, mother's age, mother's education, regional center, child's gender, child's age, and payment method

Developmental Services to qualify for services for autism or any child with an ASD diagnostic code from the DSM-IV were included in the study. The authors found that exposure to two pesticides—difocol and endosulfan—during the first 8 weeks of pregnancy was associated with a six-fold increased risk of ASD. The risk was also seen to increase with increasing poundage of pesticides applied, and to decrease with increasing distance from the site of application, implying a dose response relationship. Unlike Roberts, we did not see an association between ASD and parental occupational exposure to pesticides, herbicides, insecticides, and fungicides, nor did parents of children with ASD report increased levels of exposure to pesticides. However, we had no data on specific active ingredients or formulations, while Roberts and colleagues obtained information on the individual chemical compounds being applied and saw no significant associations with many of the pesticide formulations investigated (Roberts et al. 2007). Given the specificity of the Roberts' findings, and the lack of specificity with regard to individual pesticide chemical classes in our data on occupational exposures, there may be no real discrepancy.

Other than solvents and pesticides as previously mentioned, the study conducted by Felicetti (1981), following up on work conducted by Wiedel and Coleman (1976) indicated that occupational exposure to chemicals might be associated with autism. However, little information was given about the methods used to collect or analyze the data, making it extremely difficult to determine the validity of their findings (Felicetti 1981; Allred and Wilbur 2002).

Our study has both limitations and strengths. It was limited by the small sample size given the large number of exposures evaluated and the low prevalence of some of the exposures. Nevertheless, as one of the first studies in several decades to systematically evaluate parental job exposures and risk of ASD, this evaluation of several dozen potentially biologically relevant occupational agents provides a first pass screen from which results can be used to target future research directions. Due to the small number of exposed subjects for each group, exposures for mothers and fathers were combined. Combining parental exposures may be justified if the main route for the paternal exposure is via take-home exposures. Given that this was a pilot study, combining exposures into one variable increased the prevalence of exposure and allowed for the evaluation of occupational exposures that might occur through direct maternal contact as well as via take-home exposures of the father from contaminated clothing, body surfaces, and work materials.

Obtaining accurate exposure data is always a challenge. Here exposure data were collected using two methods, self-reported exposures and IH-assessments based on job title, task, and responsibility information. Research indicates that there are both strengths and limitations associated with self-report and industrial hygiene exposure data (Teschke et al. 2002). For example, agreement between IH data and self-report data can be highly variable. Sensitivity and

specificity have also been found to be highly variable when self-report data is compared to quantitative measurements. Recall bias may also be a potential concern with self-report data. The recall period in our population ranged from 3 to 6.6 years going back 3 months prior to conception. Because the children had already been diagnosed with ASD when the parents were asked about occupational exposures, the parents of children with ASD may have been more likely to report occupational exposures compared to the parents of children with TD, biasing the results away from the null. Under a 'universal null' hypothesis and no reporting bias, we might have expected a higher proportion of control than case parents to report about half of the exposures; in this study, very few exposures (two out of 14) were reported by a higher proportion of parents of children with TD, suggesting such bias may have been present. On the other hand, it is also possible that some of the exposures are truly associated with risk for ASD. Additionally, research indicates that there is usually little difference in the reliability and validity of exposure assessments between cases and controls, although cases have been found to be better at estimating their exposure (Teschke et al. 2002). Certain methods can also be employed to improve participant recall, and reduce bias. These methods include using common terms when asking about exposures, offering guideposts to increase the participants' accuracy when asking about amount of exposure, and asking about agents that they are able to see, hear, smell, or touch (Teschke et al. 2002). Listing exposures rather than offering open ended questions also improves sensitivity. A number of these methods were employed in this study, including listing specific agents and asking about agents that the participants could see, feel, or smell. This may have increased the likelihood that the participants were able to accurately report their exposure information.

