Abt Associates Inc.

Thimerosal and Autism

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Volume II

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The interpretation of results represent the views of the authors only, and do not necessarily represent the views of the Principal Investigators from the participating HMOs, the Centers for Disease Control and Prevention (CDC), or the study's External Expert Consultants.

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10. Introduction to Volume II

Volume I of this report presents the study background and research questions, study design, sample selection, data sources, measures, analysis approach, and results of the analyses that were used to address the primary and secondary research questions that motivated the study. Volume II 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.

11. Use of Alternative Exposure Variables

In this section we explore whether the findings from the study are sensitive to the coding of exposure variables, or to assumptions that were made regarding the ethylmercury content of immune globulins that were received by the mother during her pregnancy with the study child, but where the manufacturer was unknown.

11.1. Use of PreNatThimer_Alt, and "Amount Variables"

In this section, we fit the same models that are summarized in Exhibit 9.4.2 ("Model Summary: *PreNatThimer, Exp01mos, Exp17mos* Exposure Models), except that the exposure variables are replaced with alternatively coded exposure variables. For prenatal exposure, we replace the *PreNatThimer* variable with *PreNatThimer_Alt*. As described in Section 7.4.4, when a prenatal immune globulin receipt lacked specific information about manufacturer or lot number, we assumed that the product "Rhogam" was received and assigned an exposure amount equal to 12.75 micrograms of ethylmercury to the receipt. The *PreNatThimer* variable was created as the sum of all prenatal ethylmercury exposure from vaccines and immune globulins, including those where "Rhogam" was the assumed product type. For creation of the *PreNatThimer_Alt* variable, we made an alternative assumption that those receipts contained 50 micrograms of ethylmercury, as would have been the case if those unknowns corresponded to receipt of either Gamulin or Hypro-d products. The results shown in Exhibit 11.1 can be compared to the results in Exhibit 9.4.2 to assess whether the estimates of risk associated with prenatal exposure are sensitive to the use of the *PreNatThimer* variable or the *PreNatThimer_Alt* measure of exposure. The results do not appear to be sensitive to the use of one variable relative to the other. The parameter estimates and odds ratios from the two sets of results are very similar to one another.

As explained in Section 7.3.2, the variables *Exp01mos, Exp17mos* were constructed by dividing the amount of mercury in each vaccine receipt by the child's weight at the time of receipt, and cumulating across the appropriate age range (i.e., birth to one month, and one to seven months). The exposure variables *Amt01mos, Amt17mos* were created by summing the ethylmercury exposure amounts in each vaccine receipt within the relevant age range, but without dividing by the child's weight at the time of receipt. Thus,

comparing the results shown in Exhibit 11.1.1 to the results shown in Exhibit 9.4.2 gives an indication as to whether the estimates of risk associated with postnatal exposure are sensitive whether child's weight at the time of receipt is used in the creation of the exposure variables. The results do not appear to be sensitive to the use of *Amt01mos* and *Amt17mos* variables in place of the measures *Exp01mos* and *Exp17mos.* Because the exposure variables used in the two sets of models are on different scales, the parameter estimates are not directly comparable to one another. But, the odds ratios are comparable to one another and are very similar across the two sets of results.

Exhibit 11.1.1. Model Summary: *PreNatThimer_Alt* , *Amt01mos, Amt17mos* Exposure Models

Outcome	N	Exposure Measure	Estimate	Stderr	Prob ChiSq		One Unit Chg. OR[a]	Lower 95% CL	Upper 95% CL	1/OR	2 SD Unit Chg. OR[b]	1/OR
ASD_Outc	1008	*PreNatThimer_Alt*	0.0038	0.0055	0.490		1.004	0.993	1.015		1.11	
ASD_Outc	1008	*Amt01mos*	-0.0032	0.0138	0.817		0.997	0.970	1.024	1.003	0.96	1.04
ASD_Outc	1008	*Amt17mos*	-0.0053	0.0032	0.097	~	0.995	0.988	1.001	1.005	0.65	1.55
AD_Outc	911	*PreNatThimer_Alt*	0.0066	0.0063	0.299		1.007	0.994	1.019		1.20	
AD_Outc	911	*Amt01mos*	0.0144	0.0154	0.349		1.015	0.984	1.046		1.20	
AD_Outc	911	*Amt17mos*	-0.0091	0.0036	0.013	*	0.991	0.984	0.998	1.009	0.48	2.10
ASD_Only	773	*PreNatThimer_Alt*	-0.0047	0.0108	0.666		0.995	0.974	1.017	1.005	0.88	1.14
ASD_Only	773	*Amt01mos*	-0.0594	0.0292	0.042	*	0.942	0.890	0.998	1.061	0.47	2.15
ASD_Only	773	*Amt17mos*	0.0011	0.0063	0.859		1.001	0.989	1.013		1.10	
ASD_Regr	701	*PreNatThimer_Alt*	0.0121	0.0107	0.259		1.012	0.991	1.034		1.39	
ASD_Regr	701	*Amt01mos*	-0.0168	0.0258	0.516		0.983	0.935	1.034	1.017	0.81	1.24
ASD_Regr	701	*Amt17mos*	-0.0138	0.0062	0.025	*	0.986	0.974	0.998	1.014	0.32	3.09
AD_ExLoCF	884	*PreNatThimer_Alt*	0.0069	0.0065	0.290		1.007	0.994	1.020		1.21	
AD_ExLoCF	884	*Amt01mos*	0.0041	0.0165	0.804		1.004	0.972	1.037		1.05	
AD_ExLoCF	884	*Amt17mos*	-0.0104	0.0039	0.008	**	0.990	0.982	0.997	1.010	0.43	2.34
ASD_Scr	821	*PreNatThimer_Alt*	0.0035	0.0059	0.547		1.004	0.992	1.015		1.10	
ASD_Scr	821	*Amt01mos*	-0.0153	0.0145	0.290		0.985	0.957	1.013	1.015	0.82	1.22
ASD_Scr	821	*Amt17mos*	-0.0077	0.0035	0.029	*	0.992	0.985	0.999	1.008	0.53	1.88
AD_Scr	728	*PreNatThimer_Alt*	0.0076	0.0069	0.277		1.008	0.994	1.021		1.23	
AD_Scr	728	*Amt01mos*	0.0039	0.0166	0.814		1.004	0.972	1.037		1.05	
AD_Scr	728	*Amt17mos*	-0.0128	0.0042	0.002	**	0.987	0.979	0.995	1.013	0.35	2.85

~ 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.

11.2. Exposure Cumulated Over Both Prenatal and Postnatal Periods

In this section we present results of analyses designed to address the following question:

> Are there associations between autism outcomes and cumulative exposure over both the prenatal and postnatal periods?

We note that this question was not specified during the planning phase of the study, but arose after results of preliminary analyses were presented to the group of External Expert Consultants and Principal Investigators from the CDC and the HMOs. In order to address this question we created two new measures. The first is a measure of cumulative exposure prenatal through seven months postnatal, the second covers the prenatal period through 20 months postnatal. Since there was no obvious way to combine the measure of postnatal exposure that was divided by weight at time of vaccine receipt with the prenatal measures (that do not have weight as part of the measure), we created the measures by summing the prenatal exposure amounts with the postnatal "amount variables", where the "amount variables" are the cumulative mercury amounts with no division by weight at time of receipt. The new cumulative measures were defined as follows:

Exposure Measure	**Definition**
CumPre07mos	*= PreNatThimer+Amt07mos*
CumPre020mos	*= PreNatThimer+Amt020mos*
where	
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.
Amt07mos	= "Amount zero to 7 months" = Amount of ethylmercury per vaccine receipt summed over all vaccines and immune globulins received by the child during the age range from birth to seven months of age (1 to 214 days).
Amt020mos	= "Amount zero to 20 months" = Amount of ethylmercury per vaccine receipt summed over all vaccines and immune globulins received by the child during the age range from birth to twenty months of age (1 to 609 days).

Models were of the form:

$$\log(\frac{\pi}{1-\pi}) = \alpha_i + \beta_1 Cumpre07mos + \sum_j \alpha_j oe_j + \sum_k \alpha_{j+k} cf_k$$

and

$$\log(\frac{\pi}{1-\pi}) = \alpha_i + \beta_1 Cumpre020mos + \sum_j \alpha_j oe_j + \sum_k \alpha_{j+k} cf_k$$

Model results are summarized in Exhibits 11.2.1 and 11.2.2. There are no indications that increased cumulative exposure over both prenatal and postnatal periods is associated with increased risk of autism. For the contrasts of ASD to the screened control group, and AD

to the screened control group, higher cumulative exposure prenatal through seven months was associated with decreased risk of ASD and AD.

Exhibit 11.2.1. Model Summary: *CumPre07mos* Exposure Models

Outcome	N	Exposure Measure	Estimate	Stderr	Prob ChiSq		One Unit Chg. OR[a]	Lower 95% CL	Upper 95% CL	1/OR	2 SD Unit Chg. OR[b]	1/OR
ASD_Outc	1008	*CumPre07mos*	-0.0040	0.0029	0.167		0.99598	0.990	1.002	1.004	0.702	1.42
AD_Outc	911	*CumPre07mos*	-0.0059	0.0033	0.077	~	0.99417	0.988	1.001	1.006	0.598	1.67
ASD_Only	773	*CumPre07mos*	-0.0031	0.0056	0.581		0.99694	0.986	1.008	1.003	0.764	1.31
ASD_Regr	701	*CumPre07mos*	-0.0108	0.0058	0.061	~	0.98927	0.978	1.001	1.011	0.388	2.58
AD_ExLoIQ	884	*CumPre07mos*	-0.0068	0.0036	0.055	~	0.99318	0.986	1.000	1.007	0.548	1.82
ASD_Scr	821	*CumPre07mos*	-0.0067	0.0032	0.038	*	0.99331	0.987	1.000	1.007	0.554	1.80
AD_Scr	728	*CumPre07mos*	-0.0094	0.0038	0.014	*	0.99066	0.983	0.998	1.009	0.439	2.28

~ 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 11.2.2. Model Summary: *CumPre020mos* Exposure Models

Outcome	N	Exposure Measure	Estimate	Stderr	Prob ChiSq	One Unit Chg. OR[a]	Lower 95% CL	Upper 95% CL	1/OR	2 SD Unit Chg. OR[b]	1/OR
ASD_Outc	1008	*CumPre020mos*	-0.0029	0.0027	0.297	0.997	0.992	1.003	1.003	0.73	1.38
AD_Outc	911	*CumPre020mos*	-0.0040	0.0031	0.195	0.996	0.990	1.002	1.004	0.63	1.58
ASD_Only	773	*CumPre020mos*	-0.0023	0.0050	0.641	0.998	0.988	1.007	1.002	0.77	1.30
ASD_Regr	701	*CumPre020mos*	-0.0047	0.0054	0.380	0.995	0.985	1.006	1.005	0.59	1.70
AD_ExLoIQ	884	*CumPre020mos*	-0.0046	0.0034	0.169	0.995	0.989	1.002	1.005	0.59	1.68
ASD_Scr	821	*CumPre020mos*	-0.0038	0.0030	0.195	0.996	0.990	1.002	1.004	0.65	1.54
AD_Scr	728	*CumPre020mos*	-0.0056	0.0035	0.112	0.994	0.988	1.001	1.006	0.54	1.87

~ 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.

12. Sensitivity Analyses

This chapter is focused on exploratory analyses to determine whether the exposure effects estimated from the primary models presented in Section 9.4 ("Model Results") are sensitive to any of a variety of factors such as inclusion/exclusion of particular covariates, or inclusion/exclusion of small numbers of potentially highly influential observations.

Since the postnatal exposure measures *Exp07mos*, *Exp17mos*, and *Exp020mos* are all highly correlated with one another (see Exhibit 9.3), and the estimated effects of those exposures tend to be very similar in terms of magnitude (odds ratios) and statistical significance (p-values), we focus our sensitivity analyses on only one of the three, and we will consider those sensitivity results to be a good proxy for the other two measures. We will use the *Exp17mos* measure in our sensitivity analyses so that when we include/exclude particular observations or covariates, we can simultaneously assess the sensitivity of the *PreNatThimer* and *Exp01mos* effects to those changes.

12.1. Exploration of Functional Form, Sensitivity to Extreme Exposure Amounts, and Sensitivity to Extreme Residuals

In this section we examine partial-partial residual plots to explore three types of questions. The first is concerned with whether the functional form of the relationship between each of the exposure measures and AD risk might be something other than the linear form assumed for the models presented in Chapter 9. The second type of question addressed in this section is concerned with whether the results are sensitive to inclusion or omission of observations with unusually extreme exposure values. Finally, the third type of question is concerned with whether results are sensitive to extreme residual values.

A residual is the difference between the predicted value from a regression model, and the observed value. Plots of residuals can be very helpful for answering the types of questions described above. A partial-partial residual plot is a special type of residual plot that is created as follows. Suppose we wish to create a partial-partial residual plot corresponding to the exposure measure *Exp17mos*. Let us define the following three models:

- **Model 0**: AD case-control status is the dependent variable. The independent variables include the exposure measures *PreNatThimer*, *Exp01mos,* and *Exp17mos,* and the set of covariates described in Section 8.2.
- **Model 1:** AD case-control status is the dependent variable. The independent variables include the exposure measures *PreNatThimer*, and *Exp01mos,* and the set of covariates described in Section 8.2. Note that *Exp17mos* is not used as an independent variable in this model.
    - Let us call the residuals from this model **"Residual Set 1"**
- **Model 2:** *Exp17mos* is the dependent variable. The exposure measures *PreNatThimer*, and *Exp01mos*, and the set of covariates described in Section 8.2 are independent variables.
    - Let us call the residuals from this model **"Residual Set 2"**.

The partial-partial residual plot is obtained by making a scatter plot with *Residual Set 2* plotted along the x-axis, and *Residual Set 1* plotted along the y-axis. If Models 0, 1, and 2 are linear regression models, then the slope estimate obtained by regressing *Residual Set 2* on *Residual Set 1* is exactly the same as the slope of the *Exp17mos* effect obtained from *Model 0*. By overlaying the regression line obtained by regressing *Residual Set 2* on *Residual Set 1* on the scatter plot, we obtain a visual indication of whether there are any particular observations that might be highly influential in determining the slope of the line. Furthermore, by adding a non-parametric scatter plot smother to the plot, we obtain an indication of whether a non-linear relationship may exist.

In the current study, Model 0 (i.e., the model results summarized in Exhibit 9.4.2) is not a linear model, but is instead a conditional logistic regression model. The model that produced the results summarized in Exhibit 9.4.2 was fit to the data using SAS Proc PHREG with the ties=Discrete option. Several types of residuals can be output from the PHREG procedure that can be used for making residual plots, but none are a

straightforward difference between observed and predicted values, as described above. In order to produce residual plots that would have more straightforward interpretations than those that could be obtained from the conditional logistic regression models, we produced residual plots using two alternative approaches.

The first alternative approach involved fitting unconditional logistic regression models to the data for Model 0 and Model 1, above (in all approaches, Model 2 is a linear regression model). This type of model was fit to the data using SAS Proc Logistic, and included the use of dummy variables for the matching strata. We show in Exhibit 12.1.1 that the parameter estimates, and their standard errors and p-values for the three exposure variables in Model 0 are very close to the values reported from the conditional logistic regression model in Exhibit 9.4.2. The advantage of this approach is that we can obtain residuals from Model 2 that have straightforward interpretations. From this model we obtain a predicted probability of being an AD case for each observation, and define the residuals as the difference between the predicted probability and the observed case control status dependent variable[1]. For the residual plots, we plot Residual Set 2 against Residual Set 1. While the regression of Residual Set 2 on Residual Set 1 does not produce a slope parameter that is identical to the slope of the *Exp17mos* effect obtained from *Model 0*, it is has the same sign and a similar p-value, and overlaying the regression line on the residual plot does help to identify points of potentially high influence.

The second alternative approach involved fitting linear regression models to the data for Model 0 and Model 1. This type of model was fit to the data using SAS Proc GLM, and included the use of dummy variables for the matching strata. We show in Exhibit 12.1.1 that the while the parameter estimates, and their standard errors are different than the previous models, the signs are the same as, and the p-values are close to those reported from the conditional logistic regression model in Exhibit 9.4.2. Thus, in terms of statistical significance, the linear model provides a very good approximation to the conditional logistic regression model results. The advantage of the linear model is that regression of *Residual Set 2* on *Residual Set 1* produces a slope that is identical to the slope estimate of the *Exp17mos* effect from Model 0.

Exhibit 12.1.2 shows partial-partial residual plots for the two alternative approaches described above. Each scatter plot is overlaid with a linear regression line, and a non-parametric scatter plot smoother line (orange dotted line). These plots do not suggest a curved or some other non-linear relationship between exposure and AD risk. Since the two plots are almost identical, subsequent plots use Model 1 residuals from the unconditional logistic regression.

Exhibit 12.1.3 was created to assess whether the *Exp17mos* exposure effect might be sensitive to extreme values of *Exp17mos* measure, or to extreme residual values. The exhibit has plots in two columns and three rows. The three plots in the left-side column are partial-partial residual plots as described above. The left-side top row plot corresponds to the full data set and is identical to the plot shown in Exhibit 12.1.2. The

[1] Due to the case-control sampling design, the predicted probabilities do not represent true probabilities of case – control status.

plots in the right-side column are Model 1 residual plotted against the *Exp17mos* exposure variable. The right-side plots are provided to give the reader a clearer understanding of the relationship of the Model 2 residuals to the *Exp17mos* exposure variable. The plots in the middle panels correspond to models fit to a reduced data set wherein observations with extreme exposure amounts were omitted. For the purpose of these plots, we defined extreme as *Exp17mos* =0 and *Exp17mos* >40. The middle plot on the left-side shows that omitting the observations with extreme values of the *Exp17mos* results in a flatter slope relative to the full model. However, the slope is still negative, and regression of the Model 2 residuals on Model 1 residuals indicates a slope that is still significantly different than zero (slope coefficient = -0.0074, SE = 0.0034, p=0.031). This slope can be compared to the slope obtained from the full data set and displayed in the top panel of Exhibit 12.1.1 (slope coefficient = -0.0088, SE = 0.0031, p=0.0046).

Similarly, the bottom row shows the effect on the *Exp17mos* slope of omitting observations with extreme Model 2 residual values. After omitting these observations, the slope is steeper than the slope from the full model, and is negative and significantly different than zero (coef = -0.0105, SE = 0.0038, p=0.007).

