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An Evaluation of Surrogate Chemical Exposure Measures and Autism Prevalence in Texas

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There is currently considerable discussion in the scientific community as well as within the general public concerning the role mercury (Hg) exposures may play in the apparent increased incidence of neurodevelopmental disorders (particularly autism) in children. Although the primary focus of this debate has focused on ethylmercury from vaccinations, linkage to other sources of Hg has been proposed. An ecologic association between 2001 Toxic Release Inventory (TRI; www.epa.gov/tri) data for Hg and 2000–2001 school district autism prevalence was previously reported in Texas. Evaluations using industrial release data as surrogate exposure measures may be problematic, particularly for chemicals like Hg that have complex environmental fates. To explore the robustness of TRI-based analyses of the Hg–autism hypothesis in Texas, a detailed analysis was undertaken examining the extent of the ecological relationship during multiple years and examining whether surrogate exposure measures would yield similar conclusions. Using multilevel Poisson regression analysis and data obtained from a number of publicly available databases, it was found that air Hg release data were significantly associated with autism prevalence in Texas school districts when considering data for 2001 and 2002 (2001: RR = 4.45, 95% CI = 1.60–12.36, 2002: RR = 2.70, 95% CI = 1.17–6.15). Significant associations were not found using data from 2003 to 2005. A significant association was not observed when considering air Hg data for 2000 or 2001 and school district autism prevalence data for 2005–2006 or 2006–2007, an analysis allowing for a 5-yr time period between presumed exposure and entry into the public school system (2000: RR = 1.03, 95% CI = 0.59–1.83, 2001: RR = 0.94, 95% CI = 0.59–1.47). Significant associations were not observed for any year nor for the time lagged analyses when censored autism counts were replaced by threes instead of zeros. An evaluation of TRI air emissions data for several other pollutants did not find significant associations except for nickel (RR = 1.71, 1.12–2.60), which has no history of being associated with neurodevelopmental disorders. An evaluation using downwind location from coal-fired power plants as the exposure surrogate variable also did not yield statistically significant results. The analysis suggests Hg emissions are not consistently associated with autism prevalence in Texas school districts. The lack of consistency across time may be the result of the influence of a more significant factor which remains unidentified. Alternatively, it may be that the significant association observed in 2001 and 2002 does not represent a true causal association.

The adverse neurodevelopmental effects of high-level mercury (Hg) exposure have been well documented in a number of historical poisoning episodes in Japan (Hamada & Osame, 1996; Choi, 1989; Tsubaki & Irukayama, 1977), Iraq (Bakir et al., 1973), and other countries (Curley et al., 1971; Elhassani, 1972). Each of these outbreaks was characterized by in utero exposure to organic mercurials via the maternal diet and gross neurological symptoms (e.g., cerebral palsy, mental retardation). The extent to which much lower organic Hg exposures produced neurodevelopmental effects is somewhat more contentious. Studies of two key island populations, the Faroe Islands (Grandjean et al., 1992, 1997; Debes et al., 2006) and the Seychelles Islands (Myers et al. 1995a, 1995b; Davidson et al., 1995, 2006), reached different conclusions regarding the adverse effects of pre- and postnatal methylmercury (MeHg) exposures despite the two studies having comparable exposure levels. The different diets of the two groups (pilot whale versus oceanic fish, respectively) were suggested as an explanation for the differing results (Myers & Davidson, 1998). The effects observed in the Faroe Islands studies (as well as smaller studies in other areas; Crump et al., 1998) were subtle effects on IQ, effects that would not be detectable on an individual basis.

The question as to the role Hg exposures may play in autism was first suggested in connection with postnatal exposures to ethylmercury from vaccines (Bernard et al., 2001). A number of analyses conducted on vaccine outcome databases as well as a case-series investigation involving autistic children suggested an association between postnatal thimerosal exposure and autism (Geier & Geier, 2003, 2006a, 2006b, 2007a; Young et al., 2008).

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However, this hypothesis has not been supported by the results of several large-scale studies and reviews (Madsen et al., 2003; Andrews et al., 2004; IOM, 2004; Parker et al., 2004; Thompson et al., 2007; Schechter & Grether, 2008) and the subject remains highly controversial (DeStefano, 2007; Baker, 2008).

Several studies have suggested that inorganic Hg exposures from environmental sources may be associated with autism prevalence (Fido & Al-Saad, 2005; Palmer et al., 2006; Windham et al., 2006). Note that the exposures considered in these studies did not clearly distinguish between pre- and postnatal exposures and did not involve the organic forms most clearly associated with neurodevelopmental effects. These ecological studies and case series are useful for hypothesis generation but lack the ability to ascertain causal relationships or individual-level associations due to the lack of information regarding individual exposure status. With regard to MeHg, it is noteworthy that the incidence of autism was not found to be different from that of Western countries among children in the Faroe Islands (Ellefsen et al., 2007), despite the fact that exposure levels (i.e., to MeHg via fish consumption) are higher than those encountered in most of the United States (Oken et al., 2005). At least one well-designed case-control study investigating individual childhood exposures to various sources of Hg and their possible association with autism is now underway but results are not yet available (Hertz-Picciotto et al., 2006).

