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Thimerosal and Autism

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1. Executive Summary

Thimerosal is a mercury-containing preservative that, up until the late 1990s, was used in several types of vaccines that were routinely administered to children during infancy. The study of Thimerosal and Autism was conducted to investigate whether prenatal and/or early childhood exposure to thimerosal-containing vaccines and immune globulin preparations is associated with increased risk of autism.

The study utilized a matched case-control design. Study participants were recruited from membership roles of three large health maintenance organizations (HMOs). Cases were children who had a diagnosis of autism spectrum disorder (ASD) recorded in their medical records, and who subsequently participated in a rigorous standardized assessment to determine if they met study criteria for ASD, or for autistic disorder (AD). Criteria were based on results of direct observation of children using the Autism Diagnostic Observation Schedule (ADOS) and administration of the Autism Diagnostic Interview-Revised (ADIR) to the mothers of case children. Controls were selected from among children that did not have ASD diagnoses in their medical records, and whose parents confirmed that they had never been told that their child had autism. To reduce the likelihood that the control group included any children with undiagnosed ASD, the Social Communication Questionnaire was used as a screener and control children that scored above criterion were omitted from the control group. Approximately three matched controls were recruited for each case. Controls were matched to cases on birth year, sex, and HMO.

Children from each HMO were eligible to participate if they were born between January 1, 1994 and December 31, 1999, had been enrolled in the HMO from birth through their second birthday, and lived within 60 miles of an assessment clinic. Children had to be able to walk on their own, and hear and see adequately using eyeglasses or hearing aids if necessary, and had to live with their biological mother an average of at least four days per week since birth. The child's family had to be fluent in English. Testing was conducted between June, 2005 and May, 2007. Children were excluded if they had the following medical conditions with known causal links to the symptoms of autism: Fragile X syndrome, tuberous sclerosis, Rett's syndrome, congenital rubella syndrome, or Angelman's syndrome. Recruitment was attempted for all eligible cases within the HMO populations. Control children were randomly selected from the HMO populations to match cases within matching strata defined by birth year, sex, and HMO.

For each child, a detailed vaccination history was created from two data sources. The first was from computer-automated records maintained by the HMOs as part of the Vaccine Safety Datalink (VSD) system and as part of their administrative record keeping systems. The second source was from detailed abstractions of the children's medical charts. Each vaccine or immune globulin receipt listed in the child's vaccine history was assigned a mercury amount based on its type, manufacturer, year, and lot number. Similarly, measures of prenatal exposure were calculated from maternal vaccination histories covering the period when the mother was pregnant with the focus child. The

maternal vaccination histories were compiled from chart abstraction of the mother's medical records, and from maternal self-report on receipts of immune globulins and flu shots during pregnancy.

Relationships between autism outcomes and exposure to ethylmercury from thimerosal-containing vaccines and immune globulin preparations were estimated using conditional logistic regression models that controlled for a range of potential confounding factors. The list of potential covariates was developed by the study's investigators and the panel of External Expert Consultants based on published research on risk factors for neurodevelopmental outcomes including autism. These included measures of birth weight, household income, maternal education, marital status, maternal and paternal age, birth order, and breast feeding duration. They also included child birth conditions including Apgar score, and indicators for birth asphyxia, respiratory distress, and hyperbilirubinemia. To control for potential confounding due to non-vaccine prenatal exposures, measures of maternal tobacco use, alcohol use, fish consumption, exposure to non-vaccine mercury sources, lead, illegal drugs, valproic acid, folic acid, and viral infections during pregnancy were created. Measures of child anemia, encephalitis, lead exposure, and pica were also tested for inclusion as covariates in the models, as were measures of maternal health care seeking behavior. Covariate measures were created from data obtained from medical chart abstraction and from parent interview. Covariates were retained in the final models if they satisfied a change-in-estimate criterion evaluated by dropping terms that resulted in less than a 10% change in exposure coefficients relative to a full model with all potential covariates.

The study protocol was developed by a design group led by Abt Associates, Inc. working in close consultation with Principal Investigators from the Centers for Disease Control and Prevention (CDC), Principal Investigators, Data Managers, and Study Managers from the each of the three HMOs, and with the study's External Expert Consultants. Prior to recruitment and data collection, a detailed analysis plan was written for the study that specified the research questions, study design, eligibility criteria, sampling plan and target sample sizes, the form of the statistical models that would be used, the specific hypotheses to be tested, decision rules for categorizing outcome classifications, the coding of exposure variables, the list of covariates to be used as statistical control variables, the coding of each of those variables, and decision rules for the retention or omission of each covariate in the final analysis models.

By agreement among the members of the design group, data analysis for the study was to be completed in two phases. In the first analysis phase, analysts at Abt Associates were to carry out as closely as possible the analyses specified in the plan and to do only the analyses specified in the plan. At the end of this phase, all members of the design group were invited to a meeting in Washington, DC where the first round, preliminary results were presented to the group. Prior to that meeting, the results of analyses linking exposures to outcomes had not been shared with anyone outside of Abt Associates. The second phase of analysis began with the meeting in Washington, DC. At that meeting, the design group considered the results and generated new hypotheses and questions that were to be pursued in the second phase. Over the ensuing months design team members

provided written comments on the results of the preliminary analyses and made suggestions for additional analyses. The current report includes results from both phases.

The analysis plan specified primary and secondary research questions. The primary questions were the *raison d'être* for the study, and guided design decisions. The secondary questions were considered to be important questions that could and should be addressed given that the study was to occur. The discussion that follows focuses first on the primary research questions. These questions were concerned with the relationships of exposures and either AD or ASD outcomes. Specifically, we asked, are there associations between a diagnosis of autistic disorder (AD) or autism spectrum disorder (ASD) and children's prenatal or early postnatal exposure to ethylmercury from thimerosal-containing vaccines and immune globulins. The questions focused on cumulative exposures in each of the following five time periods or age ranges:

- The prenatal period
- A birth exposure (defined as exposure from birth to age 28 days)
- Cumulative exposure from age 29 days through seven months
- Cumulative exposure from birth through seven months, and
- Cumulative exposure from birth through 20 months of age.

Analyses were based on 256 ASD cases and 752 matching controls, and on 187 AD cases and 724 matched controls¹. All children that met the criteria required to receive an AD classification also met the criteria for ASD. Thus, the 187 AD cases are a subset of the 256 ASD cases, and likewise the matched controls for AD cases are a subset of the matched controls for ASD cases. With such a large degree of overlap between the samples of AD and ASD cases, one would expect similar results from the two sets of analyses.

The study results did not support the hypothesis that predicted that increased thimerosal exposure would be related to increased risk of AD or ASD outcomes. There were no significant associations between prenatal exposure and either AD or ASD outcomes. Nor were there significant associations between a birth exposure and either AD or ASD outcomes. The parameter estimates for cumulative exposures birth to seven months and birth to 20 months were in a direction suggesting that increased exposure was related to decreased risk of either AD or ASD. Although these results were statistically significant², we are not aware of a plausible biological mechanism that would lead to this result. We therefore interpret this result as a chance finding. Thus, for none of the

¹ Response rates for cases and controls were 48 and 32 percent respectively. See Chapter 5, Exhibit 5.3.3 for details.

² Note that three of the measures of cumulative exposure (birth to seven months, birth to 20 months, and 29 days to seven months) are highly correlated with one another. Thus their estimated relationships to AD and ASD outcomes are similar to one another. Like the estimates for cumulative exposures birth to seven months and birth to 20 months, the estimates for cumulative exposure 29 days to seven months were in the direction of decreased risk. The measure of exposure from age 29 days to seven months had a significant negative relationship to the AD outcome, but did not meet the $p < 0.05$ criterion for statistical significance for the ASD outcome.

exposure measures was there evidence to support the hypothesis that increased thimerosal exposure would be related to increased risk of AD or ASD outcomes.

There were two types of secondary research questions specified in the analysis plan. The first type concerned relationships of exposures to subgroups of AD and ASD cases. Questions about the same previously described cumulative exposure measures for five time periods or age ranges were asked about the each of the following subgroups:

- ASD-not-AD
- ASD with regression
- AD with low cognitive functioning excluded
- ASD w/Screened Controls
- AD w/Screened Controls

ASD-not-AD is the subset of cases that met criteria for ASD, but did not meet criteria for AD. ASD with regression is a subset of ASD cases that had a definite loss of language skills. Analysis of the subgroup of AD cases where children with low cognitive functioning were excluded was motivated by the following concern. Because children who are non-responsive during the assessment process are more difficult to assess, it can sometimes be difficult to determine whether children with severe developmental delay actually have autistic disorder. If the imprecision of the assessment process for such children resulted in inclusion of children without AD in the AD group, then we would expect that the estimate of the relationship of exposure to AD risk could be attenuated. Therefore, an outcome category for AD with low cognitive functioning excluded was created and its relationship to exposure was estimated.

The rationale for examining the subsets of AD and ASD cases contrasted to “screened controls” was as follows. During the study’s design phase, the study’s External Expert Consultants expressed concern that if the control group included individuals with milder types of adverse neurodevelopmental outcomes, and if increased exposure to ethylmercury from thimerosal-containing vaccines and immune globulins was related to increased risk of those milder adverse neurodevelopmental outcomes, then inclusion of those individuals in the control group could attenuate the estimates of the risk of AD and ASD from ethylmercury exposure. Therefore, as a further precaution, the study’s External Expert Consultants urged the creation of a “screened control group” that would exclude children that had milder forms of adverse neurodevelopmental outcomes that have had hypothesized linkages to ethylmercury exposure. We therefore created a “screened control group” that excluded children who had any of the following conditions: speech delay or language delay; learning disabilities; attention deficit hyperactivity disorder (ADHD) or attention deficit disorder (ADD); or tics. Additionally, children that had had an individual education plan (IEP) in the 12 months prior to the eligibility interview were also excluded from the “screened control group.”

The results of the five subgroup analyses described above were similar to the results of the analyses for the primary research questions. That is, the results from these analyses did not support the hypothesis that increased thimerosal exposure would be related to

increased risk of these outcomes. As with the previous results, there were no significant associations between prenatal exposure and these outcomes, no indications of increased risk associated with a birth dose, and for four of the five subgroups the estimates of the relationships of cumulative exposures birth to seven months and birth to 20 months were significant and in a direction suggesting that increased exposure was related to decreased risk of autism outcomes.

Another type of secondary research question involved interaction effects. One question asked whether exposure effects varied by the sex of the child, another asked if the effects of exposure were greater if thimerosal-containing vaccines and immune globulins were received concurrently with antibiotic use³, and a third asked whether higher prenatal exposure exacerbated the effects of higher postnatal exposure. The results indicated that there were no significant differences between boys and girls in exposure effects for any of the autism outcomes, there was no evidence that higher prenatal exposure exacerbated the effects of postnatal exposure, and no evidence that exposure that was concurrent with antibiotic use was associated with adverse outcomes.

Much of the afore mentioned second phase analyses were focused on probing deeper to understand the phase I results and to try to determine if the results described above were sensitive to model specifications, to a few highly influential observations, or to potential sources of bias. Results are summarized below.

Low birth weight excluded: One line of inquiry was motivated by the question of whether mercury exposure had a more profound effect on low birth weight children. Since there were few low birth weight children in the sample, this question could not be adequately addressed by the typical approach of modeling interactions between birth weight and exposure measures. As an alternative approach, we fit models to the data where low birth weight children were excluded from the analysis and compared results to those from the full data set with low birth weight children included. The result of excluding low birth weight children was a slight attenuation of exposure effects toward zero. We concluded that the results did not provide evidence that thimerosal exposure has substantially different associations with autism for low birth weight individuals relative to higher birth weight children.

Use of alternative exposure variables: For the main analyses, measures of postnatal exposure were created by dividing the amount of mercury in each vaccine or immune globulin receipt by the child's weight in kilograms at the time of receipt, and then cumulating over the relevant age range (e.g., birth to seven months). During the design phase, consulting toxicologists had recommended that dividing by child's weight at the time of receipt would produce the most relevant measures of exposure. A question that arose in the second phase of analysis was, "are the results sensitive to the use of measures that divide by child's weight at time of exposure? Would similar results have been obtained if mercury amounts were cumulated over the relevant age range without

³ The analyses concerning thimerosal exposure concurrent with antibiotic use were motivated by animal studies that showed that excretion of orally ingested methylmercuric choride was slowed when taken concurrently with oral antibiotics (Rowland et. al, 1977, 1980, 1984). See Section 9.4.5 for details.

dividing by child's weight at the time of receipt?" Analyses with alternative measures, where there was no division by child's weight at the time of receipt, produced results that were very similar to the original results. We conclude that the results were not sensitive to division by child's weight at the time of receipt.

We also examined sensitivity of results to assumptions made about the amount of mercury in some of the immune globulins received by mothers while they were pregnant with the focus child. There were 53 prenatal immune globulin receipts where we did not have enough information to conclusively determine exactly which immune globulin product was received. For these receipts, we assumed that the most commonly used product (Rhogam) was received, and we assigned a mercury amount of 12.75 micrograms to each receipt. For an alternative analysis, we assumed that a product with a higher mercury content (50 micrograms) was received for each of these 53 receipts. We conclude that the results are not sensitive to this alternative assumption.

Exploration of functional form: The models used in the main analyses assumed a linear relationship between exposure and autism risk. We produced a series of residual plots to explore the question of whether some non-linear function (e.g., quadratic, step function, or threshold effect) would better describe the relationship between exposure and outcomes. The plots did not suggest that a non-linear functional form would be more appropriate than the linear assumption used for the main analyses.

Sensitivity to extreme exposure amounts and sensitivity to extreme residuals: We produced a series of residual plots to identify observations with potentially extreme exposure values or extreme residual values. We fit models with the potentially extreme values omitted and compared the exposure estimates to estimates from the full data set. We found no evidence that the results were highly influenced by a few extreme values.

Sensitivity to use of covariates in analysis models: The main analysis models controlled for a variety of factors that were potential confounders for the relationship of exposures to outcomes. To assess the sensitivity of the use of any covariates in the analysis models, we fit a set of models where no covariates were included. The models with no covariates did, however, include terms for the case-control matching strata in order to properly contrast cases to their matched controls. We concluded that the results for the primary research questions were sensitive to the use of covariates in the analysis models to control for potential confounding effects. In models that included only a single exposure variable as a predictor, and no other covariates other than the case-control matching strata, the relationships of postnatal exposure birth to seven months and birth to 20 months to AD and ASD outcomes were attenuated toward zero and not statistically significant. In the covariate adjusted models these exposure effects were statistically significant and in a direction that indicated that greater exposure was associated with decreased risk. For the subgroup analyses corresponding to the secondary research questions, the estimates obtained from models with no covariates were similarly attenuated toward zero, and for most, but not all outcomes, were not statistically significant.

To further explore the effects of covariates on exposure estimates we produced a set of exhibits that show the effect on the exposure estimates and their standard errors as covariates are dropped from the analysis models. At the top of each exhibit is the exposure estimate and standard error when all potential covariates were entered into the analysis model. The next row down shows the estimate and standard error after dropping the covariate with the highest p-value. The next row down shows the estimate and standard error after dropping the covariate with the next highest p-value, and so on until the last row that shows the estimate and standard error obtained from a model with no covariates. The results indicate that, with the exception of the birth weight covariate, the omission of any one particular covariate did not dramatically affect the exposure estimates. As each covariate was dropped, the general pattern was for the exposure effects to become slightly more attenuated toward zero, and the standard error of the estimate to become slightly smaller. Birth weight was the last covariate to be dropped, and after dropping it, the estimate for cumulative postnatal exposure for the age range from 29 days to seven months⁴ dropped to less than a fourth of its previous size.

As a follow up to the previous analysis, we tried dropping the birth weight covariate earlier in the sequence. The results indicate that when other covariates are included in the models, dropping the birth weight covariate does not have a dramatic effect on the estimate for cumulative exposure 29 days to seven months. Dropping the birth weight covariate did attenuate the effect somewhat, but it was still negative and statistically significant after dropping the term. We conclude that the results are sensitive to the inclusion of covariates, but that the birth weight covariate alone does not drive the result.

As specified in the analysis plan, the birth weight covariate was a categorical variable with five levels corresponding to birth weights less than one kilogram (KG); 1 to <1.5 KGs; 1.5 to <2.5 KGs; 2.5 to <4 KGs; and 4 KGs and above. We speculated that because there were very few cases and controls in the lowest birth weight categories, the sparseness of data in those categories may have caused unexpected estimation issues in the conditional logistic regression models, making the results sensitive to the coding of this variable. In order to investigate this, we tried re-running the models but with a birth weight variable that included only three categories: less than 2.5 KGs; 2.5 to <4 KGs; and 4 KGs. The results suggest that the postnatal exposure estimates were somewhat sensitive to the coding of the birth weight variable. For the primary research questions regarding AD and ASD, the use of the alternatively coded birth weight variable meant that the estimates for exposures birth to seven months, birth to 20 months, and 29 days to seven months were attenuated toward zero and not statistically significant. For the subgroup analyses used to address the secondary research questions, the estimates were also attenuated toward zero, but some remained statistically significant.

⁴ For these analyses we examined exposure estimates from models that had terms for prenatal exposure, cumulative exposure birth to 28 days, and cumulative exposure 29 days to 7 months. Because of the very high correlation between measures of exposure birth to 7 months, 29 days to 7 months, and birth to 20 months, we interpret the estimates from the exposure effects 29 days to 7 months as very good proxy for the effects of covariates on the measures for birth to 7 months and birth to 20 months.

Were overall results driven by results from one particular matching stratum? In order to assess whether the results were sensitive to the influence of one or a few highly influential observations within a single matching stratum, we tried re-fitting the analysis model to sequential subsets of data where, in each subset, all data from a single matching stratum were omitted⁵. For example, if one or a few highly influential observations were in Stratum “2”, then results from a model where the data were omitted from that stratum would be very different from the results when the data from the stratum are included. The investigation indicated that results are not sensitive to the inclusion / exclusion of data from any single matching stratum.

Were overall results driven by results from one particular HMO? To address this question we fit models separately to the data from the two largest HMOs and compared the results to the overall results⁶. The exposure estimates from each of the two large HMOs are similar in direction and magnitude to the overall results. However, they were seldom statistically significant due to the smaller sample sizes obtained when modeling separately by HMO. We conclude that the overall results were not primarily driven by the results in one particular HMO.

Analyses to assess potential physician opt-out bias: The study’s sampling and recruitment process required that physicians had an opportunity to opt-out their patients from being contacted for recruitment. During the design phase of the study, there was concern expressed among the group of External Expert Consultants that opportunity for physician opt-out could bias the results of the study if physicians selectively opted-out case families that they thought would have higher exposures. To address this concern, we planned analyses of the numbers and exposure levels of opted out families. The results indicated that at two HMOs less than one half of one percent of cases and controls were opted-out by physicians. At the third HMO, the protocol required active consent by physicians before families could be asked to participate. At this site, physician non-response was equivalent to opting-out. Consent was not obtained for 10 percent of cases and 9 percent of controls at that site. Analyses of exposure levels indicated that there was no evidence that physicians had opted out children with higher exposure levels. Additionally, there were no significant differences between the exposure levels of opted-out cases and opted-out controls.

Analyses to assess potential self-selection bias: Selection bias could have affected the results if the relationship between the decision to participate in the study and exposure was different for cases and controls. For example, if high exposure controls were more likely to participate than low exposure controls, and if exposure level was unrelated to the participation decision of cases, then mean exposure in the control group would be too high, and the estimate of the relationship of exposure to autism risk would be biased. In order to assess whether there was self-selection bias, we used VSD data, which was available for both participants and non-participants, to create measures of cumulative exposure for the age ranges birth to one month, birth to seven months, and birth to 20

⁵ This study used a case-control study design wherein controls were matched to cases within matching strata defined by birth year, sex, and HMO.

⁶ The sample size from the smallest HMO was not large enough to support separate analysis.

months. We then calculated the case-control differences in exposure amounts for the full sample, including both participants and non-participants. These are estimates of the case-control differences in exposure that would have been obtained if every sample member had chosen to participate. This represents a condition where self-selection bias could not have occurred. We also calculated the case-control differences in exposure amounts for the study participants. Comparison of the two sets of case-control differences provides an indication of whether self-selection to participate biased the exposure means in the participant group.

For the full sample, including both participants and non-participants, means of measures of cumulative exposure birth to seven months, and birth to 20 months were slightly higher for controls than for cases, but the case-control difference in exposure was not significantly different than zero. Likewise in the participant group, the control group means were slightly higher on these measures but again, the case-control difference was not significantly different than zero. The estimate of the case-control difference in the participant group was slightly larger than that estimated from the full sample, but the 95 percent confidence intervals for the case-control differences estimated from the participant group included the point estimate of the case-control difference from the full sample. These results indicate that self-selection was not a potent force affecting the results.

For the measure of exposure birth to one month, the case-control difference was positive (higher mean for cases) in the full sample, and negative in the participant sample, but both estimates of the case-control difference were close to zero and not significantly different than zero in a statistical sense. Again, the 95 percent confidence interval around the estimate from the participant group included the estimate from the full sample, so there is little evidence of self-selection bias here.

An additional analysis indicated no significant differences among participant cases, nonparticipant cases, participant controls, and nonparticipant controls in cumulative exposure amounts at ages 1, 7, or 20 months. These results suggest no evidence of self-selection bias.

An important caveat on these analyses is that the data used to create the measures of exposure used in this analysis came from VSD data only, and could not be verified using chart abstraction data as had been done in the main analyses. We did not abstract the charts of non-participants. We know that there was at least a small amount of measurement error in exposure measures that were used for this analysis.

The findings from the main analyses for the primary and secondary research questions indicated that higher levels of exposure in the age ranges birth to seven months and birth to 20 months were associated with lower risk of autism outcomes. One hypothesis was that self-selection bias was the cause of these unexpected results. The findings from the self-selection bias analyses were consistent with this hypothesis in the sense that the case-control difference in birth to seven month and birth to 20 month exposure amounts was slightly larger in the participant group than the full sample. However, in both the full

sample and the participant sample exposure levels were higher in cases than controls, and the differences between the estimates from the participant group and full sample were very small, and statistically indistinguishable from one another. We conclude from these results there was little if any evidence of self-selection bias in the participant sample.

Effects of having an older autistic sibling: The results of the main analyses indicated that higher exposure birth to seven months and birth to 20 months was associated with lower risk of autism. A factor contributing to those results was that, on average, cases had slightly lower exposure levels than controls. One set of analyses was designed to address a hypothesis that posits that the following two factors could result in lower average exposure for cases. 1) Autism risk is higher if a child has an older sibling with autism. Therefore, cases would be more likely than controls to have older siblings with autism. And 2) by the late 1990s theories regarding a vaccination-autism link were beginning to emerge. Parents that had one autistic child, or their physicians, may have been more likely to delay or decline vaccinations, or, if available, ask for thimerosal-free vaccines for subsequent children.

We found that for each exposure measure the mean exposure levels were slightly lower for children with older autistic siblings, but the differences were not statistically significant. We tried adding an indicator for having an older autistic sibling as a covariate to the analysis models but found that this addition had very little effect on the estimates of the exposure effects. We also tried fitting a set of models where children with older autistic siblings were omitted from the analyses, but again found that the exclusion of such children from the analysis had very little effect on the estimates of exposure effects.

Why were exposure levels higher in controls than cases? Was it because of a higher number of vaccines received by controls, or was it because of receipt of vaccines with higher thimerosal content? Analyses conducted to answer these questions indicated that:

- The number of vaccines received by cases and controls were close to identical.
- The cumulative amount of ethylmercury exposure from thimerosal-containing vaccines was close to identical up to about seven months of age then diverged slightly with controls having slightly higher exposure levels.
 - Differences between exposure levels of cases and controls were very small.
- The differences in exposure amounts were due to:
 - Hib receipts – cases were more likely to have thimerosal-free, or combined Hib vaccines (e.g., DTaP-Hib, HepB-Hib) than controls, resulting in lower cumulative exposure levels.
 - HepB receipts – cases were more likely to have thimerosal-free HepB vaccines than controls, resulting in lower cumulative exposure levels.

Analyses to assess potential recall bias: During the design phase of this study the issue of recall bias was identified by the Principal Investigators and External Expert

Consultants as an area of potential concern. The concern was motivated by the idea that the mothers of children with adverse health outcomes (e.g., autism) may be more likely to recall exposures that may have occurred during pregnancy or their child's infancy than the mothers of children with more positive health outcomes. For the measures of neonatal and early childhood exposure to thimerosal-containing vaccines and immune globulins, recall bias is not a concern because those measures were created from medical chart abstraction and computer automated (VSD) records. Measures of prenatal exposure to thimerosal-containing vaccines and immune globulins utilized information from both medical chart abstraction and from maternal report as part of the parent interview. Therefore measures of prenatal exposure could potentially be subject to the influence of recall bias. Additionally, some of the measures that were used as covariates in the analysis models had the potential to be influenced by recall bias.

In order to assess whether there is evidence of differential recall between mothers of case and control children, we conducted analyses that compared the agreement between data reported in medical charts and information reported during the parent interview by case and control mothers. None of the analyses produced results that support the hypothesis that there is differential ability on the part of case or control mothers to recall events or exposures during their pregnancies or during their child's early infancy.

Power analyses: The minimum detectable effects from the study were very close to what had been envisioned during the design phase. For ASD and the measure of prenatal exposure, the study had 80 percent power to detect an odds ratio of 1.39 for a 12.5 microgram increase in prenatal exposure to ethylmercury from vaccines and immune globulins. For exposures birth to one month, the study had 80 percent power to detect an odds ratio of 1.61 for a 12.5 microgram increase in exposure. For an increase of 50 micrograms of exposure to ethylmercury from vaccines and immune globulins received during the age range spanning 29 days to seven months⁷, the study had 80 percent power to detect an odds ratio of 1.56.

An alternative consideration of power is to ask, what were the minimum detectable effects for differences between low and high exposure for each of the exposure measures? As an indication of a difference between low and high exposure, we calculated the minimum detectable odds ratios for a difference of two standard deviations for each exposure measure. For these measures, a two standard deviation difference roughly corresponds to the difference between the 10th and 90th percentiles. For the ASD outcome, for each two SD increase in ethylmercury received in the prenatal, birth-to-one, birth-to-seven, and birth-to-20 month periods, the study had approximately 80% power to detect ORs of 1.5, 1.7, 2.1, and 2.2, respectively.

Refusal interviews: Refusal interviews were obtained from 10 to 20 percent of families at two HMOs that were contacted but refused to participate. Overall, 60 percent indicated that they did not participate due to time issues, and 21 percent indicated distrustful, negative or ambivalent attitudes towards research. The overall distribution of reasons for

⁷ The minimum detectable odds ratios for exposure birth to seven months and birth to 20 months were similar that described for 29 days to seven months.

non-participation, was significantly different for cases and controls. Greater proportions of controls indicated time constraints, distrustful, negative or ambivalent attitudes towards research, and child health issues, while cases were more likely to indicate that they did not want to subject their child to testing, a belief that their child was ineligible, and maternal health issues.

Health care seeking behavior: During the design phase of the study the issue of health care seeking bias was discussed in meetings that included the study's Principal Investigators and the panel of External Expert Consultants. The concept of health care seeking bias as it pertains to the current study is as follows. Suppose that people could be classified as active health care seekers, or not active health care seekers. One might expect that active health care seekers would be both more likely to get all of their child's recommended vaccines on time (thus increasing exposure), and be more likely to have their child assessed if they suspect anything unusual about their child's development (thus increasing the likelihood of getting a diagnosis of autism). While the people who are not active health care seekers would be more likely to skip or get vaccines late, and be less likely to have their child assessed.

The concern about health care seeking bias motivated the measurement of health care seeking behavior. During the design phase, the study's Principal Investigators and the panel of External Expert Consultants suggested the following three measures as proxies for an underlying, unobservable latent construct of health care seeking:

- Initiation of prenatal care;
- Frequency of pap smears;
- Frequency of blood cholesterol level tests.

The measures are selected as proxies for the underlying trait "health care seeker" on the premise that health care seekers would be more likely to initiate prenatal care early, would be more likely to have ever had a pap smear and be more likely to have had one within three years prior to the interview, and would be more likely to have ever had a cholesterol test and would be more likely to have had one within three years prior to the interview.

We conducted analyses to address the question, do mothers who are active health care seekers tend to have their children exposed to more mercury than those who are not? To be specific, models were used to examine the association between measures of mothers' health care seeking behavior and focus children's prenatal or postnatal mercury exposure. The hypothesis is that mothers who are active health care seekers would be more likely to have their children receive recommended vaccines according to the recommended schedule, and thus their children would have higher cumulative exposure amounts.

The results indicate that there were no statistically significant associations between any of the three measures of health care seeking and any of the measures of prenatal or postnatal exposure to ethylmercury from thimerosal-containing vaccines and immune globulins.

The results provide no compelling evidence to support the theory that health care seeking behavior is related to increased exposure. One possible explanation for the lack of significant associations is that the measures we used are poor proxies for the underlying latent construct of health care seeking. An alternative explanation is that the measures used are adequate proxies, but that the underlying construct (health care seeking) is not associated with increased exposure.

Study Limitations and Strengths

Our study, like all observational studies has inherent limitations. Specifically, although we were able to control for many potential confounders, there is no way of knowing if a critical confounder was omitted. The relatively low response rates suggest a potential for selection bias. However, our analyses of exposure levels of non-participants suggested that self selection was not a potent source of bias. Reporting bias can be a concern with case-control studies, particularly because of differential recall of exposures by cases and controls. Our measures of postnatal exposure were not susceptible to reporting bias because they were built from medical record abstraction and computer automated data sources. Our measures of prenatal exposure to thimerosal-containing vaccines and immune globulins were primarily built from medical record abstraction data, but also depended on maternal self-report, and hence could be susceptible to recall bias. However, none of our analyses to assess potential recall bias produced results supporting the hypothesis of differential recall of case and control mothers.

Additionally, all study children were HMO members for their first two years of life, and were members of the same HMOs six to 13 years later at the time of sample selection. If there were a relationship between a family's decision to leave or remain in the HMO that differed according to case/control status, then the results could be biased. For example, suppose that there were a family characteristic that increased the probability of missing or skipping vaccinations (resulting in lower exposure), that also increased the probability of switching insurers or leaving the area (resulting in ineligibility for the study). If there were no differential relationship, equal proportions of lower exposure cases and controls would have been excluded from the study. But suppose a greater proportion of the case families with the characteristic remained in the HMO because of the services they could get for their autistic child. If this hypothetical scenario played out, then controls would have higher average exposure than cases.

Since our analyses indicated that the number of immunizations received by cases and controls were almost identical (but that cases were more likely to have immunizations with lower mercury content), the hypothetical scenario described above does not seem likely. We do not, however, have exposure data on families that were not eligible because they left the HMOs, and we therefore cannot rule out the possibility that their omission from the study affected the results.

Conclusions

The results of this study did not support the hypothesis that higher exposure to ethylmercury from thimerosal-containing vaccines and immune globulins is related to increased risk of autism in our study population.

2. Document Overview

Volume I of the Technical Report is intended to present both study results and the technical details of study design, sampling, data sources, variable construction, and methods of analysis.

The executive summary was presented in Section 1, and Section 2 presents an overview of Volumes I and II of the Technical Report. Section 3 presents the historical factors that motivated the study, some background on mercury exposure and its effects on neurological development, the history and use of thimerosal in vaccines, a brief review of the literature on thimerosal and neurodevelopmental outcomes including autism, an introduction to the Centers for Disease Control's research program on thimerosal and vaccines, and the study's motivating research questions. Sections 4, 5, and 6 describe the study's design, sample, and data sources.

Section 7 presents detail on the construction of outcome measures, exposure measures, and covariates. This section also includes an explanation of imputations of missing values on covariates. Section 8 describes the analysis approach including a discussion of how measures of effect size are presented. Section 9 presents results. Included in Section 9 are descriptive statistics that describe the characteristics of the study participants and their amounts of exposure to ethylmercury from thimerosal-containing vaccines and immune globulins. The latter part of Section 9 presents summaries of the results of models used to estimate the size and statistical significance of associations between autism outcomes and exposure to ethylmercury from thimerosal-containing vaccines and immune globulins.

Volume II of the Technical Report provides additional detail about the study participants and the measures used in the study, and presents results of analyses that were conducted to better understand the results presented in Volume I, and whether they were sensitive to a variety of factors such as coding of variables, model specifications, covariates, potential outliers, or potential sources of bias.

3. Background and Research Questions

3.1. Statement of the Problem

Through the 1990s and into the 2000s, a dramatic increase in the nation's childhood immunization rates roughly coincided with an apparent marked increase in the prevalence of autism (California Health and Human Services Agency, 1999; Croen, Grether, Hoogstrate, & Selvin, 2002; Gurney et al., 2003; Yeargin-Allsop et al., 2003). Though the reasons for this increased prevalence are not clear, rising concern among the general public and in the scientific community has focused attention on possible associations with childhood vaccines.

Initial attention primarily focused on a possible link between the measles-mumps-rubella (MMR) combination vaccine and autism (e.g., Wakefield et al., 1998). Because autism is typically diagnosed at about the same time or soon after the standard age at which the final dose of the MMR is administered researchers and many parents of affected children called for research on autism and the MMR. A series of nine controlled observational studies, three ecological studies and two studies based on passive reporting system in Finland show evidence of no association between the MMR vaccine and autism (IOM, 2004)⁸, but concern has shifted to other possible pathways from vaccinations to autism. In particular, attention has focused on mercury. An ethylmercury-based preservative, thimerosal, had been used since the 1930's as a preservative in several regularly administered childhood vaccines. Thimerosal was used as a preservative in vaccines and immune globulins that were distributed in multi-dose vials.

One reason for the hypothesized link between ethylmercury exposure from vaccinations and the increase in autism is that between 1989 and 1998, as more vaccines with earlier administration times were added to the recommended childhood immunization schedule, average cumulative exposure to ethylmercury from vaccines subsequently rose.⁹ Calculations showed that some infants could have received, during their first year of life, doses of ethylmercury via childhood vaccines that exceed limits for methylmercury exposure established by public health and environmental agencies (Ball et al., 2001). Although Ball et al. found no evidence of harm from exposure to thimerosal in vaccines, in 1999 the U.S. Public Health Service and the American Academy of Pediatrics issued a joint statement that established the goal of removing thimerosal as soon as possible from vaccines customarily recommended for infants (AAP, 1999).

In 2001, the Institute of Medicine (IoM) reviewed then-available data on thimerosal and a variety of neurodevelopmental disorders, including autism. The IOM concluded that although the hypothesized association between thimerosal and neurodevelopmental delay

⁸ The IOM (2004) report reviews nine controlled observational studies (DeStefano et al., 2004; DeWilde et al., 2001; Farrington et al., 2001; Fombonne and Chakrabarti, 2001; Madsen et al., 2002; Makela et al., 2002; Takahashi et al., 2003; Taylor et al., 1999, 2002), three ecological studies (Dales et al., 2001; Gillberg and Heijbel, 1998; Kaye et al., 2001), and two studies based on passive reporting system in Finland (Patja et al., 2000; Peltola et al., 1998). They also reviewed two additional studies that they determined were uninterpretable due to methodological flaws.

⁹ In particular, the Haemophilus influenzae b (Hib) and hepatitis B (hepB) vaccines were added to the AAP's recommended schedule of vaccinations in 1990 and 1991 respectively. See Stehr-Green, et al., 2003.

was not well established, such a link was biologically plausible, and required further study (Stratton et al., 2001).

3.1.1. Research on the Neurotoxicity of Ethylmercury from Thimerosal-containing Vaccines and Immune Globulin Preparations

Subsequent to the recommendation to remove thimerosal from childhood vaccines several studies have been published that focus on the relationships between exposure to ethylmercury from thimerosal-containing vaccines and immune globulins and neurodevelopmental outcomes of children, including autism. These include studies by Verstraeten et al. (2003), Hviid et al. (2003), Madsen et al. (2003), Stehr-Green et al. (2003), Geier and Geier (2003a, 2003c, 2003c, 2004, 2005, 2006a, 2006b, 2006c, 2007), Heron et al. (2004), Andrews et al. (2004), Fombonne et al. (2006), Thompson et al. (2007), Miles and Takahashi (2007), Croen et al. (2008), Geier et al. (2008), Young, Geier and Geier (2008), Schechter & Grether (2008), and Tozzi et al. (2009).

The study by Verstraeten et al. (2003) calculated measures of exposure and outcomes using computerized records of three large HMOs. These records were developed and maintained as part of the Vaccine Safety Datalink (VSD) system, and as part of administrative record keeping systems. Three measures of exposure were calculated from the computerized records of vaccine receipts. These were cumulative mercury exposure from birth to 1 month, cumulative mercury exposure from birth to 3 months, and cumulative mercury exposure from birth to 7 months. Outcome measures were obtained from ICD-9 codes¹⁰ and were coded as the presence/absence of diagnoses of neurodevelopmental disorders. Outcomes included autism, “other child psychosis,” stammering, tics, sleep disorders, eating disorders, emotional disturbances, ADD, developmental language delay, developmental speech delay, speech or language delay, and coordination disorder. Results were reported separately for each of the three HMOs.

The study reported no significant associations between outcomes and 1-month cumulative exposure for any of the three HMOs. Significant findings were reported for associations between 3-month cumulative exposure and tics at one HMO, and 3-month exposure and language delay at a second HMO, and between 7-month cumulative exposure and language delay at the same HMO.

The study by Hviid et al. (2003) used computerized records corresponding to all children born in Denmark over the period January 1, 1990 to December 31, 1996 to estimate the relative risk of autism corresponding to cumulative ethylmercury exposure amounts of 0, 25, 75, and 125 micrograms. No significant associations were reported.

Madsen et al. (2003) used data from the Danish Psychiatric Central Register to examine incidence rates of autism diagnoses before and after the discontinuation of thimerosal-containing vaccines in Denmark in 1992. They concluded that there was no upward trend in

¹⁰ ICD-9 = International Classification of Diseases, Ninth Revision, Clinical Modification.

autism diagnoses before the discontinuation, but that the incidence of autism increased after the discontinuation of thimerosal-containing vaccines.

Stehr-Green et al. (2003) analyzed autism incidence rates in Denmark and in Sweden before and after discontinuation of thimerosal-containing vaccines and reported similar results to those reported by Madsen et al. (2003). In both countries, the incidence of autism diagnoses increased after discontinuation of thimerosal-containing vaccines. The source of autism cases used to calculate incidence rates in Sweden in the ecological analysis reported by Stehr-Green et al. (2003) has been criticized as being improperly restricted to inpatient hospitalization records, when most diagnoses of ASD occur in outpatient settings (Blaxhill, 2004; see Stehr-Green, 2004 for reply).

Each of the Geier and Geier (2003a, 2003c, 2003c, 2004, 2005, 2006a, 2006b, 2006c) studies report finding associations between thimerosal-containing vaccines and neurodevelopmental disorders. However, the Institute of Medicine (IOM) (2004), characterized the first four of those studies (2003a, 2003c, 2003c, 2004) as having serious methodological limitations that render the results uninterpretable. Parker et. al, (2004) also identifies multiple methodological concerns with the same studies. Like the earlier studies, the latter four papers (2005, 2006a, 2006b, 2006c) report results of analyses of the Vaccine Adverse Events Reporting System (VAERS) database. Detailed descriptions of potential biases and pitfalls that could arise from attempting to use the VAERS data to make causal inferences are provided in IOM (2004) and Parker et. al (2004).

In addition to the results from analysis of VAERS data, the Geier and Geier (2005) paper reports results from analyses of VSD data. Although the authors of the Geier and Geier (2005) paper claim to have analyzed the VSD data as independent researchers, major sections of the text and several tables match almost identically to text and tables included in a preliminary draft of the Verstraeten et. al. paper, described above¹¹. Young, Geier and Geier (2007) report results from analysis of VSD data and concluded that increased mercury exposure from thimerosal-containing vaccines was associated with each of the neurodevelopmental disorders they examined (autism, ASD, ADD/ADHD, developmental learning disorder/learning disorder not otherwise specified, disturbance of emotions specific to childhood and adolescence, and tics). The methodological abnormalities in this paper, however, render its results uninterpretable. For example, they claim to show increasing rates of neurodevelopmental disorders (NDs) over time concurrent with increases in mercury exposure over time. However, for the final two years in the time span they “augmented” the data by inflating the counts of children with NDs. They report that in the final two years, that they added the numbers 45 and 80 to the observed counts of children with autism.¹²

The results reported by Heron et al (2004) were based on a study of over 13,000 children in the United Kingdom. Exposure data came from the Bristol-based Child Health Surveillance Database. Outcome measures were created from maternal responses to the Strengths and

¹¹ Early pre-publication write-ups of the Verstraeten et. al. analyses obtained via the Freedom of Information act were posted on a web site and, at the time of this writing, are currently available on the web. See Verstraeten et. al. (2000) for details. For criticism regarding the differences in findings between preliminary and final analyses conducted by Verstraeten et. al. see Redwood (2004). For a response to criticism, see Verstraeten (2004).

¹² Additional methodological issues are described by EpiWonk at <http://epiwonk.com/>

Difficulties Questionnaire and the Child Behavior Checklist (behavior ratings), the Revised Denver Scale (fine motor development) and from other items in the maternal questionnaire (speech problems, tics, and special needs). Results of 69 hypothesis tests (23 outcomes times 3 exposure measures) from models that controlled for birth weight, gestation, maternal education, and other demographic characteristics of the child and family indicated nine significant associations between exposures and outcomes. One was in the direction of increased exposure being related to harm, the remaining 8 were in the direction of benefit. Poor prosocial behavior at 47 months of age was associated with higher 3-month exposure. Outcomes with associations in the direction of benefit were conduct problems, fine motor skills at 30 months of age, tics at 91 months of age, and two measures that are each indicators that the child has special needs. Several of these 5 beneficial outcomes had significant associations with two exposure measures, totaling 8 significant hypothesis tests.

The results reported by Andrews et al. (2004) were based on data obtained from over 103 thousand children in the United Kingdom. Exposure and outcome data were extracted from computerized medical records. Outcome measures were created from ICD-9 codes. Confounder variables used in their statistical models included gender, year of birth, and when significant, month of birth. They reported beneficial associations between increased exposure and general developmental disorders, ADD, speech or language delay, and unspecified developmental delay. In a special sub-analysis that excluded children who had not received all three recommended DTP vaccinations by one year of age, a significant harmful association between increased exposure and tics was found. In the full data set, the estimates for tics were in the harmful direction, but not statistically significant.

Fombonne et al. (2006) estimated the prevalence of pervasive developmental disorder (PDD) in cohorts of children in Montreal, Canada over a span of time that included the removal of thimerosal from childhood vaccines. They reported a statistically significant linear trend in the prevalence of PDD during the study period. They also reported that the prevalence of PDD in thimerosal-free birth cohorts was significantly higher than that in thimerosal-exposed cohorts. They concluded that thimerosal exposure was unrelated to the increasing trend in PDD prevalence in Montreal, Canada.

Schechter and Grether (2008) used data from the California Department of Developmental Services to study time trends in autism prevalence before and after the removal of thimerosal from childhood vaccines. They concluded that autism prevalence increased even after the discontinuation of thimerosal-containing childhood vaccines.

Thompson et al. (2007) used a retrospective cohort design to assess relationships between prenatal and early childhood exposure to ethylmercury from thimerosal-containing vaccines and immune globulin preparations and 42 neuropsychological outcomes. The outcome measures included speech and language indices, verbal memory, achievement, fine motor coordination, visuospatial ability, attention and executive functioning tasks, behavior regulation, tics, and general intellectual functioning. Autism was not an outcome. Among the 42 neuropsychological outcomes, only a few significant associations with exposure to mercury from thimerosal were detected. The detected associations were small and almost equally divided between positive and negative effects. Higher prenatal mercury exposure was associated with better performance on one measure of language and poorer performance on

one measure of attention and executive functioning. Increasing levels of mercury exposure from birth to 7 months were associated with better performance on one measure of fine motor coordination and on one measure of attention and executive functioning. Increasing mercury exposure from birth to 28 days was associated with poorer performance on one measure of speech articulation and better performance on one measure of fine motor coordination. The pattern of small numbers of positive and negative associations among a large number of hypothesis tests was consistent with what would be expected if exposure had no relationship to outcomes.

Tozzi et al. (2009) used data from a randomized controlled trial to compare neuropsychological performance, 10 years after vaccination of two groups of children exposed to different amounts of thimerosal from vaccinations. Twenty four outcomes were assessed including measures of memory and learning, attention, executive functioning, visuospatial functions, language, and motor skills. Comparisons were made between higher and lower exposure for the full group, for males, and for females, resulting in a total of 72 hypothesis tests. Two significant associations were found. For females, higher exposure was associated with poorer performance on the Boston Naming test and on the Finger Tapping Test with the dominant hand. Given that the expected number of false rejections of the null hypothesis for 72 tests is four, the authors concluded that the two significant findings may have been attributable to chance.

Four studies have focused on prenatal exposure to thimerosal via maternal receipt of thimerosal-containing immune globulins during pregnancy. Miles and Takahashi (2007a) calculated the proportions of autistic children, and as a comparison group, the proportions of children with down syndrome and other de novo chromosome disorders whose mothers had received a thimerosal-containing immune globulin during pregnancy. Both groups had sought care from the same university-based clinic in Missouri, but it is not clear from the paper if the eligibility criteria and selection mechanism for inclusion in the study were the same for both groups. No significant differences were found. The proportions whose mothers were Rh-negative were also compared for these two groups. Rh-negativity is used as a proxy for prenatal exposure because most the mothers would have received thimerosal-containing immune globulins during pregnancy. No significant differences were found. See Bernard et al. (2007) for criticism of the study and Miles and Takahashi (2007b) for a reply.

Croen et al. (2008) used a case-control design to assess potential association between ASD and prenatal exposure to thimerosal from maternal receipt of immune globulins during pregnancy. Cases and randomly selected controls were recruited from a large HMO. They reported finding no associations between either prenatal thimerosal exposure and ASD or between maternal Rh-negative status and ASD.

As a proxy for prenatal exposure to thimerosal-containing immune globulins, Geier and Geier (2007) compared Rh-negativity of the mothers of 53 patients with ASDs who consecutively presented their outpatient clinic for genetic/developmental evaluations in 2005 and 2006 to the Rh-negativity status of 926 pregnant women that presented to the same clinic between 1980 and 1989. It is not stated how those 926 were chosen out of all the pregnant women that presented to the clinic during that time period, or why that time period

was chosen to form a comparison group. They conclude that children with ASDs were significantly more likely to have Rh-negative mothers than the comparison group.

Geier et al. (2008) contrasted maternal Rh-negativity of children with a broader range of neurodevelopmental disorders (NDs) to the maternal Rh-negativity status of comparison groups. Data come from two clinics. At clinic A, maternal Rh-negativity status of 196 children with NDs was compared to that of 124 children without NDs. There is no information on how either set of children was selected for inclusion in the study. Clinic B is the same as reported on in the Geier and Geier (2007) paper, this time with the maternal Rh-negativity status of 87 ASD children compared to the Rh-negativity status of 1,021 pregnant women that presented to the same clinic between 1980 and 1989. Again in this paper, no explanation is given as to how this comparison group was selected or why it is appropriate. They conclude that the mothers of children with NDs were significantly more likely to be Rh-negative mothers than the comparison groups.

Some researchers have suggested that differences in the ability to metabolize mercury and other heavy metals may be related to the hypothesized association between thimerosal and autism. There may be subpopulations that do not efficiently eliminate mercury from the body (e.g., Stajich et al., 2000). Holmes et al. (2003) have reported that autistic children metabolize mercury differently from non-autistic children. It is not known whether this metabolic difference is causally linked to autism, or whether some factor associated with autism also alters the body's ability to eliminate mercury (and/or other heavy metals). The notion that thimerosal could cause autism only in certain pre-disposed individuals gained some support from a study by Hornig et al. (2004), who exposed four different strains of rats to thimerosal and reported abnormal development in only one of the rat strains, which was genetically predisposed to autoimmune diseases. Berman et al. (2008) used experimental procedures that closely followed the report by Hornig et al. (2004) but did not find evidence that the exposure caused abnormal growth or development.

3.2. Background on Autism

Autism is a neurodevelopmental disorder for which there are no biological screening tests but, rather, diagnosis is based on a set of behavioral criteria specified in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (DSM-IV-TR). These include impaired language development, profoundly disrupted social interaction and attachments, and severely-restricted play activities, which also are often characterized by a narrow range of interests and the presence of stereotyped, repetitive behaviors. Also common are an exaggerated fascination with inanimate objects and an extreme aversion to environmental changes. Boys are four to five times more likely to be autistic, and approximately 75 percent of autistic children also have some degree of mental retardation or impaired cognitive functioning. The disorder emerges early in life, and is usually diagnosed by the child's third birthday (DSM-IV-TR, 2000). Recently, systematic assessment tools have appeared, but these instruments still rely on clinical observation and parent report of child behavior.

The term "autism" is nonspecific but usually refers to one of a subset of the pervasive developmental disorders (PDDs) identified in the DSM-IV. We will follow the terminology

used in two recent reviews, Newschaffer et. al, (2002), and the British Medical Research Council (MRC, 2001). PDDs include childhood disintegrative disorder, Rett’s disorder, autistic disorder, Asperger’s syndrome, and Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS). Although these disorders share a pattern of qualitative impairment in communicative, social, and imaginative development, Rett’s disorder is distinguished by progressive physical and motor regression and is etiologically distinct from the other PDDs. Childhood disintegrative disorder is characterized by a period of normal development in language, social interaction, and play for at least two years, followed by a “devastating” regression in several of these areas before age ten (DSM-IV-TR). Clinicians and researchers also identify a subset of the PDDs, called Autism Spectrum Disorders (ASDs), that includes autistic disorder (synonymous here with “classic autism”), Asperger’s syndrome and PDD-NOS. These three PDDs appear related to one another along a continuum with respect to the intensity and severity of deficiencies (MRC, 2001; Newschaffer, et al., 2002). Exhibit 3.1 summarizes this terminology.

Between 15 and 40 percent of autistic children appear to exhibit age-appropriate development of communicative, social, and play behavior before onset of marked regression in these behavioral domains, usually at 15 to 19 months,. In these cases, children acquire relatively few words (i.e., less than 10) before deterioration becomes evident (MRC, 2001). This phenomenon is commonly referred to as “regressive autism,” a term which is not yet well-delineated. Halsey and Hyman et al. (2001) note that there is no standard definition of the term “regressive autism.” When parents report regression, they may note either an acute loss of a few words or phrases, or a loss that extended over a longer period of time. The difficulty in defining regressive autism is compounded by the fact that the onset of symptoms may actually differ from the age at which parents first notice any behavioral regression. When outside examiners view home videotapes taken of children before the parents first recognized symptoms, evidence of atypical development is sometimes apparent. Because of these challenges, researchers are actively developing new instruments to distinguish autism that appears relatively early from those cases where regression occurs after a period of ostensibly typical development.

Exhibit 3.1
Diagnostic Categories for Autism

Pervasive Developmental Disorders (PDDs)

- Childhood disintegrative disorder
 - Rett’s disorder
 - ***Autism spectrum disorders (ASDs)***
 - Autistic disorder (classic autism)
 - Asperger’s syndrome
 - Pervasive developmental disorder not otherwise specified (PDD-NOS)
-

Excluding cases of autism arising from identified chromosomal abnormalities or structural irregularities of the central nervous system (e.g., tuberous sclerosis complex (TSC); fragile-X syndrome), the etiology of ASDs is not known. However, evidence suggests a strong genetic component. Twin studies have reported significantly higher concordance rates for monozygotic than for dyzygotic twins. Evidence for a heritable component is bolstered by findings that siblings of cases are at a much higher relative risk than in the general

population. However, the absence of a single genetic model explaining the inheritance of ASDs, combined with reports of an apparent increase in the prevalence of ASDs since the 1990s, have fueled hypotheses about environmental causes, or more likely, an environmental trigger to a genetic predisposition during a critical developmental period (Newschaffer, Fallin, & Lee, 2002).

3.3. Research Questions

The study was specifically designed to answer ten primary research questions. This report distinguishes these questions from other questions that can potentially be answered by the study, or at least those that the study may shed some light on, but that ultimately were not the primary motivators of the study design. This second group of questions is relegated to the category of secondary research questions.

The primary research question of the study is whether there are associations between autism and children's prenatal or early postnatal exposure to ethylmercury from thimerosal. This research question actually involves five separate research questions corresponding to five time periods, from the prenatal period through age 20 months. In addition, each of the five research questions was asked about two primary autism outcome classifications: autistic disorder (AD) and autism spectrum disorder (ASD). The ASD category is a broader classification that includes children that satisfy diagnostic criteria for AD plus children with Asperger's syndrome and PDD-NOS.

Research questions about three other autism outcome categorizations were relegated to the status of secondary questions because the study was not specifically designed to ensure that the sample sizes of these subgroup analyses would be large enough to detect small effects. These outcomes include ASD not including AD (ASD-not-AD), ASD with regression, and AD with low cognitive function excluded. The ASD-not-AD category includes children who meet criteria for ASD but excludes children who meet criteria for AD. The ASD with regression classification consists of the subset of children that meet criteria for ASD and who also satisfy criteria for regression. The AD with low cognitive function excluded classification is the subset of children that meet criteria for AD, but where children with very low cognitive function are excluded. This subgroup analysis was motivated by the concern about whether the diagnostic instruments can accurately classify children with very low function. (The specific criteria and rationale for each of these outcome classifications are described in Chapter 7.)

Additional secondary questions concern (a) interactions between thimerosal exposure and factors such as sex and concurrent antibiotic use, and (b) comparison of ASD and AD cases to a special subset of "screened" controls. The set of screened controls excluded individuals with diagnoses that have been hypothesized to be related to thimerosal exposure.¹³ These diagnoses included: speech/language delay, learning disabilities, ADHD,

¹³ These questions were motivated by concern that if the control group included individuals with milder types of adverse neurodevelopmental outcomes, and if increased exposure to ethylmercury from thimerosal-containing vaccines and immune globulins were related to increased risk of those milder adverse neurodevelopmental, than inclusion of those individuals in the control group could attenuate the estimates of the risk of AD, ASD to ethylmercury exposure. For additional details, see Section 7.2.

and any history of tics. This “screened” control group was created as a subset of the main control group.

Primary Research Questions: Autistic Disorder

A primary research question for the study is to examine whether there are associations between a diagnosis of autistic disorder (AD) and children’s prenatal or early postnatal exposure to ethyl mercury from thimerosal. The research questions focus on five, sometimes overlapping, exposure periods:

- The prenatal period
- A birth dose (defined as exposure to thimerosal from the hepatitis B vaccine received within the first 28 days of life)
- Cumulative exposure from the 29th day of life through seven months
- Cumulative exposure from birth through seven months, and
- Cumulative exposure from birth through 20 months of age.

The five exposure periods correspond to the following five research questions:

- Is there an association between a diagnosis of autistic disorder and level of prenatal exposure to ethylmercury from thimerosal in vaccines or immune globulins received by the mother during pregnancy?
- Is there an association between a diagnosis of autistic disorder and level of exposure to ethylmercury from thimerosal-containing vaccines and immune globulins received at birth (defined as receipt of thimerosal-containing vaccines and immune globulins within the first 28 days of life), independent of vaccines received later in life?
- Is there an association between a diagnosis of autistic disorder and level of exposure to ethylmercury from thimerosal-containing vaccines and immune globulins received by the child between one through seven months of age, independent of effects from thimerosal exposure in the first 28 days of life?
- Is there an association between a diagnosis of autistic disorder and level of exposure to ethylmercury from thimerosal-containing vaccines and immune globulins received by the child from birth through seven months of age?
- Is there an association between a diagnosis of autistic disorder and level of exposure to ethylmercury from thimerosal-containing vaccines and immune globulins received by the child from birth through twenty months of age?

Primary Research Questions: Autism Spectrum Disorder

The primary research questions regarding autism spectrum disorder consist of the same questions as above, but with the child outcome *ASD* substituted in place of *autistic disorder*.

Secondary Research Questions: Subgroup Analyses

A set of secondary research questions consists of the same questions as above, but with the following child outcomes substituted in place of the outcome *autistic disorder*:

- ASD-not-AD
- *ASD with regression.*
- AD with low cognitive functioning excluded
- ASD w/Screened Controls
- AD w/Screened Controls

Secondary Research Questions: Possible Interactions with Thimerosal Exposure

The study tested for possible interactions (effect modifiers) of a small set of child characteristics on the relationship between thimerosal exposure and each of the autism outcomes (AD, ASD, ASD-not-AD, ASD with regression, AD with low cognitive function excluded, ASD w/Screened Controls, AD w/Screened controls). Two variables that will be tested for interaction effects are gender of child and concurrent antibiotic use at the time of receipt of vaccines. These variables were selected based on previous research findings on interaction effects with other developmental outcomes for children. Additional analyses will test for interactions between prenatal and postnatal exposure to thimerosal. The specific research questions concerning interactions with thimerosal exposure include:

- Does the association between autism outcomes and exposure to mercury from thimerosal in vaccines or immune globulins differ depending on the sex of the child?
- Is there an interaction effect of prenatal and postnatal exposure to mercury from thimerosal on the risk of autism outcomes?
- Does the association between autism outcomes and exposure to mercury from thimerosal in vaccines or immune globulins differ depending on the concurrent use of antibiotics by the child?

Also of interest was a possible interaction between low birth weight and thimerosal exposure. However, the number of low birth weight children in the sample was very small. Accordingly, we would expect that a traditional interaction test would have very low power to detect an effect. Therefore, our plans called for an investigation of the birth weight question from a different perspective. We planned to conduct subgroup analyses consisting of children who were of normal birth weight (>2500 grams). While these analyses do not provide estimates of exposure effects on low birth weight individuals, comparison of the parameter estimates from the normal birth weight subgroup to the full sample will provide an indication of whether the exposure estimates are sensitive to the inclusion/omission of low birth weight children in the analysis. Results of these analyses are shown Section 9.4.7.

In addition to the analyses designed to address the primary and secondary research questions specified above, some supplementary exploratory analyses were also planned. Those analyses are described and presented in the Volume II of the Technical Report.

4. Study Design

The study was designed to examine relationships between prenatal and early childhood exposure to ethylmercury from thimerosal-containing vaccines and immune globulin preparations, and risk of autism. The study used a matched case-control design, where controls were matched to cases on birth year, sex, and HMO. There was a three-to-one ratio of controls to cases. Study participants were recruited from three HMOs that participate in the CDC's Vaccine Safety Datalink.

All recruited cases had a diagnosis of autism spectrum disorder (ASD) in their medical records. Potential cases were identified via ICD-9 codes (299.0 or 299.8), text string search, or at one HMO, via autism registries. In order to ascertain whether case children met our study's criteria for ASD, autistic disorder (AD), and ASD with regression, case children were assessed in clinics using a standardized protocol which included child observation and maternal interview. Mothers of case children were administered the Autism Diagnostic Interview-Revised (ADI-R) (Rutter, LeCouteur, & Lord, 2003), and case children were directly assessed using the Autism Diagnostic Observation Schedule (ADOS) (Lord et al, 2003).

Only children who had never had a diagnosis of ASD were included in the control group. To reduce the likelihood that the control group included children with undiagnosed ASD, the Lifetime form of Social Communication Questionnaire (SCQ) (Rutter, Bailey & Lord, 2003) was administered as part of the maternal interview for children who had indications of neurodevelopmental difficulties. Children with SCQ scores 16 or above were excluded from the control group (Lord 2004).

Children's histories of vaccinations and immune globulin receipts were obtained from computer automated immunization records, and abstracted medical charts. Maternal receipts of vaccines and immune globulins during pregnancy were compiled from abstracted medical charts and self-report from maternal interviews. Mercury content of the vaccines and immune globulin preparations was determined by linking the manufacturer, lot number, and year of receipt information to published data, and manufacturer records (see Chapter 7 for details). Procedures for resolution of discrepancies between data sources or between records and recommended vaccination schedules are described in Chapter 7.

Relationships between exposure and autism outcomes were estimated using conditional logistic regression models that controlled for a range of potential confounding factors.

5. Sample

There were a total of 1,095 “full participant” children included in the study, including 321 cases and 774 controls. Full participant children (cases or controls) are defined as children for whom the study obtained all of the following: Parental consent to participate in the study; a completed parent interview; and a completed set of medical record abstractions. Full participating cases also had to have completed the clinical assessment used to verify case status. The 321 full participant cases include 256 that met the study’s criteria for ASD or AD, and 65 that were below criteria (i.e, did not meet criteria for classification as an ASD or AD case). The 774 full participant controls include 12 that were initially thought to be eligible but, upon analysis of medical chart abstracted data and parent interview data, were found to have exclusionary conditions. Those 12 full participant controls were excluded from all analyses. With 256 ASD cases and 762 matched controls the ratio of controls to cases was 2.98 to 1. Descriptions of eligibility and exclusionary conditions, sampling and recruitment processes, recruitment outcomes, and the sizes of analysis samples are provided in the sections that follow.

5.1. Eligibility and Exclusionary Criteria

Both the case and control children were recruited from three HMOs. Each HMO identified a pool of children in the appropriate range of birth years who were currently enrolled in the HMO when the study began. To be eligible for the study, in addition to falling within the specified age range, each child had to meet other eligibility criteria intended to ensure that the study would be able to obtain complete, accurate information on the child’s vaccination history. Eligibility criteria were checked at many stages during the sample creation process. First, during the creation of the sampling frame, children were excluded if the HMO’s automated data records showed evidence of the presence of an exclusionary condition. Ineligibles were also identified during recruitment and eligibility phone calls, and from analysis of parent interview data, and chart abstraction data. Eligibility and exclusionary conditions are listed below.

- **Child must have been born between January 1, 1994 and December 31, 1999.**
The sample of cases and controls for the study consisted of a cohort of children who were born into the participating HMOs between January 1, 1994 and December 31, 1999, making them 5.9 through 13 years of age at the time of the data collection. The birth date cutoffs were selected to be as broad as possible in order to maximize the size of the pool of potential cases. The rationale for the upper birth date cutoff of December 31, 1999 is that one of the HMOs switched to thimerosal-free vaccines by the spring of 2000, which means there would be little or no variation in exposure for children born later than December 31, 1999. The rationale for the lower birth date cutoff of January 1, 1994 concerns the availability of automated ICD-9 data for the identification of cases. Although automated vaccine data prior to 1995 are available at all three HMOs, there are no automated data available for identification of cases for

two of the HMOs prior to 1995. The date was extended backwards into 1994 since it was assumed that for a child born in 1994 who has autistic disorder, the diagnosis would likely not have been made until 1995, at the earliest. Therefore, autistic children born in 1994 were identifiable in the automated data.

- **Child must have been enrolled in the HMO at birth.** This requirement was intended to ensure that there are accurate data available on the child's receipt of the hepatitis B vaccination at birth and on the child's prenatal exposure from vaccines or immune globulins received by the child's mother during her pregnancy. The participating HMOs differ in how they define being "born into the HMO." At both HMO-B and HMO-C, it is defined as being born in a HMO system hospital. At HMO-A, it is defined as being born into that HMO's system, but not necessarily in an HMO-A hospital.
- **Child must have been a continuous member of the HMO for the entire first twenty-four months of life.** So that the study could obtain full information on the child's vaccinations during his/her first two years of life, the child's medical care in infancy must have been provided continuously from birth through 24 months, by the child's current HMO. "Continuous" membership was defined enrollment with no membership gaps for the age range spanning birth to 24 months.
- **Child must reside in the specified study area.** Controlling the geographic area within the HMO coverage could increase the comparability of the cases, as well as make the data collection more concentrated and therefore less expensive. During creation of the sampling frame, children that were known to live more than 60 miles from an assessment clinic were excluded from the sampling frame.

Children were excluded from the sampling frame if they had received experimental vaccine with unknown mercury content. Children were also excluded from the study if they had medical conditions with known causal links to autism symptoms, including:

- Fragile X syndrome,
- Tuberous sclerosis,
- Rett's Syndrome,
- Congenital rubella syndrome, and
- Angelman's syndrome.

Another exclusion is related to conditions that would keep a child from being able to participate fully in the child assessment.

- **Child had to be able to participate fully in the assessment,** i.e., s/he had to be able to walk on their own, and to hear or see adequately using eyeglasses or hearing aids if needed. The clinical assessment required that cases can see, hear, and walk

adequately. To maintain equivalence of the cases and controls this criterion was applied to both case and control children.

Other exclusions are related to the validity of the parent report data obtained on the children. For both case and control children, the following conditions had to be met:

- **The child's biological mother had to be available for the parent interview.** The requirement that biological mother be available for the interview was applied to ensure that data on prenatal exposures and early childhood exposures could be obtained.
- **The child must have lived with the biological mother an average of at least four days per week since birth.** This criterion was applied in order to ensure that the mother would be an accurate informant about the child's early and current medical and exposure history and behavior. (A child who had been hospitalized for a long period of time, and therefore living separately from his/her mother for some period of time, was not excluded based on this criterion, so long as the mother considered herself to be the child's primary caregiver since birth.)
- **The child's family must be fluent in English.** The mother had to understand English well enough to be interviewed in English. If verbal, the child had to use English as his/her primary language. Non-verbal children must reside in a home where English was spoken. This eligibility criterion was necessary for cases to participate fully in the clinical assessment, and was applied equally to cases and controls.

For controls, children who might have an undiagnosed ASD were excluded. Specifically,

- **For controls, children had to have a score on the Social Communication Questionnaire (SCQ) below 16.** A two-phase process was used to identify these controls. During the eligibility call, parents were asked if their child had any history of the following:
 - Attention deficit disorder or attention deficit hyperactivity disorder (ADD/ADHD);
 - A speech or language delay or impairment;
 - A diagnosed learning disability;
 - A tic disorder or Tourette's disorder; or
 - An Individualized Education Program (IEP) at school

If, during the eligibility interview, the parent indicated that a control child had a history of any of the above indicators, then the Social Communication Questionnaire (SCQ) (Rutter, Bailey, & Lord, 2003) was administered during the Parent Interview.

The SCQ, described in more detail later, asks parents about any abnormalities in social or communicative behavior or any exaggerated interests or repetitive, stereotyped play they may have noticed in the control child. Control children that scored above the criterion score (16 or above) were excluded from the analyses. This criterion score was established in consultation with Dr. Catherine Lord, co-developer of the ADOS and ADI-R assessment tools that were used in this study to confirm ASD and AD diagnoses. Seven children were excluded from the control group due to high SCQ scores.