Exhibit 12.1.1. Model Summary: AD Outcome *PreNatThimer* , *Exp01mos, Exp17mos* Exposure Effects from A) Conditional Logistic Regression Model, B) Unconditional Logistic Regression Model, and C) Linear Regression Model

Outcome	N	Exposure Measure	Estimate	Stderr	P-val.		One Unit Chg. OR[a]	Lower 95% CL	Upper 95% CL	1/OR	2 SD Unit Chg. OR[b]	1/OR
A) Conditional Logistic Regression model:												
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
B) Unconditional Logistic Regression model:												
AD_Outc	911	*PreNatThimer*	0.0145	0.0108	0.182		1.015	0.993	1.036		1.27	
AD_Outc	911	*Exp01mos*	0.0210	0.0483	0.663		1.021	0.929	1.123		1.09	
AD_Outc	911	*Exp17mos*	-0.0575	0.0212	0.007	**	0.944	0.906	0.984	1.059	0.43	2.31
C) Linear Regression Model												
AD_Outc	911	*PreNatThimer*	0.0022	0.0018	0.211							
AD_Outc	911	*Exp01mos*	0.0027	0.0076	0.724							
AD_Outc	911	*Exp17mos*	-0.0091	0.0032	0.005	**						

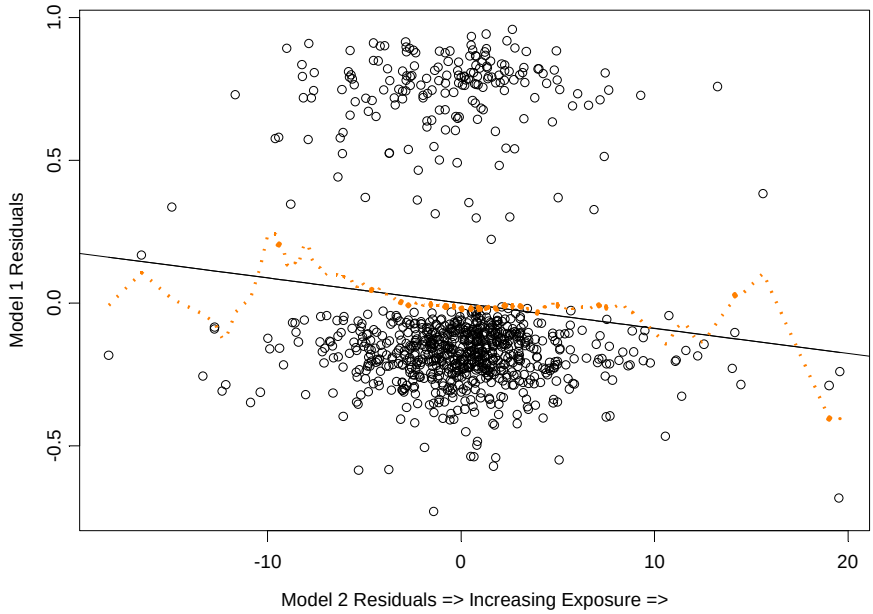
~ p<0.10; * p<0.05; ** p<0.01

[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.

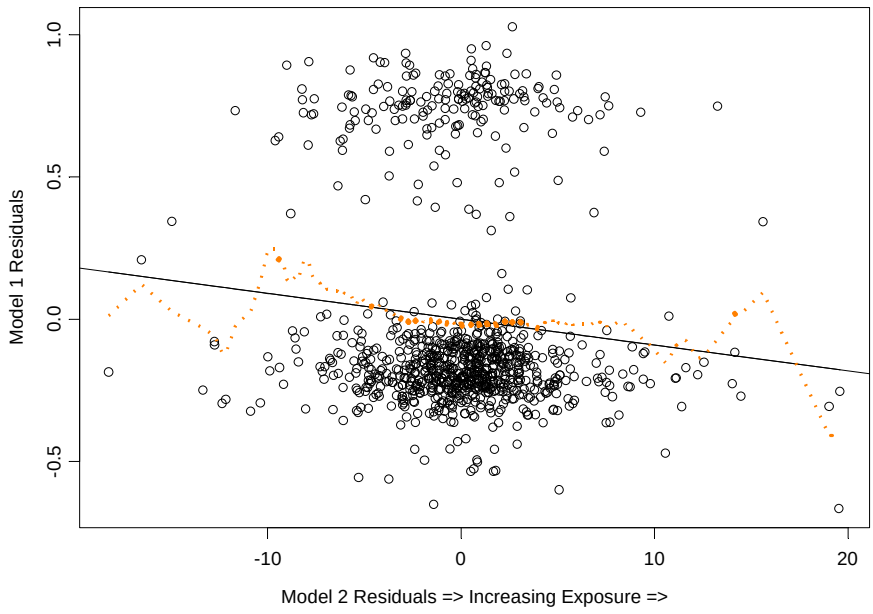
Exhibit 12.1.2. Partial-Partial Residual Plots for Exp17mos (AD Cases and Controls)

Model 1 = Unconditional Logistic Regression



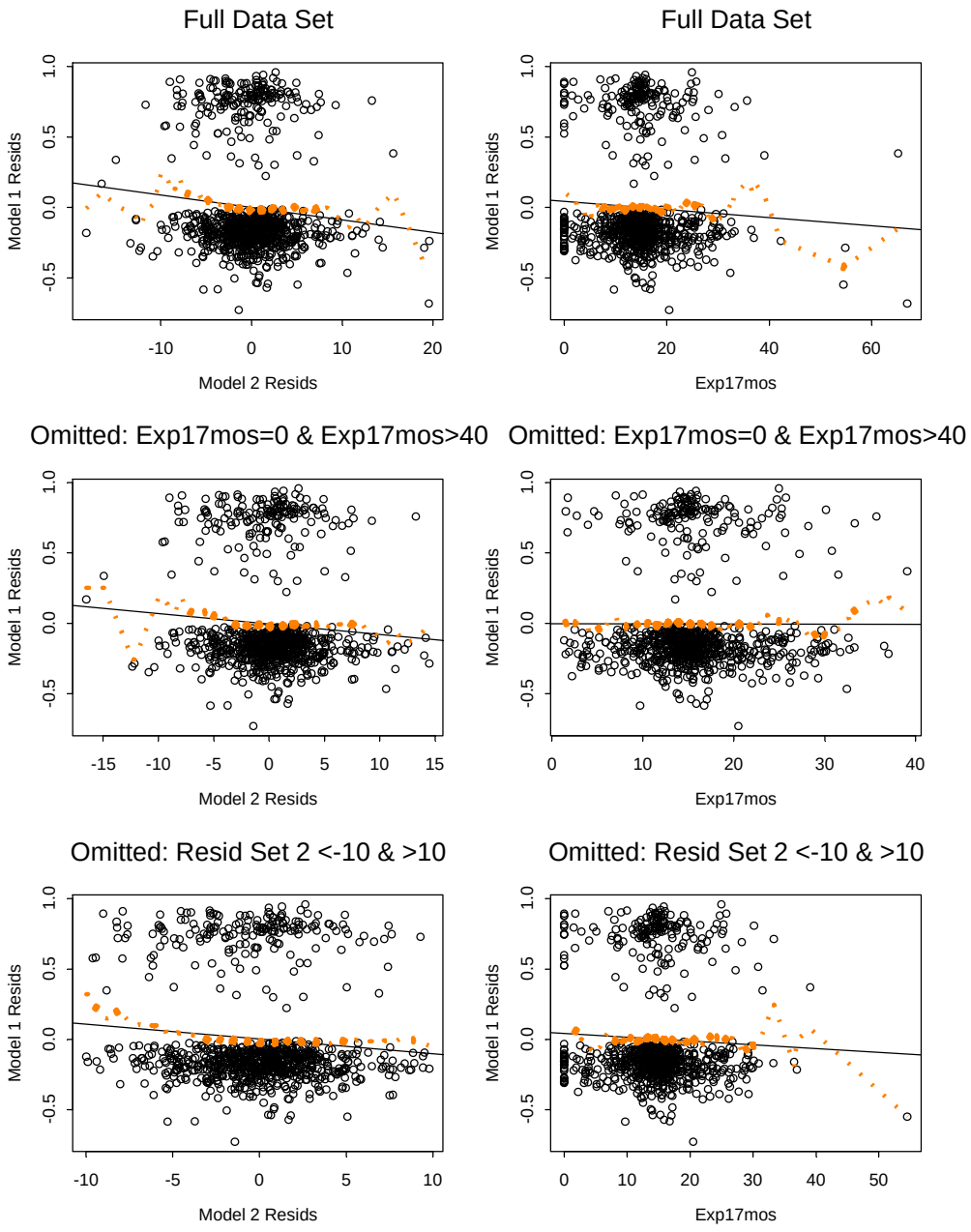
Regression:	Coef:	Value	Std. Error	t value	Pr(>|t|)
Resid Set 1 = B0 + B1(Resid Set 2) + e	(Intercept)	0	0.0128	0	1
	Resid Set 2	-0.0088	0.0031	-2.8383	0.0046

Model 1 = Linear Regression



Regression:	Coef:	Value	Std. Error	t value	Pr(>|t|)
Resid Set 1 = B0 + B1(Resid Set 2) + e	(Intercept)	0	0.0128	0	1
	Resid Set 2	-0.0091	0.0031	-2.9131	0.0037

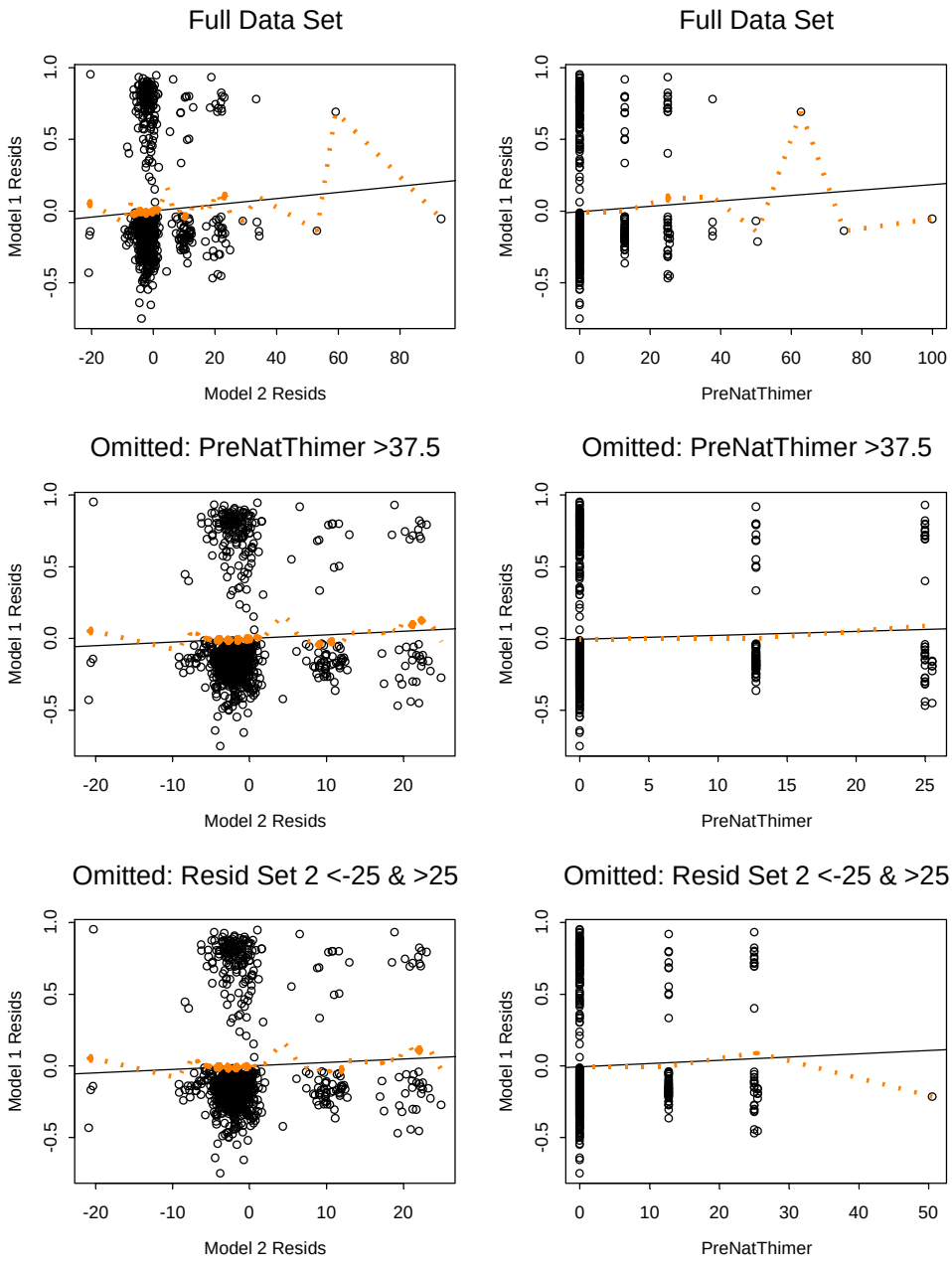
Exhibit 12.1.3. Residual Plots for Exp07mos Effect (AD Cases and Controls)
Model 1 = Unconditional Logistic Regression
Full Data Set and Reduced Data Sets (See Text for Details)



Plots in left-hand column are partial-partial residual plots (see text for explanation). Plots on the right-hand side have *Exp17mos* plotted along the x-axis. The plots on the right-hand side are provided to give the reader a clearer understanding of the relationship of Model 2 residuals to the *Exp17mos* exposure variable, and to show why 0 and >40 were chosen as cut-offs for defining "extreme".

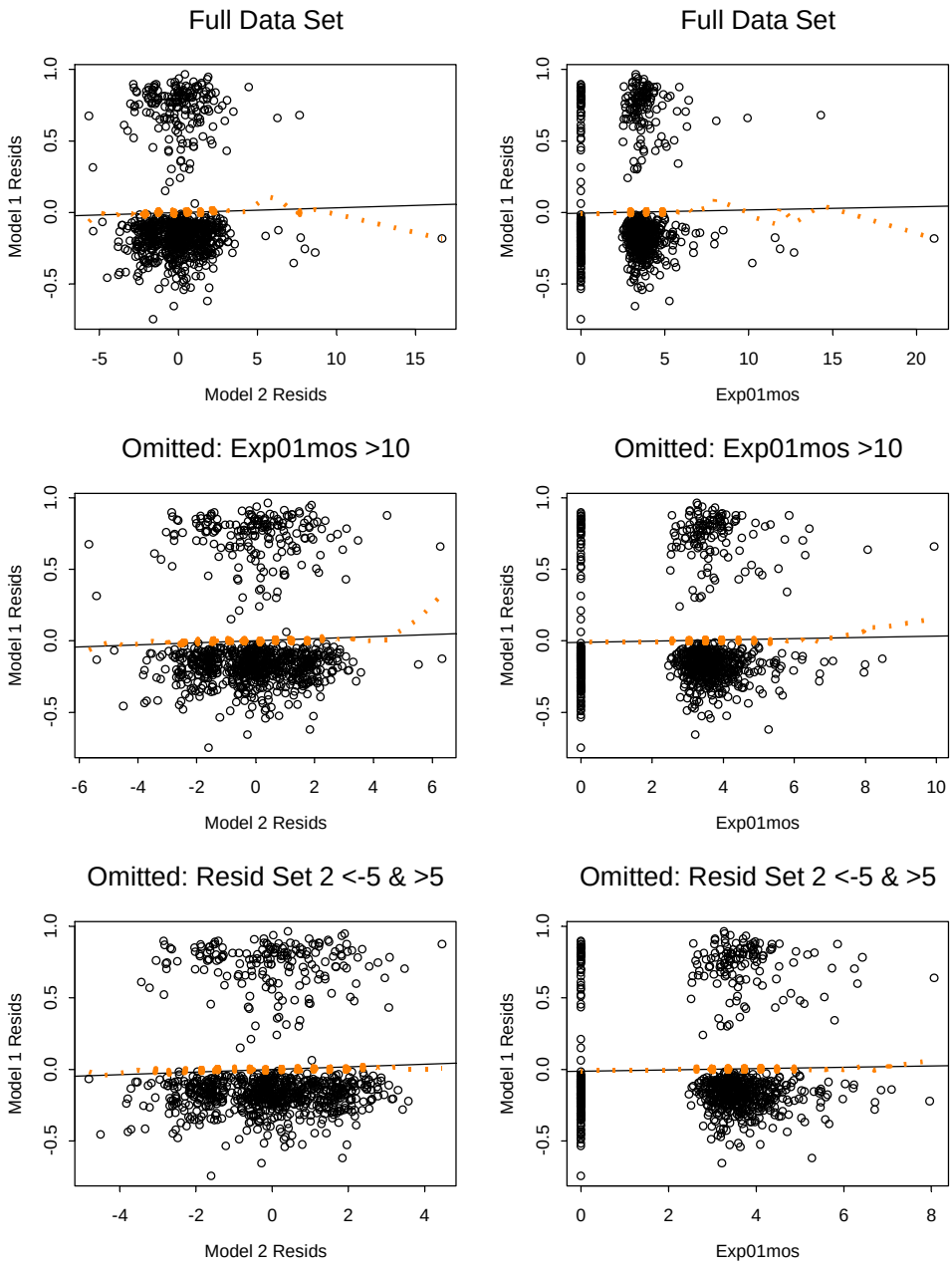
Exhibits 12.1.4 and 12.1.5 are similar to the previous exhibit but correspond to the *PrenatThimer* and *Exp01mos* exposure measures. In both cases the slopes of the exposure measures are not significantly different than zero when the models are fit to the full data set, nor are they significantly different than zero for any of the subsets of data with extreme values omitted. The plots do not suggest that a non-linear functional form would be more appropriate than the linear forms assumed for the models reported in Chapter 9.

Exhibit 12.1.4. Residual Plots for PreNatThimer Effect (AD Cases and Controls)
Model 1 = Unconditional Logistic Regression
Full Data Set and Reduced Data Sets (See Text for Details)



Plots in left-hand column are partial-partial residual plots (see text for explanation). Plots on the right-hand side have *PreNatThimer* plotted along the x-axis. The plots on the right-hand side are provided to give the reader a clearer understanding of the relationship of Model 2 residuals to the *PreNatThimer* exposure variable, and to show why >37.5 was chosen as a cut-off for defining "extreme".

Exhibit 12.1.5 Residual Plots for Exp01mos Effect (AD Cases and Controls)
Model 1 = Unconditional Logistic Regression
Full Data Set and Reduced Data Sets (See Text for Details)



Plots in left-hand column are partial-partial residual plots (see text for explanation). Plots on the right-hand side have *Exp01mos* plotted along the x-axis. The plots on the right-hand side are provided to give the reader a clearer understanding of the relationship of Model 2 residuals to the *Exp01mos* exposure variable, and to show why >10 was chosen as a cut-off for defining "extreme".

12.2. Sensitivity of Results to Inclusion/Exclusion of Particular Covariates

12.2.1. Sensitivity to the Use of Any Covariates vs No Covariates

We know, by comparison of the bivariate results shown in Section 9.3 to the model results shown in Section 9.4., that that estimate of the *Exp17mos* exposure effect is sensitive to the inclusion of *any* covariates versus no covariates. For example, in Exhibit 9.3.3 (Bivariate Relationships of Exposure Measures to AD outcome), the estimate and p-value for the *Exp17mos* effect are *est.*=-0.0114, and *p*=0.501, respectively, whereas the corresponding result from the model with covariates are *est.*=-0.0560, and p=0.008, respectively (Exhibit 9.4.2).