An association between environmental 2001 Hg release values (i.e., Toxic Release Inventory [TRI] reports) and 2000–2001 special education and autism prevalence has been reported for the State of Texas (Palmer et al., 2006, 2008). There are a number of concerns regarding the use of industrial release data such as the TRI as a surrogate variable for exposure; in addition to the normal issues with lack of detail on individual exposures, TRI data may not reflect actual concentrations present in the immediate human environment, especially where exposure pathways may be complex (Lewandowski, 2006). Moreover, such exposures must precede autism diagnoses in order to be a causal factor in the development of autism and temporal relationships may be difficult to discern with such data. To better understand some of the limitations of the TRI-based analyses, and to explore the robustness of the Hg–autism hypothesis, whether other surrogate exposure measures and other analysis methods produced similar findings was examined.

METHODS

Data Collection

Autism and Special Education Data

Data on the prevalence of autism and other special education categories for the academic years 2000–2001 through 2005–2006 were obtained from the Texas Education Agency (TEA) Academic Excellence Indicator System (AEIS, www.tea.state.tx.us/perfreport/aeis). Assignment to special education categories is based on diagnosis by state special education psychologists or private practitioners. Note that these data do not necessarily indicate the true prevalence of disability in the population but rather the number of individuals registered as having a particular condition within the public school system.

Demographic Data

Data on school district demographics for each school year (i.e., student enrollment, racial composition, school district wealth, percentage economically disadvantaged students) were also obtained from the TEA website. To assess the urban character of the school district, school district population and financial data were evaluated according to eight categories used by the TEA and described by Palmer et al. (2006).

Exposure Data

TRI air data were obtained for Hg and several other pollutants (see Table 5) for each county in Texas for the year 2001 (U.S. Environmental Protection Agency, www.epa.gov/tri). TRI air Hg data were also obtained for the years 2000 through 2005. Although TRI data encompass all forms of Hg, because the organic forms are only produced in very small quantities, TRI Hg really reflects inorganic mercury (both ionic and elemental forms). Data for total air releases were employed because this eliminates releases that are unlikely to result in widespread public exposure (e.g., releases to injection wells, on-site retention areas, or off-site landfills), at least in the timeframes of interest. Analyses were also conducted using log transformed TRI emissions estimates for highly skewed TRI datasets.

Data on the locations of coal fired power plants and associated Hg emissions (again a combination of elemental and ionic Hg) were also obtained from the TRI database (data for 2000). Downwind status relative to the coal-fired power plants was determined using wind rose data obtained for monitoring stations in various regions of Texas from the Texas Commission on Environmental Quality (summary data reflecting measurements 1984 to 1992) (TCEQ, 1984–1992). Finally, data were obtained on the location of Hg-related fish consumption advisories from the Texas Department of Parks and Wildlife (TDPW, 2008). All exposure data were determined on a countywide basis and then applied to all school districts located within the county.

Data Analysis

All analyses were conducted with the statistical computing package R using generalized linear mixed effects regression (lmer) to fit mixed Poisson regression models to the relevant data. Poisson models were used to model the autism counts, with the natural log of the district-specific student population sizes as offsets. As in previous analyses (Palmer et al., 2006, 2008), a random effect was used to account for within-county correlations in the autism counts. The lmer function returns best-fit estimates of the coefficient for each model variable, as

well as an estimate of the rate ratio (with upper and lower 95% confidence intervals) associated with each model variable.

Our first analysis involved examining the relationship between county-specific 2001 TRI air Hg and the TEA school district autism count for the 2000–2001 school year. Variables included in the mixed Poisson regression model consisted of the 2001 TRI reported air Hg releases, the percentage white students in the district, whether the district was urban or suburban, the district tax base, and the percentage economically disadvantaged children in the district. In cases where there were no TRI air Hg data reported for a county, the values were assumed to be zero. For privacy reasons the TEA does not report the number of autism cases for districts in which there are fewer than 5 autistic students and, in the data obtained, TEA coded all values from 0 to 4 as –999; counts in these districts were also assumed to be zero in our primary analyses. Because the use of zeros is likely to underestimate the autism counts in some school districts, a sensitivity analysis was also conducted in which these counts were all set to the value of 3 (the limit of detection divided by the square root of 2). Subsequent analyses used zero as the value for censored TEA autism counts except where indicated.

The possibility of whether an association was observed in later years was also considered. TRI air Hg data and autism prevalence data were evaluated for the years 2002, 2003, 2004, and 2005 (equating to school years 2001–2002, 2002–2003, 2003–2004, and 2004–2005). Demographic data were also updated for the later years.

To evaluate the potential effect of a "time lag" between prenatal exposure and autism diagnosis within the school district system, TRI air Hg data were evaluated from 2000 and 2001 with autism prevalence data in children under 6 yr of age from the 2005–2006 and 2006–2007 school years. This allows for a 5- to 6-yr time period between exposure and disease counts by the school systems, which of course do not enroll children during the first few years of life. The TEA age-specific autism data obtained for this portion of the analysis censored autism counts between 1 and 4 students but allowed determination of actual 0 counts. Thus use of a value of 3 for censored data in this analysis is probably more appropriate than a value of 0. Other variables included in the mixed Poisson regression model were those described previously. The next stage of analysis considered whether 2001 TRI air Hg data were associated with other special education categories in the 2001 TRI Hg data. This involved repeating the 2001 analysis already described but sequentially substituting data for each of the other special education categories for autism.