For cases, only children with a confirmed ASD or AD diagnosis were included in the analyses.

- For cases, ASD or AD status had to be confirmed by clinical assessment.** To be eligible for recruitment, case children had to have evidence of an ASD or AD diagnosis in the HMO’s computer automated medical records data. Cases were identified via ICD-9 codes (299.0 or 299.8) text string search, and at one HMO, via autism registries. At all three HMOs inpatient and outpatient records were searched for occurrences of ICD-9 codes equal to 299.0 or 299.8, and text string searches outpatient clinic databases were conducted to identify any records of diagnoses in the ASD spectrum. At HMO-C, ASD registries were also used to identify children that had ASD diagnoses. As part of the Eligibility Interview, case families were asked to confirm that their child had received a diagnosis of ASD or AD. In a small number of instances, a case parent reported that the child had never had a diagnosis of ASD. These cases were handled slightly differently at each HMO. At one HMO these families were not invited for clinical assessment. At another HMO the Principal Investigator made sure that the family was contacted in order to explain why they were asked to participate in the study and to invite them to come for a clinical assessment to determine their child’s diagnosis. The procedure was similar at the third HMO, with the additional step of having the study staff contact the child’s physician first to determine whether it was appropriate to invite the family to participate in a clinical assessment. Only case families that agreed to come in for a clinical assessment were later assessed. Finally, only those case children that met criteria for ASD or AD from the clinical assessment were included in the analyses. The clinical assessments and study criteria for designation as ASD and AD are described in a subsequent section.

Exhibit 5.1.1 lists the eligibility criteria and exclusion criteria and the source of the information on each.

Exhibit 5.1.1

Eligibility and Exclusion Criteria for the Sample and Source of Information

VSD	Medical	Eligibility
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	Automated Database	Record	and Parent Interviews
Eligibility Criteria			
Born between 1/1/94 and 12/31/1999	X	X	X
Child currently enrolled in HMO (at time of recruitment)	X		
Child enrolled in HMO at birth	X		
Child enrolled in HMO for entire 1st two years	X		
Child resides in study area	X		X
Exclusions: Cases and Controls			
Received experimental vaccine with unknown mercury content	X		
Fragile X syndrome, tuberous sclerosis	X	X	X
Rett's syndrome	X	X	X
Congenital rubella syndrome	X	X	X
Angelman's syndrome	X	X	X
Child not with biological mother majority of time since birth and/or currently			X
Child and/or mother do not speak/understand English fluently			X
Child unable to walk on own; hearing/vision impairments are uncorrected			X
Exclusions: Controls Only			
Previous diagnosis of autism spectrum disorder	X	X	X
Score above criterion on SCQ			X
Exclusions: Cases Only			
Child did not have previous diagnosis of autism spectrum disorder (cases)	X		X
Child did not meet study criteria for AD or ASD ^a			
^a See Section 7.1 for explanation of the use of ADOS and ADI-R assessments for defining study criteria for AD and ASD.			

5.2. Sample Selection

The study population was comprised of children born between 1/1/94 and 12/31/99 who were currently enrolled¹⁴ in any of the three participating HMOs, and were enrolled at birth, and were enrolled for their first two years of life, and who resided in the study areas. The population was also defined by the exclusionary criteria listed in Exhibit 5.1.1. For example the population was defined as including only children whose mothers could speak and understand English fluently, could walk on their own, and who did not have uncorrected vision or hearing impairments.

A sampling frame is a list of population members from which a sample can be drawn. The sampling frame for the current study was created in collaboration with the data managers

¹⁴ Currently enrolled was defined as enrolled in the third quarter of 2004.

from each of the three HMOs participating in the study. HMO data managers first created a preliminary sampling frame by selecting records from their VSD database that satisfied criteria based on birth year, HMO enrollment, and residence within study area. Abt Associates Inc. then created the final sampling frame by applying additional exclusionary criteria based on medical conditions that were identifiable in the automated data records. We note that in the sample frame creation phase, the only data sources regarding eligibility and exclusionary criteria were the VSD automated data records (see check marks for data source in Exhibit 5.1.1.) During the physician opt-out, recruitment and analysis phases, eligibility and exclusionary criteria were checked and re-checked, and in many instances, children that were included in the sampling frame and sample were subsequently found to be ineligible.

After creation of the final sampling frame, samples were drawn. All cases in the sampling frame were included in the sample. Samples of controls were drawn in two phases. In the first phase, a pool of controls was drawn. The IDs of all cases and the pool of phase I sampled controls were sent to the children's primary care physicians who were given the opportunity to opt-out any children that they thought should not be asked to participate in the study. After the physician opt-out phase was complete, the IDs of cases were sent to recruitment in batches, and the phase II sampling of controls commenced. The goal of phase II sampling of controls was to obtain approximately three confirmed controls per confirmed case within each birth year by sex by HMO matching stratum. In order to have the best chance of obtaining the target control-to-case ratio, phase II sampling and recruitment of controls lagged slightly behind recruitment and assessment of cases.

To understand the phase II sampling process, consider a matching stratum with two cases in the sample frame. If both cases participated and were confirmed in the clinical assessment as meeting criteria for ASD, then we would want to have six confirmed controls in this stratum. If, however, neither of the cases in this stratum met study criteria for ASD, then we would want to have recruited zero controls from this stratum. Any data collected from controls in this stratum would have no use in the study because these controls would not be matched to confirmed cases. To balance the need to keep the study moving with the need to approximately obtain the target ratio of controls to cases, we could not wait for cases to go through the entire process before recruiting controls. To carry the current example further, in a first batch release of sample to recruitment, we would have released the IDs of both cases to recruitment, and drawn a phase II sample of three controls from the phase I pool of controls. We would not anticipate that all three controls would participate. If neither case were confirmed in this stratum, we would have only obtained only 1 to 3 controls that were not needed. However, if one or more cases had agreed to participate or were confirmed, then additional phase II random samples of controls would be drawn in anticipation of the need for additional controls in this stratum.

In phase I, a sample was drawn that included all cases in the sampling frame and a sample of controls that was matched to cases within matching strata defined by birth years, sex, and HMO. Using SAS Proc SurveySelect, a stratified random sample of controls was selected from the sampling frame. The allocation of the number of controls to select from each birth year by sex stratum, within an HMO, was based on the number of cases in the stratum, on the

desire to have approximately three confirmed controls for each confirmed ASD case¹⁵, and on assumptions about the ratios of sampled-to-confirmed cases and controls that would be obtained. Specifically, the number of phase I controls selected from each stratum was based on assumptions that:

- The sampled-to-confirmed ratio of cases could be as low as 1 to 1 (i.e., within any particular stratum, all sampled cases could be classified as confirmed cases);
- The sampled-to-confirmed ratio of controls could be as high as 5 to 1 (i.e., within a stratum, as few as 1 out of 5 sampled controls could become confirmed controls);
- The desired ratio of confirmed controls to confirmed cases within each stratum was 3 to 1.

Therefore, for each stratum the number of controls selected for inclusion in the phase I sample was:

$$\# \text{ of sampled controls} = (\# \text{ cases}) * 1 * 5 * 3.$$

The following examples show the number of controls sampled within particular strata at HMO-A. All 30 potential cases in the sampling frame were included in the sample. Within the birth year by sex stratum defined as “1994-males” there were 5 cases. Therefore, using SAS Proc SurveySelect, a random sample of $5 * 1 * 5 * 3 = 75$ matching controls from the “1994-males” was selected into the sample. Similarly, for the stratum “1994-females” there was one case, and $1 * 1 * 5 * 3 = 15$ matched controls were selected from the stratum.

Exhibit 5.2.1 shows the numbers in the preliminary and final sampling frames, the phase I sample numbers, the numbers of physician opt-outs, and finally, the numbers of phase II sample members that were sent to recruitment. In order to allow for comparisons between the rates of diagnosed ASD cases in the sampling frames used for the current study, and ASD rates reported elsewhere, the exhibit also shows the case rate per 1,000 in the preliminary and final sampling frames for each HMO and the combined group across HMOs.

The study’s internal review boards¹⁶ (IRBs) required that, prior to recruitment, each sampled child’s primary care physician be contacted and offered the opportunity to opt-out children from the study. The numbers of cases and controls that physicians opted-out of participation are shown, by HMO, in Exhibit 5.2.1. In two of the three HMOs the numbers of opt-outs were very low for both cases and controls. In the two HMOs with low opt-out rates, the HMO’s IRBs required only that the physician be notified and had the opportunity to decline participation for families. At the third, the HMO’s IRB required written permission from the primary care physician before the child’s mother could be invited to participate. The site that required written permission from physicians had considerably higher opt-out rates, but within that site, the proportion of cases for which permission to participate was not obtained was very similar to the control proportion.

¹⁵ A “confirmed case” is a case that participated in the study, meets eligibility criteria, and meets the criteria from the clinical assessment for classification as ASD. A “confirmed control” is a control that participated in the study and meets eligibility criteria.

¹⁶ Each of the three HMOs, the CDC and Abt Associates had an IRB that reviewed all aspects of the study’s protocol.

For additional details about the sampling frame, see Chapter 22.

Exhibit 5.2.1. Numbers in Sampling Frame, Sample, Physician Opt-outs and Numbers Sent to Recruitment

	HMO-A			HMO-B			HMO-C			All		
	Case	Cntrl.	Case Rate Per 1000 ^a	Case	Cntrl.	Case Rate Per 1000 ^a	Case	Cntrl.	Case Rate Per 1000 ^a	Case	Cntrl.	Case Rate Per 1000 ^a
Preliminary Sampling Frame	30	3,745	7.9	384	43,065	8.8	549	41,689	13.0	963	88,499	10.8
Final Sampling Frame	30	3,464	8.6	303	33,188	8.7	477	34,149	13.8	810	70,801	11.3
Phase I Sample (Sent to Physicians)	30	450		303	1,887		477	2,688		810	5,025	
Identified as Ineligible by Physician	0	1		8	124		0	0		8	125	
Physician Opt-out	0	2		29	167		2	5		31	174	
Sample Remaining after Opt-outs	30	447		266	1,596		475	2,683		771	4,726	
Phase II Sample (sent to recruitment)	30	80		266	806		475	1,874		771	2,760	

^a Case rate per 1000 calculated as $1000 * (\# \text{ cases} / (\# \text{ cases} + \# \text{ controls}))$ – All available cases were included in samples, therefore the rate was not calculated for samples because it is not relevant.

5.3. Recruitment Process and Outcomes

The recruitment process included the following steps:

- A. If the physician agreed to let the study contact the parent, parents were informed of the study via an HMO recruitment letter. Parents who did not want to participate had the option to send back an opt-out card indicating their refusal to participate.
- B. Parents who did not send back the opt-out card were contacted by telephone for recruitment by the HMO.
 - a) A sample of the parents who were contacted by phone and refused to participate were administered a refusal interview.
- C. For parents who agreed to participate in the recruitment telephone call, Abt Associates Inc. conducted eligibility screening using the telephone eligibility interview.
- D. Eligible parents were then interviewed by telephone by Abt Associates Inc., using the parent interview.

- E. For cases, parents and children were asked to come to a clinic at their HMO, where the child assessments were conducted.
- F. For controls and cases that had completed the requisite parent interviews and clinical child assessments, medical records were abstracted by HMO staff.

A. HMO Recruitment Letter: Once the physicians had been informed and had a chance to let the HMO know if any particular families should not be contacted, the HMOs sent the mother of each of the remaining target families a personalized recruitment letter, with an informational brochure about the study. This letter and brochure briefly described the study and invited the family to participate. The study description included mention of the incentives that were offered to participating families. To thank them for the time they spent in the study, both cases and controls were given a \$75 American Express gift check upon completion of the telephone Parent Interview. In addition, for participation in the clinic assessment visit, case families were offered a \$150 gift check, and the case child received a \$25 gift certificate to a book/music store chain. The study description also informed parents that they would be reimbursed for any transportation and child care costs that were incurred because of the clinic visit.

A postcard was enclosed with the letter that the parent could return to the HMO indicating either wanting to opt in to the study or wanting not to be contacted. Any parent who indicated a willingness to be contacted, either by returning the postcard or by calling the toll-free number, was contacted by an HMO recruiter. Parents who did not send back the postcard within three weeks were also called by an HMO recruiter.

B. Recruitment Call: In the recruitment telephone call, the HMO recruiter described the study activities to the mother, answered any questions she might have about it, and asked if she were willing to be contacted by a representative of Abt Associates Inc. If the parent agreed, the family's contact information was passed on to Abt Associates Inc.. The recruitment of the sample was conducted on a rolling basis, depending on the timing of IRB approval at each HMO, the training of the necessary staff, and the size of the case sample provided at each HMO. **(a). Refusal Interview:** A sample of families who indicated during the Recruitment Interview that they were not going to participate in the study were asked to complete a short Refusal Interview. The Refusal Interview asked respondents to provide reasons for their refusal and for basic information on family background and child developmental status, so that the study could track non-response data and determine whether or not any systematic differences existed between the participating and non-participating families. Families were offered a \$25 American Express gift check to participate in the refusal interview.

C. Eligibility Interview: When a family agreed to participate, its contact information was provided to Abt Associates Inc. survey staff who took responsibility for conducting further screening of potential participants. Each family was contacted by telephone and was

administered an eligibility interview. The eligibility interview was programmed on CATI (Computer Assisted Telephone Interviewing).

D. Parent Interview: The parent interview was conducted with the child's biological mother via telephone for all eligible cases and controls. For a subset of controls, a portion of the parent interview comprised the second step in a two-step process to assess eligibility. This process was described previously in the section on Eligibility and Exclusionary Criteria. Additional details on the content of the parent interview are included in a subsequent section.

E. Clinical Assessment: Potential cases who had completed the parent interview were clinically assessed to determine whether they met criteria for inclusion in the study analyses as ASD or AD cases. The clinical assessment is described in a subsequent section.

F. Medical Record Abstraction: After completion of the parent interview, the clinical assessment (cases only), and consents¹⁷, medical records of participant children and their mothers were abstracted to produce study data. The medical record abstraction data are described in a subsequent section.

Recruitment outcomes are summarized overall and by HMO in Exhibit 5.3.1. The exhibit shows that of 771 cases in the sample, completed parent interviews were obtained for 386 (50%), and of 2,760 sampled controls, completed parent interviews were obtained for 774 (27%). There was considerable variation across sites in recruitment outcomes: The percentage of controls that could not be located or were passive refusals was much higher at HMO-C than at the other HMOs. The difference in participation rates between cases and controls motivates the question of whether participation was related to exposure. See Volume II, Chapter 14 for results of analyses that address this question.

Exhibit 5.3.2. shows the numbers of cases that had complete clinical assessments and who were assigned scores on both the ADOS and the ADI-R. The exhibit shows that 65 cases that had completed the parent interview did not complete the clinical assessments. These incompletes occurred when families canceled appointments for assessments and could not re-schedule, or for 18 of the 65, when the mother indicated that her child did not have ASD or AD and did not want to participate in the clinical assessment.

Medical records were abstracted for all 321 cases that had complete clinical assessments, and all 774 controls that had complete parent interviews, for a total of 1,095 full participants in the study.

We calculated response rates as described in The American Association for Public Opinion Research (AAPOR), 2008, *Standard Definitions: Final Dispositions of Case Codes and*

¹⁷ The procedures for obtaining informed consent from parents for each of the data collection activities (Parent Interview, Medical Record Abstraction, and Clinic Visit) were reviewed and approved by the Institutional Review Boards (IRBs) from the CDC, Abt, and the three HMOs.

Outcome Rates for Surveys. 5th edition. Results for cases and controls, and for the combined group of cases and controls are shown in Exhibit 5.3.3.

Exhibit 5.3.1.1. Recruitment Outcomes Through Parent Interview

Recruitment Outcome	HMO-A		HMO-B		HMO-C		All Combined									
	Case n	%	Case n	%	Case n	%	Case n	%								
Ineligible	3	10.0	4	5.0	12	4.5	62	7.7	88	18.5	250	13.3	103	13.4	316	11.4
Unlocated, Passive Refusal	0	0.0	1	1.3	9	3.4	35	4.3	19	3.8	431	23.0	27	3.5	467	16.9
Refused	11	36.7	39	48.8	88	32.0	356	44.2	159	33.5	808	43.1	255	33.1	1203	43.6
Completed Parent Interview	16	53.3	36	45.0	160	60.4	353	41.1	210	44.2	385	20.4	386	50.1	774	27.3
Total	30	100.0	80	100.0	266	100.0	806	100.0	475	100.0	1874	100.0	771	100.0	2760	100.0

“Ineligible” = Child was determined to be ineligible during recruitment call, eligibility call, or parent interview.

“Unlocated, Passive Refusal” = Family could not be reached or did not answer or return calls after repeated attempts.

“Refused” = Family was contacted and declined to participate.

“Completed Parent Interview” = Mother completed the parent interview.

“Total” = Total number of children that were invited to participate in the study.

Exhibit 5.3.2. Completion of Clinical Assessment

Recruitment Outcome	HMO-A		HMO-B		HMO-C		All Combined	
	Case n	%	Case n	%	Case n	%	Case n	%
Clinical Assessment Not Completed	6	37.5	27	16.9	32	15.2	65	16.8
Clinical Assessment Completed	10	62.5	133	83.1	178	84.8	321	83.2
Total	16	100.0	160	100.0	210	100.0	386	100.0

“Clinical Assessment Not Completed” = Number of children that did not complete both parts of the clinical assessment (ADOS and ADI-R).

“Clinical Assessment Completed” = Number of children that had completed both parts of the clinical assessment (ADOS and ADI-R) and had scores on both assessments.

“Total” = Total number of case children that had completed parent interviews and were invited to participate in the clinical assessment.

Exhibit 5.3.3. Response Rates

		<u>Cases</u>	<u>Controls</u>	<u>Total</u>
C	= Complete	321	774	1095
P	= Partial	65	0	65
Enp	= Eligible non-participant	255	1203	1458
Unp	= Unknown eligibility non-participant	27	467	494
NE	= Not eligible	103	316	419
e	= Estimated proportion of Unp that are eligible	0.86	0.86	0.86
RR1	= Response Rate 1 (minimum response rate)	0.48	0.32	0.35
RR2	= Response Rate 2 (counts partial completes as participants)	0.58	0.32	0.37
RR3	= Response Rate 3 (uses estimate of the proportion with unknown eligibility that are eligible)	0.48	0.33	0.36
RR4	= Response Rate 4 (like RR3, but includes partials as participants)	0.58	0.33	0.38

For cases, these are participants that completed the parent interview and completed the clinical assessment. For controls, these are participants that completed the parent interview.

These are cases that completed the parent interview, but did not complete the clinical assessment.

These are families that were contacted and refused to participate (active refusals).

These are families that could not be reached, or did not answer or return phone calls after repeated attempts (unlocated and passive refusals). Since these families were never contacted, eligibility status could not be ascertained.

Child was determined to be ineligible during recruitment call, eligibility call, or parent interview.

Calculated as: $e = 1 - \left(\frac{NE}{NE + C + P + Enp} \right)$

$RR1 = \frac{C}{C + P + Enp + Unp}$

$RR2 = \frac{C + P}{C + P + Enp + Unp}$

$RR3 = \frac{C}{C + P + Enp + e(Unp)}$

$RR4 = \frac{C + P}{C + P + Enp + e(Unp)}$

Response rates calculated as described in AAPOR, 2008.

5.4. Clinical Assessment Outcomes

Details on the clinical assessment process and criteria for classification of outcomes are presented in Chapter 7. A summary of outcomes of the clinical assessment of cases, overall and by HMO, is presented in Exhibit 5.4.1. Overall, 80 percent of assessed cases met study criteria for the ASD classification. Of those that met criteria for ASD, 73 percent also met criteria for classification as AD, and 19 percent also met criteria for classification of ASD with regression. Of those that met criteria for AD, 12 percent met criteria for AD with low cognitive function.

Exhibit 5.4.1. Summary of Clinical Assessment Outcomes for Cases

Assessment Outcome	HMO-A		HMO-B		HMO-C		All Combined	
	N	%	N	%	N	%	N	%
Met criteria for ASD	9	90.0	110	82.7	137	77.0	256	79.8
Did not meet criteria for ASD	1	10.0	23	17.3	41	23.0	65	20.2
Total Assessed	10	100.0	133	100.0	178	100.0	321	100.0
Met criteria for AD	7	77.8	83	75.5	97	70.8	187	73.0
Met criteria for ASD not AD	2	22.2	27	24.5	40	29.2	69	27.0
Total ASD	9	100.0	110	100.0	137	100.0	256	100.0
Met criteria for ASD with regression	4	44.4	21	19.1	24	17.5	49	19.1
ASD but did not meet criteria for regression	5	55.6	89	80.9	113	82.5	207	80.9
Total ASD	9	100.0	110	100.0	137	100.0	256	100.0
Met criteria for AD with low cognitive function	2	28.6	11	13.3	9	9.3	22	11.8
AD but did not meet criteria for low cognitive function	5	71.4	72	86.7	88	90.7	165	88.2
Total AD	7	100.0	83	100.0	97	100.0	187	100.0

5.5. Sizes of Analysis Samples

As described in the previous section, the study obtained complete data on 774 full participant controls and 321 full participant cases. However, analyses were based on smaller subsets of data for several reasons. First, 12 controls were omitted from all analysis data sets because of exclusionary conditions that were discovered upon analysis of chart abstraction or parent interview data. These included 7 that were excluded due to high SCQ scores, 2 that were excluded because the data indicated they had received a diagnosis of Asperger's syndrome, 1 because of diagnosis of tuberous sclerosis, and 2 because of diagnosis of pervasive developmental disorder. Analyses of these data sources did not reveal the presence of any exclusionary conditions among the full participant cases. Thus, after exclusion of the 12 controls described above, there were a total of 762 full participant controls and 321 full participant cases for a total of 1,083 records that could potentially be used in analyses.

Data from full participants were omitted from the analysis samples for any of three reasons. First, for cases, if their clinical assessment results indicated that they did not meet criteria for the ASD or AD condition in the target analysis, their data were excluded. For example, for a child's data to be included in the analysis for the contrast of AD cases to matched controls, the child had to meet study criteria for classification as AD. The data from case children who met criteria for ASD but not AD, and from children who did not meet criteria for ASD were omitted from this analysis. The criteria used by the study for classification into the various groups (e.g., ASD, AD, ASD with regression) are described in a subsequent section. In the current section, we simply provide the numbers of children that met the criteria for each condition and were therefore included in analytic samples.

Another reason for omission from analysis samples was applicable only to controls. Controls were matched to cases on birth year, sex, and HMO¹⁸. Controls in a matching stratum that had no corresponding matched cases were omitted from the analytic sample. For example, in the final sample frame there was one case in the matching stratum defined as males, born in 1996, in HMO-A. If that case had participated and had been a confirmed ASD case, we would have needed three matching controls in that stratum. In anticipation of the potential need for controls in that stratum, the IDs of several controls were released to recruitment, and two controls from that stratum participated. However, the single case in that stratum did not participate in the study. Therefore, the two participant controls in that stratum did not match to any cases in the study and therefore could not be used. They were excluded. There were no instances of exclusion of cases due to lack of matching controls. But there were times when we recruited controls that did not match to cases.

As another example, consider the more restrictive outcome classification "ASD with regression." There were only 49 cases that satisfied criteria for that outcome classification. For analyses where ASD with regression cases are contrasted to matched controls, we only used the controls from the same strata as those 49 cases. Thus, there were a large number of controls (110) that were not used in that analysis because they did not come from the same matching strata as the ASD with regression cases.

Exhibit 5.5.1 shows the numbers of cases and controls in each analysis data set, and the numbers that were omitted from the analyses for the reasons described above.

¹⁸ When it became clear that there were an insufficient number of potential cases in the original three HMO populations, an additional population was added to the study. This additional population came from within the HMO-C HMO system, but was geographically distinct from the original HMO-C population. Controls from the original HMO-C population are matched to cases from the original HMO-C population. And likewise, controls from the second HMO-C population were cases from the same population. Thus the matching strata were defined by six birth years (1994 - 1999), two sexes (males, females), and four HMO/regions (HMO-A, HMO-B, HMO-C region 1, HMO-C region 2), producing a total of $6 \times 2 \times 4 = 48$ matching strata.

Exhibit 5.5.1 Size of Analysis Samples

Contrast: ASD Cases vs Matched Controls		Cases	Controls	Total
Omitted from data set	Did not meet criteria for ASD classification	65		
	No matching Cases in stratum		10	
Included in data set	Size of analysis sample	256	752	1,008
	Total	321	762	1,083

Contrast: AD Cases vs Matched Controls				
Omitted from data set	Did not meet criteria for AD classification	134		
	No matching Cases in stratum		38	
Included in data set	Size of analysis sample	187	724	911
	Total	321	762	1,083

Contrast: ASD-not-AD Cases vs Matched Controls				
Omitted from data set	Did not meet criteria for ASD-not-AD classification	252		
	No matching Cases in stratum		58	
Included in data set	Size of analysis sample	69	704	773
	Total	321	762	1,083

Contrast: ASD with Regression Cases vs Matched Controls				
Omitted from data set	Did not meet criteria for ASD w/Reg. classif.	272		
	No matching Cases in stratum		110	
Included in data set	Size of analysis sample	49	652	701
	Total	321	762	1,083

Contrast: AD with Low Cognitive Functioning Excluded vs Matched Controls				
Omitted from data set	Did not meet criteria for classification	156		
	No matching Cases in stratum		43	
Included in data set	Size of analysis sample	165	719	884
	Total	321	762	1,083

Contrast: ASD Cases vs Matched "Screened" Controls		Cases	Controls	Total
Omitted from data set	Did not meet criteria for ASD classification	65		
	No matching Cases in stratum		10	
	Did not meet criteria for "Screened"		186	
	No matching Controls in stratum	1		
Included in data set	Size of analysis sample	255	566	821
	Total	321	762	1,083

Contrast: AD Cases vs Matched "Screened" Controls		Cases	Controls	Total
Omitted from data set	Did not meet criteria for AD classification	134		
	No matching Cases in stratum		38	
	Did not meet criteria for "Screened"		182	
	No matching Controls in stratum	1		
Included in data set	Size of analysis sample	186	542	728
	Total	321	762	1,083

6. Data Sources

6.1. Data Collection Overview

Data were obtained for the current study through the data collection activities listed below:

For cases and controls:

- Parent Interview with the biological mother, conducted by telephone by Abt Associates Inc.
- Maternal and child medical chart abstraction, conducted by the HMOs;
- Computer-Automated Data from the Vaccine Safety Datalink (VSD) system.

For controls with a history of one or more developmental screening indicators:

- Social Communication Questionnaire, conducted by telephone as part of the parent interview by Abt Associates Inc.

For cases (children with ASD diagnoses in medical records) only, clinic assessment visits including:

- Autism Diagnostic Interview-Revised (ADI-R), conducted in-person with case child's parent;
- Regression questions, conducted in-person with case child's parent;
- Nonverbal cognitive test, conducted in-person with the case child;
- Autism Diagnostic Observation Schedule (ADOS), conducted in-person with the case child.

Exhibit 6.1.1 Sources for Each Type of Data			
Data	Source	Data Collector	Method
Child outcomes			
<ul style="list-style-type: none"> ▪ ASD Classification ▪ AD Classification ▪ ASD-not-AD Classification 	Clinical case assessment visit at HMO	Trained clinicians	ADOS: Clinical assessment of case children. ADI-R : Clinical interview with mothers of cases
<ul style="list-style-type: none"> ▪ ASD with Regression 	Clinical case assessment visit at HMO	Trained clinicians	Regression Questions : Clinical interview with mothers of cases
<ul style="list-style-type: none"> ▪ AD with low cognitive function excluded 	Clinical case assessment visit at HMO	Trained clinicians	Nonverbal cognitive tests: Raven's Colored Progressive Matrices Mullen Scales of Early Learning
"Screened control group"	Medical chart abstraction Parent telephone interview	HMO Abt.	Data abstraction of child's medical charts Parent Interview questions regarding diagnoses of child's conditions Social Communication Questionnaire (SCQ)
Exposures			
<ul style="list-style-type: none"> ▪ Child 	Computer automated records	HMO	Data abstraction of VSD computerized database
	Medical chart abstraction	HMO	Data abstraction of child's medical charts
<ul style="list-style-type: none"> ▪ Prenatal (Mother) 	Mother medical records	HMO	Data abstraction of mother's medical charts
	Parent report as part of parent telephone interview	Abt	Parent Interview questions regarding mother's receipt of vaccinations and immune globulins during pregnancy
Covariates			
<ul style="list-style-type: none"> ▪ Characteristics of child, family, home ▪ Exposure to other toxins ▪ Medical history 	Parent report as part of parent telephone interview	Abt	Parent Interview
	Child medical records	HMO	Data abstraction of child's medical charts
	Mother medical records	HMO	Data abstraction of mother's medical charts

6.2. Parent Interview

The mothers of both cases and controls were administered a detailed Parent Interview by telephone. The Parent Interview had six major sections that produced detailed data on:

- Maternal and Child Medical Histories;
- Maternal Prenatal Fish Consumption;
- Family Educational History;
- Household Characteristics;

- Child’s and Mother’s Exposure History (for mercury, mercury-containing agents, and other toxins); and
- Mother’s and her Biological Children’s Diagnoses

6.3. Social Communication Questionnaire (SCQ)

In order to identify (and remove from the control sample) any controls who might have an undiagnosed ASD, parents of selected controls were administered the Social Communication Questionnaire (SCQ) (Rutter, Bailey, & Lord, 2003) as part of the Parent Telephone Interview. The Lifetime form of the SCQ was used in the interview, since it was the version of the SCQ recommended when the SCQ is used for diagnostic screening purposes. The SCQ includes 40 yes/no items that ask parents about any abnormalities in social or communicative behavior or any exaggerated interests or repetitive, stereotyped play they may have noticed in the control child.

The controls selected for the SCQ were those who, in the eligibility interview, reported a history of one or more developmental screening indicators, including: ADD/ADHD; a speech or language delay or impairment; a diagnosed learning disability; a tic disorder or Tourette’s syndrome; and/or an IEP in school.

A score on the SCQ was computed based on the number of abnormalities reported by the parent. Controls for whom the SCQ score was above a cutoff score (16 or above)¹⁹ were excluded from the study and replaced, while controls with SCQ scores below the cutoff remained in the study. All controls that were administered the SCQ were omitted from the “screened control group.” For families for whom the SCQ score was above the cutoff, a letter explaining the child’s diagnostic history from the developmental screening questions in the eligibility interview and the results of the SCQ was mailed to the HMO Principal Investigator, who distributed the letter to the child’s primary care physician. This letter included a telephone number for a clinical psychologist whom the physician could call for consultation, and information about resources for evaluating ASD. Within two weeks of the administration of the SCQ, this clinical psychologist called the family to discuss the results and recommended that they consult the child’s primary care physician concerning possible additional evaluation.

6.3.1. Staffing for Telephone Interviews

Abt Associates Inc. used its senior telephone interviewers from its Survey Operations Center to conduct the parent telephone interviews. Approximately 10 interviewers were trained to complete the Telephone Eligibility Interview, Parent Interview, and the SCQ. Telephone interviewers underwent a two-day training that:

¹⁹ Although the SCQ user’s manual suggests the use of a cut-off score of 15 for the lifetime form, we used a score of 16 based on the recommendation of Dr. Catherine Lord (co-developer of the SCQ, ADOS and ADI-R assessments).

- Provided a project overview, including the study’s purpose and goals as well as an explanation of the survey methodology and data collection tools;
- Reviewed the various strategies required to identify and reach respondents and the methods to gain their cooperation;
- Honed the interviewer's skills at establishing and maintaining rapport with both survey respondents and other household members who may serve as “gatekeepers;” and
- Provided trainees with the opportunity to learn the specific instruments and practice their administration.

Both the Eligibility Interview and Parent Interview (including the SCQ for controls) were addressed in several formats including question-by-question review of specifications, mock interviews, and supervision of each interviewer’s first “live” interviews.

Quality of the telephone interviews was assured by means of on-going live reviews performed by the interviewers’ on-site supervisors. In addition, other Abt Associates Inc. project staff periodically reviewed recordings of the interviews in order to make sure the questions were being asked correctly.

6.4. Medical Record Abstractions

Data from both the mother’s and child’s medical records for both cases and controls were reviewed and abstracted by experienced record abstractors from the HMO medical staff. The abstraction was developed to collect the following information from the maternal medical record: 1) pregnancy history; 2) complications, illness, procedures and treatments during the pregnancy with the target child; 3) procedures or complications of labor and delivery, including method of delivery and any drugs administered during labor; 4) maternal hepatitis B antigen status, receipt of Rhogam (or other Rh(D) immunoglobulin), and receipt of any vaccines during pregnancy with target child; and 5) maternal medical history for developmental outcomes.

Data abstracted from the child medical report included: 1) perinatal data, such as gestational age, birth weight, birth length, head circumference at birth, Apgar scores and birth plurality; 2) abnormal conditions and clinical procedures relating to the newborn; 3) infant medications; 4) all receipts of any vaccines or immune globulins; 5) all receipts of antibiotics; 6) developmental delays or conditions and psychiatric conditions, including date of the first mention of the condition in the medical chart, date of first prescribed medications, date of first referral, and type of service provider; and 7) medical conditions, such as lead poisoning and anemia/iron deficiency, including date of first mention in the medical chart.

6.4.1. Staffing for Medical Record Abstractions

The medical record abstractors were all experienced in this type of work. Each abstractor received a half-day training on study-specific issues from Abt Associates Inc. staff either by telephone or in person. HMO staff also participated in the training and supported the work of the abstractors in the field. The training session covered the background and purpose of the study; medical abstraction forms for the mother and child; maintaining subject confidentiality; transmittal of data to Abt Associates Inc.'s central office; and quality assurance. The medical abstractors were provided with training materials that included question-by-question specifications which provided explanatory information about each item required on each of the medical abstraction forms.

Hard copies of the medical abstraction forms were sent to Abt Associates Inc. where they were reviewed by a research team member for legibility and completeness. The data were then sent to a professional data entry house where all the medical record abstraction data were double entered.

6.5. Computer-automated Data

The computer-automated data, collected and maintained in accordance with the Vaccine Safety Datalink (VSD) system (Chen et. Al., 2000), were provided to the study from each of the three participating HMOs. These data were used in the creation of the sampling frame (see Section 5.2) and used in the analysis phase to create measures of exposure and covariate measures. These data sets included information on each case or control child's sex and date of birth; vaccination information including date and type of vaccine received, vaccine manufacturer and lot number and indicators of whether vaccines were received inside or outside of the HMO; inpatient and outpatient medical care information including ICD-9 codes and dates; and information about child's birth including gestational age, birth weight, Apgar score, and mother's date of birth.

6.6. The Clinical Case Assessment Visit

Cases were asked to come to a clinic at the HMO for a standardized assessment of the child and an interview with the mother. The clinical interview with case mothers and the clinical assessment of case children were both essential parts of this case ascertainment. The clinical interviews and child assessments were intended to confirm ASD diagnoses obtained from the VSD automated records via a rigorous, standardized assessment. Mothers of cases were interviewed, in person, using two measures that described the child's functioning: the Autism Diagnostic Interview-Revised (ADI-R) (Rutter, Le Couteur, & Lord, 2003) and a set of Regression Questions included as part of the ADI-R (Lord, personal communication, 2003). These were administered in person to the mother without the child present. Case children were directly assessed using a standardized measure of nonverbal cognitive functioning and the Autism Diagnostic Observation Schedule (ADOS) (Lord, Rutter, DiLavore, Risi, 2003) with a parent present. Each measure is described below and summarized in Exhibit 6.6.1.

The clinical assessment visits were conducted at the participating HMOs. At two of the three HMOs, we used HMO space during the weekends and employed assessors whom we had hired as consultants and who were unaffiliated with the HMOs. These assessors included psychologists, a speech therapist, and research staff from clinics where they regularly administered the ADI-R and/or ADOS. In the third HMO, we subcontracted the data collection to the ASD Clinic of that HMO, and members of the clinic's professional staff (clinical psychologists and a pediatrician) conducted the study assessments on weekdays as part of their daily work. At one of the HMOs, families were given the choice of coming to one of two possible locations for the clinic visit, depending upon which was more convenient for them. At the other two HMOs, the clinical assessments were all conducted at a single location.

The staff for a clinical assessment visit included one clinic coordinator and one to four clinical assessors, depending on the number of families scheduled and the configuration of the visit. The clinical assessors' responsibilities were to prepare for and administer the diagnostic measures to the parents and children, while the clinic coordinator was responsible for all other aspects of the clinic visit. A critical task for the clinic coordinators was to read the informed consent form to the parents and obtain their signed consent. Other clinic coordinator duties included scheduling families and assessors for the clinic visits; opening up the space and making sure the testing areas were ready for the assessors' use; and distributing incentives to the families and reimbursing them for any transportation and/or child care costs. Additionally, the clinic coordinators were responsible for bringing any necessary supplies for the clinical assessors, such as the testing protocols. (Clinical assessors brought their own test kits and manuals.) The clinic coordinators also videotaped approximately every third ADOS, and audiotaped approximately every third ADI-R for quality control purposes (for details, see section 6.6.4.3). Clinic coordinators took responsibility for sending all the completed ADI-R and ADOS test protocols to Abt Associates Inc.

The clinic spaces provided by the HMOs were similar in that each included a reception/waiting area where the clinic coordinators could review the consent forms with parents prior to the clinic visits and prepare other clinic paperwork. Separate, quiet rooms were available for the clinical assessors to interview parents (ADI-R) or to test the children using the ADOS protocol. The rooms for child testing were typically small and fairly bare rooms that provided the children space to move around but were free from distracting elements such as wall art or desk-top items. In the two HMOs where assessments were conducted during weekends, the videotaping of the ADOS assessments was done with a hand-held video camera. In the ASD Clinic setting, a videocamera was mounted on the wall of the testing room.

At each HMO the same steps were followed in contacting the case families. Soon after the appointment for the clinic visit was made by the clinic coordinator, a confirmation letter was mailed to the family from Abt Associates Inc's Cambridge office confirming the time and location of the clinic visit. This mailing also included a map and directions to the clinic, including parking options, a schedule outlining the timeline for a "typical" clinic visit so families would know what to expect and how much time to plan for, and a

copy of the consent form that they would sign upon arrival at the clinic. The letter also provided the family with a telephone number to reach the clinic coordinator who had scheduled the visit in case they needed to reschedule the visit. The Clinic Coordinators also made reminder calls to families the day before the scheduled assessment visits.

A number of different configurations were used to schedule the two assessments for each family (ADI-R and ADOS). Families were offered the option of completing all the assessments in a single clinic visit or across two separate visits. Most often families chose the single visit format, when typically two assessors would work with the family simultaneously, one administering the interview (ADI-R) to one parent and the other conducting the standardized observation of the child (ADOS) with the second parent present. This format required mothers to bring either the child’s father or another adult familiar to the child so that the mother could be interviewed separately. If the mother was unable to bring another familiar adult for the visit, the family was scheduled for two separate visits, one for each part of the assessment.

Exhibit 6.6.1

Developmental Assessment Battery for Cases

Clinical Interview with Case Mothers

<u>Assessment</u>	<u>Domain</u>	<u>Type of Measure</u>
Autism Diagnostic Interview-Revised (ADI-R)	Reciprocal social interaction Communication Repetitive, restricted behaviors	Parent report of child's behavior
Regression Questions	Regression in language, social interaction and communication skills	Parent report of loss of communication skills

Case Child Clinical Assessment

Autism Diagnostic Observation Schedule (ADOS)	Social Interaction Communication Communication-Social Interaction total	Behavior of child observed in semi-structured activities
Cognitive Measure^a:		
Raven’s Colored Progressive Matrices	Nonverbal reasoning ability	Nonverbal cognitive function
Mullen Scales of Early Learning	Visual reception	Nonverbal cognitive function

^a Only one of two measures was used to derive a score for each child. See Section 7.1.3.

6.6.1. Clinical Interview with Case Mothers

6.6.1.1. The Autism Diagnostic Interview-Revised (ADI-R)

This clinical semi-structured diagnostic interview is a modified and shortened version of the Autism Diagnostic Interview (ADI), and is used to differentiate ASD from other developmental delays. The ADI-R (Rutter, Le Couteur, & Lord, 2003) consists of 111 items and focuses on behaviors in three domains: quality of social interaction, communication and language, and repetitive, restricted and stereotyped interests and behavior. A fourth domain provides information on the age of first symptom manifestation. Clinicians score the child's behavior based on the mother's report; elevated scores indicate problem behavior. The measure itself establishes cut-off scores for each of three domains for a diagnosis of autism spectrum disorder. This diagnosis must be confirmed with an administration of the ADOS. Reliability and validity have been demonstrated. The ADI-R requires substantial training in administration and scoring and considerable experience with autistic children and children with other developmental delays. Administration of the ADI-R (including the Regression Questions described below) by a highly trained clinician to a mother of a child with suspected autism takes approximately three hours.

6.6.1.2. Regression Questions

The Regression Questions are 18 items developed by Dr. Catherine Lord (Lord, 2003) and colleagues that were asked in place of the ADI-R questions numbered 11-28. The Regression Questions are intended to assess regression in language, social interaction, and communication skills. Dr. Lord and colleagues developed criteria for determining whether or not developmental regression in any of these domains occurred. Approximately 25 percent of children with a diagnosis of ASD are estimated to meet the criteria for developmental regression (Lord, personal communication, December, 2003).

6.6.2. Clinical Assessment of Case Children

6.6.2.1. The Autism Diagnostic Observation Schedule (ADOS)

The ADOS (Lord, Rutter, DiLavore, & Risi, 2003) is a semi-structured observation of the child consisting of various play activities designed to elicit social and communicative behaviors. This instrument provides a measure of autism spectrum disorder that is unaffected by language. The ADOS has four modules, only one of which is given to an individual child. Each module takes approximately 35-40 minutes to administer. The appropriate module is determined based primarily on the child's level of expressive language, as well as on the child's chronological age: Module 1 is used with children who do not consistently use phrase speech; Module 2 is for children who use phrase speech but are not verbally fluent; and Module 3 or 4 is used with fluent children. The clinical assessors determined the child's level of expressive communication based on their interactions with the child during the administration of the Ravens or Mullen cognitive measure (described below). The ADOS must be administered by experienced

clinicians who have been trained in its use and have had previous experience working with autistic children and children with other non-ASD developmental delays. Inter-rater and test-retest reliability as well as internal validity have been demonstrated and the ADOS (and its previous versions) has been used for about 15 years.

6.6.2.2. Nonverbal Cognitive Measure

To assess each child's level of nonverbal cognitive functioning, clinicians administered one of two measures commonly used with this population. Because there is no single nonverbal cognitive measure that has adequate norms for the full range of developmental delays seen in this population, we used two measures: one that captures the level of functioning of autistic children above the severely delayed range, and another that distinguishes among children functioning in the very lowest range. We assessed children's nonverbal cognitive functioning using either the form board version of the Raven's Colored Progressive Matrices or the Visual Reception Scale of the Mullen Scales of Early Learning. The results from the nonverbal cognitive measures were used to identify a subset of children that had very low cognitive function. That subset of children was excluded from the subanalyses labeled "AD with low cognitive function excluded." See Chapter 7 for details.

Raven's Colored Progressive Matrices

The Raven's Progressive Matrices (Raven's) (Raven, Raven, & Court, 1998) is a widely used measure of general cognitive ability. It is a nonverbal measure that assesses fluid intelligence, the sort of intelligence involved in solving novel problems. The psychometric properties of the measure are good, both for its test-retest reliability and correlations between the Raven's and the Binet and Wechsler IQ scales. The Raven's comes in several different versions. We used the form board version of the Colored Progressive Matrices that was developed to be especially appealing to young children. The form board version presents a series of problems in the form of puzzles in which a piece has been removed. The child is shown several pieces that would all fit in the puzzle, but the child must choose the piece that will complete the pattern. We used Raven's scores derived by Dr. Catherine Lord and colleagues, by plotting a standardized regression line using percentiles and age equivalents reported in the Raven's manual for overlapping groups of children and adults. The regression line yielded a deviation cognitive score for each six-month interval from age 3 to 12 and one score for 13 - 25 years. The administration of the Raven's colored form-board matrices usually takes about 20 minutes, but this varies depending on the responsiveness of the child.

Mullen Scales of Early Learning

The Mullen (Mullen, E.M. 1995) is most appropriate for children from birth to age 5 years and 8 months, but can also be used to assess the cognitive level of lower-functioning children older than age 5 years, 8 months. The measure includes scales in five areas: Gross motor; Fine motor; Visual Reception; Expressive Language; and

Receptive Language. To be consistent with the Raven's measure of nonverbal intelligence, we administered only the Visual Reception Scale, which is the measure of nonverbal intelligence from the Mullen. This scale provided us with a T-score and an age equivalent. The Mullen Visual Reception Scale typically takes about 15 minutes to administer, but, as with the Raven's, this can vary depending on the child.

6.6.3. Clinical Assessment Visit Follow-up

Original copies of all the testing protocols used in the clinic assessment visits were sent to Abt Associates Inc. To ensure assessment data were entered correctly, the study team devised a double-entry method. One staff member entered the data from the scoring algorithm into a Microsoft Access data entry form. A second staff member then entered the data from the individual assessment booklet pages into a similar Access form. A SAS program was used to compare the data in two forms and highlight discrepancies. A third staff member then resolved these discrepancies. Only when the two forms were in complete agreement would the data be validated and a diagnosis assigned to the case. This process served two purposes: 1) to avoid simple data entry errors that could affect diagnoses, and 2) to identify and eliminate errors made by clinical assessors in transferring scores from the assessment booklet pages to the scoring algorithm.

Within a month of the assessment visit, a parent results letter was sent to the HMO for mailing to the parent and distribution to the child's primary care provider (PCP). This letter did not provide parents with a AD or ASD diagnosis, but instead reported whether the child met criteria for autism spectrum disorder on the communication and social interaction domains of the ADOS and ADI-R. The letter also reported how the child's cognitive score compared with scores of children the same age. This approach was developed in consultation with Dr. Catherine Lord, one of the developers of the ADOS and ADI-R.

6.6.4. Staffing for the Clinical Assessments of Cases

Because confirming cases' AD/ASD diagnoses using gold-standard assessments is a particular strength in this study, it was critically important to set and maintain high standards of reliability in the data collection process. The Abt Associates Inc. study team set the initial bar high by hiring only clinical assessors who had demonstrated a research level of reliability on the ADI-R and/or ADOS. This level of reliability is only achieved when assessors have demonstrated the standardized administration procedures and have shown that they understand the coding rules and can reach agreement in scoring with experts on the measures who have been identified by Dr. Catherine Lord, one of the developers of the ADI-R and ADOS and director of the University of Michigan's Autism and Communication Disorders Centers (UMACC). For the ADI-R, assessors must reach at least 90% agreement with the scoring of an expert approved by UMACC, and for the ADOS, at least 80% agreement. For each measure, these percentages apply both to the total set of coded items and to the subset of items that are included in the diagnostic algorithms. In order to ensure the highest level of inter-rater reliability on the measures, we had UMACC-approved experts check the assessors' scoring of tapes of testing

sessions provided by UMACC, instead of having the assessors score themselves against a master scoring template. In order to ensure that high standards were maintained throughout the study, we also developed and implemented quality control measures to conduct on-going review of the assessors' fidelity in administering the measures and their reliability in scoring.

6.6.4.1. Training on the ADI-R and ADOS

By the end of the study, fifteen different assessors had administered the ADI-R and/or the ADOS. The data collection occurred sequentially in one HMO after another, in large part because of the lack of research reliable assessors in two of our data collection sites. In the first HMO in which we collected data, we quickly identified three assessors who had experience with both the ADI-R and ADOS because of work on other autism-related research. Because these assessors had already completed many of the steps towards establishing research reliability on both measures, it did not take long for them to achieve research reliability and begin collecting data. This was not the case, however, in the other two HMO data collection sites. In one we found no one experienced on either measure and, in the other site, it was only after many months that we were able to identify some individuals on research staffs of other autism projects with experience. For those individual assessors without any training on either the ADOS or ADI-R and for those who may have used the measures clinically but needed to achieve research reliability, the project supported the training that they needed to become research reliable on one or both measures. The project only supported the training of those future assessors who met the prerequisites, including: extensive experience with children with autism spectrum disorders, and familiarity with other types of developmental delays and with typical development in children in the age range of the study. Abt Associates Inc. recruited assessors both from highly trained groups, such as clinical psychologists, and pediatricians, as well as from among experienced treatment and research center staff that had extensive experience on the ADOS and ADI-R. See Exhibit 6.6.2 for a summary of characteristics of clinical assessors.

Below, we describe the specific steps required to achieve research level certification on the ADOS and ADI-R, as prescribed by Dr. Catherine Lord, one of the instrument developers. These are the steps that were used in 2004-2005 when we were supporting the assessors' efforts to become research reliable.

For the ADOS, the following reliability training was required:

- An initial two-day clinical training provided by the ADOS publisher, Western Psychological Services (WPS)
- An additional two and a half days of research/reliability training at the University of Michigan's Autism and Related Communication Disorders Center (UMACC), or with UMACC staff off site; and establishing reliability of at least 80% with a member of UMACC or another group of expert assessors (as designated by UMACC). This involved scoring two taped ADOS administrations and submitting videotapes of two of the trainee's ADOS administrations (of specific types of

children) so that an expert assessor can compare the trainee’s administration and scoring to standard criteria.

For several assessors that did not have previous experience with administration of the ADOS, the process of becoming research-reliable on the ADOS took many months. One of the factors that influenced the length of time it took to become research reliable was the availability of appropriate children with specific kinds of developmental delays for the trainee to assess for both practice and for reliability tapes (and who were not the age of potential subjects in the study). Another factor was the availability of an expert assessor to review the trainees’ tapes. Of course, the individual learning trajectory of each trainee also influenced the length of time it took to achieve reliability.

The process of training and establishing reliability for the ADI-R was somewhat shorter than what is required to be research-certified on the ADOS. To become research-certified on the ADI-R, trainees had to:

- Attend an approved training program (either at UMACC or with one of their approved trainers) and pass on-site competency requirements;
- Submit one to two videotaped interviews for review by an expert assessor at (or certified by) UMACC; and
- Submit their codings of two teaching videotapes to an expert assessor who is already research certified (by UMACC) and achieve at least 90% agreement.

Exhibit 6.6.2. Characteristics of Clinical Assessors

Assessor	HMO	Degree or Profession	# ADI-R administered in study	#ADOS administered in study	Previous experience with ADI-R	Previous experience with ADOS
Assessor 1	A	Psychologist*	1	3	Yes	Yes
Assessor 2	A	Speech/lang. Pathologist**	4	4	Yes	Yes
Assessor 3	A	Grad student** (PhD program in psychology)	5	3	Yes	Yes
Assessor 4	B	Psychologist	59	58	No	No
Assessor 5	B	Psychologist	60	63	No	No
Assessor 6	B	Pediatrician	9	9	No	No
Assessor 7	B	Psychologist	6	3	No	No
Assessor 8	C	Research staff** (BA)	11	45	Yes	Yes
Assessor 9	C	Psychologist	0	28	N/A	Yes-ADOS trainer
Assessor 10	C	Research staff** (BS)	53	0	Yes	N/A
Assessor 11	C	Psychologist	0	45	N/A	No
Assessor 12	C	LCSW (Autism specialist)	45	8	No	No
Assessor 13	C	Research staff** (BA)	0	9	N/A	Yes
Assessor 14	C	Research staff** (BA)	0	45	N/A	Yes
Assessor 15	C	Research staff.** (MPH)	69	0	Yes – in-clinic trainer on ADI-R	N/A

*Psychologists were all Ph.D. clinical psychologists

** Research staff all had previous experience conducting assessments as part of large autism studies

*** HMO B assessors all worked in the HMO’s ASD clinic and conducted autism assessments regularly as part of their regular work

6.6.4.2. Project-Specific Training

Once the clinical assessors attained research reliability on the ADI-R and/or ADOS, Abt Associates Inc. staff and consultants conducted study-specific training. These training sessions lasted two to three days and included training for both the clinical assessors and the clinic coordinators. A highly experienced educational psychologist taught the clinical assessors how to administer the cognitive measures, and Abt Associates Inc. staff introduced the Regression Questions. The clinic coordinators were trained on obtaining signed informed consent for the clinic visit from parents, on clinic protocols and logistics, and on procedures for delivering the data to Abt Associates Inc. In addition, both assessors and clinic coordinators were also trained on protocols for handling emergencies and reporting suspected child abuse and/or neglect and on how to videotape the ADOS administrations.

6.6.4.3. ADI-R and ADOS Quality Control Procedures

To ensure that the assessments continued to be of high quality throughout the study, we hired experienced trainers of the ADI-R and ADOS to serve as quality control (QC) monitors. These individuals reviewed tapes of assessments (audiotapes for the ADI-R and videotapes for the ADOS) to check on the assessors' administrative fidelity and to assess the appropriateness of their interactions with the parents and children. One tape was reviewed for every ten assessments of each measure for each assessor. Our approach to collecting the tapes to be reviewed was to have clinical assessors or clinic coordinators videotape every third ADOS and audiotape every third ADI-R that each clinical assessor administered. These tapes were sent to Abt Associates Inc., where a study team member randomly selected one of every three ADI-R tapes and/or one of every three ADOS tapes for quality control review.

All three quality control (QC) monitors were clinical psychologists. They listened to/viewed the audio- and videotapes, recorded their comments using the appropriate protocols, and mailed the materials back to Abt Associates Inc. Abt Associates Inc. staff then reviewed their comments and sent them to the clinic assessors. For the ADI-R and ADOS, the QC monitors used protocols developed by the Abt Associates Inc. study team in consultation with experts. To assess the quality of the ADOS administration, the QC monitors also used a detailed, module-specific set of protocols developed by Dr. Catherine Lord's research team. This process provided clinic assessors with ongoing feedback, allowing them to make adjustments in their administration of the measures as needed. With regard to the assessors' interactions with the parents and children, the QC monitors made no negative comments. With regard to the assessors' administrative fidelity, the QC monitors were also positive overall. The few suggestions they made included recommending that one assessor go more quickly when administering the ADI-R and that another assessor follow questions with more prompts on the ADI-R and make sure that ADOS items were administered in the correct order.

Because the ongoing QC process did not focus on scoring, halfway through the data collection process, we re-examined the reliability of the assessors still working on the study at that time. The goal of this review was to determine whether the assessors were still meeting the level of agreement with the expert's scoring that was required to be considered research reliable (90% for the ADI-R and 80% for the ADOS, for both the total item set and for the algorithm items). The procedure used was to send the QC monitor a tape of the administration as well as a copy of the assessor's scored assessment booklet. The QC consultant listened to/viewed the tape and scored her own assessment booklet before comparing it to the assessor's scoring. Any discrepancies in scoring or general comments were recorded. The QC monitor then contacted the assessor to discuss any discrepancies in scoring and to decide on final scores, if needed. These consensus scores were then transmitted to the Abt Associates Inc. study team and entered in the project database as final scores.

We used the same criteria for re-checking reliability as had been used at the start of the study (90 percent agreement for the ADI-R and 80 percent agreement for the ADOS). The assessors were found to have maintained the high level of reliability found at the start. We checked the scoring of the measure the assessor administered most often, unless they administered both frequently, and, in that case, we checked their scoring on both measures. Of the five assessors whose ADI-R scoring was checked, all but one met at least the required 90 percent level of agreement with the expert scorer. The one assessor who did not meet the criterion, had an agreement level of about 88 percent and met the 90 percent cutoff in the second tape that was reviewed for scoring, which was administered after the QC monitor provided some additional technical assistance to the assessor. Three of the ADI-R's checked agreed with the expert's scoring 100 percent. Scores for five of the assessors were also double checked for the ADOS, and all met at least the required 80 percent level of agreement, with one achieving 100 percent reliability.

7. Measures

7.1. Outcome Classifications for Cases

The data sources for making outcome classifications for cases were described in Chapter 6. In the sections that follow, the decision rules for making the outcome classifications for cases shown in Exhibit 7.1.1 are described. Cases that did not meet criteria for a particular outcome classification (e.g., ASD) were excluded from the case-control analyses corresponding to that outcome.

Exhibit 7.1.1

Outcome Classifications

Variable	Definition	Form
Autistic disorder (AD)	Algorithm for classification based on results from ADI-R and ADOS.	Binary (yes/no) ^a
Autistic spectrum disorder (ASD)	Algorithm for classification based on results from ADI-R and ADOS.	Binary (yes/no) ^a
ASD without AD (ASD-not-AD)	Cases with ASD excluding those with AD	Binary (yes/no) ^a
ASD with regression	Meets criteria for autism spectrum disorder and criteria for regression from Regression Instrument	Binary (yes/no) ^a
AD with low cognitive function omitted	Meets criteria for autistic disorder, but cases with very low cognitive function are omitted	Binary (yes/no) ^a

Binary (yes/no)^a: Yes = meets criteria for classification; No = does not meet criteria (and excluded from analyses corresponding to that outcome classification).

7.1.1. Decision Rules for Categorizing Autistic Disorder and ASD Outcomes

The decision rules for categorizing AD and ASD cases were developed in the planning stages of the current study, prior to data collection, and specified in the study's analysis plan. They were developed in consultation with Dr. Catherine Lord and Dr. Susan Risi. It is expected that the criteria used by the current study to categorize ASD cases are stricter than those defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), such that 100 percent of cases that meet the current study's criteria for ASD would also meet DSM-IV criteria²⁰. To develop the decision rules, we relied on work by Dr. Susan Risi, Dr. Catherine Lord, and colleagues that focused on several different options regarding algorithms for using the ADI-R and ADOS to

²⁰ Personal communication from Dr. Catherine Lord.

make the classifications of *Autistic Disorder* and *Autism Spectrum Disorder*. The competing algorithms have different implications for the sensitivity and specificity of the diagnostic tests. Their analyses were based on a population of children that had been referred to a communicative disorders clinic. They compared various scoring options from the ADOS and ADI-R to a “gold standard” diagnosis and calculated the sensitivity and specificity of the various options²¹. We used their results to help guide our decisions regarding specification of criteria for making the classifications²². Their results are summarized in Exhibits 7.1.2 and 7.1.3. The first of the two exhibits shows sensitivity and specificity estimates for various criteria for making an ASD categorization. The second exhibit shows similar data for making an autistic disorder categorization. The rows of the exhibits show notations representing different ADOS and ADI-R scoring criteria. The cell entries in the tables show various statistics including the sensitivity and specificity achieved in their study when the criteria indicated in the row were applied. For each of the two tables, we chose the row criteria that we believe gives the best trade-off in terms of sensitivity and specificity, for the purposes of the current study. For reference, the terms *sensitivity*, and *specificity* are defined in Exhibit 7.1.4. In the discussion that follows, we first explain our logic for deciding which row criteria we thought was most suitable. We then explain how the criteria we have chosen translate into decision rules for making categorizations from the ADOS and ADI-R.

²¹ The “gold standard” used for these purposes was classification based on consensus from a group of autism experts that had reviewed a complete set of clinical notes.

²² In the period between the design phase (when we made our decisions how to use ADOS and ADI-R results to classify potential cases as meeting or not meeting criteria for ASD or AD), and the writing of this report, Risi et al. (2006) published additional data on the sensitivity and specificity of the diagnostic tests. We report in the current chapter the actual data that we used for making decisions. However, if we had used the more recent data, reported in Risi et al. (2006), we would have made the same decisions on how to use the ADOS and ADI-R results classify AD and ASD cases as we describe in the current report.

Exhibit 7.1.2.**Sensitivity and Specificity Estimates for Autism Spectrum Disorder (ASD) (n = 553)**

Criteria	True Positive (n)	False Positive (n)	True Negative (n)	False Negative (n)	Sensitivity	Specificity
ADI-R (Social + 1 Domain) <u>or</u> ADOS (ASD)	429	54	50	20	95.6%	48.1%
ADI-R (Social + 1 Domain) <u>and</u> ADOS (ASD)	364	13	91	85	81.1%	87.5%
ADI-R (Social + 1 Domain) <u>and</u> ADOS (ASD Social)	376	22	82	73	83.7%	78.9%
ADI-R (Social + 1 Domain) <u>and</u> ADOS (ASD Social minus 1 point)	385	31	73	64	85.8%	70.2%
ADI-R (Social + 1 Domain)	393	42	62	56	87.5%	59.6%
ADOS (ASD)	400	25	79	49	89.1%	76.0%

Source: "Standardizing Diagnostic Criteria Using the the ADI-R and ADOS". Unpublished analyses by S. Risi, C. Lord, A. Pickles, D. Anderson, S. Qiu, E. Cook, & B. Leventhal

Exhibit 7.1.3.**Sensitivity and Specificity Estimates for Autistic Disorder (AD) (n = 492)**

Criteria	True Positive (n)	False Positive (n)	True Negative (n)	False Negative (n)	Sensitivity	Specificity
ADI-R and ADOS (ASD)	246	61	157	28	89.8%	72.0%
ADI-R <u>and</u> ADOS (AD)	234	32	186	40	85.4%	85.3%
ADI-R <u>or</u> ADOS (AD)	272	120	98	2	99.3%	44.95%
ADI-R	249	100	118	25	90.9%	54.1%
ADOS (AD)	257	52	166	17	93.8%	76.2%
ADOS (ASD)	271	106	112	3	98.9%	51.4%

Source: "Standardizing Diagnostic Criteria Using the the ADI-R and ADOS". Unpublished analyses by S. Risi, C. Lord, A. Pickles, D. Anderson, S. Qiu, E. Cook, & B. Leventhal

Exhibit 7.1.4
Definitions of Sensitivity and Specificity

$$\text{Sensitivity} = \frac{\text{True positives}}{\text{All with disease}} = \frac{\text{True positives}}{\text{True pos} + \text{False neg}}$$

$$\text{Specificity} = \frac{\text{True negatives}}{\text{All without disease}} = \frac{\text{True negatives}}{\text{True neg} + \text{False pos}}$$

7.1.1.1. Rationale for Choice of Criteria Based on Sensitivity and Specificity

All of the potential cases that were assessed in this study had been identified in their medical records as having ASD. The ADOS and ADI-R were used so that the study could identify and exclude from the analyses any children that were misdiagnosed in the medical records. This objective argues for utilizing the criteria that maximize specificity. At the same time, the study wanted to protect against throwing out true cases from our analysis because that would reduce the size of the analysis sample. That argues for being mindful of the sensitivity of the test.

For the ASD classification, the criteria yielding the maximum specificity are shown in Row 2 (shown as shaded in the Exhibit 7.1.2). In the Risi et. al. study, those criteria identified 87.5 percent of the children that did not have disease (according to the gold standard) and as not having ASD according to the test. This criterion also did well on keeping the children with disease and classifying them as having ASD. The test identified as ASD 81.1 percent of the children that really had the disorder. We therefore choose to use the criteria indicated in Row 2 for making the ASD classification.

Similarly, for the autistic disorder classification, the criteria yielding the maximum specificity are shown in Row 2 (shown as shaded in the Exhibit 7.1.3). We therefore choose to use the criteria indicated in Row 2 for making the AD classification.

7.1.1.2. Decision Rules

For this study, we adopted the following classification rules:²³

For a diagnosis of autistic disorder, a child had to meet the following criteria:

²³ It is important to remember that the ADI-R only provides for a diagnosis of the broader autism spectrum disorder, of which autistic disorder is a more specific diagnosis. The ADOS provides for a diagnosis of either autistic disorder or the more general autism spectrum disorder.

1. Age of onset prior to 36 months (Domain D on the ADI-R); and
2. On the ADI-R, above the threshold score for a diagnosis of ASD on all three domains:
 - ✓ Reciprocal social interaction (Domain A)
 - ✓ Communication (Domain B)
 - ✓ Repetitive, restricted behaviors (Domain C);
3. On the ADOS, above the threshold score for a diagnosis of autistic disorder on both domains and the total:
 - ✓ Social Interaction domain
 - ✓ Communication domain
 - ✓ Communication-Social Interaction total.

For a diagnosis of autism spectrum disorder (ASD), a child must meet the following criteria:

A. Either or both of the following must be met:

1. Age of onset 36 months or later, **AND**
2. All of the other criteria above for a diagnosis of autistic disorder

OR

B. All of the following must be met:

1. On the ADOS, above the threshold for a diagnosis of autism spectrum disorder on both domains and the total:
 - ✓ Social Interaction domain
 - ✓ Communication domain
 - ✓ Communication-Social Interaction total
2. On the ADI-R, above threshold for a diagnosis of autism spectrum disorder on one domain:
 - ✓ Reciprocal social interaction (Domain A);
3. On the ADI-R, above threshold for a diagnosis of autism spectrum disorder on one or both of the following:
 - ✓ Communication (Domain B)
 - ✓ Repetitive, restricted behaviors (Domain C).

If a child fails to meet the criteria for either autistic disorder or autism spectrum disorder, the child is classified as ***not ASD***. These classification rules are summarized in Exhibit 7.1.5.

Exhibit 7.1.5. Summary of ASD and AD Classification Rules			
ADI-R Domains A,B,C	ADOS Domains A,B,C	Age at Onset Domain D	Classification
Above cut-off on all three domains	Above autistic disorder cut-off on all three domains	<36 months	AD
Above cut-off on all three domains	Above autistic disorder cut-off on all three domains	>=36 months	ASD
Above cut-off on social and one additional domain	Above ASD cut-off on all three domains	N/A	ASD

For a diagnosis of ASD-not-AD a child must meet the following criteria:

- ✓ Must meet criteria for ASD; and
- ✓ Must NOT meet criteria for AD.

Exhibit 7.1.6 shows the ADOS and ADI-R scores and the resultant classifications as AD, ASD, or Below Criteria (did not meet criteria AD or ASD) for all 321 children in the current sample with complete ADOS and ADI-R assessments. The first 65 rows of the exhibit correspond to the 65 children that did not meet study criteria for the AD or the ASD classification. For example, the children represented in the first two rows did not meet criteria for ASD on either the ADI-R or ADOS assessments. The children represented in rows 3 and 4 scored above criteria on the ADOS assessments, but below criteria on the ADI-R assessments.

The children represented in rows 66 – 134 meet criteria for ASD but not for AD. For example, the child represented in row 66 did not meet AD criteria on domain C (Patterns of Behavior) on the ADI-R. The children in rows 67 – 70 met all of the ADI-R criteria, and met ADOS criteria for ASD, but did not meet ADOS criteria for AD.