Similar comparisons between bivariate (Exhibit 9.3.3) and multivariable (Exhibit 9.2.4) model results for *PreNatThimer* and *Exp01mos* exposure effects suggest that these estimates are not highly sensitive to whether effects are estimated with or without controlling for confounders. The estimates and p-values for the *PreNatThimer* effect are very similar in the two exhibits. They are *est*. = 0.0101, *p*=0.302 in the bivariate results table, and *est*. = 0.0106, *p*=0.318 from the model with covariates. The estimates for the *Exp01mos* effect are not significantly different than zero in either table. They are *est*. = 0.0097, *p*=0.826, and *est*. = 0.0284, *p*=0.562, in the bivariate and multivariable results tables, respectively.

12.2.2. Change in Estimate When Each Covariate is Dropped

The tables in this section show the effects of dropping covariates from the multivariable models on the estimates and standard errors of prenatal exposure effects (*PreNatThimer*), neonatal (birth to one month) exposure effects (*Exp01mos*), and cumulative exposure during the age range spanning one to seven months (*Exp17mos*). The tables show how the estimate and standard error for each exposure effect change as each covariate is dropped from the model. Each table is read from top to bottom as in the following example.

Exhibit 12.2.1 shows results for the ASD outcome analysis. The first model fitted to this outcome included all covariates. (See Chapter 8, Section 8.2 for a description of model fitting decision rules and an explanation of the coding of each covariate.) The exposure parameter estimates and standard errors from that model are shown in the row labeled "Full Model". Based on examination of the full model results, the variable "*Enceph*" was dropped from the subsequent model. The row labeled "*Enceph*" shows exposure parameter estimates and standard errors obtained from the model after dropping the "*Enceph*" covariate[2]. This row shows, for example, that relative to the Full Model, the coefficient for *PreNatThimer* changed from 0.00636 to 0.00638 after "*Enceph*" was

[2] For the definition of each covariate, see Volume I, Exhibit 7.5.1.

dropped, and the standard error did not change. Since the change in estimate was less than 10 percent, relative to the Full Model, a zero is shown in the column labeled "*C.I.E. PreNatThimer*". Similarly, dropping "*Enceph*" from the model did not result in change-in-estimates of the *Exp01mos* or *Exp17mos* effects that exceeded the 10 percent criterion, and therefore zeros are entered in the corresponding columns. The table also shows the p-value for the test of the null hypothesis that the coefficient for *"Enceph"* was equal to zero (p=0.920). The next row down in the table shows similar quantities after dropping the *Bilirubin* covariate. Each row of the table shows the results after dropping an additional covariate. Thus, the results shown in the row labeled "*Bilirubin*" are from a model where the terms for *Enceph* and *Bilirubin* had been dropped.

The variables in the shaded rows are the variables that were retained in the final, reduced model. As explained in Chapter 8, these variables were retained in the final model because dropping any one of them resulted in a change-in-estimate of 10 percent or more of at least one of the exposure effects, relative to the full model. Note that dropping each covariate generally resulted in small reductions of the standard errors of the parameter estimates. With the exception of the *birthweight* covariate, the dropping of any single covariate resulted in only very small changes to the estimates or standard errors. Examination of the last row of Exhibit 12.2.1 indicates that the coefficient for the *Exp17mos* exposure effect changed substantially when the *birthweight* variable was dropped.

The remaining tables are read in a similar fashion to that described above.

Exhibit 12.2.1 Outcome: ASD
Effects of Dropping Covariates on Estimates and Standard Errors of Exposure Effects

Dropped Covariate	Exposure Estimates and Standard Errors						Dropped Covariate		C.I.E.[a]	C.I.E.	C.I.E.
	PreNatThimer		*Exp01mos*		*Exp17mos*				PreNat-	Exp-	Exp-
Name	Estimate	S.E.	Estimate	S.E.	Estimate	S.E.	df	P-val	Thimer	01mos	17mos
Full Model	0.00636	0.00966	-0.02919	0.04556	-0.03190	0.01865	.	.	.	.	.
Enceph	0.00638	0.00966	-0.02928	0.04555	-0.03205	0.01858	1	0.920	0	0	0
Bilirubin	0.00637	0.00965	-0.02923	0.04552	-0.03201	0.01855	1	0.972	0	0	0
PreNatTuna	0.00634	0.00965	-0.02913	0.04550	-0.03203	0.01855	1	0.939	0	0	0
PreNatValproi	0.00626	0.00964	-0.02907	0.04550	-0.03202	0.01855	1	0.861	0	0	0
RespDistress	0.00629	0.00964	-0.02789	0.04532	-0.03263	0.01844	1	0.751	0	0	0
SingleParent	0.00627	0.00963	-0.02788	0.04541	-0.03269	0.01844	1	0.645	0	0	0
PreNatNicotin	0.00618	0.00959	-0.02821	0.04536	-0.03251	0.01843	1	0.679	0	0	0
Multiple	0.00612	0.00958	-0.02766	0.04525	-0.03237	0.01842	1	0.743	0	0	0
PreNatFilling	0.00612	0.00958	-0.02774	0.04526	-0.03255	0.01841	1	0.678	0	0	0
C5APGAR	0.00611	0.00958	-0.02808	0.04522	-0.03277	0.01838	1	0.863	0	0	0
PreNatIllDrug	0.00634	0.00956	-0.02908	0.04519	-0.03297	0.01836	1	0.616	0	0	0
PreNatOthMerc	0.00679	0.00950	-0.03094	0.04512	-0.03389	0.01833	1	0.094	0	0	0
PreNatFish	0.00697	0.00951	-0.02955	0.04501	-0.03443	0.01836	1	0.286	0	0	0
ChildLead	0.00719	0.00950	-0.03090	0.04501	-0.03408	0.01837	1	0.330	1	0	0
Dad_Age	0.00749	0.00946	-0.03065	0.04495	-0.03390	0.01832	3	0.908	1	0	0
MomEduc_cat	0.00687	0.00942	-0.03042	0.04474	-0.03359	0.01816	3	0.546	0	0	0
PreNatViralIn	0.00741	0.00938	-0.02823	0.04456	-0.03282	0.01810	1	0.330	1	0	0
PreNatLead_1	0.00723	0.00937	-0.02936	0.04459	-0.03297	0.01815	1	0.311	1	0	0
PreNatAlcohol	0.00776	0.00943	-0.02985	0.04457	-0.03176	0.01804	1	0.226	1	0	0
Anemia	0.00845	0.00941	-0.03339	0.04436	-0.03285	0.01804	1	0.281	1	1	0
BrstFeed	0.00786	0.00939	-0.02973	0.04405	-0.03344	0.01799	2	0.228	1	0	0
MomAge	0.00909	0.00933	-0.02086	0.04392	-0.02791	0.01770	4	0.023	1	1	1
HC_PAP	0.01044	0.00935	-0.02468	0.04373	-0.02816	0.01761	2	0.106	1	1	1
HC_Cholest	0.01041	0.00924	-0.02119	0.04311	-0.02573	0.01755	2	0.025	1	1	1
HC_InitInad_1	0.01060	0.00922	-0.02094	0.04297	-0.02642	0.01757	1	0.175	1	1	1
ChildPica	0.00959	0.00912	-0.02275	0.04265	-0.02423	0.01743	1	<.0001	1	1	1
Folic_PNVit_M	0.01053	0.00910	-0.02063	0.04272	-0.02416	0.01739	1	0.021	1	1	1
PovertyRatio1	0.00814	0.00901	-0.01887	0.04296	-0.02441	0.01740	1	0.002	1	1	1
BirthOrder	0.00852	0.00889	-0.02132	0.04222	-0.02449	0.01733	2	0.042	1	1	1
Birthwt	0.00731	0.00887	-0.02754	0.04110	-0.00525	0.01475	4	0.162	1	0	1

[a] C.I.E. = "Change in estimate" and is equal to "1" if dropping a covariate changes the exposure estimate by more than 10 percent, relative to the estimates shown for the "full model".

Read Table: Estimate of PreNatThimer effect from full model (all covariate included) is 0.00636. After dropping "Enceph" the estimate for PreNatThimer is 0.00638.

Exhibit 12.2.2 Outcome: AD
Effects of Dropping Covariates on Estimates and Standard Errors of Exposure Effects

Dropped Covariate Name	Exposure Estimates and Standard Errors						Dropped Covariate		C.I.E.[a] PreNat-Thimer	C.I.E. Exp-01mos	C.I.E. Exp-17mos
	PreNatThimer		*Exp01mos*		*Exp17mos*						
	Estimate	S.E.	Estimate	S.E.	Estimate	S.E.	df	P-val			
Full Model	0.01157	0.01103	0.02982	0.05043	-0.05796	0.02187	.	.	.	.	.
Bilirubin	0.01155	0.01103	0.02997	0.05038	-0.05784	0.02182	1	0.935	0	0	0
PreNatTuna	0.01117	0.01095	0.03081	0.05045	-0.05770	0.02178	1	0.395	0	0	0
PreNatValproi	0.01129	0.01094	0.03061	0.05044	-0.05769	0.02178	1	0.790	0	0	0
RespDistress	0.01134	0.01094	0.03192	0.05023	-0.05847	0.02163	1	0.749	0	0	0
SingleParent	0.01134	0.01094	0.03192	0.05022	-0.05848	0.02162	1	0.990	0	0	0
PreNatNicotin	0.01101	0.01083	0.03208	0.05011	-0.05797	0.02160	1	0.487	0	0	0
Multiple	0.01054	0.01079	0.03280	0.04957	-0.05711	0.02151	1	0.153	0	0	0
PreNatFilling	0.01058	0.01078	0.03253	0.04953	-0.05665	0.02148	1	0.675	0	0	0
C5APGAR	0.01039	0.01077	0.03062	0.04952	-0.05797	0.02150	1	0.354	1	0	0
PreNatIllDrug	0.01057	0.01074	0.03014	0.04951	-0.05812	0.02148	1	0.781	0	0	0
PreNatOthMerc	0.01096	0.01065	0.02998	0.04945	-0.05850	0.02146	1	0.507	0	0	0
PreNatFish	0.01102	0.01064	0.03030	0.04939	-0.05870	0.02145	1	0.872	0	0	0
ChildLead	0.01155	0.01064	0.02676	0.04942	-0.05834	0.02148	1	0.124	0	1	0
Dad_Age	0.01180	0.01061	0.02722	0.04942	-0.05806	0.02144	3	0.967	0	0	0
MomEduc_cat	0.01051	0.01052	0.02891	0.04895	-0.05679	0.02119	3	0.424	0	0	0
PreNatViralIn	0.01051	0.01052	0.02893	0.04888	-0.05679	0.02118	1	0.995	0	0	0
PreNatLead_1	0.01033	0.01053	0.02839	0.04887	-0.05720	0.02120	1	0.722	1	0	0
PreNatAlcohol	0.01057	0.01059	0.02837	0.04888	-0.05599	0.02106	1	0.472	0	0	0
Anemia	0.01196	0.01049	0.01475	0.04831	-0.05697	0.02107	1	0.074	0	1	0
BrstFeed	0.01162	0.01048	0.01687	0.04800	-0.05654	0.02097	2	0.471	0	1	0
MomAge	0.01260	0.01042	0.02645	0.04788	-0.05019	0.02061	4	0.047	0	1	1
HC_PAP	0.01478	0.01044	0.02182	0.04768	-0.05032	0.02048	2	0.066	1	1	1
HC_Cholest	0.01503	0.01024	0.02627	0.04655	-0.04750	0.02041	2	0.024	1	1	1
HC_InitInad_1	0.01512	0.01024	0.02628	0.04653	-0.04775	0.02043	1	0.715	1	1	1
ChildPica	0.01351	0.01017	0.02109	0.04623	-0.04483	0.02018	1	0.000	1	1	1
Folic_PNVit_M	0.01436	0.01015	0.02321	0.04636	-0.04493	0.02009	1	0.033	1	1	1
PovertyRatio1	0.01134	0.00998	0.02702	0.04649	-0.04489	0.02007	1	0.001	0	0	1
BirthOrder	0.01179	0.00982	0.02127	0.04565	-0.04426	0.01995	2	0.055	0	1	1
Birthwt	0.01010	0.00979	0.01026	0.04419	-0.01156	0.01703	4	0.046	1	1	1

[a] C.I.E. = "Change in estimate" and is equal to "1" if dropping a covariate changes the exposure estimate by more than 10 percent, relative to the estimates shown for the "full model".
Read Table: Estimate of PreNatThimer effect from full model (all covariate included) is 0.01157. After dropping "Bilirubin" the estimate for PreNatThimer is 0.01155.

Exhibit 12.2.3 Outcome: ASD-not-AD
Effects of Dropping Covariates on Estimates and Standard Errors of Exposure Effects

Dropped Covariate Name	Exposure Estimates and Standard Errors						Dropped Covariate		C.I.E.[a]	C.I.E.	C.I.E.
	PreNatThimer		*Exp01mos*		*Exp17mos*				PreNat-	Exp-	Exp-
	Estimate	S.E.	Estimate	S.E.	Estimate	S.E.	df	P-val	Thimer	01mos	17mos
Full Model	-0.00420	0.01974	-0.21625	0.09521	0.00113	0.03067	.	.	.	.	.
Bilirubin	-0.00519	0.01971	-0.21810	0.09451	0.00347	0.03025	1	0.891	1	0	1
momeduc	-0.00498	0.01976	-0.21959	0.09443	0.00227	0.03001	3	0.982	1	0	1
HC_PAP_2	-0.00508	0.01978	-0.22082	0.09441	0.00202	0.03000	1	0.733	1	0	1
Birthwt	-0.00652	0.01971	-0.22437	0.09346	0.00158	0.02891	2	0.645	1	0	1
ChildLead	-0.00610	0.01963	-0.22279	0.09340	0.00280	0.02872	1	0.708	1	0	1
SingleParent	-0.00685	0.01964	-0.22336	0.09332	0.00245	0.02872	1	0.494	1	0	1
RespDistress	-0.00633	0.01963	-0.21115	0.09204	-0.00680	0.02607	1	0.409	1	0	1
PovertyRatio1	-0.00724	0.01971	-0.21201	0.09221	-0.00595	0.02617	1	0.327	1	0	1
PreNatAlcohol_1	-0.00555	0.01977	-0.20914	0.09177	-0.00521	0.02596	1	0.227	1	0	1
BrstFeed	-0.00734	0.01968	-0.19995	0.09022	-0.00090	0.02559	2	0.228	1	0	1
BirthOrder	-0.00805	0.02032	-0.19389	0.08996	-0.00155	0.02519	2	0.239	1	1	1
HC_Cholest	-0.00802	0.02038	-0.19304	0.09020	0.00044	0.02517	2	0.384	1	1	1
momage	-0.00723	0.02021	-0.19012	0.09029	0.00339	0.02493	2	0.573	1	1	1
PreNatTuna	-0.00717	0.02057	-0.19134	0.09035	0.00077	0.02479	1	0.156	1	1	1
PreNatFish	-0.00794	0.02047	-0.18723	0.08998	0.00569	0.02447	1	0.064	1	1	1
PreNatOthMerc_An	-0.00856	0.02008	-0.19918	0.08973	0.00408	0.02452	1	0.013	1	0	1
PreNatFillings_1	-0.00896	0.02030	-0.19982	0.08993	0.00326	0.02439	1	0.119	1	0	1
PreNatIllDrug	-0.00716	0.02002	-0.20068	0.08980	0.00345	0.02434	1	0.275	1	0	1
PreNatLead_1	-0.00625	0.01969	-0.20189	0.09008	0.00499	0.02445	1	0.178	1	0	1
Folic_PNVit_Mult	-0.00463	0.01952	-0.20118	0.09045	0.00674	0.02446	1	0.236	1	0	1
C5APGAR	-0.00367	0.01949	-0.19023	0.08961	0.00489	0.02387	1	0.141	1	1	1
Anemia	-0.00387	0.01942	-0.18529	0.08907	0.00563	0.02375	1	0.291	0	1	1
prenatviralinf	-0.00332	0.02013	-0.17812	0.08904	0.00673	0.02361	1	0.069	1	1	1
HC_InitInad_1	-0.00427	0.02001	-0.18899	0.08981	0.01415	0.02485	1	0.055	0	1	1
ChildPica	-0.00206	0.01956	-0.18959	0.08896	0.01431	0.02444	1	0.017	1	1	1

[a] C.I.E. = "Change in estimate" and is equal to "1" if dropping a covariate changes the exposure estimate by more than 10 percent, relative to the estimates shown for the "full model".

Read Table: Estimate of PreNatThimer effect from full model (all covariate included) is -0.00420. After dropping "Bilirubin" the estimate for PreNatThimer is -0.00519.

Exhibit 12.2.4 Outcome: ASD with Regression
Effects of Dropping Covariates on Estimates and Standard Errors of Exposure Effects

Dropped Covariate	Exposure Estimates and Standard Errors						Dropped Covariate		C.I.E.[a]	C.I.E.	C.I.E.
	PreNatThimer		*Exp01mos*		*Exp17mos*				PreNat-	Exp-	Exp-
Name	Estimate	S.E.	Estimate	S.E.	Estimate	S.E.	df	P-val	Thimer	01mos	17mos
Full Model	0.04131	0.02298	-0.11291	0.09680	-0.10768	0.04093	.	.	.	.	.
Bilirubin	0.03854	0.02288	-0.10410	0.09470	-0.11452	0.04046	1	0.305	0	0	0
HC_PAP_2	0.03899	0.02278	-0.10683	0.09501	-0.11583	0.04053	1	0.565	0	0	0
prenatviralinf	0.03909	0.02276	-0.10560	0.09457	-0.11458	0.03993	1	0.830	0	0	0
PreNatFillings_1	0.03908	0.02270	-0.10560	0.09451	-0.11458	0.03974	1	0.998	0	0	0
SingleParent	0.03952	0.02264	-0.10615	0.09442	-0.11470	0.03978	1	0.803	0	0	0
RespDistress	0.03923	0.02265	-0.11442	0.09314	-0.11336	0.03974	1	0.640	0	0	0
PreNatLead_1	0.03924	0.02264	-0.11413	0.09288	-0.11343	0.03972	1	0.966	0	0	0
PreNatFish	0.03867	0.02262	-0.11306	0.09272	-0.11336	0.03967	1	0.704	0	0	0
PreNatTuna	0.03777	0.02258	-0.11150	0.09231	-0.11261	0.03956	1	0.573	0	0	0
PreNatOthMerc_An	0.03781	0.02263	-0.10868	0.09195	-0.11411	0.0395	1	0.579	0	0	0
ChildLead	0.03900	0.02250	-0.11020	0.09195	-0.11299	0.03958	1	0.338	0	0	0
Brstfeed	0.03966	0.02234	-0.11502	0.09112	-0.11612	0.03942	2	0.773	0	0	0
HC_InitInad_1	0.03906	0.02241	-0.11290	0.09121	-0.11773	0.03995	1	0.243	0	0	0
cholest	0.04052	0.02240	-0.10672	0.09039	-0.11378	0.0393	2	0.451	0	0	0
Birthorder	0.04093	0.02231	-0.12025	0.08978	-0.11304	0.03909	2	0.448	0	0	0
C5APGAR	0.03908	0.02250	-0.11806	0.08905	-0.11133	0.03932	1	0.115	0	0	0
ChildPica	0.03958	0.02121	-0.11999	0.08715	-0.10298	0.03799	1	<.0001	0	0	0
Anemia	0.03795	0.02114	-0.10429	0.08627	-0.09803	0.03773	1	0.197	0	0	0
PreNatAlcohol_1	0.03848	0.02104	-0.10342	0.08569	-0.09496	0.03746	1	0.283	0	0	1
PovertyRatio1	0.03468	0.02033	-0.07482	0.08836	-0.09153	0.03773	1	0.004	1	1	1
Educ	0.03395	0.02027	-0.06914	0.08668	-0.09290	0.03745	2	0.533	1	1	1
MomAge	0.03579	0.02012	-0.06419	0.08793	-0.08709	0.03688	2	0.347	1	1	1
birthwt	0.03353	0.01983	-0.04262	0.08795	-0.07501	0.03616	2	0.364	1	1	1

[a] C.I.E. = "Change in estimate" and is equal to "1" if dropping a covariate changes the exposure estimate by more than 10 percent, relative to the estimates shown for the "full model".