An association between TRI air release data for other chemicals and autism prevalence was next explored. Retaining 2001 as the year of interest, TRI air Hg was substituted with TRI air release data for the other chemicals listed in Table 1. Whether the existence of a coal fired power plant within, or upwind of, a county was associated with autism prevalence in the school districts located within that county was next explored. To determine upwind/downwind status, the percentage of county land area that was downwind of a coal-burning power plant in terms of the annual average prevailing wind direction from National Weather Service wind roses was calculated. This was done using the graphic information system program ArcView (ESRI, Danvers, MA). Downwind was defined as having a certain percentage (50, 70, or 85%) of the county land area within a 40-mile radius of a plant in the downwind direction. A Poisson regression analysis was conducted using the percentage of county land area downwind of a coal burning power plant as the exposure variable (i.e., in lieu of TRI data). A similar analysis was conducted using a weighted variable: the percentage of county land area downwind of the power plant(s) multiplied by the amount of Hg released from the nearby power plant(s). The weighted variable follows the rationale that if autism prevalence is related to Hg release, the highest prevalence should be apparent in localities where most of the land area is downwind of a large quantity Hg source. The collected data were also plotted graphically as a way of understanding how patterns of Hg release and autism prevalence varied by geographical region.

RESULTS

Table 1 provides descriptive measures of the 2001 data used in the analysis. Overall, for 2001 there were 4,057,712 students recorded in the TEA records, of whom 7022 were registered in the autism category. Statistics for datasets representing other years were similar. Table 1 also summarizes data obtained for 2001 from the TRI database.

TRI Air Hg and Autism Prevalence

Using 2001 air TRI Hg and 2001–2002 autism prevalence data, our analysis did find a statistically significant association between TRI air Hg and autism (Table 2). The relative risk (RR) value for TRI air Hg was 4.45 (95% CI = 1.60,12.36). The effect of TRI air Hg was substantially less than those of the urbanicity variables [urban district = TRUE, RR = 28.73 (10.18–81.06), suburban district = TRUE, RR = 23.63 (8.39–66.53]. The number of economically disadvantaged students in the district was negatively correlated with autism prevalence (RR = 0.1 (0.07–0.15), whereas the effects of race (percent white) and district wealth (i.e., tax base) were minimal.

Whether this association persisted for later years was next considered; summary statistics for the data analyzed are shown in Table 3 and results of the analysis are shown in Table 4. For the primary analysis using zeros for censored autism counts, statistically significant associations were only observed with the 2001 and 2002 data. The RR for 2002 (2.70, CI = 1.17–6.15) was only about 60% of that observed in 2001. Analysis of subsequent years did not yield statistically significant associations. The relative contributions of other covariates were similar to those observed in 2001 (data not shown).

TABLE 1
Summary of Data Used in Base Case Analysis (2000–2001 Data)

Variable	Number of school districts	Mean	SD	Minimum	Maximum
Total student count per district	1181	3436	11,003	6	208,462
Autism count (per district)	1201	5.86	24.5	0	450
Percent economically disadvantaged	1199	47.6	21.8	0	100
Percent European American	1199	57.4	29.85	0	100
District wealth ($)	1199	204,855	283,266	0	3,154,183
Percent urban	1030	3.3	na	na	na
Percent suburban	1030	20.6	na	na	na
Percent rural	1030	45.7	na	na	na
Percent other	1030	30.4	na	na	na
TRI air mercury (lb)	na	325	423	0.1	1579
TRI air antimony (lb)	na	705	1065	2	3133
TRI air lead (lb)	na	1109	5159	0.03	48,652
TRI air manganese (lb)	na	2727	7119	2	50,485
TRI air nickel (lb)	na	598	1071	1	7004
TRI air zinc (lb)	na	7101	29,394	3	213,346
TRI air benzene (lb)	na	45,452	123,900	0	722,578
TRI air ethylbenzene (lb)	na	5564	11,619	6	43,868
TRI air naphthalene (lb)	na	6893	22,512	3	125,979
TRI air trichloroethylene (lb)	na	18,155	16,109	45	54,511
TRI air sulfuric acid (lb)	na	128,810	272,269	111	1,262,856

Note. Mean and standard deviations are based on data from counties reporting nonzero release amounts. Counties reporting zero emissions for a particular chemical were included in the multilevel Poisson regression analyses (see Table 3).

TABLE 2
Results for Multilevel Poisson Regression Model Evaluating the Association Between 2001 TRI Air Mercury Releases and 2001–2002 Texas Education Association Autism Prevalence Data

Parameter	Estimate	SE	RR	Lower	Upper
TRI air Hg (per 1000 lb)	1.494	0.521	4.45	1.60	12.36
Percentage of white students	–0.011	0.002	0.99	0.99	0.99
District tax base	–0.008	0.017	1.01	0.98	1.04
Percentage of economically disadvantaged students	–2.291	0.206	0.10	0.07	0.15
Urban district (TRUE)	3.358	0.529	28.73	10.18	81.06
Suburban district (TRUE)	3.162	0.528	23.63	8.39	66.53
Other district type (TRUE)	2.991	0.527	19.91	7.09	55.91

Note. All covariates shown in the table were included as predictors in the regression model. When special education was included as a variable in the model, results were only minimally affected (e.g., the RR for TRI air Hg was 4.86 [1.42–16.59]).