Similar to self-report exposure data, IH exposure data can also be highly variable. Although recall bias does not affect the IH data, factors that affect accurate reporting can include IH familiarity with specific jobs, access to detailed job information, and knowledge about participants' use of personal protective equipment while on the job (Teschke et al. 2002). Research also indicates that the sensitivity of IH data is highly inconsistent. However, the specificity is often found to be highly stable. The combination of an inconsistent sensitivity, but a stable specificity results in the likelihood of lower misclassification bias. Most significantly, if a panel of three or more IHs is used, as was done in this study, expert-assessed occupational exposures have been found to be both valid and reliable (Fritschi et al. 2003; Siemiatycki et al. 1997; Stewart and Stewart 1994). One method that further increases the accuracy of IH data is to request estimations for broad classes of chemicals rather than just specific chemicals, which was done in this study. If only job title is available, misclassification errors are a potential source of bias (Benke et al. 2001; Teschke et al. 2002). However, this type of bias can be reduced if sufficient work information is available, such as responsibilities and tasks, another approach taken in the CHARGE Study.

The consistency and accuracy of the case definition and ascertainment procedures are two strengths of this study. Two standardized instruments, the ADI-R and ADOS, were used to diagnose the cases for this study and were administered at either the UC Davis MIND Institute or the UCLA Neuropsychiatric Institute by a small well-trained staff with established reliability, thus, ensuring consistency and accuracy (Hertz-Picciotto et al. 2006). Similarly, ASD symptoms were ruled out in controls using a standardized screening tool (SCQ).

The methods used to identify the participants for this study were designed to reduce selection bias and are a strength of this study. It is estimated that the California Department of Developmental Services (DDS) represents 75–80% of the total population of children in California diagnosed with autism (Croen et al. 2002); by drawing from this sampling frame, this study had a better chance than is typical of clinic-based studies to capture cases that are likely fairly representative of the case population in California. Use of the birth files to identify controls does the same for the control population. The representativeness of the regional centers reduces the chances of selection bias affecting our results, increasing generalizability, even though parents with lower education tend to be underrepresented in all study groups (Hertz-Picciotto et al. 2006).

A potential weakness of this study is that the participation rate for the control population was approximately 27%. Whether occupational exposures are correlated with refusal patterns is difficult to determine, and could depend on the nature of the specific exposure.

Research indicates that the prevalence of ASD has risen over the last few decades (Blaxill 2004). Although some of this trend may be associated with improved and standardized diagnostic criteria, greater awareness, and wider availability of funds for services, to date these factors do not appear to account for all of the increase (Blaxill 2004; Frombonne 2003; Gurney et al. 2003; Hertz-Picciotto 2009; King and Bearman 2009). The remaining causes of this rise are not clear, but because the greatest increase has occurred over the last few decades, it seems unlikely that genetic factors are acting alone; rather genotype probably confers susceptibility that acts in conjunction with an environmental exposure to increase risk of ASD.

Findings of de novo mutations, chromosomal rearrangements, and epigenetic alterations in ASD also support a role of environmental insults, and difference in gene

expression may be one of several pathways by which chemical exposures may alter brain development. Nevertheless, our specific findings should be viewed cautiously until larger studies have been undertaken; moreover, understanding of mechanisms is primitive at this stage. Whereas a number of chemicals did not appear to be associated with ASD, as a pilot study, our null results should also not be construed as definitive.

Although some prior research has evaluated occupational exposures and autism (Wiedel and Coleman 1976; Felicetti 1981; Gillberg and Coleman 2000; Allred and Wilbur 2002), this study improves upon other designs previously used by: confirmation of ASD cases, use of a larger and better characterized sample, evaluation of individual- rather than group-level information on chemical exposures, and the collection of specific detailed exposure and occupational information evaluated by a team of three experienced IH experts.

Overall, these results add to mounting evidence that individual level exposures may be important in the etiology of ASD. However, it must be stressed that these results are preliminary and are not conclusive, and that none were significant after correcting for multiple comparisons. Additional research is required to confirm and extend these initial findings. Further advances can come through studies that employ larger sample sizes, that investigate interactions with genetic factors, and that examine functionally relevant exposures.