Read Table: Estimate of PreNatThimer effect from full model (all covariate included) is 0.04131. After dropping "Bilirubin" the estimate for PreNatThimer is 0.03854.

Exhibit 12.2.5 Outcome: AD with Low CF Excluded
Effects of Dropping Covariates on Estimates and Standard Errors of Exposure Effects

Dropped Covariate	Exposure Estimates and Standard Errors						Dropped Covariate		C.I.E.[a]	C.I.E.	C.I.E.
	PreNatThimer		*Exp01mos*		*Exp17mos*				PreNat-	Exp-	Exp-
Name	Estimate	S.E.	Estimate	S.E.	Estimate	S.E.	df	P-val	Thimer	01mos	17mos
Full Model	0.01626	0.01101	-0.01018	0.05441	-0.06277	0.02329	.	.	.	.	.
Bilirubin	0.01625	0.01101	-0.00935	0.05427	-0.06243	0.02327	1	0.775	0	0	0
PreNatTuna	0.01554	0.01088	-0.00738	0.05427	-0.06180	0.02317	1	0.186	0	1	0
PreNatValproi	0.01573	0.01086	-0.00788	0.05426	-0.06176	0.02317	1	0.685	0	1	0
RespDistress	0.01576	0.01086	-0.00727	0.05402	-0.06209	0.02301	1	0.903	0	1	0
SingleParent	0.01575	0.01085	-0.00739	0.05405	-0.06194	0.023	1	0.829	0	1	0
PreNatNicotin	0.01527	0.01073	-0.00593	0.05396	-0.06123	0.02297	1	0.456	0	1	0
Multiple	0.01484	0.01069	-0.00613	0.05360	-0.06066	0.02292	1	0.224	0	1	0
PreNatFilling	0.01484	0.01069	-0.00606	0.05361	-0.06077	0.02289	1	0.921	0	1	0
C5APGAR	0.01462	0.01068	-0.00825	0.05358	-0.06262	0.02291	1	0.323	1	1	0
PreNatIllDrug	0.01479	0.01065	-0.00878	0.05356	-0.06277	0.02289	1	0.789	0	1	0
PreNatOthMerc	0.01516	0.01055	-0.00950	0.05342	-0.06356	0.02286	1	0.253	0	0	0
PreNatFish	0.01517	0.01054	-0.00944	0.05337	-0.06359	0.02285	1	0.977	0	0	0
ChildLead	0.01530	0.01055	-0.01058	0.05341	-0.06354	0.02289	1	0.504	0	0	0
Dad_Age	0.01546	0.01051	-0.01033	0.05331	-0.06324	0.02282	3	0.979	0	0	0
MomEduc_cat	0.01401	0.01044	-0.00767	0.05286	-0.06240	0.02252	3	0.430	1	1	0
PreNatViralIn	0.01395	0.01043	-0.00831	0.05279	-0.06256	0.02252	1	0.832	1	1	0
PreNatLead_1	0.01381	0.01044	-0.00889	0.05276	-0.06288	0.02255	1	0.798	1	1	0
PreNatAlcohol	0.01420	0.01048	-0.00892	0.05277	-0.06131	0.02238	1	0.429	1	1	0
BrstFeed	0.01401	0.01045	-0.00885	0.05255	-0.06024	0.02224	2	0.542	1	1	0
MomAge	0.01514	0.01040	0.00036	0.05247	-0.05429	0.02191	4	0.095	0	1	1
HC_PAP	0.01807	0.01043	-0.00520	0.05212	-0.05446	0.02171	2	0.016	1	1	1
HC_Cholest	0.01831	0.01021	-0.00325	0.05042	-0.05100	0.02163	2	0.015	1	1	1
HC_InitInad_1	0.01834	0.01021	-0.00332	0.05041	-0.05109	0.02164	1	0.885	1	1	1
ChildPica	0.01694	0.01018	-0.00836	0.05010	-0.04829	0.02136	1	0.000	0	1	1
Folic_PNVit_M	0.01775	0.01018	-0.00753	0.05025	-0.04854	0.02131	1	0.070	0	1	1
PovertyRatio1	0.01551	0.01001	-0.00661	0.05029	-0.04965	0.02133	1	0.003	0	1	1
BirthOrder	0.01584	0.00996	-0.00874	0.04959	-0.04942	0.02122	2	0.151	0	1	1
Birthwt	0.01378	0.00990	-0.01866	0.04865	-0.00972	0.0179	4	0.022	1	1	1

[a] C.I.E. = "Change in estimate" and is equal to "1" if dropping a covariate changes the exposure estimate by more than 10 percent, relative to the estimates shown for the "full model".

Read Table: Estimate of PreNatThimer effect from full model (all covariate included) is 0.01626. After dropping "Bilirubin" the estimate for PreNatThimer is 0.01625.

Exhibit 12.2.6 Outcome: ASD with Screened Controls
Effects of Dropping Covariates on Estimates and Standard Errors of Exposure Effects

Dropped Covariate	Exposure Estimates and Standard Errors						Dropped Covariate		C.I.E.[a]	C.I.E.	C.I.E.
	PreNatThimer		*Exp01mos*		*Exp17mos*				PreNat-	Exp-	Exp-
Name	Estimate	S.E.	Estimate	S.E.	Estimate	S.E.	df	P-val	Thimer	01mos	17mos
Full Model	0.00493	0.01019	-0.06410	0.04884	-0.03927	0.0207	.	.	.	.	.
Bilirubin	0.00502	0.01018	-0.06483	0.04885	-0.03971	0.0207	1	0.643	0	0	0
PreNatTuna	0.00489	0.01017	-0.06427	0.04883	-0.03989	0.0207	1	0.737	0	0	0
PreNatValproi	0.00481	0.01015	-0.06425	0.04883	-0.03991	0.0207	1	0.902	0	0	0
RespDistress	0.00486	0.01013	-0.06637	0.04882	-0.03848	0.0206	1	0.372	0	0	0
SingleParent	0.00481	0.01012	-0.06681	0.04890	-0.03874	0.0206	1	0.640	0	0	0
PreNatNicotin	0.00446	0.01003	-0.06752	0.04880	-0.03836	0.0206	1	0.500	0	0	0
Multiple	0.00403	0.01001	-0.06652	0.04851	-0.03874	0.0205	1	0.267	1	0	0
PreNatFilling	0.00420	0.01002	-0.06563	0.04846	-0.03929	0.0205	1	0.450	1	0	0
C5APGAR	0.00428	0.01001	-0.06650	0.04843	-0.03955	0.0205	1	0.663	1	0	0
PreNatIllDrug	0.00441	0.00999	-0.06743	0.04829	-0.03975	0.0205	1	0.811	1	0	0
PreNatOthMerc	0.00486	0.00994	-0.07000	0.04807	-0.03980	0.0204	1	0.040	0	0	0
PreNatFish	0.00495	0.00992	-0.06726	0.04789	-0.04024	0.0204	1	0.156	0	0	0
ChildLead	0.00516	0.00991	-0.06864	0.04786	-0.03998	0.0204	1	0.562	0	0	0
Dad_Age	0.00550	0.00984	-0.06761	0.04764	-0.03972	0.0204	3	0.893	1	0	0
MomEduc_cat	0.00468	0.00980	-0.06724	0.04734	-0.03995	0.0202	3	0.486	0	0	0
PreNatViralIn	0.00541	0.00975	-0.06533	0.04715	-0.03913	0.0202	1	0.352	0	0	0
PreNatLead_1	0.00543	0.00974	-0.06521	0.04715	-0.03906	0.0202	1	0.649	1	0	0
PreNatAlcohol	0.00597	0.00978	-0.06549	0.04711	-0.03760	0.0201	1	0.308	1	0	0
Anemia	0.00636	0.00979	-0.06932	0.04692	-0.03912	0.0201	1	0.361	1	0	0
BrstFeed	0.00602	0.00980	-0.06231	0.04638	-0.03949	0.0200	2	0.122	1	0	0
MomAge	0.00782	0.00966	-0.05496	0.04620	-0.03375	0.0196	4	0.029	1	1	1
HC_PAP	0.00933	0.00966	-0.05802	0.04589	-0.03462	0.0195	2	0.140	1	0	1
HC_Cholest	0.00953	0.00954	-0.05533	0.04525	-0.03239	0.0195	2	0.068	1	1	1
HC_InitInad_1	0.00987	0.00951	-0.05658	0.04512	-0.03374	0.0194	1	0.187	1	1	1
ChildPica	0.00986	0.00938	-0.05723	0.04460	-0.02953	0.0192	1	<.0001	1	1	1
Folic_PNVit_M	0.01105	0.00934	-0.05231	0.04452	-0.03025	0.0191	1	0.010	1	1	1
PovertyRatio1	0.00889	0.00920	-0.04959	0.04480	-0.03134	0.0192	1	0.009	1	1	1
BirthOrder	0.00864	0.00913	-0.05251	0.04421	-0.03089	0.0191	2	0.215	1	1	1
Birthwt	0.00742	0.00908	-0.04873	0.04295	-0.00530	0.0166	4	0.047	1	1	1

[a] C.I.E. = "Change in estimate" and is equal to "1" if dropping a covariate changes the exposure estimate by more than 10 percent, relative to the estimates shown for the "full model".
Read Table: Estimate of PreNatThimer effect from full model (all covariate included) is 0.00493. After dropping "Bilirubin" the estimate for PreNatThimer is 0.00502.

Exhibit 12.2.7 Outcome: AD with Screened Controls
Effects of Dropping Covariates on Estimates and Standard Errors of Exposure Effects

Dropped Covariate	Exposure Estimates and Standard Errors						Dropped Covariate		C.I.E.[a]	C.I.E.	C.I.E.
	PreNatThimer		*Exp01mos*		*Exp17mos*				PreNat-	Exp-	Exp-
Name	Estimate	S.E.	Estimate	S.E.	Estimate	S.E.	df	P-val	Thimer	01mos	17mos
Full Model	0.01183	0.01159	-0.00259	0.05382	-0.07065	0.0248	.	.	.	.	.
Bilirubin	0.01188	0.01158	-0.00326	0.05381	-0.07098	0.02476	1	0.775	0	1	0
PreNatTuna	0.01144	0.01152	-0.00155	0.05383	-0.07100	0.02469	1	0.297	0	1	0
PreNatValproi	0.01166	0.01150	-0.00173	0.05382	-0.07089	0.02468	1	0.741	0	1	0
RespDistress	0.01166	0.01147	-0.00344	0.05381	-0.06904	0.02457	1	0.445	0	1	0
SingleParent	0.01166	0.01149	-0.00330	0.05374	-0.06907	0.02457	1	0.878	0	1	0
PreNatNicotin	0.01081	0.01131	-0.00336	0.05358	-0.06806	0.02452	1	0.362	0	1	0
Multiple	0.00941	0.01125	-0.00353	0.05264	-0.06898	0.02428	1	0.043	1	1	0
PreNatFilling	0.00936	0.01124	-0.00417	0.05256	-0.06854	0.02421	1	0.809	1	1	0
C5APGAR	0.00936	0.01122	-0.00655	0.05252	-0.06920	0.02423	1	0.213	1	1	0
PreNatIllDrug	0.00945	0.01118	-0.00693	0.05241	-0.06933	0.0242	1	0.915	1	1	0
PreNatOthMerc	0.01026	0.01109	-0.00752	0.05223	-0.06909	0.0241	1	0.225	1	1	0
PreNatFish	0.01032	0.01108	-0.00549	0.05204	-0.06977	0.0241	1	0.535	1	1	0
ChildLead	0.01090	0.01106	-0.01028	0.05201	-0.06976	0.02417	1	0.240	0	1	0
Dad_Age	0.01112	0.01101	-0.00885	0.05184	-0.06955	0.02413	3	0.936	0	1	0
MomEduc_cat	0.00928	0.01098	-0.00675	0.05121	-0.06840	0.02382	3	0.314	1	1	0
PreNatViralIn	0.00920	0.01097	-0.00726	0.05118	-0.06854	0.02382	1	0.851	1	1	0
PreNatLead_1	0.00922	0.01097	-0.00704	0.05117	-0.06843	0.02381	1	0.869	1	1	0
PreNatAlcohol	0.00956	0.01101	-0.00712	0.05116	-0.06683	0.02364	1	0.514	1	1	0
Anemia	0.01025	0.01101	-0.02360	0.05070	-0.06881	0.02361	1	0.080	1	1	0
BrstFeed	0.01004	0.01104	-0.01828	0.05009	-0.06823	0.02352	2	0.318	1	1	0
MomAge	0.01165	0.01085	-0.01060	0.04991	-0.06122	0.02309	4	0.056	0	1	1
HC_PAP	0.01397	0.01077	-0.01469	0.04961	-0.06204	0.02294	2	0.099	1	1	1
HC_Cholest	0.01456	0.01062	-0.01129	0.04829	-0.05947	0.02286	2	0.040	1	1	1
HC_InitInad_1	0.01471	0.01061	-0.01163	0.04826	-0.05996	0.02283	1	0.741	1	1	1
ChildPica	0.01424	0.01044	-0.01600	0.04781	-0.05333	0.02241	1	<.0001	1	1	1
Folic_PNVit_M	0.01535	0.01039	-0.01147	0.04781	-0.05414	0.02224	1	0.019	1	1	1
PovertyRatio1	0.01230	0.01016	-0.00658	0.04799	-0.05561	0.02226	1	0.006	0	1	1
BirthOrder	0.01197	0.01009	-0.01221	0.04728	-0.05435	0.02214	2	0.177	0	1	1
Birthwt	0.01061	0.01003	-0.01060	0.04578	-0.01362	0.01896	4	0.016	1	1	1

[a] C.I.E. = "Change in estimate" and is equal to "1" if dropping a covariate changes the exposure estimate by more than 10 percent, relative to the estimates shown for the "full model".

Read Table: Estimate of PreNatThimer effect from full model (all covariate included) is 0.01183. After dropping "Bilirubin" the estimate for PreNatThimer is 0.01188.

12.2.3. Sensitivity to the Inclusion of Birth Weight as a Covariate

The previous section (Section 12.2.2) showed how the estimates change as covariates are sequentially dropped from the models. Exhibit 12.2.2 corresponds to the comparison of AD to matched controls. It shows that the estimate of the *Exp17mos* exposure effect does not change radically as each covariate is dropped, until the last covariate in the sequence (*Birthwt*) is omitted from the model. Relative to the estimate from the model that immediately preceded it, dropping the *Birthwt* covariate results in a change-in-estimate from -0.0442 to -0.0116. This suggests that the *Exp17mos* exposure effect may be sensitive to the inclusion or exclusion of the *Birthwt* covariate.

To explore effect of *Birthwt* on the *Exp17mos* effect further, we tried dropping *Birthwt* earlier in the sequence to evaluate whether its inclusion/exclusion made a big difference for the *Exp17mos* effect when other covariates were included in the model. The results, summarized in Exhibit 12.2.8, indicate that when other covariates are included in the model, dropping *Birthwt* does not have a dramatic effect on the *Exp17mos* exposure effect. Dropping *Birthwt* did attenuate the *Exp17mos* exposure effect somewhat, but the effect was still negative and significantly different than zero (p=0.044).