Evaluation of TRI air Hg data from 2000 and 2001 with autism prevalence data (ages 5 to 6 yr only) from the 2005–2006 and 2006–2007 school years to examine the effect of a time lag between exposure and evaluation resulted in RRs of 1.56 (95% CI = 0.36, 6.87) and 2.49 (95% CI = 0.63–9.39), respectively, indicating a lack of statistical significance (Table 4). However, these two estimates may be unreliable due to high collinearity with urbanicity, for which the RR estimates and confidence intervals were unrealistically large and unstable. As noted previously, use of zero as a value for censored data in the 5–6 yr old data set is probably unrealistic.

Sensitivity Analysis for Method of Handling Censored Autism Counts

Results of a secondary analysis substituting the value 3 for all censored autism counts (counts below 5 in any district) are also shown in Table 4. RRs for the single-year analyses varied

TABLE 3
Summary of Input Data Used in Modeling of Years Subsequent to Base Case

Parameter	2000–2001	2001–2002	2002–2003	2003–2004	2004–2005	2005–2006	2006–2007
Students							
Mean	3436	3417	3480	3527	3570	577[a]	593[a]
Standard deviation	11,003	11,068	11,220	11,281	11,313	1906[a]	1935[a]
Minimum	6	12	6	6	13	1[a]	3[a]
Maximum	208,462	210,670	211,762	211,157	208,454	34,975[a]	34,698[a]
Autism count							
Mean (per district)	5.86	6.75	8.09	9.74	11.4	1.5[b]	1.8[b]
Standard deviation (per district)	24.5	27.49	32.26	37.74	43.2	7.5[b]	8.8[b]
Statewide total	7022	8233	9900	11,956	14,017	1876[b]	2177[b]
Percent economically disadvantaged							
Mean	47.6	49.42	51.8	52.9	54.8	55.8	55.7
Standard deviation	21.8	21.86	21.2	20.7	20.9	20.7	20.8
Percent white	57.4	56.22	55.2	54.4	53.4	52.8	52.1
District wealth (tax base dollars per student)							
Mean	$205,000	$235,000	$243,000	$240,000	$266,000	$300,000	$356,000
Standard deviation	$283,000	$348,000	$364,000	$317,000	$376,000	$460,000	$608,000
Percent urban	3.3	3.3	3.3	3.3	3.3	3.3	3.3
TRI air Hg (lb)[c]							
Mean	146.7	153.9	88.3	97.8	99.8	166.8	165.6
Standard deviation	380	400.1	226.8	260.2	266.1	417.2	409.6
Minimum	0	0	0	0	0	0	0
Maximum	1579	1800	1404	1744	1705	2056	1579

[a]For children in kindergarten and first grade only, which serves as the denominator for children in the 5–6 yr age range.
[b]For children ages 5 to 6 yr only.
[c]For the first five columns, data correspond to the calendar year coinciding with the second half of the academic year indicated in each column. For the last two columns, data are for the calendar years 2000 and 2001, respectively. Statistics include data for counties reporting zero emissions.

from 1.03 to 1.28; none were statistically significant. The time lag analysis using this approach produced stable estimates for all parameters, with RRs of 1.03 (95% CI = 0.59, 1.83) for 2000 TRI air Hg and 2005–2006 autism counts, and 0.94 (95% CI = 0.59, 1.47) for 2001 TRI air Hg and 2006–2007 autism counts.

Relationship of TRI Hg with Other Special Education Categories

Most of the other TEA special education classes were not significantly associated with TRI air Hg (Table 5). However, traumatic brain injury was associated with TRI air Hg (RR = 5.06 95% CI = 1.26–20.30). Note that this association is even stronger than that reported for autism.

Evaluations Using TRI Air Data for Other Chemicals

The 2001 air TRI concentrations for most other chemicals evaluated were not significantly associated with autism prevalence, exhibiting RR between 1.0 and 1.2 (Table 6). The only chemical besides Hg that was significantly associated with autism prevalence was TRI air nickel (Ni), which produced a RR of 1.71 (95% CI = 1.12–2.60). The TRI data for Ni are highly skewed, with data for Harris County being substantially higher than elsewhere. When this data point was excluded from the analysis, the RR for the association between TRI air Ni and autism increased to 3.59 (95% CI = 1.63–7.94).

Exploring Associations Between Autism Prevalence and Power Plant Locations

To consider the effect of being located downwind of coal-fired power plants, *t*-tests were first run looking at autism prevalence in those counties downwind versus those not downwind of coal-fired power plants. None of the *t*-tests produced a significant result, suggesting that "downwind status" is not related to autism prevalence (data not shown). Mixed Poisson regression analyses were also conducted using percentage of county land area downwind of a coal-burning power plant as the exposure variable (i.e., in lieu of TRI data). All other variables were retained from the earlier models. No significant association

TABLE 4

Results for Multilevel Poisson Regression Model Evaluating the Association Between TRI Air Mercury Releases and TEA Autism Prevalence Data (Data From Years Subsequent to the Base Analysis), Adjusting for Urbanicity, Percent White Students, District Tax Base, and Percentage of Economically Disadvantaged Students