Acknowledgments The authors would like to thank the families who participated in the CHARGE research project. It is because of their time and commitment that we were able to conduct this research. The authors would also like to thank Lora Delwiche at the University of California, Davis for her help with data management during this project. Grant sponsor: National Institutes of Health, Grant numbers: 1 P01 ES11269, 1 R01 ES015359, Grant sponsor: U.S. Environmental Protection Agency through the Science to Achieve Results (STAR) program, Grant numbers: R829388, R833292.

References

Allred, M., & Wilbur, S. (2002). Hazardous substance exposures and autism. In C. DeRosa, J. Holler, & M. Mehlman (Eds.), *Advances in modern toxicology* (pp. 453–473). Princeton, NJ: International Toxicology Books, Inc.

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed. Text Revision). Washington, DC: American Psychiatric Association.

Benke, G., Sim, M., Fritschi, L., Aldred, G., Forbes, A., & Kauppinen, T. (2001). Comparison of occupational exposure using three different methods: Hygiene panel, job exposure matrix (JEM), and self reports. *Applied Occupational and Environmental Hygiene, 16*(1), 84–91.

Blaxill, M. F. (2004). What's going on? The question of time trends in autism. *Public Health Reports, 119*, 536–551.

Bove, F. J., Fulcomer, M. C., Klotz, J. B., Esmart, J., Dufficy, E. M., & Savrin, J. E. (1995). Public drinking water contamination and birth outcomes. *American Journal of Epidemiology, 141*(9), 850–862.

Courchesne, E. (2004). Brain development in autism: Early overgrowth followed by premature arrest of growth. *Mental Retardation and Developmental Disabilities Research Reviews, 10*(2), 106–111.

Courchesne, E., Redcay, E., & Kennedy, D. P. (2004). The autistic brain: Birth through adulthood 5. *Current Opinion in Neurology, 17*(4), 489–496.

Croen, L. A., Grether, J. K., & Selvin, S. (2002). Descriptive epidemiology of autism in a California population: who is at risk? *Journal of Autism and Developmental Disorders, 32*(3), 217–224.

Dietert, R. R., & Dietert, J. M. (2008). Potential for early-life immune insult including developmental immunotoxicity in autism and autism spectrum disorders: Focus on critical windows of immune vulnerability. *Journal of Toxicology and Environmental Health. Part B, Critical Reviews, 11*(8), 660–680.

Doumouchtsis, K. K., Doumouchtsis, S. K., Doumouchtsis, E. K., & Perrea, D. N. (2009). The effect of lead intoxication on endocrine functions. *Journal of Endocrinological Investigation, 32*(2), 175–183.

Felicetti, T. (1981). Parents of autistic children: Some notes on a chemical connection. *Milieu therapy, 1*(1), 13–16.

Fritschi, L., Nadon, L., Benke, G., Lakhani, R., Latreille, B., Parent, M. E., et al. (2003). Validation of expert assessment of occupational exposures. *American Journal of Industrial Medicine, 43*(5), 519–522.

Frombonne, E. (2003). The prevalence of autism. *The Journal of the American Medical Association, 289*(1), 87–89.

Gillberg, C., & Coleman, M. (2000). *The biology of the autistic syndromes* (3rd ed.). London: Mac Keith Press.

Glasson, E. J., Bower, C., Petterson, B., de Klerk, N., Chaney, G., & Hallmayer, J. F. (2004). Perinatal factors and the development of autism: A population study. *Archives of General Psychiatry, 61*(6), 618–627.

Grandjean, P., & Landrigan, P. J. (2006). Developmental neurotoxicity of industrial chemicals. *Lancet, 368*(9553), 2167–2178.

Gurney, J. G., Fritz, M. S., Ness, K. K., Sievers, P., Newschaffer, C. J., & Shapiro, E. G. (2003). Analysis of prevalence trends of autism spectrum disorder in Minnesota. *Archives of Pediatrics and Adolescent Medicine, 157*(7), 622–627.

Hertz-Picciotto, I. (2009). Commentary: Diagnostic change and the increased prevalence of autism. *International Journal of Epidemiology, 38*, 1239–1241.