The children represented in rows 135 – 321 met criteria for AD.

Exhibit 7.1.6 Observed ADOS and ADI-R Scores and the Resulting AD, ASD and Below Criteria Classifications																	
Row Number	Classification: 0=Below Criteria	ADI-R				ADOS Module 1				ADOS Module 2				ADOS Module 3			
		Domain A Reciprocal Interaction	Domain B Communication - Verbal Total	Domain C Patterns of Behavior Total	Domain D Abnormality of Development Total	Communication Total	Reciprocal Social Interaction Total	Communication and Social Interaction Total	Communication Total	Reciprocal Social Interaction Total	Communication and Social Interaction Total	Communication Total	Reciprocal Social Interaction Total	Communication Total	Reciprocal Social Interaction Total		
ASD Cut Point =>		10	8	3	1	2	4	7	3	4	5	8	3	4	2	4	7
AD Cut Point =>						4	7	12	5	6	12	5	6	3	3	6	10
1	0	0	0	2	2	2	2	2	2	2	2	2	2	2	2	2	2
2	0	0	7	2	0	2	0	2	0	2	0	2	0	2	0	2	0
3	0	1	1	1	0	1	0	1	0	1	0	1	0	1	0	1	0
4	0	1	6	1	2	1	2	1	2	1	2	1	2	1	2	1	2
5	0	2	4	3	0	3	0	3	0	3	0	3	0	3	0	3	0
6	0	2	5	1	2	1	2	1	2	1	2	1	2	1	2	1	2
7	0	4	0	2	1	2	1	2	1	2	1	2	1	2	1	2	1
8	0	4	4	4	0	4	0	4	0	4	0	4	0	4	0	4	0
9	0	4	7	1	5	1	5	1	5	1	5	1	5	1	5	1	5
10	0	5	4	2	0	2	0	2	0	2	0	2	0	2	0	2	0
11	0	5	8	7	1	7	1	7	1	7	1	7	1	7	1	7	1
12	0	6	8	6	5	6	5	6	5	6	5	6	5	6	5	6	5
13	0	6	8	2	5	2	5	2	5	2	5	2	5	2	5	2	5
14	0	6	10	1	3	1	3	1	3	1	3	1	3	1	3	1	3
15	0	6	10	6	2	6	2	6	2	6	2	6	2	6	2	6	2
16	0	6	15	2	1	2	1	2	1	2	1	2	1	2	1	2	1
17	0	6	16	4	1	4	1	4	1	4	1	4	1	4	1	4	1
18	0	7	5	6	3	6	3	6	3	6	3	6	3	6	3	6	3
19	0	7	6	1	5	1	5	1	5	1	5	1	5	1	5	1	5
20	0	7	8	3	3	3	3	3	3	3	3	3	3	3	3	3	3
21	0	8	12	3	2	3	2	3	2	3	2	3	2	3	2	3	2
22	0	8	15	4	3	4	3	4	3	4	3	4	3	4	3	4	3
23	0	9	5	3	0	3	0	3	0	3	0	3	0	3	0	3	0
24	0	9	6	4	0	4	0	4	0	4	0	4	0	4	0	4	0
25	0	9	7	6	0	6	0	6	0	6	0	6	0	6	0	6	0
26	0	9	10	7	3	7	3	7	3	7	3	7	3	7	3	7	3
27	0	9	11	4	5	4	5	4	5	4	5	4	5	4	5	4	5
28	0	10	13	5	0	5	0	5	0	5	0	5	0	5	0	5	0
29	0	11	13	6	0	6	0	6	0	6	0	6	0	6	0	6	0
30	0	11	14	3	5	3	5	3	5	3	5	3	5	3	5	3	5

Scores that are below AD but above ASD cut points are highlighted in Blue

Scores that are below ASD cut points are highlighted in Yellow

Exhibit 7.1.6 Observed ADOS and ADI-R Scores and the Resulting AD, ASD and Below Criteria Classifications

Row Number	Classification: 0=Below Criteria	ADI-R			ADOS Module 1			ADOS Module 2			ADOS Module 3				
		Domain A Reciprocal Social Interaction	Domain B Communication - Verbal Total	Domain B Communication - Non-Verbal Total	Domain C Patterns of Behavior Total	Domain D Abnormality of Development Total	Communication Total	Reciprocal Social Interaction Total	Communication and Social Interaction Total	Communication Total	Reciprocal Social Interaction Total	Communication and Social Interaction Total			
ASD Cut Point =>		10	8	7	3	1	2	4	3	5	4	3	2	4	7
AD Cut Point =>															10
Scores that are below AD but above ASD cut points are highlighted in Blue															
31	0	13	16	.	5	2	1	5	6
32	0	13	18	.	5	2	0	3	4
33	0	14	6	.	4	0	1	0	1
34	0	14	14	.	4	5	1	1	2
35	0	15	7	.	6	5	3	3	6
36	0	15	14	.	5	5	2	3	5
37	0	16	10	.	12	5	2	2	4
38	0	16	13	.	6	3	1	7	8
39	0	17	12	.	3	5	1	3	4
40	0	17	13	.	6	3	1	5	6
41	0	17	14	.	6	5	2	4	6
42	0	17	16	.	2	5	0	1	1
43	0	18	11	.	3	0	1	4	5
44	0	18	15	.	5	4	2	4	6
45	0	18	19	.	8	3	1	6	7
46	0	18	21	.	6	5	3	4	7
47	0	20	18	.	8	5	1	8	9
48	0	21	13	.	4	3	3	1	4
49	0	21	15	.	4	1	1	3	4
50	0	22	21	.	8	5	1	3	4
51	0	23	12	.	5	2	1	4	5
52	0	23	18	.	5	5	1	7	8
53	0	23	21	.	6	1	1	4	5
54	0	24	16	.	8	3	2	4	6
55	0	24	16	.	8	4	1	3	4
56	0	24	20	.	11	3	1	5	6
57	0	24	20	.	8	5	0	3	3
58	0	24	22	.	5	1	0	3	3
59	0	25	24	.	4	5	0	2	2
60	0	25	24	.	5	5	1	10	11
61	0	26	18	.	7	5	1	6	7
62	0	26	19	.	8	3	1	8	9

Exhibit 7.1.6 Observed ADOS and ADI-R Scores and the Resulting AD, ASD and Below Criteria Classifications

Row Number	Classification: 0=Below Criteria	ADI-R			ADOS Module 1			ADOS Module 2			ADOS Module 3													
		Domain A Reciprocal Social Interaction	Domain B Communication - Verbal Total	Domain B Communication - Non-Verbal Total	Domain C Patterns of Behavior Total	Domain D Abnormality of Development Total	Communication Total	Reciprocal Social Interaction Total	Communication and Social Interaction Total	Communication Total	Reciprocal Social Interaction Total	Communication Total	Reciprocal Social Interaction Total	Communication and Social Interaction Total										
ASD Cut Point =>		10	8	7	3	1	2	4	3	4	3	4	2	4	7	8	12	5	6	3	4	6	10	
AD Cut Point =>		Scores that are below AD but above ASD cut points are highlighted in Blue																						
63	0	26	19	.	6	3	3	3	3	6	6
64	0	27	15	.	7	4	2	4	2	4	6
65	0	27	18	.	11	3	0	4	0	4	4
66	ASD	10	8	.	0	4	5	7	5	7	12
67	ASD	10	12	.	6	5	3	5	3	5	8
68	ASD	11	11	.	3	4	2	6	2	6	8
69	ASD	11	16	.	3	3	2	6	2	6	8
70	ASD	13	10	.	5	1	2	7	2	7	9
71	ASD	13	10	.	10	0	5	6	5	6	11
72	ASD	13	13	.	3	0	5	10	5	10	15
73	ASD	14	10	.	2	3	4	10	4	10	14
74	ASD	14	11	.	5	5	2	9	2	9	11
75	ASD	14	12	.	8	4	3	4	3	4	7
76	ASD	15	10	.	3	5	4	5	4	5	9
77	ASD	15	14	.	5	4	3	6	3	6	9
78	ASD	15	15	.	7	5	4	4	4	4	8
79	ASD	15	16	.	2	4	4	6	4	6	10
80	ASD	15	18	.	6	5	2	7	2	7	9
81	ASD	15	19	.	1	5	4	7	4	7	11
82	ASD	16	5	.	3	4	3	6	3	6	9
83	ASD	16	9	.	9	2	4	4	4	4	8
84	ASD	16	21	.	5	4	2	7	2	7	9
85	ASD	17	11	.	2	0	3	6	3	6	9
86	ASD	17	14	.	0	5	6	10	6	10	16
87	ASD	17	15	.	4	1	2	6	2	6	8
88	ASD	17	17	.	8	2	3	6	3	6	9
89	ASD	17	18	.	6	5	2	5	2	5	7
90	ASD	18	10	.	4	4	2	9	2	9	11
91	ASD	18	11	.	4	5	3	6	3	6	9
92	ASD	18	12	.	1	3	3	9	3	9	12
93	ASD	18	17	.	6	5	3	4	3	4	7
94	ASD	19	18	.	8	5	2	9	2	9	11

Exhibit 7.1.6 Observed ADOS and ADI-R Scores and the Resulting AD, ASD and Below Criteria Classifications

Row Number	Classification: 0=Below Criteria	ADI-R				ADOS Module 1			ADOS Module 2			ADOS Module 3				
		Domain A Reciprocal Social Interaction	Domain B Communication - Verbal Total	Domain B Communication - Non-Verbal Total	Domain C Patterns of Behavior Total	Domain D Abnormality of Development Total	Communication and Social Interaction Total	Reciprocal Social Interaction Total	Communication Total	Reciprocal Social Interaction Total	Communication Total	Reciprocal Social Interaction Total	Communication Total	Reciprocal Social Interaction Total		
ASD Cut Point =>		10	8	7	3	1	2	4	3	5	4	3	6	4	7	10
AD Cut Point =>		Scores that are below AD but above ASD cut points are highlighted in Blue														
95	ASD	20	12	.	4	3	2	5	7
96	ASD	20	12	.	3	3	2	8	10
97	ASD	20	13	.	2	2	6	12	18
98	ASD	20	16	.	8	3	3	4	7
99	ASD	20	19	.	3	5	2	7	9
100	ASD	21	5	.	6	5	4	9	13
101	ASD	21	19	.	8	5	2	5	7
102	ASD	22	17	.	3	4	2	7	9
103	ASD	22	21	.	7	2	2	6	8
104	ASD	23	10	.	7	2	3	6	9
105	ASD	23	13	.	4	2	3	5	8
106	ASD	23	14	.	5	4	.	.	.	4	7	11
107	ASD	23	15	.	2	5	.	.	.	7	11	18
108	ASD	23	16	.	2	5	.	.	.	3	6	9
109	ASD	23	17	.	5	3	.	.	.	2	10	16
110	ASD	23	18	.	0	4	.	.	.	6	10	16
111	ASD	23	23	.	6	3	3	6	10
112	ASD	23	24	.	6	5	5	5	10
113	ASD	24	9	.	7	5	3	6	9
114	ASD	24	16	.	2	4	3	10	13
115	ASD	24	17	.	6	4	3	6	9
116	ASD	24	20	.	10	3	2	6	8
117	ASD	25	9	.	2	2	4	11	15
118	ASD	25	21	.	4	5	2	10	12
119	ASD	25	.	12	2	3	5	10	15
120	ASD	26	11	.	2	2	4	12	16
121	ASD	26	17	.	3	4	4	4	8
122	ASD	26	18	.	8	5	3	4	7
123	ASD	26	19	.	5	5	3	6	9
124	ASD	27	14	.	6	2	2	10	12
125	ASD	27	17	.	6	5	2	6	8
126	ASD	27	25	.	10	5	2	7	9

Exhibit 7.1.6 Observed ADOS and ADI-R Scores and the Resulting AD, ASD and Below Criteria Classifications

Row Number	Classification: 0=Below Criteria	ADI-R			ADOS Module 1			ADOS Module 2			ADOS Module 3				
		Domain A Reciprocal Social Interaction	Domain B Communication - Verbal Total	Domain B Communication - Non-Verbal Total	Domain C Patterns of Behavior Total	Domain D Abnormality of Development Total	Communication Total	Reciprocal Social Interaction Total	Communication and Social Interaction Total	Communication Total	Reciprocal Social Interaction Total	Communication and Social Interaction Total			
ASD Cut Point =>		10	8	7	3	1	2	4	7	12	3	4	2	4	7
AD Cut Point =>							4	7	12	5	6	6	3	6	10
Scores that are below AD but above ASD cut points are highlighted in Blue															
127	ASD	27	25	.	6	5	2	10	12
128	ASD	28	15	.	8	3	2	5	7
129	ASD	28	17	.	5	5	2	8	10
130	ASD	28	19	.	10	5	3	5	8
131	ASD	28	21	.	11	5	2	8	10
132	ASD	28	24	.	12	3	2	5	7
133	ASD	28	25	.	8	4	2	9	11
134	ASD	29	22	.	9	5	3	4	7
135	AD	11	10	.	4	3	5	11	16
136	AD	11	10	.	6	4
137	AD	11	12	.	5	3	4	10	14
138	AD	11	13	.	5	3	4	9	13
139	AD	11	13	.	7	3	6	13	19
140	AD	12	14	.	6	1	4	7	11
141	AD	13	9	.	6	5	5	7	12
142	AD	13	11	.	8	5	7	12	19
143	AD	13	17	.	5	2	5	10	15
144	AD	14	8	.	4	5	5	8	13
145	AD	14	8	.	5	4	3	8	11
146	AD	14	11	.	6	5	6	12	18
147	AD	14	15	.	5	4	7	11	18
148	AD	15	14	.	5	3	4	6	10
149	AD	15	14	.	5	5	6	13	19
150	AD	15	15	.	7	4	5	11	16
151	AD	16	11	.	8	1	3	9	12
152	AD	16	12	.	3	3	5	9	14
153	AD	16	13	.	3	3	4	10	14
154	AD	16	13	.	6	2	4	8	12
155	AD	16	15	.	11	4	4	10	14
156	AD	16	15	.	4	1	4	11	15
157	AD	16	16	.	5	5	3	9	12
158	AD	16	16	.	7	3	8	10	18

Exhibit 7.1.6 Observed ADOS and ADI-R Scores and the Resulting AD, ASD and Below Criteria Classifications

Row Number	Classification: 0=Below Criteria	ADI-R			ADOS Module 1			ADOS Module 2			ADOS Module 3				
		Domain A Reciprocal Social Interaction	Domain B Communication - Verbal Total	Domain C Communication - Non-Verbal Total	Domain D Abnormality of Development Total	Communication Total	Reciprocal Social Interaction Total	Communication and Social Interaction Total	Communication Total	Reciprocal Social Interaction Total	Communication and Social Interaction Total	Communication Total	Reciprocal Social Interaction Total	Communication and Social Interaction Total	
ASD Cut Point =>		10	8	7	1	2	4	7	12	8	4	6	3	4	7
AD Cut Point =>						4	7	12	12	6	6	5	3	6	10
Scores that are below AD but above ASD cut points are highlighted in Blue															
159	AD	16	16	.	3	3	7	10
160	AD	16	19	.	3	7	12	19
161	AD	16	19	.	3	5	13	18
162	AD	17	14	.	2	3	9	12
163	AD	17	14	.	5	7	10	17
164	AD	17	15	.	3	3	9	12
165	AD	17	15	.	5	3	7	10
166	AD	17	19	.	4	8	11	.	
167	AD	17	22	.	5	7	12	19
168	AD	18	11	.	3	8	7	15
169	AD	18	12	.	3	4	7	11
170	AD	18	13	.	3	3	10	13
171	AD	18	14	.	1	3	10	13
172	AD	18	18	.	4	5	11	18
173	AD	19	10	.	2	6	11	17
174	AD	19	11	.	2	5	13	18
175	AD	19	12	.	4	6	9	15
176	AD	19	13	.	5	3	11	14
177	AD	19	13	.	4	4	10	14
178	AD	19	16	.	5	3	7	10
179	AD	19	19	.	3	6	13	19
180	AD	19	19	.	3	6	10	16
181	AD	19	20	.	5	7	10	17
182	AD	20	15	.	5	3	10	13
183	AD	20	15	.	5
184	AD	20	16	.	5	8	13	21
185	AD	20	18	.	4	7	11	18
186	AD	20	18	.	3	3	8	11
187	AD	20	19	.	3	3	8	11
188	AD	20	20	.	3	5	12	17
189	AD	21	11	.	4	4	12	16
190	AD	21	11	.	4	7	14	21

Exhibit 7.1.6 Observed ADOS and ADI-R Scores and the Resulting AD, ASD and Below Criteria Classifications

Row Number	Classification: 0=Below Criteria	ADI-R			ADOS Module 1			ADOS Module 2			ADOS Module 3				
		Domain A Reciprocal Social Interaction	Domain B Communication - Verbal Total	Domain B Communication - Non-Verbal Total	Domain C Patterns of Behavior Total	Domain D Abnormality of Development Total	Communication Total	Reciprocal Social Interaction Total	Communication and Social Interaction Total	Communication Total	Reciprocal Social Interaction Total	Communication and Social Interaction Total			
ASD Cut Point =>		10	8	7	3	1	2	4	3	4	3	4	2	4	7
AD Cut Point =>							4	7	5	6	12	12	3	6	10
Scores that are below AD but above ASD cut points are highlighted in Blue															
191	AD	21	17	.	6	5	5	13	18
192	AD	21	19	.	11	1	3	7	10
193	AD	21	19	.	4	5	3	10	13
194	AD	21	19	.	5	3	3	10	13
195	AD	21	20	.	7	5	5	12	17
196	AD	21	20	.	4	5	6	11	17
197	AD	21	20	.	10	3	6	11	17
198	AD	21	21	.	8	4	5	11	16
199	AD	21	22	.	5	3	4	13	17
200	AD	21	22	.	7	5	5	12	17
201	AD	21	23	.	4	5	4	9	13
202	AD	22	11	.	9	5	5	11	16
203	AD	22	15	.	5	2	7	14	21
204	AD	22	16	.	4	3	4	11	15
205	AD	22	17	.	5	4	3	9	12
206	AD	22	17	.	9	5	5	11	16
207	AD	22	18	.	7	2	5	7	12
208	AD	22	20	.	5	3	5	13	18
209	AD	22	21	.	4	3	4	9	13
210	AD	22	22	.	8	5	7	14	21
211	AD	22	.	12	8	4	5	10	15
212	AD	22	.	13	3	5	5	12	17
213	AD	23	15	.	8	5	7	12	19
214	AD	23	16	.	5	2	5	12	17
215	AD	23	17	.	9	5	7	14	21
216	AD	23	18	.	10	5	7	12	19
217	AD	23	19	.	10	5	5	9	14
218	AD	23	19	.	6	5	4	11	15
219	AD	23	19	.	10	4	4	7	11
220	AD	23	20	.	3	5	4	10	14
221	AD	23	20	.	10	5	8	12	14
222	AD	23	21	.	4	2	8	14	22

Exhibit 7.1.6 Observed ADOS and ADI-R Scores and the Resulting AD, ASD and Below Criteria Classifications

Row Number	Classification: 0=Below Criteria	ADI-R			ADOS Module 1			ADOS Module 2			ADOS Module 3				
		Domain A Reciprocal Social Interaction	Domain B Communication - Verbal Total	Domain B Communication - Non-Verbal Total	Domain C Patterns of Behavior Total	Domain D Abnormality of Development Total	Communication Total	Reciprocal Social Interaction Total	Communication and Social Interaction Total	Communication Total	Reciprocal Social Interaction Total	Communication and Social Interaction Total			
ASD Cut Point =>		10	8	7	3	1	2	4	7	3	4	8	2	4	7
AD Cut Point =>							4	7	12	5	6	12	3	6	10
Scores that are below AD but above ASD cut points are highlighted in Blue															
223	AD	24	13	.	9	4	5	11	16
224	AD	24	14	.	4	5	7	11	18
225	AD	24	15	.	11	5	3	7	10
226	AD	24	16	.	9	5	4	6	10
227	AD	24	17	.	8	5	.	.	.	5	10	15	.	.	.
228	AD	24	18	.	6	5	7	11	18
229	AD	24	18	.	8	3	5	10	15
230	AD	24	21	.	8	5	3	9	12
231	AD	24	22	.	8	5	.	.	.	6	10	16	.	.	.
232	AD	24	22	.	4	4	4	13	17
233	AD	24	22	.	9	3	6	12	18
234	AD	24	23	.	4	4	.	.	.	8	8	16	.	.	.
235	AD	25	16	.	6	4	5	13	18
236	AD	25	16	.	5	4	8	11	19
237	AD	25	16	.	7	2	.	.	.	7	11	18	.	.	.
238	AD	25	17	.	5	4	.	.	.	5	10	15	.	.	.
239	AD	25	18	.	7	4	3	9	12
240	AD	25	19	.	9	3	7	12	19
241	AD	25	19	.	6	3	5	11	16
242	AD	25	19	.	7	4	5	8	13
243	AD	25	19	.	5	3	.	.	.	10	9	19	.	.	.
244	AD	25	22	.	8	5	7	13	20
245	AD	25	22	.	8	2	5	10	15
246	AD	25	26	.	10	5	6	14	20
247	AD	25	.	13	7	4	5	9	14
248	AD	26	15	.	8	5	7	8	15
249	AD	26	16	.	6	3	7	14	21
250	AD	26	16	.	6	3	6	12	18
251	AD	26	17	.	10	4	.	.	.	10	14	24	.	.	.
252	AD	26	19	.	6	5	7	12	19
253	AD	26	20	.	12	5	4	10	14
254	AD	26	22	.	9	4	5	11	16

Exhibit 7.1.6 Observed ADOS and ADI-R Scores and the Resulting AD, ASD and Below Criteria Classifications

Row Number	Classification: 0=Below Criteria	ADI-R			ADOS Module 1			ADOS Module 2			ADOS Module 3				
		Domain A Reciprocal Social Interaction	Domain B Communication - Verbal Total	Domain B Communication - Non-Verbal Total	Domain C Patterns of Behavior Total	Domain D Abnormality of Development Total	Communication Total	Reciprocal Social Interaction Total	Communication and Social Interaction Total	Communication Total	Reciprocal Social Interaction Total	Communication and Social Interaction Total			
ASD Cut Point =>		10	8	7	3	1	2	4	7	3	4	8	2	4	7
AD Cut Point =>							4	7	12	5	6	12	3	6	10
Scores that are below AD but above ASD cut points are highlighted in Blue															
255	AD	26	23	.	10	4	7	13	20
256	AD	26	23	.	12	5	7	13	20
257	AD	26	.	13	8	4	5	11	16
258	AD	26	.	12	6	5	7	13	20
259	AD	26	.	13	6	5	7	10	17
260	AD	26	.	13	8	5	.	.	.	8	14	22	.	.	.
261	AD	26	.	14	6	5	6	11	17
262	AD	27	14	.	5	5	5	10	15
263	AD	27	14	.	5	3	.	.	.	8	13	21	.	.	.
264	AD	27	16	.	8	2	3	10	13
265	AD	27	17	.	6	5	4	6	10
266	AD	27	17	.	8	4	7	11	18
267	AD	27	17	.	6	3	4	9	13
268	AD	27	19	.	8	5	.	.	.	8	13	21	.	.	.
269	AD	27	19	.	8	4	4	9	13
270	AD	27	20	.	10	3	6	12	18
271	AD	27	20	.	8	5	5	11	16
272	AD	27	20	.	9	5	5	9	14
273	AD	27	20	.	8	5	8	9	17
274	AD	27	20	.	4	5	6	7	13
275	AD	27	20	.	8	5	3	8	11
276	AD	27	21	.	10	2	5	12	17
277	AD	27	21	.	9	5	.	.	.	8	14	22	.	.	.
278	AD	27	22	.	9	3	6	7	13
279	AD	27	23	.	3	4	.	.	.	7	14	21	.	.	.
280	AD	27	23	.	4	4	6	11	17
281	AD	27	24	.	12	5	5	13	18
282	AD	27	24	.	8	4	.	.	.	8	11	19	.	.	.
283	AD	27	.	11	4	4	6	11	17
284	AD	27	.	12	6	4	6	13	19
285	AD	27	.	14	4	4	5	12	17
286	AD	28	14	.	6	5	7	14	21

Exhibit 7.1.6 Observed ADOS and ADI-R Scores and the Resulting AD, ASD and Below Criteria Classifications

Row Number	Classification: 0=Below Criteria	ADI-R			ADOS Module 1			ADOS Module 2			ADOS Module 3				
		Domain A Reciprocal Social Interaction	Domain B Communication - Verbal Total	Domain B Communication - Non-Verbal Total	Domain C Patterns of Behavior Total	Domain D Abnormality of Development Total	Communication Total	Reciprocal Social Interaction Total	Communication and Social Interaction Total	Communication Total	Reciprocal Social Interaction Total	Communication and Social Interaction Total			
ASD Cut Point =>		10	8	7	3	1	2	4	7	3	4	8	2	4	7
AD Cut Point =>							4	7	12	5	6	12	3	6	10
Scores that are below AD but above ASD cut points are highlighted in Blue															
287	AD	28	17	.	8	5	5	11	16
288	AD	28	18	.	8	3	6	13	19
289	AD	28	19	.	5	4	.	.	.	5	11	16	.	.	.
290	AD	28	20	.	6	5	3	10	13
291	AD	28	20	.	8	5	.	.	.	7	12	19	.	.	.
292	AD	28	20	.	4	5	6	14	20
293	AD	28	20	.	7	5	.	.	.	8	9	17	.	.	.
294	AD	28	21	.	7	4	5	12	17
295	AD	28	21	.	6	5	.	.	.	8	12	20	.	.	.
296	AD	28	22	.	9	3	4	11	15
297	AD	28	24	.	8	5	4	11	15
298	AD	28	.	12	4	2	6	12	18
299	AD	28	.	13	8	3	6	10	16
300	AD	28	.	14	8	5	10	12	22
301	AD	29	12	.	8	5	8	10	18
302	AD	29	17	.	5	5	3	9	12
303	AD	29	18	.	7	4	.	.	.	8	11	19	.	.	.
304	AD	29	19	.	5	5	5	9	14
305	AD	29	19	.	5	3	3	8	11
306	AD	29	21	.	8	4	.	.	.	8	14	22	.	.	.
307	AD	29	22	.	12	5	7	12	19
308	AD	29	24	.	5	3	.	.	.	6	9	15	.	.	.
309	AD	29	.	14	4	4	6	10	16
310	AD	29	.	14	6	4	8	13	21
311	AD	29	.	13	7	5	5	10	15
312	AD	29	.	13	5	5	8	14	22
313	AD	29	.	14	6	4	4	8	12
314	AD	30	14	.	7	5	4	8	12
315	AD	30	18	.	8	5	4	12	16
316	AD	30	19	.	8	5	8	11	19
317	AD	30	21	.	12	5	4	10	14
318	AD	30	.	14	8	4	6	11	17

Exhibit 7.1.6 Observed ADOS and ADI-R Scores and the Resulting AD, ASD and Below Criteria Classifications																			
Row Number	Classification: 0=Below Criteria	ADI-R			ADOS Module 1			ADOS Module 2			ADOS Module 3								
		Domain A Reciprocal Social Interaction	Domain B Communication - Verbal Total	Domain B Communication - Non-Verbal Total	Domain C Patterns of Behavior Total	Domain D Abnormality of Development Total	Communication Total	Reciprocal Social Interaction Total	Communication and Social Interaction Total	Communication Total	Reciprocal Social Interaction Total	Communication Total	Reciprocal Social Interaction Total	Communication and Social Interaction Total					
ASD Cut Point =>		10	8	7	3	1	2	4	7	12	3	5	8	12	2	3	4	6	7
AD Cut Point =>		Scores that are below AD but above ASD cut points are highlighted in Blue																	
319	AD	30	.	14	4	2	8	11	19
320	AD	30	.	13	8	5	6	9	15
321	AD	30	.	12	6	5	7	13	20

7.1.2. Decision Rules for Categorizing ASD with Regression Outcomes

In order for a child to be categorized as ASD with regression, the child had to meet both the criteria for ASD and the criteria for regression. The criteria for regression were based on the “regression questions” that were administered along with the ADI-R. Those questions are shown in Exhibits 7.1.7 and 7.1.8. Case children met criteria for the regression classification if:

- The response to *Regression Item 11* was a “2” (Definite loss of 3 or more words (not including “mama” and “dada”) for at least a month)

or

- 25% or more of the skills listed in *Regression Item 12b* that a child had before 24 months, were lost for a month or more before 36 months.

For example, if a child had 6 of the 7 skills listed *Regression Item 12b* before 24 months, and had stopped using 2 of those six skills for a month or more before 36 months, then the child would have lost 33% of the skills, and this percentage of skills lost meets the criterion for regression.

Among the 256 cases that met criteria for ASD:

- 207 (81%) did not meet criteria for regression
- 49 (19%) did meet criteria for regression.

Among the 49 that met criteria for regression:

- 40 met criteria based on *Regression Item 11* (definite loss of 3 or more words).
- 9 did not meet criteria based on *Regression Item 11* but did meet criteria based on *Regression Item 12b*. (See Exhibit 7.1.9)
- 43 met criteria for AD.

Exhibit 7.1.7 Regression Item 11.

11. LOSS OF LANGUAGE SKILLS AFTER ACQUISITION

This item is to determine whether, ONCE THE SUBJECT HAS DEVELOPED COMMUNICATIVE LANGUAGE, THERE WAS A DEFINITE PERIOD OF LOSS OF SKILLS THAT LASTED AT LEAST 1 MONTH. USE THE FOLLOWING DEFINITIONS:

- LANGUAGE BEFORE LOSS: COMMUNICATIVE USE OF AT LEAST FIVE DIFFERENT WORDS (OTHER THAN “MAMA” AND “DADA”) ON A DAILY BASIS FOR AT LEAST 1 MONTH.
- LANGUAGE LOSS: LOSS FOR AT LEAST 1 MONTH OF A LANGUAGE SKILL PREVIOUSLY ESTABLISHED, AS SPECIFIED ABOVE.

Were you ever concerned that [SUBJECT] might have lost language or communication skills during the first years of his/her life?

Was there ever a time that s/he stopped speaking for some months after having learned to talk?

(IF YES) How much language did s/he have before stopping? Was s/he using at least five different words (other than “mama” and “dada”) on a daily basis for as long as 1 month?

Exhibit 7.1.7 Regression Item 11.

List at least 5 words used on a daily basis.

Score: _____

0 = Definitely no loss

1 = Probable loss of specified skill, including language (<3 words or not clear loss) or communication skills

2 = Definite loss of 3 or more words (not including “mama” and “dada”) for at least a month

8 = Insufficient language and other skills to measure change in quality

9 = N/K or not asked

IF ITEM 11 =0 OR 8, SKIP TO ITEM 20, ELSE CONTINUE TO ITEM 12

Exhibit 7.1.8 Regression Item 12b.

12b. EARLY LANGUAGE SKILLS

Now I want to ask you about some specific skills that SUBJECT might have been able to do either recently or when s/he was younger. I'll ask you whether s/he ever lost these skills, how old s/he was when the loss of this skill first became apparent and whether s/he ever regained the skills that were lost. (FILL IN ALL BOXES)

Skill	Had skill before 24 months	Stopped using the skill for a month or more before 36 months	Can do now	Never had
Respond to name				
Say or understand “Uh oh”				
Say or understand “Mommy”				
React to “There’s Mommy/Daddy”				
Say or understand “Hi”				
Understand “Come here/Come on”				
Understand “Look/Look here”				

Exhibit 7.1.9. Percent of Skills Lost for 9 ASD Cases That Met Criteria for Regression Based on Regression Item 12b

Number of Skills Prior to 24 Months	Number of Skills Lost	Percent Lost	Frequency	Cumulative Frequency
3	1	33	1	1
7	7	100	3	4
3	1	33	1	5
3	2	67	1	6
6	4	67	1	7
7	7	100	2	9

7.1.3. Decision Rules for Categorizing Autistic Disorder with Low Cognitive Function Excluded

The rationale for creating an outcome category “*AD with Low Cognitive Function Excluded*” was that it can be difficult to determine whether children with severe developmental delay actually have autistic disorder. Children who are non-responsive during the assessment process are more difficult to assess. If the imprecision of the assessment process for children with severe developmental delays resulted in the inclusion of children without AD in the AD group, then we would expect the estimates of AD risk associated with exposure to ethylmercury from vaccines and immune globulins would be attenuated, relative to estimates based on a group with non-AD children excluded from the AD group. Put another way, we are more confident that all of the children in the group classified as *AD with Low Cognitive Function Excluded* really do have autistic disorder, than we are of the group with the more general *AD* classification.

To be categorized as *AD with Low Cognitive Function Excluded*, the child had to meet the study criteria for autistic disorder and also had to not meet the study criteria for *Low Cognitive Function*. As described in Chapter 6, there was no single assessment instrument that could adequately measure cognitive functioning across the full range of developmental delays in the population autistic disorder cases. Therefore, both the Raven's Colored Matrices and the Visual Reception Scale of the Mullen were available to assess the case children's cognitive functioning. The clinical assessors always began with the Raven's and only administered the Mullen scale if the child's Raven's score was below a cut-off recommended by Dr. Catherine Lord.

Raven's raw scores were converted to standard scores using the standard scores derived by Dr. Catherine Lord and colleagues and described in Section 6.6.2.2. Lord et. al derived the scores by plotting a standardized regression line using percentiles and age equivalents reported in the Raven's manuals for overlapping groups of children and adults. Results from the Mullen assessment are expressed as “Mullen Years” and “Mullen Months” where, for example a result of 3 years, 1 month means that the child's level of cognitive functioning is estimated to be equivalent to that of an average child who is 3 years, 1 month. The Mullen scores were converted into a ratio cognitive function score (or “*Ratio CF*”) in the following manner. First the Mullen Years and Months scores were converted into a *Mullen Age in Years* score as follows:

- $Mullen\ Age\ in\ Years = Mullen_Years + (Mullen_Months / 12).$

For example, a score of 3 years, 1 month is equal to:

- $Mullen\ Age\ in\ Years = 3 + (1 / 12) = 3.086.$

The child's chronological age at the time of assessment was expressed in a likewise fashion. The *Ratio CF* was calculated as the ratio of *Mullen Age in Years* to the child's chronological age in years, multiplied by 100, as shown in the following example:

- $Ratio\ CF = 100 * (Mullen\ Age\ in\ Years / Child\ Age\ at\ Assessment)$

$$\begin{aligned} &= 100*(3.086 / 10.089) \\ &= 100*(.306) \\ &= 30.6 \end{aligned}$$

Using the advice of Dr. Catherine Lord, who drew on her experiences with the levels of cognitive functioning where confidence in the AD classification drops off, we used the following criteria to mark cases for exclusion from the *AD with Low Cognitive Function Excluded* group. A child was marked for exclusion from the group if he or she had either:

- A Raven's score of below 35; or
- A Mullen Ratio CF score of below 35.

Two additional cases were marked for exclusion from the *AD with Low Cognitive Function Excluded* group because they were unable to complete either the Raven's or the Mullen. One could not understand the Raven's and could not pay attention to the Mullen. The other could not be tested due high activity level and erratic behavior.

The Raven's and Mullen of the assessed cases are shown in Exhibit 7.1.10. The exhibit shows each child's AD, ASD, or Below Criteria status, child's age, Raven and Mullen Scores, and an indicator for whether the child met the study's criteria for "Low Cognitive Function". Records marked as "Low CF = 1" were excluded from the *AD with Low Cognitive Function Excluded* group.

Exhibit 7.1.10								
Raven's, Mullen, and Ratio Cognitive Function Scores and Classification of "Low Cognitive Function"								
(Low CF = Yes Marked for Exclusion from "AD with Low Cognitive Function Excluded" Group)								
Row	AD, ASD Classification	Child Age	Ravens_ Score_n	Mullen_ Years_n	Mullen_ Months_n	Mullen_ Age	Ratio CF	Low CF 1=Yes
1	Below Criteria	8.4	140	0
2	ASD	6.4	140	0
3	Below Criteria	8.6	140	0
4	ASD	8.1	140	0
5	AD	7.5	138	0
6	AD	7.3	137	0
7	AD	8.4	136	0
8	AD	9.1	136	0
9	ASD	9.1	136	0
10	AD	7.7	136	0
11	Below Criteria	8.5	133	0
12	Below Criteria	9.5	133	0
13	ASD	9.2	133	0
14	ASD	10.0	131	0
15	AD	10.2	131	0
16	AD	10.0	131	0
17	Below Criteria	7.1	131	0
18	ASD	10.5	130	0
19	AD	10.6	130	0
20	AD	10.8	130	0
21	ASD	7.3	129	0
22	AD	8.4	129	0
23	AD	8.7	129	0
24	AD	9.0	129	0
25	AD	8.9	129	0
26	AD	9.0	129	0
27	Below Criteria	7.3	128	0
28	AD	6.3	128	0
29	AD	7.8	128	0
30	AD	7.6	128	0
31	ASD	7.3	128	0
32	Below Criteria	9.8	127	0
33	Below Criteria	10.2	127	0
34	AD	7.9	125	0
35	ASD	10.4	125	0
36	AD	8.9	125	0
37	ASD	8.3	125	0
38	Below Criteria	11.7	125	0
39	ASD	10.4	125	0
40	Below Criteria	8.7	125	0
41	AD	8.6	125	0
42	ASD	9.6	125	0
43	Below Criteria	9.3	125	0

Exhibit 7.1.10

Raven's, Mullen, and Ratio Cognitive Function Scores and Classification of "Low Cognitive Function"

(Low CF = Yes Marked for Exclusion from "AD with Low Cognitive Function Excluded" Group)

Row	AD, ASD Classification	Child Age	Ravens_ Score_n	Mullen_ Years_n	Mullen_ Months_n	Mullen_ Age	Ratio CF	Low CF 1=Yes
44	ASD	9.6	125	0
45	ASD	9.3	125	0
46	AD	9.9	125	0
47	Below Criteria	9.7	125	0
48	Below Criteria	9.7	125	0
49	AD	8.6	122	0
50	AD	9.7	122	0
51	ASD	8.7	122	0
52	AD	8.4	122	0
53	Below Criteria	8.5	122	0
54	Below Criteria	9.2	122	0
55	ASD	8.6	122	0
56	Below Criteria	9.0	122	0
57	Below Criteria	11.2	119	0
58	AD	7.9	119	0
59	ASD	11.6	119	0
60	Below Criteria	9.3	119	0
61	ASD	10.6	119	0
62	ASD	10.1	119	0
63	AD	7.4	119	0
64	AD	9.4	119	0
65	ASD	7.5	119	0
66	AD	7.8	119	0
67	AD	11.6	119	0
68	Below Criteria	7.5	119	0
69	AD	8.8	119	0
70	AD	8.1	119	0
71	Below Criteria	10.0	119	0
72	ASD	10.3	119	0
73	AD	8.9	119	0
74	ASD	10.1	119	0
75	ASD	9.1	119	0
76	Below Criteria	8.4	119	0
77	AD	6.1	117	0
78	AD	7.9	116	0
79	AD	7.7	116	0
80	ASD	9.8	114	0
81	AD	11.4	114	0
82	AD	11.1	114	0
83	AD	10.0	114	0
84	Below Criteria	11.1	114	0
85	AD	10.7	114	0
86	ASD	7.3	114	0
87	ASD	11.4	114	0

Exhibit 7.1.10

Raven's, Mullen, and Ratio Cognitive Function Scores and Classification of "Low Cognitive Function"

(Low CF = Yes Marked for Exclusion from "AD with Low Cognitive Function Excluded" Group)

Row	AD, ASD Classification	Child Age	Ravens_ Score_n	Mullen_ Years_n	Mullen_ Months_n	Mullen_ Age	Ratio CF	Low CF 1=Yes
88	Below Criteria	8.0	114	0
89	Below Criteria	10.2	114	0
90	Below Criteria	8.8	114	0
91	AD	10.7	114	0
92	Below Criteria	11.9	114	0
93	AD	9.5	114	0
94	Below Criteria	8.8	114	0
95	AD	10.6	114	0
96	ASD	9.0	114	0
97	AD	11.7	114	0
98	ASD	9.7	114	0
99	Below Criteria	8.0	114	0
100	Below Criteria	7.9	114	0
101	ASD	11.6	114	0
102	AD	12.2	114	0
103	AD	7.6	113	0
104	AD	5.9	112	0
105	AD	6.3	112	0
106	ASD	6.1	112	0
107	ASD	6.9	112	0
108	ASD	7.2	112	0
109	AD	10.0	110	0
110	Below Criteria	11.0	110	0
111	AD	10.9	110	0
112	Below Criteria	9.3	110	0
113	AD	8.1	110	0
114	AD	10.9	110	0
115	AD	11.8	110	0
116	Below Criteria	6.1	110	0
117	AD	10.0	110	0
118	AD	11.2	110	0
119	AD	6.6	110	0
120	AD	6.6	110	0
121	AD	11.9	110	0
122	ASD	9.1	110	0
123	ASD	8.0	110	0
124	Below Criteria	11.5	110	0
125	Below Criteria	7.5	110	0
126	Below Criteria	7.5	110	0
127	AD	8.0	108	0
128	AD	7.4	108	0
129	AD	8.4	108	0
130	ASD	6.2	108	0
131	AD	6.5	108	0

Exhibit 7.1.10

Raven's, Mullen, and Ratio Cognitive Function Scores and Classification of "Low Cognitive Function"

(Low CF = Yes Marked for Exclusion from "AD with Low Cognitive Function Excluded" Group)

Row	AD, ASD Classification	Child Age	Ravens_ Score_n	Mullen_ Years_n	Mullen_ Months_n	Mullen_ Age	Ratio CF	Low CF 1=Yes
132	AD	10.4	107	0
133	Below Criteria	10.2	107	0
134	AD	11.5	107	0
135	ASD	11.2	107	0
136	Below Criteria	9.5	107	0
137	AD	9.8	107	0
138	Below Criteria	11.6	107	0
139	AD	11.1	107	0
140	Below Criteria	11.7	107	0
141	ASD	11.7	107	0
142	AD	9.2	107	0
143	ASD	10.4	107	0
144	AD	9.5	107	0
145	AD	7.5	105	0
146	AD	6.2	105	0
147	Below Criteria	6.5	105	0
148	AD	7.3	105	0
149	ASD	7.1	105	0
150	AD	7.3	105	0
151	AD	11.7	104	0
152	ASD	9.0	104	0
153	ASD	10.4	104	0
154	AD	9.1	104	0
155	Below Criteria	11.9	104	0
156	ASD	9.9	104	0
157	Below Criteria	12.2	104	0
158	AD	9.4	104	0
159	AD	10.7	104	0
160	AD	7.0	103	0
161	Below Criteria	6.1	103	0
162	ASD	7.7	103	0
163	ASD	8.2	103	0
164	AD	8.4	103	0
165	AD	8.5	103	0
166	AD	6.2	103	0
167	AD	7.0	103	0
168	ASD	7.5	100	0
169	AD	10.8	100	0
170	AD	9.4	100	0
171	AD	7.2	100	0
172	AD	7.6	100	0
173	AD	7.6	100	0
174	ASD	9.8	100	0
175	AD	11.9	100	0

Exhibit 7.1.10

Raven’s, Mullen, and Ratio Cognitive Function Scores and Classification of “Low Cognitive Function”

(Low CF = Yes Marked for Exclusion from “AD with Low Cognitive Function Excluded” Group)

Row	AD, ASD Classification	Child Age	Ravens_ Score_n	Mullen_ Years_n	Mullen_ Months_n	Mullen_ Age	Ratio CF	Low CF 1=Yes
176	Below Criteria	8.9	100	0
177	AD	7.9	100	0
178	AD	9.9	100	0
179	AD	9.8	100	0
180	AD	8.6	100	0
181	AD	11.6	100	0
182	Below Criteria	12.4	100	0
183	AD	8.0	98	0
184	Below Criteria	8.6	98	0
185	AD	9.5	98	0
186	AD	8.3	98	0
187	ASD	8.3	98	0
188	AD	9.1	98	0
189	AD	9.6	98	0
190	Below Criteria	10.0	98	0
191	AD	7.4	98	0
192	Below Criteria	7.5	98	0
193	AD	11.7	97	0
194	AD	11.4	97	0
195	AD	10.9	97	0
196	ASD	10.5	97	0
197	AD	8.0	95	0
198	Below Criteria	10.0	95	0
199	ASD	7.3	95	0
200	AD	9.6	95	0
201	ASD	9.0	95	0
202	AD	8.4	95	0
203	AD	7.7	95	0
204	AD	9.9	95	0
205	AD	7.9	95	0
206	AD	6.5	95	0
207	AD	6.7	95	0
208	ASD	6.6	95	0
209	AD	9.6	95	0
210	AD	10.0	95	0
211	AD	8.2	95	0
212	AD	9.4	95	0
213	Below Criteria	11.4	94	0
214	AD	11.2	94	0
215	AD	10.0	94	0
216	ASD	10.5	94	0
217	AD	7.0	93	0
218	AD	7.1	93	0
219	AD	8.1	93	0

Exhibit 7.1.10

Raven's, Mullen, and Ratio Cognitive Function Scores and Classification of "Low Cognitive Function"

(Low CF = Yes Marked for Exclusion from "AD with Low Cognitive Function Excluded" Group)

Row	AD, ASD Classification	Child Age	Ravens_ Score_n	Mullen_ Years_n	Mullen_ Months_n	Mullen_ Age	Ratio CF	Low CF 1=Yes
220	AD	7.2	93	0
221	Below Criteria	9.3	93	0
222	ASD	8.0	93	0
223	AD	8.3	93	0
224	Below Criteria	7.5	93	0
225	ASD	9.1	90	0
226	AD	10.6	90	0
227	Below Criteria	6.8	90	0
228	ASD	9.5	90	0
229	AD	6.9	90	0
230	AD	10.0	90	0
231	ASD	7.2	90	0
232	AD	8.0	90	0
233	AD	5.9	88	0
234	ASD	9.4	88	0
235	ASD	10.9	88	0
236	ASD	11.4	88	0
237	AD	10.2	88	0
238	AD	6.4	88	0
239	AD	7.7	88	0
240	Below Criteria	7.0	88	0
241	AD	7.1	88	0
242	AD	12.0	88	0
243	AD	12.7	88	0
244	Below Criteria	8.9	88	0
245	AD	13.1	88	0
246	AD	7.0	85	0
247	Below Criteria	9.3	85	0
248	AD	11.3	85	0
249	AD	10.1	85	0
250	Below Criteria	12.8	85	0
251	Below Criteria	11.9	83	0
252	AD	11.6	83	0
253	Below Criteria	11.4	83	0
254	Below Criteria	10.6	83	0
255	AD	8.7	83	0
256	AD	9.4	83	0
257	ASD	12.1	83	0
258	Below Criteria	8.6	83	0
259	AD	8.9	80	0
260	AD	9.6	80	0
261	AD	7.7	80	0
262	ASD	8.6	80	0
263	AD	11.8	80	0

Exhibit 7.1.10
Raven's, Mullen, and Ratio Cognitive Function Scores and Classification of "Low Cognitive Function"
(Low CF = Yes Marked for Exclusion from "AD with Low Cognitive Function Excluded" Group)

Row	AD, ASD Classification	Child Age	Ravens_ Score_n	Mullen_ Years_n	Mullen_ Months_n	Mullen_ Age	Ratio CF	Low CF 1=Yes
264	ASD	8.4	80	0
265	Below Criteria	12.7	80	0
266	AD	9.3	78	0
267	AD	12.0	78	0
268	ASD	6.9	78	0
269	AD	9.6	75	0
270	AD	10.2	75	0
271	Below Criteria	7.3	75	0
272	AD	7.9	75	0
273	AD	9.2	75	0
274	AD	11.8	73	0
275	ASD	9.3	73	0
276	AD	8.1	73	0
277	AD	11.5	73	0
278	Below Criteria	7.3	73	0
279	AD	8.0	70	0
280	AD	10.9	70	0
281	ASD	10.7	70	0
282	AD	10.4	70	0
283	AD	8.2	70	0
284	AD	9.2	70	0
285	AD	9.3	68	0
286	AD	8.6	68	0
287	ASD	8.1	68	0
288	AD	7.4	63	0
289	AD	10.4	60	0
290	ASD	11.9	58	0
291	AD	11.8	58	0
292	AD	11.5	55	0
293	ASD	9.5	50	0
294	AD	9.1	50	0
295	AD	11.3	45	0
296	AD	12.7	35	0
297	Below Criteria	6.2	18	1
298	AD	10.0	6	1
299	AD	7.9	.	5	6	5.5	69.6	0
300	AD	11.0	.	.	45	3.8	34.1	1
301	AD	6.0	.	.	24	2.0	33.6	1
302	AD	7.9	.	.	31	2.6	32.9	1
303	AD	8.0	.	.	30	2.5	31.1	1
304	AD	6.7	.	.	25	2.1	30.9	1
305	AD	6.5	.	.	24	2.0	30.8	1
306	AD	10.1	.	3	1	3.1	30.6	1
307	AD	8.8	.	2	6	2.5	28.4	1

Exhibit 7.1.10 Raven's, Mullen, and Ratio Cognitive Function Scores and Classification of "Low Cognitive Function" (Low CF = Yes Marked for Exclusion from "AD with Low Cognitive Function Excluded" Group)									
Row	AD, ASD Classification	Child Age	Ravens_ Score_n	Mullen_ Years_n	Mullen_ Months_n	Mullen_ Age	Ratio CF	Low CF 1=Yes	
308	AD	7.7	.	.	26	2.2	28.1	1	
309	AD	8.5	.	1	13	2.1	24.5	1	
310	AD	11.6	.	.	33	2.8	23.6	1	
311	AD	8.5	.	2	0	2.0	23.6	1	
312	AD	11.5	.	.	31	2.6	22.5	1	
313	AD	7.1	.	.	19	1.6	22.4	1	
314	AD	7.9	.	.	21	1.8	22.1	1	
315	AD	9.0	.	.	23	1.9	21.4	1	
316	AD	12.1	.	2	6	2.5	20.7	1	
317	AD	11.6	.	.	25	2.1	18.0	1	
318	AD	7.6	.	1	3	1.3	16.5	1	
319	AD	10.4	.	.	11	0.9	8.8	1	
320	AD	8.4	No score. Unable to understand Ravens, could not pay attention to Mullen						1
321	ASD	8.7	No cog testing possible due to high activity level, not possible to compute score due to erratic behavior.						1

7.2. Creation of "Screened Control Group"

The study utilized a matched case-control design wherein controls were matched to cases on birth year, sex, and HMO. As described in Chapter 5 (Sampling), in addition to the eligibility interview, the computer automated data, chart abstraction data, and parent interview data sources were analyzed to ensure that individuals sampled as controls did not have AD, ASD, or any exclusionary conditions specified for the study. Furthermore, the Social Communication Questionnaire was used to identify and exclude from the control group, any individuals that might have undiagnosed ASD. The explicit goal of the study is to assess whether higher levels of exposure to thimerosal containing vaccines and immune globulins is associated with increased risk of adverse neurodevelopmental outcomes – specifically, AD, ASD, and ASD with regression. During the study's design phase, the study's External Expert Consultants expressed concern that if the control group included individuals with milder types of adverse neurodevelopmental outcomes, and if increased exposure to ethylmercury from thimerosal-containing vaccines and immune globulins were related to increased risk of those milder adverse neurodevelopmental outcomes, then inclusion of those individuals in the control group could attenuate the estimates of the risk of AD, and ASD from ethylmercury exposure. Therefore, as a further precaution, the study's External Expert Consultants urged the creation of a "screened control group" that would exclude children that had milder forms of adverse neurodevelopmental outcomes that have had hypothesized linkages to

ethylmercury exposure²⁴. We therefore created a “screened control group” that excluded children for which records indicated any of the following:

- Speech delay or language delay;
- Learning disabilities;
- Attention deficit hyperactivity disorder (ADHD) or attention deficit disorder (ADD); or
- Tics.

Additionally, children that had had an individual education plan (IEP)²⁵ in the 12 months prior to the eligibility interview were also excluded from the “screened control group”. Children with any of the conditions listed above are likely to have had an IEP. However, this criterion will have likely excluded some children from the “screened control group” for reasons other than those conditions (e.g., behavioral problems, physical or sensory issues).

To identify children with any of those conditions, we used three data sources:

- Eligibility interview;
- Parent interview;
- Medical chart abstraction.

The use of each of those three data sources is described in Chapter 6.

7.3. Measures of Postnatal Exposure to Ethylmercury

7.3.1. Introduction to the Vaccination Histories File

Two sources of postnatal vaccination data (computer-automated and chart abstraction) were combined to create a *Vaccination Histories File*. This file contains the vaccination histories of the n=1,095 full participant children. Each row of the Vaccination Histories File represents a record of a vaccine received on a particular day. Thus, the file has many records per child. The file includes each child’s “resolved vaccine history,” and also includes the raw, original, un-cleaned vaccine data from each of the two data sources. The resolved vaccine histories were obtained from cleaning the raw, original data and resolving any discrepancies among the two data sources and any discrepancies between the records and recommended childhood vaccination schedules. Cumulative exposure amounts were calculated from each child’s resolved vaccine history. Data cleaning procedures are described subsequently.

²⁴ For results of studies of ethylmercury exposure and neurodevelopmental outcomes, see Verstaeten et. al, (2000); Thompson, Price, Goodson et. al (2007); Price, Goodson, Stewart (2007) and other studies referenced in Section 3.1.1.

²⁵ An IEP is an educational program specifically designed by a team of professionals to meet the needs of a student with difficulties in the classroom or developmental issues.

Exhibit 7.3.1.1 shows an example resolved vaccine history for one child. The column “Res_Vacdays1” shows the child’s age in days at the time of each vaccine receipt. The exhibit shows that the child received vaccines on the day she/he was born (day 1), and at ages 63, 126, and 183 days. The next three columns to the right show the type of vaccine received (Res_VacType), the manufacturer (Res_Mfr), and the ethylmercury amount, expressed in micrograms (μg), contained in each vaccine (MercAmt). Additional detail is provided subsequently in this document regarding vaccine types and the assignments of mercury amounts associated with each receipt. The column labeled “RecptWtKG1” shows the child’s weight (in kilograms) at the time of vaccine receipt. And the final column (Amt_wt1) shows the mercury amount for each receipt divided by the child’s weight at the time of the vaccine receipt. To create the exposure variables used in the analyses, the values of “Amt_wt1” were summed over particular age ranges.

Exhibit 7.3.1.1 Example of a Resolved Vaccine History

ChildID	Res_Vacdays1	Res_VacType	Res_MFR	MercAmt	RecptWtKG1	Amt_wt1
0001	1	HepB	SKB	12.50	3.65	3.42
0001	63	DTP	CON	25.00	5.90	4.24
0001	63	Hib	MSD	12.50	5.90	2.12
0001	63	HepB	SKB	12.50	5.90	2.12
0001	63	Polio	LED	0.00	5.90	0.00
0001	126	DTP	CON	25.00	7.17	3.49
0001	126	Hib	MSD	12.50	7.17	1.74
0001	126	Polio	LED	0.00	7.17	0.00
0001	183	DTP	CON	25.00	8.51	2.94
0001	183	HepB	SKB	12.50	8.51	1.47
0001	183	Polio	LED	0.00	8.51	0.00

Res_Vacdays1 is child’s age in days at time of vaccine receipt (day of birth = day 1).

MercAmt is micrograms of ethylmercury in a single receipt of the vaccine.

RecptWtKG1 is child’s weight in kilograms at the time of vaccine receipt.

Amt_wt1 was calculated as $MercAmt / RecptWtKG1$

7.3.2. Overview of Steps from Raw Data to Creation of Analysis Variables

Data on early childhood exposure to ethylmercury from thimerosal-containing vaccines and immune globulins were obtained from two sources: From computer-automated data files and from abstractions of each child’s medical records. Information provided in the parent interview was also used to verify the data. An overview of the data processing steps from the receipt of raw data files to the creation of the exposure variables used in analyses is as follows:

1. The master list of study IDs was merged to each of the two vaccine files (computer-automated and chart abstraction immunization records). Any problems with ID discrepancies were resolved at this stage. Each of the two files contained many records per child ID, where each record represented a single vaccine

- receipt. Each file contained fields for child's ID, type of vaccine received, and either the date the vaccine was received or the child's age in days at the time of vaccine receipt. The computer-automated and chart abstracted data sets also contained fields for vaccine manufacturer and lot number. The master list of study IDs contained each child's ID and date of birth.
2. For each of the two files (chart, computer automated) a new *VacType* (vaccine type) variable was created, where the possible values taken by the variable and the spelling of each vaccine type were standardized across both data sources. For example, in the computer-automated data set, the codes 08, 43, and 45 took the value "HepB" on the *VacType* variable. In the chart data set, entries originally recorded as "HEP B", "HEP-B", "HEP B RECOMB", and several others were assigned the value "HepB" on the *VacType* variable. The common coding of the *VacType* variable made possible the merging and alignment of the two data sources on receipts of particular types of vaccines. All recodes were discussed and confirmed during weekly conference calls with the whole study team (the team included CDC staff, principal investigators from each of the HMOs, many of whom are pediatricians, data managers from each of the HMOs, and Abt Associates Inc. staff).
 3. For the chart abstraction, each child's age in days corresponding to each vaccine receipt was calculated. The computer-automated data set was delivered to Abt Associates Inc. with a field for child's age in days at time of vaccine receipt.
 4. The two files were merged by child's ID, child's age in days at time of vaccine receipt, and vaccine type.
 5. The next step was to resolve discrepancies in vaccine histories. Discrepancies included differences between the two data sources regarding the receipt of a vaccine on a particular day, or between the vaccine history indicated in the data set and the recommended vaccine schedule. An example of the former is a case where the medical chart abstraction data set indicated receipt of hepatitis B vaccine for a child on day 1 (i.e. on day child was born), but where the computer-automated data showed no receipt on that day. An example of the latter is when a particular data source (e.g. chart or computer automated) indicated receipt of two full series of DTaP, Hib, and HepB only two days apart. Receipt of two full series separated by only two days represents a major discrepancy from recommended vaccine schedules. It is exceedingly unlikely that a child would have received these series two days apart. It is much more likely that the duplicate records are due to clerical errors. Resolution of discrepancies was a major task and is considered in greater detail in Section 7.3.3. This data cleaning phase focused exclusively on vaccines and immune globulins received during the age range from birth to two years. Resolution of discrepancies resulted in a "resolved vaccine history" for each child.
 6. In the next step we assigned a mercury exposure amount corresponding to each vaccine receipt shown in each child's resolved vaccine history. For example, polio vaccine receipts were assigned an exposure amount equal to zero micrograms of ethylmercury, and Hib vaccines were assigned values of 0, 12.5, or 25 micrograms depending on the type of Hib vaccine received. Additional details

on the exposure amounts corresponding to each vaccine type are provided in Section 7.3.4.

7. Next, we needed to obtain the child's weight (in kilograms) corresponding to each age (in days) that the child received a vaccine. For most records the process was straightforward because children's weights are often recorded in medical records at the same time that vaccines are administered. In some cases, however, the data on children's weights were incomplete or did not align perfectly to the dates of vaccine receipt. When a vaccine receipt did not have a corresponding weight, one of two methods was used to impute a weight. If there were recorded weights before and after the vaccine receipt, then linear interpolation was used to predict the child's weight on the day of vaccine receipt. If there were no recorded weights after the vaccine receipt, then all of the child's recorded weights were used in a growth curve model to predict the child's weight at the time of the vaccine receipt. The predictions from the growth curve models aligned very closely with the growth curves published in the *2000 CDC Growth Charts for the United States: Methods and Developments*.
8. For each vaccine receipt, the mercury exposure amount (expressed as micrograms of ethylmercury contained in the vaccine) was divided by the child's weight (in kilograms) at the time of vaccine receipt, resulting in a measure of *exposure per kilogram per vaccine receipt*. For example, if a child weighed 8 kilograms at the time of receipt of a vaccine containing 12.5 micrograms of ethylmercury, then the value on this variable corresponding to this vaccine receipt would be equal to $12.5 / 8 = 1.56$ micrograms per kilogram.
9. Finally, for each child, the variables representing *exposure per kilogram per vaccine receipt* were summed over all vaccines and immune globulins received within each of four age ranges (0 to 7 months; 0 to 1 month; 1 to 7 months; 0 to 20 months) to produce the following three variables that were used in the analytical models:
 - *Exp07mos* = "Exposure zero to 7 months" = Exposure per kilogram per vaccine receipt summed over all vaccines and immune globulins received during the age range from birth to seven months of age (1 to 214 days).
 - *Exp01mos* = "Exposure zero to 1 month" = Exposure per kilogram per vaccine receipt summed over all vaccines and immune globulins received during the age range from birth to one month of age (1 to 28 days).
 - *Exp17mos* = "Exposure one to 7 months" = Exposure per kilogram per vaccine receipt summed over all vaccines received during the age range from one to seven months of age (29 to 214 days).
 - *Exp020mos* = "Exposure zero to 20 months" = Exposure per kilogram per vaccine receipt summed over all vaccines received during the age range from birth to twenty months of age (1 to 609 days).

Several additional exposure variables were created and used in models to estimate exposure effects when the receipt of thimerosal-containing vaccines coincided with antibiotic treatment. Those variables are described in the section titled "Concurrent Antibiotics-by-Exposure Interaction Models" (Section 9.2.6).

Three additional variables were created that were not used in the analytical models, but were used for descriptive purposes. These three variables were similar to those defined above, except that there was no division by the child's weight at the time of vaccine receipt. They are:

- Amt07mos = “Amount zero to 7 months” = Amount of ethylmercury per vaccine receipt summed over all vaccines and immune globulins received during the age range from birth to seven months of age (1 to 214 days).
- Amt01mos = “Amount zero to 1 month” = Amount of ethylmercury per vaccine receipt summed over all vaccines and immune globulins received during the age range from birth to one month of age (1 to 28 days).
- Amt17mos = “Amount one to 7 months” = Amount of ethylmercury per vaccine receipt summed over all vaccines received during the age range from one to seven months of age (29 to 214 days).
- Amt020mos = “Amount zero to 20 months” = Amount of ethylmercury per vaccine receipt summed over all vaccines and immune globulins received during the age range from birth to twenty months of age (1 to 609 days).

7.3.3. Data Cleaning for Child Vaccination Histories

Data on early childhood exposure to thimerosal from vaccines and hepatitis B immune globulins were obtained from two sources: computer automated data files²⁶, and abstractions of each child's medical records. Information provided by the child's mother during the parent interview was also used to verify the vaccine histories. Section 7.3.2 provided an overview of the data processing steps from the receipt of raw data files to the creation of the exposure variables. The purpose of the current section is to provide detail on the data cleaning procedures used to derive a “resolved vaccine history” for each child. The term “resolved vaccine history” is used to mean the final vaccine history for a child after having resolved any discrepancies among the two data sources regarding the receipt of a vaccine on a particular day, or between the vaccine history indicated in the raw data set and the recommended vaccine schedule. While the exposure variables include measures of cumulative exposure up to age 20 months, we applied the data cleaning procedures to cover an age range that went beyond 20 months. The data cleaning procedures described in this section were undertaken to obtain a resolved vaccine history for each child for the period spanning birth to 24 months (1-730 days).

The sections that follow describe each of several data cleaning procedures that were applied to the combined data set. Explanations of these procedures are accompanied by examples. The data cleaning procedures were originally developed as part of the study of *Infant Environmental Exposure to Thimerosal and Neuropsychological Outcomes at Ages 7 to 10 Years* (Price, Goodson, Stewart (2007); Thompson, Price, Goodson et al (2007)) in close consultation with data managers and investigators at each of the four HMOs that

²⁶ Each HMO that participated in the study maintains computer-automated vaccine records for administrative use and for research purposes. These computer-automated files are part of the Vaccine Safety Datalink system.

participated in that study, and with investigators at the CDC. This team included several pediatricians with firsthand experience in administering childhood vaccinations and in-depth knowledge of vaccination policies and practices used during the time period covered by the study. The team also included data managers and analysts from the HMOs who had a great deal of experience in the use of vaccination data for research purposes.

In a process spanning several months, the entire team scrutinized records to help develop and validate the data cleaning procedures. As computer automated cleaning algorithms were developed, samples of resulting vaccine histories, shown along with the raw data from each of the data sources, were sent out to all team members and were discussed during weekly telephone conferences. Near the end of the process, in order to validate that the computerized algorithms did not generate any unexpected results, Abt Associates Inc. staff scrutinized printouts showing the resolved histories and the raw data for every child in the data set.

7.3.3.1. Step 1: Preliminary Vaccine History

After combining vaccination data from both sources (chart and computer-automated) we preliminarily assumed that when a vaccine receipt appears in one but not in both data sources, that the vaccine was received by the child. In other words, a vaccine did not need to appear in both data sources in order to be counted. That is because we assumed that it was possible for a received vaccine to be listed in one source, but missed in the other source. As will be shown later, the assumption is preliminary because application of subsequent cleaning rules may remove one or more of the vaccines from the resolved history. An example of the application of this assumption is shown in Exhibit 7.3.3.1, where the resolved vaccine history includes a hepatitis B vaccine receipt at age 2-days. The right-hand panel of the exhibit shows the vaccine records from the chart and computer-automated data sets. The relevance of the columns for manufacturer and lot number will become apparent in subsequent examples. As shown in the exhibit, this receipt was indicated in the chart data, but was not present in the computer-automated data. The left-hand panel of the exhibit shows the resolved vaccine history for ID # 258. This child received hepatitis B vaccines at ages 2, 54, and 282 days, and several other vaccines on ages 60, 178, and 233 days. The resolved vaccine history includes only vaccines received during the age range spanning from birth to 730 days, i.e. from age (in days) = 1 to 730. The columns of the middle panel of the exhibit are for indicators for decision rules. None of those rules were applied in this example, but will be discussed in a subsequent section.

7.3.3.2. Step 2: Application of 30-day and 15-day Algorithms

A set of algorithms was developed to detect duplicate records of receipts of HepB, Hib, DTP, DTaP, combined DTP-Hib, combined DTaP-Hib, and polio vaccines within the first year of life. Since polio vaccines did not contain thimerosal, it was not strictly necessary to include them in the cleaning processes, but they were included nonetheless. However, for the other vaccines listed above, failure to identify and remove duplicate

records from the resolved vaccine history would result in an overestimate of a child's mercury exposure. Checks for other, less commonly administered childhood vaccines are described in a subsequent section of this document.