TEA academic year	TRI air Hg reporting year	Value used for censored autism counts[a]	TRI air Hg RR (CI)	Urban school district RR (CI)
2000–2001	2001	0	4.45 (1.60–12.4)	28.7 (10.2–81.1)
		3	1.28 (0.95–1.72)	0.93 (0.77–1.12)
2001–2002	2002	0	2.70 (1.17–6.15)	33.0 (11.5–94.5)
		3	1.51 (0.91–1.47)	0.92 (0.77–1.10)
2002–2003	2003	0	2.07 (0.84–5.13)	26.8 (11.5–62.6)
		3	1.12 (0.83–1.50)	0.93 (0.79–1.09)
2003–2004	2004	0	1.41 (0.56–3.53)	53.5 (14.0–204)
		3	1.06 (0.81–1.38)	0.944 (0.81–1.10)
2004–2005	2005	0	1.19 (0.54–2.61)	33.2 (12.6–87.8)
		3	1.03 (0.81–1.31)	0.96 (0.82–1.11)
Time lag analysis (limited to children 5 to 6 yr of age)				
2005–2006	2000	0	1.56[b] (0.36–6.87)	8,900,000[b] (0–infinity)
		3	1.03 (0.59–1.83)	1.15 (0.82–1.59)
2006–2007	2001	0	2.49[b] (0.63–9.39)	10,000,000[b] (0–infinity)
		3	0.94 (0.59–1.47)	1.01 (0.75–1.36)

[a]TEA autism counts are not publicly reported when fewer than five individuals are in a given category for any school district. While many of the actual counts may be zero, 3 reflects the limit of detection divided by the square root of 2, a common value to substitute for left censored data such as these.

[b]Parameter estimates for these two marked time-lag analyses were unstable, as indicated by the unrealistically large relative risks and confidence intervals for the effect of urbanicity. Analyses conducted with 3 as the value for the censored autism count data are believed to be more appropriate since true "0" counts could be deduced in the age-specific TEA autism data set.

TABLE 5

Results of Multilevel Poisson Regression Analysis of 2001 TRI Air Mercury Data and Different Special Education Categories Reported in the 2001–2002 TEA Database, Adjusting for Urbanicity, Percent White Students, District Tax Base, and Percentage of Economically Disadvantaged Students

Special education category	Number of students in state in category	Relative risk	95% Confidence interval
Autism	7022	4.45	1.60–12.36
Learning disability	260,791	0.91	0.58–1.44
Mental retardation	27,979	1.42	0.80–2.48
Orthopedic impairment	6322	1.89	0.34–10.57
Speech impairment	97,791	0.94	0.62–1.40
Emotional disturbance	34,639	1.98	0.38–10.29
Visual impairment	2552	1.73	0.60–4.96
Auditory impairment	5629	1.73	0.19–16.03
Non-categorical early childhood disability	1913	20.69	0.22–1936.64
Other health impairment	39,116	1.31	0.58–2.98
Traumatic brain injury	573	5.06	1.26–20.30

Note. The categories "Developmental delay" and "Deaf/blind" were not evaluated due to a limited number of data points associated with only a few counties.

TABLE 6
Multilevel Poisson Regression Model Results: 2001 TRI Air Chemical Data and Same Year TEA Autism Prevalence, Adjusting for Urbanicity, Percentage of White Students, District Tax Base, and Percentage of Economically Disadvantaged Students

Chemical	RR	95% CI
Mercury	4.45	1.60–12.36
Antimony	1.95	0.89–4.25
Lead	1.04	0.97–1.11
Manganese	1.16	0.97–1.37
Nickel	1.71	1.12–2.60
Zinc	1.01	0.99–1.03
Benzene	1.00	1.00–1.00
Ethylbenzene	1.01	1.00–1.02
Naphthalene	1.02	1.00–1.05
Trichloroethylene	1.05	1.01–1.09
Sulfuric acid	1.02	1.00–1.04
Nickel excluding Harris County[a]	3.59	1.63–7.94
LN sulfuric acid	1.12	1.04–1.19
LN Lead	1.22	1.10–1.35
LN Benzene	1.12	1.04–1.21

Note. Each chemical was fitted in a separate regression model.
[a]7004 lb of TRI air emissions in 2001, 3.5 times higher than next highest county.

between downwind status and autism prevalence were found (Table 7). Use of the weighted variable to characterize estimate Hg exposure also did not indicate a significant association between downwind status and autism prevalence (RR = 1.15, CI = 0.52–2.55). There was no statistically significant association between the existence of an Hg-based fish consumption advisory and autism prevalence (RR = 1.39, 95% CI = 0.61–3.15).

Graphical Evaluations

Along with conducting the statistical analyses, TRI air Hg and autism prevalence were also graphically examined (Figure 1). Such graphical representations may help suggest other variables that should be considered. For example in Figure 1, 2000–2001 autism prevalence appears to be associated with the highest TRI 2001 Hg data in the areas around Houston and San Antonio but does not appear to be similarly associated in the Dallas/Fort Worth area. Autism prevalence also appears to be relatively low in areas of northeastern Texas where TRI air Hg is high. This figure also illustrates the highly significant influence of urbanicity on autism prevalence. Figure 2 depicts 2001–2002 autism prevalence versus the locations of coal-fired power plants with prevailing wind directions indicated. A review of this figure indicates that areas of elevated autism prevalence do not consistently correspond to downwind status. Autism prevalence appears to be fairly low in northeastern Texas, an area of significant coal-fired power plant emissions.