Exhibit 12.2.8 Outcome: AD ** Birth Weight Dropped Early in Sequence **
Effects of Dropping Covariates on Estimates and Standard Errors of Exposure Effect

Dropped Covariate	Exposure Estimates and Standard Errors						Dropped Covariate		C.I.E.[a]	C.I.E.	C.I.E.
	PreNatThimer		*Exp01mos*		*Exp17mos*				PreNat-	Exp-	Exp-
Name	Estimate	S.E.	Estimate	S.E.	Estimate	S.E.	df	P-val	Thimer	01mos	17mos
Full Model	0.01157	0.01103	0.02982	0.05043	-0.05796	0.02187	.	.	.	.	.
Birthwt	0.01096	0.01102	0.01121	0.04897	**-0.03967**	0.01968	4	0.200	0	1	1
Bilirubin	0.01092	0.01101	0.01171	0.04887	-0.03922	0.01955	1	0.848	0	1	1
PreNatTuna	0.01059	0.01094	0.01214	0.04896	-0.03925	0.01955	1	0.377	0	1	1
PreNatValproi	0.01071	0.01093	0.01197	0.04895	-0.03925	0.01955	1	0.797	0	1	1
RespDistress	0.01069	0.01093	0.01106	0.04866	-0.03847	0.01897	1	0.872	0	1	1
SingleParent	0.01067	0.01093	0.01109	0.04863	-0.03848	0.01896	1	0.928	0	1	1
PreNatNicotin	0.01036	0.01083	0.01128	0.04853	-0.03802	0.01894	1	0.502	1	1	1
Multiple	0.00946	0.01078	0.01936	0.04803	-0.03177	0.01869	1	0.062	1	1	1
PreNatFilling	0.00950	0.01077	0.01954	0.04799	-0.03123	0.01860	1	0.729	1	1	1
C5APGAR	0.00911	0.01074	0.01289	0.04798	-0.03009	0.01874	1	0.103	1	1	1
PreNatIllDrug	0.00932	0.01070	0.01232	0.04797	-0.03029	0.01872	1	0.761	1	1	1
PreNatOthMerc	0.00971	0.01062	0.01204	0.04789	-0.03079	0.01870	1	0.500	1	1	1
PreNatFish	0.00982	0.01061	0.01256	0.04782	-0.03109	0.01870	1	0.802	1	1	1
ChildLead	0.01024	0.01060	0.00933	0.04786	-0.03051	0.01869	1	0.124	1	1	1
Dad_Age	0.01050	0.01056	0.00908	0.04775	-0.03036	0.01865	3	0.950	0	1	1
MomEduc_cat	0.01051	0.01052	0.02891	0.04895	-0.05679	0.02119	3	0.424	0	0	0
PreNatViralIn	0.00908	0.01047	0.01071	0.04708	-0.02888	0.01831	1	0.933	1	1	1
PreNatLead_1	0.00876	0.01048	0.01055	0.04712	-0.02924	0.01838	1	0.577	1	1	1
PreNatAlcohol	0.00899	0.01053	0.01021	0.04707	-0.02862	0.01828	1	0.602	1	1	1
Anemia	0.01040	0.01045	-0.00254	0.04666	-0.02879	0.01827	1	0.073	1	1	1
BrstFeed	0.00988	0.01043	0.00098	0.04633	-0.02811	0.01828	2	0.394	1	1	1
MomAge	0.01118	0.01036	0.00900	0.04637	-0.02214	0.01797	4	0.048	0	1	1
HC_PAP	0.01338	0.01039	0.00401	0.04612	-0.02207	0.01785	2	0.054	1	1	1
HC_Cholest	0.01367	0.01022	0.00956	0.04489	-0.01854	0.01777	2	0.022	1	1	1
HC_InitInad_1	0.01382	0.01020	0.00791	0.04504	-0.01465	0.01790	1	0.150	1	1	1
ChildPica	0.01237	0.01011	0.00523	0.04470	-0.01323	0.01758	1	0.000	0	1	1
Folic_PNVit_M	0.01315	0.01009	0.00846	0.04469	-0.01388	0.01726	1	0.058	1	1	1
PovertyRatio1	0.00963	0.00994	0.01261	0.04517	-0.01167	0.01738	1	0.001	1	1	1
BirthOrder	0.01010	0.00979	0.01026	0.04419	-0.01156	0.01703	2	0.093	1	1	1

[a] C.I.E. = "Change in estimate" and is equal to "1" if dropping a covariate changes the exposure estimate by more than 10 percent, relative to the estimates shown for the "full model".

Read Table: Estimate of PreNatThimer effect from full model (all covariate included) is 0.01157. After dropping "Bilirubin" the estimate for PreNatThimer is 0.01092.

12.2.4. Sensitivity to Potentially Endogenous Covariates

A covariate is endogenous with exposure if the exposure has a causal affect on the value of the covariate. For example, if thimerosal exposure caused autism, and having an autistic child caused families, on average, to have lower income, then a measure of income would be endogenous, because in this hypothetical scenario, exposure causes lower income. Controlling for an endogenous covariate could partial out some of the exposure effect, such that effects that really should be attributed to the exposure get mistakenly attributed to the covariate. Covariates that are measured prior to exposure cannot be endogenous. In the current study, many of the covariates represent things that were measured after exposure, and are theorized to be possibly related to both exposure and outcomes, but not to be causally affected by exposure level. For example, while breast feeding is expected to result in higher probability of healthy development (outcome), and may represent a proxy for some characteristic of mothers that would make them more or less likely to get all of their child's vaccinations on time (exposure), one would not expect that thimerosal exposure would have a causal relationship to breastfeeding duration. However, since breastfeeding is concurrent with postnatal exposure, it is impossible to rule out the possibility that the measure of breast feeding duration is endogenous. Of the covariates that were retained in the final, reduced model for the AD outcome (the shaded variables in Exhibit 12.2.2) the only measures that could not possibly be endogenous with postnatal exposure are mother's age, and child's birth weight. While the measures of prenatal folic acid use (*Folic_PNVit*) and inadequacy of initiation of prenatal care *(HC_InitInad)* are measures of events that occurred prior to postnatal exposure, both measures are based on both medical record data and maternal self report, and could therefore have a component of endogeneity. One could even argue that, since birth comes after potential prenatal exposure to thimerosal from maternal receipts of vaccines or immune globulins, that even birth weight could have an element of endogeneity.

In order to evaluate whether the *Exp17mos* exposure estimates are sensitive to the inclusion of any covariates that could possibly be endogenous, we created a subset of data comprised only of AD cases and matched controls that had zero exposure on the *PreNatThimer* measure, and fit a model which included only measures of birth weight and maternal age as covariates. The results, shown in Exhibit 12.2.9, indicate that for this subset of data, and with only the birth weight and mother's age covariates, the estimate for *Exp07mos* is still negative (*est.* = -0.04164) and significantly different than zero (p=0.0486). These results suggest that estimated effect of Exp07mos exposure is not particularly sensitive to the inclusion of potentially endogenous variables as covariates.

Exhibit 12.2.9
Model Results for AD vs Matched Controls
Where *PreNatThimer = 0*, and Only Covariates are Birth Weight and Maternal Age

Based on n=804 Observations Where *PreNatThimer = 0*

Variable	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Odds Ratio	Variable Label
Exp01mos	1	-0.01261	0.04818	0.0685	0.7935	0.987	Amt/Wt(KGs) birth-28 days
Exp17mos	1	-0.04164	0.02112	3.8886	0.0486	0.959	Amt/Wt(KGs) 29-214 days
<1 Kg is reference category							
BW1_1p5k	1	-2.71334	1.52365	3.1713	0.0749	0.066	=1 if Birth wgt 1.0 Kg to 1.499 Kg
BW1p5_2p5k	1	-2.70145	1.16018	5.4218	0.0199	0.067	=1 if Birth wgt 1.5 Kg to 2.499 Kg
BW2p5_4k	1	-3.09445	1.13896	7.3816	0.0066	0.045	=1 if Birth wgt 2.5 Kg to 3.999 Kg
BW4kup	1	-3.19692	1.17502	7.4024	0.0065	0.041	=1 if Birth wgt 4.0 Kg and up
<20 year is reference category							
Mom20_24	1	-0.85418	0.68644	1.5484	0.2134	0.426	Mom Age at child birth 20 - 24
Mom25_29	1	-0.37658	0.62497	0.3631	0.5468	0.686	Mom Age at child birth 25 - 29
Mom30_34	1	-0.42537	0.62097	0.4692	0.4933	0.654	Mom Age at child birth 30 - 34
MomGE35	1	-0.27336	0.61671	0.1965	0.6576	0.761	Mom Age at child birth ge 35

12.3. Sensitivity of Results to Coding of Birth Weight Covariate

The results in Chapter 10 indicated that when low birth weight children were omitted from the analyses, there was a small amount of attenuation toward zero of the exposure estimates. The results in Sections 12.2.1 and 12.2.2 indicated that exposure estimates were somewhat sensitive to the inclusion or omission of birth weight as a covariate. Those results indicated that when birth weight was dropped as a covariate, that the postnatal exposure estimates changed more that when any other single covariate was dropped from the models. Those results also showed that when a full set of other covariates was included, and birth weight was the only covariate that was dropped, postnatal exposure estimates were still often signficantly different than zero. In the current section, we explore the question of whether the postnatal exposure estimates are sensitive to the coding of birth weight as a covariate.

The coding used in the original analyses had been specified in advance, during the study design phase, and included four dummy variables to represent five birth weight categories: 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. As indicated in Exhibit 9.2.1, only one percent of the participant children had birth weights in the lowest birth weight category, and only one percent had birth weights in the second lowest category. We speculated that the sparseness of data in the lowest birth weight categories might cause unexpected estimation issues in the

conditional logistic regression models that could make 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[3]. Results are shown in Exhibits 12.3.1-12.3.3, and should be compared to the results in Exhibits 9.4.1 – 9.4.3. Collapsing of the birth weight categories resulted in attenuation of the estimated effects of postnatal exposure. For several outcomes and for several estimates of the effects of exposure, the estimates were still significantly different than zero after collapsing of birth weight categories. We do conclude, however, that the results are sensitive to the coding of the birth weight covariate.

Exhibit 12.3.1 Model Summary: *PreNatThimer* and *Exp07mos* Exposure Models When Low Birth Weight Categories are Collapsed

Outcome	N	Exposure Measure	Estimate	Stderr	Prob ChiSq		One Unit Chg. OR[a]	Lower 95% CL	Upper 95% CL	1/OR	2 SD Unit Chg. OR[b]	1/OR
ASD_Outc	1008	PreNatThimer	0.0062	0.0094	0.513		1.006	0.988	1.025		1.11	
ASD_Outc	1008	Exp07mos	-0.0257	0.0158	0.103		0.975	0.945	1.005	1.026	0.67	1.49
AD_Outc	911	PreNatThimer	0.0097	0.0105	0.355		1.010	0.989	1.031		1.17	
AD_Outc	911	Exp07mos	-0.0299	0.0180	0.097	~	0.971	0.937	1.005	1.030	0.63	1.59
ASD_Only[c]	773	PreNatThimer	-0.0022	0.0200	0.913		0.998	0.959	1.038	1.002	0.96	1.04
ASD_Only[c]	773	Exp07mos	-0.0246	0.0294	0.401		0.976	0.921	1.033	1.025	0.68	1.47
ASD_Regr[c]	701	PreNatThimer	0.0380	0.0211	0.072	~	1.039	0.997	1.083		1.86	
ASD_Regr[c]	701	Exp07mos	-0.0991	0.0338	0.003	**	0.906	0.848	0.968	1.104	0.21	4.68
AD_ExLoIQ	884	PreNatThimer	0.0145	0.0105	0.167		1.015	0.994	1.036		1.27	
AD_ExLoIQ	884	Exp07mos	-0.0378	0.0195	0.053	~	0.963	0.927	1.000	1.039	0.56	1.80
ASD_Scr	821	PreNatThimer	0.0039	0.0098	0.689		1.004	0.985	1.024		1.07	
ASD_Scr	821	Exp07mos	-0.0339	0.0180	0.059	~	0.967	0.933	1.001	1.035	0.59	1.70
AD_Scr	728	PreNatThimer	0.0116	0.0115	0.314		1.012	0.989	1.035		1.21	
AD_Scr	728	Exp07mos	-0.0479	0.0212	0.024	*	0.953	0.914	0.994	1.049	0.47	2.11

~ 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.

[c] Because of small cell sizes the low birth wieght groups were already collapsed in original models (i.e., models reported in Exhibit 9.4.1) for these outcomes. See Section 8.2 for details on covariates used. Consequently, the estimates shown in the current exhibit for these outcomes are unchanged from the original estimates reported in Chapter 9.

[3] Other variables that were used as covariates for one or more outcomes and that had low sample proportions within some categories included measures of mother's age at the time her child was born, father age, the measure of frequency of pap smears, the measure of inadequacy of initiatation of prenatal care, prenatal use of illegal drugs, and prenatal use of valproic acid. We also tried collapsing cell categories for those variables but the results did not appear to be sensitive to the coding of these variables.

Exhibit 12.3.2. Model Summary: *PreNatThimer*, *Exp01mos* , *Exp17mos* Exposure Models When Low Birth Weight Categories are Collapsed

Outcome	N	Exposure Measure	Estimate	Stderr	Prob ChiSq		One Unit Chg. OR[a]	Lower 95% CL	Upper 95% CL	1/OR	2 SD Unit Chg. OR[b]	1/OR
ASD_Outc	1008	PreNatThimer	0.0062	0.0094	0.509		1.006	0.988	1.025		1.11	
ASD_Outc	1008	Exp01mos	-0.0413	0.0439	0.347		0.960	0.880	1.046	1.042	0.84	1.18
ASD_Outc	1008	Exp17mos	-0.0236	0.0166	0.155		0.977	0.945	1.009	1.024	0.71	1.41
AD_Outc	911	PreNatThimer	0.0094	0.0106	0.374		1.009	0.989	1.031		1.17	
AD_Outc	911	Exp01mos	0.0024	0.0479	0.960		1.002	0.913	1.101		1.01	
AD_Outc	911	Exp17mos	-0.0345	0.0193	0.075	~	0.966	0.930	1.003	1.035	0.61	1.65
ASD_Only[c]	773	PreNatThimer	-0.0042	0.0197	0.831		0.996	0.958	1.035	1.004	0.93	1.07
ASD_Only[c]	773	Exp01mos	-0.2163	0.0952	0.023	*	0.806	0.668	0.971	1.241	0.41	2.42
ASD_Only[c]	773	Exp17mos	0.0011	0.0307	0.971		1.001	0.943	1.063		1.02	
ASD_Regr[c]	701	PreNatThimer	0.0380	0.0211	0.073	~	1.039	0.997	1.083		1.86	
ASD_Regr[c]	701	Exp01mos	-0.1043	0.0863	0.227		0.901	0.761	1.067	1.110	0.65	1.53
ASD_Regr[c]	701	Exp17mos	-0.0980	0.0377	0.009	**	0.907	0.842	0.976	1.103	0.24	4.16
AD_ExLoIQ	884	PreNatThimer	0.0145	0.0105	0.167		1.015	0.994	1.036		1.27	
AD_ExLoIQ	884	Exp01mos	-0.0380	0.0524	0.469		0.963	0.869	1.067	1.039	0.86	1.17
AD_ExLoIQ	884	Exp17mos	-0.0378	0.0208	0.070	~	0.963	0.924	1.003	1.039	0.58	1.73
ASD_Scr	821	PreNatThimer	0.0040	0.0098	0.685		1.004	0.985	1.023		1.07	
ASD_Scr	821	Exp01mos	-0.0794	0.0468	0.090	~	0.924	0.843	1.013	1.083	0.72	1.38
ASD_Scr	821	Exp17mos	-0.0269	0.0189	0.155		0.973	0.938	1.010	1.027	0.68	1.48
AD_Scr	728	PreNatThimer	0.0112	0.0116	0.336		1.011	0.988	1.035		1.20	
AD_Scr	728	Exp01mos	-0.0154	0.0533	0.773		0.985	0.887	1.093	1.016	0.94	1.06
AD_Scr	728	Exp17mos	-0.0532	0.0229	0.020	*	0.948	0.907	0.992	1.055	0.46	2.17

~ 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.

[c] Because of small cell sizes the low birth wieght groups were already collapsed in original models (i.e., models reported in Exhibit 9.4.2) for these outcomes. See Section 8.2 for details on covariates used. Consequently, the estimates shown in the current exhibit for these outcomes are unchanged from the original estimates reported in Chapter 9.

Exhibit 12.3.3. Model Summary: *PreNatThimer* and *Exp020mos* Exposure Models When Low Birth Weight Categories are Collapsed

Outcome	N	Exposure Measure	Estimate	Stderr	Prob ChiSq		One Unit Chg. OR[a]	Lower 95% CL	Upper 95% CL	1/OR	2 SD Unit Chg. OR[b]	1/OR
ASD_Outc	1008	PreNatThimer	0.0060	0.0094	0.522		1.006	0.988	1.025		1.10	
ASD_Outc	1008	Exp020mos	-0.0252	0.0152	0.098	~	0.975	0.946	1.005	1.026	0.64	1.57
AD_Outc	911	PreNatThimer	0.0093	0.0105	0.375		1.009	0.989	1.030		1.16	
AD_Outc	911	Exp020mos	-0.0262	0.0172	0.129		0.974	0.942	1.008	1.027	0.63	1.60
ASD_Only[c]	773	PreNatThimer	-0.0019	0.0201	0.924		0.998	0.960	1.038	1.002	0.97	1.03
ASD_Only[c]	773	Exp020mos	-0.0270	0.0277	0.331		0.973	0.922	1.028	1.027	0.62	1.62
ASD_Regr[c]	701	PreNatThimer	0.0364	0.0207	0.080	~	1.037	0.996	1.080		1.81	
ASD_Regr[c]	701	Exp020mos	-0.0780	0.0321	0.015	*	0.925	0.869	0.985	1.081	0.25	4.02
AD_ExLoIQ	884	PreNatThimer	0.0141	0.0105	0.179		1.014	0.994	1.035		1.26	
AD_ExLoIQ	884	Exp020mos	-0.0325	0.0187	0.082	~	0.968	0.933	1.004	1.033	0.56	1.79
ASD_Scr	821	PreNatThimer	0.0038	0.0099	0.703		1.004	0.985	1.023		1.06	
ASD_Scr	821	Exp020mos	-0.0286	0.0171	0.094	~	0.972	0.940	1.005	1.029	0.60	1.67
AD_Scr	728	PreNatThimer	0.0111	0.0116	0.336		1.011	0.989	1.034		1.20	
AD_Scr	728	Exp020mos	-0.0383	0.0200	0.056	~	0.962	0.925	1.001	1.039	0.51	1.98

~ 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.

[c] Because of small cell sizes the low birth wieght groups were already collapsed in original models (i.e., models reported in Exhibit 9.4.3) for these outcomes. See Section 8.2 for details on covariates used. Consequently, the estimates shown in the current exhibit for these outcomes are unchanged from the original estimates reported in Chapter 9.

12.4. Are Overall Results Driven by Results in One Particular 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 for the AD outcome to sequential subsets of data where, in each subset, all data from a single stratum were omitted[4]. 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 results of this exploratory analysis are summarized in Exhibit 12.4.1. The first row of the exhibit shows the exposure parameter estimates, standard errors, and p-values from the model fit to the full data set with all strata included. The second row shows the estimates, standard errors, and p-values when the data from "Stratum 2" are omitted[5]. The results do not appear to be sensitive to the inclusion / exclusion of data from "Stratum 2". Similar results on third row indicate that results do not appear to be sensitive to the inclusion / exclusion of data from "Stratum 3". Examination of the entire table suggests that the results are not particularly sensitive to the inclusion / exclusion of data from any single matching stratum.

Exhibit 12.4.1. AD Outcome:
Parameter Estimates When Observations from One Stratum at a Time are Omitted

Omitted Stratum	NObsUsed	Est1_Pre NatThimer	SE1_Pre NatThimer	PVal1_ PreNat Thimer	Est1_ Exp01mos	SE1_ Exp01mos	PVal1_ Exp01mos	Est1_ Exp17mos	SE1_ Exp17mos	PVal1_ Exp17mos
Full Data Set	911	0.011	0.011	0.318	0.028	0.049	0.562	-0.056	0.021	0.008
2	905	0.015	0.011	0.179	0.027	0.049	0.584	-0.058	0.021	0.007
3	907	0.011	0.011	0.321	0.009	0.050	0.864	-0.056	0.021	0.008
5	906	0.009	0.011	0.418	0.029	0.049	0.551	-0.054	0.021	0.010
7	908	0.011	0.011	0.290	0.028	0.049	0.571	-0.056	0.021	0.008
9	908	0.011	0.011	0.294	0.029	0.049	0.551	-0.057	0.021	0.007
10	906	0.012	0.011	0.277	0.029	0.049	0.555	-0.056	0.021	0.008
12	906	0.010	0.011	0.328	0.032	0.049	0.517	-0.056	0.021	0.008
13	892	0.014	0.012	0.234	0.033	0.049	0.503	-0.059	0.021	0.006
14	827	0.009	0.012	0.444	0.020	0.053	0.697	-0.063	0.022	0.004
15	889	0.012	0.011	0.254	0.051	0.054	0.338	-0.059	0.021	0.006
16	849	0.013	0.011	0.232	0.014	0.051	0.784	-0.057	0.021	0.008
17	904	0.011	0.011	0.295	0.028	0.049	0.563	-0.056	0.021	0.008
18	853	0.008	0.011	0.432	0.049	0.049	0.318	-0.050	0.021	0.019

[4] This study used a case-control study design wherein controls were matched to cases within matching strata defined by birth year, sex, and HMO. See Volume I, Chapter 5 for details.