For all of the vaccine types listed above, except HepB, the algorithms were based on an assumption that two receipts of a single type of vaccine separated by a period of 30 days or less represents a major discrepancy from the recommended vaccination schedule. When such cases were detected, the algorithms marked one of the assumed duplicates for removal, and retained the other in the resolved vaccine history. The process for deciding which to keep and which to remove is described subsequently. These algorithms were created with the full awareness that, in the rare instance that a child was mistakenly administered one or more of these vaccines twice in a period of less than 30 days, the application of the algorithm would result in an underestimate of the child's actual exposure. However, there was consensus among the study team that those instances were expected to be exceedingly rare, whereas duplicate entries of the same vaccine were known to be common. Therefore, the algorithms focused on solving the common problem, hence preventing overestimates of exposure, while simultaneously, in rare instances, potentially causing underestimates.

The assumptions underlying the algorithms for HepB were similar to those described above, except that, when one of the receipts is a HepB that was received in the first month of life, it is plausible for two doses to be separated by a period of less than 30 days. This occurs, for example, in cases when a child receives a late birth dose of HepB, or an early month-1 dose of HepB. Examples include records of children who received HepB vaccinations on days 1 and 29, on days 15 and 43, and on days 2 and 31. The team considered it to be implausible to receive two doses within a period of 15 days or less when one of the receipts occurs in the first month of life, so the algorithm was programmed accordingly. When neither receipt fell within the first 30 days of life, the 30-day algorithm as previously described was applied for HepB vaccinations.

Detecting duplicate records for DTPs and Hibs was complicated by the fact that some discrepancies were caused by situations such as a record of a combined DTP-Hib vaccine in one data source, but separate DTP and Hib vaccines in another source, or entry of a DTP in one source, but entry of a DTaP in another source. The algorithms were designed to detect duplicates in all permutations of individual DTP, DTaP, DT (or TD), experimental DTaP, and Hib vaccines, and combined DTP, DTaP, and Hib vaccines.

When duplicate records were detected, a set of decision rules was applied to determine which of the two records should be omitted and which should be retained in the resolved vaccine history. The first decision rule was dependent on which of the two records had non-missing information on manufacturer and/or lot number. The record containing information on manufacturer and lot number was deemed to be more reliable and was therefore retained. In order to facilitate the comparisons, a ***manufacturer and lot number information score*** was computed for each record as follows. The combined data set included two variables from the chart data set that listed vaccine manufacture and lot number, and two additional variables listing vaccine manufacture and lot number from

the computer-automated data set. For each of those four variables, we created a corresponding dummy variable that took the value “1” if the manufacturer or lot number was non-missing, and took the value “0” otherwise. We then calculated the sum of the four dummy variables to obtain the *manufacturer and lot number information score* for each vaccine record. Possible values on this score were 0, 1, 2, 3, or 4. If one of the two duplicates had a higher score, it was retained, and the other was omitted.

Exhibit 7.3.3.2 shows an example where combined DTP-Hib vaccines were retained on days 121, and 185, while separate DTP and Hibs were omitted from the same days because the former had non-missing manufacturer and lot number, while the latter did not. This example also shows same-day-duplicate Hibs that were omitted on day 63. In the “decision rules” columns of the exhibit, “1”s indicate omitted duplicates.

In cases of a tie on the *manufacturer and lot information score*, then one was chosen at random to retain, and the other was omitted. An example is presented in Exhibit 7.3.3.4, where records of Hib and polio receipts on day 130 were omitted, but records of the same vaccines received on day 131 were retained in the resolved vaccine history. The choice of which to omit and which to retain was random.

7.3.3.3. Step 3: Check, Verify or Fix

This section summarizes a set of checks that were carried out on the children’s vaccine histories to identify potential errors. Vaccine histories identified by this set of checks were scrutinized by the study team during weekly phone conferences and decisions were made either verifying that the history was already correct, or that fixes were needed. Often a decision was made that a child’s medical records should be pulled and studied for clues on how to resolve potential discrepancies. The process of checking and fixing was iterative, such that after programming code was written and executed resulting in a change in a set of resolved vaccine histories, the set of checks was run again. The programming code used to make changes was applied only to the resolved vaccine history. The original data from the chart and computer-automated sources were never changed. A summary of the set of checks is as follows:

- 1) Verify that there are no two receipts of vaccines of a single type separated by less than 30 days, unless one is a HepB that was received during the first month of life.
- 2) Check for any receipts shown as having occurred before the child was born.

This type of error was caused by incorrect date entries. These errors were rectified by examination of the child’s full vaccine history, followed by a decision regarding the most likely correct date of receipt. For example, in one case a DTP-Hib vaccine was shown as having been received 180 days prior to the birth of the child. By changing the date of receipt by one year, the vaccine lined up with other vaccine receipts that occurred when the child was 185 days old.

- 3) Check for receipts of anything other than HepB during first 30 days of life.

Receipts of anything other than HepB or HepB immune globulin were treated as data entry errors. Examples include a record of a receipt of Hib at age 2-days, and for a different child, a receipt of DTP at age 1-day. In both cases the children received HepB vaccinations on those days. In both cases it was believed that the entries of the Hib and DTP vaccines were inadvertent.

- 4) Identify and check any histories indicating more than 3 HepB receipts in the first year of life.

The vaccine histories of children with more than three HepB receipts during the first year of life were examined by the study team. In instances where the receipts occurred around birth, 2 months, 4 months, and 6 to 12 months, the histories were deemed to be plausible and no further action was taken. When the four receipts deviated considerably from that pattern, staff from the relevant HMO went back to the child's medical charts to look for clues as to what might have happened. In one example, receipts were listed at birth, around 1 month, around 6 months, and around 7 months. Review of the charts indicated that the record of receipt near 7 months was an error. That receipt was omitted from the child's resolved vaccine history.

- 5) Identify and check any histories indicating more than 3 DT receipts in the first year of life. Included in the count of DT receipts were any receipts of DTs (or TDs), DTPs, DTaPs, experimental DTaP vaccines, and any combination vaccines that included DT i.e., DTaP-Hib, DTP-Hib, and DTaP-HepB.

The vaccine histories of children with more than three DT receipts during the first year of life were examined by the study team. In instances where the receipts occurred around 2, 4, 6, and 12 months, the histories were deemed to be plausible and no further action was taken. When the four receipts deviated considerably from that pattern, staff from the relevant HMO went back to the child's medical charts to look for clues as to what might have happened. In one example, receipts were listed at days 66, 121, 154, and 188. Review of the charts indicated that the record of receipt at 154 days was an error. That receipt was omitted from the child's resolved vaccine history.

- 6) Identify and check any histories indicating more than 4 Hib receipts (including combination vaccines with DTP or DTaP) in the first year of life.

A finding that a child's vaccine history indicated more than 4 Hib receipts triggered a chart review by staff at the relevant HMO. In one case, the receipt of 5 Hibs by a single child within the first year of life was deemed to be accurate.

- 7) Identify and check any histories indicating a receipt of an influenza vaccine in the first 120 days of life.

It would be unusual to receive a flu shot in this age range. None were found.

8) Checks for Hepatitis-A, MMR, varicella and polio vaccines.

These vaccines never contained thimerosal, so obtaining clean histories was not critical for these vaccines. However, checks were run to help identify anomalies in the children's histories. Checks included identification of histories where either varicella or MMR vaccine was received in the first 180 days of life, histories where any hepatitis-A vaccine was received before age 1 year, and histories indicating more than three polio receipts in the first year.

A list of all vaccine types remaining in the resolved vaccine histories of all children and the amount and the mercury amount assigned to each receipt is shown in Section 7.3.4.

Exhibit 7.3.3.1

Example Vaccine History: Record of HepB Vaccine Receipt at Age 2-Days Shown in Chart Data, but no Corresponding Record in Computer-Automated Data.

<u>Resolved Vaccine History</u>				<u>Decision Rule Indicators</u>						<u>Chart and Computer-automated Immunization Data</u>										
ID	Age Days	Res. Vac.	Res. Mfr.	HepB R1	HepB R2	Polio R1	Polio R2	DTP Hib R1	DTP Hib R2	Same Day Dup.	Bad Date	Look up	Age Days	Chart Vac.	Cmptr Vac.	Chart Mfr.	Cmptr Mfr.	Chart Lot	Cmptr Lot	
258	2	HepB	MIS										2	HepB		MIS			MIS	
258	54	HepB	SKB										54	HepB	HepB	ENG	SKB	ENG	110	
258	60	DTP	CON										60	DTP	DTP	CON	CON	2B4	2B4	
258	60	Hib	PRX										60	Hib	Hib	PRA	PRX	M13	M13	
258	60	Polio	LED										60	Polio	Polio	LED	LED	67	67	
258	178	DTP	LED										178	DTP	DTP	LED	LED	350	350	
258	178	Hib	PRX										178	Hib	Hib	PRA	PRX	M13	M13	
258	178	Polio	LED										178	Polio	Polio	LED	LED	352	352	
258	233	DTP	CON										233	DTP	DTP	CON	CON	3J4	3J4	
258	233	Hib	PRX										233	Hib	Hib	PRA	PRX	M13	M13	
258	233	Polio	LED										233	Polio	Polio	LED	LED	352	352	
258	282	HepB	SKB										282	HepB	HepB	ENG	SKB	128	128	
258													465	DTP	DTP	CON	CON	3F5	3F5	
258													465	Hib	Hib	PRA	PRX	M71	M71	
258													465	MMR	MMR	MSD	MSD	116	116	

Notes: For brevity, manufacturer and lot numbers are truncated to three characters. Actual values span more characters and may include blank spaces. Resolved vaccine history includes only vaccines received in the age range of 1 to 730 days.

Exhibit 7.3.3.2
Example Vaccine History: Combined DTP-Hib Vaccines Retained on Days 121 and 185 While Separate DTP and Hibs Omitted from Same Days Because Former Had Manufacturer and Lot Number. Same-Day-Duplicate Hibs Omitted on Day 63.

<u>Resolved Vaccine</u>				<u>Decision Rule Indicators</u>				<u>Chart and Computer-automated Immunization Data</u>						
<u>History</u>				HepB	DTP	Hib	Look	Age	Chart	Cmptr	Chart	Cmptr	Chart	Cmptr
ID	Age	Res.	Res.	Polio	Hib	R1	up	Days	Vac.	Vac.	Mfr.	Mfr.	Lot	Lot
	Days	Vac.	Mfr.	R1	R2	R2	Day							
							Dup.							
26	1	HepB	MIS					1	HepB	HepB	MIS	UNK	MIS	
26	63						1	63	Hib	Hib	MSD	MSD		136
26	63						1	63	Hib	Hib	UNK	UNK		
26	63	DTP	CON					63	DTP	DTP	MIS	CON	MIS	3D5
26	63	Hib	MSD					63	Hib	Hib	MIS	MSD	MIS	136
26	63	HepB	SKB					63	HepB	HepB	MIS	SKB	MIS	ENG
26	63	Polio	LED					63	Polio	Polio	MIS	LED	MIS	71
26	121	DTP-Hib	LED					121	DTP-Hib	DTP-Hib	LED	LED	MIS	390
26	121					1		121	DTP	DTP	MIS	UNK	MIS	
26	121					1		121	Hib	Hib	MIS	UNK	MIS	
26	121	Polio	LED					121	Polio	Polio	MIS	LED	MIS	71
26	185	DTP-Hib	LED					185	DTP-Hib	DTP-Hib	LED	LED	MIS	390
26	185					1		185	DTP	DTP	MIS	UNK	MIS	
26	185					1		185	Hib	Hib	MIS	UNK	MIS	
26	185	HepB	SKB					185	HepB	HepB	MIS	SKB	MIS	ENG
26	185	Polio	LED					185	Polio	Polio	MIS	LED	MIS	71
26	371							371	DTP-Hib	DTP-Hib	UNK	UNK	MIS	
26	371							371	MMR	MMR	UNK	UNK	MIS	
26	371							371	DTP	DTP	MIS	UNK	MIS	
26	371	Hib	LED					371	Hib	Hib	MIS	UNK	MIS	

Notes: For brevity, manufacturer and lot numbers are truncated to three characters. Actual values span more characters and may include blank spaces. Resolved vaccine history includes only vaccines received in the age range of 1 to 730 days.

**Exhibit 7.3.3.4
 Example Vaccine History: Hib and Polio Receipts from Day 130 Omitted, Same Vaccines Received on Day 131 Retained.
 Choice of Which to Omit and Which to Retain was Random.**

Resolved Vaccine History				Decision Rule Indicators				Chart and Computer-automated Immunization Data									
ID	Age Days	Res. Vac.	Res. Mfr.	HepB R1	HepB R2	DTP Hib R1	DTP Hib R2	Same Day Dup.	Bad Date Dup.	Look up	Age Days	Chart Vac.	Cmptr Vac.	Chart Mfr.	Cmptr Mfr.	Chart Lot	Cmptr Lot
300	11	HepB	SKB								11	HepB		SKB			139
300	60	Hib	PRX								60	Hib	Hib	PRA	PRX	M17	M17
300	60	HepB	SKB								60	HepB	HepB	SKB	SKB	ENG	ENG
300	60	Polio	PMC								60	Polio	Polio	PAS	PMC	J06	J06
300							1				130	Hib		PRA		M28	
300											130	Polio		PAS		J11	
300	131	Hib	PRX								131		Hib		PRX		M28
300	131	Polio	PMC								131		Polio		PMC		J11
300	183	Hib	PRX								183	Hib	Hib	PRA	PRX	M28	M28
300	183	Polio	PMC								183	Polio	Polio	CON	PMC	J11	J11

Notes: For brevity, manufacturer and lot numbers are truncated to three characters. Actual values span more characters and include may blank spaces. Resolved vaccine history includes only vaccines received in the age range of 1 to 730 days.

7.3.4. Mercury Amount Assigned to Each Childhood Vaccine or Immune Globulin Receipt

Each vaccine or immune globulin listed in each child's resolved vaccine history was assigned a mercury amount. The dates of vaccine and immune globulin receipts in the resolved vaccine history file ranged from January of 1994 to October of 2001. During that time frame some vaccine types never contained thimerosal, (e.g., polio, MMR, varicella vaccines). For the thimerosal-containing vaccines and immune globulins (e.g., HepB, Hib, DTaP), the amount of ethylmercury contained in a single dose varied depending on the year and manufacturer. The vaccine types that never contained thimerosal during the relevant time frame were identified using the following sources of information: The 1995 and 2000 Physician's Desk References (PDRs), Pediatrics (1999), Plotkin & Orenstein (1999), Plotkin & Mortimer (1994), the Food and Drug Administration (FDA) website (accessed on 2/28/2003), and personal communication with vaccine experts at the FDA. The mercury amounts contained in experimental vaccines were provided by the participating HMOs, using data from their own records. For vaccines and immune globulins types that ever contained thimerosal, Abt Associates Inc. produced a spreadsheet corresponding to each manufacturer that showed frequencies of lot numbers by vaccine or immune globulin type and year of receipt. These spreadsheets were sent to the CDC who then contacted each manufacturer. Each manufacturer then provided the amount of ethylmercury contained in a single dose of vaccine or immune globulin corresponding to each lot number.

There were some vaccine and immune globulin receipts in the vaccine histories file that had unknown or unrecognized lot numbers. In those cases the most frequently occurring ethylmercury amount for the particular vaccine type, manufacturer, year of receipt, and HMO was assigned. In instances where the manufacturer and the lot number were unknown, the most frequently occurring ethylmercury amount for the particular vaccine type, year of receipt and HMO was assigned. For example, hepatitis B vaccines received in the years 1994 -1998 that had unknown manufacturers and lot numbers were assigned ethylmercury amounts of 12.5 micrograms because that was the amount contained in all hepatitis B vaccines in those years, regardless of manufacturer. In 1999 and 2000 thimerosal-free HepB vaccines were sometimes used. But, in those years, within this study sample, the thimerosal-containing HepB vaccines were used more frequently in each of the HMOs. Therefore, HepB vaccines that were received in 1999 and 2000 that had unknown manufacturers and lot numbers were assigned an ethylmercury amount of 12.5 micrograms. Less than 2 percent of vaccine receipts were assigned mercury amounts in this manner.

Exhibit 7.3.4.1 shows a frequency tabulation of the types of vaccines and immune globulins in the resolved vaccine histories file and the ethylmercury amount assigned to each receipt. Manufacturer abbreviations are shown at the bottom of the table. The column labeled "Have Lot #?" has the value "Yes" if the lot number was known, has the value "No" if the lot number was unknown, and has the value "N/A" if the lot number was not applicable to the mercury amount assignment because the vaccine type never contained thimerosal during the relevant time period.

For the “IG GG” (immune globulin) receipts in 1998 and 1999 that had unknown manufacturers, the manufacturer was assumed to be MBL because Armour had stopped producing “IG GG” in 1996. The MBL “IG GG” product did not contain thimerosal, therefore the ethyl mercury amount was set to zero for those receipts.

The single “Vari-IG” (varicella immune globulin) receipt was assigned an ethylmercury amount of 62.5 micrograms based on the lot number and an assumed dose of 1.25 ml and thimerosal concentration of 0.01%. To assign an ethyl mercury amount to the Rabies receipt, we looked at the weight of the child at the time of the receipt and assumed a child of that weight would receive 0.4 ml of the rabies vaccine, which contained 50 micrograms of ethylmercury per 1 ml. This resulted in an assigned amount of 20 micrograms of ethylmercury.

**Exhibit 7.3.4.1
Vaccine and Immune Globulin Types and Amount of Ethylmercury in Each Receipt**

Vaccine Type	Manufacturer	Year	Have Lot#	MercAmt	Frequency	Cumulative Frequency
DT TD	LED	1994	Yes	25	1	1
DT TD	LED	1995	Yes	25	1	2
DT TD	LED	1999	Yes	25	1	3
DT TD	LED	2000	Yes	25	1	4
DT TD	PMC	1995	Yes	25	1	5
DT TD	PMC	1996	Yes	25	4	9
DT TD	PMC	1997	Yes	25	2	11
DT TD	PMC	1998	Yes	25	1	12
DT TD	PMC	1999	Yes	25	1	13
DT TD	unknown	1996	No	25	1	14
DTP	LED	1994	Yes	25	1	15
DTP	LED	1995	Yes	25	8	23
DTP	LED	1996	Yes	25	7	30
DTP	LED	1998	Yes	25	2	32
DTP	MBL	1994	Yes	24.12	1	33
DTP	MBL	1994	Yes	24.38	2	35
DTP	MBL	1994	Yes	24.6	6	41
DTP	MBL	1994	Yes	25.46	6	47
DTP	MBL	1994	Yes	25.75	1	48
DTP	MBL	1995	Yes	24.27	18	66
DTP	MBL	1995	Yes	25.04	2	68
DTP	MBL	1995	Yes	25.89	6	74
DTP	MBL	1995	Yes	26.75	1	75
DTP	MBL	1996	Yes	22.67	3	78
DTP	MBL	1996	Yes	23.28	7	85
DTP	MBL	1996	Yes	24.27	5	90
DTP	MBL	1996	Yes	25.89	1	91
DTP	MBL	1996	Yes	26.75	10	101
DTP	MBL	1997	Yes	26.75	1	102
DTP	PMC	1994	Yes	25	84	186

Exhibit 7.3.4.1**Vaccine and Immune Globulin Types and Amount of Ethylmercury in Each Receipt**

Vaccine Type	Manufacturer	Year	Have Lot#	MercAmt	Frequency	Cumulative Frequency
DTP	PMC	1995	Yes	25	34	220
DTP	PMC	1996	Yes	25	8	228
DTP	PMC	1997	Yes	25	1	229
DTP	PMC	1998	Yes	25	1	230
DTP	PMC	1999	Yes	25	2	232
DTP	unknown	1994	No	25	3	235
DTP	unknown	1995	No	25	7	242
DTP	unknown	1996	No	25	3	245
DTP	unknown	1997	No	25	2	247
DTP	unknown	1998	No	25	2	249
DTP-Hib	LED	1994	Yes	25	234	483
DTP-Hib	LED	1995	No	25	5	488
DTP-Hib	LED	1995	Yes	25	485	973
DTP-Hib	LED	1996	No	25	7	980
DTP-Hib	LED	1996	Yes	25	588	1568
DTP-Hib	LED	1997	Yes	25	221	1789
DTP-Hib	LED	1998	Yes	25	90	1879
DTP-Hib	LED	1999	Yes	25	19	1898
DTP-Hib	LED	2000	Yes	25	1	1899
DTP-Hib	PMC	1995	Yes	25	1	1900
DTP-Hib	unknown	1994	No	25	1	1901
DTP-Hib	unknown	1995	No	25	3	1904
DTP-Hib	unknown	1996	No	25	3	1907
DTP-Hib	unknown	1998	No	25	1	1908
DTaP	LED	1994	Yes	25	2	1910
DTaP	LED	1995	Yes	25	23	1933
DTaP	LED	1996	Yes	25	37	1970
DTaP	LED	1997	Yes	25	126	2096
DTaP	LED	1998	Yes	25	227	2323
DTaP	LED	1999	Yes	25	65	2388
DTaP	LED	2000	Yes	25	12	2400
DTaP	PMC	1996	Yes	25	5	2405
DTaP	PMC	1997	No	25	1	2406
DTaP	PMC	1997	Yes	25	433	2839
DTaP	PMC	1998	Yes	25	507	3346
DTaP	PMC	1999	Yes	0	24	3370
DTaP	PMC	1999	Yes	25	149	3519
DTaP	PMC	2000	Yes	0	5	3524
DTaP	PMC	2000	Yes	25	40	3564
DTaP	PMC	2001	Yes	25	1	3565
DTaP	SKB	1996	No	25	1	3566
DTaP	SKB	1998	Yes	0	1	3567
DTaP	SKB	1999	No	0	1	3568
DTaP	SKB	1999	Yes	0	419	3987
DTaP	SKB	2000	Yes	0	279	4266

Exhibit 7.3.4.1**Vaccine and Immune Globulin Types and Amount of Ethylmercury in Each Receipt**

Vaccine Type	Manufacturer	Year	Have Lot#	MercAmt	Frequency	Cumulative Frequency
DTaP	SKB	2001	Yes	0	48	4314
DTaP	unknown	1997	No	25	16	4330
DTaP	unknown	1998	No	25	14	4344
DTaP	unknown	1999	No	0	5	4349
DTaP	unknown	1999	No	25	1	4350
DTaP	unknown	2000	No	0	4	4354
DTaPHepB	SKB	1995	Yes	0	3	4357
Flu	LED	1995	Yes	12.5	4	4361
Flu	LED	1996	No	12.5	1	4362
Flu	LED	1996	Yes	12.5	13	4375
Flu	LED	1997	Yes	12.5	12	4387
Flu	LED	1998	Yes	12.5	18	4405
Flu	LED	1999	Yes	12.5	23	4428
Flu	LED	2000	Yes	12.5	11	4439
Flu	LED	2001	Yes	12.5	3	4442
Flu	PMC	1998	Yes	0	2	4444
Flu	PMC	1999	Yes	0	1	4445
Flu	PMC	1999	Yes	12.5	2	4447
Flu	PMC	2000	Yes	0	2	4449
Flu	unknown	1998	No	12.5	3	4452
HBIG	ABBOTT	1995	Yes	25	1	4453
HBIG	ABBOTT	1996	Yes	25	1	4454
HBIG	ABBOTT	1997	Yes	25	1	4455
HBIG	unknown	1994	No	25	1	4456
HBIG	unknown	1995	No	25	2	4458
HBIG	unknown	1996	No	25	1	4459
Hib	LED	1994	Yes	0	1	4460
Hib	LED	1994	Yes	25	18	4478
Hib	LED	1995	Yes	0	3	4481
Hib	LED	1995	Yes	25	70	4551
Hib	LED	1996	Yes	0	3	4554
Hib	LED	1996	Yes	25	70	4624
Hib	LED	1997	Yes	0	7	4631
Hib	LED	1997	Yes	25	147	4778
Hib	LED	1998	Yes	0	1	4779
Hib	LED	1998	Yes	25	265	5044
Hib	LED	1999	Yes	25	219	5263
Hib	LED	2000	Yes	0	38	5301
Hib	LED	2000	Yes	25	31	5332
Hib	LED	2001	Yes	0	11	5343
Hib	MSD	1994	No	12.5	3	5346
Hib	MSD	1994	Yes	12.5	67	5413
Hib	MSD	1995	No	12.5	1	5414
Hib	MSD	1995	Yes	12.5	17	5431
Hib	MSD	1996	No	12.5	1	5432

Exhibit 7.3.4.1**Vaccine and Immune Globulin Types and Amount of Ethylmercury in Each Receipt**

Vaccine Type	Manufacturer	Year	Have Lot#	MercAmt	Frequency	Cumulative Frequency
Hib	MSD	1996	Yes	12.5	2	5434
Hib	MSD	1997	No	0	6	5440
Hib	MSD	1997	Yes	0	352	5792
Hib	MSD	1997	Yes	12.5	11	5803
Hib	MSD	1998	Yes	0	352	6155
Hib	MSD	1999	Yes	0	263	6418
Hib	MSD	2000	Yes	0	50	6468
Hib	MSD	2001	Yes	0	2	6470
Hib	PMC	1995	Yes	0	5	6475
Hib	PMC	1996	Yes	0	2	6477
Hib	PMC	1996	Yes	25	2	6479
Hib	PMC	1997	Yes	25	1	6480
Hib	PMC	1998	Yes	0	1	6481
Hib	PMC	1999	Yes	0	7	6488
Hib	PMC	2000	Yes	0	37	6525
Hib	SKB	1996	Yes	0	1	6526
Hib	unknown	1995	No	12.5	7	6533
Hib	unknown	1995	No	25	1	6534
Hib	unknown	1996	No	0	4	6538
Hib	unknown	1996	No	25	3	6541
Hib	unknown	1997	No	0	14	6555
Hib	unknown	1997	No	25	2	6557
Hib	unknown	1998	No	0	11	6568
Hib	unknown	1998	No	25	1	6569
Hib	unknown	1999	No	0	11	6580
Hib	unknown	2000	No	25	2	6582
HepA	MSD	1995	N/A	0	4	6586
HepA	MSD	1996	N/A	0	4	6590
HepA	MSD	1999	N/A	0	1	6591
HepA	MSD	2000	N/A	0	6	6597
HepA	MSD	2001	N/A	0	2	6599
HepA	SKB	1996	N/A	0	2	6601
HepA	unknown	1999	N/A	0	1	6602
HepA	unknown	2001	N/A	0	2	6604
HepB	MSD	1994	Yes	12.5	226	6830
HepB	MSD	1995	No	12.5	1	6831
HepB	MSD	1995	Yes	12.5	301	7132
HepB	MSD	1996	Yes	12.5	275	7407
HepB	MSD	1997	No	12.5	2	7409
HepB	MSD	1997	Yes	12.5	168	7577
HepB	MSD	1998	Yes	12.5	46	7623
HepB	MSD	1999	Yes	0	18	7641
HepB	MSD	1999	Yes	12.5	9	7650
HepB	MSD	2000	Yes	0	44	7694
HepB	MSD	2001	Yes	0	2	7696

Exhibit 7.3.4.1**Vaccine and Immune Globulin Types and Amount of Ethylmercury in Each Receipt**

Vaccine Type	Manufacturer	Year	Have Lot#	MercAmt	Frequency	Cumulative Frequency
HepB	SKB	1994	Yes	12.5	108	7804
HepB	SKB	1995	Yes	12.5	160	7964
HepB	SKB	1996	No	12.5	1	7965
HepB	SKB	1996	Yes	12.5	266	8231
HepB	SKB	1997	Yes	12.5	436	8667
HepB	SKB	1998	No	12.5	1	8668
HepB	SKB	1998	Yes	12.5	545	9213
HepB	SKB	1999	Yes	12.5	339	9552
HepB	SKB	2000	Yes	12.5	22	9574
HepB	unknown	1994	No	12.5	11	9585
HepB	unknown	1995	No	12.5	21	9606
HepB	unknown	1996	No	12.5	18	9624
HepB	unknown	1997	No	12.5	27	9651
HepB	unknown	1998	No	12.5	22	9673
HepB	unknown	1999	No	12.5	13	9686
HepB	unknown	2000	No	12.5	3	9689
HepB-Hib	MSD	1995	Yes	0	6 ^b	9695
HepB-Hib	MSD	1997	Yes	0	1	9696
HepB-Hib	MSD	1999	No	0	1	9697
HepB-Hib	MSD	1999	Yes	0	63	9760
HepB-Hib	MSD	2000	Yes	0	130	9890
HepB-Hib	MSD	2001	Yes	0	8	9898
HepB-Hib	PMC	1999	Yes	0	1	9899
HepB-Hib	unknown	1999	No	0	1	9900
HepB-Hib	unknown	2000	No	0	4	9904
IG GG	ARMOUR	1994	Yes	50	2	9906
IG GG	ARMOUR	1995	Yes	50	1	9907
IG GG	MBL	2001	Yes	0	1	9908
IG GG	unknown	1998	No	0	1	9909
IG GG	unknown	1999	No	0	1	9910
MMR	MSD	1994	N/A	0	1	9911
MMR	MSD	1995	N/A	0	144	10055
MMR	MSD	1996	N/A	0	145	10200
MMR	MSD	1997	N/A	0	193	10393
MMR	MSD	1998	N/A	0	211	10604
MMR	MSD	1999	N/A	0	200	10804
MMR	MSD	2000	N/A	0	159	10963
MMR	MSD	2001	N/A	0	15	10978
MMR	unknown	1995	N/A	0	3	10981
MMR	unknown	1996	N/A	0	9	10990
MMR	unknown	1997	N/A	0	5	10995
MMR	unknown	1998	N/A	0	3	10998
MMR	unknown	1999	N/A	0	2	11000
MMR	unknown	2000	N/A	0	3	11003
Measles	MSD	1998	N/A	0	1	11004

Exhibit 7.3.4.1**Vaccine and Immune Globulin Types and Amount of Ethylmercury in Each Receipt**

Vaccine Type	Manufacturer	Year	Have Lot#	MercAmt	Frequency	Cumulative Frequency
Measles	MSD	1999	N/A	0	1	11005
Mening	LED	1995	Yes	0	7	11012
Mening	LED	1996	Yes	0	93	11105
Mening	LED	1997	Yes	0	87	11192
Mening	LED	1998	Yes	0	79	11271
Mening	LED	1999	Yes	0	19	11290
Mumps	MSD	1998	N/A	0	1	11291
Pneumo	LED	1995	Yes	0	12	11303
Pneumo	LED	1996	Yes	0	79	11382
Pneumo	LED	1997	Yes	0	99	11481
Pneumo	LED	1998	Yes	0	82	11563
Pneumo	LED	1999	Yes	0	37	11600
Pneumo	LED	2000	Yes	0	316	11916
Pneumo	LED	2000	Yes	25 ^a	1	11917
Pneumo	LED	2001	Yes	0	56	11973
Pneumo	MSD	1995	Yes	0	6	11979
Pneumo	MSD	1996	Yes	0	2	11981
Pneumo	MSD	2000	Yes	0	3	11984
Pneumo	MSD	2001	Yes	0	1	11985
Pneumo	unknown	2000	No	0	3	11988
Pneumo	unknown	2001	No	0	1	11989
Polio	LED	1994	N/A	0	320	12309
Polio	LED	1995	N/A	0	484	12793
Polio	LED	1996	N/A	0	565	13358
Polio	LED	1997	N/A	0	466	13824
Polio	LED	1998	N/A	0	194	14018
Polio	LED	1999	N/A	0	145	14163
Polio	LED	2000	N/A	0	3	14166
Polio	MSD	1996	N/A	0	2	14168
Polio	MSD	1997	N/A	0	3	14171
Polio	MSD	1998	N/A	0	9	14180
Polio	MSD	1999	N/A	0	4	14184
Polio	MSD	2000	N/A	0	2	14186
Polio	PMC	1995	N/A	0	6	14192
Polio	PMC	1996	N/A	0	6	14198
Polio	PMC	1997	N/A	0	133	14331
Polio	PMC	1998	N/A	0	347	14678
Polio	PMC	1999	N/A	0	359	15037
Polio	PMC	2000	N/A	0	257	15294
Polio	PMC	2001	N/A	0	10	15304
Polio	SKB	1996	N/A	0	1	15305
Polio	Sanofi	1999	N/A	0	1	15306
Polio	unknown	1994	N/A	0	3	15309
Polio	unknown	1995	N/A	0	11	15320
Polio	unknown	1996	N/A	0	9	15329

Exhibit 7.3.4.1**Vaccine and Immune Globulin Types and Amount of Ethylmercury in Each Receipt**

Vaccine Type	Manufacturer	Year	Have Lot#	MercAmt	Frequency	Cumulative Frequency
Polio	unknown	1997	N/A	0	21	15350
Polio	unknown	1998	N/A	0	12	15362
Polio	unknown	1999	N/A	0	8	15370
Polio	unknown	2000	N/A	0	4	15374
RSV	MBL	1998	N/A	0	1	15375
RSV	MEDIMUN	1998	N/A	0	4	15379
RSV	MEDIMUN	1999	N/A	0	8	15387
RSV	unknown	1998	N/A	0	5	15392
RSV	unknown	1999	N/A	0	6	15398
Rabies	unknown	1995	No	20	1	15399
Rota	LED	1998	N/A	0	2	15401
Rota	LED	1999	N/A	0	54	15455
Rota	unknown	1999	N/A	0	1	15456
Rubella	MSD	1998	N/A	0	1	15457
Rubeola	MSD	1997	N/A	0	1	15458
Typhoid	LED	1998	N/A	0	2	15460
Typhoid	LED	1999	N/A	0	2	15462
Vari-IG	unknown	1996	No	62.5	1	15463
Varicel	MSD	1995	N/A	0	72	15535
Varicel	MSD	1996	N/A	0	126	15661
Varicel	MSD	1997	N/A	0	150	15811
Varicel	MSD	1998	N/A	0	200	16011
Varicel	MSD	1999	N/A	0	182	16193
Varicel	MSD	2000	N/A	0	152	16345
Varicel	MSD	2001	N/A	0	16	16361
Varicel	Other	1996	N/A	0	1	16362
Varicel	PMC	2000	N/A	0	1	16363
Varicel	unknown	1996	N/A	0	8	16371
Varicel	unknown	1997	N/A	0	1	16372
Varicel	unknown	1998	N/A	0	2	16374
Varicel	unknown	1999	N/A	0	3	16377
Varicel	unknown	2000	N/A	0	3	16380
Yellow	PMC	1997	N/A	0	1	16381

^a One child received the Pnu-Immune product, which is normally given to adults. This product contained 25 micrograms of ethylmercury.

^b The six HepB-Hib receipts in 1995 were administered as part of a Comvax trial.

MercAmt is micrograms of ethylmercury in a single receipt of the vaccine.

LED = Lederle, Praxis, Wyeth, Ayerst

MBL = Massachusetts Biologic Laboratories

MSD = Merck, Sharp, Dohme

PMC = Pasteur, Merieux, Connaught, Aventis

SKB = Smithkline, Beecham, Glaxo

7.4. Measures of Prenatal Exposure to Ethylmercury

7.4.1. Introduction to the Prenatal Ethylmercury Exposures File

Two sources of prenatal vaccination data (maternal medical chart abstraction and maternal interview) were combined to create a *Prenatal Ethylmercury Exposures File*. This file contains data on maternal exposure to ethylmercury from thimerosal-containing vaccines and immune globulins received by the mothers of study participants during their pregnancies with the focus children. The file contains one record per mother of each full participant child (n=1,095). Each record lists the types of vaccines and immune globulins received, the amounts of ethylmercury corresponding to each receipt, and the timing of each receipt. The timing of receipt is expressed as the number of months from the receipt to the birth of the focus child.

Examples of several prenatal records are shown in Exhibit 7.4.1.1. The first record (ID = “1”) corresponds to a mother who received a Gamulin injection (an immune globulin) 3.0 months prior to the birth of the focus child. The mercury amount corresponding to a Gamulin receipt was assigned as 50 micrograms of ethylmercury. The example in the second row (ID= “2”) is a mother who received a Rhogam injection (an immune globulin) 2.8 months prior to the birth of the focus child. Rhogam is assumed to have contained 12.75 micrograms of ethylmercury per receipt²⁷. ID “3” received two immune globulin injections during her pregnancy, each containing 50 micrograms of ethylmercury, resulting in a total prenatal exposure amount equal to 100 micrograms.

ID “4” received an immune globulin 2.6 months before the focus child was born, and received another on the day the child was born. Receipts on the day of the birth of the focus child were assumed to have occurred after delivery, and are therefore not counted in the total prenatal exposure amount. ID “5” received adult dose influenza and tetanus vaccines during her pregnancy, resulting in a total exposure amount equal to 50 micrograms. ID “6” received a hepatitis B vaccination resulting in 12.5 micrograms of ethylmercury exposure. And, ID “7” did not receive any vaccinations or immune globulins during her pregnancy with the focus child.

We note that it is possible that the weight of the mother at the time of receipt and gestational age might both be factors that could influence any effects that exposure might have on the child’s development. However, the study design team, including consulting toxicologists, could not identify a basis from which to include those factors in the exposure measure. Therefore, the prenatal exposure measure is simply a sum of total micrograms of ethylmercury from vaccines and immune globulins received during pregnancy. The factors of mother’s weight and gestational age are not part of the measure.

²⁷ Additional detail is provided in Section 7.3.3

Exhibit 7.4.1.1

Example Records of Prenatal Ethylmercury Exposures from Thimerosal-containing Vaccines and Immune Globulins

ID	Prenat-thimer	Immune Globulin 1				Immune Globulin 2				Flu		HepB		Tetanus		DT	
		Type	Amt	Mos	Dose	Type	Amt	Mos	Dose	Amt	Mos	Amt	Mos	Amt	Mos	Amt	Mos
1	50	GAMULIN	50	3.0	1CC												
2	12.75	RHOGAM	12.75	2.8	SINGLE DOS												
3	100	GAMULIN	50	5.3	UNK (FULL)	GAMULIN	50	2.5	UNK (FULL)								
4	50	GAMULIN	50	2.6	J23003	GAMULIN	0	0	J24110								
5	50									25	7.0			25	0.8		
6	12.5											12.5	6.6				
7	0																

PrenatThimer = total ethylmercury exposure (micrograms) from vaccines and immune globulins during pregnancy with focus child.

Columns labeled "Amt" show the ethylmercury amount (micrograms) corresponding to a vaccine or immune globulin receipt. Columns labeled "Mos" show the number of months between receipt and birth of the focus child.

"Flu" = influenza vaccine, "HepB" = hepatitis B vaccine, "Tetanus" = tetanus, and "DT" = diphtheria-tetanus. Records indicated that these were the only types of thimerosal-containing vaccines received by the mothers of study participants during their pregnancies with the focus children.

7.4.2. Overview of Steps from Raw Data to Creation of Analysis Variables

Data on prenatal exposure to ethylmercury from thimerosal containing vaccines and immune globulins were obtained from two sources: Abstractions of maternal medical charts covering the period that the mother was pregnant with the focus child and from questionnaire items from the parent interview. An overview of the data processing steps from the receipt of raw data files to the creation of the exposure variables used in analyses is as follows:

1. The master list of study IDs was merged to the maternal medical chart and parent interview files. Any problems with ID discrepancies were resolved at this stage. The master list of IDs, the maternal medical chart, and the parent interview data files each contained one record per child ID. The master list of study IDs contained each child's ID and date of birth. The maternal chart file contained a field for Rh-blood group status of the mother. It also contained fields for the date, dosage, manufacturer, and product names of immune globulins received, and for dates and types of vaccines received by the mother. The parent interview file contained data from questionnaire items that explained that women with Rh-negative blood types often receive Rhogam or other immune globulins during pregnancy to prevent problems with blood incompatibility, and asked the mother if she had received any Rhogam or other immune globulins during her pregnancy with the focus child, or during the period when she was breastfeeding (if the

- mother had indicated that she had breastfed her child)²⁸. Another item asked if she received a flu shot during pregnancy or breastfeeding periods.
2. For chart records, all entries indicating the type of immune globulin received were recoded to correct spelling errors and variations in abbreviations. For example, an incorrectly spelled entry indicating receipt of “rhogan” would have been recoded to take the value “RHOGAM”.
 3. Next, we calculated the number of months between vaccine or immune globulin receipt and the date of delivery. Only those receipts that occurred within the period spanning ten months (256 days) prior to the delivery date were counted towards the total amount of prenatal exposure to ethylmercury from thimerosal. Immune globulins received on the day of delivery were assumed to have occurred after delivery, and were therefore not counted in the calculation of prenatal exposure.
 4. In the next step, discrepancies between the maternal medical chart-abstracted data and the parent interview data on receipt of immune globulins during pregnancy were resolved. During the weekly conference calls, the entire study team reviewed all available data for discrepant cases. If the mother was Rh-negative, and either of the two data sources indicated receipt of an immune globulin during pregnancy, then it was assumed that a receipt had occurred. Additional details on this step are provided in Section 7.4.3 of this document.
 5. A mercury exposure amount was assigned to each vaccine or immune globulin receipt. See Section 7.4.4 for details.
 6. Finally, a measure of total ethylmercury exposure from vaccine and immune globulins received during pregnancy was created. For example, a child whose mother received two vaccines during her pregnancy that each contained 25 micrograms of ethylmercury, e.g., a flu shot and a tetanus shot, would have received a value of 50 micrograms on this measure. This measure was used in the analytical models and was defined as follows:
 - *PrenatThimer* = “Prenatal exposure to ethylmercury from thimerosal” = The sum total of mercury amounts from all thimerosal containing vaccines and immune globulins received by the mother during her pregnancy with the focus child.

7.4.3. Cleaning of Prenatal Ethylmercury Exposures Data

The chart-abstracted data on vaccine receipts during pregnancy were straightforward. The records listed the types of and dates of vaccine receipts. Using the date of vaccine receipt and the child’s date of birth, we calculated the number of months from receipt to birth and assigned an exposure amount to the vaccine receipt only if the receipt occurred before the child was born, and less than 10 months prior to the birth of the child. Although the rule we applied would have counted receipts 10 months prior to birth (to account for the possibility of late births) there were no receipts listed in the data set that were near 10 months. In these data we found one occurrence of a diphtheria-tetanus (DT)

²⁸ Questions about maternal receipt of thimerosal-containing vaccines or immune globulins during breastfeeding were intended to clarify the timing of the receipts. Maternal receipts during breastfeeding were not included in the measures of prenatal or early childhood exposure to ethylmercury.

receipt that was 8.7 months prior to the birth of the child. All other vaccine receipts that were counted toward the total exposure amounts were less than 8.7 months prior to birth.

The chart-abstracted data included records of receipts of the following thimerosal-containing vaccines: Influenza, tetanus, diphtheria-tetanus, and hepatitis B. There were also records of rubella vaccine receipts, but the rubella vaccines did not contain thimerosal and were therefore of no consequence to the analyses. The chart abstraction forms also had areas for entry of pneumococcal, meningococcal, rabies, and any other vaccines received (in an “other – specify” field), but none of those types of receipts were recorded.

The data on immune globulin receipts were less straightforward for several reasons. The first was that the information on the product name and manufacturer sometimes conflicted with one another, or was sometimes missing entirely. This was a problem because the amount of mercury included in a dose varied according to the product received. A second potential conflict was between the mother’s recorded Rh-status and immune globulin receipt. The expectation is that Rh-positive mothers would not receive immune globulins and Rh-negative mothers would usually receive immune globulins, although this was not always the case. Finally, there was the potential for discrepancy between the mother’s recollection of immune globulin receipt, as reported in the parent interview, and the data recorded in the medical charts. The resolutions for each of these types of discrepancies are described below. Similarly, because flu receipts were abstracted from the mother’s medical charts, and mothers were asked if they received a flu shot during pregnancy, there were sometimes discrepancies between the two data sources. The procedures for resolving such discrepancies are described subsequently.

An example of a discrepancy between an immune globulin product name (type) and the product manufacturer is a record that indicates that the product received was Rhogam and the manufacturer was Armour. The product made by Armour was called Gamulin, and thimerosal content in Gamulin was different than that of Rhogam. This discrepancy probably occurred because, even though Rhogam is a specific product, the name “Rhogam” is often used as a generic term similar to the way “Kleenex” is often used as a generic term to refer to facial tissues, even though Kleenex is a specific product. Therefore, whenever a manufacturer or lot number was listed in the record that pointed toward the receipt of a specific product, the manufacturer or lot number information took precedence over the information listed in the product type field. The Prenatal Ethylmercury Exposures File includes the original text for product type and manufacturer, as well as the resolved product type. The resolved product type represents our best estimate of what was actually received, and was used for the purpose of assigning a mercury exposure amount.

Rhogam was the most commonly listed type of immune globulin at all three HMOs. In cases where the evidence pointed to the receipt of an immune globulin, but where there was no information on product type, manufacturer, or lot number, we assumed the receipt was Rhogam. Section 7.4.4 describes variables that were created and analyses that were conducted to evaluate the sensitivity of the model results to this assumption.

For each record we had to make a judgment, based on the available evidence, as to whether the mother received one or more immune globulins during her pregnancy with the focus child. And, as described in a subsequent section, we then assigned an ethylmercury exposure amount to each receipt. The set of codes shown below was developed to document the determinations regarding if and how many immune globulins were received during pregnancy. Exhibit 7.4.3.1 shows the frequency that each decision code was applied. The “prenatal immune globulin decision codes” were defined as follows:

Decision Codes 1.01 – 1.06 : One immune globulin received during pregnancy.

- Decision code 1.01 = prenatal immune globulin received: The chart indicated that the mother was Rh-negative, and indicated that an immune globulin was received within the period spanning ten months prior to the birth of the child. The mother reported having received an immune globulin during her pregnancy with the focus child.
- Decision code 1.02 = prenatal immune globulin received: The chart indicated that the mother was Rh-negative, and indicated that an immune globulin was received within the period spanning ten months prior to the birth of the child. The mother reported having received an immune globulin, but could not remember if it was received during pregnancy or during the period when she was breastfeeding the focus child.
- Decision code 1.03 = prenatal immune globulin received: The chart indicated that the mother was Rh-negative, and indicated that an immune globulin was received within the period spanning ten months prior to the birth of the child. The mother reported having received an immune globulin during the period when she was breastfeeding the focus child, but did not report having received an immune globulin during pregnancy. We assume that the chart is correct and that the mother’s memory of no receipt during pregnancy is incorrect.
- Decision code 1.04 = prenatal immune globulin received: The chart indicated that the mother was Rh-negative, and indicated that an immune globulin was received within the period spanning ten months prior to the birth of the child. The mother either reported that she did not receive an immune globulin during pregnancy or she did not know if she had received one. We assume that the chart data are correct.
- Decision code 1.05 = prenatal immune globulin received: The chart data indicated that it was unknown whether mother had received an immune globulin during pregnancy. The mother was Rh-negative, and she said that she had received an immune globulin during pregnancy, so we assume that she did receive an immune globulin during pregnancy.

- Decision code 1.06 = prenatal immune globulin received: The chart data indicated that it was unknown whether mother had received an immune globulin during pregnancy. The mother's Rh-status is unknown, but she said that she had received an immune globulin during pregnancy, so we assume that she did receive an immune globulin during pregnancy.
- Decision code 1.07 = prenatal immune globulin received: The regular section of chart did not show a Rhogam receipt, but in the Maternal Chart Abstraction, (in Section 2 Maternal Medications during pregnancy), the text in the "Other (Specify)" field listed Rhogam. This mother also said in the parent interview that she received Rhogam during pregnancy.

Decision Codes 2.01 – 2.04 : Two immune globulins received during pregnancy

- Decision code 2.01 = prenatal immune globulin received: The chart indicated that the mother was Rh-negative, and indicated that a second immune globulin was received within the period spanning ten months prior to the birth of the child. The mother reported having received an immune globulin during her pregnancy with the focus child.
- Decision code 2.02 = prenatal immune globulin received: The chart indicated that the mother was Rh-negative, and indicated that a second immune globulin was received within the period spanning ten months prior to the birth of the child. The mother reported having received an immune globulin, but could not remember if it was received during pregnancy or during the period when she was breastfeeding the focus child.
- Decision code 2.03 = prenatal immune globulin received: The chart indicated that the mother was Rh-negative, and indicated that a second immune globulin was received within the period spanning ten months prior to the birth of the child. The mother reported having received an immune globulin during the period when she was breastfeeding the focus child, but did not report having received an immune globulin during pregnancy. We assume that the chart is correct and that the mother's memory of no receipt during pregnancy is incorrect.
- Decision code 2.04 = prenatal immune globulin received: The chart indicated that the mother was Rh-negative, and indicated that a second immune globulin was received within the period spanning ten months prior to the birth of the child. The mother reported that she did not know if she had received an immune globulin during pregnancy. We assume that the chart data are correct.

Decision Codes 3.00 : Three immune globulins received during pregnancy

- Decision code 3.00 = prenatal immune globulin received. Notes written in the comments section of the chart abstraction clearly indicated receipt of third immune globulin during pregnancy.

Decision Codes 4.01 – 4.11: No immune globulins received during pregnancy

- Decision code 4.01 = no prenatal immune globulin received: The charts indicated that the mother was Rh-positive and contained no indication of immune globulin receipt. The mothers in this group either said ‘no’ or they did not know whether they had received an immune globulin during their pregnancies with the focus children.
- Decision code 4.02 = no prenatal immune globulin received: The charts indicated that the mother was Rh-negative and contained no indication of immune globulin receipt during pregnancy. The mothers in this group either said ‘no’ or they did not know whether they had received an immune globulin during their pregnancies with the focus children. Two mothers in this group received immune globulin injections after the birth of the focus child.
- Decision code 4.03 = no prenatal immune globulin received: The chart data listed Rh-status as unknown, and contained no indication of immune globulin receipt. The mothers in this group said that they did not receive an immune globulin during their pregnancies with the focus children.
- Decision code 4.04 = no prenatal immune globulin received: The chart data listed the mother’s Rh-status as positive, and contained no indication of immune globulin receipt. The mothers in this group said that they did receive an immune globulin during their pregnancies with the focus children. We assume that since the mothers were Rh-positive and would have no need for an immune globulin, since there was no indication of an immune globulin receipt in the chart, that the chart is correct.
- Decision code 4.05 = no prenatal immune globulin received: Comments on chart abstraction form indicated that these mothers did not receive an immune globulin because the father was Rh-negative also.
- Decision code 4.06 = no prenatal immune globulin received: Mother said that she received an immune globulin during breastfeeding period. Review of medical record data confirmed that immune globulin receipt was after the birth of the child.
- Decision code 4.07 = no prenatal immune globulin received: Mother said she received an immune globulin during pregnancy. Chart data indicates that mother did not receive immune globulin during pregnancy, but did receive an immune globulin just after delivery of child. We assume that the chart is correct.

- Decision code 4.08 = no prenatal immune globulin received: Chart review indicated no immune globulin receipt.
- Decision code 4.09 = no prenatal immune globulin received: Chart review indicated no immune globulin receipt. We assume that chart review is correct.
- Decision code 4.10 = no prenatal immune globulin received: Mother said she received an immune globulin during breastfeeding period, not during pregnancy. Chart shows no receipt during pregnancy.
- Decision code 4.11 = no prenatal immune globulin received: Chart provides no information on Rh-status or on whether an immune globulin was received during pregnancy. Mother said she did not receive and immune globulin during pregnancy. We assume that the mother is correct.

Exhibit 7.4.3.1
Data Cleaning Decision Codes for Prenatal Immune Globulin Receipts

Number IGs Recv'd	Dec- ion Code	Mother		IG Receipt # 1		IG Receipt # 2		Frequency
		Report Of Receipt	Rh Status	Months Prior to Birth	Product Type	Months Prior to Birth	Product Type	
1	1.01	YesBoth	RhNeg	1.81	RHOGAM	.		1
1	1.01	YesBoth	RhNeg	1.91	RHOGAM	.		1
1	1.01	YesBoth	RhNeg	2.14	RHOGAM	.		1
1	1.01	YesBoth	RhNeg	2.2	RHOGAM	.		1
1	1.01	YesBoth	RhNeg	2.3	RHOGAM	-0.03		1
1	1.01	YesBoth	RhNeg	2.8	RHOGAM	-0.03		1
1	1.01	YesBoth	RhNeg	2.8	RHOGAM	0		1
1	1.01	YesBoth	RhNeg	2.86	RHOGAM	-0.03		1
1	1.01	YesBoth	RhNeg	2.89	RHOGAM	0		1
1	1.01	YesBoth	RhNeg	2.93	RHOGAM	.		1
1	1.01	YesBoth	RhNeg	3.03	RHOGAM	.		1
1	1.01	YesBoth	RhNeg	3.06	RHOGAM	.		1
1	1.01	YesBoth	RhNeg	3.26	RHOGAM	.		1
1	1.01	YesBoth	RhNeg	3.29	RHOGAM	.		1
1	1.01	YesBoth	RhNeg	3.32	RHOGAM	.		1
1	1.01	YesBoth	RhNeg	3.98	RHOGAM	0		1
1	1.01	YesBoth	RhNeg	5.1	RHOGAM	0		1
1	1.01	YesBoth	RhNeg	5.66	RHOGAM	.		1
1	1.01	YesPreg	RhNeg	1.28	RHOGAM	.		1
1	1.01	YesPreg	RhNeg	1.38	RHOGAM	.		1
1	1.01	YesPreg	RhNeg	1.58	RHOGAM	.		1
1	1.01	YesPreg	RhNeg	2.01	RHOGAM	0		1
1	1.01	YesPreg	RhNeg	2.14	RHOGAM	.		1
1	1.01	YesPreg	RhNeg	2.17	RHOGAM	-0.03		1
1	1.01	YesPreg	RhNeg	2.2	RHOGAM	.		1
1	1.01	YesPreg	RhNeg	2.24	RHOGAM	.		1
1	1.01	YesPreg	RhNeg	2.24	RHOGAM	0		1

Exhibit 7.4.3.1
Data Cleaning Decision Codes for Prenatal Immune Globulin Receipts

Number IGs Recv'd	Dec- ision Code	Mother		IG Receipt # 1		IG Receipt # 2		Frequency
		Report Of Receipt	Rh Status	Months Prior to Birth	Product Type	Months Prior to Birth	Product Type	
1	1.01	YesPreg	RhNeg	2.27	RHOGAM	.		1
1	1.01	YesPreg	RhNeg	2.3	RHOGAM	.		1
1	1.01	YesPreg	RhNeg	2.37	RHOGAM	.		1
1	1.01	YesPreg	RhNeg	2.37	RHOGAM	-0.03		1
1	1.01	YesPreg	RhNeg	2.4	RHOGAM	.		2
1	1.01	YesPreg	RhNeg	2.4	RHOGAM	0		1
1	1.01	YesPreg	RhNeg	2.5	RHOGAM	-0.03		1
1	1.01	YesPreg	RhNeg	2.57	RHOGAM	.		1
1	1.01	YesPreg	RhNeg	2.76	RHOGAM	.		1
1	1.01	YesPreg	RhNeg	2.86	RHOGAM	.		1
1	1.01	YesPreg	RhNeg	3.16	RHOGAM	.		1
1	1.01	YesPreg	RhNeg	3.29	RHOGAM	.		1
1	1.01	YesPreg	RhNeg	3.36	RHOGAM	-0.03		1
1	1.01	YesPreg	RhNeg	3.39	RHOGAM	.		1
1	1.01	YesPreg	RhNeg	5.43	RHOGAM	-0.03		1
1	1.01	YesPreg	RhNeg	5.56	RHOGAM	0		1
1	1.01	YesPreg	RhNeg	5.59	RHOGAM	.		1
1	1.01	YesPreg	RhNeg	5.89	RHOGAM	.		1
1	1.02	YesDK	RhNeg	2.4	RHOGAM	-0.03		1
1	1.02	YesDK	RhNeg	2.5	RHOGAM	.		1
1	1.02	YesDK	RhNeg	2.53	RHOGAM	-0.03		1
1	1.02	YesDK	RhNeg	3.19	GAMULIN	-0.03		1
1	1.03	YesBrst	RhNeg	1.84	RHOGAM	.		1
1	1.03	YesBrst	RhNeg	1.97	RHOGAM	0		1
1	1.03	YesBrst	RhNeg	2.76	RHOGAM	0		1
1	1.03	YesBrst	RhNeg	2.83	RHOGAM	.		2
1	1.03	YesBrst	RhNeg	2.86	RHOGAM	.		1
1	1.03	YesBrst	RhNeg	2.86	RHOGAM	-0.07		1
1	1.03	YesBrst	RhNeg	2.96	RHOGAM	.		1
1	1.03	YesBrst	RhNeg	2.99	RHOGAM	-0.03		1
1	1.03	YesBrst	RhNeg	3.49	RHOGAM	0		1
1	1.03	YesBrst	RhNeg	19.74		3.16	RHOGAM	1
1	1.04	DK	RhNeg	1.35	RHOGAM	-0.03		1
1	1.04	DK	RhNeg	2.57	RHOGAM	.		1
1	1.04	DK	RhNeg	2.63	RHOGAM	.		1
1	1.04	DK	RhNeg	2.66	RHOGAM	.		1
1	1.04	DK	RhNeg	2.73	RHOGAM	.		1
1	1.04	DK	RhNeg	2.8	RHOGAM	.		1
1	1.04	DK	RhNeg	3.26	RHOGAM	0		1
1	1.04	No	RhNeg	1.94	RHOGAM	.		1
1	1.04	No	RhNeg	2.93	RHOGAM	0		1
1	1.04	No	RhNeg	5.76	RHOGAM	0		1
1	1.05	YesBoth	RhNeg	.	RHOGAM	.		3
1	1.06	YesBoth	RhUnk	.	RHOGAM	.		3

Exhibit 7.4.3.1
Data Cleaning Decision Codes for Prenatal Immune Globulin Receipts

Number IGs Recv'd	Dec- ision Code	Mother Report Of Receipt		IG Receipt # 1		IG Receipt # 2		Frequency
		Rh Status	Months Prior to Birth	Product Type	Months Prior to Birth	Product Type		
1	1.07	YesBoth	RhNeg	.	RHOGAM	.		1
2	2.01	YesBoth	RhNeg	5.36	RHOGAM	2.89	RHOGAM	1
2	2.01	YesPreg	RhNeg	5.13	RHOGAM	2.14	RHOGAM	1
2	2.01	YesPreg	RhNeg	5.82	RHOGAM	2.7	RHOGAM	1
2	2.01	YesPreg	RhNeg	5.99	RHOGAM	2.99	RHOGAM	1
2	2.01	YesPreg	RhNeg	6.15	HYPRHO-D	2.89	RHOGAM	1
2	2.02	YesDK	RhNeg	2.73	RHOGAM	0.03	RHOGAM	1
2	2.03	YesBrst	RhNeg	5.16	RHOGAM	2.76	RHOGAM	1
2	2.03	YesBrst	RhNeg	6.38	GAMULIN	2.99	HYPRHO-D	1
2	2.03	YesBrst	RhNeg	7.4	RHOGAM	2.37	RHOGAM	1
2	2.04	DK	RhNeg	2.8	RHOGAM	5.59	RHOGAM	1
3	3.00	YesPreg	RhNeg	7.47	MICRHOGAM	5.43	RHOGAM	1
0	4.01	DK	RhPos	.		.		30
0	4.01	No	RhPos	.		.		939
0	4.02	DK	RhNeg	.		.		1
0	4.02	DK	RhNeg	.		-0.03		1
0	4.02	DK	RhNeg	0		.		1
0	4.02	No	RhNeg	.		.		3
0	4.03	No	RhUnk	.		.		1
0	4.04	YesPreg	RhPos	.		.		8
0	4.05	YesBoth	RhNeg	.		.		2
0	4.06	YesBrst	RhNeg	.		.		1
0	4.07	YesBoth	RhNeg	.		0		1
0	4.07	YesBoth	RhNeg	0		.		2
0	4.07	YesBrst	RhNeg	0		.		1
0	4.07	YesPreg	RhUnk	-0.03		.		1
0	4.07	YesPreg	RhPos	.		0		1
0	4.07	YesPreg	RhNeg	.		0		1
0	4.08	DK	RhNeg	.		.		1
0	4.09	YesBoth	RhNeg	.		.		1
0	4.10	YesBrst	RhNeg	.		.		1
0	4.11	No	RhUnk	.		.		9
Total:								1095

Number IGs Received and Decision Code: See text

Mother Report of Receipt: From Parent interview – Mother responses included “YesPreg” = Yes, received an immune globulin during pregnancy; “Yes Brst” = Yes, received immune globulin during breast feeding; “Yes Both” = Yes received immune globulins during both pregnancy and breastfeeding periods; “YesDK” = Yes received an immune globulin during pregnancy or breasfeed, but don’t known which; “No” = did not receive during either period; “DK” = don’t know.

Rh Status = Mother’s Rh status as recorded in chart.

Months Prior to Birth = The number of months from receipt of immune globulin to birth of child. “0” = receipt on day of birth, which was assumed to have occurred just after the birth of the child. Negative values indicate receipt after birth of the child (in months).

A set of decision codes was also developed corresponding to the question of if and how many flu shots each mother received during her pregnancy with the focus child. The decisions were based on data from both the maternal medical chart abstractions and responses to items in the parent interview. Neither source indicated that any of the mothers received more than one flu shot during pregnancy. The frequency of application of each decision code is shown in Exhibit 7.4.3.2. The decision codes were defined as follows:

Flu Decision Codes 1.1 – 1.4 : One influenza vaccine received during pregnancy

- Decision code 1.1 = One influenza vaccine received during pregnancy: The mother said that she did not receive a flu shot during pregnancy. However, the chart clearly shows she did, and the record indicates receipt was in November, when flu shots are given. We assume chart is correct and the mother’s memory is incorrect.
- Decision code 1.2 = One influenza vaccine received during pregnancy: The mother said that she did receive a flu shot during pregnancy. The chart shows she did receive a flu shot during pregnancy.
- Decision code 1.3 = One influenza vaccine received during pregnancy: The mother said that she received a flu shot during her pregnancy, but that she received it outside of the HMO. There is no flu shot during pregnancy shown in chart, but if it were received outside of the HMO, it is likely that it would not have appeared in her chart. We assume that mother’s memory is the best information we have and therefore assume that she did receive a flu shot during pregnancy.
- Decision code 1.4 = One influenza vaccine received during pregnancy: The mother said that she received a flu shot during her pregnancy, and she said that she received it at the current HMO. There is no flu shot during pregnancy shown in chart. Consultations with pediatricians and data managers at the HMOs indicated that due to the routine nature of flu shots, and that fact that flu shots are often administered in group settings and in clinic settings that are outside of the regular prenatal care clinics, it plausible that these mothers could have received a flu shot but that the receipt was not recorded in her chart. We assume that mother’s memory is the best information we have and therefore assume that she did receive a flu shot during pregnancy.

Flu Decision Codes 2.1 – 2.4: No influenza vaccines received during pregnancy

- Decision code 2.1 = No influenza vaccine received during pregnancy: The mother said that she did not receive a flu shot during pregnancy, and the chart indicates no receipt.

- Decision code 2.2 = No influenza vaccine received during pregnancy: The mother said that she did not know if she received a flu shot during pregnancy, and the chart indicates no receipt.
- Decision code 2.3= No influenza vaccine received during pregnancy: The mother said that she did not receive a flu shot during pregnancy, and the chart abstraction indicated that flu receipt during pregnancy was unknown.
- Decision code 2.4= No influenza vaccine received during pregnancy: The mother said that she received a flu shot during either pregnancy or breastfeeding, but could not remember which. The chart indicates no receipt. The child was born in early November, which suggests a higher probability of receipt during the breastfeeding period. We assume the chart is correct.

Exhibit 7.4.3.2
Data Cleaning Decision Codes for Prenatal Flu Shot Receipts

Number of Flu Shots Received	Decision Code	Mother Report Of Receipt	Flu Receipt Recorded In Chart	Months Prior To Birth	Frequency
1	1.1	None	Yes	8.88	1
1	1.2	Recd out of HMO	Yes	1.18	1
1	1.2	Recd in HMO	Yes	1.12	1
1	1.3	Recd out of HMO	No	.	2
1	1.4	Recd in HMO	No	.	37
0	2.1	None	No	.	885
0	2.1	Recd in HMO	No	.	4
0	2.1	DK	No	.	1
0	2.2	None	No	.	98
0	2.3	None	No	.	63
0	2.3	Recd in HMO	No	.	1
0	2.4	Recd in HMO	No	.	1
				Total:	1095

Number flu shots received and Decision Code: see text.

Mother Report of Receipt: In parent interview, mother was asked if she received a flu shot during pregnancy, and if so, was it received within the HMO.

Flu Receipt Recorded in Chart = "Yes" if a flu receipt was recorded in mother's chart for the period spanning 10 months prior to birth of the focus child.

Months Prior to Birth: = number of months from flu shot (as recorded in chart) to birth of the focus child.

7.4.4. Mercury Amount Assigned to Each Prenatal Vaccine or Immune Globulin Receipt

Similar to the process described for childhood vaccine receipts, each vaccine or immune globulin received by the mother during the prenatal period was assigned a mercury amount. Our reference sources for determining the amount of mercury contained in each vaccine receipt included the 1995 and 2000 Physician's Desk References (PDRs), Pediatrics (1999), Plotkin & Orenstein (1999), Plotkin & Mortimer (1994), the Food and Drug Administration (FDA) website (accessed on 2/28/2003).

Final determination of the amounts of ethylmercury in prenatal immune globulins was made in consultation with experts at the FDA and with the manufacturers of immune globulin products. The amounts assigned were as follows:

- Rhogam: Between 1993 and 1997 the fill volumes ranged from 0.5 to 1.2 milliliters (*ml*), with an assumed average fill volume of 0.85 ml. Thimerosal was present in Rhogam at 0.003% w/v, which is equivalent to 30 micrograms (μg) per *ml*. Thimerosal was 50 percent ethylmercury by weight. Multiplying the three quantities gives $30 \frac{\mu\text{g}}{\text{ml}} \times 0.85\text{ml} \times 0.50 = 12.75\mu\text{g}$ of ethylmercury per receipt.
- MicRhogam: Between 1993 and 1997 the fill volumes ranged from 0.3 to 1.2 milliliters (*ml*), with an assumed average fill volume of 0.75 ml. Thimerosal was present in MicRhogam at 0.003% w/v, which is equivalent to 30 μg per *ml*. thimerosal was 50 percent ethylmercury by weight. Multiplying the three quantities gives $30 \frac{\mu\text{g}}{\text{ml}} \times 0.75\text{ml} \times 0.50 = 11.25\mu\text{g}$ of ethylmercury per receipt.
- Gamulin and Hyprho-d: The average fill volumes for Gamulin and Hyprho-d used between 1993 and 1997 are assumed to be 1.0 ml. thimerosal was present in each type at 0.01% w/v, which is equivalent to 100 micrograms μg per *ml*. Thimerosal was 50 percent ethylmercury by weight. Multiplying the three quantities gives $100 \frac{\mu\text{g}}{\text{ml}} \times 1.0\text{ml} \times 0.50 = 50\mu\text{g}$ of ethylmercury per receipt.