Hertz-Picciotto, I., Croen, L. A., Hansen, R., Jones, C. R., van de Water, J., & Pessah, I. N. (2006). The CHARGE study: An epidemiologic investigation of genetic and environmental factors contributing to autism. *Environmental Health Perspectives, 114*(7), 1119–1125.

Hertz-Picciotto, I., Park, H. Y., Dostal, M., Kocan, A., Trnovec, T., & Sram, R. (2008). Prenatal exposures to persistent and non-persistent organic compounds and effects on immune system development. *Basic & Clinical Pharmacology & Toxicology, 102*(2), 146–154.

Hooiveld, M., Haveman, W., Roskes, K., Bretveld, R., Burstyn, I., & Roeleveld, N. (2006). Adverse reproductive outcomes among male painters with occupational exposure to organic solvents. *Occupational and Environmental Medicine, 63*(8), 538–544.

Irgens, A., Kruger, K., Skorve, A. H., & Irgens, L. M. (1998). Reproductive outcome in offspring of parents occupationally exposed to lead in Norway. *American Journal of Industrial Medicine, 34*(5), 431–437.

Kalkbrenner, A. E., Daniels, J. L., Chen, J., Poole, C., Emch, M., & Morrissey, J. (2010). Perinatal exposure to hazardous air pollutants and autism spectrum disorders at age 8. *Epidemiology, 21*(5), 631–641.

Key, M. M., Henschel, A. F., Butler, J., Ligo, R. N., & Tabershaw, I. R. (Eds.). (1977). *Occupational diseases. A guide to their recognition*. Washington, DC: DHEW (NIOSH).

King, M., & Bearman, P. (2009). Diagnostic change and the increased prevalence of autism. *International Journal of Epidemiology, 38*, 1224–1234.

Klin, A., Jones, W., Schultz, R., Volkmar, F., & Cohen, D. (2002). Defining and quantifying the social phenotype in autism. *American Journal of Psychiatry, 159*(6), 895–908.

Larsson, H. J., Eaton, W. W., Madsen, K. M., Vestergaard, M., Olesen, A. V., Agerbo, E., et al. (2005). Risk factors for autism: Perinatal factors, parental psychiatric history, and socioeconomic status. *American Journal of Epidemiology, 161*(10), 916–925.

Laslo-Baker, D., Barrera, M., Knittel-Keren, D., Kozer, E., Wolpin, J., Khattak, S., et al. (2004). Child neurodevelopmental outcome and maternal occupational exposure to solvents. *Archives of Pediatrics and Adolescent Medicine, 158*(10), 956–961.

Logman, J. F., de Vries, L. E., Hemels, M. E., Khattak, S., & Einarson, T. R. (2005). Paternal organic solvent exposure and adverse pregnancy outcomes: A meta-analysis. *American Journal of Industrial Medicine, 47*(1), 37–44.

Lord, C., Risi, S., Lambrecht, L., Cook, E. H, Jr, Leventhal, B. L., DiLavore, P. C., et al. (2000). The autism diagnostic observation schedule-generic: A standard measure of social and communication deficits associated with the spectrum of autism. *Journal of Autism and Developmental Disorders, 30*(3), 205–223.

Lord, C., Rutter, M., & Le Couteur, A. (1994). Autism diagnostic interview-revised: A revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *Journal of Autism and Developmental Disorders, 24*(5), 659–685.

McMartin, K. I., Chu, M., Kopecky, E., Einarson, T. R., & Koren, G. (1998). Pregnancy outcome following maternal organic solvent exposure: A meta-analysis of epidemiologic studies. *American Journal of Industrial Medicine, 34*(3), 288–292.

Moore, S. J., Turnpenny, P., Quinn, A., Glover, S., Lloyd, D. J., Montgomery, T., et al. (2000). A clinical study of 57 children with fetal anticonvulsant syndromes. *Journal of Medical Genetics, 37*(7), 489–497.

Mullen, E. M. (1995). *Mullen's scales of early learning*. Circle Pines, MN: American Guidance Services Inc.