[5] Note that there was no "Stratum 1" in the data set used for analysis of AD cases and matched controls. Although "Stratum 1" included ASD cases and matching controls, there were no AD cases in "Stratum 1". Consequently, "Stratum 1" does not appear in this exhibit. Other strata, e.g. "Stratum 4", are not included in the exhibit for the same reason

Exhibit 12.4.1. AD Outcome:
Parameter Estimates When Observations from One Stratum at a Time are Omitted

Omitted Stratum	NObsUsed	Est1_Pre NatThimer	SE1_Pre NatThimer	PVal1_ PreNat Thimer	Est1_ Exp01mos	SE1_ Exp01mos	PVal1_ Exp01mos	Est1_ Exp17mos	SE1_ Exp17mos	PVal1_ Exp17mos
19	895	0.010	0.011	0.323	0.017	0.050	0.727	-0.059	0.022	0.007
20	844	0.012	0.011	0.283	0.018	0.051	0.719	-0.048	0.023	0.038
21	905	0.011	0.011	0.316	0.024	0.049	0.620	-0.053	0.021	0.012
22	850	0.003	0.012	0.787	0.006	0.053	0.903	-0.079	0.024	0.001
24	887	0.009	0.011	0.432	0.040	0.049	0.418	-0.045	0.021	0.037
25	902	0.011	0.011	0.297	0.028	0.049	0.566	-0.055	0.021	0.010
26	897	0.011	0.011	0.305	0.027	0.049	0.583	-0.056	0.021	0.008
28	889	0.012	0.011	0.268	0.027	0.049	0.574	-0.059	0.021	0.005
29	899	0.011	0.011	0.310	0.027	0.049	0.581	-0.057	0.021	0.007
30	859	0.010	0.011	0.346	0.041	0.050	0.415	-0.055	0.021	0.010
32	865	0.014	0.011	0.186	0.033	0.049	0.503	-0.058	0.022	0.008
33	904	0.011	0.011	0.319	0.030	0.049	0.543	-0.055	0.021	0.010
34	850	0.008	0.011	0.490	0.039	0.050	0.431	-0.056	0.022	0.011
36	863	0.010	0.011	0.373	0.040	0.050	0.428	-0.048	0.021	0.025
38	897	0.011	0.011	0.316	0.033	0.049	0.501	-0.052	0.021	0.014
40	885	0.010	0.011	0.333	0.019	0.050	0.701	-0.053	0.021	0.012
42	879	0.009	0.011	0.405	0.032	0.050	0.518	-0.057	0.021	0.007
43	907	0.011	0.011	0.309	0.029	0.049	0.548	-0.056	0.021	0.008
44	864	0.010	0.011	0.347	0.038	0.050	0.452	-0.055	0.022	0.011
46	887	0.011	0.011	0.292	0.025	0.049	0.609	-0.055	0.021	0.010
48	875	0.010	0.011	0.352	0.013	0.050	0.792	-0.061	0.022	0.005

12.5. Are Overall Results Driven by Results From One Particular HMO?

The results presented in this section are from analyses that were conducted to determine whether the findings from the main models, summarized in Volume I Exhibits 9.4.1 – 9.4.3, were being driven by results from one HMO, or whether the pattern of results is replicated across HMOs. To address this question, we fit models of the same form as described in Volume I Sections 9.4.1 – 9.4.3 separately to data from the two largest HMOs, to obtain separate estimates from each of those two HMOs. The sample size in the smallest HMO (HMO-A) was not large enough to support estimimation in a model with a full set of covariates. Therefore, HMO-A was not used for the current analyses.

In order to assess whether the results in the main analyses are being driven by results in a particular HMO, we made the following comparisons:

Vol II, Exhibits 12.5.1 & 12.5.2	to	Vol I, Exhibit 9.4.1
Vol II, Exhibits 12.5.3 & 12.5.4	to	Vol I, Exhibit 9.4.2
Vol II, Exhibits 12.5.5 & 12.5.6	to	Vol I, Exhibit 9.4.3

Generally, the results at each of the two larger sites are similar to the overall results presented in Exhibits 9.4.1 – 9.4.3 of Volume I. With the few exceptions noted below, the parameter estimates for the exposure coefficients have the same sign (positive or negative) at each of the two larger HMOs (HMO-B and HMO-C) as they did in the overall combined estimates from all three HMOs presented in Volume I. For postnatal exposure birth to one month, birth to seven months, and one to seven months, the magnitudes of effects are generally larger for HMO-C than HMO-B, with the combined estimates from all three HMOs falling between the two. For exposures birth to 20 months, the situation is reversed with larger magnitudes at HMO-B than HMO-C, with the combined estimates from all three HMOs falling between the two.

In summary, it appears that the estimated effects are similar in the two large sites, and generally only become statistically significant when the sample size is increased by combining data from all three sites. In particular:

- Estimates for postnatal exposure birth to seven months (*Exp07mos*) are:
  - Negative for all outcomes at HMO-B
    - Statistically significant for 1 of the 7 outcomes
  - Negative for all outcomes at HMO-C
    - Statistically significant for 2 of the 7 outcomes
  - Negative for all outcomes in main table (HMOs A, B, and C)
    - Statistically significant for 6 of the 7 outcomes

- Estimates for postnatal exposure birth to one month (*Exp01mos*) are:
  - Negative for 6 out of 7 outcomes at HMO-B
    - Statistically significant for 0 of the 7 outcomes
  - Negative for all outcomes at HMO-C
    - Statistically significant for 0 of the 7 outcomes

    - Negative for 6 of the 7 outcomes in main table (HMOs A, B, and C)
        - Statistically significant 0 of the 7 outcomes

- Estimates for postnatal exposure birth to twenty months (*Exp020mos*) are:
    - Negative for all outcomes at HMO-B
        - Statistically significant for 2 of the 7 outcomes
    - Negative for all outcomes at HMO-C
        - Statistically significant for 0 of the 7 outcomes
    - Negative for all outcomes in main table (HMOs A, B, and C)
        - Statistically significant for 6 of the 7 outcomes

- Estimates for prenatal exposure (*PreNatThimer*) are:
    - Non-significant for all outcomes at HMO-B
    - Non-significant for all outcomes at HMO-C
    - Non-significant for all outcomes main table (HMOs A, B, and C)

Thus it does not appear that the results from the main analyses are being driven by data from one particular site.

Exhibit 12.5.1 Model Summary: *PreNatThimer* and *Exp07mos* Exposure Models (HMO=HMO-B)

Outcome	N	Exposure Measure	Estimate	Stderr	Prob ChiSq		One Unit Chg. OR[a]	Lower 95% CL	Upper 95% CL	1/OR	2 SD Unit Chg. OR[b]	1/OR
ASD_Outc	459	PreNatThimer	0.0098	0.0125	0.434		1.010	0.985	1.035	0.990	1.18	
ASD_Outc	459	Exp07mos	-0.0203	0.0227	0.372		0.980	0.937	1.025	1.020	0.73	1.37
AD_Outc	426	PreNatThimer	0.0148	0.0143	0.302		1.015	0.987	1.044	0.985	1.28	
AD_Outc	426	Exp07mos	-0.0241	0.0254	0.342		0.976	0.929	1.026	1.024	0.68	1.46
ASD_Only	355	PreNatThimer	0.0062	0.0261	0.813		1.006	0.956	1.059	0.994	1.11	
ASD_Only	355	Exp07mos	-0.0010	0.0465	0.982		0.999	0.912	1.094	1.001	0.98	1.02
ASD_Regr	342	PreNatThimer	0.0452	0.0378	0.231		1.046	0.972	1.127	0.956	2.14	
ASD_Regr	342	Exp07mos	-0.1217	0.0463	0.009	**	0.885	0.809	0.969	1.129	0.15	6.76
AD_ExLoIQ	415	PreNatThimer	0.0179	0.0150	0.232		1.018	0.989	1.049	0.982	1.35	
AD_ExLoIQ	415	Exp07mos	-0.0331	0.0281	0.240		0.967	0.916	1.022	1.034	0.59	1.68
ASD_Scr	365	PreNatThimer	0.0047	0.0129	0.713		1.005	0.980	1.030	0.995	1.08	
ASD_Scr	365	Exp07mos	-0.0381	0.0254	0.134		0.963	0.916	1.012	1.039	0.55	1.82
AD_Scr	332	PreNatThimer	0.0109	0.0174	0.531		1.011	0.977	1.046	0.989	1.20	
AD_Scr	332	Exp07mos	-0.0496	0.0319	0.120		0.952	0.894	1.013	1.051	0.46	2.18

~ 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 12.5.2 Model Summary: *PreNatThimer* and *Exp07mos* Exposure Models (HMO= HMO-C)

Outcome	N	Exposure Measure	Estimate	Stderr	Prob ChiSq		One Unit Chg. OR[a]	Lower 95% CL	Upper 95% CL	1/OR	2 SD Unit Chg. OR[b]	1/OR
ASD_Outc	508	PreNatThimer	-0.0054	0.0183	0.769		0.995	0.960	1.031	1.005	0.93	1.07
ASD_Outc	508	Exp07mos	-0.0449	0.0285	0.115		0.956	0.904	1.011	1.046	0.54	1.85
AD_Outc	454	PreNatThimer	0.0091	0.0195	0.639		1.009	0.971	1.048	0.991	1.12	
AD_Outc	454	Exp07mos	-0.0616	0.0329	0.061	~	0.940	0.882	1.003	1.064	0.43	2.32
ASD_Only	408	PreNatThimer	-0.0210	0.0420	0.617		0.979	0.902	1.063	1.021	0.76	1.31
ASD_Only	408	Exp07mos	-0.0195	0.0483	0.686		0.981	0.892	1.078	1.020	0.77	1.31
ASD_Regr	340	PreNatThimer	0.0273	0.0316	0.387		1.028	0.966	1.093	0.973	1.42	
ASD_Regr	340	Exp07mos	-0.1016	0.0597	0.089	~	0.903	0.804	1.016	1.107	0.25	4.00
AD_ExLoIQ	445	PreNatThimer	0.0185	0.0200	0.356		1.019	0.979	1.059	0.982	1.27	
AD_ExLoIQ	445	Exp07mos	-0.0752	0.0361	0.037	*	0.928	0.864	0.996	1.078	0.36	2.79
ASD_Scr	422	PreNatThimer	-0.0084	0.0183	0.647		0.992	0.957	1.028	1.008	0.90	1.11
ASD_Scr	422	Exp07mos	-0.0597	0.0313	0.057	~	0.942	0.886	1.002	1.062	0.44	2.26
AD_Scr	371	PreNatThimer	0.0163	0.0210	0.438		1.016	0.975	1.059	0.984	1.23	
AD_Scr	371	Exp07mos	-0.1045	0.0398	0.009	**	0.901	0.833	0.974	1.110	0.24	4.17

~ 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 12.5.3 Model Summary: *PreNatThimer*, *Exp01mos* , *Exp17mos* Exposure Models (HMO= HMO-B)

Outcome	N	Exposure Measure	Estimate	Stderr	Prob ChiSq	One Unit Chg. OR[a]	Lower 95% CL	Upper 95% CL	1/OR	2 SD Unit Chg. OR[b]	1/OR
ASD_Outc	459	PreNatThimer	0.0098	0.0125	0.434	1.010	0.985	1.035	0.990	1.18	
ASD_Outc	459	Exp01mos	-0.0154	0.0567	0.786	0.985	0.881	1.100	1.016	0.93	1.07
ASD_Outc	459	Exp17mos	-0.0211	0.0245	0.389	0.979	0.933	1.027	1.021	0.73	1.37
AD_Outc	426	PreNatThimer	0.0147	0.0144	0.309	1.015	0.987	1.044	0.985	1.28	
AD_Outc	426	Exp01mos	0.0235	0.0615	0.702	1.024	0.908	1.155	0.977	1.11	
AD_Outc	426	Exp17mos	-0.0333	0.0278	0.232	0.967	0.916	1.022	1.034	0.61	1.63
ASD_Only	355	PreNatThimer	0.0026	0.0267	0.923	1.003	0.951	1.056	0.997	1.04	
ASD_Only	355	Exp01mos	-0.1873	0.1282	0.144	0.829	0.645	1.066	1.206	0.44	2.30
ASD_Only	355	Exp17mos	0.0245	0.0485	0.613	1.025	0.932	1.127	0.976	1.44	
ASD_Regr	342	PreNatThimer	0.0452	0.0378	0.231	1.046	0.972	1.127	0.956	2.14	
ASD_Regr	342	Exp01mos	-0.1179	0.1180	0.318	0.889	0.705	1.120	1.125	0.59	1.69
ASD_Regr	342	Exp17mos	-0.1224	0.0507	0.016 *	0.885	0.801	0.977	1.130	0.16	6.09
AD_ExLoIQ	415	PreNatThimer	0.0180	0.0151	0.233	1.018	0.989	1.049	0.982	1.35	
AD_ExLoIQ	415	Exp01mos	0.0323	0.0673	0.632	1.033	0.905	1.178	0.968	1.15	
AD_ExLoIQ	415	Exp17mos	-0.0460	0.0311	0.140	0.955	0.899	1.015	1.047	0.51	1.97
ASD_Scr	365	PreNatThimer	0.0047	0.0129	0.717	1.005	0.980	1.030	0.995	1.08	
ASD_Scr	365	Exp01mos	-0.0743	0.0633	0.241	0.928	0.820	1.051	1.077	0.72	1.39
ASD_Scr	365	Exp17mos	-0.0322	0.0270	0.233	0.968	0.918	1.021	1.033	0.62	1.61
AD_Scr	332	PreNatThimer	0.0109	0.0174	0.533	1.011	0.977	1.046	0.989	1.20	
AD_Scr	332	Exp01mos	-0.0387	0.0760	0.611	0.962	0.829	1.117	1.039	0.84	1.19
AD_Scr	332	Exp17mos	-0.0517	0.0348	0.137	0.950	0.887	1.017	1.053	0.47	2.15

~ 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 12.5.4 Model Summary: *PreNatThimer*, *Exp01mos* , *Exp17mos* Exposure Models (HMO= HMO-C)

Outcome	N	Exposure Measure	Estimate	Stderr	Prob ChiSq		One Unit Chg. OR[a]	Lower 95% CL	Upper 95% CL	1/OR	2 SD Unit Chg. OR[b]	1/OR
ASD_Outc	508	PreNatThimer	-0.0050	0.0182	0.785		0.995	0.960	1.031	1.005	0.94	1.07
ASD_Outc	508	Exp01mos	-0.1159	0.0843	0.169		0.891	0.755	1.051	1.123	0.69	1.45
ASD_Outc	508	Exp17mos	-0.0289	0.0333	0.386		0.972	0.910	1.037	1.029	0.71	1.41
AD_Outc	454	PreNatThimer	0.0091	0.0195	0.640		1.009	0.971	1.048	0.991	1.12	
AD_Outc	454	Exp01mos	-0.0575	0.0903	0.524		0.944	0.791	1.127	1.059	0.83	1.20
AD_Outc	454	Exp17mos	-0.0627	0.0395	0.113		0.939	0.869	1.015	1.065	0.47	2.11
ASD_Only	408	PreNatThimer	-0.0264	0.0430	0.539		0.974	0.895	1.060	1.027	0.71	1.40
ASD_Only	408	Exp01mos	-0.2213	0.1904	0.245		0.801	0.552	1.164	1.248	0.49	2.03
ASD_Only	408	Exp17mos	0.0206	0.0585	0.725		1.021	0.910	1.145	0.980	1.28	
ASD_Regr	340	PreNatThimer	0.0287	0.0315	0.361		1.029	0.968	1.095	0.972	1.44	
ASD_Regr	340	Exp01mos	-0.3068	0.1826	0.093	~	0.736	0.514	1.052	1.359	0.37	2.67
ASD_Regr	340	Exp17mos	-0.0611	0.0681	0.369		0.941	0.823	1.075	1.063	0.48	2.07
AD_ExLoIQ	445	PreNatThimer	0.0186	0.0200	0.352		1.019	0.980	1.060	0.982	1.27	
AD_ExLoIQ	445	Exp01mos	-0.0930	0.0993	0.349		0.911	0.750	1.107	1.097	0.74	1.35
AD_ExLoIQ	445	Exp17mos	-0.0707	0.0428	0.099	~	0.932	0.857	1.013	1.073	0.43	2.32
ASD_Scr	422	PreNatThimer	-0.0080	0.0183	0.660		0.992	0.957	1.028	1.008	0.90	1.11
ASD_Scr	422	Exp01mos	-0.1485	0.0884	0.093	~	0.862	0.725	1.025	1.160	0.62	1.61
ASD_Scr	422	Exp17mos	-0.0394	0.0360	0.274		0.961	0.896	1.032	1.040	0.63	1.60
AD_Scr	371	PreNatThimer	0.0163	0.0210	0.439		1.016	0.975	1.059	0.984	1.23	
AD_Scr	371	Exp01mos	-0.0905	0.1005	0.368		0.913	0.750	1.112	1.095	0.75	1.34
AD_Scr	371	Exp17mos	-0.1081	0.0465	0.020	*	0.898	0.819	0.983	1.114	0.28	3.62

~ 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 12.5.5 Model Summary: *PreNatThimer* and *Exp020mos* Exposure Models (HMO= HMO-B)