Exhibit 7.4.4.1 lists all of the thimerosal-containing vaccines and immune globulins received by the mothers during their pregnancies with the focus children. The exhibit also shows the amount of ethylmercury assigned to each receipt.

As described previously, the word "Rhogam" is often used as a generic term even though it is a specific product. Since lot numbers and manufacturers were infrequently listed in the medical charts, there are many instances where the product type was listed as "Rhogam", but where we are uncertain whether the term was being used generically or

was referring to the specific product “Rhogam”. If the term was being used generically, then we may have assigned the wrong mercury amount to the receipt. For example, if a Gamulin was administered, but the administering physician wrote in the chart that “Rhogam” was given, then we would have mistakenly assigned the receipt a mercury amount equal to 12.75, instead of 50. The data set includes two variables, corresponding to IG receipts 1 and 2, that each reflect the level of uncertainty regarding the type of immune globulin received. Recall that up to two immune globulins were listed in the chart abstracted data.

For receipt number 1, we defined a variable named *PN_ProductInfo1* that could take the values “1” or “0”. A value of “1” reflects a high level of confidence that we have the correct information on the type of product that was administered. The variable took the value “1” if the lot number or the manufacturer, or a product other than “Rhogam” was recorded in the chart. These pieces of information provided specifics about the product that was received prenatally. Immune globulin receipts where *PN_ProductInfo1* takes the value “0” are those where we lack the specific information on the product received. In several cases we assumed that Rhogam was received because we had no information on product type. In the remaining cases the chart listed the type as “Rhogam”, but we are unsure of whether the term “Rhogam” was being used generically or was a reference to the specific product. For receipt number 2, the same type of variable was created and named *PN_ProductInfo2*.

We used the variables *PN_ProductInfo1* and *PN_ProductInfo2* in the following way. Our primary set of analyses utilized the prenatal mercury amounts listed in Exhibit 7.4.4.1. This is equivalent to an assumption that all receipts with low levels of certainty about the product types were Rhogam receipts, and hence contained 12.75 micrograms of ethylmercury. To evaluate the sensitivity of the model results to the potential misspecification of the type of immune globulin received (and hence the total prenatal mercury exposure amount) we fit an alternate set of models where we made an alternative assumption that all receipts with low levels of certainty about the product types were Gamulin or Hyprho-d receipts, with 50 micrograms of ethylmercury. In these alternative models, if *PN_ProductInfo1* or *PN_ProductInfo2* was equal to zero, than mercury amount for the corresponding immune globulin receipt was set to 50 micrograms.

Exhibit 7.4.4.2 shows a three-way cross-tabulation of the variable *PN_ProductInfo1* with the variable containing the primary mercury amount assignments for immune globulin receipt number one (*PN_IG1_Amt*), and with the variable containing the alternate mercury amount assignments for immune globulin receipt number one (*PN_IG1_Amt_Alt*). The exhibit shows that there were 50 immune globulin receipts where the value of *PN_ProductInfo1* was 0 and the primary mercury amount was assigned as 12.75 micrograms. The alternate value for these 50 receipts was set to 50 micrograms. The same type of cross-tabulation for variables corresponding to immune globulin receipt numbers two and three are shown in Exhibits 7.4.4.3 and 7.4.4.4. Finally, Exhibit 7.4.4.5 shows a cross-tabulation of the primary variable measuring total prenatal mercury exposure from thimerosal (*PreNatThimer*), with the variable measuring total exposure calculated using the alternate amounts (*PreNatThimer_Alt*).

Exhibit 7.4.4.1**Receipts of Prenatal Vaccines and Immune Globulins and Amount of Ethylmercury in Each Receipt**

<u>Vaccine or Immune Globulin Type</u>	<u>Mercury Amount (Micrograms)</u>	<u>Freq.</u>	<u>Comment</u>
Rhogam	12.75	95	Immune globulin
Michrogam	11.25	1	Immune globulin
Gamulin	50	2	Immune globulin
Hyprho-d	50	3	Immune globulin
Influenza	25	42	Influenza (Adult Dose)
TT	25	1	Tetanus Toxoid
TD	25	4	Diphtheria-tetanus
Rubella	0	9	
HepB	n/a	0	Hepatitis – B
Pneumo	n/a	0	Pneumococcal
Mening	n/a	0	Meningococcal
Rabies	n/a	0	Rabies
Other	n/a	0	Other (specify)

Exhibit 7.4.4.2**Cross-tabulation of PN_ProductInfo1, PN_IG1_Amt, and PN_IG1_Amt_Alt Variables**

<u>PN_ProductInfo1</u>	<u>PN_IG1_Amt</u>	<u>PN_IG1_Amt_Alt</u>	<u>Frequency</u>	<u>Cumulative Frequency</u>
.	.	.	1006	1006
0	12.75	50	50	1056
1	11.25	11.25	1	1057
1	12.75	12.75	35	1091
1	50	50	3	1095

Exhibit 7.4.4.3**Cross-tabulation of PN_ProductInfo2, PN_IG2_Amt, and PN_IG_Amt_Alt Variables**

<u>PN_ProductInfo2</u>	<u>PN_IG2_Amt</u>	<u>PN_IG2_Amt_Alt</u>	<u>Frequency</u>	<u>Cumulative Frequency</u>
.	.	.	1083	1083
0	12.75	50	3	1086
1	12.75	12.75	8	1094
1	50	50	1	1095

Exhibit 7.4.4.4**Cross-tabulation of PN_ProductInfo3, PN_IG3_Amt, and PN_IG_Amt_Alt Variables**

<u>PN_ProductInfo3</u>	<u>PN_IG3_Amt</u>	<u>PN_IG3_Amt_Alt</u>	<u>Frequency</u>	<u>Cumulative Frequency</u>
.	.	.	1094	1094
1	50	50	1	1095

Exhibit 7.4.4.5
Cross-tabulation of PreNatThimer and PreNatThimer_Alt Variables

PreNatThimer	PreNatThimer_Alt	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	0	967	88.31	967	88.31
12.75	12.75	27	2.47	994	90.78
12.75	50	45	4.11	1039	94.89
25	25	37	3.38	1076	98.26
25.5	25.5	5	0.46	1081	98.72
25.5	62.75	2	0.18	1083	98.9
37.75	37.75	2	0.18	1085	99.09
37.75	75	4	0.37	1089	99.45
50	50	1	0.09	1090	99.54
50.5	50.5	1	0.09	1091	99.63
62.75	100	1	0.09	1092	99.73
74	111.25	1	0.09	1093	99.82
75	75	1	0.09	1094	99.91
100	100	1	0.09	1095	100

7.5. Covariates

Exhibit 7.5.1 summarizes the data sources and construction of all variables that were used as covariates in the analytic models.

Exhibit 7.5.1 Data Sources and Construction of Variables Used as Covariates in Analytical Models

Variable	Description	Data Sources			Additional Details
		Parent Interview	Medical Abstract	Computer Automated	
<i>Birth weight</i>	1 = <1.0 kilograms (KG) 2 = 1.0 to 1.4999 KGs 3 = 1.5 to 2.4999 KGs 4 = 2.5 to 3.4999 KGs 5 = 4.0 + KGs		X	X	The five category variable was made into four dummy variables for use in analytical models. Category 1 (<1.0 KGs) is omitted category in models.
<i>PovertyRatio</i>	Ratio of household income to poverty line. Values below 1 correspond to families living below the poverty line. Values above 1 correspond to families living above the poverty line.	X			Percent of poverty line calculated from household (HH) size, household income, and the 2004 poverty guidelines for the 48 contiguous states and the District of Columbia shown in Department of Health and Human Services Annual Update of the HHS Poverty Guidelines; Federal Register, Vol. 69, No. 30, February 13, 2004 / Notices according to the following algorithm: if HH size=2 then PovertyRatio=HH Income/12490; if HH size=3 then PovertyRatio =HH Income/15670; if HH size=4 then PovertyRatio=HH Income/18850; if HH size=5 then PovertyRatio=HH Income/22030; if HH size=6 then PovertyRatio=HH Income/25210; if HH size=7 then PovertyRatio=HH Income/28390; if HH size=8 then PovertyRatio=HH Income/31570; if HH size=9 then PovertyRatio=HH Inc./(31570+3180); if HH size=10 then PovertyRatio=HH nc./(31570+6360)
<i>Maternal Education</i>	0= No high school degree 1=High school diploma or GED 2=attended some college, but no degree 3=Associate's degree or higher	X			The four category variable was made into three dummy variables for use in analytical models. Category 1 (No high school degree) is omitted category in models.
<i>SingleParent</i>	Child lives in a single parent household (0=no, 1=yes)	X			
Child and Family Characteristics					

Exhibit 7.5.1 Data Sources and Construction of Variables Used as Covariates in Analytical Models

Variable	Description	Data Sources			Additional Details
		Parent Interview	Medical Abstract	Computer Automated	
<i>Maternal Age</i>	Age at birth of child 1 = <20 years old 2 = 20 – 24 years 3 = 25 – 29 years 4 = 30 – 34 years 5 = 35 years or older	X	X	X	The five category variable was made into four dummy variables for use in analytical models. Category 1 (<20 years old) is omitted category in models.
<i>Paternal Age</i>	Age at birth of child 1 = <20 years old 2 = 20 – 29 years 3 = 30 – 39 years 4 = 40 – 49 years 5 = 50 years or older	X	X		The five category variable was made into four dummy variables for use in analytical models. Category 1 (<20 years old) is omitted category in models.
<i>BirthOrder</i>	1=Child is first born 2=Child is second born 3=Child is third born or later	X			The three category variable was made into two dummy variables for use in analytical models. Category 1 (first born) is omitted category in models.
<i>Multiple</i>	Plurality =1 if child was a multiple (twin, triplet) =0 if child was a singleton	X	X		
<i>Breast Feeding (Duration)</i>	0 = Breast Fed: <1 month 1 =Breast Fed: 1-6 months 2 = Breast Fed: 6+ months	X			The three category variable was made into two dummy variables for use in analytical models. Category 1 (<1 month) is omitted category in models.
Child Birth Conditions					
<i>C5APGARImpVal1</i>	5-minute apgar		X		Child's score on the 5 minute APGAR, which is a test given to newborns five minutes after birth to measure activity, pulse, grimace, appearance, and respiration.
<i>BirthAsphyxia</i>	=1 if medical record indicates birth asphyxia =0 else		X		
<i>RespDistress</i>	=1 if medical record indicates		X		

Exhibit 7.5.1 Data Sources and Construction of Variables Used as Covariates in Analytical Models

Variable	Description	Data Sources			Additional Details
		Parent Interview	Medical Abstract	Computer Automated	
<i>Bilirubin</i>	respiratory distress =0 else =1 if neonatal hyperbilirubinemia =0 else		X		=1 if total bilirubin >10 on day 1; or If total bilirubin > 12 on day 2; or If total bilirubin >15 on day 3; or If any of the following treatments: phototherapy, biliites, bilirubin lights, exchange transfusion, or type and cross match blood.
Prenatal Exposures (non-vaccine related)					
<i>PreNatNicotine_1</i>	Used tobacco during pregnancy	X	X		= 1 if mother used any tobacco products during pregnancy. 0= none
<i>PreNatAlcohol_1</i>	Alcohol use during pregnancy:	X	X		1= occasional (1-4 drinks per month) 2= light (20-24 drinks/month or 5-6 per week) 3=moderate(10-15 drinks per week) 4=heavy (more than 15 drinks per week) Entered in models as linear term.
<i>Tuna Consumption</i>	Maternal tuna consumption during pregnancy	X			0= no consumption of tuna during pregnancy. 1 = moderate consumption (less than one serving per week) 2 = high consumption (more than one serving per week) Entered in models as linear term.
<i>PreNatFish_1</i>	High consumption of fish during pregnancy.	X			1= if mother reported eating tuna, and ocean fish, and home-caught fish during pregnancy. 0 = else.
<i>PreNatOthMerc_Any</i>	=1 if any prenatal non-vac merc exposures1	X			PreNat non-vac mercury exposures: PreNatChin= 1=used chinese herbal ball prep PreNatMex= 1=used native Am or Mex folk meds PreNatFolk= 1= used folk to treat empacho PreNatRelig= 1=materials Santeria,espiritismo,oth relig PreNatContacts= 1=used thim-containing contact soln PreNatNasal= 1=used thim-containing nasal soln PreNatEyeDrops= 1=used thim-containing eye drops

Exhibit 7.5.1 Data Sources and Construction of Variables Used as Covariates in Analytical Models

Variable	Description	Data Sources			Additional Details
		Parent Interview	Medical Abstract	Computer Automated	
<i>PreNatFillings_1</i>	Mercury-containing dental amalgams	X			PreNatEar = 1=used thim-containing ear wax soln PreNatSkin= 1=used skin lightening cream PreNatTherm= 1=exposed to broken merc-contain thermometer PreNatBulb= 1=exposed to broken florescent bulb PreNatShoes= 1=exposed to broken pre-97 shoe lights PreNatGauge= 1=exposed to broken electronic swithes,relays,gauges
<i>PreNatlead_1</i>	Prenatal exposure to lead from occupational or residential sources	X			Amalgam fillings during pregnancy: 0 = mother had no amalgam fillings 1 = had amalgam filling, but no dental work and did not chew gum during pregnancy 2= had amalgam fillings and had dental work or chewed gum during pregnancy. = 1 if during pregnancy mother worked in: Smelting, soldering, construction, or demolition or if during pregnancy mother lived in : a pre-1950 home, or a pre-1978 home that underwent painting or renovation during her pregnancy.
<i>PreNatIIIDrug</i>	1=Cocaine or Narcotic		X		1=if maternal medical chart indicated suspected use of cocaine or narcotics during pregnancy. 0 = else.
<i>PreNatValproic</i>	= 1 if mother took valproic acid during pregnancy =0 else.	X	X		If chart or parent interview indicated that mother took valproic acid during pregnancy, or phenobarbital, depakote, monistat, macrodantin during pregnancy.
<i>PreNatFolic</i>	= 1 if mother took folic acid or prenatal vitamins or multivitamins during pregnancy =0 else.	X	X		If chart or parent interview indicated that mother took folic acid or prenatal vitamins or multivitamins during pregnancy.
<i>PreNatViralInf</i>	= 1 if medical chart indicated that		X		

Exhibit 7.5.1 Data Sources and Construction of Variables Used as Covariates in Analytical Models

Variable	Description	Data Sources			Additional Details
		Parent Interview	Medical Abstract	Computer Automated	
	mother had any viral infection (e.g., herpes simplex virus outbreak, chlamydia, strep infection, upper respiratory viral infection, viral enteritis) at anytime during pregnancy = 0 otherwise.				
Child Medical Conditions					
Anemia	Anemia or iron deficiency		X		= 1 if any records of anemia and iron deficiency in child's chart. =0 else.
Enceph	= 1 if child had encephalitis or any CNS infection prior to 36 months of age =0 else		X		
ChildLead	= 1 if child had lead test levels over 10 or child was exposed to lead from home before age 3 =0 else				= 1 if lead poisoning before age three indicated in chart; or Parent said child had an elevated lead test level before age 3; or before age 3, Child lived in home where water was tested and found to have high lead content; or Child had pica and child lived in a pre-1950 home; or Child had pica and child lived in a pre-1978 home that underwent painting or renovation; or Child had pica and parent said paint or floor varnish was tested and had high lead content;
ChildPica	= 1 if child exhibited pica before his/her third birthday.	X	X		Pica is characterized by persistent and compulsive cravings (lasting one month or longer) to eat nonfood items.

Exhibit 7.5.1 Data Sources and Construction of Variables Used as Covariates in Analytical Models

Variable	Description	Data Sources			Additional Details
		Parent Interview	Medical Abstract	Computer Automated	
<i>HC_InitInad</i>	= 1 if Kotelchuck initiation of prenatal care index in "inadequate" range = 0 else	X	X		If date of initiation of prenatal care is missing from chart, then used information from parent interview
<i>HC_Pap</i>	= 0 if mother has never had a pap smear. = 1 if mother has ever had a pap smear, but not within the three years prior to interview = 2 if mother had a pap smear within three years.		X		The three category variable was made into two dummy variables for use in analytical models. Category 0 (Never) is omitted category in models. This variable was considered to be a proxy measure for health care seeking behavior.
<i>HC_Cholest</i>	= 0 if mother has never had a cholesterol test. = 1 if mother has ever had a cholesterol test, but not within the three years prior to interview = 2 if mother had a cholesterol test within the three years.		X		The three category variable was made into two dummy variables for use in analytical models. Category 0 (Never) is omitted category in models. This variable was considered to be a proxy measure for health care seeking behavior.

7.5.1. Imputation of Missing Values for Covariates

Exhibit 7.5.2 describes the procedures used to impute missing values for covariates. Note that the analysis data set contained no missing values on outcome classifications (i.e., case / control status) or on measures of ethylmercury exposure from thimerosal-containing vaccines and immune globulins. The postnatal exposure measures were calculated as the amount of mercury contained in a received vaccine or immune globulin, divided by the child's weight at time of vaccine receipt, and summed over the appropriate age range. Thus, there was a requirement for data on each child's weight at the time of vaccine receipt. An explanation of imputation of missing weight data is provided in Chapter 18.

Exhibit 7.5.2. Imputation of Missing Values for Covariates

Covariate with Missing Values	Description	# of Missing Values	Imputation Method
PovertyRatio	Ratio of income to poverty line	26	The <i>PovertyRatio</i> variable was created from measures of family income, family size, and poverty line thresholds. There were no missing values for family size, but there were missing values for income. Missing values for income were replaced by the sample mean of income, plus a randomly selected residual from a model of the form $Y = B0 + e$. Adding the randomly selected residual ensured that the variation of imputed values was the same as the variation in observed values.
MomEduc	Maternal education level 0=NoHSDip;1=HS_GED; 2=SomeCollege; 3= CollDegree(BA, Associate's or above)	1	The imputed value was generated to have the following probabilities of being in one of the education level categories: 0.03 for <i>MomEduc</i> =0, 0.155 for <i>MomEduc</i> =1, 0.211 for <i>MomEduc</i> =2, and 0.603 for <i>MomEduc</i> =3. These probabilities correspond to the percentages of mothers with non-missing education levels that were in each education category.
BioDadAgeCat	Biological father's age at birth of child 1=0-19, 2=20-29, 3=30-39, 4=40-49, 5=49+	2	Predicted values of paternal age were obtained from a model of the form: $Y = B0 + B1(\text{maternal age}) + e$. Missing values were replaced with the model-predicted value plus a randomly selected residual. The imputed values were placed into the categories of <i>BioDadAgeCat</i> , as shown.
BirthOrderCat	Child birth order 1=1st,2=2nd,3=3rd or higher	1	The imputed value was generated to have the following probabilities of being in one of the birth order categories: 0.40 for

Exhibit 7.5.2. Imputation of Missing Values for Covariates		
Covariate with Missing Values	Description	# of Missing Values
		Imputation Method
		<i>BirthOrderCat</i> =1, 0.40 for <i>BirthOrderCat</i> =2, 0.20 for <i>BirthOrderCat</i> =3. These probabilities correspond to the sample percentages of children that were in each birth order category.
<i>PreNatNicotine</i>	Tobacco use during pregnancy =1 if any tobacco use; pregnancy	1
		The imputed value was generated to have the following probability of taking the value “1” (yes): 0.052. This corresponds to the sample percentage of mothers that used tobacco during pregnancy.
<i>PreNatAlcohol</i>	Alcohol use during pregnancy 0=Never, 1=Occasional, 2=light, 3=moderate, 4=heavy	3
		The imputed values were generated to have the following probability of being in each of the alcohol use categories: 0.924 for <i>PreNatAlcohol</i> =0, 0.071 for <i>PreNatAlcohol</i> =1, 0.002 for <i>PreNatAlcohol</i> =2, 0.003 for <i>PreNatAlcohol</i> =3 and 0 <i>PreNatAlcohol</i> =4. These probabilities correspond to the sample percentages among those with non-missing data.
<i>PreNatTuna</i>	Prenatal Tuna (0=none, 1=moderate, 2=high)	69
		For the 69 mothers who could not remember how often they ate tuna during pregnancy, we assumed that if they never ate tuna, they would be likely to remember, or if they ate tuna regularly, they would be likely to remember. We therefore guessed that they were most likely to have eaten tuna occasionally (less than one serving per week). The 69 with missing values were given imputed values of <i>PreNatTuna</i> =1 (moderate).
<i>PreNatOceanFresh</i>	Hi Prenatal OceanFresh (1= ate other OceanFresh often or very often)	34
		The variable <i>PreNatOceanFresh</i> was not used as a covariate, but was used in the construction of the variable <i>PreNatFish</i> . For the 34 mothers who could not remember how much ocean fish, or home-caught fresh fish they ate, we assumed that if they ate a lot of these types of fish, they were be more likely to remember. We therefore assumed that these mothers did not eat either ocean or home-caught fresh water fish often or very often, and set the value of <i>PreNatOceanFresh</i> to “0”.
<i>PreNatFish</i>	=1 if <i>PreNatTuna</i> =Hi or <i>PreNatOceanFresh</i> in(Often,VeryOften)	84
		The variable <i>PreNatFish</i> was constructed from the variables <i>PreNatTuna</i> and <i>PreNatOceanFresh</i> .
<i>PreNatFillings</i>	0=None, 1=Have(noWrk,Grnd,gum)2=Have(YesWrk,Grnd or Gum)	89
		The variable <i>PreNatFillings</i> was constructed from information on whether or not mother had amalgam fillings, whether or not mother had dental work done during pregnancy, whether or not mother

Exhibit 7.5.2. Imputation of Missing Values for Covariates

Covariate with Missing Values	Description	# of Missing Values	Imputation Method
PreNatLead	=1 if PreNatResiLead or PreNatOccupLead=1	32	<p>chewed gum during pregnancy, and whether or not mother ground her teeth during pregnancy. Of the 89 with missing values on <i>PreNatFillings</i>, all had non-missing information on one or more of the variables used for construction, but they did not have non-missing values on all of the variables. The imputed values were generated from the conditional probabilities, given the non-missing components. For example, if mother had fillings, but did not grind her teeth, then the conditional probability of <i>PreNatFillings=0</i> is 0.00, <i>PreNatFillings=1</i> is .28 and <i>PreNatFillings=2</i> is 0.71. (Many mothers reported that they chewed gum, so even if a mother did not grind her teeth, if she had amalgam fillings, her chances of being in category <i>PreNatFillings=2</i> were still high.)</p> <p>The <i>PreNatLead</i> variable was constructed from measures of residential lead exposure during pregnancy, and occupational lead exposure during pregnancy. The measure of residential lead exposure was created from information on whether the mother lived in a pre-1950 home, or lived in a pre-1978 home that underwent painting or renovation during her pregnancy. Imputed values on the residential lead variable were generated from conditional probabilities, given the amount of information available. For example, among mothers that lived in pre-1978 homes, 33% had <i>PreNatResiLead=1</i>. Therefore, if a mother lived in a pre-1978 home, but could not remember if it was renovated or painted during her pregnancy, her imputed value on <i>PreNatResiLead</i> had a 33% chance of taking the value 1, and a 67% chance of taking the value "0". Only one mother had a missing value on the measure of occupational lead exposure. She was employed during her pregnancy. Therefore, her imputed value was generated with a probability equal to the proportion of employed mothers who had occupational lead exposure.</p>
HC_InitInad	=1 if Kotelchuck initiation of prenatal care index is in "inadequate" range	7	<p>The imputed value was generated to have the following probability of taking the value "1" (yes): 0.030. This corresponds to the percentage of mothers that had values of <i>HC_InitInad_1</i> = 1.</p>

8. Analysis Approach

During the design phase of this study an analysis plan was developed that detailed the child outcomes that were to be measured, data sources, how exposure measures and covariates would be coded, the forms of the statistical models that would be fit to the data, and the method for deciding which covariates were to be retained or dropped for inclusion in the models for any particular outcome variable. The analysis plan went through several iterations of review and comment by the Principal Investigators at the CDC, at each of the three participating HMOs, and at Abt Associates Inc., and by the study's External Expert Consultants²⁹.

Variable construction and the modeling approach followed very closely to that analysis plan. In the first phase of analysis, only models that were specified in the analysis plan were fit to the data. Following an agreed upon protocol, none of the preliminary results were shown to or discussed with anyone outside of the analysis team at Abt Associates Inc. prior to a meeting that took place on May 29, 2008. At that meeting the preliminary results from those models were presented to the group of Principal Investigators and the study's External Expert Consultants. The second phase of analysis began after the May 29, 2008 meeting. The phase one results generated new ideas and motivated new lines of inquiry. The group of Principal Investigators and the study's External Expert Consultants were asked to submit their ideas for phase two analyses within a two month period after the meeting. Phase two analyses are presented in Volume II of this technical report.

The data sources and construction of measures were described previously in Chapter 6 and 7. The remainder of Chapter 8 focuses on the analytical models used and on model selection (i.e., which covariates are included in each model).

Section 8.1 presents an example model specification and introduces notation that is used throughout the remainder of the report. The full set of analysis models is documented in Chapter 9. The model specifications are presented in that section in order to clarify the interpretation of the results that are presented there.

Section 8.2 documents the methods used for model selection. A description of how we reported effect sizes is provided in Section 8.3.

8.1. Overview of Analytical Models

Shown below is an example model specification that introduces notation and terminology that will be used in the discussion of statistical models. The example model shown below corresponds to the research question regarding the extent to which the timing of children's exposure to ethylmercury from thimerosal in vaccines or immune globulins may be associated with a diagnosis of autistic disorder.

²⁹ See Acknowledgements section for listing of the Panel of External Consultants.

$$\log\left(\frac{\pi}{1-\pi}\right) = \alpha_i + \beta_1 preNatThimer + \beta_2 Exp01mos + \beta_3 Exp17mos + \sum_j \gamma_j oe_j + \sum_k \gamma_{j+k} cf_k$$

The model is specified as a conditional logistic regression model³⁰. The left-hand side of the equation shows the logistic link for the probability of an outcome classification, e.g., autism disorder (AD). There are four classes of right-hand-side variables in the model. The first class represented by the term α_i represents indicators for the matched sets of cases and controls, where matching was on birth year, sex, and HMO. The second class consists of the thimerosal exposure variables. In this model, the *preNatThimer* variable is a measure of prenatal exposure to ethylmercury from thimerosal-containing vaccines and immune globulins, the variable *Exp01mos* represents exposure to ethylmercury from thimerosal-containing hepatitis B vaccines or immune globulins administered in the first 28 days of life, and *Exp17mos* is a measure of exposure to ethylmercury from thimerosal-containing vaccines received in the age range of one to seven months (29-214 days).

The third class of right-hand-side variables represents other prenatal exposures to neurotoxins that may be related to the risk of autism. These variables are included in the model to account for relationships between exposures to other neurotoxins and the outcome measures when making inferences about the effects of thimerosal exposure on the outcome variable. Examples include maternal alcohol use and maternal smoking during pregnancy. These terms are represented in the model specification by oe_j , where “oe” stands for “other exposures”, and the γ_j represent fixed effect parameters. The summation symbol means that we will have 0, 1, 2, 3... up to “j” such terms in the model specification.

The fourth class of right-hand-side variables is labeled as “child and family statistical control variables”. This class of variables includes child and family demographic factors that we want to control for when making inferences about the relationship of thimerosal exposure to the outcome variable. Examples include maternal age and family socio-economic status. This class of variables is represented in the model specification by cf_k , where “cf” stands for “child and family”, and the subscript “k” indicates that we will have 1, 2, 3, ... up to “k” such terms in the model. The corresponding parameters are numbered “j + k” to indicate that the numbering follows sequentially after the “other exposures” variables. For example, if there were two “other exposures” variables, then the first child and family statistical control variable in the model would be subscripted with a 3 (j + k = 2 + 1 = 3). The second *cf* variable would be numbered 4, (j + k = 2+2=4), etc.

There are three hypotheses to be tested using the model shown in the example above.

1. The test of the null hypothesis that there is no linear relationship of prenatal exposure to thimerosal to the risk of AD.

³⁰ Conditional logistic regression models were fit to the data using SAS (version 9.1) Proc PhReg, and using the “ties = discrete” option.

2. The test of whether there is a relationship between receipt thimerosal-containing vaccines and immune globulins in the first 28 days of life, and AD risk.
3. The test for a linear relationship between exposure to thimerosal received in the age range of one month to seven months, and AD risk. We will use the following notation for these three tests:

$$H_0 : \beta_1 = 0 \quad \text{vs} \quad H_a : \beta_1 \neq 0 ,$$

$$H_0 : \beta_2 = 0 \quad \text{vs} \quad H_a : \beta_2 \neq 0 ,$$

$$H_0 : \beta_3 = 0 \quad \text{vs} \quad H_a : \beta_3 \neq 0 .$$

8.2. Inclusion of Covariates

Consulting pediatricians, neurotoxicologists, and other experts identified a long list of factors that could plausibly have relationships with the outcome variables in this study. It is not feasible to implement an experimental design that would strictly eliminate the potential influence of all of these factors on the outcome measures. However, by specifying some or all of them as covariates in our statistical models, we attempt to adjust for the influences of these factors on the outcome variables when making inferences about the relationship between exposure to ethylmercury and the outcome measures. In this section we describe our methodology for choosing which variables were retained as covariates in the final analytical models (in addition to the thimerosal exposure variables which are always retained). The goal of the covariate selection methodology is to find the set of variables for the final models that will simultaneously produce precise estimates of exposure effects (small standard errors) while controlling for potential confounding. These are decisions about what variables will be included in the terms represented by oe_j and cf_j in the models specified in the previous section.

Other than the interactions already specified in Section 3.3, no additional tests for interactions are planned. In order to limit the proliferation of statistical tests which would increase the probability of spurious findings, our strategy was to specify the biologically plausible interactions in advance, and test only those interactions. Therefore, the covariate selection strategy is limited to the problem of deciding what variables should be retained as main effect covariates.

In the analysis plan for a study that preceded the current study (the Thimerosal Follow-Up study, “*Infant Environmental Exposures and Neuropsychological Outcomes at Ages 7-10 Years*” (Price, Goodson and Stewart, 2007)), we discussed three different approaches to covariate selection. The three methods are not necessarily mutually exclusive. We referred to the first method as the *a priori* selection method. In this approach, model covariates are selected during the design phase, well before data are collected. This method is based on the assumption that there is strong prior knowledge about the relationships between outcomes and the variables that are being considered as covariates and/or the relationships between thimerosal exposure and the variables that are being considered as covariates. For many of the outcome measures used in the Thimerosal Follow-Up study, strong prior knowledge did exist. For example, for most of

the outcome measures for that study, we knew, *a priori*, that the age of the child at the time of testing would be related to the outcome. For the autism outcomes being considered in the current study, there are no variables on our list, other than the matching variables, for which we have sufficient prior knowledge to specify in advance that they need to be included as covariates in the final models. Therefore, other than the matching variables and the exposure variables, there were no additional independent variables that we specified *a priori* for inclusion in all of the final models.

We refer to the second method as *backwards elimination*. This is a very commonly used method of covariate selection in which one begins a step-wise process by fitting a model with a full set of covariates, and identifying the covariate with the largest p-value. That variable is dropped in the second iteration and a new model is fit, and the process is repeated. This procedure continues until all covariates that do not reach a pre-set significance criterion are dropped from the model.

Several consulting statisticians on the Thimerosal Follow-Up study advocated the use of a third methodology for covariate selection, the *change-in-estimate* methodology. In this approach, the decision of whether or not to include a variable as a covariate is decided by fitting models with and without the covariate and comparing the estimates of the target parameter(s) (i.e., the exposure variable(s)) in the two models. If the difference between the estimates target parameter(s) from the two models changes by more than some pre-determined cut-off level (e.g., 10%), then the covariate is retained in subsequent models, otherwise it is dropped. In this strategy, it is assumed that a model that includes all of the potential covariates (called *the full model*) is unbiased. The final model should include the subset of potential covariates that result in exposure estimates that are similar in magnitude to those obtained from *the full model*, but that have better precision.

For the Thimerosal Follow-Up study, the outcomes were continuous measures and were to be fit to linear regression models. A strategy involving a mix of *a priori* selected covariates, backwards elimination, and change-in-estimate was planned. The model selection strategy for the Thimerosal Follow-Up study was guided by research by Budz-Joregnsen et al. (2001) on covariate selection strategies. The Budz-Joregnsen et al. (2001) paper was especially relevant to the Thimerosal Follow-Up study because they examined selection strategies for similarly specified least squares linear regression models, with some of the same outcome measures and covariates as those in the Thimerosal Follow-Up study. Furthermore, both studies had similar exposure measures and sample sizes. The outcome measures and the type of statistical models are quite different for the current autism study. In the autism study, the outcomes are binary and were analyzed in Cox proportional hazards models. For the autism case-control study we utilized a change-in-estimate type of strategy for covariate selection, following the methodologies outlined in Kleinbaum and Klein (2002), and Hosmer and Lemeshow (2000).

In this methodology, a full model including all potential covariates is fit to the data. Starting with the covariate that has the highest p-value³¹, the covariate was dropped and the exposure estimates from the reduced model were compared to the estimates from the full model. If the omission of that covariate does not change the parameter estimates corresponding to *PrenatThimer* or *Exp01mos* or *Exp17mos* by more than 10 percent relative to the estimates from the full model, the variable is dropped. The process continues through all of the remaining potential covariates. Covariates that have small p-values but that do not change any of the exposure parameter estimates by more than 10 percent are omitted from the reduced model. Otherwise, the covariate is retained on the right-hand side of the regression equation. This process has the result that the parameter estimates from the final, reduced model are not more than 10 percent different than the estimates from the full model, but the standard errors of the estimates from the reduced model are smaller than those of the full model. Section 12.2.2 of Volume II of the Technical Report shows the parameter estimates and standard errors for each of the exposure variables for the full model and the reduced model. The displays in that chapter show the amount of change to each exposure estimate as each covariate was dropped. Thus, the displays in that chapter show the sensitivity of the model results to the inclusion or exclusion of any particular covariate.

At the outset of the model selection process, it became clear that covariates that had little or no variation in values were causing estimation problems. For example, for the analysis of the ASD outcome, only one observation had a value of ‘1’ on the *BirthAsphyxia* covariate, and the remaining n=1,007 observations in the data set had the value ‘0’ on that variable. When this variable entered the analytic model as a covariate, the estimate and its standard error were nonsensically large. The standard error was 47 times as large as the estimate, and the odds ratio was well over five hundred thousand to one. Because of these nonsensical estimates, we dropped *BirthAsphyxia* from the full model and all subsequent models. The analyses of other outcomes utilized smaller data sets, and as the data sets got smaller, estimation problems with other covariates arose. For the analysis of the AD outcome, only one observation out of n=911 had a value of ‘1’ on the encephalitis covariate (*enceph*), resulting in similarly absurd estimates. It too was omitted from the full and subsequent models. Exhibit 8.1 shows, for each outcome model, the list of covariates that were not included in the models because lack of variation caused the kind of estimation problem described above. In some cases, covariates were not completely omitted, but to avoid estimation problems, the levels were collapsed. For example, for the ASD-not-AD outcome model, birth weight entered the model as a potential covariate, but it was entered as a three category variable (<2.5 kg; 2.5 – 3.999 kg ; 4+ kg) instead of entering in its original form as a five category variable (<1kg; 1-1.4.999 kg; 1.5-2.4.999 kg; 2.5 – 4 kg ; 4+ kg).

Exhibit 8.2 shows the covariates included in the final reduced model for each outcome. For two of the outcomes, ASD-not-AD, and AD w/Scr (AD compared to “screened control group”), the initial estimates of at least one of the three exposure effects from the

³¹ P-values were not part of the decision process regarding which covariates to drop and which to retain in the final reduced model. They were only used as a rough guide as to which variables to drop first in the process.

full model was so close to zero, that even a very small numerical change in the estimate resulting from dropping a covariate amounted to more than a 10 percent change, relative to the estimate from the full model. For the ASD-not-AD outcome, the initial estimate for the *PreNatThimer* effect was very close to zero, and dropping any covariate resulted in a change of more than 10 percent. Thus, using the selection criteria specified in the analysis plan and described above resulted in decision rules that meant that none of the covariates could be dropped. Therefore, the final model is the full model. Similarly, for the ASD w/Scr outcome, it was the *Exp01mos* effect that was very close to zero in the full model, and dropping any covariate resulted in a change of more than 10 percent. For this outcome, the final model is the same as the full model. The results in Section 12.2.2 show, however, that our inferences about the exposure effects are not sensitive to the issue of whether the full model or a reduced model is used for these outcomes.

For each outcome, the covariate set shown in Exhibit 8.2 was used for all models for that outcome. For example, for the ASD outcome, the covariate set shown in the exhibit was also used in models where the exposure variables were *PreNatThimer* and *Exp07mos*, models where the exposure variables were *PreNatThimer* and *Exp020mos*, and the exposure-by-sex, and exposure-by-concurrent antibiotics interaction models.

Exhibit 8.1 Covariates Omitted From Each Outcome Model Due to Estimation Problems			
Contrast: ASD Cases vs Matched Controls	Cases n=256	Controls n=752	Total n=1,008
Covariates Omitted from Analysis Model Because of Estimation Problems:			
<i>BirthAsphyxia</i>			
Contrast: AD Cases vs Matched Controls	187	724	911
<i>BirthAsphyxia</i>			
<i>Enceph</i>			
Contrast: ASD-not-AD Cases vs Matched Controls	69	704	773
<i>BirthAsphyxia</i>			
<i>Enceph</i>			
PreNatValproic			
Birth weight categories collapsed to three (<2.5 kg; 2.5 – 4 kg ; >4 kg)			
Mother's age categories collapsed to three (<30 years; 30-34 years; >35 years)			
Father's age categories collapsed to three (<40 years; 40-49 years; >49 years)			
<i>Multiple</i>			
<i>HC_Pap</i> collapsed to two categories (1 & 2 ; 3) (Never & >3Yrs vs within 3 years)			
Contrast: ASD with Regression Cases vs Matched Controls	49	652	701
<i>BirthAsphyxia</i>			
<i>Enceph</i>			
PreNatValproic			
PreNatIIIIDrug			
Folic_PNVit_Multi			
Birth weight categories collapsed to three (<2.5; 2.5 – 4 kg ; >4 kg)			
Mother's age categories collapsed to three (<30 years; 30-34 years; >35 years)			
Mother's education collapsed to three (No HS & HS; Some College; College)			
Father's Age			
<i>HC_Pap</i> collapsed to two categories (1 & 2 ; 3) (Never & >3Yrs vs within 3 years)			
AD with Low Cognitive Function Excluded Cases vs Matched Controls	165	719	884
<i>BirthAsphyxia</i>			
<i>Enceph</i>			
<i>Anemia</i>			
Contrast: ASD Cases vs "Screened" Matched Controls	255	566	821
<i>BirthAsphyxia</i>			
<i>Enceph</i>			
Contrast: AD Cases vs "Screened" Matched Controls	186	542	728
<i>BirthAsphyxia</i>			
<i>Enceph</i>			

Exhibit 8.2. Covariates Tested For Inclusion in the Reduced Model for Each Outcome								
Symbols Key:		Outcome Model						
X = Variable included as covariate b = omitted "baseline" comparison category - = Variable not included due to estimation problems		ASD	AD	ASD -not- AD	ASD w/Reg	AD w/o Lo CF	ASD w/ Scr	AD w/ Scr
Variable	Label							
MomLt20	Mom Age at child birth lt 20	b	b	b	b	b	b	b
Mom20_24	Mom Age at child birth 20 - 24	X	X	b	b	X	X	X
Mom25_29	Mom Age at child birth 25 - 29	X	X	b	b	X	X	X
Mom30_34	Mom Age at child birth 30 - 34	X	X	X	X	X	X	X
MomGE35	Mom Age at child birth ge 35	X	X	X	X	X	X	X
BirthOrder1_1	=1 if 1st born	b	b	b		b	b	b
BirthOrder2_1	=1 if 2nd born	X	X	X		X	X	X
BirthOrderGE3_1	=1 if 3rd born or higher	X	X	X		X	X	X
Multiple	=1 if twin or triplet			-				
BFNone	=1 if Breastfed 0 months	b	b	b		b	b	b
BF1_6mos	=1 if Breastfed 1-5.99 months	X	X	X		X	X	X
BFgt6mos	=1 if Breastfed 6+ months	X	X	X		X	X	X
PovertyRatio1		X	X	X	X	X	X	X
MomEduc_NoHSDip	=1 if Mom did not graduate high school			b	b	b		b
MomEduc_HS	=1 if Mom HS Grad			X	b	X		X
MomEduc_Some	=1 if Mom Some Coll			X	X	X		X
MomEduc_Coll	=1 if Mom Coll Grad			X	X	X		X
SingleParent	Child lives in a single parent household			X				X
Dadlt20_i1	Dad <20 years old			b	-			b
Dad20_29_i1	Dad 20-29 years old			b	-			X
Dad30_39_i1	Dad 30-39 years old			b	-			X
Dad40_49_i1	Dad 40-49 years old			X	-			X
DadGE49_i1	Dad >49 years old			X	-			X
HC_InitInad	1= if Kotel Init PNC =INADEQ	X	X	X		X	X	X
HC_Cholest_0	0=never	b	b	b		b	b	b
HC_Cholest_1	1=>3yrs	X	X	X		X	X	X
HC_Cholest_2	2=w/in3yrs	X	X	X		X	X	X
HC_PAP_0	0=never	b	b	b		b	b	b
HC_PAP_1	1=>3yrs	X	X	b		X	X	X
HC_PAP_2	2=w/in3yrs	X	X	X		X	X	X
PreNatTuna	Prenatal Tuna (0=none, 1=moderate, 2=hig			X				X
PreNatFish	=1 if PreNatTuna=Hi or PreNatOceanFresh			X				X
PreNatOthMerc_Any	=1 if any prenat non-vac merc exposures			X				X
PreNatFillings_1	0=None,1=Have(noWrk,Grnd,gum)2=Have(YesW			X				X
PreNatNicotine_1	=1 if any tobacco use: pregnancy			X				X
PreNatAlcohol_1	0=Never,1=Occasional,2=light,3=moderate	X		X	X	X	X	X
PreNatIllDrug	=1 if Cocaine or Narcotic use during pre			X	-			X
PreNatValproic	Used Prenatal Valproic acid			-	-			X
Folic_PNVit_Multi	=1 if Folic,PreNatVit or Multivit prenat	X	X	X	-	X	X	X
PreNatVirallnf	=1 if any prenatal viral infections	X		X		X	X	X
PreNatLead_1	=1 if PreNatResilLead or PreNatOccupLead=	X		X		X	X	X

Exhibit 8.2. Covariates Tested For Inclusion in the Reduced Model for Each Outcome

Symbols Key:		Outcome Model						
X = Variable included as covariate b = omitted "baseline" comparison category - = Variable not included due to estimation problems		ASD	AD	ASD -not- AD	ASD w/Reg	AD w/o Lo CF	ASD w/ Scr	AD w/ Scr
Variable	Label							
BWLt1k	=1 if Birth wgt < 1 Kg	b	b	b	b	b	b	b
BW1_1p5k	=1 if Birth wgt 1.0 Kg to 1.499 Kg	X	X	b	b	X	X	X
BW1p5_2p5k	=1 if Birth wgt 1.5 Kg to 2.499 Kg	X	X	b	b	X	X	X
BW2p5_4k	=1 if Birth wgt 2.5 Kg to 3.999 Kg	X	X	X	X	X	X	X
BW4kup	=1 if Birth wgt 4.0 Kg and up	X	X	X	X	X	X	X
C5APGAR	5 minute Apgar score			X				X
BirthAsphyxia	=1 if Birth asphyxia	-	-	-	-	-	-	-
RespDistress	=1 if Resp Distress Syndrome (hyaline)			X				X
Bilirubin	=1 if hyperbilirubinemia			X				X
Anemia	=1 if anemia 6-30 mos	X	X	X		-	X	X
ChildLead	=1 if child exposure to lead			X		-		X
ChildPica	=1 if child had pica	X	X	X		X	X	X
Enceph	=1 if Encephalitis or any CNS infection		-	-	-	-	-	-

8.3. Reporting Effect Sizes

The parameter estimates corresponding to the thimerosal exposure variables in the conditional logistic regression models lack intuitively obvious interpretations. Only the sign (positive or negative) corresponding to the estimates is easy to interpret. A positive coefficient means that the predicted risk of autism increases with increasing exposure, a negative coefficient means the opposite. To report quantities of the size of the exposure effects, we convert the coefficient into odds ratios. Unlike the exposure estimates themselves, the odds ratios convey something about the magnitude of the exposure effect. Many readers will be familiar with the use of odds ratios as measures of effect sizes, but most of the familiarity will be in the context of studies where exposure is a dichotomous event, coded as “1” if exposed, and “0” if unexposed. In the current study, exposures are measured on continuous scales. We therefore explain in this section how we calculate, present, and interpret odds ratios in the current report. We start by explaining odds ratios for the simpler case of dichotomous exposure, then explain how they are interpreted in the current study with continuous exposure measures.

8.3.1. Odds Ratio in Case-Control Studies when Exposure is Dichotomous

Let the 2x2 table shown below represent the data from a case-control study, with dichotomous exposure, and no adjustments for confounding (i.e., no covariate

adjustments). Let each cell represent a table proportion³², such that, “a”, for example, represents exposed cases, and “c” cases that were not exposed.

		Disease		
		Case	Control	
Exposure	Yes	a	b	
	No	c	d	
		a+c	b+d	a+b+c+d=1

The “odds” of exposure for cases is the proportion that were cases and exposed (“a”) divided by the proportion that were cases and not exposed (“c”), which is “a/c”.

Similarly, the “odds” of exposure for controls is the proportion that were controls and exposed (“b”) divided by the proportion that were controls and not exposed (“d”), which is “b/d”.

The odds ratio is the ratio of “a/c” divided by “b/d” ($a/c / b/d = ad/bc$). For example, if we had equal proportions of case and controls, and if about two thirds cases were exposed, but only half of controls were exposed, then the values of a, b, c, and d might be 0.34, 0.16, 0.25, and 0.25 respectively. Then the odds of exposure for cases is $(.34/.16)=2.125$. One can think of odds in the following way. Suppose you had 34 red marbles and 16 blue marbles in a jar. If you mixed them up and closed your eyes and reached into the jar and picked out one, you would have 34 chances of picking red, 16 chances of picking blue. The odds of picking red are $34/16=2.125$ (or 2.125 to 1). In this example the odds of exposure for controls is $(.5/.5)=1$. The odds ratio is $(.34/.16)/(.5/.5) = 2.125$. If you had two jars, and in jar 1 there were 34 red and 16 blue marbles, and in jar 2 there were 50 red and 50 blue marbles, you know that if you reached into jar 1 your chances of grabbing a red marble would be 2.125 times greater than if you reached into jar 2. In terms of exposure, in this example, the odds of exposure is 2.125 times greater for cases than controls.

Perhaps more importantly, one can also use the same data to estimate odds of disease given exposure, the odds of disease given no exposure, and the ratio of those odds. As will be shown, that odds ratio is exactly the same as that described above.

The estimated odds of disease given exposure is calculated as “a/b”, the odds of disease given no exposure is “c/d” and the odds ratio is $a/b / c/d = ad/bc$, which is the same as above. Thus, in this example, the odds of disease is a little over two times as great if exposed than if unexposed. The odds ratio is a measure of the magnitude of the exposure effect.

³² The concepts discussed here work equally well if the cell entries are counts.

Another measure of the magnitude of an exposure effect is the relative risk. Suppose we had a study design wherein we drew samples of exposed and unexposed, then waited for a period of time to see who developed and did not develop disease. We could produce a 2x2 table like the following:

		Disease		
		Yes	No	
Exposure	Yes	p1	p2	p1+p2
	No	p3	p4	p3+p4
				$p1+p2+p3+p4=1$

Where p1 is the proportion that was exposed and got the disease, and p2 is the proportion that was exposed and did not get the disease.

In this design, the risk of disease given exposure (i.e., the incidence of disease among exposed) can be estimated as $p1 / (p1+p2)$, i.e., the proportion of exposed that got the disease. The risk of disease given no exposure is estimated as $p3 / (p3+p4)$, and the relative risk is $[p1 / (p1+p2)] / [p3 / (p3+p4)]$. Note that in a case-control study one cannot directly estimate the risk of disease because the sample is selected by choosing a fixed number of cases and controls, and it is therefore not possible to estimate disease incidence.

When the disease is rare, so that the risk for both exposed and non-exposed is small in absolute terms, then the odds ratio will be an approximation of the relative risk, where relative risk is the ratio of the risk of disease if exposed to the risk of disease if not exposed (Mausner and Kramer, 1985). That is because, if the disease is rare, then p1 is very small relative to p2, and $p1 / (p1+p2)$ is approximately equal to $p1 / p2$. Likewise, if the disease is rare, then p3 is very small relative to p4, and $p3 / (p3+p4)$ becomes approximately equal to $p3 / p4$. Then, the relative risk is approximately equal to $[p1 / p2] / [p3 / p4]$, which can be rewritten as $p1p4 / p2p3$, which is the same as the odds ratio formula (ad/bc), shown above.

Since the autism outcomes in the current study are rare, relative to the size of the populations without those outcomes, the odds ratios reported in the current study can be thought of as good approximations of the relative risk, and we will often refer to odds ratios that are significantly different than one as being indicators of increased or decreased risk associated with increased exposure.

We can obtain the same type of odds ratio estimates from a conditional logistic regression model where the inferences about the difference in risk due to exposure are made after controlling for potential confounders. Taking the exponent of the exposure parameter estimate gives the odds ratio for a one unit change in exposure. If the exposure is dichotomous, coded as 1 if exposed, and 0 if unexposed, then odds ratio is an estimate of the difference in risk associated with a one unit difference in exposure, where the one-unit difference in exposure represents the difference from unexposed to exposed. In the

previous example, we would say that the one unit difference from unexposed to exposed is associated with an odds ratio of 2.125, or a little over a doubling of the risk.

8.3.2. Odds Ratio in Case-Control Studies when Exposure is Continuous

When the exposure variable is measured on a continuous scale, as are the exposure measures in the current study (e.g., *PreNatThimer*, *Exp01mos*, *Exp07mos*, *Exp17mos*, and *Exp020mos*), taking the exponent of the parameter estimate from the conditional logistic regression model is interpreted as the odds ratio for a one unit change in exposure, which is the same interpretation as discussed in the previous section. However, in the discussion in the previous section, a one unit change in exposure corresponded to the difference between exposed and unexposed. For *PreNatThimer* a one unit difference in exposure corresponds to a difference of one microgram of prenatal ethylmercury exposure from vaccines or immune globulins. Since the difference between getting and not getting a prenatal Rhogam injection corresponds to a difference of 12.75 micrograms of exposure, the odds ratio corresponding to a one microgram difference is not particularly meaningful. Similarly, it is not intuitively obvious what a one unit difference means for the measures of postnatal exposure. For a child weighing 12.5 kilograms at the time of receipt of a vaccine containing 12.5 micrograms of ethylmercury, than a one unit difference would correspond to the difference between receipt and no receipt of the vaccine. Since children's weights at time of vaccine receipt varied, as did the amount of vaccine contained within a single dose, the one unit difference metric for the odds ratios is not ideal.

In order to display effect sizes (the odds ratios) in a metric that would have more intuitive meaning, we present them in terms of what could be thought of as the difference in risk associated with a difference in exposure that roughly corresponds to the difference between low exposure and high exposure. One way to think about low and high exposure is to consider the exposure distribution in the sample. One could imagine defining low exposure as the exposure amount at the 10th or 25th percentiles of the distribution. At the 10th percentile, only 10 percent of sample members have that exposure amount or lower. At the 25th percentile, only 25 percent of sample members have that exposure amount or lower. We would call those low exposure amounts because relatively few sample members have exposure levels that low or lower. Similarly, we could imagine defining higher exposure as amounts corresponding to the 75th or 95th percentiles.

Another way to define the difference between low and high exposure would be to present the differences in terms of differences in standard deviation units of the exposure measures. One could think of the difference in risk associated with a difference of say, one, or two standard deviation units of exposure as corresponding to the difference between low and high exposure.

Exhibit 8.3 shows various descriptive statistics including means, minimums, maximums, standard deviations and percentiles for each of the exposure measures for the largest analysis data set (the ASD vs matched controls data set, n=1,008). On the far right-hand side of the table, the column labeled “75th -25th” shows the difference between the 75th

and 25th percentiles. The column labeled “2xSD” shows the standard deviation multiplied by two. And the column labeled “90th – 10th” shows the difference between the 90th and 10th percentiles. For most of the measures, the values in “2xSD” fell somewhere between the differences in the columns labeled “75th -25th” and “90th – 10th”. For two of the measures (*PreNatThimer*, and *Amt01mos*) the value in “2xSD” was greater than the value in “90th – 10th”, but was still well below the difference between the minimum and maximum values. Based on the results shown in this table, we reasoned that a two standard deviation difference in each exposure measure represented a good, “rough proxy” for the difference between low and high exposure.

Therefore, in summary tables of model results shown later in this document, we show the odds ratio corresponding to a two standard deviation difference in the exposure measure. We interpret these results as the estimated difference in risk of the autism outcome corresponding to the difference between low and high exposure. The estimates were calculated as in the following example. Suppose that $\hat{\beta}_1$ was the parameter estimate corresponding to the *PreNatThimer* exposure effect from a conditional logistic regression model. Then the odds ratio corresponding to a two-standard deviation difference on the exposure measure (i.e., the difference roughly corresponding to the difference between low and high exposure) would be calculated as $\exp(\hat{\beta}_1 * 16.34)$.

8.3.3. Inverse Odds Ratio (1/OR)

Finally, when the estimated odds ratio is less than one, the summary tables also show the inverse of the odd ratio (1 / OR). These are shown because, with odds ratios, it is not always obvious how odds ratios that are less one correspond in magnitude to odds ratios that are greater than one. For example, an OR of 0.66 indicates an effect of the same magnitude as an OR of 1.5. For a dichotomous exposure, the OR of 1.5 means disease risk is 1.5 times higher in exposed than unexposed. The OR of 0.66 can be expressed as 1/OR = 1.5, which means that disease risk is 1.5 times higher in the *unexposed* than the exposed.

For our study with continuous measures of exposure, a value of 1/OR that is greater than one represents the magnitude of increased autism risk associated with having *lower exposure*, relative to higher exposure.

**Exhibit 8.3 Exposure Variable Descriptives –
Two Times the Standard Deviation Roughly Corresponds to the Difference Between High and Low Exposure**

Variable	Label	N	Mean	Std Dev	Min	10th Pctl	25th Pctl	75th Pctl	90th Pctl	Max	75-25th	2XSD	90-10th
PreNatThimer	PreNat Exp Amt	1008	2.44	8.17	0	0	0	0	12.75	100	0	16.34	12.75
Exp01mos	Amt/Wt(KGs) birth-28 days	1008	2.66	2.04	0	0	0	3.76	4.38	21.04	3.76	4.08	4.38
Exp07mos	Amt/Wt(KGs) birth-214 days	1008	17.41	7.78	0	7.42	14.13	20.48	26.58	66.94	6.35	15.56	19.16
Exp17mos	Amt/Wt(KGs) 29-214 days	1008	14.75	7.27	0	5.15	12.16	17.3	23.18	66.94	5.14	14.54	18.03
Exp020mos	Amt/Wt(KGs) birth-609 days	1008	20.69	8.91	0	8.98	17.56	24.24	31.3	76.74	6.68	17.82	22.32
Amt01mos	Amt Merc birth-28 days	1008	9	6.43	0	0	0	12.5	12.5	50	12.5	12.86	12.5
Amt07mos	Amt Merc birth-214 days	1008	102.93	42.22	0	37.5	87.5	112.5	174.43	190.83	25	84.44	136.93
Amt17mos	Amt Merc 29-214 days	1008	93.93	40.95	0	25	75	100	161.93	187.5	25	81.9	136.93
Amt020mos	Amt Merc birth-609 days	1008	136.13	54.79	0	50	112.5	162.5	212.5	300	50	109.58	162.5

Note: the variables below are measures of exposure concurrent with or not concurrent with receipt of antibiotics. See Section 9.4.5 for details.

AbExp01mos	Concur Amt/Wt(KGs) birth-28 days	1008	0.26	1.01	0	0	0	0	0	6.71	0	2.03	0
AbExp17mos	Concur Amt/Wt(KGs) birth-214 days	1008	0.97	3.1	0	0	0	0	4.21	54.85	0	6.21	4.21
AbExp07mos	Concur Amt/Wt(KGs) 29-214 days	1008	1.22	3.28	0	0	0	0	4.69	54.85	0	6.55	4.69
AbExp020mos	Concur Amt/Wt(KGs) birth-609 days	1008	1.74	3.65	0	0	0	2.57	6.12	54.85	2.57	7.3	6.12
ncAbExp01mos	NonConcur Amt/Wt(KGs) birth-28 days	1008	2.41	2.09	0	0	0	3.7	4.28	21.04	3.7	4.18	4.28
ncAbExp17mos	NonConcur Amt/Wt(KGs) birth-214 days	1008	13.78	6.97	0	4.39	10.31	16.62	21.3	65.17	6.32	13.93	16.91
ncAbExp07mos	NonConcur Amt/Wt(KGs) 29-214 days	1008	16.18	7.49	0	6.35	12.56	19.78	24.92	65.17	7.21	14.98	18.57
ncAbExp020mos	NonConcur Amt/Wt(KGs) birth-609 days	1008	18.94	8.58	0	7.17	14.97	22.74	28.55	70.3	7.78	17.16	21.38

9. Results

9.1. Descriptive Statistics: Demographics and Exposures

Exhibit 9.1.1 shows descriptive statistics that help characterize the sample of study participants. Additional descriptive information on study participants is available in the summary tables in Section 9.2.

Exhibit 9.1.1. Descriptive Statistics About Study Participants				
		ASD (n=256)	Control (n=752)	Total (n=1,008)
		%	%	%
HMO	HMO-A	4	4	4
	HMO-B	43	46	46
	HMO-C	<u>54</u>	<u>49</u>	<u>50</u>
		100	100	100
Child's Year of Birth	1994	14	16	15
	1995	15	15	15
	1996	16	18	18
	1997	21	19	20
	1998	19	17	18
	1999	<u>14</u>	<u>14</u>	<u>14</u>
		100	100	100
Child's Age at Time of Assessment (in Years) ^a	6	10	5	7
	7	21	18	18
	8	17	18	18
	9	21	19	20
	10	14	17	16
	11	14	17	16
	12	2	5	5
	13	<u>0.4</u>	<u>0.3</u>	<u>0.3</u>
		100	100	100
Sex	Female	13	15	15
	Male	<u>87</u>	<u>85</u>	<u>85</u>
		100	100	100
Birth Weight (Kilograms)	< 1.0	2	0.3	1
	1.0 - 1.499	0.4	1	1
	1.5 - 2.499	7	5	6
	2.5 - 3.99	76	79	78
	> 4.0	<u>16</u>	<u>15</u>	<u>15</u>
		100	100	100
Biological Mother's Age	<20	2	1	1

Exhibit 9.1.1. Descriptive Statistics About Study Participants

		ASD (n=256)	Control (n=752)	Total (n=1,008)
		%	%	%
At Birth of Child	20-24	5	9	8
	25-29	23	23	23
	30-34	36	36	36
	35 +	<u>35</u>	<u>30</u>	<u>31</u>
		100	100	100
Biological Father's Age At Birth of Child	<20	1	1	1
	20-29	20	24	23
	30-39	60	56	57
	40-49	17	17	17
	49 +	<u>2</u>	<u>2</u>	<u>2</u>
	100	100	100	
Mother's Education Level	No Diploma	3	3	3
	H.S. Grad	15	15	15
	Some Coll.	19	22	21
	College Grad.	<u>63</u>	<u>60</u>	<u>61</u>
		100	100	100
Single Parent	No	82	85	84
	Yes	<u>18</u>	<u>15</u>	<u>16</u>
		100	100	100

^a Recruitment of controls lagged behind cases so that controls could be recruited to match cases that had agreed to participate within birth year, sex, and MCO matching strata. The lagged recruitment meant that controls were an average of 3 months older than cases at the time of interview / assessment. Note: Percentages of cases and controls were not exactly identical on matching variables (birth year, sex, MCO) because we did not always get exactly three matched controls per case within each matching stratum.

Exhibits 9.1.2 – 9.1.5 display descriptive statistics on exposure measures. Additional descriptive information on exposure amounts can be found in Exhibit 8.3, and in the exhibits in Section 9.3.

Exhibit 9.1.2 shows the most commonly occurring patterns of vaccine receipt and mercury exposure amounts for the age range spanning birth to seven months, for participants at each of the three HMOs.

Exhibit 9.1.3 shows the correlation among the exposure variables. It shows that prenatal exposure has weak, positive correlations with postnatal exposure measures. This indicates that on average, children that were exposed prenatally were likely to have slightly higher postnatal exposure. But the correlation coefficients were quite small, indicating that prenatal exposure is a poor predictor of postnatal exposure.

The exhibit also indicates that exposure in the first month (*Exp01mos*) only has a weak, but positive, correlation with cumulative exposure in the the age range from 1 to 7 months ($\rho = 0.12$). Thus, when we fit models that include terms for *PreNatThimer*, *Exp01mos*, and *Exp17mos*, we need not be concerned that the terms are highly correlated.

Additionally, the postnatal exposure measures defined as mercury amount divided by weight at the time of vaccine receipt (i.e., the measures with the prefix “*Exp*”) were highly correlated with exposure measures that did not divide by weight at the time of exposure (i.e., the measures with the prefix “*Amt*”). This indicates that the former measures are determined more by thimerosal amount than by child’s weight. This also suggests that would expect similar results from models that use the “*Amt*” variables in place of the “*Exp*” variables.

A scatter plot of exposure amount versus number of HepB, DTP, and Hib vaccines received is shown in Exhibit 9.1.4. This plot shows that variation among children in exposure amounts was due to variation in mercury content of vaccine and immune globulin products (e.g., Hib vaccines in use at the time contained 0, 12.5, or 25 micrograms of ethylmercury), use of combined versus separate vaccines (e.g., separate receipts of DTP and Hib vaccines could result in twice the mercury exposure as receipt of a combined DTP-Hib vaccine) and due to variation in the number of vaccines received. For example, among children that received a total of eight HepB, DTP, and Hib vaccines in the age range from birth to seven months, exposure amount varied from zero to 190.83 micrograms of mercury.

Exhibit 9.1.2.
Pattern of Receipts of Thimerosal-containing Vaccines Resulting in
Maximum Cumulative Exposure Birth to 7 Months
and
Modal Patterns of Receipts at Each HMO

<u>Age</u>	<u>Vaccine</u>	<u>Typical Pattern Resulting in Maximum Cumulative Exposure^a</u>	<u>Modal Patterns at each HMO</u>		
			<u>HMO-A</u>	<u>HMO-B</u>	<u>HMO-C</u>
Birth (1-28 days)	HepB	12.5	12.5	.	12.5
1-2 months	HepB		12.5	.	
3-4 months	HepB	12.5	.	12.5	12.5
5-7 months	HepB	12.5	.	12.5	12.5
2 months	DTaP	25	25	.	25
2 months	Hib	25	25	.	0
2 months	DTaP-Hib	.	.	25	.
4 months	DTaP	25	25	.	25
4 months	Hib	25	25	.	0
4 months	DTaP-Hib	.	.	25	.
6 months	DTaP	25	25	.	25
6 months	Hib	25	25	.	.
6 months	DTaP-Hib	.	.	25	.
Cumulative Exposure Birth to 7 months:		187.5	175	100	112.5

^a Ball et al (2001) estimated that a thimerosal-containing influenza vaccine that would have been recommended for children in selected populations could have been added to the maximum pattern shown above, resulting in 200 micrograms of cumulative exposure. It is also conceptually possible for a child to have received more than 187.5 micrograms of cumulative exposure in the first seven months if the child had received a hepatitis B immune globulin, in addition to all the vaccines depicted in the maximum pattern. That scenario, however, did not occur in the sample of children analyzed in the current study. One child's cumulative exposure exceeded 187.5 because (s)he had a pattern of receipts similar to that shown above, except that (s)he did not receive a third HepB in the 5-7 months age range, but (s)he did receive a rabies shot that contained 20 micrograms of ethylmercury within the first seven months. The mercury amounts assigned to her/his DTaP receipts were not the typical 25 microgram amounts but were instead 24.27, 23.28, and 23.28, respectively. Thus her/his total exposure amount was 195.83. For additional information on the mercury amounts contained in each vaccine received, see Chapter 7.