Newschaffer, C. J., Croen, L. A., Daniels, J., Giarelli, E., Grether, J. K., Levy, S. E., et al. (2007). The epidemiology of autism spectrum disorders. *Annual Review of Public Health, 28*, 235–258.

NIOSH. (2001) Registry of toxic effects of chemical substances (RTECS®). Cincinnati, OH: National Institute for Occupational Safety and Health. Available: http://www.cdc.gov/niosh/rtecs/RTECSaccess.html. Assessed 20 December 2010.

Pardo, C. A., & Eberhart, C. G. (2007). The neurobiology of autism. *Brain Pathology, 17*(4), 434–447.

Perera, F. P., Jedrychowski, W., Rauh, V., & Whyatt, R. M. (1999). Molecular epidemiologic research on the effects of environmental pollutants on the fetus. *Environmental Health Perspectives, 107*(Suppl 3), 451–460.

Pessah, I. N., Seegal, R. F., Lein, P. J., LaSalle, J., Yee, B. K., Van De Water, J., et al. (2008). Immunologic and neurodevelopmental susceptibilities of autism. *Neurotoxicology, 29*(3), 532–545.

Roberts, E. M., English, P. B., Grether, J. K., Windham, G. C., Somberg, L., & Wolff, C. (2007). Maternal residence near agricultural pesticide applications and autism spectrum disorders among children in the California Central Valley. *Environmental Health Perspectives, 115*(10), 1482–1489.

Roman, E., Doyle, P., Ansell, P., Bull, D., & Beral, V. (1996). Health of children born to medical radiographers. *Occupational and Environmental Medicine, 53*(2), 73–79.

Siemiatycki, J., Fritschi, L., Nadon, L., & Gerin, M. (1997). Reliability of an expert rating procedure for retrospective assessment of occupational exposures in community-based case-control studies. *American Journal of Industrial Medicine, 31*(3), 280–286.

Sparrow, S. S., Balla, D. A., & Cicchetti, D. V. (1984). *Vineland adaptive behavior scales*. Circle Pines, MN: American Guidance Services, Inc.

Stewart, P. A., & Stewart, W. F. (1994). Occupational case-control studies: II. Recommendations for exposure assessment. *American Journal of Industrial Medicine, 26*(3), 313–326.

Stromland, K., Nordin, V., Miller, M., Akerstrom, B., & Gillberg, C. (1994). Autism in thalidomide embryopathy: A population study. *Developmental Medicine and Child Neurology, 36*(4), 351–356.

Szatmari, P. (2003). The causes of autism spectrum disorders. *British Medical Journal, 326*(7382), 173–174.

Teschke, K., Olshan, A. F., Daniels, J. L., De Roos, A. J., Parks, C. G., Schulz, M., et al. (2002). Occupational exposure assessment in case-control studies: Opportunities for improvement. *Occupational and Environmental Medicine, 59*(9), 575–593. (discussion 594).

Volk, H. E., Hertz-Picciotto, I., Delwiche, L., Lurmann, F., & McConnell, R. (2011). Residential proximity to freeways and autism in the CHARGE study. *Environmental Health Perspectives, 119*(6), 873–877.

Wiedel, L., & Coleman, M. (1976). The autistic and control population of this study. Demographic, historical and attitudinal data. In M. Coleman (Ed.), *The autistic syndromes* (pp. 11–20). Amsterdam, Holland: North Holland Publishing.

Wiest, M. M., German, J. B., Harvey, D. J., Watkins, S. M., & Hertz-Picciotto, I. (2009). Plasma fatty acid profiles in autism: A case-control study. *Prostaglandins Leukotrienes and Essential Fatty Acids, 80*(4), 221–227.

Windham, G. C., Zhang, L., Gunier, R., Croen, L. A., & Grether, J. K. (2006). Autism spectrum disorders in relation to distribution of hazardous air pollutants in the San Francisco Bay area. *Environmental Health Perspectives, 114*(9), 1438–1444.

Xu, X., Cho, S. I., Sammel, M., You, L., Cui, S., Huang, Y., et al. (1998). Association of petrochemical exposure with spontaneous abortion. *Occupational and Environmental Medicine, 55*(1), 31–36.