DISCUSSION

The possibility that Hg has a causative role in neurodevelopmental diseases such as autism has stimulated considerable research and discussion. Data supporting a link between Hg exposure (whether organic or inorganic Hg) and autism remain speculative. A number of studies suggest that autistic children exhibit altered metabolism and increased susceptibility to chemicals capable of producing oxidative stress (James et al., 2004, 2006; Zoroglu et al., 2004; Yao et al., 2006; Williams et al., 2007; Geier & Geier, 2007b). The role for early-life immune-system insults (including those produced by metals) as a causal factor in autism was also explored in detail by Dietert and Dietert (2008). The extent to which these effects have a role in the causation of autism versus being downstream consequences of the disease itself is not clear. However, the cited studies do suggest autistic children may be at higher risk for chemical exposure.

The analysis described here showed that TRI air Hg data reported in 2001 and 2002 were significantly associated with autism prevalence data collected by the TEA in the same years as long as censored data were treated as zeros. The association was not statistically significant in analyses of data from 2003 through 2005, which would be expected if the association represented a true biological phenomenon. However, our analysis of same-year TRI and TEA autism data neglects the latency period that would occur between exposure in utero first entry into the TEA record system at approximately age 5 yr. Such an analysis is only valid if the Hg exposure variable is stable over time, such that Hg data at age 5 or 6 yr also reflect conditions 5 to 6 yr earlier. An analysis of TRI data shows that average TRI air Hg was relatively stable between 2000 and 2005 (ranging from 14,000 to 17,000 pounds as a statewide total), whereas statewide TEA autism prevalence more than doubled, from 0.16% in 2000–2001 to 0.37% in 2005–2006. Although stability of exposure may therefore be a reasonable assumption, analyses conducted using a 5- to 6-yr time lag between TRI air Hg data and TEA autism data also did not demonstrate a significant association. This also suggests that the 2001 and 2002 findings may be isolated results.

The limitations of ecological studies are well known, and epidemiologists warn researchers not to interpret group-level associations as if they were individual-level associations (Szklo & Nieto, 1993). Moreover, ecological studies are particularly susceptible to bias produced by confounding (Piantadosi et al., 1988). In the present analyses urbanicity is a strong confounding variable assessed using discrete categories, creating a strong potential for residual confounding. In the analysis of the 2001 data (with censored data treated as zeros), living in an urban environment was associated with an RR for autism of 28, a finding that was statistically significant. This strong association

TABLE 7
Multilevel Poisson Regression Model Evaluations for Downwind Location From Coal-Fired Power Plants, Adjusting for Urbanicity, Percentage of White Students, District Tax Base, and Percentage of Economically Disadvantaged Students

Criterion	RR	95% CI
County area at least 50% downwind	1.46	0.64–3.36
County area at least 70% downwind	1.11	0.41–3.04
County area at least 85% downwind	1.47	0.25–8.68
Weighted Variables		
Exposure estimated based on weighted location-emission variable 1*[a]	1.15	0.52–2.55

Note. Each location criterion was fitted in a separate regression model.
[a]Percent of county land area downwind of coal-fired power plant location(s) multiplied by the amount of mercury released by the nearby power plant(s).

was also noted elsewhere (Williams et al., 2006; Deb & Prasad, 1994), yet the reason for this association remains unknown. Race and income do not appear to be involved, as the relationship persists even when these factors are included as variables in the regression analysis. Is the effect due to differences in diagnosis or a tendency of parents of autistic children to move to larger cities where support services may be better? Or is the effect due to some environmental factor for which "urbanicity" serves as a surrogate? Additional research into the basis for the association between urbanicity and autism prevalence is clearly needed.

Our analysis of other TEA disability categories found that traumatic brain injury was also associated with 2001 TRI air Hg, an association that was even stronger than that reported for autism. According to Texas State Regulations, this category is reserved for injuries resulting from physical trauma and specifically excludes those that are congenital or degenerative. One would therefore not expect Hg exposure to be causally related to traumatic brain injury, and the association is likely due to chance or confounding.

Our evaluation of the potential impact of power plant locations on autism prevalence indicated no association. Although coal-fired power plants are considerable sources of inorganic Hg, this is not the form strongly associated with neurodevelopmental effects. While elemental and inorganic Hg may be converted to MeHg in aquatic systems, human exposures to MeHg via local fish consumption are not likely to be characterized sufficiently by emissions data to allow prediction of any potential adverse health effects. Moreover, it is well established that the majority of power plant Hg air emissions travel far from the point of release (Seigneur et al., 2006) and thus any impact of power plants on nearby residents is likely to be obscured by other potential Hg exposures (e.g., in utero exposure to Hg from maternal amalgam fillings).