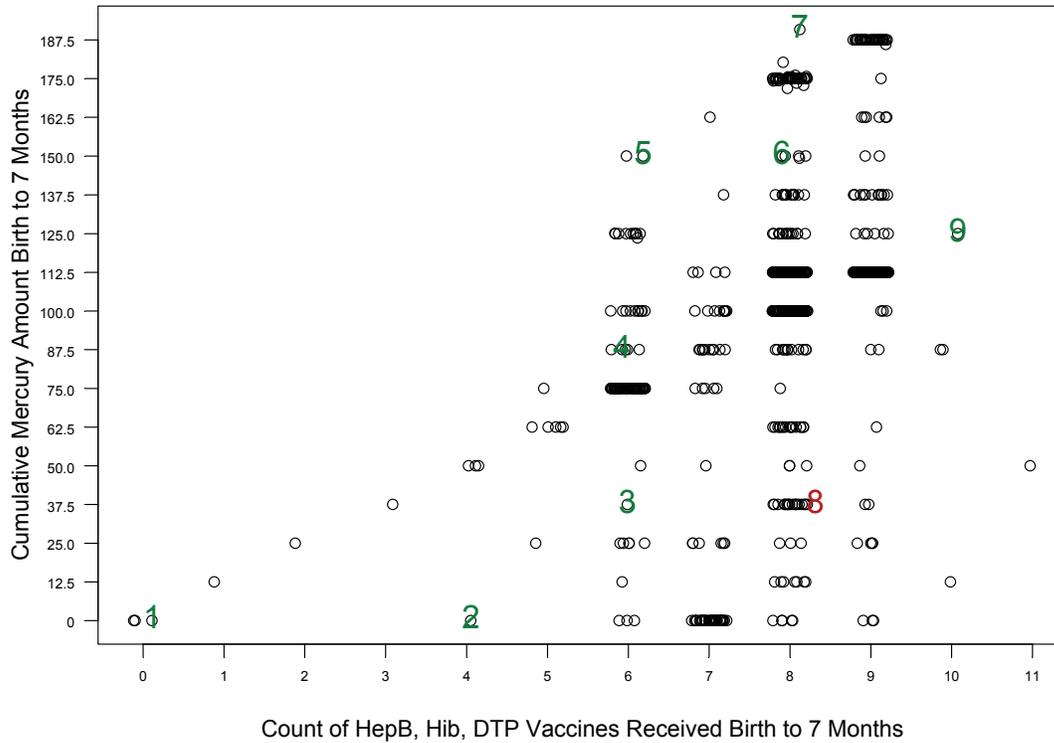
Exhibit 9.1.3. Pearson Correlation Coefficients for Correlations Among Exposure Variables

Variable	Label	PreNat Thimer	Exp01 mos	Exp17 mos	Exp07 mos	Exp020 mos	Amt01 mos	Amt 17mos	Amt 07mos
PreNatThimer	PreNat Exp Amt	1							
Exp01mos	Amt/Wt(KGs) birth-28 days	0.03	1						
Exp17mos	Amt/Wt(KGs) 29-214 days	0.10	0.12	1					
Exp07mos	Amt/Wt(KGs) birth-214 days	0.11	0.37	0.97	1				
Exp020mos	Amt/Wt(KGs) birth-609 days	0.10	0.32	0.94	0.96	1			
Amt01mos	Amt Merc birth-28 days	0.04	0.95	0.07	0.32	0.26	1		
Amt17mos	Amt Merc 29-214 days	0.11	0.12	0.90	0.87	0.84	0.12	1	
Amt07mos	Amt Merc birth-214 days	0.12	0.26	0.88	0.89	0.86	0.27	0.99	1
Amt020mos	Amt Merc birth-609 days	0.10	0.18	0.82	0.81	0.89	0.18	0.90	0.90

For information on the definition of each exposure variable, see Chapter 7.

All Pearson correlation coefficients shown that are 0.10 or greater were statistically significantly different than zero ($p < 0.05$).

Exhibit 9.1.4. Variation in Cumulative Mercury Amount for Age Range Birth to 7 Months



Each circle in the plot shows the amount of mercury received by a child in the age range birth to seven months, and the number of HepB, Hib, and DTP vaccines received by the child. Examples indicated by numbers are described below.

x-axis shows count of HepB, Hib, and DTP vaccines received birth to seven months – Included in the count of number of HepBs received are all receipts of HepB, HepB-Hib, and DTaP-HepB; Included in count of number of Hibs received are all receipts of DTP-Hib, Hib, and HepB-Hib; Included in count of number of DTPs received are all receipts DT TD, DTP, DTP-Hib, DTaP, and DTaP-HepB. Plotted points are jittered along the x-axis to make more points will be visible.

y-axis shows cumulative mercury amount from all thimerosal-containing vaccines and immune globulins received during the age range from birth to seven months.

Example 1. Child had zero micrograms of mercury exposure – (s)he received no vaccines birth to seven months.

Example 2. Child received: 2 DTaPs and 2 Hibs birth to seven months, each contained 0 micrograms of mercury.

Example 3. Child received: 2 DTaPs with 0 micrograms of mercury; 1 Hib with 25 micrograms of mercury; 1 Hib with 0 micrograms of mercury; 1 HepB w/ 12.5 micrograms of mercury; 1 HepB w/ 0 micrograms of mercury.

Example 4. Child received: 2 HepBs each with 12.5 micrograms of mercury; 1 DTP-Hib with 25 micrograms of mercury; 1 DT TD with 25 micrograms of mercury; 1 Hib with 12.5 micrograms of mercury.

Example 5. Child received: 3 DTaPs each with 25 micrograms of mercury; 3 Hibs each with 25 micrograms of mercury.

Example 6. Child received: 1 DTP-Hib with 25 micrograms of mercury; 2 HepBs each with 12.5 micrograms of mercury; 2 DT TDs each with 25 micrograms of mercury; 2 Hibs each with 25 micrograms of mercury.

Example 7. Child received: 2 HepBs each with 12.5 micrograms of mercury; 3 DTPs containing 24.3, 23.3, and 23.3 micrograms of mercury; 3 Hibs each with 25 micrograms of mercury; 1 rabies with 20 micrograms of mercury.

Example 8. Child received: 3 HepBs each with 12.5 micrograms of mercury; 4 DTaPs each containing 0 micrograms of mercury; 3 Hibs each with 0 micrograms of mercury.

Example 9. Child received: 4 HepBs each with 12.5 micrograms of mercury; 3 DTPs each containing 25 micrograms of mercury; 3 Hibs each with 0 micrograms of mercury.

9.2. Descriptive Statistics from Clinical Assessment of Cases

Section 7.1 describes the clinical assessment procedure and decision rules that were used for classifying cases. For the 256 cases that completed clinical assessments, Exhibit 9.2.1 shows results of each type of assessment (ADI-R, ADOS, cognitive function, and regression assessment) by outcome classification (AD, non-ASD, and below criteria) and by HMO. Across all three HMOs, the mean reciprocal social interaction and verbal communication scores were higher (greater impairments or abnormalities) for AD cases than non-AD ASD cases, which were in turn higher than mean scores of the children that were below criteria for ASD. As was indicated previously in Exhibit 7.1.6, AD cases were more likely to have a non-verbal communication score than non-AD ASD cases or the below criterion individuals. The means of the patterns of behavior and abnormality of development scores did not follow the same descending pattern across the AD, non-AD ASD, and below-criteria groups.

The pattern of descending means across groups held for all three HMOs for the ADOS communication, reciprocal social interaction, and total scores. At all three HMOs, Ravens scores (cognitive function) were lower for AD than non-AD ASD cases, and the former were more likely to have taken the Mullen's test, which was required when cognitive function levels were lower. Greater numbers of AD than non-AD ASD cases or below criteria individuals met criteria for regression.

Exhibit 9.2.1. Descriptive Statistics from ADI-R, ADOS, Cognitive Functioning, and Regression Assessments													
Assessment Type	AD			Non-AD ASD ^a			Below Criteria ^b			All (ASD) ^c			
	HMO-A	HMO-B	HMO-C	HMO-A	HMO-B	HMO-C	HMO-A	HMO-B	HMO-C	HMO-A	HMO-B	HMO-C	
Number Clinically Assessed													
N (Number Assessed)	7	83	97	2	27	40	1	23	41	9	110	137	
ADI-R													
Mean: Reciprocal Social Interaction	24.71	23.05	22.75	16.50	21.33	20.03	16.00	11.17	15.02	22.89	22.63	21.96	
Mean: Verbal Communication	15.25	17.49	17.47	13.00	15.42	15.53	10.00	10.26	13.66	14.50	16.94	16.86	
Mean: Non-verbal Communication	12.33	13.09	13.33		12.00					12.33	13.00	13.33	
Mean: Patterns of Behavior	6.43	6.93	6.37	8.50	5.22	4.85	12.00	4.09	5.12	6.89	6.51	5.93	
Mean: Abnormality of Development	3.86	4.12	3.84	2.00	3.48	3.95	5.00	2.70	2.80	3.44	3.96	3.87	
ADOS													
Number Using Module 1	5	17	14	0	2	0	0	0	0	5	19	14	
Number Using Module 2	1	11	14	0	3	1	0	0	1	1	14	15	
Number Using Module 3	1	55	69	2	22	39	1	23	40	3	77	108	
Number Total	7	83	97	2	27	40	1	23	41	9	110	137	
Mean: Communication	5.14	5.45	5.59	3.50	3.11	3.05	2.00	2.09	1.61	4.78	4.87	2.22	
Mean: Reciprocal Social Interaction	10.86	10.96	10.39	5.00	7.48	6.78	2.00	6.26	4.44	9.56	10.11	3.12	
Mean: Total (Comm. + Recip)	16.00	16.43	15.98	8.50	10.59	9.85	4.00	8.35	6.07	14.33	15.00	4.56	
Cognitive Function													
Number Using Ravens	6	71	88	2	26	40	1	23	41	8	97	128	
Number Using Mullen	1	11	9	0	0	0	0	0	0	1	11	9	
Number Unable to Test	0	1	0	0	1	0	0	0	0	0	2	0	
Number Tested + Untested Total	7	83	97	2	27	40	1	23	41	9	110	137	
Mean: Ravens Score	70.33	102.25	100.00	107.00	104.08	107.68	18.00	110.13	107.15	79.50	102.74	102.40	
Mean: Mullen Score	16.52	28.29	27.40	0	0	0	0	0	0	16.52	28.29	27.40	
Number w/ Low Cognitive Function	2	11	9	0	1	0	1	0	0	2	12	9	
Regression													
Number w/ Regression	4	17	22	0	4	2	0	2	5	4	21	24	

^a These are cases that met study criteria for classification as ASD but did not meet criteria for classification as AD.

^b These are individuals that did not meet study criteria for classification as ASD.

^c These are cases that met study criteria for classification as AD or ASD (includes the AD and the non-AD ASD groups).

9.3. Bivariate Relationships

9.3.1. Bivariate Relationships of Covariates to Case-Control Outcomes

Exhibit 9.3.1 summarizes bivariate relationships between the ASD outcome measures and each of the many measures that were tested for inclusion in the analysis models as covariates. For example, the first row of the table shows that for the overall combined sample of ASD cases and controls, the mothers' mean age in years at the time of the birth of the focus child was 31.7 years, with the minimum and maximum ages ranging from 15 to 46 years. The mean, minimum and maximum ages of mothers were very similar in both the ASD and control groups. A test of the null hypothesis of equivalence of mothers' ages between ASD and control groups was conducted using SAS Proc PHReg to fit a conditional logistic regression model of the form:

$$\log\left(\frac{\pi}{1-\pi}\right) = \alpha_j + \beta_1(MomAgeBirth)$$

where the left-hand side of the equation shows the logistic link for the probability of the outcome classification ASD, α_j represents indicators for the matching strata (cases were frequency matched to controls within birth-year, sex, and HMO strata), and $MomAgeBirth$ is the mother's age at the time of birth of the focus child, measured in years. We refer to this as a bivariate relationship to distinguish these results from the results of multivariable models, described subsequently, and to draw attention to the fact that, other than the matching strata, the only independent variable on the right hand side of the model is the measure of the mother age. In other words, this model results in a test of the equivalence of the mean of mothers ages in the ASD and control groups, in a model that does not control for any other factors (except for the matching strata). In Exhibit 9.3.1, the column labeled "Est." is the parameter estimate from the model $\hat{\beta}_1$, the column labeled "S.E." is the standard error of $\hat{\beta}_1$, and the chi-square value and p-value correspond to a two-sided test of the form: $H_0 : \beta_1 = 0$ vs $H_a : \beta_1 \neq 0$. Note that this is a one degree of freedom test. The column labeled "O.R." gives the odds ratio for ASD associated with a one unit (in this case one year) increase in the independent variable.

In the case of the measure of the mother's age at the time of birth of the focus child, the previous example used a continuous measure of mother's age that was coded in years. Rows 2-7 of the exhibit correspond to a categorical coding of mother's age into five discrete age categories. The categorical coding of age, as shown in rows 2-7, correspond to the specification in the study's analysis plan as to how age was to be coded. The first row in this section shows the p-value (0.2334) corresponding to a four degree of freedom test of the null hypothesis that the age distribution (i.e., the proportion of mothers in each of the five age categories) is equivalent for ASD and control group mothers. While it

may be somewhat redundant to show results for both continuous and categorical versions of the mother's age variable, we thought that for descriptive purposes, both forms would be useful. Other variables in the table that have both continuous and categorical versions are measures of father's age at birth of child, and birth weight.

The model for the relationship of the categorical version of mother's age to the ASD outcome was of the form:

$$\log\left(\frac{\pi}{1-\pi}\right) = \alpha_j + \beta_1(Mom20_24) + \beta_2(Mom25_29) + \beta_3(Mom30_34) + \beta_4(MomGE35)$$

where the age category corresponding to ages less than 20 years are omitted, and therefore comprises the baseline comparison category. Thus, $\hat{\beta}_1$ gives the estimated difference in the log odds of ASD for children with 20 to 24 year-old mothers, relative to children with mothers that were under 20 years at the time of their birth.

The relationships of the ASD outcome to the remaining variables in the exhibit were examined in the same manner as described above. Noteworthy relationships were:

- **Birth order** was marginally related to the ASD outcome (p=0.0593). ASD children were more likely to be first or second born, and less likely to be third born or higher than their matched control counterparts.
- **Household income level** relative to family size, (expressed as a percent of poverty line) was higher for controls than for ASD cases.
- **Inadequacy of prenatal care** (as measured using the Kotelchuck index) was marginally related to the ASD outcome (p=0.066). A higher proportion of ASD mothers had late prenatal care than control mothers.
- A higher proportion of ASD mothers had had their **cholesterol checked** within three years of the assessment/interview, and higher proportions of control mothers had never had their cholesterol checked or had had their cholesterol checked more than three years prior to the assessment/interview.
- **Use of prenatal vitamins containing folic acid** was associated with a higher odds ratio of ASD.
- **Child lead exposure and child pica** were associated with higher odds ratios for ASD. There was a high degree of overlap between child lead exposure and child pica - almost all children that had high lead exposure had pica, and vice versa.

The high degree of overlap between the pica and child lead measures was due in large part to the definition of the child lead exposure variable, where having pica and living in a home where lead was likely to be present was a criterion that resulted in a positive score on the child lead variable.

The finding that a greater proportion of ASD than control children had a positive value on the child lead exposure measure generated the question of whether the difference was due to more children with ASD diagnoses being tested, or among those tested, whether more ASD children had a positive test result, or whether more ASD children had pica and

lived in a home where lead was present. The table below was created to provide an answer to the question. It shows the four ways that a child could receive a positive value on the child lead exposure variable and the frequency and percent of ASD case and control children that had positive values on the measure. It shows that the primary reason for the difference was that a greater proportion of ASD children had pica and lived in a home that was likely to have had lead present. Few children, cases or controls, had elevated lead test levels before age three or lived in a home where the water was known to have high lead content.

Reason that "ChildLead" variable had the value "1"				Controls		ASD Cases	
				Freq.	Percent (out of n=752)	Freq.	Percent (out of n=256)
Lead poisoning before age three indicated in chart;	Parent said child had an elevated lead test level before age 3	Child lived in home where water was tested and found to have high lead content;	Child had pica and child lived in a pre-1950 home; ==or == Child had pica and child lived in a pre-1978 home that underwent painting or renovation == or == Child had pica and parent said paint or floor varnish was tested and had high lead content;				
		X	X	1	0.1%		0.0%
			X	16	2.1	19	7.4
			X	X	0.0	1	0.4
X	X X			1	0.1	1	0.4
					0.0	1	0.4
			Total	18	2.4	22	8.6

Exhibit 9.3.1. Bivariate Relationships Of Covariates to ASD Outcome

Variable	Label	Overall (n=1008)			ASD (n=256)			Control (n=752)			Estimates from PH Model				O.R.	
		Mean	Min	Max	Mean	Min	Max	Mean	Min	Max	df	Est.	S.E.	ChiSq		P-Val
MomAgeBirth	Mom age at child Birth (Years)	31.74	15	46	32.14	15	46	31.61	15	45	1	0.0204	0.0137	2.2140	0.1368	1.02
Mom Age	Categories	4	.	.	5.5729	0.2334	.
MomL120	Mom Age at child birth < 20	0.01	0	1	0.02	0	1	0.01	0	1
Mom20_24	Mom Age at child birth 20 - 24	0.08	0	1	0.05	0	1	0.09	0	1	1	-0.6762	0.6635	1.0388	0.3081	0.509
Mom25_29	Mom Age at child birth 25 - 29	0.23	0	1	0.23	0	1	0.23	0	1	1	-0.0713	0.6109	0.1136	0.9070	0.9310
Mom30_34	Mom Age at child birth 30 - 34	0.36	0	1	0.36	0	1	0.36	0	1	1	-0.0264	0.6069	0.0019	0.9654	0.9740
MomGE35	Mom Age at child birth >= 35	0.31	0	1	0.35	0	1	0.30	0	1	1	0.0962	0.6054	0.0253	0.8737	1.1010
Birth Order	Categories	2	.	.	5.6500	0.0593~	.
BirthOrder1_1	=1 if 1st born	0.42	0	1	0.45	0	1	0.42	0	1	1	0.4701	0.2097	5.0243	0.0250*	1.6000
BirthOrder2_1	=1 if 2nd born	0.37	0	1	0.40	0	1	0.36	0	1	1	0.4576	0.2134	4.5994	0.0320*	1.5800
BirthOrderGE3_1	=1 if 3rd born or higher	0.20	0	1	0.15	0	1	0.22	0	1
Multiple	=1 if twin or triplet	0.05	0	1	0.06	0	1	0.05	0	1	1	0.3246	0.3126	1.0783	0.2991	1.3830
Breast Feeding	Categories	2	.	.	1.1578	0.5605	.
BFNone	=1 if Breastfed 0 months	0.23	0	1	0.25	0	1	0.22	0	1
BF1_6mos	=1 if Breastfed 1-5.99 months	0.36	0	1	0.35	0	1	0.36	0	1	1	-0.1734	0.1920	0.8152	0.3666	0.8410
BFgt6mos	=1 if Breastfed 6+ months	0.41	0	1	0.39	0	1	0.42	0	1	1	-0.1912	0.1883	1.0311	0.3099	0.8260
PovertyRatio1		4.68	0.185	20	4.19	0.65	18.46	4.85	0.185	20	1	-0.0796	0.0272	8.5449	0.0035*	0.9240
Education	Categories	2	.	.	1.1543	0.5615	.
MomEduc_HS	=1 if Mom HS Grad	0.15	0	1	0.15	0	1	0.15	0	1	1	-0.0110	0.2071	0.0028	0.9575	0.9890
MomEduc_Some	=1 if Mom Some Coll	0.21	0	1	0.19	0	1	0.22	0	1	1	-0.1987	0.1875	1.1231	0.2892	0.8200
MomEduc_Coll	=1 if Mom Coll Grad	0.61	0	1	0.63	0	1	0.60	0	1
SingleParent	Child lives in a single parent household	0.16	0	1	0.18	0	1	0.15	0	1	1	0.1712	0.1933	0.7851	0.3756	1.1870
BioDadYearsImpVal1	Dad age in years	34.24	17	62	34.83	17	62	34.04	17	61	1	0.0175	0.0111	2.4840	0.1150	1.0180
Dad Age Categories	Categories	4	.	.	2.9322	0.5692	.
Dadlt20_i1	Dad <20 years old	0.01	0	1	0.01	0	1	0.01	0	1
Dad20_29_i1	Dad 20-29 years old	0.23	0	1	0.2	0	1	0.24	0	1	1	0.0083	0.8225	0.0001	0.9920	1.0080
Dad30_39_i1	Dad 30-39 years old	0.57	0	1	0.6	0	1	0.56	0	1	1	0.2905	0.8166	0.1265	0.7221	1.3370

Exhibit 9.3.1. Bivariate Relationships Of Covariates to ASD Outcome

Variable	Label	Overall (n=1008)		ASD (n=256)		Control (n=752)		Estimates from PH Model					O.R.
		Mean	Min Max	Mean	Min Max	Mean	Min Max	df	Est.	S.E.	ChiSq	P-Val	
Dad40_49_i1	Dad 40-49 years old	0.17	0 1	0.17	0 1	0.17	0 1	1	0.1883	0.8277	0.0518	0.8200	1.2070
DadGE49_i1	Dad >49 years old	0.02	0 1	0.02	0 1	0.02	0 1	1	0.6040	0.9591	0.3966	0.5288	1.8290
HC_InitInad_1	1= if Kotel Init PNC =INADEQ	0.03	0 1	0.05	0 1	0.02	0 1	1	0.6988	0.3805	3.3739	0.0662~	2.0110
HC_Cholesterol	Last Cholesterol Check	2	.	.	6.6827	0.0354*	.
HC_Cholest_0	0=never	0.16	0 1	0.13	0 1	0.17	0 1
HC_Cholest_1	1=>3yrs	0.13	0 1	0.09	0 1	0.14	0 1	1	-0.1113	0.3011	0.1367	0.7116	0.8950
HC_Cholest_2	2=w/in3yrs	0.71	0 1	0.78	0 1	0.69	0 1	1	0.3949	0.2166	3.3257	0.0682~	1.4840
HC_PAP	Last Pap Smear (Categorical)	2	.	.	2.5146	0.2844	.
HC_PAP_0	0=never	0.00	0 1	0.00	0 1	0.00	0 1
HC_PAP_1	1=>3yrs	0.07	0 1	0.09	0 1	0.06	0 1	1	0.5487	1.1834	0.2150	0.6429	1.7310
HC_PAP_2	2=w/in3yrs	0.93	0 1	0.91	0 1	0.93	0 1	1	0.1252	1.1581	0.0117	0.9139	1.1330
PreNatTuna	Prenatal Tuna (0=none, 1=moderate, 2=hig	0.69	0 2	0.71	0 2	0.68	0 2	1	0.0883	0.1362	0.4199	0.5170	1.0920
PreNatFish	=1 if PreNatTuna=Hi or PreNatOceanFresh	0.12	0 1	0.15	0 1	0.11	0 1	1	0.3149	0.2108	2.2307	0.1353	1.3700
PreNatOthMerc	Sum of prenatal non-vac merc exposures	0.13	0 2	0.15	0 2	0.13	0 2	1	0.2143	0.1896	1.2772	0.2584	1.2390
PreNatOthMerc Any	=1 if any prenatal non-vac merc exposures	0.12	0 1	0.15	0 1	0.11	0 1	1	0.3519	0.2113	2.7745	0.0958~	1.4220
PreNatFillings_1	0=None, 1=Have(noWrk,Grnd,gum)2=Have(YesW	1.32	0 2	1.34	0 2	1.31	0 2	1	0.0721	0.0853	0.7133	0.3983	1.0750
PreNatNicotine_1	=1 if any tobacco use: pregnancy	0.05	0 1	0.05	0 1	0.05	0 1	1	-0.0572	0.3468	0.0272	0.8690	0.9440
PreNatAlcohol_1	0=Never, 1=Occasional, 2=light, 3=moderate	0.08	0 3	0.09	0 3	0.08	0 3	1	0.1920	0.2276	0.7112	0.3991	1.2120
PreNatIlDrug	=1 if Cocaine or Narcotic use during pre	0.01	0 1	0.01	0 1	0.01	0 1	1	0.5843	0.7376	0.6275	0.4283	1.7940
PreNatValproic	Used Prenatal Valproic acid	0	0 1	0	0 1	0.01	0 1	1	-0.2923	1.1206	0.0680	0.7942	0.7470
Folic_PNVit_Multi	=1 if Folic PreNatVit or Multivit prenatal	0.93	0 1	0.96	0 1	0.91	0 1	1	0.8276	0.3488	5.6314	0.0176*	2.2880
PreNatVirallnf	=1 if any viral infections during pregnancy	0.06	0 1	0.07	0 1	0.05	0 1	1	0.3010	0.2989	1.0143	0.3139	1.3510
PreNatLead_1	=1 if PreNatResiLead or PreNatOccupLead=1	0.25	0 1	0.23	0 1	0.25	0 1	1	-0.0926	0.1699	0.2971	0.5857	0.9120
Birthwgt	Weight at birth in grams	3442.68	705 11000	3462.3	705 11000	3436	805 5260	1	0.0001	0.0001	0.3295	0.5659	1.0000
Birth Weight	Categorical	4	.	.	4.9038	0.2973	.
BWL1tk	=1 if Birth wgt < 1 Kg	0.01	0 1	0.02	0 1	0	0 1
BW1_1p5k	=1 if Birth wgt 1.0 Kg to 1.499 Kg	0.01	0 1	0	0 1	0.01	0 1	1	-2.3073	1.3998	2.7169	0.0993~	0.1000
BW1p5_2p5k	=1 if Birth wgt 1.5 Kg to 2.499 Kg	0.06	0 1	0.07	0 1	0.05	0 1	1	-1.4114	0.9161	2.3739	0.1234	0.2440

Exhibit 9.3.1. Bivariate Relationships Of Covariates to ASD Outcome

Variable	Label	Overall (n=1008)			ASD (n=256)			Control (n=752)			Estimates from PH Model					
		Mean	Min	Max	Mean	Min	Max	Mean	Min	Max	df	Est.	S.E.	ChiSq	P-Val	O.R.
BW2p5_4k	=1 if Birth wgt 2.5 Kg to 3.999 Kg	0.78	0	1	0.76	0	1	0.79	0	1	1	-1.6773	0.8738	3.6845	0.0549~	0.1870
BW4kup	=1 if Birth wgt 4.0 Kg and up	0.15	0	1	0.16	0	1	0.15	0	1	1	-1.5552	0.8884	3.0642	0.0800~	0.2110
C5APGAR	5 minute Apgar Score	8.93	5	10	8.92	6	10	8.94	5	10	1	-0.0910	0.1521	0.3579	0.5497	0.9130
RespDistress	=1 if Resp Distress Syndrome (hyaline)	0.03	0	1	0.04	0	1	0.03	0	1	1	0.1746	0.4076	0.1835	0.6684	1.1910
Bilirubin	=1 if hyperbilirubinemia	0.08	0	1	0.09	0	1	0.08	0	1	1	0.2036	0.2626	0.6016	0.4380	1.2260
Anemia	=1 if anemia 6-30 mos	0.03	0	1	0.02	0	1	0.03	0	1	1	-0.5033	0.5519	0.8317	0.3618	0.6050
ChildLead	=1 if child exposure to lead	0.04	0	1	0.09	0	1	0.02	0	1	1	1.3200	0.3284	16.1604	0.0001*	3.7430
ChildPica	=1 if child had pica	0.04	0	1	0.09	0	1	0.02	0	1	1	1.3014	0.3282	15.7276	0.0001*	3.6740
Enceph	=1 if Encephalitis or any CNS infection	0	0	1	0	0	1	0	0	1	1	1.1340	1.4278	0.6308	0.4271	3.1080

9.3.2. Bivariate Relationships of Exposure Measures to Case-Control Outcomes

Bivariate relationships of exposure measures to outcomes were estimated using the same type of models as described in the previous section on bivariate relationships of covariates to case-control outcomes.

Exhibit 9.3.2 shows the bivariate relationships of the ASD outcome to each of the study's measures of prenatal and postnatal exposure to ethylmercury from thimerosal containing vaccines and immune globulins. The odds ratios for each of the postnatal exposure measures are slightly below 1 and the odds ratios for each of the prenatal exposure measures are slightly above 1, but none is significantly different from zero.

Exhibits 9.3.3 – 9.3.8 show similar tables corresponding to the outcomes: AD, ASD-not-AD (ASD Only), ASD with Regression, AD with Low Cognitive Function Excluded, ASD with Screened Control Group, and AD with Screened Control Group. The patterns are similar to that of Exhibit 9.3.2. Most of the odds ratios for postnatal exposure are slightly below one, while most of the odds ratios for prenatal exposure are slightly above one. Some of the effects are individually statistically significant at the 0.05 or 0.10 level. All of these are associated with odds ratios below one.

Exhibit 9.3.2 Bivariate Relationships Of Exposure Measures to ASD Outcome

Variable	Label	Overall (n=1008)			ASD (n=256)			Control (n=752)			Estimates from PH Model					
		Mean	Min	Max	Mean	Min	Max	Mean	Min	Max	df	Est.	S.E.	ChiSq	P-Val	O.R.
Exp07mos	Amt/Wt(KGs) birth-214 days	17.41	0	66.94	17.30	0	65.17	17.45	0	66.94	1	-0.0077	0.0138	0.3132	0.5758	0.992
Exp01mos	Amt/Wt(KGs) birth-28 days	2.66	0	21.04	2.65	0	14.30	2.66	0	21.04	1	-0.0275	0.0409	0.4527	0.5011	0.973
Exp17mos	Amt/Wt(KGs) 29-214 days	14.75	0	66.94	14.65	0	65.17	14.78	0	66.94	1	-0.0053	0.0148	0.1260	0.7227	0.995
Exp020mos	Amt/Wt(KGs) birth-609 days	20.69	0	76.74	20.45	0	70.30	20.77	0	76.74	1	-0.0095	0.0131	0.5242	0.4691	0.991
Amt07mos	Amt Merc birth-214 days	102.93	0	190.83	101.13	0	190.83	103.54	0	187.50	1	-0.0039	0.0029	1.8005	0.1796	0.996
Amt01mos	Amt Merc birth-28 days	9.00	0	50.00	9.01	0	45.00	8.99	0	50.00	1	-0.0072	0.0131	0.2982	0.5850	0.993
Amt17mos	Amt Merc 29-214 days	93.93	0	187.50	92.11	0	187.50	94.55	0	187.50	1	-0.0038	0.0030	1.5918	0.2071	0.996
Amt020mos	Amt Merc birth-609 days	136.13	0	300.00	133.58	0	300.00	137.00	0	262.50	1	-0.0033	0.0027	1.5330	0.2157	0.997
PreNatThimer	PreNat Exp Amt	2.44	0	100.00	2.70	0	74.00	2.35	0	100.00	1	0.0072	0.0089	0.6532	0.4190	1.007
PreNatThimer_Alt	PreNat Exp Amt (Alt)	4.32	0	111.25	4.74	0	111.25	4.18	0	100.00	1	0.0037	0.0052	0.4957	0.4814	1.004

Exhibit 9.3.3 Bivariate Relationships Of Exposure Measures to AD Outcome

Variable	Label	Overall (n=1008)			AD (n=187)			Control (n=724)			Estimates from PH Model					
		Mean	Min	Max	Mean	Min	Max	Mean	Min	Max	df	Est.	S.E.	ChiSq	P-Val	O.R.
Exp07mos	Amt/Wt(KGs) birth-214 days	17.61	0	66.94	17.53	0	65.17	17.63	0	66.94	1	-0.0086	0.0155	0.3064	0.5799	0.991
Exp01mos	Amt/Wt(KGs) birth-28 days	2.70	0	21.04	2.79	0	14.30	2.68	0	21.04	1	0.0097	0.0439	0.0484	0.8258	1.010
Exp17mos	Amt/Wt(KGs) 29-214 days	14.91	0	66.94	14.75	0	65.17	14.95	0	66.94	1	-0.0114	0.0169	0.4532	0.5008	0.989
Exp020mos	Amt/Wt(KGs) birth-609 days	20.95	0	76.74	20.80	0	70.30	20.99	0	76.74	1	-0.0080	0.0147	0.2937	0.5879	0.992
Amt07mos	Amt Merc birth-214 days	103.99	0	190.83	101.42	0	190.83	104.65	0	187.50	1	-0.0058	0.0033	3.0482	0.0808~	0.994
Amt01mos	Amt Merc birth-28 days	9.09	0	50.00	9.40	0	45.00	9.01	0	50.00	1	0.0042	0.0143	0.0854	0.7701	1.004
Amt17mos	Amt Merc 29-214 days	94.90	0	187.50	92.03	0	187.50	95.64	0	187.50	1	-0.0064	0.0034	3.5066	0.0611~	0.994
Amt020mos	Amt Merc birth-609 days	137.74	0	262.50	134.64	0	253.33	138.54	0	262.50	1	-0.0043	0.0031	1.9986	0.1574	0.996
PreNatThimer	PreNat Exp Amt	2.42	0	100.00	2.96	0	62.75	2.28	0	100.00	1	0.0101	0.0098	1.0652	0.3020	1.010
PreNatThimer_Alt	PreNat Exp Amt (Alt)	4.26	0	100.00	5.15	0	100.00	4.03	0	100.00	1	0.0058	0.0059	0.9789	0.3225	1.006

Exhibit 9.3.4 Bivariate Relationships Of Exposure Measures to ASD-not-AD Outcome

Variable	Label	Overall (n=773)			ASD-not-AD (n=69)			Control (n=704)			Estimates from PH Model					
		Mean	Min	Max	Mean	Min	Max	Mean	Min	Max	df	Est.	S.E.	ChiSq	P-Val	O.R.
Exp07mos	AmtWt(KGs) birth-214 days	16.90	0	66.94	16.65	0	34.90	16.92	0	66.94	1	-0.0083	0.0252	0.1092	0.7410	0.992
Exp01mos	AmtWt(KGs) birth-28 days	2.61	0	21.04	2.29	0	5.52	2.64	0	21.04	1	-0.1864	0.0888	4.4108	0.0357*	0.830
Exp17mos	AmtWt(KGs) 29-214 days	14.29	0	66.94	14.36	0	31.63	14.29	0	66.94	1	0.0108	0.0259	0.1725	0.6779	1.011
Exp020mos	AmtWt(KGs) birth-609 days	20.07	0	76.74	19.51	0	40.97	20.13	0	76.74	1	-0.0166	0.0245	0.4603	0.4975	0.983
Amt07mos	Amt Merc birth-214 days	100.70	0	187.50	100.32	0	187.50	100.74	0	187.50	1	0.0006	0.0052	0.0118	0.9134	1.001
Amt01mos	Amt Merc birth-28 days	8.85	0	50.00	7.97	0	12.50	8.93	0	50.00	1	-0.0515	0.0268	3.6837	0.0549~	0.950
Amt17mos	Amt Merc 29-214 days	91.86	0	187.50	92.35	0	187.50	91.81	0	187.50	1	0.0030	0.0055	0.3074	0.5793	1.003
Amt020mos	Amt Merc birth-609 days	132.93	0	300.00	130.72	0	300.00	133.15	0	250.00	1	-0.0009	0.0047	0.0334	0.8550	0.999
PreNatThimer	PreNat Exp Amt	1.93	0	74.00	2.00	0	74.00	1.92	0	37.75	1	-0.0016	0.0197	0.0067	0.9349	0.998
PreNatThimer_Alt	PreNat Exp Amt (Alt)	3.76	0	111.25	3.62	0	111.25	3.77	0	75.00	1	-0.0024	0.0103	0.0561	0.8128	0.998

Exhibit 9.3.5 Bivariate Relationships Of Exposure Measures to ASD with Regression Outcome

Variable	Label	Overall (n=701)			ASD w/Regress. (n=49)			Control (n=652)			Estimates from PH Model					
		Mean	Min	Max	Mean	Min	Max	Mean	Min	Max	df	Est.	S.E.	ChiSq	P-Val	O.R.
Exp07mos	AmtWt(KGs) birth-214 days	17.30	0	66.94	16.69	0	39.96	17.34	0	66.94	1	-0.0666	0.0311	4.5967	0.0320*	0.936
Exp01mos	AmtWt(KGs) birth-28 days	2.64	0	21.04	2.59	0	14.30	2.64	0	21.04	1	-0.0642	0.0849	0.5717	0.4496	0.938
Exp17mos	AmtWt(KGs) 29-214 days	14.66	0	66.94	14.10	0	30.48	14.70	0	66.94	1	-0.0735	0.0353	4.3310	0.0374*	0.929
Exp020mos	AmtWt(KGs) birth-609 days	20.65	0	76.74	20.51	0	46.62	20.66	0	76.74	1	-0.0481	0.0290	2.7465	0.0975~	0.953
Amt07mos	Amt Merc birth-214 days	103.13	0	190.83	101.09	0	190.83	103.28	0	187.50	1	-0.0113	0.0057	3.9736	0.0462*	0.989
Amt01mos	Amt Merc birth-28 days	8.93	0	50.00	9.08	0	45.00	8.92	0	50.00	1	-0.0091	0.0261	0.1215	0.7274	0.991
Amt17mos	Amt Merc 29-214 days	94.20	0	187.50	92.01	0	187.50	94.37	0	187.50	1	-0.0118	0.0059	3.9226	0.0476*	0.988
Amt020mos	Amt Merc birth-609 days	137.03	0	262.50	140.12	0	253.33	136.80	0	262.50	1	-0.0048	0.0053	0.8207	0.3650	0.995
PreNatThimer	PreNat Exp Amt	1.97	0	37.75	3.34	0	25.00	1.86	0	37.75	1	0.0308	0.0195	2.4935	0.1143	1.031
PreNatThimer_Alt	PreNat Exp Amt (Alt)	3.72	0	75.00	5.62	0	50.00	3.58	0	75.00	1	0.0122	0.0104	1.3814	0.2399	1.012

Exhibit 9.3.6 Bivariate Relationships Of Exposure Measures to AD with Low Cognitive Function Excluded Outcome																
Variable	Label	Overall (n=884)			AD Low Cog. Ex. (n=165)			Control (n=719)			Estimates from PH Model					
		Mean	Min	Max	Mean	Min	Max	Mean	Min	Max	df	Est.	S.E.	ChiSq	P-Val	O.R.
Exp07mos	Amt/Wt(KGs) birth-214 days	17.51	0	66.94	17.39	0	65.17	17.53	0	66.94	1	-0.0106	0.0166	0.4088	0.5226	0.989
Exp01mos	Amt/Wt(KGs) birth-28 days	2.67	0	21.04	2.70	0	9.93	2.67	0	21.04	1	-0.0185	0.0482	0.1469	0.7015	0.982
Exp17mos	Amt/Wt(KGs) 29-214 days	14.83	0	66.94	14.69	0	65.17	14.86	0	66.94	1	-0.0097	0.0179	0.2963	0.5862	0.990
Exp020mos	Amt/Wt(KGs) birth-609 days	20.82	0	76.74	20.67	0	70.30	20.86	0	76.74	1	-0.0079	0.0156	0.2574	0.6119	0.992
Amt07mos	Amt Merc birth-214 days	103.58	0	187.50	100.84	0	187.50	104.21	0	187.50	1	-0.0065	0.0035	3.3830	0.0659~	0.994
Amt01mos	Amt Merc birth-28 days	9.02	0	50.00	9.17	0	37.50	8.99	0	50.00	1	-0.0042	0.0155	0.0748	0.7845	0.996
Amt17mos	Amt Merc 29-214 days	94.56	0	187.50	91.67	0	187.50	95.23	0	187.50	1	-0.0067	0.0037	3.3630	0.0667~	0.993
Amt020mos	Amt Merc birth-609 days	137.12	0	262.50	134.09	0	237.50	137.82	0	262.50	1	-0.0043	0.0033	1.7112	0.1908	0.996
PreNatThimer	PreNat Exp Amt	2.34	0	100.00	3.05	0	62.75	2.18	0	100.00	1	0.0137	0.0099	1.9217	0.1657	1.014
PreNatThimer_Alt	PreNat Exp Amt (Alt)	4.15	0	100.00	5.08	0	100.00	3.94	0	100.00	1	0.0064	0.0061	1.0971	0.2949	1.006

Exhibit 9.3.7 Bivariate Relationships Of Exposure Measures to ASD Outcome with Screened Control Group																
Variable	Label	Overall (n=821)			ASD (n=255)			Scr. Control (n=566)			Estimates from PH Model					
		Mean	Min	Max	Mean	Min	Max	Mean	Min	Max	df	Est.	S.E.	ChiSq	P-Val	O.R.
Exp07mos	Amt/Wt(KGs) birth-214 days	17.42	0	65.17	17.20	0	65.17	17.52	0	54.50	1	-0.0110	0.0155	0.5056	0.4771	0.989
Exp01mos	Amt/Wt(KGs) birth-28 days	2.72	0	21.04	2.65	0	14.30	2.75	0	21.04	1	-0.0484	0.0428	1.2806	0.2578	0.953
Exp17mos	Amt/Wt(KGs) 29-214 days	14.70	0	65.17	14.55	0	65.17	14.77	0	54.50	1	-0.0052	0.0166	0.0979	0.7544	0.995
Exp020mos	Amt/Wt(KGs) birth-609 days	20.62	0	70.30	20.33	0	70.30	20.75	0	57.01	1	-0.0106	0.0147	0.5187	0.4714	0.989
Amt07mos	Amt Merc birth-214 days	103.55	0	190.83	100.84	0	190.83	104.78	0	187.50	1	-0.0064	0.0032	3.9576	0.0467*	0.994
Amt01mos	Amt Merc birth-28 days	9.21	0	50.00	9.00	0	45.00	9.30	0	50.00	1	-0.0157	0.0136	1.3320	0.2485	0.984
Amt17mos	Amt Merc 29-214 days	94.35	0	187.50	91.84	0	187.50	95.48	0	187.50	1	-0.0058	0.0033	3.0920	0.0787~	0.994
Amt020mos	Amt Merc birth-609 days	136.15	0	300.00	133.18	0	300.00	137.48	0	262.50	1	-0.0046	0.0029	2.4884	0.1147	0.995
PreNatThimer	PreNat Exp Amt	2.36	0	100.00	2.61	0	74.00	2.25	0	100.00	1	0.0073	0.0091	0.6377	0.4245	1.007
PreNatThimer_Alt	PreNat Exp Amt (Alt)	4.13	0	111.25	4.66	0	111.25	3.90	0	100.00	1	0.0044	0.0054	0.6653	0.4147	1.004

Exhibit 9.3.8 Bivariate Relationships Of Exposure Measures to AD Outcome with Screened Control Group

Variable	Label	Overall (n=728)			ASD (n=186)			Scr. Control (n=542)			Estimates from PH Model					
		Mean	Min	Max	Mean	Min	Max	Mean	Min	Max	df	Est.	S.E.	ChiSq	P-Val	O.R.
Exp07mos	Amt/Wt(KGs) birth-214 days	17.65	0	65.17	17.40	0	65.17	17.74	0	54.50	1	-0.0132	0.0174	0.5749	0.4483	0.987
Exp01mos	Amt/Wt(KGs) birth-28 days	2.77	0	21.04	2.78	0	14.30	2.77	0	21.04	1	-0.0102	0.0454	0.0508	0.8217	0.990
Exp17mos	Amt/Wt(KGs) 29-214 days	14.88	0	65.17	14.62	0	65.17	14.97	0	54.50	1	-0.0137	0.0189	0.5282	0.4674	0.986
Exp020mos	Amt/Wt(KGs) birth-609 days	20.91	0	70.30	20.63	0	70.30	21.01	0	57.01	1	-0.0096	0.0164	0.3418	0.5588	0.990
Ami07mos	Amt Merc birth-214 days	104.80	0	190.83	101.03	0	190.83	106.10	0	187.50	1	-0.0090	0.0037	5.9142	0.0150*	0.991
Ami01mos	Amt Merc birth-28 days	9.35	0	50.00	9.38	0	45.00	9.34	0	50.00	1	-0.0044	0.0147	0.0892	0.7652	0.996
Ami17mos	Amt Merc 29-214 days	95.45	0	187.50	91.65	0	187.50	96.76	0	187.50	1	-0.0091	0.0038	5.8113	0.0159*	0.991
Ami020mos	Amt Merc birth-609 days	137.94	0	262.50	134.09	0	253.33	139.26	0	262.50	1	-0.0058	0.0033	3.0998	0.0783~	0.994
PreNatThimer	PreNat Exp Amt	2.34	0	100.00	2.84	0	62.75	2.17	0	100.00	1	0.0106	0.0100	1.1266	0.2885	1.011
PreNatThimer_Alt	PreNat Exp Amt (Alt)	4.08	0	100.00	5.04	0	100.00	3.75	0	100.00	1	0.0064	0.0061	1.1238	0.2891	1.006

9.3.3. Bivariate Relationships of Covariates to Exposure Measures

In this section we show the bivariate relationships of covariate measures to exposure measures (*PreNatThimer*, *Exp01mos*, *Exp07mos*, and *Exp020mos*). The relationships were calculated separately for ASD cases and controls. We summarize the relationships in four sections that follow:

- Relationships that were similar for both cases and controls
- Relationships for controls, but not cases
- Unordered relationships
- Significant relationships but where group sizes were very small

The full set of bivariate results is shown in Exhibits 9.3.9 and 9.3.10.

9.3.3.1. Relationships That Were Similar for Both Cases and Controls

Mother's age at birth of child – Although mother's age was entered as a categorical variable in the main analysis models, we looked at the relationships of exposure measures to both the categorically coded age variable and a continuous measure of mother's age to the exposure measures. The results indicated several significant linear associations between the continuous age measure and exposures. Increased maternal age was associated with:

- Higher prenatal exposure in both cases and controls
- Higher cumulative exposure birth to seven months in both cases and controls
- Higher cumulative exposure birth to twenty months in both cases and controls

Father's age at birth of child – Similar to mother's age, father's age was entered as a categorical variable in the main analysis models, but we looked at the relationships of exposure measures to both the categorically coded age variable and a continuous measure of father's age to the exposure measures. The results indicated several significant and near significant linear associations between the continuous age measure and exposures. Increased paternal age was associated with:

- Higher cumulative exposure birth to seven months in cases³³ (p=0.053) and controls (p<0.05)
- Higher birth to 20 month exposures in cases (p=0.066) and controls (p<0.05)
- Higher birth to 1 month exposures for controls (p<0.05)
- Higher prenatal exposures for controls (p=0.09)

Multiples (twins or triplets) -

³³ In these summaries, relationships where p-value is greater than 0.05 criterion, but less than 0.10 are shown in parentheses.

- In both cases and controls, twins or triplets had higher exposures birth to 7 months and birth to 20 months, than singletons.

Education level –

- For both cases and controls higher education was associated with higher cumulative exposure birth to 7 months (for cases, $p=0.066$) and birth to 20 months (for cases, $p=0.069$)

Birth weight –

- For both cases and controls, lower birth weight was associated with higher exposure birth to seven months and birth to 20 months
- For both cases and controls, for birth weight categories 1.5-2.5 kilograms and above, lower birth weight was associated with higher exposure birth to one month. The number of children with birth weight less than 1.5 kilograms was very low and among those groups the means did not follow an ordered pattern.

Respiratory Distress--

- Among both cases and controls, respiratory distress syndrome was associated with lower exposure birth to 1 month.
- Among both cases and controls, respiratory distress syndrome was associated with higher exposure birth to 7 months and birth to 20 months.

Hyperbilirubinemia--

- Among both cases and controls, hyperbilirubinemia was associated with higher exposure birth to 7 months and birth to 20 months.

Prenatal Viral Infections--

- For cases, prenatal exposure was higher among those whose mother's had viral infections during pregnancy.
- For controls birth to 7 month and birth to 20 month exposures were higher among children whose mothers had prenatal viral infections.

9.3.3.2. Relationships for Controls, but not Cases

Income Level -

- For controls higher income (higher poverty ratio) was associated with greater prenatal, birth to seven month ($p=0.053$) and birth to 20 month exposures.
- For cases there were no significant associations between poverty ratio and exposure levels.

Prenatal Lead—

- For controls, prenatal lead exposure was associated with higher prenatal exposure.

9.3.3.3. Unordered relationships

We would characterize the associations as ordered if, for example, first borns had lower exposure levels than second borns, who in turn had lower exposure levels than third borns. The associations described in this section were unordered.

Birth order – Birth order has some associations with exposures. None of the associations between birth order and exposure were ordered.

- For cases, exposure birth to 7 months and birth to 20 months, first borns and third borns had higher mean exposure levels than second borns.
- For controls, exposure birth to 1 month, first borns and third borns had higher mean exposure levels than second borns.

Breast feeding -

- Controls only, birth to 20 months exposures were higher among those that did not breast feed, or breast fed for more than 6 months, as compared to those that breast fed for 1 to 6 months.

9.3.3.4. Significant Relationships But Where Group Sizes were Very Small

Prenatal Use of Illegal Drugs--

- The number of case and control mothers that reported use of illegal drugs during pregnancy was very low. There were two significant associations with exposure, but the number were so low the number might not be reliable.

Five Minute Apgar Scores –

- For both cases and controls there was significant variation of exposure means among groups having different apgar scores, but the numbers of children in many of the apgar score groups were very small, and the relationships did not appear to follow any particular order.

9.3.3.5. Summary Tables – Bivariate Relationships of Covariates to Exposure Measures

Variable		Covariate Level		PreNatThimer		Exp07mos		Exp020mos			
		Mean	SD	ProbF	Mean	SD	ProbF	Mean	SD		
MomAgeBirth	Mom age at child Birth (Years)	256		0.0077	0.28 ^a	0.7321	-0.01 ^a	0.0436	0.20 ^a	0.0381	0.24 ^a
MomAge	Categories			0.2873		0.8943		0.1034		0.1210	
MomL20	Mom Age at child birth <20	4	0.00	0.00	0.00	3.35	0.29	15.86	1.04	18.19	1.37
Mom20_24	Mom Age at child birth 20-24	13	0.00	0.00	0.00	2.59	1.54	15.50	4.85	19.69	5.56
Mom25_29	Mom Age at child birth 25-29	58	1.30	5.09	2.83	2.01	17.26	7.85	8.81	19.92	8.81
Mom30_34	Mom Age at child birth 30-34	92	2.88	7.48	2.58	1.85	15.89	6.78	18.94	7.98	7.98
MomGE35	Mom Age at child birth >= 35	89	3.94	11.82	2.58	2.33	19.09	9.97	22.57	11.54	11.54
BirthOrder	Categories			0.2482		0.5911		0.0084		0.0040	
BirthOrder1_1	=1 if 1st born	115	3.59	10.27	2.75	1.89	17.51	8.22	20.73	9.74	9.74
BirthOrder2_1	=1 if 2nd born	102	2.23	7.99	2.49	1.97	15.81	6.45	18.61	7.24	7.24
BirthOrderGE3_1	=1 if 3rd born or higher	39	1.31	3.92	2.78	2.58	20.54	11.12	24.46	12.45	12.45
Multiple				0.1996		0.5302		0.0084		0.0015	
Multiple	0=not twin or triplet	240	2.88	8.94	2.63	2.00	16.95	7.78	19.97	8.96	8.96
Multiple	1=twin or triplet	16	0.00	0.00	2.96	2.50	22.53	12.43	27.70	13.84	13.84
Breast Feeding				0.5095		0.1150		0.5180		0.6306	
BFNone	=1 if Breastfed 0 months	65	1.74	5.82	3.09	2.40	16.30	6.67	19.51	8.29	8.29
BF1_6mos	=1 if Breastfed 1-5.99 months	90	2.66	7.18	2.58	1.88	17.49	7.72	20.59	8.69	8.69
BF6gmoms	=1 if Breastfed 6+ months	101	3.35	11.13	2.43	1.88	17.76	9.49	20.94	10.85	10.85
PovertyRatio1		256	0.3063	0.20 ^a	0.7475	-0.01 ^a	0.4301	-0.15 ^a	0.4180	-0.17 ^a	
Education				0.4774		0.8481		0.0659		0.0689	
MomEduc NoHS	=1 if no HS Dipl	7	3.57	9.45	1.98	1.87	9.87	8.01	12.19	8.81	8.81
MomEduc HS	=1 if Mom HS Grad	39	0.97	4.45	2.64	1.90	16.20	6.85	19.09	7.75	7.75
MomEduc_Some	=1 if Mom Some Coll	49	3.86	10.64	2.64	1.68	17.37	7.85	20.32	8.67	8.67
MomEduc Coll	=1 if Mom Coll Grad	161	2.73	8.78	2.69	2.18	17.86	8.52	21.18	10.00	10.00
Single Parent				0.8377		0.9202		0.8861		0.5847	
Single Parent	0=child does not live in a single parent household	210	2.75	8.36	2.65	1.93	17.26	8.36	20.03	9.67	9.67
Single Parent	1=child lives in a single parent household	46	2.46	10.12	2.68	2.47	17.45	7.66	21.15	8.68	8.68
BioDadYearsImpVal1	Dad age in years	256	0.6658	0.04 ^a	0.9914	0.00 ^a	0.9914	0.00 ^a	0.0537	0.15 ^a	0.0662
DadAge Categories				0.0944		0.9730		0.2287		0.1509	
DadH20_11	Dad < 20 years old	2	0.00	0.00	3.92	0.49	16.09	0.08	18.69	0.43	0.43
Dad20_29_11	Dad 20-29 years old	51	0.98	4.90	2.73	1.65	15.93	6.03	19.00	7.04	7.04
Dad30_39_11	Dad 30-39 years old	153	3.94	10.48	2.61	2.22	17.10	8.35	20.17	9.68	9.68
Dad40_49_11	Dad 40-49 years old	44	0.86	4.19	2.62	1.91	19.77	10.01	23.58	11.27	11.27
DadGE49_11	Dad >49 years old	6	0.00	0.00	3.00	1.62	16.18	5.12	17.60	6.16	6.16
HC_InitInad_1				0.5501		0.5747		0.4358		0.1218	
HC_InitInad_1	0 else	244	2.63	8.65	2.67	1.99	17.21	8.28	20.25	9.48	9.48
HC_InitInad_1	1=if Kotel Init PNC = INADEQ	12	4.17	9.73	2.33	2.82	19.11	7.02	24.59	9.18	9.18
HC_Cholesterol	Last Cholesterol Check			0.8204		0.4145		0.9663		0.9801	
HC_Cholest_0	0=Never	33	3.45	8.49	2.41	2.22	17.08	6.63	20.56	7.55	7.55
HC_Cholest_1	1=> 3 yrs	24	3.12	6.71	2.25	1.67	17.00	6.85	20.09	7.76	7.76
HC_Cholest_2	2=w/in 3 yrs	199	2.52	8.95	2.74	2.04	17.37	8.63	20.48	9.99	9.99
HC_PAP	Last Pap Smear (Categorical)			0.4209		0.5245		0.9879		0.9943	
HC_PAP_0	0=never	1	0.00		3.70		18.54		20.75		
HC_PAP_1	1 => 3 yrs	23	4.92	15.03	2.24	1.99	17.23	6.55	20.26	7.68	7.68
HC_PAP_2	2=w/in 3 yrs	232	2.49	7.82	2.69	2.04	17.30	8.40	20.47	9.69	9.69

Exhibit 9.3.9. Relationships of Covariates to Exposure Measures for n=256 ASD Cases

Variable	Covariate Level		PreNatThimer		Exp0Imos		Exp07mos		Exp020mos			
	ProbF	Mean	SD	ProbF	Mean	SD	ProbF	Mean	SD	ProbF	Mean	SD
PreNatTuna	0.5569	1.96	8.18	0.8566	2.61	2.04	0.7563	16.88	8.10	0.5799	19.91	9.38
None		3.02	8.98		2.65	2.09		17.63	8.51		20.94	9.80
Moderate		3.92	8.82		2.92	1.50		16.52	6.17		18.95	7.02
High												
PreNatFish	0.8299	2.65	8.90	0.3426	2.70	2.08	0.1327	17.62	8.41	0.1171	20.84	9.72
0= PreNatTuna not HI or no PreNatOceanFresh		2.98	7.40		2.36	1.77		15.44	6.89		18.22	7.82
PreNatFish	0.8350	2.60	8.80	0.4891	2.71	2.07	0.4353	17.56	8.39	0.3268	20.82	9.69
1= PreNatTuna=HI or PreNatOceanFresh		3.39	8.16		2.31	1.80		15.69	7.15		18.31	8.20
0		0.00			3.59			19.00			19.01	
1												
2												
PreNatOthMerc_Any	0.6440	2.60	8.80	0.3062	2.71	2.07	0.2193	17.56	8.39	0.1348	20.82	9.69
PreNatOthMerc_Any		3.30	8.07		2.34	1.78		15.78	7.07		17.33	8.09
PreNatOthMerc_Any												
PreNatFillings_1	0.7498	2.07	6.14	0.5079	2.74	1.76	0.9647	17.22	8.50	0.7589	19.94	9.19
None		2.46	6.81		2.33	1.87		17.05	8.84		19.92	10.44
no Wrk. Grnd. gum		3.03	10.01		2.71	2.19		17.40	7.97		20.83	9.36
YesWrk. Grnd. or Gum												
PreNatNicotine_1	0.8147	2.73	8.83	0.6830	2.64	1.90	0.2805	17.42	8.12	0.2613	20.60	9.37
PreNatNicotine_1		2.13	4.96		2.89	3.99		14.79	10.24		17.44	11.80
PreNatNicotine_1												
0=Never		2.46	7.56		2.74	2.03		17.23	8.42		20.29	9.73
1=Occasional		6.21	18.10		1.84	1.93		18.24	5.82		22.50	6.16
2=Light		0.00	0.00		0.00	0.00		16.07	1.25		20.69	0.09
3=Moderate												
PreNatIIDrug	0.5890	2.73	8.73	0.0229	2.68	2.03	0.6944	17.32	8.26	0.7771	20.47	9.54
PreNatIIDrug		0.00	0.00		0.00	0.00		15.44	3.63		18.91	3.11
PreNatIIDrug												
0=No Cocaine or Narcotic use during Pregnancy												
1=Cocaine or Narcotic use during Pregnancy												
PreNatValproic	0.0098	2.61	8.59	0.8394	2.65	2.04	0.7445	17.29	8.24	0.8030	20.44	9.51
0= did not use Prenatal Valproic acid		25.00			3.07			19.98			22.82	
PreNatValproic												
1= Used Prenatal Valproic acid												
Folic_PNVit_Multi	0.3169	0.00	0.00	0.0554	1.44	1.87	0.1925	20.62	17.13	0.1721	24.47	17.87
Folic_PNVit_Multi		2.81	8.84		2.70	2.03		17.16	7.69		20.29	9.02
Folic_PNVit_Multi												
0=no Folic, PreNatVit or Multivit prenatal												
1= Folic, PreNatVit or Multivit prenatal												
PreNatViralInf	0.0041	2.27	7.26	0.8959	2.65	1.95	0.9184	17.28	8.32	0.6583	20.38	9.56
PreNatViralInf		8.33	19.00		2.71	3.00		17.49	7.09		21.41	8.69
PreNatViralInf												
0= no viral infections during pregnancy												
1= any viral infections during pregnancy												
PreNatLead_1	0.5417	2.88	9.32	0.9706	2.65	2.05	0.9421	17.28	8.59	0.7114	20.33	9.98
PreNatLead_1 =0 if PreNatResilLead ne 1 AND PreNatOccupLead ne 1		2.10	6.19		2.66	2.01		17.36	6.94		20.85	7.75
PreNatLead_1 =1 if PreNatResilLead or PreNatOccupLead=1												
Birthwgt	0.8142	0.00		0.0139	-0.00		<0.0001	-0.00		<0.0001	-0.00	
Birth Weight	0.8009	0.00	0.00	0.0001	0.00	0.00	<0.0001	33.93	22.12	<0.0001	39.93	23.34
BW11k		0.00	0.00		0.00	0.00		21.62	7.48		29.14	8.58
BW1_1p5k		2.97	7.08		4.08	2.80		17.43	7.48		25.28	10.33
BW1p5_2p5k		2.46	8.16		2.75	1.35		17.43	7.48		20.66	8.58
BW2p5_4k		4.08	11.84		1.91	1.35		13.20	6.74		15.21	7.73
BW4kup												

Exhibit 9.3.9. Relationships of Covariates to Exposure Measures for n=256 ASD Cases

Variable	Covariate Level	N	PreNatThimer			Exp0Imos			Exp07mos			Exp020mos		
			ProbF	Mean	SD	ProbF	Mean	SD	ProbF	Mean	SD	ProbF	Mean	SD
CSAPGAR	5 minute Apgar Score		0.4986			0.4258			0.0061			0.0129		
CSAPGAR	6	3		4.25	7.36		1.29	2.23		18.27	13.43		22.82	17.27
CSAPGAR	7	2		12.50	17.68		1.70	2.40		8.12	11.48		10.12	14.31
CSAPGAR	8	13		3.88	7.93		2.51	2.26		24.14	14.91		27.79	16.43
CSAPGAR	9	233		2.48	8.64		2.66	2.03		16.87	7.50		19.98	8.72
CSAPGAR	10	5		5.00	11.18		3.94	0.80		22.49	4.05		25.88	6.58
RespDistress			0.9783			0.0361			0.0348			0.0516		
RespDistress	0= no Resp Distress Syndrome (hyaline)	247		2.70	8.71		2.70	2.02		17.09	7.51		20.23	8.75
RespDistress	1= Resp Distress Syndrome (hyaline)	9		2.78	8.33		1.26	1.92		22.97	19.55		26.50	21.75
Bilirubin			0.9871			0.7240			0.0042			0.0063		
Bilirubin	0= no hyperbilirubinemia	233		2.70	8.81		2.67	2.00		16.84	7.30		19.95	8.54
Bilirubin	1= hyperbilirubinemia	23		2.73	7.51		2.51	2.42		21.95	14.06		25.59	15.64
Anemia			0.5319			0.0967			0.0182			0.0195		
Anemia	0= no anemia 6-30 mos	252		2.74	8.75		2.62	1.90		17.14	8.12		20.28	9.37
Anemia	1= anemia 6-30 mos	4		0.00	0.00		4.33	6.80		26.91	10.43		31.43	12.54
ChildLead			0.5880			0.4025			0.6153			0.6702		
ChildLead	0= no child exposure to lead	234		2.79	8.98		2.62	2.07		17.22	8.43		20.37	9.76
ChildLead	1=child exposure to lead	22		1.74	4.48		3.00	1.58		18.14	5.67		21.28	6.02
ChildPica			0.5880			0.2266			0.3724			0.4710		
ChildPica	0= child did not have pica	234		2.79	8.98		2.60	2.08		17.15	8.40		20.32	9.73
ChildPica	1=child had pica	22		1.74	4.48		3.15	1.43		18.79	6.00		21.85	6.51
Enceph			0.7561			0.2952			0.4863			0.5930		
Enceph	0=no Encephalitis or CNS infection	255		2.71	8.70		2.64	2.03		17.27	8.23		20.43	9.51
Enceph	1=Encephalitis or any CNS infection	1		0.00			4.78			23.02			25.53	

^a For variables on a continuous scale (mother age in years, poverty ratio, and father's age in years) the number shown in the "Mean" column is the regression coefficient from a simple linear regression of the variable on the exposure measure.