Outcome	N	Exposure Measure	Estimate	Stderr	Prob ChiSq		One Unit Chg. OR[a]	Lower 95% CL	Upper 95% CL	1/OR	2 SD Unit Chg. OR[b]	1/OR
ASD_Outc	459	PreNatThimer	0.0095	0.0125	0.445		1.010	0.985	1.035	0.991	1.17	
ASD_Outc	459	Exp020mos	-0.0307	0.0217	0.158		0.970	0.929	1.012	1.031	0.60	1.67
AD_Outc	426	PreNatThimer	0.0139	0.0144	0.332		1.014	0.986	1.043	0.986	1.26	
AD_Outc	426	Exp020mos	-0.0369	0.0244	0.130		0.964	0.919	1.011	1.038	0.54	1.86
ASD_Only	355	PreNatThimer	0.0065	0.0260	0.803		1.007	0.956	1.059	0.994	1.12	
ASD_Only	355	Exp020mos	-0.0101	0.0433	0.816		0.990	0.909	1.078	1.010	0.84	1.18
ASD_Regr	342	PreNatThimer	0.0444	0.0369	0.229		1.045	0.972	1.124	0.957	2.11	
ASD_Regr	342	Exp020mos	-0.1284	0.0447	0.004	**	0.880	0.806	0.960	1.137	0.12	8.63
AD_ExLoIQ	415	PreNatThimer	0.0171	0.0151	0.257		1.017	0.988	1.048	0.983	1.33	
AD_ExLoIQ	415	Exp020mos	-0.0494	0.0269	0.066	~	0.952	0.903	1.003	1.051	0.44	2.29
ASD_Scr	365	PreNatThimer	0.0045	0.0128	0.723		1.005	0.980	1.030	0.995	1.08	
ASD_Scr	365	Exp020mos	-0.0443	0.0242	0.067	~	0.957	0.912	1.003	1.045	0.48	2.10
AD_Scr	332	PreNatThimer	0.0098	0.0175	0.578		1.010	0.976	1.045	0.990	1.18	
AD_Scr	332	Exp020mos	-0.0634	0.0311	0.042	*	0.939	0.883	0.998	1.065	0.35	2.90

~ 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 12.5.6 Model Summary: *PreNatThimer* and *Exp020mos* Exposure Models (HMO= HMO-C)

Outcome	N	Exposure Measure	Estimate	Stderr	Prob ChiSq	One Unit Chg. OR[a]	Lower 95% CL	Upper 95% CL	1/OR	2 SD Unit Chg. OR[b]	1/OR
ASD_Outc	508	PreNatThimer	-0.0062	0.0183	0.736	0.994	0.959	1.030	1.006	0.92	1.08
ASD_Outc	508	Exp020mos	-0.0256	0.0272	0.347	0.975	0.924	1.028	1.026	0.67	1.49
AD_Outc	454	PreNatThimer	0.0075	0.0195	0.700	1.008	0.970	1.047	0.993	1.10	
AD_Outc	454	Exp020mos	-0.0279	0.0314	0.375	0.973	0.914	1.034	1.028	0.65	1.55
ASD_Only	408	PreNatThimer	-0.0200	0.0419	0.634	0.980	0.903	1.064	1.020	0.78	1.29
ASD_Only	408	Exp020mos	-0.0285	0.0456	0.531	0.972	0.889	1.063	1.029	0.64	1.56
ASD_Regr	340	PreNatThimer	0.0232	0.0312	0.459	1.023	0.963	1.088	0.977	1.34	
ASD_Regr	340	Exp020mos	-0.0189	0.0559	0.736	0.981	0.880	1.095	1.019	0.74	1.34
AD_ExLoIQ	445	PreNatThimer	0.0162	0.0201	0.419	1.016	0.977	1.057	0.984	1.23	
AD_ExLoIQ	445	Exp020mos	-0.0350	0.0342	0.306	0.966	0.903	1.033	1.036	0.58	1.73
ASD_Scr	422	PreNatThimer	-0.0094	0.0183	0.607	0.991	0.956	1.027	1.009	0.89	1.13
ASD_Scr	422	Exp020mos	-0.0337	0.0296	0.255	0.967	0.912	1.025	1.034	0.59	1.69
AD_Scr	371	PreNatThimer	0.0143	0.0210	0.496	1.014	0.974	1.057	0.986	1.20	
AD_Scr	371	Exp020mos	-0.0612	0.0378	0.105	0.941	0.873	1.013	1.063	0.38	2.60

~ 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.

12.6. Are Results Sensitive to Calculation of Weight at Time of Vaccine Receipt?

The main results reported in Volume I, Section 9.4.1 – 9.4.3 used measures of postnatal exposure where the mercury amount in each vaccine or immune globulin received was divided by the child's weight in kilograms at the time of receipt, and then summed over the relevant age range (e.g., birth to seven months). The creation of the postnatal exposure measures are explained in Volume I, Section 7.3, and as noted in that section, usually each child's weight was recorded on their medical charts at the same time that the child received a vaccine, but there were times when vaccines were recieived but no weight was recorded. In those instances the weight at time of vaccine receipt was interpolated or extrapolated from other recorded weights for the child. In current section we address the question of whether the main results reported in Volume I, Section 9.4.1 – 9.4.3 might be sensitive to the imputation of missing weights.

To answer this question, we compared the results from the main models where the exposure measures included division by weight at time of receipt (Exhibit 9.4.2) to the results from models where exposure measures were created without dividing by weight at time of receipt (Exhibit 11.1.1). The results in the two exhibits are very similar. We interpret this to mean that the results were not sensitive to the use of weights in the postnatal exposure measures, and therefore the results are not sensitive to the use of imputed weights.

For further detail on weight at time of vaccine receipt and the frequency that weights were imputed, see Volume II, Section 18 "Additional Detail on Weight at Time of Vaccine Receipt".

13. 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. (See Section 5.2 for more details). During the design phase of the study, there was concern expressed among the panel 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.

13.1.1. Summary of Results

Analyses of the numbers of cases and controls that were opted-out indicated that:

- At two HMOs, very few sample members were opted-out by physicians
  - Less that a half a percent of sampled cases and controls were opted-out at HMOs A and C
- At HMO-B, 10 percent of sampled cases and 9 percent of sampled controls were opted out by physicians
  - At this HMO, the protocol required active consent by physicians. Children whose primary care physicians did not respond to the request for consent were opted-out.

Analyses of exposure levels of opted-out cases and controls provided no evidence of bias of exposure levels due to physician-opt outs:

- There were no significant differences in exposure levels between opted-out cases and opted-out controls.
- Physcians did not opt-out children with higher exposure. For three of four exposure measures, there were no significant differences between the exposure levels of opted-out children and children that were not opted out.
  - For exposure birth to one month, opted-out children had lower average exposure levels than children that were not opted-out ($p=0.049$)
- The cases-control differences for opted-out children did not differ significantly from the case-control differences of children that were not opted-out.
- If all of the opted-out children had been allowed to participate, and all had been found to be eligible and had participated, their inclusion in the participant group would have had very little effect on the case-control differences in exposure levels.
  - Estimates of the case-control differences in exposure amounts for the n=1,018 study participants were very close to estimates of the case-control differences for a group comprised of both study participants and opted out children.

13.1.2. Numbers of Cases and Controls that were Opted-out

The numbers of cases and controls that physicians opted-out of participation are shown by HMO, in Exhibit 13.1. In two of the three HMOs the number of opt-outs was very low

for both cases and controls. In two HMOs, the HMO's Internal Review Board (IRB) required only that the physician be notified and had the opportunity to decline participation for families, while 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.

Exhibit 13.1. Numbers of Case and Control Physcian Opt-outs, by HMO

HMO-A:

- Cases: 0 physician opt-outs out of 30 in sample
- Controls: 2 physician opt-outs out of 450 in sample (2/450 = 0.0044, i.e, 0.4 percent)

HMO-B:

- Cases: 29 physician opt-outs out of 303 in sample (29/303 = 0.09570, i.e., 10 percent)
  - (Note: an additional 8 were excluded in physician opt-out stage because they were identified as ineligible because the mothers did not speak English. 303-37=266 is the number of case IDs was sent to recruitment)
- Controls: 167 physician opt-outs out of 1887 in sample (167/1887 = 0.0885, i.e., 9 percent)
  - (Note: an additional 124 were excluded in physician opt-out stage because they were identified as ineligible because the mothers did not speak English.

HMO-C:

- Cases: 2 physician opt-outs out of 477 in sample (2/477 = 0.0042, i.e., 0.4 percent)
- Controls: 5 physician opt-outs out of 1351 in sample (5/1351 = 0.0037, i.e., 0.4 percent)

13.1.3. Exposure Levels of Opted-out Cases and Controls

The results presented in this section are from analyses that were conducted to answer the following four questions:

1. Were the exposure levels of opted-out cases different than the exposure levels of opted-out controls?
2. Were exposure levels of opted-out children (both cases and controls) different than the exposure levels of children that were not opted out (both cases and controls)?
3. Was the case-control difference in exposure for opted-out children different than the case-control difference in exposure among children that were not opted-out?
4. If there had been no physician opt-outs, and all of the children that were opted-out had been found to be eligible, and all had participated, how would their inclusion in the participant group have affected the case-control difference in exposure measures for the participant group?

Methods and Results for Question 1

To address the first question, we used the computer automated vaccination records that were maintained as part of the Vaccine Safety Datalink system (VSD data) to calculate cumulative ethylmercury exposure amounts for the for the 205 physician opt-out children

(31 cases and 174 controls). The VSD vaccination data was cleaned and coded, and ethylmercury exposure amounts were assigned to each vaccine receipt in a manner similar to that described in Chapter 7. However, unlike the process described in Chapter 7, where the final "resolved vaccine histories" for study participants were obtained from both VSD and medical chart abstracted vaccination records, the analyses described in the current chapter are based on data from the VSD source only. We did not abstract medical record charts for the study non-participants. Using the VSD data source, we calculated the following four exposure measures:

$Amt07mos_{VSD}$	=	Cumulative amount of ethylmercury from vaccines and immune globulins received during the age range spanning birth to seven months (1 – 214 days), calculated using VSD data.
$Amt01mos_{VSD}$	=	Cumulative amount of ethylmercury from vaccines and immune globulins received during the age range spanning birth to one month (1 – 28 days), calculated using VSD data.
$Amt17mos_{VSD}$	=	Cumulative amount of ethylmercury from vaccines and immune globulins received during the age range spanning one to seven months (29 – 214 days), calculated using VSD data.
$Amt020mos_{VSD}$	=	Cumulative amount of ethylmercury from vaccines and immune globulins received during the age range spanning birth to 20 months (1 – 609 days), calculated using VSD data.

We then estimated the case-control difference in exposure amount in models that controlled for birth year by sex by HMO matching strata. The models were of the form:

$$Amt07mos_{VSD} = \beta_0 + \beta_1(ASD) + \sum_{m}^{M-1} \beta_{1+m}(MatchingStratum_m) + \varepsilon$$

ASD = an indicator of case control status. Note that *ASD =1* if selected as a case in the sampling phase, and =0 if selected as part of the control sample. This case/control status indicator comes from medical records, and was not verified via clinical assessment as was done for the study participants used in the main analyses.

$MatchingStratum_m$ = 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 exposure amount, 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:

$$\hat{Y}_{Case} = \hat{\beta}_0 + \hat{\beta}_1(1) + \sum_{m}^{M-1} \hat{\beta}_{1+m}(mean(MatchingStratum_m)),$$

where *mean(MatchingStratum$_m$)* is the proportion of the sample that is in the m^{th} matching stratum.

The least squares mean for the control group is obtained as:

$$\hat{Y}_{Control} = \hat{\beta}_0 + \hat{\beta}_1(0) + \sum_{m}^{M-1} \hat{\beta}_{1+m}(mean(MatchingStratum_m))$$

The results summarized in Exhibit 13.2 indicate that there were no significant differences between opted-out cases and opted-out controls for any of exposure measures.

Exhibit 13.2.
Summary of Model Results to Estimate Case / Control Differences in Cumulative Exposure Measures for Physician Opt-Out Children, Using VSD Data

	Number			Case - Control Difference			Least Squares	
	of Records			Difference		$H_0 : \beta_1 = 0$	Means	
Exposure Measure	Total	Case	Control	$\hat{\beta}_1$	S.E.	p-value	Case	Control
$Amt07mos_{VSD}$	205	31	174	1.06	6.14	0.86	106.9	105.8
$Amt01mos_{VSD}$	205	31	174	-0.032	1.40	0.82	7.0	7.3
$Amt17mos_{VSD}$	205	31	174	1.38	6.19	0.82	99.9	98.5
$Amt020mos_{VSD}$	205	31	174	7.51	6.60	0.26	146.3	138.8

Methods and Results for Question 2

> Question 2: Were exposure levels of opted-out children (both cases and controls) different than the exposure levels of children that were not opted out (both cases and controls)?

To address Question 2, we used VSD data to calculate cumulative exposure amounts for the originally selected sample members that where not opted-out by physicians. The not-opted-out group included children that participated in the study and children that did not participate in the study. We excluded from this not-opted-out group any children who

were known to be ineligible[6]. For the purpose of comparison, we included in the not-opted-out group only the children that were matched to opted-out children on matching strata. For example, we retained not-opted-out children in analysis from the stratum 1994 females from HMO-B because there were opted-out children from that stratum. We omitted from the analysis the not-opted-out children from the stratum 1999 females from HMO-A because there were no opted-out children from that stratum. Using these criteria, the analysis was based on the exposure amounts of 205 opted-out children and 1793 not-opted-out children.

We estimated differences in exposure between opted-out and not-opted-out using models of the following form:

$$Amt07mos_{VSD} = \beta_0 + \beta_1(OptOut) + \beta_2(ASD) + \sum_{m}^{M-1} \beta_{2+m}(MatchingStratum_m) + \varepsilon$$

OptOut = 1 if child was opted-out, = 0 if not opted-out.

And other terms are as described previously.

$\hat{\beta}_1$ = the OLS estimate of the difference in exposure amount between opted-outs and not-opted-out children, controlling for ASD status and matching strata.

The results shown in Exhibit 13.3 show that for three of the four exposure measures, there were no significant differences between exposure levels of opted-out and not-opted out children. The results do indicate that opted-out children had lower average cumulative exposures in the the first month of life, than children that were not opted-out.

[6] In the recruitment process, many children were found to be ineligible during either the recruitment or eligibility call (see Chapter 5 for details). The passive non-participants and unlocated families will have also included some ineligibles, but they are impossible to identify and exclude.

Exhibit 13.3.
Summary of Model Results to Estimate Differences Between Opted-out and Not-opted-out Children in Cumulative Exposure Measures, Using VSD Data

	Number			Opt-Out Difference			Least Squares	
	of Records			Difference		$H_0 : \beta_1 = 0$	Means	
Exposure Measure	Total	Opted-out	Not-Opted-Out	$\hat{\beta}_1$	S.E.	p-value	Opt-out	Not-Opt-Out
$Amt07mos_{VSD}$	1998	205	1793	-1.48	2.08	0.48	106.1	107.6
$Amt01mos_{VSD}$	1998	205	1793	-0.94	0.48	0.049 *	7.49	8.43
$Amt17mos_{VSD}$	1998	205	1793	-0.51	2.04	0.80	98.6	99.1
$Amt020mos_{VSD}$	1998	205	1793	-0.52	2.32	0.82	141.3	141.8

Methods and Results for Question 3

> Question 3: Was the case-control difference in exposure for opted-out children different than the case-control difference in exposure among children that were not opted-out?

To address Question 3, we used the same data set as was used for Question 2, but fit models to test for an interaction between physician opt-out and case-control status. The models were of the following form:

$$Amt07mos_{VSD} = \beta_0 + \beta_1(OptOut) + \beta_2(ASD) + \beta_3(OptOut * ASD) + \sum_{m}^{M-1} \beta_{2+m}(MatchingStratum_m) + \varepsilon$$

where the test $H_0 : \beta_3 = 0 \; vs. \; H_a : \beta_3 \neq 0$ is a test of whether the case-control difference for physician opt-out children is different than the case-control difference among children that were not opted-out.

Results are summarized in Exhibit 13.4. None of the tests for interaction effects were statistically significant.

Exhibit 13.4.
Summary of Model Results to Test for Interaction Between Physician Opt-out and ASD Status on Exposure Measures, Using VSD Data

		Number of Records			Interaction Test p-value for Test	Least Squares Means	
Exposure Measure	Group	Total	Case	Control	$H_0 : \beta_3 = 0 \; vs. \; H_a : \beta_3 \neq 0$	Case	Control
$Amt07mos_{VSD}$	Opted-Out	205	31	174	0.80	107.0	106.4
	Not-Opted-Out	1793	412	1381		106.7	108.1
$Amt01mos_{VSD}$	Opted-Out	205	31	174	0.67	7.3	7.3
	Not-Opted-Out	1793	412	1381		8.7	8.2
$Amt17mos_{VSD}$	Opted-Out	205	31	174	0.71	99.4	99.1
	Not-Opted-Out	1793	412	1381		98.2	99.9
$Amt020mos_{VSD}$	Opted-Out	205	31	174	0.24	146.1	141.2
	Not-Opted-Out	1793	412	1381		140.5	142.8

Note that since the least squares means are model-estimated means which are dependent on the independent variables used in the regression equation, it is expected that the least square means for opted-out cases and controls will not be exactly the same as the least squares means for opted-out cases and controls shown in Exhibit 13.2.

Methods and Results for Question 4

> Question 4: If there had been no physician opt-outs, and all of the children that were opted-out had been found to be eligible, and all had participated, how would their inclusion in the participant group have affected the case-control difference in exposure measures for the participant group?

This question asks whether physician opt-outs biased the estimates of case-control differences in exposure levels. That is, how would the mean exposure level change if all physician opt-outs had participated? To answer this question, we used VSD data to estimate the case-control difference in exposure levels for the 1,018 study participants, and the calculated the same estimates using data from the group of 1,223 children that are obtained by combining the records of the 1,018 participants with the 205 physician opt-out children. For each data set, case-control differences and least-squares means were estimated using models of the form:

$$Amt07mos_{VSD} = \beta_0 + \beta_1(ASD) + \sum_{m}^{M-1} \beta_{1+m}(MatchingStratum_m) + \varepsilon$$

For each exposure measure Exhibit 13.5 shows the estimated case-control difference in average exposure of the 1,018 study participants, and the estimated case-control difference for the group that would have been obtained if all of the physcian opt-outs had been allowed to participate, and all did participate. Each pair of estimates is very close to one another. For example, for birth to seven months exposure, the case-control difference for participants was 1.67 micrograms of ethylmercury, while the estimate for the combined participant plus opt-out group was 1.68 micrograms. The 95 percent confidence interval for the first group spans the estimate of the second group, and likewise the 95 percent confidence interval for the second group spans the estimate for the first group. Differences between the two groups on each measure were small and the 95 percent confidence intervals for each group spanned the estimate for the other group. These results suggest that physician opt-outs resulted in little, if any, bias in the exposure levels of cases and controls.