Our results for the analysis of 2001 data (both TRI air Hg and TEA autism prevalence) are qualitatively similar to those reported by Palmer et al. (2006) for the same time frame. Quantitative differences appear to be due to the use of different TRI data (TRI air release vs. total release) and perhaps differences in the calculated urbanicity factor. It was not possible to replicate the TRI release values summarized in the Palmer et al. (2006), which may be due to updates made to the TRI database. Companies are allowed to revise TRI submittals, a fact that is problematic in terms of using the data reproducibly. Differences may also be due to statistical software differences. Palmer et al. (2006) used a multilevel Poisson regression model and an earlier version of the MLWIN software package for their analyses, but did not specify the estimation method used to fit the model. Several estimation methods are used for generalized linear mixed models in MLWIN and are based on different likelihood function approximations and may produce different results. The early default MLWIN method, marginal quasi-likelihood, is only appropriate when the variance for the random effect is small (Molenberghs & Verbeke, 2005). Our analysis used a Laplace approximation in combination with partial quasi-likelihood. Although this method appears to be currently favored by statisticians, implementations vary widely across software packages, and even within this context results may vary widely. Our analyses using the 2000–2001 data show a range of relative risks for total Hg versus autism, depending on the estimation algorithm. For example, using three different algorithm choices for the multilevel Poisson model, the results for the 2001 data (using total Hg rather than air Hg) yield RR values of 1.29 (95% CI = 1.09–1.49), 1.67 (95% CI = 1.23–2.28), and 2.025 (95% CI = 1.23–3.34). This is a surprising result given that the same data are being used in the analysis. Epidemiologists need to be aware of these limitations of existing algorithms for fitting generalized linear mixed models; this extreme sensitivity to choice of algorithm may be a particular problem for rare outcomes (Breslow & Lin, 1995).

Our sensitivity analyses also indicate an extremely high degree of sensitivity to the method used to handle censoring, with relative risks shrinking toward 1 as larger values below the limit of detection are substituted for the left-censored

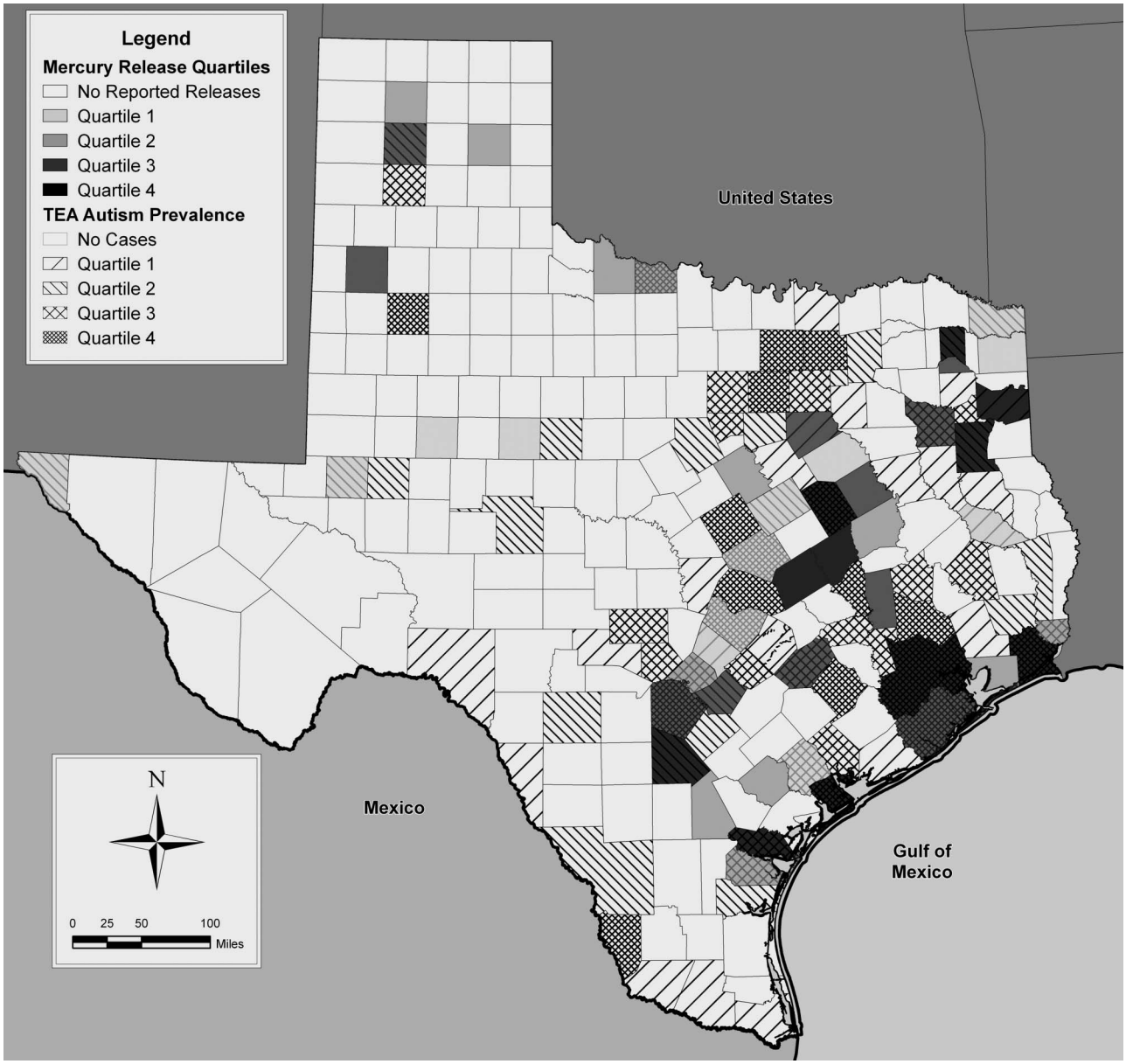

FIG. 1. 2001 TRI air mercury release data and 2000–2001 TEA autism prevalence. Data are grouped by quartiles.

autism counts. Various substitutions including 0, half the limit of detection, and the limit of detection divided by the square root of 2 are commonly used for left-censored data, particularly in the setting of chemical concentrations (Barr et al., 2006). Although these findings highlight some limitations of public use data sets, more sophisticated methods such as Monte Carlo simulation or maximizing an approximation to the left-censored multilevel Poisson likelihood function might be more reliable when uncensored data cannot be obtained. A likelihood-based approach that accounts for the size of the district might be particularly important, as the censored autism counts for larger districts are more likely to actually be nonzero counts than the censored autism counts for smaller districts.