Exhibit 9.3.10. Relationships of Covariates to Exposure Measures for n=752 Controls														
Variable	Covariate Level	N	PreNatThimer			Exp01mos			Exp07mos			Exp020mos		
			ProbF	Mean	SD	ProbF	Mean	SD	ProbF	Mean	SD	ProbF	Mean	SD
MomAgeBirth	Mom age at child Birth (Years)	752	0.0484	0.11 ^a		0.1838	0.02 ^a		0.0136	0.13 ^a		0.0143	0.14 ^a	
MomAge	Categories		0.5334			0.3486			0.2530			0.2234		
MomI_20	Mom Age at child birth < 20	11	0.00	0.00		1.96	1.88		16.42	6.93		19.54	8.27	
Mom20_24	Mom Age at child birth 20-24	68	2.60	7.71		2.61	1.71		15.96	7.64		18.98	8.80	
Mom25_29	Mom Age at child birth 25-29	173	1.83	6.16		2.67	2.05		16.87	7.33		20.12	8.17	
Mom30_34	Mom Age at child birth 30-34	274	2.21	7.97		2.54	2.01		17.84	7.30		21.36	8.41	
MomGE35	Mom Age at child birth >= 35	226	2.96	9.42		2.86	2.19		17.91	8.23		21.14	9.41	
Birth Order	Categories		0.8667			0.0186			0.5641			0.8485		
BirthOrder1_1	= 1 if 1st born	313	2.53	8.36		2.85	2.04		17.80	7.53		20.98	8.62	
BirthOrder2_1	= 1 if 2nd born	273	2.23	6.57		2.39	1.86		17.19	7.83		20.59	8.89	
BirthOrderGE3_1	= 1 if 3rd born or higher	166	2.20	9.36		2.78	2.31		17.20	7.52		20.65	8.64	
Multiple	Categories		0.7151			0.0129			<0.0001			<0.0001		
Multiple	0=not twin or triplet	718	2.37	8.10		2.62	2.00		17.16	7.26		20.42	8.32	
Multiple	1=twin or triplet	34	1.86	5.49		3.52	2.71		23.51	11.89		28.07	12.83	
Breast Feeding	Categories		0.1867			0.2110			0.0679			0.0345		
BFNone	= 1 if Breastfed 0 months	165	2.29	8.01		2.90	1.90		18.03	7.91		21.34	9.20	
BFI_6mos	= 1 if Breastfed 1-5.99 months	273	1.72	5.42		2.64	2.22		16.59	7.97		19.68	9.09	
BFG6mos	= 1 if Breastfed 6+ months	314	2.93	9.67		2.56	1.96		17.88	7.13		21.41	8.02	
PovertyRatio1	Categories		0.0003			0.4379	-0.02 ^a		0.0530	0.17 ^a		0.0302	0.22 ^a	
Education	Categories		0.5862			0.9461			0.0255			0.0332		
MomEduc_NoHS	= 1 if no HS Dipl	24	1.59	4.31		2.71	1.68		13.96	5.62		16.78	7.17	
MomEduc_HS	= 1 if Mom HS Grad	113	1.68	5.47		2.57	1.93		16.57	5.98		20.03	6.80	
MomEduc_Some	= 1 if Mom Some Coll	166	2.05	9.19		2.71	2.22		17.06	8.99		20.20	10.15	
MomEduc_Coll	= 1 if Mom Coll Grad	449	2.67	8.20		2.67	2.03		18.00	7.49		21.37	8.58	
Single Parent	Categories		0.6124			0.3365			0.1258			0.0878		
Single Parent	0=child does not live in a single parent household	638	2.41	8.25		2.63	1.98		17.63	7.39		21.00	8.41	
Single Parent	1=child lives in a single parent household	114	2.00	6.42		2.83	2.42		16.44	8.86		19.48	10.19	
BioDadYcarsImpVal1	Dad age in years	752	0.0933	0.08 ^a		0.0021	0.04 ^a		0.0405	0.09 ^a		0.0304	0.11 ^a	
DadAge Categories	Categories		0.1557			0.0414			0.0894			0.0816		
DadI20_11	Dad < 20 years old	7	0.00	0.00		2.08	1.95		18.04	1.70		20.34	3.60	
Dad20_29_11	Dad 20-29 years old	181	1.61	6.23		2.47	1.94		16.40	7.64		19.64	8.63	
Dad30_39_11	Dad 30-39 years old	424	2.26	7.45		2.60	1.91		17.71	7.36		21.02	8.54	
Dad40_49_11	Dad 40-49 years old	128	3.55	11.24		3.14	2.53		17.59	8.56		21.01	9.45	
DadGE49_11	Dad >49 years old	12	5.23	9.93		3.04	2.12		21.89	6.84		26.27	8.12	
HC_InitInad_1	Categories		0.6166			0.8827			<0.0001			<0.0001		
HC_InitInad_1	0 else	735	2.37	8.07		2.66	2.04		17.22	7.09		20.51	8.19	
HC_InitInad_1	1=if Kotel Init PNC = INADEQ	18	1.42	4.12		2.73	2.33		26.76	17.63		31.12	18.51	
HC_Cholesterol	Last Cholesterol Check		0.7384			0.3944			0.7608			0.5065		
HC_Cholest_0	0=Never	126	2.40	10.37		2.57	1.74		17.21	6.71		20.72	7.59	
HC_Cholest_1	1=>3 yrs	106	1.79	5.62		2.46	2.64		17.92	6.88		21.68	7.81	
HC_Cholest_2	2=w/in 3 yrs	520	2.45	7.75		2.73	1.98		17.41	7.99		20.59	9.14	
HC_PAP	Last Pap Smear (Categorical)		0.3853			0.1686			0.7779			0.9005		
HC_PAP_0	0=never	3	0.00	0.00		1.46	2.53		14.78	3.58		18.47	7.37	
HC_PAP_1	1 >= 3 yrs	46	3.83	15.35		2.20	1.92		17.06	6.33		20.76	7.58	
HC_PAP_2	2=w/in 3 yrs	703	2.26	7.29		2.70	2.05		17.48	7.73		20.78	8.80	

Exhibit 9.3.10. Relationships of Covariates to Exposure Measures for n=752 Controls

Variable	Covariate Level	N	PreNatThimer			Exp01mos			Exp07mos			Exp020mos		
			ProbF	Mean	SD	ProbF	Mean	SD	ProbF	Mean	SD	ProbF	Mean	SD
PreNatTuna	Prenatal Tuna (0=none, 1=moderate, 2=high)		0.9054			0.6413			0.4398			0.3319		
None		256	2.17	6.99	2.75	2.20	17.58	8.52	20.91	9.65				
Moderate		477	2.43	8.50	2.63	1.97	17.46	7.12	20.81	8.15				
High		19	2.63	7.88	2.40	2.00	15.26	7.40	17.85	9.06				
PreNatFish	0= PreNatTuna not Hi or no PreNatOceanFresh 1= PreNatTuna=Hi or PreNatOceanFresh	669	0.6524	2.30	7.72	0.3130	2.64	2.05	0.8449	17.43	7.35	0.9630	20.77	8.39
PreNatFish		83	2.72	9.98	2.88	2.01	17.60	9.67	20.72	11.04				
PreNatOthMerc	Sum of prenatal non-vac merc exposures	667	0.3037	2.25	7.55	0.3076	2.67	2.06	0.9644	17.46	7.82	0.8956	20.74	8.95
0		76	3.48	11.50	2.51	1.92	17.37	5.85	21.11	6.34				
1		9	0.00	0.00	3.61	1.86	16.81	7.38	19.87	9.19				
2														
PreNatOthMerc	Any	667	0.3530	2.25	7.55	0.8534	2.70	2.06	0.8659	17.46	7.82	0.8089	20.74	8.95
PreNatOthMerc	Any	85	3.11	10.92	2.63	1.82	17.31	5.98	20.98	6.64				
PreNatFillings_1	Categorical		0.7317	2.07	7.92	0.6527	2.73	1.90	0.1176	17.81	7.61	0.1291	21.11	8.68
None		201	2.80	7.95	2.51	2.70	18.51	8.15	22.01	9.06				
no Wrk. Grnd. gum		117	2.36	8.05	2.67	1.92	16.99	7.48	20.27	8.61				
YesWrk. Grnd. or Gum		434												
PreNatNicotine_1	0=no tobacco use: pregnancy 1=any tobacco use: pregnancy	714	0.0726	2.23	7.21	0.5260	2.68	2.06	0.2834	17.52	7.77	0.2057	20.86	8.87
PreNatNicotine_1		38	4.62	17.06	2.46	1.76	16.15	4.15	19.02	4.49				
PreNatAlcohol_1	Categorical		0.4993	2.23	7.26	0.1056	2.71	2.05	0.7058	17.42	7.72	0.6266	20.75	8.81
0=Never		695	3.90	14.44	2.04	1.89	17.80	6.58	21.12	7.49				
1=Occasional		55	0.00	0.00	4.30	0.00	20.95	9.55	20.95	9.55				
2=Light		1	0.00	0.00	3.01	0.00	0.00	0.00	0.00	0.00				
3=Moderate		1												
PreNatIIDrug	0=No Cocaine or Narcotic use during Pregnancy 1=Cocaine or Narcotic use during Pregnancy	47	0.0317	2.30	7.93	0.5755	2.67	2.05	0.8132	17.44	7.66	0.9894	20.77	8.74
PreNatIIDrug		5	10.00	13.69	2.15	1.99	18.25	2.63	20.82	2.28				
PreNatValproic	Used Prenatal Valproic acid	748	0.8337	2.35	8.01	0.4566	2.67	2.05	0.2191	17.47	7.64	0.1671	20.80	8.71
PreNatValproic	0= did not use Prenatal Valproic acid 1= Used Prenatal Valproic acid	4	3.19	6.38	1.90	2.20	12.77	6.23	0.4922	14.76	7.57			
Folic_PNVit_Multi	0=no Folic, PreNatVit or Multivit prenatal 1= Folic, PreNatVit or Multivit prenatal	64	0.2243	1.19	4.34	0.4425	2.48	1.75	0.7222	17.77	8.01	0.4922	21.48	8.82
Folic_PNVit_Multi		688	2.46	8.25	2.68	2.07	17.42	7.60	20.70	8.71				
PreNatViralInf	0= no viral infections during pregnancy 1= any viral infections during pregnancy	712	0.8788	2.34	8.04	0.7984	2.66	2.03	0.0025	17.25	7.61	0.0066	20.56	8.71
PreNatViralInf		40	2.54	7.15	2.74	2.30	20.99	7.31	0.4198	20.57	8.84	0.2888	20.57	8.84
PreNatLead_1	=0 else	563	0.0371	2.00	7.25	0.6834	2.65	2.08	0.4198	17.32	7.76	0.2888	20.57	8.84
PreNatLead_1	=1 if PreNatResiLead or PreNatOccupLead=1	189	3.40	9.83	2.72	1.95	17.83	7.26	0.4198	17.32	7.76	0.2888	20.57	8.84
Birthwgt	Weight at birth in grams	752	0.2835	0.00	5.31	<0.0001	5.31	-0.00	<0.0001	-0.00	<0.0001	<0.0001	-0.00	<0.0001
Birth Weight	Categorical		0.8009	0.00	0.00	<0.0001	0.00	0.00	<0.0001	60.72	8.80	<0.0001	66.87	13.95
BW<1kg	=1 if Birth wgt < 1 Kg	2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	60.72	8.80	<0.0001	66.87	13.95
BW_1_1p5k	=1 if Birth wgt 1.0Kg to 1.499 Kg	5	2.55	5.70	2.54	3.48	29.95	16.88	32.66	17.06				
BW_1p5_2p5k	=1 if Birth wgt 1.5 kg to 2.499 Kg	40	1.89	6.06	4.27	3.78	22.58	9.26	26.47	10.76				
BW2p5_4k	=1 if Birth wgt 2.5 Kg to 3.999 Kg	595	2.31	7.84	2.71	1.90	17.11	7.04	20.34	8.17				
BW4kup	=1 if Birth wgt 4.0 Kg and up	110	2.75	9.52	1.86	1.42	16.05	5.97	19.63	6.77				

Exhibit 9.3.10. Relationships of Covariates to Exposure Measures for n=752 Controls

Variable	Covariate Level	N	PreNatThimer		Exp01mos		Exp07mos		Exp020mos					
			ProbF	Mean	SD	ProbF	Mean	SD	ProbF	Mean	SD			
CSAPGAR	5 minute Apgar Score	4	0.4986	0.00	0.00	0.4934	2.20	1.47	<0.0001	12.61	6.65	0.0003	13.53	6.32
CSAPGAR	6	1		0.00	0.00		0.00			54.50			57.01	
CSAPGAR	7	8		0.00	0.00		2.26	1.91		17.43	5.74		19.47	7.04
CSAPGAR	8	37		2.03	6.92		2.19	2.04		15.86	8.00		19.22	9.10
CSAPGAR	9	678		2.42	8.19		2.70	2.06		17.41	7.52		20.77	8.63
CSAPGAR	10	24		2.10	6.06		2.77	1.74		20.18	6.94		23.15	7.80
RespDistress			0.7061			0.0012			<0.0001			<0.0001		
RespDistress	0= no Resp Distress Syndrome (hyaline)	730		2.37	8.05		2.71	2.04		17.25	7.18		20.55	8.28
RespDistress	1= Resp Distress Syndrome (hyaline)	22		1.72	5.87		1.27	1.99		24.09	15.77		28.00	16.69
Bilirubin			0.5765			0.3268			<0.0001			<0.0001		
Bilirubin	0= no hyperbilirubinemia	695		2.40	8.19		2.69	2.04		17.14	6.99		20.40	8.07
Bilirubin	1= hyperbilirubinemia	57		1.78	5.03		2.41	2.10		21.18	12.64		25.27	13.71
Anemia			0.4500			0.8385			0.0205			0.0024		
Anemia	0= no anemia 6-30 mos	729		2.39	8.09		2.66	2.05		17.33	7.63		20.59	8.69
Anemia	1= anemia 6-30 mos	23		1.11	3.67		2.75	1.92		21.07	6.92		26.20	7.89
ChildLead			0.1704			0.7542			0.3766			0.4936		
ChildLead	0= no child exposure to lead	734		2.29	7.94		2.67	2.05		17.41	7.66		20.73	8.73
ChildLead	1=child exposure to lead	18		4.90	9.79		2.51	1.91		19.01	6.67		22.16	8.10
ChildPica			0.5321			0.8725			0.8940			0.7841		
ChildPica	0= child did not have pica	734		2.32	7.99		2.67	2.05		17.45	7.65		20.78	8.72
ChildPica	1=child had pica	18		3.51	8.46		2.59	1.97		17.21	7.19		20.21	8.67
Enceph			0.7689			0.1931			<0.0001			<0.0001		
Enceph	0=no Encephalitis or CNS infection	751		2.35	8.00		2.67	2.05		17.38	7.42		20.69	8.48
Enceph	1=Encephalitis or any CNS infection	1		0.00			0.00			66.94			76.74	

* For variables on a continuous scale (mother age in years, poverty ratio, and father's age in years) the number shown in the "Mean" column is the regression coefficient from a simple linear regression of the variable on the exposure measure.

9.4. Model Results

The model results summarized in this section are organized by exposure model type, and then by outcome type. For example, the first section that follows corresponds to models with exposure effects for prenatal exposure (*PreNatThimer*) and cumulative exposure for the period spanning birth to seven months (*Exp07mos*). Within that section there are model summaries for exposure effects corresponding to each of the seven outcome classifications, (i.e., ASD, AD, ASD-not-AD, ASD w/ Regression, AD w/Low cognitive function excluded, ASD w/ screened control group, and AD with screened control group). There are sections and summaries for the following exposure model types:

- Prenatal and birth to seven month exposures – *PreNatThimer*, *Exp07mos*
- Prenatal and birth to one month, and one to 7 month exposures – *PreNatThimer*, *Exp01mos*, *Exp17mos*
- Prenatal and birth to twenty month exposures – *PreNatThimer*, *Exp020mos*
- Sex by exposure interactions- Sex by: *PreNatThimer*, *Exp07mos*
- Sex by exposure interactions- Sex by: *PreNatThimer*, *Exp01mos*, *Exp17mos*
- Sex by exposure interactions- Sex by: *PreNatThimer*, *Exp020mos*
- Prenatal by postnatal exposure interactions
- Concurrent antibiotics by exposure interactions

For explanation of exposure variables, please see Chapter 7, Sections 7.3, and 7.4. For explanation of outcome classifications, see Chapter 7, Section 7.1. For explanation of analysis sample size see Chapter 5, Section 5.4. And for covariate selection procedures, see Chapter 8, Section 8.2. All models were fit to the data using the SAS software's PhReg procedure with the "ties = discrete" option (SAS version 9.1).

Each model summary shows the parameter estimates and standard errors of exposure effects, as well as p-values for the null hypotheses that the exposure effects are equal to zero. Odds ratios and 95 percent confidence intervals corresponding to a one-unit increase in the exposure measure are shown. In many studies, a one-unit increase in exposure represents the difference between 'exposed' and 'not exposed', and for those studies this kind of odds ratio has intuitive relevance. However, for the current study a one-unit increase in the postnatal exposure measures correspond to a one microgram per kilogram increase in exposure, which lacks intuitive meaning. Accordingly we also show the odds ratio corresponding to a two standard deviation unit increase in the exposure measure. We show these in order to serve as guidelines as to the odds ratios associated with an increase in exposure that roughly corresponds to the difference between low and high exposure. See Chapter 8, Section 8.3 for more details on the use of the odds ratio corresponding to a two standard deviation increase in exposure as a measure of effect size.

Additionally, when the estimated odds ratio is less than one, the summary tables show the inverse of the odd ratio ($1 / OR$). For example, if the estimated odds ratio were 0.66, then taking its inverse yields the value 1.5, which can be interpreted as indicating that the odds of disease is one and a half times higher for the unexposed than for the exposed. See Chapter 8, section 8.3 for more details

9.4.1. Main Effect Models

9.4.1.1. Birth through Seven Months and Prenatal Exposures

Models of the form shown below were used to address the research question of whether there is an association between autism risk and either prenatal thimerosal exposure, or cumulative thimerosal exposure from birth through seven months of age. For definitions of model terms and the list of covariates used for each outcome, see Chapter 8, section 8.2.

$$\log\left(\frac{\pi}{1-\pi}\right) = \alpha_i + \beta_1 preNatThimer + \beta_2 Exp07mos + \sum_j \alpha_j oe_j + \sum_k \alpha_{j+k} cf_k$$

$$H_0 : \beta_1 = 0 \quad vs \quad H_a : \beta_1 \neq 0$$

$$H_0 : \beta_2 = 0 \quad vs \quad H_a : \beta_2 \neq 0$$

The results are summarized in Exhibit 9.4.1. For selected examples of full model results, including parameter estimates for covariate terms, see Volume II, Chapter 19.

Exhibit 9.4.1. Model Summary: PreNatThimer and Exp07mos Exposure Models

Outcome	N	Exposure Measure	Estimate	Stderr	Prob ChiSq	One Unit Chg.				2 SD Unit Chg.	
						OR ^a	Lower 95% CL	Upper 95% CL	1/OR	OR ^b	1/OR
ASD_Outc	1008	PreNatThimer	0.0069	0.0094	0.466	1.007	0.988	1.026	1.034	1.12	
ASD_Outc	1008	Exp07mos	-0.0331	0.0166	0.046 *	0.967	0.937	0.999	1.034	0.60	1.67
AD_Outc	911	PreNatThimer	0.0110	0.0105	0.296	1.011	0.990	1.032	1.043	1.20	
AD_Outc	911	Exp07mos	-0.0425	0.0188	0.024 *	0.958	0.924	0.994	1.043	0.52	1.94
ASD_Only	773	PreNatThimer	-0.0022	0.0200	0.913	0.998	0.959	1.038	1.002	0.96	1.04
ASD_Only	773	Exp07mos	-0.0246	0.0294	0.401	0.976	0.921	1.033	1.025	0.68	1.47
ASD_Regr	701	PreNatThimer	0.0380	0.0211	0.072 ~	1.039	0.997	1.083	1.104	1.86	
ASD_Regr	701	Exp07mos	-0.0991	0.0338	0.003 **	0.906	0.848	0.968	1.104	0.21	4.68
AD_ExLoCF	884	PreNatThimer	0.0156	0.0105	0.137	1.016	0.995	1.037	1.056	1.29	
AD_ExLoCF	884	Exp07mos	-0.0547	0.0204	0.008 **	0.947	0.910	0.985	1.056	0.43	2.34
ASD_Scr	821	PreNatThimer	0.0047	0.0098	0.631	1.005	0.986	1.024	1.045	1.08	
ASD_Scr	821	Exp07mos	-0.0442	0.0186	0.017 *	0.957	0.922	0.992	1.045	0.50	1.99
AD_Scr	728	PreNatThimer	0.0124	0.0115	0.280	1.012	0.990	1.036	1.061	1.22	
AD_Scr	728	Exp07mos	-0.0591	0.0224	0.008 *	0.943	0.902	0.985	1.061	0.40	2.51

~ p<0.10; * p<0.05; ** p<0.01

^a Odds ratio corresponding to a one-unit increase in exposure measure

^b Odds ratio corresponding to a two-standard deviation unit increase in the exposure measure. This difference can be thought of as roughly corresponding to the difference between low and high exposure.

9.4.1.2. Birth Dose, One to Seven Months, and Prenatal Exposures

The model shown below corresponds to the research question concerning the link between autism risk and the timing of thimerosal exposure. In this model, postnatal exposure measures are split into two time periods. The first time period corresponds to birth dose, which usually corresponds to a hepatitis B vaccine received on the day of birth, or shortly thereafter. Small numbers of children also received an immune globulin within a few days of birth. The exposure term *Exp01mos* corresponds to cumulative exposures for the period from birth to one month (1 to 28 days). The second time period corresponds to cumulative exposures for the period spanning one to seven months (29 – 214 days).

$$\log\left(\frac{\pi}{1-\pi}\right) = \alpha_i + \beta_1 \text{preNatThimer} + \beta_2 \text{Exp01mos} + \beta_3 \text{Exp17mos} + \sum_j \alpha_j o e_j + \sum_k \alpha_{j+k} c f_k$$

$$H_0 : \beta_1 = 0 \quad \text{vs} \quad H_a : \beta_1 \neq 0$$

$$H_0 : \beta_2 = 0 \quad \text{vs} \quad H_a : \beta_2 \neq 0$$

$$H_0 : \beta_3 = 0 \quad \text{vs} \quad H_a : \beta_3 \neq 0$$

The results are summarized in Exhibit 9.4.2.

Exhibit 9.4.2. Model Summary: PreNatThimer , Exp01mos, Exp17mos Exposure Models

Outcome	N	Exposure Measure	Estimate	Stderr	Prob ChiSq	One				2 SD	
						Unit Chg. OR ^a	Lower 95% CL	Upper 95% CL	1/OR	Unit Chg. OR ^b	1/OR
ASD_Outc	1008	PreNatThimer	0.0069	0.0094	0.466	1.007	0.988	1.026		1.12	
ASD_Outc	1008	Exp01mos	-0.0304	0.0447	0.497	0.970	0.889	1.059	1.031	0.88	1.13
ASD_Outc	1008	Exp17mos	-0.0336	0.0182	0.064 ~	0.967	0.933	1.002	1.034	0.61	1.63
AD_Outc	911	PreNatThimer	0.0106	0.0106	0.318	1.011	0.990	1.032		1.19	
AD_Outc	911	Exp01mos	0.0284	0.0489	0.562	1.029	0.935	1.132		1.12	
AD_Outc	911	Exp17mos	-0.0560	0.0211	0.008 **	0.946	0.907	0.985	1.058	0.44	2.26
ASD_Only	773	PreNatThimer	-0.0042	0.0197	0.831	0.996	0.958	1.035	1.004	0.93	1.07
ASD_Only	773	Exp01mos	-0.2163	0.0952	0.023 *	0.806	0.668	0.971	1.241	0.41	2.42
ASD_Only	773	Exp17mos	0.0011	0.0307	0.971	1.001	0.943	1.063		1.02	
ASD_Regr	701	PreNatThimer	0.0380	0.0211	0.073 ~	1.039	0.997	1.083		1.86	
ASD_Regr	701	Exp01mos	-0.1043	0.0863	0.227	0.901	0.761	1.067	1.110	0.65	1.53
ASD_Regr	701	Exp17mos	-0.0980	0.0377	0.009 **	0.907	0.842	0.976	1.103	0.24	4.16
AD_ExLoCF	884	PreNatThimer	0.0155	0.0105	0.141	1.016	0.995	1.037		1.29	
AD_ExLoCF	884	Exp01mos	-0.0103	0.0533	0.846	0.990	0.892	1.099	1.010	0.96	1.04
AD_ExLoCF	884	Exp17mos	-0.0632	0.0228	0.006 **	0.939	0.898	0.982	1.065	0.40	2.51
ASD_Scr	821	PreNatThimer	0.0047	0.0098	0.633	1.005	0.986	1.024		1.08	
ASD_Scr	821	Exp01mos	-0.0672	0.0473	0.156	0.935	0.852	1.026	1.070	0.76	1.32
ASD_Scr	821	Exp17mos	-0.0400	0.0202	0.048 *	0.961	0.923	1.000	1.041	0.56	1.79
AD_Scr	728	PreNatThimer	0.0118	0.0116	0.307	1.012	0.989	1.035		1.21	
AD_Scr	728	Exp01mos	-0.0026	0.0538	0.962	0.997	0.898	1.108	1.003	0.99	1.01
AD_Scr	728	Exp17mos	-0.0707	0.0248	0.004 **	0.932	0.888	0.978	1.073	0.36	2.79

~ p<0.10; * p<0.05; ** p<0.01

^a Odds ratio corresponding to a one-unit increase in exposure measure

^b Odds ratio corresponding to a two-standard deviation unit increase in the exposure measure. This difference can be thought of as roughly corresponding to the difference between low and high exposure.

9.4.1.3. Birth through Twenty Months and Prenatal Exposures

Models of the form shown below were used to address the research question of whether there is an association between autism risk and either prenatal thimerosal exposure, or cumulative thimerosal exposure from birth through twenty months of age.

$$\log\left(\frac{\pi}{1-\pi}\right) = \alpha_i + \beta_1 preNatThimer + \beta_2 Exp020mos + \sum_j \alpha_j oe_j + \sum_k \alpha_{j+k} cf_k$$

$$H_0 : \beta_1 = 0 \quad \text{vs} \quad H_a : \beta_1 \neq 0$$

$$H_0 : \beta_2 = 0 \quad \text{vs} \quad H_a : \beta_2 \neq 0$$

Exhibit 9.4.3. Model Summary: PreNatThimer and Exp020mos Exposure Models

Outcome	N	Exposure Measure	Estimate	Stderr	Prob ChiSq	One				2 SD	
						Unit Chg. OR ^a	Lower 95% CL	Upper 95% CL	1/OR	Unit Chg. OR ^b	1/OR
ASD_Outc	1008	PreNatThimer	0.0067	0.0094	0.476	1.007	0.988	1.026		1.12	
ASD_Outc	1008	Exp020mos	-0.0330	0.0160	0.039 *	0.968	0.938	0.998	1.034	0.56	1.80
AD_Outc	911	PreNatThimer	0.0104	0.0105	0.322	1.010	0.990	1.032		1.19	
AD_Outc	911	Exp020mos	-0.0391	0.0181	0.031 *	0.962	0.928	0.996	1.040	0.50	2.01
ASD_Only	773	PreNatThimer	-0.0019	0.0201	0.924	0.998	0.960	1.038	1.002	0.97	1.03
ASD_Only	773	Exp020mos	-0.0270	0.0277	0.331	0.973	0.922	1.028	1.027	0.62	1.62
ASD_Regr	701	PreNatThimer	0.0364	0.0207	0.080 ~	1.037	0.996	1.080		1.81	
ASD_Regr	701	Exp020mos	-0.0780	0.0321	0.015 *	0.925	0.869	0.985	1.081	0.25	4.02
AD_ExLoCF	884	PreNatThimer	0.0150	0.0105	0.154	1.015	0.994	1.036		1.28	
AD_ExLoCF	884	Exp020mos	-0.0493	0.0196	0.012 *	0.952	0.916	0.989	1.051	0.42	2.41
ASD_Scr	821	PreNatThimer	0.0045	0.0098	0.648	1.005	0.985	1.024		1.08	
ASD_Scr	821	Exp020mos	-0.0384	0.0177	0.030 *	0.962	0.929	0.996	1.039	0.50	1.98
AD_Scr	728	PreNatThimer	0.0118	0.0115	0.308	1.012	0.989	1.035		1.21	
AD_Scr	728	Exp020mos	-0.0486	0.0212	0.022 *	0.953	0.914	0.993	1.050	0.42	2.38

~ p<0.10; * p<0.05; ** p<0.01

^a Odds ratio corresponding to a one-unit increase in exposure measure

^b Odds ratio corresponding to a two-standard deviation unit increase in the exposure measure. This difference can be thought of as roughly corresponding to the difference between low and high exposure.

9.4.2. Sex by Exposure Interaction Models

9.4.2.1. Sex by: PreNatThimer, Exp07mos

Since sex is a matching factor, its main effect is already contained in the model via the conditioning on matching strata. In order to address the secondary research question about whether there are different exposure effects for boys and girls, we specify models that have sex-by-exposure interaction terms, but no main effects term for sex, since that effect is already carried by the conditioning on the matching strata. This strategy is described in Kleinbaum and Klein (2002). The models shown illustrate this strategy. The first model results in tests of whether sex is an effect modifier for either thimerosal

exposure during the prenatal period or cumulative exposures from birth up through seven months of age. The results of the second and third sex by exposure interaction models are summarized in the sections the follow. The second model results in three interaction tests, corresponding to the exposures in the prenatal period, the birth to one month period, and the cumulative exposures from ages 1 to 7 months period. The third model includes a test for an interaction between sex and prenatal and cumulative exposures from birth through 20 months. The *Sexmale* variable is a dummy variable (1 if the child is male, 0 if the child is female). There is no main effect term for *Sexmale* specified in these models because sex is a matching variable.

$$\log\left(\frac{\pi}{1-\pi}\right) = \alpha_i + \beta_1 preNatThimer + \beta_2 Exp07mos + \beta_3 preNatThimer * Sexmale + \beta_4 Exp07mos * Sexmale + \sum_j \alpha_j oe_j + \sum_k \alpha_{j+k} cf_k$$

In the summary table, the estimates corresponding to the *FemPreNatThimer* effect is the estimate $\hat{\beta}_1$ from the model above. The estimates corresponding to the *MalPreNatThimer* effect was calculated as the sum of the estimates $\hat{\beta}_1 + \hat{\beta}_3$. The *SexbyPreNatThimer* effect is $\hat{\beta}_3$. Similarly, the effects *FemExp07mos*, *MalExp07mos*, *SexByExp07mos* correspond to $\hat{\beta}_2$, $\hat{\beta}_2 + \hat{\beta}_4$, and $\hat{\beta}_4$, respectively.

Exhibit 9.4.4. Model Summary: Sex by PreNatThimer, Exp07mos Interaction Models

Outcome	N	Exposure Measure	Estimate	Stderr	Prob ChiSq	One				2 SD	
						Unit Chg. OR ^a	Lower 95% CL	Upper 95% CL	1/OR	Unit Chg. OR ^b	1/OR
ASD_Outc	1008	FemPreNatThimer	-0.0219	0.0360	0.543	0.978	0.912	1.050	1.022	0.70	1.43
ASD_Outc	1008	MalPreNatThimer	0.0119	0.0106	0.259	1.012	0.991	1.033		1.22	
ASD_Outc	1008	SexByPreNatThimer	0.0338	0.0376	0.369						
ASD_Outc	1008	FemExp07mos	-0.0038	0.0397	0.925	0.996	0.922	1.077	1.004	0.94	1.06
ASD_Outc	1008	MalExp07mos	-0.0394	0.0179	0.028*	0.961	0.928	0.996	1.040	0.54	1.85
ASD_Outc	1008	SexByExp07mos	-0.0356	0.0427	0.404						
AD_Outc	911	FemPreNatThimer	-0.0387	0.0499	0.438	0.962	0.872	1.061	1.039	0.53	1.88
AD_Outc	911	MalPreNatThimer	0.0184	0.0121	0.128	1.019	0.995	1.043		1.35	
AD_Outc	911	SexByPreNatThimer	0.0571	0.0515	0.267						
AD_Outc	911	FemExp07mos	-0.0359	0.0514	0.486	0.965	0.872	1.067	1.037	0.57	1.75
AD_Outc	911	MalExp07mos	-0.0449	0.0200	0.025*	0.956	0.919	0.994	1.046	0.50	2.01
AD_Outc	911	SexByExp07mos	-0.0091	0.0543	0.868						
ASD_Only	773	FemPreNatThimer	0.0145	0.0613	0.813	1.015	0.900	1.144		1.27	

<i>ASD_Only</i>	773	<i>MalPreNatThimer</i>	-0.0024	0.0213	0.912	0.998	0.957	1.040	1.002	0.96	1.04
<i>ASD_Only</i>	773	<i>SexByPreNatThimer</i>	-0.0168	0.0648	0.795						
<i>ASD_Only</i>	773	<i>FemExp07mos</i>	0.0740	0.0754	0.327	1.077	0.929	1.248		3.16	
<i>ASD_Only</i>	773	<i>MalExp07mos</i>	-0.0401	0.0319	0.209	0.961	0.902	1.023	1.041	0.54	1.87
<i>ASD_Only</i>	773	<i>SexByExp07mos</i>	-0.1141	0.0805	0.156						
<i>ASD_Regr</i>	701	<i>FemPreNatThimer</i>	0.0330	0.0554	0.551	1.034	0.927	1.152		1.71	
<i>ASD_Regr</i>	701	<i>MalPreNatThimer</i>	0.0385	0.0231	0.097 [~]	1.039	0.993	1.087		1.88	
<i>ASD_Regr</i>	701	<i>SexByPreNatThimer</i>	0.0055	0.0606	0.928						
<i>ASD_Regr</i>	701	<i>FemExp07mos</i>	-0.1118	0.0714	0.118	0.894	0.777	1.029	1.118	0.18	5.70
<i>ASD_Regr</i>	701	<i>MalExp07mos</i>	-0.0962	0.0379	0.011 [*]	0.908	0.843	0.978	1.101	0.22	4.47
<i>ASD_Regr</i>	701	<i>SexByExp07mos</i>	0.0155	0.0786	0.843						
<i>AD_ExLoCF</i>	884	<i>FemPreNatThimer</i>	-0.0391	0.0509	0.442	0.962	0.870	1.062	1.040	0.53	1.90
<i>AD_ExLoCF</i>	884	<i>MalPreNatThimer</i>	0.0245	0.0124	0.048 [*]	1.025	1.000	1.050		1.49	
<i>AD_ExLoCF</i>	884	<i>SexByPreNatThimer</i>	0.0636	0.0526	0.226						
<i>AD_ExLoCF</i>	884	<i>FemExp07mos</i>	-0.0938	0.0619	0.130	0.910	0.806	1.028	1.098	0.23	4.30
<i>AD_ExLoCF</i>	884	<i>MalExp07mos</i>	-0.0520	0.0216	0.016 [*]	0.949	0.910	0.990	1.053	0.45	2.25
<i>AD_ExLoCF</i>	884	<i>SexByExp07mos</i>	0.0418	0.0645	0.517						
<i>ASD_Scr</i>	821	<i>FemPreNatThimer</i>	-0.0111	0.0287	0.699	0.989	0.935	1.046	1.011	0.83	1.20
<i>ASD_Scr</i>	821	<i>MalPreNatThimer</i>	0.0088	0.0113	0.434	1.009	0.987	1.031		1.15	
<i>ASD_Scr</i>	821	<i>SexByPreNatThimer</i>	0.0199	0.0308	0.519						
<i>ASD_Scr</i>	821	<i>FemExp07mos</i>	-0.0265	0.0456	0.561	0.974	0.891	1.065	1.027	0.66	1.51
<i>ASD_Scr</i>	821	<i>MalExp07mos</i>	-0.0480	0.0199	0.016 [*]	0.953	0.917	0.991	1.049	0.47	2.11
<i>ASD_Scr</i>	821	<i>SexByExp07mos</i>	-0.0215	0.0485	0.658						
<i>AD_Scr</i>	728	<i>FemPreNatThimer</i>	-0.0175	0.0462	0.704	0.983	0.898	1.076	1.018	0.75	1.33
<i>AD_Scr</i>	728	<i>MalPreNatThimer</i>	0.0174	0.0132	0.187	1.018	0.992	1.044		1.33	
<i>AD_Scr</i>	728	<i>SexByPreNatThimer</i>	0.0349	0.0482	0.468						
<i>AD_Scr</i>	728	<i>FemExp07mos</i>	-0.0764	0.0714	0.285	0.926	0.805	1.066	1.079	0.30	3.28
<i>AD_Scr</i>	728	<i>MalExp07mos</i>	-0.0588	0.0232	0.011 [*]	0.943	0.901	0.987	1.061	0.40	2.50
<i>AD_Scr</i>	728	<i>SexByExp07mos</i>	0.0175	0.0734	0.811						

~ p<0.10; * p<0.05; ** p<0.01

^a Odds ratio corresponding to a one-unit increase in exposure measure

^b Odds ratio corresponding to a two-standard deviation unit increase in the exposure measure. This difference can be thought of as roughly corresponding to the difference between low and high exposure.

9.4.2.2. Sex by: PreNatThimer, Exp01mos, Exp17mos

The model shown below was used to test whether sex is an effect modifier for exposure at three time points: prenatal thimerosal exposure, thimerosal exposure in the first month of life, and thimerosal exposure during the age range of one to seven months.

$$\log\left(\frac{\pi}{1-\pi}\right) = \alpha_i + \beta_1 preNatThimer + \beta_2 HepB + \beta_3 Exp17mos + \beta_4 preNatThimer * sexmale + \beta_5 HepB * sexmale + \beta_6 Exp17mos * sexmale + \sum_j \alpha_j oe_j + \sum_k \alpha_{j+k} cf_k$$

Exhibit 9.4.5. Model Summary: Sex by PreNatThimer, Exp01mos, Exp17mos Interaction Models

Outcome	N	Exposure Measure	Estimate	Stderr	Prob ChiSq	One Unit Chg.				2 SD Unit Chg.	
						OR ^a	95% CL	95% CL	1/OR	OR ^b	1/OR
ASD_Outc	1008	FemPreNatThimer	-0.0224	0.0362	0.536	0.978	0.911	1.050	1.023	0.69	1.44
ASD_Outc	1008	MalPreNatThimer	0.0120	0.0106	0.258	1.012	0.991	1.033		1.22	
ASD_Outc	1008	SexByPreNatThimer	0.0343	0.0379	0.364						
ASD_Outc	1008	FemExp01mos	-0.0166	0.0839	0.844	0.984	0.834	1.159	1.017	0.93	1.07
ASD_Outc	1008	MalExp01mos	-0.0403	0.0516	0.435	0.960	0.868	1.063	1.041	0.85	1.18
ASD_Outc	1008	SexByExp01mos	-0.0238	0.0973	0.807						
ASD_Outc	1008	FemExp17mos	0.0010	0.0480	0.984	1.001	0.911	1.100		1.01	
ASD_Outc	1008	MalExp17mos	-0.0393	0.0196	0.044 *	0.961	0.925	0.999	1.040	0.56	1.77
ASD_Outc	1008	SexByExp17mos	-0.0403	0.0515	0.434						
AD_Outc	911	FemPreNatThimer	-0.0366	0.0495	0.460	0.964	0.875	1.062	1.037	0.55	1.82
AD_Outc	911	MalPreNatThimer	0.0174	0.0122	0.152	1.018	0.994	1.042		1.33	
AD_Outc	911	SexByPreNatThimer	0.0540	0.0512	0.292						
AD_Outc	911	FemExp01mos	0.0302	0.0913	0.741	1.031	0.862	1.233		1.13	
AD_Outc	911	MalExp01mos	0.0203	0.0567	0.720	1.021	0.913	1.140		1.09	
AD_Outc	911	SexByExp01mos	-0.0099	0.1056	0.926						
AD_Outc	911	FemExp17mos	-0.0596	0.0619	0.336	0.942	0.835	1.064	1.061	0.42	2.38
AD_Outc	911	MalExp17mos	-0.0560	0.0225	0.013 *	0.946	0.905	0.988	1.058	0.44	2.26
AD_Outc	911	SexByExp17mos	0.0036	0.0656	0.956						
ASD_Only	773	FemPreNatThimer	0.0174	0.0599	0.771	1.018	0.905	1.144		1.33	
ASD_Only	773	MalPreNatThimer	-0.0040	0.0210	0.847	0.996	0.956	1.038	1.004	0.94	1.07
ASD_Only	773	SexByPreNatThimer	-0.0215	0.0633	0.735						
ASD_Only	773	FemExp01mos	-0.2297	0.2670	0.390	0.795	0.471	1.341	1.258	0.39	2.56
ASD_Only	773	MalExp01mos	-0.2303	0.1033	0.026 *	0.794	0.649	0.973	1.259	0.39	2.56
ASD_Only	773	SexByExp01mos	-0.0007	0.2838	0.998						
ASD_Only	773	FemExp17mos	0.1537	0.0979	0.117	1.166	0.962	1.413		9.35	
ASD_Only	773	MalExp17mos	-0.0173	0.0327	0.597	0.983	0.922	1.048	1.017	0.78	1.29
ASD_Only	773	SexByExp17mos	-0.1710	0.1037	0.099 ~						
ASD_Regr	701	FemPreNatThimer	0.0374	0.0579	0.518	1.038	0.927	1.163		1.84	
ASD_Regr	701	MalPreNatThimer	0.0389	0.0232	0.093 ~	1.040	0.994	1.088		1.89	
ASD_Regr	701	SexByPreNatThimer	0.0015	0.0629	0.982						
ASD_Regr	701	FemExp01mos	0.0136	0.1175	0.908	1.014	0.805	1.276		1.06	
ASD_Regr	701	MalExp01mos	-0.1778	0.1080	0.100	0.837	0.677	1.034	1.195	0.48	2.07

ASD_Regr	701	SexByExp01mos	-0.1914	0.1580	0.226						
ASD_Regr	701	FemExp17mos	-0.1804	0.0999	0.071	~	0.835	0.687	1.015	1.198	0.07 13.78
ASD_Regr	701	MalExp17mos	-0.0809	0.0403	0.045	*	0.922	0.852	0.998	1.084	0.31 3.24
ASD_Regr	701	SexByExp17mos	0.0995	0.1069	0.352						
AD_ExLoCF	884	FemPreNatThimer	-0.0401	0.0513	0.434		0.961	0.869	1.062	1.041	0.52 1.93
AD_ExLoCF	884	MalPreNatThimer	0.0239	0.0124	0.054	~	1.024	1.000	1.049		1.48
AD_ExLoCF	884	SexByPreNatThimer	0.0640	0.0530	0.227						
AD_ExLoCF	884	FemExp01mos	-0.1156	0.1311	0.378		0.891	0.689	1.152	1.123	0.62 1.60
AD_ExLoCF	884	MalExp01mos	0.0028	0.0598	0.963		1.003	0.892	1.127		1.01
AD_ExLoCF	884	SexByExp01mos	0.1184	0.1428	0.407						
AD_ExLoCF	884	FemExp17mos	-0.0858	0.0695	0.217		0.918	0.801	1.052	1.090	0.29 3.48
AD_ExLoCF	884	MalExp17mos	-0.0624	0.0244	0.010	*	0.939	0.896	0.985	1.064	0.40 2.48
AD_ExLoCF	884	SexByExp17mos	0.0234	0.0732	0.749						
ASD_Scr	821	FemPreNatThimer	-0.0110	0.0288	0.702		0.989	0.935	1.046	1.011	0.84 1.20
ASD_Scr	821	MalPreNatThimer	0.0091	0.0113	0.422		1.009	0.987	1.032		1.16
ASD_Scr	821	SexByPreNatThimer	0.0201	0.0310	0.517						
ASD_Scr	821	FemExp01mos	-0.0285	0.0826	0.730		0.972	0.827	1.143	1.029	0.89 1.12
ASD_Scr	821	MalExp01mos	-0.0864	0.0551	0.117		0.917	0.823	1.022	1.090	0.70 1.42
ASD_Scr	821	SexByExp01mos	-0.0580	0.0976	0.553						
ASD_Scr	821	FemExp17mos	-0.0269	0.0560	0.630		0.973	0.872	1.086	1.027	0.68 1.48
ASD_Scr	821	MalExp17mos	-0.0417	0.0215	0.052	~	0.959	0.920	1.000	1.043	0.55 1.83
ASD_Scr	821	SexByExp17mos	-0.0148	0.0593	0.803						
AD_Scr	728	FemPreNatThimer	-0.0158	0.0461	0.732		0.984	0.899	1.077	1.016	0.77 1.29
AD_Scr	728	MalPreNatThimer	0.0164	0.0132	0.213		1.017	0.991	1.043		1.31
AD_Scr	728	SexByPreNatThimer	0.0322	0.0481	0.503						
AD_Scr	728	FemExp01mos	0.0347	0.1004	0.730		1.035	0.850	1.261		1.15
AD_Scr	728	MalExp01mos	-0.0257	0.0618	0.678		0.975	0.863	1.100	1.026	0.90 1.11
AD_Scr	728	SexByExp01mos	-0.0603	0.1159	0.603						
AD_Scr	728	FemExp17mos	-0.1395	0.0935	0.136		0.870	0.724	1.045	1.150	0.13 7.60
AD_Scr	728	MalExp17mos	-0.0649	0.0257	0.012	*	0.937	0.891	0.986	1.067	0.39 2.57
AD_Scr	728	SexByExp17mos	0.0745	0.0960	0.438						

~ p<0.10; * p<0.05; ** p<0.01

^a Odds ratio corresponding to a one-unit increase in exposure measure

^b Odds ratio corresponding to a two-standard deviation unit increase in the exposure measure. This difference can be thought of as roughly corresponding to the difference between low and high exposure.

9.4.2.3. Sex by: PreNatThimer, Exp020mos

The third model included a test for an interaction between sex and cumulative exposures from birth through 20 months.

$$\log\left(\frac{\pi}{1-\pi}\right) = \alpha_i + \beta_1 preNatThimer + \beta_2 Exp020mos + \beta_3 preNatThimer * Sexmale + \beta_4 Exp020mos * Sexmale + \sum_j \alpha_j oe_j + \sum_k \alpha_{j+k} cf_k$$

Exhibit 9.4.6. Model Summary: Sex by PreNatThimer, Exp020mos Interaction Models

Outcome	N	Exposure Measure	Estimate	Stderr	Prob ChiSq	One Unit				2 SD Unit	
						Chg. OR ^a	Lower 95% CL	Upper 95% CL	1/OR	Chg. OR ^b	1/OR
ASD_Outc	1008	FemPreNatThimer	-0.0230	0.0362	0.526	0.977	0.910	1.049	1.023	0.69	1.46
ASD_Outc	1008	MalPreNatThimer	0.0115	0.0105	0.274	1.012	0.991	1.033		1.21	
ASD_Outc	1008	SexByPreNatThimer	0.0345	0.0378	0.362						
ASD_Outc	1008	FemExp020mos	-0.0228	0.0380	0.550	0.978	0.907	1.053	1.023	0.67	1.50
ASD_Outc	1008	MalExp020mos	-0.0358	0.0173	0.038 *	0.965	0.933	0.998	1.036	0.53	1.89
ASD_Outc	1008	SexByExp020mos	-0.0131	0.0408	0.749						
AD_Outc	911	FemPreNatThimer	-0.0405	0.0505	0.423	0.960	0.870	1.060	1.041	0.52	1.94
AD_Outc	911	MalPreNatThimer	0.0177	0.0121	0.144	1.018	0.994	1.042		1.34	
AD_Outc	911	SexByPreNatThimer	0.0582	0.0521	0.264						
AD_Outc	911	FemExp020mos	-0.0424	0.0478	0.376	0.959	0.873	1.053	1.043	0.47	2.13
AD_Outc	911	MalExp020mos	-0.0399	0.0192	0.038 *	0.961	0.925	0.998	1.041	0.49	2.04
AD_Outc	911	SexByExp020mos	0.0025	0.0505	0.961						
ASD_Only	773	FemPreNatThimer	0.0091	0.0616	0.883	1.009	0.894	1.139		1.16	
ASD_Only	773	MalPreNatThimer	-0.0028	0.0214	0.896	0.997	0.956	1.040	1.003	0.96	1.05
ASD_Only	773	SexByPreNatThimer	-0.0119	0.0651	0.855	0.988	0.870	1.123	1.012		
ASD_Only	773	FemExp020mos	0.0094	0.0694	0.892	1.009	0.881	1.156		1.18	
ASD_Only	773	MalExp020mos	-0.0331	0.0300	0.270	0.967	0.912	1.026	1.034	0.55	1.80
ASD_Only	773	SexByExp020mos	-0.0425	0.0742	0.567						
ASD_Regr	701	FemPreNatThimer	0.0309	0.0561	0.581	1.031	0.924	1.151		1.66	
ASD_Regr	701	MalPreNatThimer	0.0352	0.0227	0.121	1.036	0.991	1.083		1.78	
ASD_Regr	701	SexByPreNatThimer	0.0043	0.0609	0.944						
ASD_Regr	701	FemExp020mos	-0.1506	0.0764	0.049 *	0.860	0.741	0.999	1.163	0.07	14.66
ASD_Regr	701	MalExp020mos	-0.0602	0.0351	0.086	0.942	0.879	1.009	1.062	0.34	2.93
ASD_Regr	701	SexByExp020mos	0.0904	0.0822	0.271						
AD_ExLoCF	884	FemPreNatThimer	-0.0399	0.0511	0.435	0.961	0.869	1.062	1.041	0.52	1.92
AD_ExLoCF	884	MalPreNatThimer	0.0236	0.0124	0.057 ~	1.024	0.999	1.049		1.47	
AD_ExLoCF	884	SexByPreNatThimer	0.0636	0.0528	0.229						
AD_ExLoCF	884	FemExp020mos	-0.0914	0.0548	0.095 ~	0.913	0.820	1.016	1.096	0.20	5.10

<i>AD_ExLoCF</i>	884	<i>MalExp020mos</i>	-0.0450	0.0208	0.030*	0.956	0.918	0.996	1.046	0.45	2.23
<i>AD_ExLoCF</i>	884	<i>SexByExp020mos</i>	0.0464	0.0572	0.418						
<i>ASD_Scr</i>	821	<i>FemPreNatThimer</i>	-0.0123	0.0292	0.674	0.988	0.933	1.046	1.012	0.82	1.22
<i>ASD_Scr</i>	821	<i>MalPreNatThimer</i>	0.0082	0.0112	0.467	1.008	0.986	1.031		1.14	
<i>ASD_Scr</i>	821	<i>SexByPreNatThimer</i>	0.0204	0.0313	0.514						
<i>ASD_Scr</i>	821	<i>FemExp020mos</i>	-0.0473	0.0438	0.281	0.954	0.875	1.039	1.048	0.43	2.32
<i>ASD_Scr</i>	821	<i>MalExp020mos</i>	-0.0377	0.0189	0.046*	0.963	0.928	0.999	1.038	0.51	1.96
<i>ASD_Scr</i>	821	<i>SexByExp020mos</i>	0.0096	0.0464	0.837						
<i>AD_Scr</i>	728	<i>FemPreNatThimer</i>	-0.0195	0.0476	0.682	0.981	0.893	1.077	1.020	0.73	1.37
<i>AD_Scr</i>	728	<i>MalPreNatThimer</i>	0.0164	0.0131	0.212	1.017	0.991	1.043		1.31	
<i>AD_Scr</i>	728	<i>SexByPreNatThimer</i>	0.0359	0.0495	0.469	1.037	0.941	1.142			
<i>AD_Scr</i>	728	<i>FemExp020mos</i>	-0.0818	0.0656	0.212	0.921	0.810	1.048	1.085	0.23	4.30
<i>AD_Scr</i>	728	<i>MalExp020mos</i>	-0.0464	0.0221	0.036*	0.955	0.914	0.997	1.047	0.44	2.28
<i>AD_Scr</i>	728	<i>SexByExp020mos</i>	0.0355	0.0675	0.599						

~ p<0.10; * p<0.05; ** p<0.01

^a Odds ratio corresponding to a one-unit increase in exposure measure

^b Odds ratio corresponding to a two-standard deviation unit increase in the exposure measure. This difference can be thought of as roughly corresponding to the difference between low and high exposure.

9.4.3. Interaction Effects of Prenatal and Postnatal Exposure

The analyses in this section were motivated by a hypothesis that prenatal exposure to ethylmercury from thimerosal-containing vaccines and immune globulins received by the mother during pregnancy could alter the the effects of postnatal exposure on the risk of autism. The three models described below were used to test whether there were interaction effects of prenatal and postnatal exposure on the risk of autistic disorder

9.4.3.1. PreNatThimer by Exp07mos

The first model included a test for an interaction between prenatal exposure and cumulative exposures from birth through 7 months.

$$\log\left(\frac{\pi}{1-\pi}\right) = \alpha_i + \beta_1 preNatThimer + \beta_2 Exp07mos + \beta_3 preNatThimer * Exp07mos + \sum_j \alpha_j oe_j + \sum_k \alpha_{j+k} cf_k$$

The estimate $\hat{\beta}_1$ is interpreted as the model-estimated effect of prenatal exposure to thimerosal from vaccines and immune globulins when postnatal cumulative exposure (*Exp07mos*) is zero. Similarly, the term $\hat{\beta}_2$ is interpreted as the as the model-estimated effect of postnatal exposure when prenatal exposure is zero. The interaction effect $\hat{\beta}_3$ is

the effect of both prenatal and postnatal exposure, above and beyond the additive effects of prenatal exposure by itself, and postnatal exposure independent of prenatal exposure.

Exhibit 9.4.7. Model Summary: PreNatThimer by Exp07mos Interaction Models

Outcome	N	Exposure Measure	Estimate	Stderr	Prob ChiSq	One	Lower	Upper	1/OR	2 SD	1/OR
						Unit Chg. ^a	95% CL	95% CL		Unit Chg. ^b	
ASD_Outc	1008	PreNatThimer	0.0000	0.0307	0.999	1.000	0.942	1.062	1.000	1.00	1.00
ASD_Outc	1008	Exp07mos	-0.0337	0.0167	0.044 *	0.967	0.936	0.999	1.034	0.59	1.69
ASD_Outc	1008	PreNatBy07Mos	0.0004	0.0015	0.813						
AD_Outc	911	PreNatThimer	0.0318	0.0325	0.328	1.032	0.969	1.100		1.68	
AD_Outc	911	Exp07mos	-0.0408	0.0190	0.032 *	0.960	0.925	0.996	1.042	0.53	1.89
AD_Outc	911	PreNatBy07Mos	-0.0011	0.0016	0.503						
ASD_Only	773	PreNatThimer	-0.2090	0.1139	0.067 ~	0.811	0.649	1.014	1.232	0.03	30.44
ASD_Only	773	Exp07mos	-0.0307	0.0299	0.304	0.970	0.915	1.028	1.031	0.62	1.61
ASD_Only	773	PreNatBy07Mos	0.0097	0.0050	0.053						
ASD_Regr	701	PreNatThimer	0.1326	0.0506	0.009 **	1.142	1.034	1.261		8.73	
ASD_Regr	701	Exp07mos	-0.0933	0.0342	0.006 **	0.911	0.852	0.974	1.098	0.23	4.28
ASD_Regr	701	PreNatBy07Mos	-0.0054	0.0028	0.054 ~						
AD_ExLoCF	884	PreNatThimer	0.0510	0.0337	0.130	1.052	0.985	1.124		2.30	
AD_ExLoCF	884	Exp07mos	-0.0519	0.0205	0.012 *	0.949	0.912	0.988	1.053	0.45	2.24
AD_ExLoCF	884	PreNatBy07Mos	-0.0018	0.0017	0.277						
ASD_Scr	821	PreNatThimer	-0.0179	0.0319	0.575	0.982	0.923	1.046	1.018	0.75	1.34
ASD_Scr	821	Exp07mos	-0.0464	0.0189	0.014 *	0.955	0.920	0.991	1.047	0.49	2.06
ASD_Scr	821	PreNatBy07Mos	0.0012	0.0016	0.452						
AD_Scr	728	PreNatThimer	0.0262	0.0352	0.456	1.027	0.958	1.100		1.53	
AD_Scr	728	Exp07mos	-0.0579	0.0226	0.010 *	0.944	0.903	0.986	1.060	0.41	2.46
AD_Scr	728	PreNatBy07Mos	-0.0007	0.0018	0.679						

~ p<0.10; * p<0.05; ** p<0.01

^a Odds ratio corresponding to a one-unit increase in exposure measure

^b Odds ratio corresponding to a two-standard deviation unit increase in the exposure measure. This difference can be thought of as roughly corresponding to the difference between low and high exposure.

9.4.3.2. PreNatThimer by Exp01mos, Exp17mos

The second model included tests for interactions between prenatal exposure and neonatal exposure (*Exp01mos*) and between prenatal exposure and cumulative exposures from one through 7 months (*Exp17mos*).

$$\begin{aligned} \log\left(\frac{\pi}{1-\pi}\right) = & \alpha_i + \beta_1 preNatThimer + \beta_2 HepB + \beta_3 Exp17mo + \\ & \beta_4 preNatThimer * HepB + \\ & \beta_5 preNatThimer * Exp17mos + \\ & \sum_j \alpha_j oe_j + \sum_k \alpha_{j+k} cf_k \end{aligned}$$

Exhibit 9.4.8. Model Summary: PreNatThimer by Exp01mos , Exp17mos Interaction Models

Outcome	N	Exposure Measure	Estimate	Stderr	Prob ChiSq	One				2 SD	
						Unit Chg.	Lower 95% CL	Upper 95% CL	1/OR	Unit Chg.	1/OR
ASD_Outc	1008	PreNatThimer	-0.0019	0.0314	0.952	0.998	0.939	1.061	1.002	0.97	1.03
ASD_Outc	1008	Exp01mos	-0.0384	0.0461	0.405	0.962	0.879	1.053	1.039	0.85	1.17
ASD_Outc	1008	Exp17mos	-0.0333	0.0183	0.070 ~	0.967	0.933	1.003	1.034	0.62	1.62
ASD_Outc	1008	PreNatBy01Mos	0.0042	0.0053	0.432						
ASD_Outc	1008	PreNatBy17Mos	-0.0001	0.0016	0.950						
AD_Outc	911	PreNatThimer	0.0171	0.0375	0.649	1.017	0.945	1.095		1.32	
AD_Outc	911	Exp01mos	0.0058	0.0513	0.910	1.006	0.910	1.112		1.02	
AD_Outc	911	Exp17mos	-0.0527	0.0212	0.013 *	0.949	0.910	0.989	1.054	0.46	2.15
AD_Outc	911	PreNatBy01Mos	0.0157	0.0088	0.074 ~						
AD_Outc	911	PreNatBy17Mos	-0.0033	0.0020	0.092 ~						
ASD_Only	773	PreNatThimer	-0.2895	0.1588	0.068 ~	0.749	0.548	1.022	1.336	0.01	113.59
ASD_Only	773	Exp01mos	-0.2022	0.0976	0.038 *	0.817	0.675	0.989	1.224	0.44	2.29
ASD_Only	773	Exp17mos	-0.0076	0.0310	0.807	0.992	0.934	1.055	1.008	0.90	1.12
ASD_Only	773	PreNatBy01Mos	-0.0065	0.0125	0.602						
ASD_Only	773	PreNatBy17Mos	0.0146	0.0073	0.045 *						
ASD_Regr	701	PreNatThimer	0.1073	0.0564	0.057 ~	1.113	0.997	1.243		5.77	
ASD_Regr	701	Exp01mos	-0.1303	0.0899	0.147	0.878	0.736	1.047	1.139	0.59	1.70
ASD_Regr	701	Exp17mos	-0.0923	0.0378	0.015 *	0.912	0.847	0.982	1.097	0.26	3.83
ASD_Regr	701	PreNatBy01Mos	0.0112	0.0170	0.510						
ASD_Regr	701	PreNatBy17Mos	-0.0069	0.0031	0.028 *						
AD_ExLoCF	884	PreNatThimer	0.0385	0.0389	0.322	1.039	0.963	1.122		1.88	
AD_ExLoCF	884	Exp01mos	-0.0433	0.0564	0.443	0.958	0.857	1.070	1.044	0.84	1.19
AD_ExLoCF	884	Exp17mos	-0.0594	0.0229	0.010 *	0.942	0.901	0.986	1.061	0.42	2.37
AD_ExLoCF	884	PreNatBy01Mos	0.0186	0.0093	0.045 *						
AD_ExLoCF	884	PreNatBy17Mos	-0.0048	0.0022	0.027 *						
ASD_Scr	821	PreNatThimer	-0.0188	0.0323	0.561	0.981	0.921	1.045	1.019	0.74	1.36
ASD_Scr	821	Exp01mos	-0.0769	0.0489	0.116	0.926	0.841	1.019	1.080	0.73	1.37
ASD_Scr	821	Exp17mos	-0.0414	0.0205	0.044 *	0.960	0.922	0.999	1.042	0.55	1.83
ASD_Scr	821	PreNatBy01Mos	0.0048	0.0053	0.361						
ASD_Scr	821	PreNatBy17Mos	0.0007	0.0017	0.668						
AD_Scr	728	PreNatThimer	0.0126	0.0391	0.748	1.013	0.938	1.093		1.23	
AD_Scr	728	Exp01mos	-0.0264	0.0563	0.639	0.974	0.872	1.088	1.027	0.90	1.11
AD_Scr	728	Exp17mos	-0.0700	0.0249	0.005 **	0.932	0.888	0.979	1.072	0.36	2.77
AD_Scr	728	PreNatBy01Mos	0.0165	0.0094	0.081 ~						
AD_Scr	728	PreNatBy17Mos	-0.0033	0.0022	0.136						

~ p<0.10; * p<0.05; ** p<0.01

^a Odds ratio corresponding to a one-unit increase in exposure measure

^b Odds ratio corresponding to a two-standard deviation unit increase in the exposure measure. This difference can be thought of as roughly corresponding to the difference between low and high exposure.

9.4.3.3. PreNatThimer by Exp020mos

The third model included a test for an interaction between prenatal exposure and cumulative exposures from birth through 20 months.

$$\log\left(\frac{\pi}{1-\pi}\right) = \alpha_i + \beta_1 preNatThimer + \beta_2 Exp020mos +$$

$$\beta_3 preNatThimer * Exp020mos +$$

$$\sum_j \alpha_j oe_j + \sum_k \alpha_{j+k} cf_k$$

Exhibit 9.4.9. Model Summary: PreNatThimer by Exp020mos Interaction Models

Outcome	N	Exposure Measure	Estimate	Stderr	Prob ChiSq	One	Lower	Upper	1/OR	2 SD	1/OR
						Unit Chg. OR ^a	95% CL	95% CL		Unit Chg. OR ^b	
ASD_Outc	1008	PreNatThimer	0.0012	0.0302	0.969	1.001	0.944	1.062	0.999	1.02	
ASD_Outc	1008	Exp020mos	-0.0334	0.0161	0.039 *	0.967	0.937	0.998	1.034	0.55	1.81
ASD_Outc	1008	PreNatBy020Mos	0.0002	0.0012	0.847	1.000	0.998	1.003	1.000	.	.
AD_Outc	911	PreNatThimer	0.0317	0.0328	0.333	1.032	0.968	1.101	0.969	1.68	
AD_Outc	911	Exp020mos	-0.0375	0.0182	0.040 *	0.963	0.929	0.998	1.038	0.51	1.95
AD_Outc	911	PreNatBy020Mos	-0.0009	0.0014	0.496	0.999	0.996	1.002	1.001	.	.
ASD_Only	773	PreNatThimer	-0.2327	0.1274	0.068 ~	0.792	0.617	1.017	1.262	0.02	44.88
ASD_Only	773	Exp020mos	-0.0310	0.0281	0.269	0.969	0.918	1.024	1.032	0.58	1.74
ASD_Only	773	PreNatBy020Mos	0.0090	0.0047	0.054 ~	1.009	1.000	1.018	0.991	.	.
ASD_Regr	701	PreNatThimer	0.1249	0.0498	0.012 *	1.133	1.028	1.249	0.883	7.70	
ASD_Regr	701	Exp020mos	-0.0738	0.0323	0.022 *	0.929	0.872	0.989	1.077	0.27	3.73
ASD_Regr	701	PreNatBy020Mos	-0.0042	0.0023	0.066 ~	0.996	0.991	1.000	1.004	.	.
AD_ExLolQ	884	PreNatThimer	0.0509	0.0340	0.135	1.052	0.984	1.125	0.950	2.30	
AD_ExLolQ	884	Exp020mos	-0.0469	0.0197	0.017 *	0.954	0.918	0.992	1.048	0.43	2.31
AD_ExLolQ	884	PreNatBy020Mos	-0.0016	0.0015	0.274	0.998	0.996	1.001	1.002	.	.
ASD_TClIn	821	PreNatThimer	-0.0179	0.0318	0.573	0.982	0.923	1.045	1.018	0.75	1.34
ASD_TClIn	821	Exp020mos	-0.0403	0.0180	0.025 *	0.961	0.927	0.995	1.041	0.49	2.05
ASD_TClIn	821	PreNatBy020Mos	0.0010	0.0013	0.455	1.001	0.998	1.004	0.999	.	.
AD_TClIn	728	PreNatThimer	0.0250	0.0358	0.486	1.025	0.956	1.100	0.975	1.50	
AD_TClIn	728	Exp020mos	-0.0477	0.0214	0.026 *	0.953	0.914	0.994	1.049	0.43	2.34
AD_TClIn	728	PreNatBy020Mos	-0.0006	0.0015	0.698	0.999	0.996	1.002	1.001	.	.

~ p<0.10; * p<0.05; ** p<0.01

^a Odds ratio corresponding to a one-unit increase in exposure measure

^b Odds ratio corresponding to a two-standard deviation unit increase in the exposure measure. This difference

9.4.4. Models for Multiple Sources of Prenatal Exposure Interacted with Postnatal Exposure from Thimerosal

9.4.4.1. Introduction

The models summarized in this section were motivated by the same hypothesis as described in the previous section – that is, children who had prenatal exposure to mercury could be more susceptible to additional doses of postnatal exposure than children who were not exposed in utero. In the current section, however, a broader measure of prenatal exposure is introduced and modeled. The broader measure of prenatal exposure includes mercury exposures from thimerosal in vaccines and immune globulins, maternal fish consumption, maternal use of mercury containing health care products (contact lens, nasal, ear, eye drops), maternal exposure from home products, and from amalgam fillings. This new measure was modeled as an interaction effect with cumulative exposure from birth through seven months.

We caution the reader that the broader measure of prenatal exposure from multiple mercury sources defined and analyzed in this section may not be a reliable estimate of total prenatal mercury exposure. It suffers from four potentially important sources of measurement error. First, it is created from multiple items, many of which are solely dependent on maternal recall of exposures that occurred six to 13 years prior to the parent interview (e.g., use of mercury containing health care products, consumption of fish). Second, the amount of mercury in many of the sources is unknown. Third, there may be other important sources of prenatal mercury exposure not captured by the measure, e.g., air pollution. And fourth, since there is no obvious way to sum the total exposure across the multiple sources, we used an ad-hoc method (described subsequently) to create a sum score of total prenatal mercury exposure. We consider the resulting measure to be a very crude measure of total prenatal exposure to mercury from multiple mercury sources.

The broader measure of prenatal exposure was created by dichotomizing the component variables³⁴ into categories “1 = any exposure”, and “0 = no exposure”, and summing to create a composite score. The following variables were summed to create the composite (named *PreNatAllMerc*):

<u>Variable</u>		<u>Definition</u>	
<i>Pre_VacIG</i>	{	= 0 if <i>PreNatThimer</i> = 0	}
		= 1 if <i>PreNatThimer</i> > 0	
<i>Pre_Tuna</i>	{	= 1 if <i>PreNatTuna</i> > 0	}
		= 0 if <i>PreNatTuna</i> = 0	
<i>PreAmalgam</i>	{	= 0 if <i>PreNatFillings_1</i> = 0	}
		= 1 if <i>PreNatFillings_1</i> > 0	
<i>PreNatFish</i>	=	<i>PreNatFish</i> variable as currently defined (0/1).	

³⁴ For definitions of component variables, see Section 7.5.

PreNatOthMerc_Any = *PreNatOthMerc_Any* variable as currently defined (0/1).

PreNatAllMerc = *Pre_VaciG* + *Pre_Tuna* + *PreAmalgam* + *PreNatFish* + *PreNatOthMerc_Any*

A frequency crosstab of the *PreNatAllMerc* variable crossed with the components used in its creation is shown in Exhibit 9.4.10.