Palmer et al. (2008) published another analysis of TEA autism data looking specifically at TRI Hg emissions from coal-burning power plants and reported that power plant Hg release in 1998 was significantly associated with 2002 autism prevalence and that distance from a coal burning power plant was a predictor of autism risk. It is not clear from the publication whether the findings were also the same in later years or only valid for the 1998/2002 comparison.

This study represents an ecological analysis and has the limitations associated with the lack of individual-level exposure data. Although the associations found for 2001 and 2002 (using the same year's autism prevalence and TRI data and a value of zero for censored TEA data) were statistically significant, the

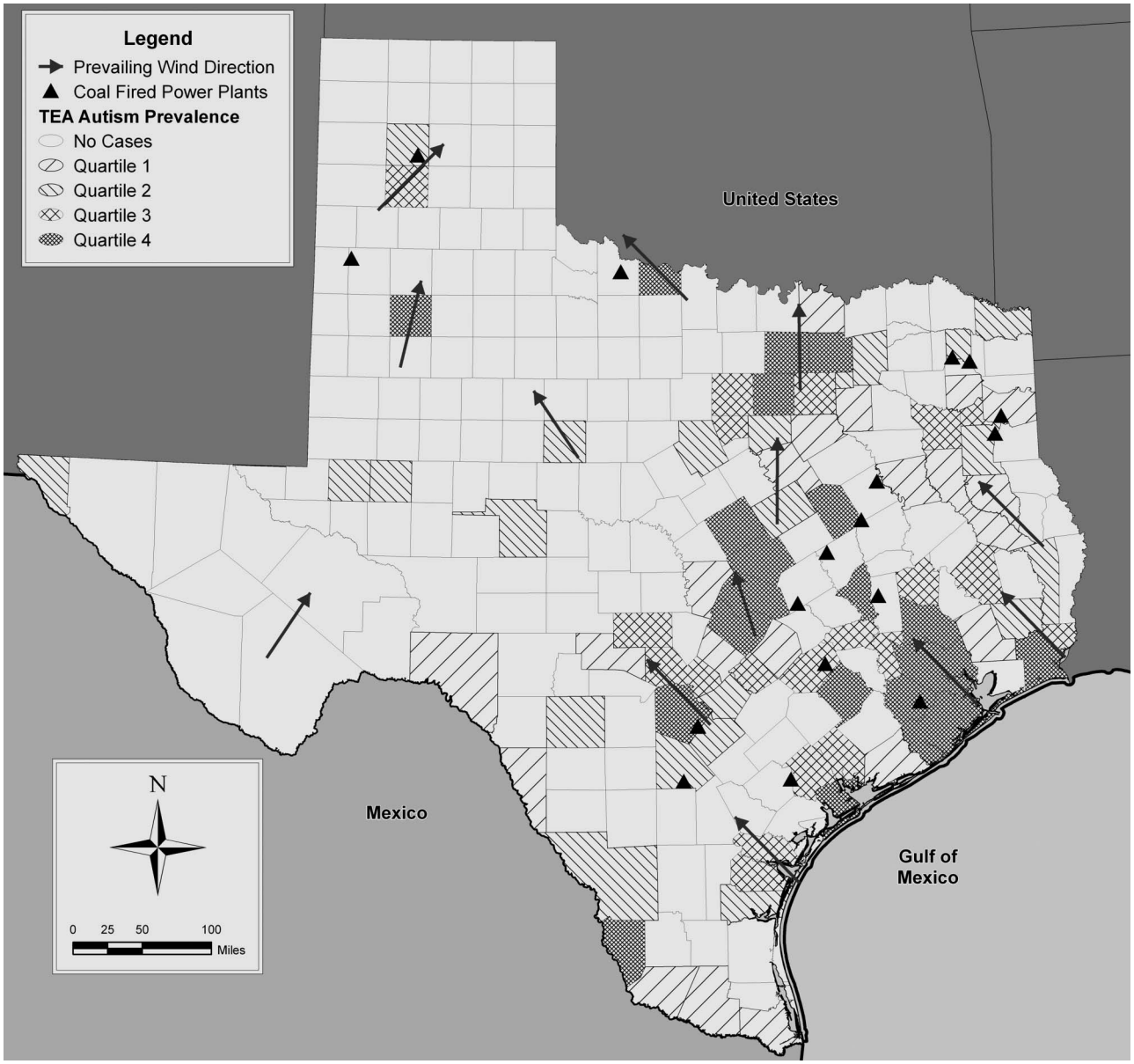

FIG. 2. 2001–2002 TEA autism prevalence, coal-fired power plant locations, and prevailing average annual wind directions.

fact that a significant association was not observed over subsequent years or in the time lagged analysis is problematic. It might be that some other more significant factor in autism prevalence became stronger in 2003–2005, thus diminishing the strength of association of TRI Hg below that detectable in our analysis. Conversely, it may be that the significant association in 2001 and 2002 does not represent a true causal association.

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