Exhibit 9.4.10. PreNatAllMerc Crossed with Five Component Variables Used to Construct It									
PreNat AllMerc	PreNat Thimer	PreNat Tuna	PreNat Fish	PreNat OthMerc_Any	PreNat Fillings	Freq.	Percent	Cum. Freq.	Cum. Percent
0	0	0	0	0	0	84	8.33	84	8.33
1	0	0	0	0	1	48	4.76	132	13.1
1	0	0	0	0	2	130	12.9	262	25.99
1	0	0	0	1	0	8	0.79	270	26.79
1	0	0	1	0	0	5	0.5	275	27.28
1	0	1	0	0	0	105	10.42	380	37.7
1	12.75	0	0	0	0	5	0.5	385	38.19
1	25	0	0	0	0	2	0.2	387	38.39
2	0	0	0	1	1	6	0.6	393	38.99
2	0	0	0	1	2	18	1.79	411	40.77
2	0	0	1	0	1	4	0.4	415	41.17
2	0	0	1	0	2	4	0.4	419	41.57
2	0	0	1	1	0	1	0.1	420	41.67
2	0	1	0	0	1	64	6.35	484	48.02
2	0	1	0	0	2	264	26.19	748	74.21
2	0	1	0	1	0	10	0.99	758	75.2
2	0	1	1	0	0	14	1.39	772	76.59
2	0	2	1	0	0	3	0.3	775	76.88
2	12.75	0	0	0	1	4	0.4	779	77.28
2	12.75	0	0	0	2	10	0.99	789	78.27
2	12.75	0	1	0	0	1	0.1	790	78.37
2	12.75	1	0	0	0	5	0.5	795	78.87
2	25	0	0	0	1	2	0.2	797	79.07
2	25	0	0	0	2	3	0.3	800	79.37
2	25	0	1	0	0	1	0.1	801	79.46
2	25	1	0	0	0	2	0.2	803	79.66
2	25.5	0	0	0	1	1	0.1	804	79.76
2	25.5	1	0	0	0	1	0.1	805	79.86
2	37.75	0	0	0	2	1	0.1	806	79.96
2	37.75	1	0	0	0	1	0.1	807	80.06
2	50.5	0	0	0	1	1	0.1	808	80.16
2	62.75	0	0	0	2	1	0.1	809	80.26
3	0	0	1	1	1	1	0.1	810	80.36
3	0	1	0	1	1	10	0.99	820	81.35
3	0	1	0	1	2	37	3.67	857	85.02
3	0	1	1	0	1	2	0.2	859	85.22
3	0	1	1	0	2	38	3.77	897	88.99
3	0	1	1	1	0	4	0.4	901	89.38
3	0	2	1	0	1	5	0.5	906	89.88

Exhibit 9.4.10. PreNatAllMerc Crossed with Five Component Variables Used to Construct It

PreNat AllMerc	PreNat Thimer	PreNat Tuna	PreNat Fish	PreNat OthMerc_Any	PreNat Fillings	Freq.	Percent	Cum. Freq.	Cum. Percent
3	0	2	1	0	2	13	1.29	919	91.17
3	0	2	1	1	0	3	0.3	922	91.47
3	12.75	0	0	1	1	1	0.1	923	91.57
3	12.75	0	0	1	2	2	0.2	925	91.77
3	12.75	0	1	0	2	1	0.1	926	91.87
3	12.75	1	0	0	1	5	0.5	931	92.36
3	12.75	1	0	0	2	26	2.58	957	94.94
3	25	1	0	0	1	5	0.5	962	95.44
3	25	1	0	0	2	8	0.79	970	96.23
3	25	1	0	1	0	2	0.2	972	96.43
3	25	2	1	0	0	2	0.2	974	96.63
3	25.5	1	0	0	2	3	0.3	977	96.92
3	25.5	1	0	1	0	1	0.1	978	97.02
3	37.75	1	0	0	2	3	0.3	981	97.32
3	50	0	0	1	2	1	0.1	982	97.42
3	74	1	0	0	2	1	0.1	983	97.52
3	100	1	0	0	2	1	0.1	984	97.62
4	0	1	1	1	2	3	0.3	987	97.92
4	0	2	1	1	1	1	0.1	988	98.02
4	0	2	1	1	2	5	0.5	993	98.51
4	12.75	1	0	1	2	2	0.2	995	98.71
4	12.75	1	1	0	1	1	0.1	996	98.81
4	12.75	1	1	0	2	1	0.1	997	98.91
4	12.75	1	1	1	0	1	0.1	998	99.01
4	12.75	2	1	0	2	1	0.1	999	99.11
4	25	1	0	1	1	1	0.1	1000	99.21
4	25	1	0	1	2	2	0.2	1002	99.4
4	25	1	1	0	1	1	0.1	1003	99.5
4	25	1	1	0	2	1	0.1	1004	99.6
4	25	2	1	0	2	1	0.1	1005	99.7
4	75	1	1	1	0	1	0.1	1006	99.8
5	12.75	1	1	1	2	1	0.1	1007	99.9
5	25	2	1	1	2	1	0.1	1008	100

9.4.4.2. Model Specifications

We fit two types of models. The first is a main effects model that is used to answer the question, is higher prenatal exposure to a variety of sources of mercury (as measured by the *preNatAllMerc* variable) associated with risk of autism outcomes? The second type of model is an interaction model, and is more closely aligned to the question that motivated these analyses. That question is, does higher prenatal exposure to a variety of sources of mercury (as measured by the *preNatAllMerc* variable) modify the relationship of postnatal exposures to autism outcomes? In other words, does high prenatal exposure increase the risk of autism outcome when postnatal exposure is high? We fit models of the forms specified below.

Model (1): Main Effect Model

$$\log\left(\frac{\pi}{1-\pi}\right) = \alpha_i + \beta_1 preNatAllMerc + \beta_2 Exp07mos + \sum_j \alpha_j oe_j + \sum_k \alpha_{j+k} cf_k$$

$$H_0 : \beta_1 = 0 \quad vs \quad H_a : \beta_1 \neq 0$$

where

preNatAllMerc = a measure of prenatal exposure to ethylmercury and methylmercury from vaccines and immune globulins (ethylmercury), or from consumption of fish, household products, and dental amalgams.

Model (2): Interaction Model

$$\log\left(\frac{\pi}{1-\pi}\right) = \alpha_i + \beta_1 preNatAllMerc + \beta_2 Exp07mos + \beta_3 preNatAllMerc * Exp07mos + \sum_j \alpha_j oe_j + \sum_k \alpha_{j+k} cf_k$$

$$H_0 : \beta_3 = 0 \quad vs \quad H_a : \beta_3 \neq 0$$

9.4.4.3. Results

Exhibit 9.4.11 indicates that there are no significant main effect associations between prenatal exposure to a variety of sources of mercury, as measured by the *preNatAllMerc* variable, and any of the autism outcomes.

The results in Exhibit 9.4.12 provide no evidence to support the hypothesis that prenatal exposure to a variety of sources of ethylmercury and methylmercury, as measured by the *preNatAllMerc* variable, exacerbate the effects of postnatal exposure to ethylmercury from vaccines and immune globulins.

Again, we stress that the *preNatAllMerc* variable is a crude measure of prenatal exposure, as it is heavily dependent on maternal recall, and only crudely captures the amount of exposure. The authors of this report do not consider the *preNatAllMerc* variable to be measured with anywhere near the same accuracy as were the measures of prenatal and postnatal exposure to ethylmercury from vaccines and immune globulins.

We also note that we fit models with interactions between *preNatAllMerc* and other postnatal exposure measures (*Exp01mos*, *Exp07mos*, and *Exp020mos*), and none of the interaction effects were significant. Those results are not shown.

Exhibit 9.4.11. Model Summary: PreNatAllMerc and Exp07mos Exposure Models

Outcome	N	Exposure Measure	Estimate	Stderr	Prob ChiSq	One	Lower	Upper	2 SD		
						Unit Chg. OR ^a	95% CL	95% CL	1/OR	Unit Chg. OR ^b	1/OR
ASD_Outc	1008	PreNatAllMerc	0.1206	0.0855	0.158	1.128	0.954	1.334		1.25	
ASD_Outc	1008	Exp07mos	-0.0323	0.0165	0.051 ~	0.968	0.937	1.000	1.033	0.61	1.65
AD_Outc	911	PreNatAllMerc	0.0277	0.0980	0.778	1.028	0.848	1.246		1.05	
AD_Outc	911	Exp07mos	-0.0415	0.0188	0.027 *	0.959	0.925	0.995	1.042	0.52	1.91
ASD_Only	773	PreNatAllMerc	-0.4767	0.3914	0.223	0.621	0.288	1.337	1.611	0.41	2.41
ASD_Only	773	Exp07mos	-0.0219	0.0294	0.456	0.978	0.924	1.036	1.022	0.71	1.41
ASD_Regr	701	PreNatAllMerc	0.1418	0.1752	0.418	1.152	0.817	1.625		1.30	
ASD_Regr	701	Exp07mos	-0.0956	0.0334	0.004 **	0.909	0.851	0.970	1.100	0.23	4.43
AD_ExLoIQ	884	PreNatAllMerc	0.0416	0.1045	0.691	1.042	0.849	1.279		1.08	
AD_ExLoIQ	884	Exp07mos	-0.0532	0.0203	0.009 **	0.948	0.911	0.987	1.055	0.44	2.29
ASD_TCIIn	821	PreNatAllMerc	0.1561	0.0891	0.080	1.169	0.982	1.392		1.33	
ASD_TCIIn	821	Exp07mos	-0.0439	0.0186	0.019 *	0.957	0.923	0.993	1.045	0.50	1.98
AD_TCIIn	728	PreNatAllMerc	0.2851	0.2420	0.239	1.330	0.828	2.137		1.69	
AD_TCIIn	728	Exp07mos	-0.0578	0.0224	0.010 *	0.944	0.903	0.986	1.060	0.41	2.46

~ p<0.10; * p<0.05; ** p<0.01

^a Odds ratio corresponding to a one-unit increase in exposure measure

^b Odds ratio corresponding to a two-standard deviation unit increase in the exposure measure. This difference can be thought of as roughly corresponding to the difference between low and high exposure.

Exhibit 9.4.12. Model Summary: PreNatAllMerc by Exp07mos Interaction Models

Outcome	N	Exposure Measure	Estimate	Stderr	Prob ChiSq	One				2 SD	
						Unit Chg. OR ^a	Lower 95% CL	Upper 95% CL	1/OR	Unit Chg. OR ^b	1/OR
ASD_Outc	1008	PreNatAllMerc	0.0315	0.2088	0.880	1.032	0.685	1.554	0.969	1.06	
ASD_Outc	1008	Exp07mos	-0.0410	0.0250	0.101	0.960	0.914	1.008	1.042	0.53	1.89
ASD_Outc	1008	PreNatAllMerc* Exp07mos	0.0052	0.0111	0.640	1.005	0.984	1.027	0.995	.	.
AD_Outc	911	PreNatAllMerc	0.0365	0.2431	0.881	1.037	0.644	1.670	0.964	1.07	
AD_Outc	911	Exp07mos	-0.0407	0.0278	0.143	0.960	0.909	1.014	1.042	0.53	1.88
AD_Outc	911	PreNatAllMerc* Exp07mos	-0.0005	0.0126	0.968	1.000	0.975	1.024	1.001	.	.
ASD_Only	773	PreNatAllMerc	-0.9398	0.5279	0.075 ~	0.391	0.139	1.100	2.560	0.18	5.68
ASD_Only	773	Exp07mos	-0.0744	0.0505	0.141	0.928	0.841	1.025	1.077	0.31	3.18
ASD_Only	773	PreNatAllMerc* Exp07mos	0.0278	0.0216	0.199	1.028	0.986	1.073	0.973	.	.
ASD_Regr	701	PreNatAllMerc	0.2411	0.4151	0.561	1.273	0.564	2.871	0.786	1.56	
ASD_Regr	701	Exp07mos	-0.0859	0.0493	0.081 ~	0.918	0.833	1.011	1.090	0.26	3.81
ASD_Regr	701	PreNatAllMerc* Exp07mos	-0.0058	0.0219	0.792	0.994	0.952	1.038	1.006	.	.
AD_ExLoIQ	884	PreNatAllMerc	0.0207	0.2611	0.937	1.021	0.612	1.703	0.980	1.04	
AD_ExLoIQ	884	Exp07mos	-0.0551	0.0302	0.068 ~	0.946	0.892	1.004	1.057	0.42	2.36
AD_ExLoIQ	884	PreNatAllMerc* Exp07mos	0.0012	0.0136	0.930	1.001	0.975	1.028	0.999	.	.
ASD_TCIIn	821	PreNatAllMerc	0.0160	0.2244	0.943	1.016	0.655	1.577	0.984	1.03	
ASD_TCIIn	821	Exp07mos	-0.0571	0.0271	0.035 *	0.944	0.896	0.996	1.059	0.41	2.43
ASD_TCIIn	821	PreNatAllMerc* Exp07mos	0.0081	0.0120	0.498	1.008	0.985	1.032	0.992	.	.
AD_TCIIn	728	PreNatAllMerc	0.3108	0.3646	0.394	1.364	0.668	2.788	0.733	1.78	
AD_TCIIn	728	Exp07mos	-0.0558	0.0313	0.075 ~	0.946	0.890	1.006	1.057	0.42	2.38
AD_TCIIn	728	PreNatAllMerc* Exp07mos	-0.0014	0.0144	0.925	0.999	0.971	1.027	1.001	.	.

~ p<0.10; * p<0.05; ** p<0.01

^a Odds ratio corresponding to a one-unit increase in exposure measure

^b Odds ratio corresponding to a two-standard deviation unit increase in the exposure measure. This difference can be thought of as roughly corresponding to the difference between low and high exposure.

9.4.5. Models for Estimation of the Effect of Exposure That is Concurrent with Antibiotic Treatment

9.4.5.1. Introduction

Several studies of the rates of excretion of methylmercuric chloride in rodents have indicated that oral antibiotics taken concurrently with oral ingestion of methylmercuric chloride is associated with slower excretion (Rowland et. al., 1977, 1980, 1984). The results of these studies suggest that antibiotics may interact with mercury in a way that may alter the effects of mercury. These findings motivate the hypothesis that, in children, antibiotics may interact with exposure to ethylmercury from thimerosal in vaccines, to have an effect that is different from exposure to ethylmercury from vaccines absent antibiotics use.

The models summarized in this section were fit to the data in order to explore the concurrent antibiotics hypothesis. Exposure to ethylmercury from thimerosal was defined as “concurrent with antibiotic receipt” if the thimerosal-containing vaccine was received during the course of antibiotic treatment, or was received up to 4 days prior to initiation of antibiotic treatment, or was received up to 14 days after the last day of antibiotic treatment. This definition of “concurrent with antibiotics” was the subject of much discussion and debate among the study’s External Expert Consultants and Principal Investigators, and after consultation with the literature and several experts in toxicology, the current definition was considered to be the best available option. The rationale for this definition is as follows.

If we operate on the theory that the loss of normal gut flora by antibiotic treatment causes the thimerosal to be excreted more slowly from the body, we must include a period of time after antibiotic usage stops during which the flora returns to normal. Pediatric experts advised that *E. coli* (the most common gut bacteria) typically returns to normal levels within two weeks of antibiotic use. Therefore, we include as concurrent any vaccine received within a period of up to two weeks after the last day of antibiotic treatment.

The rationale for the window prior to antibiotic use is based on the notion that it takes time for the mercury to be excreted, and if antibiotic treatment starts after receipt of a thimerosal containing vaccine, the antibiotic could slow the excretion rate of the previously received, but unexcreted mercury. In a previous study, “Infant Environmental Exposure to Thimerosal and Neuropsychological Outcomes at Ages 7 to 10 Years” (Price, Goodson, & Stewart, 2007), a 14 day window prior to antibiotic use had been used, as described in the following passage that was excerpted from that report:

“A consulting toxicologist advised that both animal and human data indicate demethylation and fecal excretion of the inorganic species is the predominant route of elimination of ethylmercury from the body. Unfortunately there are no precise numbers for the rate or biological half time of this process. Data from human infants (Pichichero et al, 2002), and infant monkeys (Burbacher et

al., 2005) suggested that 14 days would be a reasonable guess at the length of one half-life for excretion.”

A more recent study by Pichichero et al, (2008), however, estimated the half life for ethylmercury excretion to be 3.7 days. Based on this new information, we used a four day window prior to antibiotic use for the current study’s definition of exposure concurrent with antibiotics.

We fit models to test for associations between autism outcomes and exposure effects for the age ranges of birth to seven months, birth to one month, one to seven months, and birth to 20 months. In each model we tested for effects of exposure concurrent with antibiotics, exposure not concurrent with antibiotics, and the difference between the effects of concurrent and non-concurrent exposure. In the sections that follow we provide a brief summary of results, model specifications, and model results.

9.4.5.2. Summary of Results

Models for the seven outcomes (ASD, AD, ASD-only, ASD with regression, AD with low cognitive function excluded, ASD with screened control group, AD with screened control group), crossed with the four exposure periods (birth to seven months, birth to one month, one to seven months, and birth to 20 months) resulted in 28 tests for the difference between effects of exposure that was concurrent versus not concurrent with antibiotics. Of those 28 tests, five were significant at the $p < 0.05$ level. In each of the five the results indicated that exposure concurrent with antibiotics was associated with a greater decrease in risk of autism than exposure that was not concurrent with antibiotics. Also in each of the five, the estimates for exposure that was concurrent and exposure that was not concurrent with antibiotics were both in the direction of lower risk for greater exposure.

We conclude that these results do not support the hypothesis that exposure that is concurrent with antibiotic use produces greater risk of autism outcomes.

9.4.5.3. Model (1): Concurrent Antibiotics from Birth to 7 Months

$$\log\left(\frac{\pi}{1-\pi}\right) = \alpha_i + \beta_1 preNatThimer + \beta_2 AbExp07mos + \beta_3 ncAbExp07mos + \beta_4 AbDays07mos + \sum_j \alpha_j oe_j + \sum_k \alpha_{j+k} cf_k$$

$$H_0 : \beta_2 = 0 \quad vs \quad H_a : \beta_2 \neq 0$$

$$H_0 : \beta_3 = 0 \quad vs \quad H_a : \beta_3 \neq 0$$

$$H_0 : \beta_2 - \beta_3 = 0 \quad vs \quad H_a : \beta_2 - \beta_3 \neq 0$$

where

AbExp07mos = a cumulative measure of ethylmercury exposure from thimerosal in vaccines received **concurrent with antibiotics** during the age range from birth through seven months (1 – 214 days), expressed in microgram units per kilograms of body weight at the time of vaccine receipt,

ncAbExp07mos = a cumulative measure of ethylmercury exposure from thimerosal in vaccines received **without concurrent antibiotics use** during the age range from birth through seven months (1 – 214 days), expressed in microgram units per kilograms of body weight at the time of vaccine receipt,

and

AbDays07mos = a count of the number of days that child received antibiotics, during the age range of 1 to 214 days.

The parameter estimates have the following interpretations:

$\hat{\beta}_2$ is an estimate of the effect of exposure with concurrent antibiotic use.

$\hat{\beta}_3$ is an estimate of the effect of exposure without concurrent antibiotic use.

$\hat{\beta}_4$ is an estimate of the effect of antibiotic use (note: not *concurrent* antibiotics, but antibiotics in and of themselves).

$\hat{\beta}_2 - \hat{\beta}_3$ is an estimate of the difference between exposure effects with concurrent antibiotic use and exposure effects without antibiotic use.

Exhibit 9.4.13. Model Summary: Concurrent Antibiotics - Birth to 7 Months

Outcome	N	Exposure Measure	Estimate	Stderr	Prob ChiSq	One				2 SD	
						Unit Chg. OR ^a	Lower 95% CL	Upper 95% CL	1/OR	Unit Chg. OR ^b	1/OR
ASD_Out	1008	PreNatThimer	0.0076	0.0095	0.420	1.008	0.989	1.026		1.13	
ASD_Out	1008	AbExp07mos	-0.1186	0.0427	0.006 **	0.888	0.817	0.966	1.126	0.46	2.18
ASD_Out	1008	ncAbExp07mos	-0.0234	0.0171	0.171	0.977	0.945	1.010	1.024	0.70	1.42
ASD_Out	1008	AbDays07mos	0.0068	0.0108	0.529	1.007	0.986	1.028		1.15	
ASD_Out	1008	Diff ^c			0.024 *						
AD_Out	911	PreNatThimer	0.0117	0.0105	0.268	1.012	0.991	1.033		1.21	
AD_Out	911	AbExp07mos	-0.1197	0.0488	0.014 *	0.887	0.806	0.976	1.127	0.46	2.19
AD_Out	911	ncAbExp07mos	-0.0319	0.0196	0.104	0.969	0.932	1.007	1.032	0.62	1.61
AD_Out	911	AbDays07mos	0.0016	0.0127	0.903	1.002	0.977	1.027		1.03	
AD_Out	911	Diff ^c			0.071 ~						
ASD_Only	773	PreNatThimer	0.0002	0.0200	0.992	1.000	0.962	1.040		1.00	
ASD_Only	773	AbExp07mos	-0.1088	0.0733	0.138	0.897	0.777	1.035	1.115	0.49	2.04
ASD_Only	773	ncAbExp07mos	-0.0128	0.0316	0.684	0.987	0.928	1.050	1.013	0.83	1.21
ASD_Only	773	AbDays07mos	0.0214	0.0181	0.237	1.022	0.986	1.058		1.55	
ASD_Only	773	Diff ^c			0.189						

ASD_Regr	701	PreNatThimer	0.0402	0.0213	0.059	~	1.041	0.999	1.085		1.93
ASD_Regr	701	AbExp07mos	-0.1407	0.1068	0.188		0.869	0.705	1.071	1.151	0.40 2.51
ASD_Regr	701	ncAbExp07mos	-0.0964	0.0346	0.005	**	0.908	0.849	0.972	1.101	0.24 4.23
ASD_Regr	701	AbDays07mos	-0.0347	0.0293	0.235		0.966	0.912	1.023	1.035	0.49 2.05
ASD_Regr	701	Diff ^c			0.675						
AD_ExLoCF	884	PreNatThimer	0.0159	0.0105	0.130		1.016	0.995	1.037		1.30
AD_ExLoCF	884	AbExp07mos	-0.0958	0.0478	0.045	*	0.909	0.827	0.998	1.100	0.53 1.87
AD_ExLoCF	884	ncAbExp07mos	-0.0477	0.0212	0.024	*	0.953	0.915	0.994	1.049	0.49 2.04
AD_ExLoCF	884	AbDays07mos	-0.0037	0.0134	0.784		0.996	0.971	1.023	1.004	0.93 1.08
AD_ExLoCF	884	Diff ^c			0.311						
ASD_TCIln	821	PreNatThimer	0.0058	0.0099	0.556		1.006	0.987	1.026		1.10
ASD_TCIln	821	AbExp07mos	-0.1240	0.0486	0.011	*	0.883	0.803	0.972	1.133	0.44 2.25
ASD_TCIln	821	ncAbExp07mos	-0.0382	0.0189	0.043	*	0.962	0.928	0.999	1.040	0.56 1.77
ASD_TCIln	821	AbDays07mos	0.0101	0.0118	0.394		1.010	0.987	1.034		1.23
ASD_TCIln	821	Diff ^c			0.073	~					
AD_TCIln	728	PreNatThimer	0.0140	0.0115	0.225		1.014	0.991	1.037	0.986	1.26
AD_TCIln	728	AbExp07mos	-0.1359	0.0576	0.018	*	0.873	0.780	0.977	1.145	0.41 2.44
AD_TCIln	728	ncAbExp07mos	-0.0521	0.0228	0.023	*	0.949	0.908	0.993	1.054	0.46 2.18
AD_TCIln	728	AbDays07mos	0.0082	0.0142	0.565		1.008	0.981	1.037	0.992	1.18
AD_TCIln	728	Diff ^c			0.141						

~ p<0.10; * p<0.05; ** p<0.01

^a Odds ratio corresponding to a one-unit increase in exposure measure

^b Odds ratio corresponding to a two-standard deviation unit increase in the exposure measure. This difference can be thought of as roughly corresponding to the difference between low and high exposure. See Exhibit 8.3 for details.

^c The p-value shown for "Diff" is the test $H_0 : \beta_2 - \beta_3 = 0$ vs $H_a : \beta_2 - \beta_3 \neq 0$

9.4.5.4. Model (2): Concurrent Antibiotics from Birth to 1 Month, and 1 to 7 Months

$$\log\left(\frac{\pi}{1-\pi}\right) = \alpha_i + \beta_1 preNatThimer + \beta_2 AbExp01mos + \beta_3 ncAbExp01mos + \beta_4 AbDays01mos + \beta_5 AbExp17mos + \beta_6 ncAbExp17mos + \beta_7 AbDays17mos + \sum_j \alpha_j oe_j + \sum_k \alpha_{j+k} cf_k$$

$$H_0 : \beta_2 = 0 \quad \text{vs} \quad H_a : \beta_2 \neq 0$$

$$H_0 : \beta_3 = 0 \quad \text{vs} \quad H_a : \beta_3 \neq 0$$

$$H_0 : \beta_5 = 0 \quad \text{vs} \quad H_a : \beta_5 \neq 0$$

$$H_0 : \beta_6 = 0 \quad \text{vs} \quad H_a : \beta_6 \neq 0$$

$$H_0 : \beta_2 - \beta_3 = 0 \quad \text{vs} \quad H_a : \beta_2 - \beta_3 \neq 0$$

$$H_0 : \beta_5 - \beta_6 = 0 \quad \text{vs} \quad H_a : \beta_5 - \beta_6 \neq 0$$

where

AbDays01mos = a count of the number of days that child received antibiotics, during the first month of life (age range of 1 to 28 days),

AbDays17mos = a count of the number of days that child received antibiotics, during the during the age range of 1 to 7 months (age range of 29 to 214 days),

AbExp01mos = a cumulative measure of ethylmercury exposure from thimerosal in vaccines received **concurrent with antibiotics** during the age ranges from birth through one month (1 – 28 days), expressed in microgram units per kilograms of body weight at the time of vaccine receipt,

ncAbExp01mos = a cumulative measure of ethylmercury exposure from thimerosal in vaccines received **without concurrent antibiotics use** during the age ranges from birth through one month (1 – 28 days), expressed in microgram units per kilograms of body weight at the time of vaccine receipt,

AbExp17mos = a cumulative measure of ethylmercury exposure from thimerosal in vaccines received **concurrent with antibiotics** during the age ranges from one through seven months (29 – 214 days), expressed in microgram units per kilograms of body weight at the time of vaccine receipt,

and

ncAbExp17mos = a cumulative measure of ethylmercury exposure from thimerosal in vaccines received **without concurrent antibiotics use** during the age ranges from one through seven months (29 – 214 days), expressed in microgram units per kilograms of body weight at the time of vaccine receipt, and all other terms are as defined in the analysis plan.

The parameter estimates have the following interpretations:

$\hat{\beta}_2$ is an estimate of the effect of exposure with concurrent antibiotic use (during the age range spanning birth to 28 days).

$\hat{\beta}_3$ is an estimate of the effect of exposure without concurrent antibiotic use (during the age range spanning birth to 28 days).

$\hat{\beta}_4$ is an estimate of the effect of antibiotic use during the age range spanning birth to 28 days. (note: not *concurrent* antibiotics, but antibiotics in and of themselves).

$\hat{\beta}_5$ is an estimate of the effect of exposure with concurrent antibiotic use (during the age range spanning 29 days to seven months).

$\hat{\beta}_6$ is an estimate of the effect of exposure without concurrent antibiotic use (during the age range spanning 29 days to seven months).

$\hat{\beta}_7$ is an estimate of the effect of antibiotic use during the age range spanning 29 days to seven months. (note: not *concurrent* antibiotics, but antibiotics in and of themselves).

$\hat{\beta}_2 - \hat{\beta}_3$ is an estimate of the difference between exposure effects with concurrent antibiotic use and exposure effects without antibiotic use, for the age range spanning birth to 28 days.

$\hat{\beta}_5 - \hat{\beta}_6$ is an estimate of the difference between exposure effects with concurrent antibiotic use and exposure effects without antibiotic use, for the age range spanning 29 days to seven months.

Exhibit 9.4.14. Model Summary: Concurrent Antibiotics - Birth to 1 Month and 1 to 7 Months

Outcome	N	Exposure Measure	Estimate	Stderr	Prob ChiSq	One				2 SD	
						Unit Chg.	Lower 95% CL	Upper 95% CL	1/OR	Unit Chg.	1/OR
ASD_Out	1008	PreNatThimer	0.0082	0.0095	0.384	1.008	0.990	1.027		1.14	
ASD_Out	1008	AbExp01mos	-0.0510	0.0890	0.566	0.950	0.798	1.131	1.053	0.90	1.11
ASD_Out	1008	ncAbExp01mos	-0.0244	0.0458	0.594	0.976	0.892	1.068	1.025	0.90	1.11
ASD_Out	1008	AbDays01mos	0.0300	0.0425	0.480	1.030	0.948	1.120		1.15	
ASD_Out	1008	AbExp17mos	-0.1472	0.0524	0.005**	0.863	0.779	0.956	1.159	0.40	2.49
ASD_Out	1008	ncAbExp17mos	-0.0232	0.0187	0.216	0.977	0.942	1.014	1.024	0.72	1.38
ASD_Out	1008	AbDays17mos	0.0095	0.0117	0.418	1.010	0.987	1.033		1.21	
ASD_Out	1008	Diff01 ^c			0.756						
ASD_Out	1008	Diff17 ^d			0.016*						
AD_Out	911	PreNatThimer	0.0122	0.0106	0.251	1.012	0.991	1.034		1.22	
AD_Out	911	AbExp01mos	-0.0108	0.0994	0.914	0.989	0.814	1.202	1.011	0.98	1.02
AD_Out	911	ncAbExp01mos	0.0403	0.0499	0.419	1.041	0.944	1.148		1.18	
AD_Out	911	AbDays01mos	0.0523	0.0458	0.253	1.054	0.963	1.153		1.28	
AD_Out	911	AbExp17mos	-0.1618	0.0613	0.008**	0.851	0.754	0.959	1.175	0.37	2.73
AD_Out	911	ncAbExp17mos	-0.0452	0.0218	0.039*	0.956	0.916	0.998	1.046	0.53	1.88
AD_Out	911	AbDays17mos	0.0020	0.0141	0.886	1.002	0.975	1.030		1.04	
AD_Out	911	Diff01 ^c			0.595						
AD_Out	911	Diff17 ^d			0.053~						
ASD_Only	773	PreNatThimer	-0.0025	0.0200	0.899	0.997	0.959	1.037	1.003	0.96	1.04
ASD_Only	773	AbExp01mos	-0.1120	0.1695	0.509	0.894	0.641	1.246	1.119	0.80	1.25
ASD_Only	773	ncAbExp01mos	-0.2373	0.0985	0.016*	0.789	0.650	0.957	1.267	0.37	2.70
ASD_Only	773	AbDays01mos	-0.0360	0.0949	0.704	0.965	0.801	1.162	1.036	0.84	1.18
ASD_Only	773	AbExp17mos	-0.1311	0.0955	0.170	0.877	0.727	1.058	1.140	0.44	2.26
ASD_Only	773	ncAbExp17mos	0.0258	0.0344	0.454	1.026	0.959	1.098		1.43	

ASD_Only	773	AbDays17mos	0.0310	0.0191	0.104	1.032	0.994	1.071		1.86	
ASD_Only	773	Diff01 ^c			0.435						
ASD_Only	773	Diff17 ^d			0.099						~
ASD_Regr	701	PreNatThimer	0.0468	0.0218	0.032	1.048	1.004	1.094		2.15	
ASD_Regr	701	AbExp01mos	0.0329	0.1478	0.824	1.033	0.774	1.381		1.07	
ASD_Regr	701	ncAbExp01mos	-0.1084	0.0914	0.235	0.897	0.750	1.073	1.115	0.64	1.57
ASD_Regr	701	AbDays01mos	0.0750	0.0696	0.281	1.078	0.940	1.235		1.42	
ASD_Regr	701	AbExp17mos	-0.3410	0.1770	0.054	0.711	0.503	1.006	1.406	0.12	8.31
ASD_Regr	701	ncAbExp17mos	-0.0999	0.0384	0.009	0.905	0.839	0.976	1.105	0.25	4.02
ASD_Regr	701	AbDays17mos	-0.0248	0.0340	0.465	0.975	0.913	1.043	1.026	0.61	1.64
ASD_Regr	701	Diff01 ^c			0.328						
ASD_Regr	701	Diff17 ^d			0.162						
AD_ExLoCF	884	PreNatThimer	0.0169	0.0106	0.110	1.017	0.996	1.038		1.32	
AD_ExLoCF	884	AbExp01mos	0.0029	0.1011	0.977	1.003	0.823	1.223		1.01	
AD_ExLoCF	884	ncAbExp01mos	-0.0053	0.0548	0.923	0.995	0.893	1.107	1.005	0.98	1.02
AD_ExLoCF	884	AbDays01mos	0.0359	0.0467	0.442	1.037	0.946	1.136		1.18	
AD_ExLoCF	884	AbExp17mos	-0.1318	0.0608	0.030	0.877	0.778	0.987	1.140	0.44	2.27
AD_ExLoCF	884	ncAbExp17mos	-0.0553	0.0236	0.019	0.946	0.903	0.991	1.057	0.46	2.16
AD_ExLoCF	884	AbDays17mos	-0.0025	0.0149	0.868	0.998	0.969	1.027	1.002	0.95	1.05
AD_ExLoCF	884	Diff01 ^c			0.933						
AD_ExLoCF	884	Diff17 ^d			0.200						
ASD_TClIn	821	PreNatThimer	0.0062	0.0099	0.528	1.006	0.987	1.026		1.11	
ASD_TClIn	821	AbExp01mos	-0.0933	0.0951	0.327	0.911	0.756	1.098	1.098	0.83	1.21
ASD_TClIn	821	ncAbExp01mos	-0.0597	0.0482	0.216	0.942	0.857	1.035	1.062	0.78	1.28
ASD_TClIn	821	AbDays01mos	0.0363	0.0487	0.456	1.037	0.943	1.141		1.19	
ASD_TClIn	821	AbExp17mos	-0.1467	0.0598	0.014	0.864	0.768	0.971	1.157	0.40	2.49
ASD_TClIn	821	ncAbExp17mos	-0.0347	0.0204	0.088	0.966	0.928	1.005	1.035	0.62	1.62
ASD_TClIn	821	AbDays17mos	0.0121	0.0129	0.346	1.012	0.987	1.038		1.27	
ASD_TClIn	821	Diff01 ^c			0.714						
ASD_TClIn	821	Diff17 ^d			0.055						~
AD_TClIn	728	PreNatThimer	0.0145	0.0117	0.214	1.015	0.992	1.038		1.27	
AD_TClIn	728	AbExp01mos	-0.0391	0.1104	0.723	0.962	0.775	1.194	1.040	0.92	1.08
AD_TClIn	728	ncAbExp01mos	0.0084	0.0551	0.879	1.008	0.905	1.123		1.04	
AD_TClIn	728	AbDays01mos	0.0627	0.0552	0.256	1.065	0.955	1.186		1.34	
AD_TClIn	728	AbExp17mos	-0.1788	0.0722	0.013	0.836	0.726	0.963	1.196	0.33	3.04
AD_TClIn	728	ncAbExp17mos	-0.0635	0.0253	0.012	0.938	0.893	0.986	1.066	0.41	2.42
AD_TClIn	728	AbDays17mos	0.0093	0.0157	0.553	1.009	0.979	1.041		1.20	
AD_TClIn	728	Diff01 ^c			0.656						
AD_TClIn	728	Diff17 ^d			0.103						

~ p<0.10; * p<0.05; ** p<0.01

^a Odds ratio corresponding to a one-unit increase in exposure measure

^b Odds ratio corresponding to a two-standard deviation unit increase in the exposure measure. This difference can be thought of as roughly corresponding to the difference between low and high exposure. See Exhibit 8.3 for details.

^c The p-value shown for "Diff" is the test $H_0 : \beta_2 - \beta_3 = 0$ vs $H_a : \beta_2 - \beta_3 \neq 0$

^d The p-value shown for "Diff" is the test $H_0 : \beta_5 - \beta_6 = 0$ vs $H_a : \beta_5 - \beta_6 \neq 0$

9.4.5.5. Model (3): Concurrent Antibiotics from Birth to 20 Months

$$\log\left(\frac{\pi}{1-\pi}\right) = \alpha_i + \beta_1 preNatThimer + \beta_2 AbExp020mos + \beta_3 ncAbExp020mos + \beta_4 AbDays020mos + \sum_j \alpha_j oe_j + \sum_k \alpha_{j+k} cf_k$$

$$H_0 : \beta_2 = 0 \quad vs \quad H_a : \beta_2 \neq 0$$

$$H_0 : \beta_3 = 0 \quad vs \quad H_a : \beta_3 \neq 0$$

$$H_0 : \beta_2 - \beta_3 = 0 \quad vs \quad H_a : \beta_2 - \beta_3 \neq 0$$

where

AbExp020mos = a cumulative measure of ethylmercury exposure from thimerosal in vaccines received **concurrent with antibiotics** during the age range from birth through twenty months (1 – 609 days), expressed in microgram units per kilograms of body weight at the time of vaccine receipt,

ncAbExp020mos = a cumulative measure of ethylmercury exposure from thimerosal in vaccines received **without concurrent antibiotics use** during the age range from birth through twenty months (1 – 609 days), expressed in microgram units per kilograms of body weight at the time of vaccine receipt, and

AbDays020mos = a count of the number of days that child received antibiotics, during the age range of 1 to 609 days.

The parameter estimates have the following interpretations:

$\hat{\beta}_2$ is an estimate of the effect of exposure with concurrent antibiotic use.

$\hat{\beta}_3$ is an estimate of the effect of exposure without concurrent antibiotic use.

$\hat{\beta}_4$ is an estimate of the effect of antibiotic use (note: not *concurrent* antibiotics, but antibiotics in and of themselves).

$\hat{\beta}_2 - \hat{\beta}_3$ is an estimate of the difference between exposure effects with concurrent antibiotic use and exposure effects without antibiotic use.

Exhibit 9.4.15. Model Summary: Concurrent Antibiotics - Birth to 20 Months

Outcome	N	Exposure Measure	Estimate	Stderr	Prob ChiSq	One				2 SD	
						Unit Chg. OR ^a	Lower 95% CL	Upper 95% CL	1/OR	Unit Chg. OR ^b	1/OR
ASD_Out	1008	PreNatThimer	0.0076	0.0094	0.422	1.008	0.989	1.026	1.110	1.13	
ASD_Out	1008	AbExp020mos	-0.1039	0.0339	0.002**	0.901	0.843	0.963	1.110	0.47	2.14
ASD_Out	1008	ncAbExp020mos	-0.0250	0.0163	0.125	0.975	0.945	1.007	1.026	0.65	1.54

ASD_Out	1008	AbDays020mos	-0.0001	0.0031	0.975	1.000	0.994	1.006		0.99	1.01
ASD_Out	1008	Diff ^c			0.015 *						
AD_Out	911	PreNatThimer	0.0113	0.0106	0.285	1.011	0.991	1.033		1.20	
AD_Out	911	AbExp020mos	-0.1058	0.0388	0.006 **	0.900	0.834	0.971	1.111	0.46	2.16
AD_Out	911	ncAbExp020mos	-0.0295	0.0186	0.113	0.971	0.936	1.007	1.030	0.60	1.66
AD_Out	911	AbDays020mos	-0.0031	0.0037	0.411	0.997	0.990	1.004	1.003	0.82	1.21
AD_Out	911	Diff ^c			0.041 *						
ASD_Only	773	PreNatThimer	0.0005	0.0200	0.981	1.000	0.962	1.041		1.01	
ASD_Only	773	AbExp020mos	-0.0839	0.0572	0.143	0.920	0.822	1.029	1.087	0.54	1.84
ASD_Only	773	ncAbExp020mos	-0.0169	0.0294	0.566	0.983	0.928	1.042	1.017	0.75	1.34
ASD_Only	773	AbDays020mos	0.0045	0.0051	0.379	1.005	0.994	1.015		1.33	
ASD_Only	773	Diff ^c			0.225						
ASD_Regr	701	PreNatThimer	0.0406	0.0209	0.052 ~	1.041	1.000	1.085		1.94	
ASD_Regr	701	AbExp020mos	-0.1616	0.0822	0.049 *	0.851	0.724	0.999	1.175	0.31	3.25
ASD_Regr	701	ncAbExp020mos	-0.0724	0.0323	0.025 *	0.930	0.873	0.991	1.075	0.29	3.46
ASD_Regr	701	AbDays020mos	-0.0064	0.0074	0.383	0.994	0.979	1.008	1.006	0.66	1.51
ASD_Regr	701	Diff			0.248						
AD_ExLoCF	884	PreNatThimer	0.0153	0.0106	0.148	1.015	0.995	1.037		1.28	
AD_ExLoCF	884	AbExp020mos	-0.0837	0.0377	0.026 *	0.920	0.854	0.990	1.087	0.54	1.84
AD_ExLoCF	884	ncAbExp020mos	-0.0430	0.0201	0.033 *	0.958	0.921	0.996	1.044	0.48	2.09
AD_ExLoCF	884	AbDays020mos	-0.0045	0.0039	0.251	0.996	0.988	1.003	1.004	0.75	1.33
AD_ExLoCF	884	Diff ^c			0.261						
ASD_TcIn	821	PreNatThimer	0.0059	0.0099	0.550	1.006	0.987	1.026		1.10	
ASD_TcIn	821	AbExp020mos	-0.1104	0.0389	0.005 **	0.895	0.830	0.966	1.117	0.45	2.24
ASD_TcIn	821	ncAbExp020mos	-0.0334	0.0178	0.061 ~	0.967	0.934	1.002	1.034	0.56	1.77
ASD_TcIn	821	AbDays020mos	0.0020	0.0034	0.559	1.002	0.995	1.009		1.14	
ASD_TcIn	821	Diff ^c			0.037 *						
AD_TcIn	728	PreNatThimer	0.0139	0.0116	0.231	1.014	0.991	1.037		1.25	
AD_TcIn	728	AbExp020mos	-0.1116	0.0464	0.016 *	0.894	0.817	0.979	1.119	0.44	2.26
AD_TcIn	728	ncAbExp020mos	-0.0425	0.0215	0.048 *	0.958	0.919	1.000	1.044	0.48	2.07
AD_TcIn	728	AbDays020mos	-0.0021	0.0042	0.624	0.998	0.990	1.006	1.002	0.88	1.14
AD_TcIn	728	Diff ^c			0.122						

~ p<0.10; * p<0.05; ** p<0.01

^a Odds ratio corresponding to a one-unit increase in exposure measure

^b Odds ratio corresponding to a two-standard deviation unit increase in the exposure measure. This difference can be thought of as roughly corresponding to the difference between low and high exposure. See Exhibit 8.3 for details.

^c The p-value shown for "Diff" is the test $H_0 : \beta_2 - \beta_3 = 0$ vs $H_a : \beta_2 - \beta_3 \neq 0$

9.4.6. Antibiotic Use Among ASD Cases and Controls

Niehus R and Lord C. (2006) abstracted medical record abstractions of 75 children with ASD diagnoses, and 24 typically developing children and reported that the children with ASD were significantly more likely to have had ear infections and have used antibiotics in the first two years of life. In order to assess whether there was evidence of greater antibiotic use for ASD cases in the current study sample we 1) calculated the proportions of ASD cases and controls that had received any antibiotics each of several age ranges (birth to 1 month, 1 to 7 months, birth to 7 months, and birth to 20 months), 2) calculated the mean number of days that ASD cases and controls were on antibiotics in each of those age ranges, and 3) fit models to test whether the mean number of days or the proportion that used any antibiotics was different for ASD cases and controls, for each age range. The models were of the form:

$$Y = \beta_0 + \beta_1(ASD) + \sum_m^{M-1} \beta_{1+m}(MatchingStratum_m) + \varepsilon$$

where

Y = any of the antibiotic use variables shown in Exhibit x.x.

ASD = an indicator of case control status.

$MatchingStratum_m = 1$ if individual belongs to m^{th} matching stratum, =0 else. Matching strata are defined by birth year, sex, and HMO.

$\hat{\beta}_1$ = the OLS estimate of the case / control difference in antibiotic use, controlling for matching strata.

In the model results summaries that follow, in addition to showing the estimated case control difference ($\hat{\beta}_1$), we also show the model-estimated least squares means for the case and control groups. Least squares means are covariate adjusted means. In this case, the model adjusts for any imbalance in the case control ratio within matching strata. Specifically the least squares means are the model-predicted means when the coefficients for all of the control covariates, i.e., the coefficients corresponding to the matching strata, are multiplied by the sample means of each of those covariates. That is, the least squares mean for the case group is obtained as:

$$\hat{Y}_{Case} = \hat{\beta}_0 + \hat{\beta}_1(1) + \sum_m^{M-1} \hat{\beta}_{1+m}(\text{mean}(MatchingStratum_m)),$$

where $\text{mean}(MatchingStratum_m)$ is the proportion of the sample (either participant group or full sample) that is in the m^{th} matching stratum.

The least squares mean for the control group is obtained as:

$$\hat{Y}_{Control} = \hat{\beta}_0 + \hat{\beta}_1(0) + \sum_m^{M-1} \hat{\beta}_{1+m}(\text{mean}(MatchingStratum_m))$$

Unadjusted means of antibiotic use measures are displayed in Exhibit 9.4.16. The exhibit suggest that antibiotic use was higher for ASD cases than controls in the first month, but that the means of measures of antibiotic use were greater for controls at older ages.

The model results are summarized in Exhibit 9.4.17. They indicated that:

- ASD cases were significantly more likely to have received antibiotics in the age range from birth to 28 days ($p=0.047$)
 - 16.3% of ASD cases, 11.5% of controls were given antibiotics in the first month.
- There were no statistically significant differences between ASD case and controls on any of the other measures of antibiotic use.

Exhibit 9.4.16 Proportions of ASD Cases and Controls that had Any Antibiotics, and Mean Number of Days on Antibiotics

Variable	Label	ASD Cases				Controls			
		N	Mean	Min.	Max.	N	Mean	Min.	Max.
Any Antibiotics									
AnyAb01mos	=1 if any Antibiotics 0-1 mos. (1-28 days)	256	0.164	0	1	752	0.114	0	1
AnyAb17mos	=1 if any Antibiotics 1-7 mos. (29-214 days)	256	0.285	0	1	752	0.344	0	1
AnyAb07mos	=1 if any Antibiotics 0-7 mos. (1-214 days)	256	0.395	0	1	752	0.419	0	1
AnyAb020mos	=1 if any Antibiotics 0-20 mos. (1-609 days)	256	0.746	0	1	752	0.785	0	1
Number of Days on Antibiotics									
AbDays01mos	# days on Antibiotics 0-1 mos. (1-28 days)	256	0.887	0	28	752	0.594	0	22
AbDays17mos	# days on Antibiotics 1-7 mos. (29-214 days)	256	4.352	0	50	752	5.608	0	69
AbDays07mos	# days on Antibiotics 0-7 mos. (1-214 days)	256	5.238	0	50	752	6.202	0	69
AbDays020mos	# days on Antibiotics 0-20 mos. (1-609 days)	256	24.590	0	149	752	29.481	0	216

Exhibit 9.4.17.

Summary of Model Results to Estimate Case / Control Difference in Antibiotic Use Measures									
Antibiotic Use Measure (Y)	of Records		Case / Control Difference			Least Squares			
	Total	Case	Control	Difference	$\hat{\beta}_1$	S.E.	$H_0 : \beta_1 = 0$	Means	
							p-value	Case	Control
Any Antibiotics									
AnyAb01mos	1008	256	752	0.048	0.024	0.024	0.047 *	0.163	0.115
AnyAb17mos	1008	256	752	-0.055	0.033	0.033	0.103	0.319	0.373
AnyAb07mos	1008	256	752	-0.020	0.035	0.035	0.578	0.427	0.446
AnyAb020mos	1008	256	752	-0.033	0.030	0.030	0.276	0.742	0.775
Number of Days on Antibiotics									
AbDays01mos	1008	256	752	0.287	0.172	0.172	0.094 ~	0.830	0.543
AbDays17mos	1008	256	752	-1.095	0.706	0.706	0.121	4.817	5.911
AbDays07mos	1008	256	752	-0.807	0.732	0.732	0.270	5.65	6.45
AbDays020mos	1008	256	752	-4.284	2.203	2.203	0.052 ~	25.51	29.80

~ p<0.10; * p<0.05; ** p<0.01

9.4.7. Low Birth Weight Children Excluded

As described in Section 3.3 (“Research Questions”) there was interest in whether there might be an interaction between low birth weight and thimerosal exposure. Because the number of low birth weight children in the sample was very small, we would expect that a traditional interaction test would have very low power to detect an effect. Therefore, our plans called for an investigation of the low birth weight question from a different perspective. We planned to conduct subgroup analyses consisting of children who were of normal birth weight (>2500 grams). This provides estimates of exposure risk for normal birth weight children, and shows whether results are sensitive to the inclusion/exclusion of low birth weight children.

Exhibit 9.4.18 shows the numbers of low birth weight cases and controls in each of the seven outcome classification data sets. The exhibit shows, for example, that for the ASD outcome data set, there were 69 low birth weight children (<2500 grams) including 22 ASD cases and 47 matched controls.

Exhibit 9.4.19 is a summary of the results from the “birth through seven months and prenatal exposures model” (i.e., with exposure terms *PreNatThimer* and *Exp07mos*) for each outcome when low birth weight cases and controls are excluded from the analysis. Exhibit 9.4.19 can be compared to Exhibit 9.4.1, which summarizes results from the same models but without the exclusion of low birth weight individuals. Comparison of the two sets of results shows that for the postnatal exposure term (*Exp07mos*), and each of the outcome sets, exclusion of the low birth weight individuals results in exposure estimates that attenuated (i.e., they are closer to zero), relative to results that include the low birth weight individuals. In the full data sets, higher cumulative exposure during the age range spanning birth to seven months was associated with lower risk of the autism outcomes. With the low birth weight individuals excluded the risk estimate moves closer to zero. Comparison of odds ratios from the two sets of results indicates that the differences were very small.

For six of the eight outcome sets, exclusion of low birth weight individuals attenuated the *PreNatThimer* estimates. For the ASD-not-AD and ASD with Regression outcomes, exclusion of low birth weight individuals made the estimates of the *PreNatThimer* effect larger and more positive. In summary, these exploratory analyses based on small numbers of low birth weight individuals do not provide compelling evidence that thimerosal exposure has radically different risks or protective associations for low birth weight individuals relative to higher birth weight individuals.

Exhibit 9.4.20 shows results from models with exposure terms *PreNatThimer*, *Exp01mos*, and *Exp17mos*, and Exhibit 9.4.21 shows results from models with exposure terms *PreNatThimer*, and *Exp020mos*. These exhibits should be compared with Exhibit 9.4.3 and 9.4.4, respectively. Similar to the results described above, exclusion of low birth weight individuals results in only very small differences in the parameter estimates, and those differences were usually in the direction of attenuation.

As an additional exploratory step, we estimated bivariate associations between exposure and autism risk for the subsets of low birth weight individuals for the ASD, AD, and ASD with Regression outcome sets. We did this for the first two outcome sets because they are the primary outcomes and the third because the analyses described above showed slight increases in the *PreNatThimer* effect when the low birth weight individuals were excluded. We fit bivariate models (no covariates) because the small sample sizes would cause estimation problems in models with covariates. The summaries of bivariate relationships are shown in Exhibits 9.4.22, 9.4.23, and 9.4.24, and were calculated in the same manner as described in Section 9.1. The corresponding exhibits for bivariate relationships for the full data set are shown in Chapter 9, Exhibits 9.2.1, 9.2.2, and 9.2.4.

The results from the bivariate models for the low birth weight individuals did not look substantially different than the results estimated from the full data sets (Chapter 9). Unlike the covariate adjusted results described above, which suggested that there may be less of an estimated protective effect of higher birth to seven months cumulative exposure (*Exp07mos*) for low birth weight individuals, the postnatal exposure coefficients from the bivariate models for low birth weight individuals were slightly farther from zero in the negative direction (protective). But, the differences were exceedingly small. The results in Exhibit 9.4.18 show that the four low birth weight ASD with regression individuals had zero prenatal exposure. Thus, these data provide no evidence that prenatal exposure for low birth weight individuals is related to increased risk of ASD with regression. Similar to the results described above, these exploratory analyses based on small numbers of low birth weight individuals do not provide compelling evidence that thimerosal exposure has radically different risks or protective associations for low birth weight individuals relative to higher birth weight individuals.

Exhibit 9.4.19. Model Summary: *PreNatThimer* and *Exp07mos* Exposure Models with Low Birth Weight Cases and Controls Excluded

Outcome	N	Exposure Measure	Estimate	Stderr	Prob ChiSq	One				2 SD	
						Unit Chg. OR ^a	Lower 95% CL	Upper 95% CL	1/OR	Unit Chg. OR ^b	1/OR
<i>ASD_Outc</i>	939	<i>PreNatThimer</i>	0.0050	0.0095	0.603	1.005	0.986	1.024		1.08	
<i>ASD_Outc</i>	939	<i>Exp07mos</i>	-0.0230	0.0179	0.198	0.977	0.944	1.012	1.023	0.70	1.43
<i>AD_Outc</i>	847	<i>PreNatThimer</i>	0.0089	0.0105	0.399	1.009	0.988	1.030		1.16	
<i>AD_Outc</i>	847	<i>Exp07mos</i>	-0.0350	0.0205	0.088 ~	0.966	0.928	1.005	1.036	0.58	1.72
<i>ASD_Only</i>	729	<i>PreNatThimer</i>	-0.0038	0.0201	0.849	0.996	0.958	1.036	1.004	0.94	1.06
<i>ASD_Only</i>	729	<i>Exp07mos</i>	-0.0051	0.0327	0.875	0.995	0.933	1.061	1.005	0.92	1.08
<i>ASD_Regr</i>	657	<i>PreNatThimer</i>	0.0399	0.0212	0.060 ~	1.041	0.998	1.085		1.92	
<i>ASD_Regr</i>	657	<i>Exp07mos</i>	-0.0843	0.0360	0.019 *	0.919	0.857	0.986	1.088	0.27	3.71
<i>AD_ExLoCF</i>	822	<i>PreNatThimer</i>	0.0140	0.0106	0.188	1.014	0.993	1.035		1.26	
<i>AD_ExLoCF</i>	822	<i>Exp07mos</i>	-0.0490	0.0224	0.029 *	0.952	0.911	0.995	1.050	0.47	2.14
<i>ASD_Scr</i>	773	<i>PreNatThimer</i>	0.0040	0.0099	0.684	1.004	0.985	1.024		1.07	
<i>ASD_Scr</i>	773	<i>Exp07mos</i>	-0.0381	0.0197	0.053 ~	0.963	0.926	1.000	1.039	0.55	1.81
<i>AD_Scr</i>	685	<i>PreNatThimer</i>	0.0122	0.0116	0.292	1.012	0.990	1.036		1.22	
<i>AD_Scr</i>	685	<i>Exp07mos</i>	-0.0595	0.0241	0.014 *	0.942	0.899	0.988	1.061	0.40	2.52

~ p<0.10; * p<0.05; ** p<0.01

^a Odds ratio corresponding to a one-unit increase in exposure measure

^b Odds ratio corresponding to a two-standard deviation unit increase in the exposure measure. This difference can be thought of as roughly corresponding to the difference between low and high exposure.

Exhibit 9.4.20. Model Summary: PreNatThimer , Exp01mos, Exp17mos Exposure Models with Low Birth Weight Cases and Controls Excluded

Outcome	N	Exposure Measure	Estimate	Stderr	Prob ChiSq	One	Lower	Upper	2 SD	
						Unit Chg. OR ^a	95% CL	95% CL	1/OR	Unit Chg. OR ^b
ASD_Outc	939	PreNatThimer	0.0050	0.0095	0.603	1.005	0.986	1.024		1.08
ASD_Outc	939	Exp01mos	-0.0266	0.0503	0.597	0.974	0.882	1.075	1.027	0.90 1.11
ASD_Outc	939	Exp17mos	-0.0224	0.0197	0.254	0.978	0.941	1.016	1.023	0.72 1.39
AD_Outc	847	PreNatThimer	0.0087	0.0106	0.411	1.009	0.988	1.030		1.15
AD_Outc	847	Exp01mos	0.0333	0.0559	0.551	1.034	0.927	1.154		1.15
AD_Outc	847	Exp17mos	-0.0479	0.0230	0.037 *	0.953	0.911	0.997	1.049	0.50 2.01
ASD_Only	729	PreNatThimer	-0.0056	0.0199	0.780	0.994	0.956	1.034	1.006	0.91 1.10
ASD_Only	729	Exp01mos	-0.2034	0.1033	0.049 *	0.816	0.666	0.999	1.226	0.44 2.30
ASD_Only	729	Exp17mos	0.0254	0.0352	0.470	1.026	0.957	1.099		1.45
ASD_Regr	657	PreNatThimer	0.0401	0.0212	0.059 ~	1.041	0.999	1.085		1.92
ASD_Regr	657	Exp01mos	-0.0244	0.0911	0.789	0.976	0.816	1.167	1.025	0.90 1.10
ASD_Regr	657	Exp17mos	-0.0977	0.0413	0.018 *	0.907	0.836	0.983	1.103	0.24 4.14
AD_ExLoCF	822	PreNatThimer	0.0140	0.0107	0.188	1.014	0.993	1.036		1.26
AD_ExLoCF	822	Exp01mos	-0.0152	0.0604	0.802	0.985	0.875	1.109	1.015	0.94 1.06
AD_ExLoCF	822	Exp17mos	-0.0557	0.0252	0.027 *	0.946	0.900	0.994	1.057	0.44 2.25
ASD_Scr	773	PreNatThimer	0.0040	0.0099	0.690	1.004	0.985	1.024		1.07
ASD_Scr	773	Exp01mos	-0.0592	0.0522	0.256	0.942	0.851	1.044	1.061	0.79 1.27
ASD_Scr	773	Exp17mos	-0.0346	0.0212	0.104	0.966	0.927	1.007	1.035	0.60 1.65
AD_Scr	685	PreNatThimer	0.0119	0.0117	0.309	1.012	0.989	1.035		1.21
AD_Scr	685	Exp01mos	-0.0052	0.0598	0.931	0.995	0.885	1.119	1.005	0.98 1.02
AD_Scr	685	Exp17mos	-0.0698	0.0265	0.008 *	0.933	0.885	0.982	1.072	0.36 2.76

~ p<0.10; * p<0.05; ** p<0.01

^a Odds ratio corresponding to a one-unit increase in exposure measure

^b Odds ratio corresponding to a two-standard deviation unit increase in the exposure measure. This difference can be thought of as roughly corresponding to the difference between low and high exposure.

Exhibit 9.4.21. Model Summary: *PreNatThimer* and *Exp07mos* Exposure Models with Low Birth Weight Cases and Controls Excluded

Outcome	N	Exposure Measure	Estimate	Stderr	Prob ChiSq	One	Lower	Upper	2 SD		
						Unit Chg. OR ^a	95% CL	95% CL	1/OR	Unit Chg. OR ^b	1/OR
ASD_Outc	939	<i>PreNatThimer</i>	0.0048	0.0095	0.612	1.005	0.986	1.024		1.08	
ASD_Outc	939	<i>Exp020mos</i>	-0.0250	0.0173	0.148	0.975	0.943	1.009	1.025	0.64	1.56
AD_Outc	847	<i>PreNatThimer</i>	0.0084	0.0106	0.426	1.008	0.988	1.030		1.15	
AD_Outc	847	<i>Exp020mos</i>	-0.0358	0.0197	0.069 ~	0.965	0.928	1.003	1.036	0.53	1.89
ASD_Only	729	<i>PreNatThimer</i>	-0.0038	0.0201	0.852	0.996	0.958	1.036	1.004	0.94	1.06
ASD_Only	729	<i>Exp020mos</i>	-0.0060	0.0308	0.846	0.994	0.936	1.056	1.006	0.90	1.11
ASD_Regr	657	<i>PreNatThimer</i>	0.0391	0.0209	0.062 ~	1.040	0.998	1.083		1.89	
ASD_Regr	657	<i>Exp020mos</i>	-0.0774	0.0350	0.027 *	0.926	0.864	0.991	1.080	0.25	3.97
AD_ExLoCF	822	<i>PreNatThimer</i>	0.0134	0.0107	0.207	1.014	0.993	1.035		1.25	
AD_ExLoCF	822	<i>Exp020mos</i>	-0.0470	0.0215	0.029 *	0.954	0.915	0.995	1.048	0.43	2.31
ASD_Scr	773	<i>PreNatThimer</i>	0.0038	0.0099	0.702	1.004	0.984	1.024		1.06	
ASD_Scr	773	<i>Exp020mos</i>	-0.0372	0.0189	0.049 *	0.963	0.928	1.000	1.038	0.52	1.94
AD_Scr	685	<i>PreNatThimer</i>	0.0115	0.0116	0.324	1.012	0.989	1.035		1.21	
AD_Scr	685	<i>Exp020mos</i>	-0.0569	0.0231	0.014 *	0.945	0.903	0.988	1.059	0.36	2.76

~ p<0.10; * p<0.05; ** p<0.01

^a Odds ratio corresponding to a one-unit increase in exposure measure

^b Odds ratio corresponding to a two-standard deviation unit increase in the exposure measure. This difference can be thought of as roughly corresponding to the difference between low and high exposure.

Exhibit 9.4.22 Bivariate Relationships Of Exposure Measures to ASD Outcome For Low Birth Weight Cases and Controls

Variable	Label	Overall (n=69)			ASD (n=22)			Control (n=47)			Estimates from PH Model					
		Mean	Min	Max	Mean	Min	Max	Mean	Min	Max	df	Est.	S.E.	ChiSq	P-Val	O.R.
Exp07mos	Amt/Wt(KGs) birth-214 days	24.53	0	66.94	23.55	0	65.17	24.99	2.91	66.94	1	-0.0212	0.0343	0.3819	0.5366	0.979
Exp01mos	Amt/Wt(KGs) birth-28 days	3.66	0	21.04	3.15	0	8.07	3.91	0.00	21.04	1	-0.0571	0.0848	0.4540	0.5005	0.944
Exp17mos	Amt/Wt(KGs) 29-214 days	20.87	0	66.94	20.40	0	65.17	21.08	0.00	66.94	1	-0.0098	0.0306	0.1019	0.7495	0.990
Exp020mos	Amt/Wt(KGs) birth-609 days	28.62	0	76.74	28.12	0	70.30	28.85	5.03	76.74	1	-0.0152	0.0337	0.2035	0.6519	0.985
Amt07mos	Amt Merc birth-214 days	105.98	0	187.50	96.59	0	187.50	110.37	12.50	187.50	1	-0.0167	0.0122	1.8815	0.1702	0.983
Amt01mos	Amt Merc birth-28 days	8.15	0	50.00	6.82	0	12.50	8.78	0.00	50.00	1	-0.0333	0.0388	0.7393	0.3899	0.967
Amt17mos	Amt Merc 29-214 days	97.83	0	187.50	89.77	0	187.50	101.60	0.00	187.50	1	-0.0133	0.0119	1.2518	0.2632	0.987
Amt020mos	Amt Merc birth-609 days	141.85	0	250.00	133.52	0	225.00	145.75	12.50	250.00	1	-0.0199	0.0143	1.9374	0.1640	0.980
PreNatThimer	PreNat Exp Amt	2.01	0	25.00	2.30	0	25.00	1.88	0.00	25.00	1	0.0231	0.0532	0.1889	0.6638	1.023
PreNatThimer_Alt	PreNat Exp Amt (Alt)	2.55	0	50.00	2.30	0	25.00	2.67	0.00	50.00	1	-0.0052	0.0365	0.0204	0.8864	0.995

Exhibit 9.4.23 Bivariate Relationships Of Exposure Measures to AD Outcome For Low Birth Weight Cases and Controls

Variable	Label	Overall (n=64)			AD (n=18)			Control (n=46)			Estimates from PH Model					
		Mean	Min	Max	Mean	Min	Max	Mean	Min	Max	df	Est.	S.E.	ChiSq	P-Val	O.R.
Exp07mos	Amt/Wt(KGs) birth-214 days	25.26	2.91	66.94	25.14	5.14	65.17	25.30	2.91	66.94	1	-0.0102	0.0339	0.0913	0.7625	0.990
Exp01mos	Amt/Wt(KGs) birth-28 days	3.69	0	21.04	3.25	0	8.07	3.87	0	21.04	1	-0.0294	0.0850	0.1197	0.7293	0.971
Exp17mos	Amt/Wt(KGs) 29-214 days	21.56	0	66.94	21.89	5.14	65.17	21.44	0	66.94	1	-0.0046	0.0305	0.0228	0.8801	0.995
Exp020mos	Amt/Wt(KGs) birth-609 days	29.59	5.03	76.74	30.46	5.14	70.30	29.25	5.03	76.74	1	0.0012	0.0326	0.0014	0.9704	1.001
Amt07mos	Amt Merc birth-214 days	108.20	12.50	187.50	98.61	25.00	187.50	111.96	12.50	187.50	1	-0.0173	0.0129	1.7873	0.1812	0.983
Amt01mos	Amt Merc birth-28 days	8.20	0	50.00	6.94	0	12.50	8.70	0	50.00	1	-0.0231	0.0386	0.3590	0.5491	0.977
Amt17mos	Amt Merc 29-214 days	100.00	0	187.50	91.67	25.00	187.50	103.26	0	187.50	1	-0.0149	0.0127	1.3698	0.2418	0.985
Amt020mos	Amt Merc birth-609 days	146.09	12.50	250.00	140.97	25.00	225.00	148.10	12.50	250.00	1	-0.0135	0.0142	0.9052	0.3414	0.987
PreNatThimer	PreNat Exp Amt	1.97	0	25.00	2.10	0	25.00	1.92	0	25.00	1	0.0623	0.0804	0.6011	0.4382	1.064
PreNatThimer_Alt	PreNat Exp Amt (Alt)	2.55	0	50.00	2.10	0	25.00	2.73	0	50.00	1	0.0001	0.0394	0.0000	0.9974	1.000

Exhibit 9.4.24 Bivariate Relationships Of Exposure Measures to ASD with Regression Outcome For Low Birth Weight Cases and Controls

Variable	Label	Overall (n=44)			ASD w/Reg. (n=4)			Control (n=40)			Estimates from PH Model					
		Mean	Min	Max	Mean	Min	Max	Mean	Min	Max	df	Est.	S.E.	ChiSq	P-Val	O.R.
Exp07mos	Amt/Wt(KGs) birth-214 days	24.84	2.91	66.94	18.49	5.14	25.04	25.47	2.91	66.944	1	-0.2483	0.2246	1.2220	0.2690	0.780
Exp01mos	Amt/Wt(KGs) birth-28 days	3.83	0	21.04	1.58	0	6.31	4.04	0	21.044	1	-0.2572	0.2108	1.4883	0.2225	0.773
Exp17mos	Amt/Wt(KGs) 29-214 days	21.02	0	66.94	16.91	5.14	22.16	21.43	0	66.944	1	-0.0405	0.0899	0.2032	0.6521	0.960
Exp020mos	Amt/Wt(KGs) birth-609 days	28.98	5.03	76.74	25.29	5.14	35.40	29.35	5.03	76.74	1	-0.0273	0.0808	0.1146	0.7350	0.973
Amt07mos	Amt Merc birth-214 days	108.52	12.50	187.5	75	25	125	111.88	12.5	187.5	1	-0.5291	342.78	0.0000	0.9988	0.589
Amt01mos	Amt Merc birth-28 days	8.52	0	50	3.13	0	12.50	9.06	0	50	1	-0.1307	0.0992	1.7352	0.1878	0.877
Amt17mos	Amt Merc 29-214 days	100	0	187.5	71.88	25	112.50	102.81	0	187.5	1	-0.0728	0.0614	1.4078	0.2354	0.930
Amt020mos	Amt Merc birth-609 days	144.89	12.50	250	121.88	25	187.50	147.19	12.5	250	1	-0.0696	0.0808	0.7436	0.3885	0.933
PreNatThimer	PreNat Exp Amt	1.44	0	25	0	0	0	1.58	0	25	0	0.0000				
PreNatThimer_Alt	PreNat Exp Amt (Alt)	2.28	0	50	0	0	0	2.51	0	50	0	0.0000				

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