Exhibit 13.5.
Summary of Model Results to Estimate Case / Control Difference in Study Participants and in Group that Includes Both Study Participants and Physcian Opt-outs, Using VSD Data

		Number			Case / Control Difference				Least Squares	
		of Records			Difference		$H_0 : \beta_1 = 0$	95%	Means	
Exposure Measure	Data Set	Total	Case	Control	$\hat{\beta}_1$	S.E.	p-value	Confidence Interval	Case	Control
$Amt07mos_{VSD}$	Participants	1,018	256	762	-1.67	1.82	0.36	(-5.23, 1.90)	114.4	116.1
	Participants + Opt-outs	1,223	287	936	-1.68	1.75	0.34	(-5.11, 1.75)	114.4	116.1
$Amt01mos_{VSD}$	Participants	1,018	256	762	-0.18	0.41	0.67	(-0.98, 0.63)	9.59	9.76
	Participants + Opt-outs	1,223	287	936	-0.09	0.40	0.83	(-0.87, 0.69)	9.69	9.78
$Amt17mos_{VSD}$	Participants	1,018	256	762	-1.49	1.75	0.39	(-4.92, 1.94)	104.8	106.3
	Participants + Opt-outs	1,223	287	936	-1.60	1.70	0.35	(-4.93, 1.73)	104.7	106.3
$Amt020mos_{VSD}$	Participants	1,018	256	762	-1.87	1.99	0.35	(-5.78, 2.03)	153.21	155.09
	Participants + Opt-outs	1,223	287	936	-1.29	1.92	0.50	(-5.05, 2.47)	153.5	154.8

14. Analyses to Assess Potential Self-selection Bias

The results in Chapter 9 indicated that for some of the exposure measures, higher exposure was associated with decreased risk of ASD outcomes. This means that on average, the covariate adjusted mean exposure levels for the ASD cases were lower than the covariate adjusted mean exposure levels of their matched control counterparts. This finding motivates the question as to why controls would have higher exposure levels than cases. At the meeting on May 29th, 2008, where preliminary results of first round analyses were presented to the Study Principal Investigators and the External Expert Consultants, a hypothesis was generated that posited that selection bias could be a factor.

Selection bias could have affected the results if the relationship between the decision to participate and exposure was different for cases and controls. For example, if controls that chose to participate in the study had systematically higher exposure levels than non-participants, then the case-control difference in mean exposure levels would be biased towards higher exposure for controls. Likewise, if the cases that chose to participate had systematically lower exposure levels than non-participants, than the case-control difference in mean exposure levels would be biased towards higher exposure for controls.

It is common to approach the issue by considering whether exposure differs between participants and non-participants. While we conducted and report on results from this approach, and believe the results to be informative, we note that the difference between participants and non-participants is, by itself, not a measure of bias. Non-participants could be very different that participants, but if the participation rate is high, bias will be low. That is, estimates from the participant group will still be very similar to estimates from the full sample. Alternatively, the participation rate could be low, but if the difference between participants and non-participants is also low, there would again be low bias.

To estimate bias, we compared results from the participant sample to results from full sample (i.e. the full group that includes both participants and non-participants). Bias, by definition, is the difference between an estimate and the true population parameter. The random sampling process used to draw the sample from the sampling frame ensures that the sampled individuals within each birth year by sex by HMO stratum are representative of the populations within each stratum. If everyone participated, (i.e., if there were zero non-participants), our parameter estimates would come from the full sample, and we know that these would be unbiased estimates of true population parameters[7]. Therefore, in this chapter we create measures of bias that are measures of the difference between estimates obtained from the participant group and estimates obtained from the full sample.

In Section 14.1 we describe the preparation of Vaccine Safety Datalink system (VSD) data, which was available for both participants and non-participants, to investigate the selection bias. In Section 14.2 we described the statistical models and results for analyses of potential self selection bias. We focus on the case-control exposure difference in participants, as compared to the case-

[7] The full sample is representative of a population defined by HMO membership, birth year criteria, and other eligibility criteria defined in Chapter 5.

control exposure difference in the full sample. The results from the full sample are very similar to those of the participant sample, which suggests that self-selection bias was not a potent force affecting the results.

In Section 14.3 we explore whether exposure amounts differed between participants and non-participants. Specifically, we test whether the mean ethylmercury exposure amounts varied among the four groups defined as participant cases, non-participant cases, participant controls, and non-participant controls. The results indicate no significant variation among the four groups. We also estimated the differences in mean exposure levels between participant and non-particpant cases, and between participant and non-participant controls. There were no significant differences for these contrasts. These results support those reported in Section 14.2, suggesting that self-selection did not have a substantial impact on the results.

14.1. Data Preparation

The VSD vaccination data was cleaned and coded, and ethylmercury exposure amounts were assigned to each vaccine receipt in a manner similar to that described in Chapter 7. However, unlike the process described in Chapter 7, where the final "resolved vaccine histories" for study participants were obtained from both VSD and medical chart abstracted vaccination records, the analyses described in the current chapter are based on data from the VSD source only. We did not abstract medical record charts for the study non-participants. In order to make the measures of exposure amounts comparable for participants and non-participants, for the current analyses we calculated exposure amounts even for the study participants using only the VSD data.

Note that for the current analyses, the exposure measures are cumulative ethylmercury exposure amounts. There was no division by weight at time of vaccine receipt for these measures. Weight at the time of vaccine receipt was not available on the VSD data set used for these analyses. The weight data used in the main analyses shown in Chapter 9 were obtained from medical chart abstraction.

In our comparisons of study participants to the full sample, we excluded from both groups all individuals that were known to be ineligible. In the participant group, we included n=256 confirmed ASD cases and the n=762 eligible controls (total n = 1,018). The full sample group includes both participants and non-participants. The non-participant group is comprised of active refusers, passive refusers or unlocatables, and individuals that were sampled as ASD cases, but who did not meet study criteria for ASD, or did not complete the clinical assessments. The numbers in each group are shown in Exhibit 14.1. The full sample group had a total sample size of 3,100, including 668 cases and 2,432 controls.

Exhibit 14.2 shows a comparison of the VSD only exposure amounts, to the "resolved vaccine history" exposure amounts for the 1,083 eligible study participants that had both types of measures[8]. The means of the exposure measures calculated from the VSD only data were lower than those from the resolved vaccine histories. Paired t-tests for the differences between VSD

[8] The 1,083 includes 774 controls that completed parent interview, minus 12 that were found to be ineligible during analysis of parent interview data, plus 256 ASD confirmed cases, plus 65 that were below criteria for ASD.

only and resolved vaccine histories data were significant for each of the measures. One way to assess the magnitude of the difference between the VSD only and the resolved measures is to express the difference as a proportion of a standard deviation unit of the measure. Expressed in this manner, the differences appear to be very small, only 2 to 3 percent of a standard deviation unit. Furthermore, the correlation between the VSD only and the resolved vaccine history measure of exposure was quite high for each of the measures, ranging from 0.96 to 0.98. We conclude from these comparisons that while there is some measurement error in the VSD only data, that the VSD only data are well aligned with the more accurate measures that used both VSD and chart abstraction sources of information and will therefore be suitable for use in the analyses that follow.

Exhibit 14.1 Recruitment and Assessment Outcomes

		Case		Control	
Recruitment Outcome	**Assessment Outcome**	**n**	**%**	**n**	**%**
Ineligible		103	13.4	316	11.5
Unlocated, Passive Refusal		27	3.5	467	16.9
Refused		255	33.1	1,203	43.6
Completed Parent Interview	**ASD Case Confirmed**	**256**	**33.2**	**774[a]**	**28.0**
	Below Criteria	**65**	**8.4**		
	Clinical assessment not completed	**65**	**8.4**		
Total		771	100.0	2,760	100.0

	Case	**Control**	**Total**
Full Sample Group = Total Excluding Known Ineligibles[b]	668	2,432	3,100

[a] Includes 12 that completed parent interview but that were subsequently found to be ineligible using information from parent interview.

[b] This total excludes *known* ineligibles. The "unlocated / passive refusal" group and the "refused" group contain an unknown number of ineligibles. Since most other members of these groups never completed an eligibility interview, and none completed the parent interview, their eligibility status could not be confirmed in the same manner that it was for the study participants, or for those that completed the eligibility interview but who were found to be ineligible.

Exhibit 14.2 Comparison of VSD Exposure Amount to Exposure Amounts in Resolved Vaccine History

Exposure Measure	VSD Mean	Resolved[a] Mean	Difference VSD-Resolved[a] Mean	Paired T-test p-value	Resolved[a] Standard Deviation	Difference as proportion of Standard Deviation	Correlation Between Resolved[a] and VSD
Amt07mos	101.98	102.85	-0.88	0.0008	42.17	-0.02	0.98
Amt01mos	8.85	9.04	-0.20	0.0007	6.49	-0.03	0.96
Amt17mos	93.13	93.81	-0.68	0.0045	40.94	-0.02	0.98
Amt020mos	134.84	136.04	-1.20	0.0004	54.90	-0.02	0.98

Means, differences, and correlations for n=1,083 eligible participant cases and controls.

[a] Exposure amounts from "resolved vaccine histories" based on both VSD and chart abstracted data. See Chapter 7 for details.

14.2. Comparison Between Study Participants and Entire Sample on Case/Control Difference in Expososure

14.2.1. Analysis Model

In this section we describe the analysis model used to estimate the case - control difference in cumulative exposure for the age range spanning birth to seven months. Models of the same form were also used to estimate case - control differences for cumulative exposures birth to 1 month, and birth to 20 months. The form of the model was identical whether the model was fit to data from the n=1,018 participants or the n=3,100 in the full sample group.

The analytic model used to estimate the case - control difference was an ordinary least squares (OLS) regression model of the form:

$$Amt07mos_{VSD} = \beta_0 + \beta_1(ASD) + \sum_{m}^{M-1} \beta_{1+m}(MatchingStratum_m) + \varepsilon$$

where

$Amt07mos_{VSD}$ = cumulative amount of ethylmercury from vaccines and immune globulins received by the child during the age range spanning birth to seven months (1 – 214 days), calculated using VSD data.

ASD = an indicator of case control status. For the analysis based on study participants, *ASD =1* if confirmed case, and =0 if matched control; For analysis based on the full sample, *ASD =1* if selected as a case in the sampling phase, and =0 if selected as part of the control sample (known ineligibles were excluded from case and control groups).

$MatchingStratum_m$ = 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 exposure amount, 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:

$$\hat{Y}_{Case} = \hat{\beta}_0 + \hat{\beta}_1(1) + \sum_{m}^{M-1} \hat{\beta}_{1+m}(mean(MatchingStratum_m)),$$

where *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:

$$\hat{Y}_{Control} = \hat{\beta}_0 + \hat{\beta}_1(0) + \sum_{m}^{M-1} \hat{\beta}_{1+m}(mean(MatchingStratum_m))$$

14.2.2. Results

For the study participants, including confirmed cases and their matched control counterparts, the estimated case - control difference in cumulative exposure from birth to seven months, controlling for matching strata, was -1.67 micrograms of ethylmercury (Exhibit 14.3). This estimate indicates that cases had slightly lower exposure than their control counterparts. Noting that most of the vaccinations received by the sample children during the age range of one to seven months contained 0, 12.5, or 25 micrograms of ethylmercury, we note that the difference of -1.67 micrograms corresponds to around one seventh of the amount of ethylmercury contained in a single 12.5 microgram-containing vaccine. In statistical terms, the -1.67 microgram case-control difference was not significantly different than zero.

The case - control difference estimated from the full selected sample was -0.77 micrograms. Again, this estimate indicates that for the full selected sample, cases had lower mean exposure amounts than controls, but in statistical terms, this difference was not significantly different than zero.

An estimate of the self-selection bias can be obtained as the difference of the case-control differences from the participant and full samples. The difference between the two case-control difference estimates was 0.9 micrograms.

The difference between the participant group and full sample estimates of the case-control difference is in a direction that supports the hypothesis that selection bias may have contributed to the participant group difference between cases and controls in mean cumulative exposure birth to seven months. However, in both the participant and full samples, cases had slightly lower mean exposure levels than controls, in neither sample was the case control difference significantly different than zero, and the difference between the case-control differences in the participant and full sample is so small that we must conclude that any effect of selection bias is very small. The following points may be relevant in interpreting these results:

- The 95 percent confidence interval for the case-control difference ($\hat{\beta}_1$) for the participant group includes the estimate from the full sample.
- The 95 percent confidence interval for the case-control difference ($\hat{\beta}_1$) for the full sample group includes the estimate from the participant group.
- This size of the bias estimate (0.9 micrograms) is very small relative to a standard deviation unit of the measure of cumulative exposure from birth to 7 months (sd = 42.22). The bias estimate is only two percent of the size of the standard deviation of the measure (0.9 / 42.22 = 0.02).

Similar results were obtained for measures of cumulative exposure birth to one month, and birth to 20 months. For both measures, the estimated case-control differences in exposure amounts for

participants were very close to those of the the full sample, and none were significantly different than zero. In both sets of analyses the 95 percent confidence interval for the case-control difference for the participant group included the estimate from the full sample, and the 95 percent confidence interval for the full sample included the estimate from the participant sample (Exhibits 14.4 and 14.5) suggesting no evidence of differences in the underlying paramters being estimated. The sizes of the bias estimates (.53 micrograms, and 0.83 micrograms for measures *Amt01mos* and *Amt020mos*¸ respectively) were small when expressed as either a proportion of mercury contained in a single 12.5 microgram-containing vaccine, (about one twenty-fifth, and one fifteenth of a single shot, respectively) or as a percent of a standard deviation unit (8% and 1.5% for measures *Amt01mos* and *Amt020mos*¸ respectively).

In summary, the results for case-control differences were generally consistent with the selection bias hypotheses in that the differences were smaller in the full sample group than in the participant group[9]. But, all differences were very small. And estimates from from the full sample, like the participant sample, indicated that cases had lower mean exposure levels than controls for periods birth to 7 months and birth to 20 months, although in neither group were the case-control differences significantly different than zero. The participant group and full sample group estimates of case-control differences were very similar to one another and there was a very high degree of overlap of the 95 percent confidence intervals from both sets of estimates. The differences between mean exposure levels of participants when estimated from VSD data versus estimates from the resolved vaccine histories (Exhibit 14.2) caution us to keep in mind that measurement error in the VSD data may have muddied the picture somewhat. However, in total the evidence presented here suggests that any effects of selection bias were very small and that selection bias by itself was not large enough to have caused the unexpected findings which indicated that greater exposure levels were associated with lower risk of ASDs.

[9] For exposures birth to one month, the absolute value of the difference was not smaller, but the direction of the effect was consistent with the hypothesis.

Exhibit 14.3.
Summary of Model Results to Estimate Case - Control Difference in *Amt07mos* Measure for Study Participants and Full Selected Sample, Using VSD Data

	Number			Case - Control Difference				Least Squares	
	of Records			Difference		$H_0 : \beta_1 = 0$	95%	Means	
Data Set	Total	Case	Control	$\hat{\beta}_1$	S.E.	p-value	Confidence Interval	Case	Control
Participants	1,018	256	762	-1.67	1.82	0.36	(-5.23, 1.90)	114.4	116.1
Full Sample	3,100	668	2,432	-0.77	1.15	0.50	(-3.02, 1.50)	114.0	114.8

Exhibit 14.4.
Summary of Model Results to Estimate Case - Control Difference in *Amt01mos* Measure for Study Participants and Full Selected Sample, Using VSD Data

	Number			Case - Control Difference				Least Squares	
	of Records			Difference		$H_0 : \beta_1 = 0$	95%	Means	
Data Set	Total	Case	Control	$\hat{\beta}_1$	S.E.	p-value	Confidence Interval	Case	Control
Participants	1,018	256	762	-0.18	0.41	0.67	(-0.98, 0.63)	9.59	9.76
Full Sample	3,100	668	2,432	0.35	0.24	0.15	(-0.12, 0.81)	10.07	9.72

Exhibit 14.5.
Summary of Model Results to Estimate Case - Control Difference in *Amt020mos* Measure for Study Participants and Full Selected Sample, Using VSD Data

	Number			Case - Control Difference				Least Squares	
	of Records			Difference		$H_0 : \beta_1 = 0$	95%	Means	
Data Set	Total	Case	Control	$\hat{\beta}_1$	S.E.	p-value	Confidence Interval	Case	Control
Participants	1,018	256	762	-1.87	1.99	0.35	(-5.78, 2.03)	153.21	155.09
Full Sample	3,100	668	2,432	-1.04	1.27	0.41	(-3.53, 1.44)	151.02	152.07

14.3. Comparison of Mean Exposure Amounts Among Participant and Non-Participant Cases and Controls

14.3.1. Analysis Model

In this section we describe the analysis model used to test whether there was variation in exposure amounts among participant cases, non-participant cases, participant controls, and non-participant controls. The model shown corresponds to mean cumulative exposure for the age range spanning birth to seven months. Models of the same form were also used to estimate cases control differences for cumulative exposures birth to 1 month, and birth to 20 months.

The analytic model used to estimate the case - control difference was an ordinary least squares (OLS) regression model of the form:

$$Amt07mos_{VSD} = \beta_0 + \beta_1(NonPar.Case) + \beta_2(NonPar.Cntrl) + \beta_3(Par.Case) + \sum_{m}^{M-1} \beta_{3+m}(MatchingStratum_m) + \varepsilon$$

where

$Amt07mos_{VSD}$ = cumulative amount of ethylmercury from vaccines and immune globulins received during the age range spanning birth to seven months (1 – 214 days), calculated using VSD data.

$NonPar.Case$ = 1 if individual was sampled as a case, but not included in the analysis data set because (s)he was unlocated, refused, did not meet study criteria for ASD, or the clinical assessment was not completed (n=412)
= 0 otherwise

$NonPar.Cntrl$ = 1 if individual was sampled as a control, but not included in the analysis data set because (s)he was unlocated, or refused (n=1670)
= 0 otherwise

$Par.Case$ = 1 if individual was sampled as a case and fully participated in the study and met study criteria for ASD (n=256)
= 0 otherwise

$Par.Cntrl$ = 1 if individual was sampled as a control and fully participated in the study (n=762) [This group was the omitted reference group in the model]
= 0 otherwise

$MatchingStratum_m$ = 1 if individual belongs to m^{th} matching stratum, =0 else. Matching strata are defined by birth year, sex, and HMO.

A three degree of freedom F-test was conducted of the null hypothesis of no variation in exposure amount amount the four groups. The test was of the form

$$H_0: \begin{bmatrix} \beta_1 \\ \beta_2 \\ \beta_3 \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ 0 \end{bmatrix} \quad vs. \quad H_a: \begin{bmatrix} \beta_1 \\ \beta_2 \\ \beta_3 \end{bmatrix} \neq \begin{bmatrix} 0 \\ 0 \\ 0 \end{bmatrix}$$

Additionally, we used model results to estimate differences between non-participant and participant cases, and differences between non-participant and participant controls. For each contrast a t-test of the null hypothesis of zero difference between groups was conducted.

Difference	Estimate	Test
NonPar.Case - *Par .Case*	$\hat{\beta}_1 - \hat{\beta}_3$	$H_0: (\beta_1 - \beta_3) = 0 \quad vs. \quad H_a: (\beta_1 - \beta_3) \neq 0$
NonPar.Cntrl - *Par.Cntrl*	$\hat{\beta}_2$	$H_0: \beta_2 = 0 \quad vs. \quad H_a: \beta_2 \neq 0$

14.3.2. Results

The results summarized in Exhibits 14.6-14.11 show that there were no significant differences in cumulative exposure amounts for the periods spanning birth to one month, birth to 7 months, or birth to 20 months, among participant and non-participant cases and controls. Likewise, the pair-wise contrasts between participant and non-participant cases and between participant and non-participant controls showed no significant differences in cumulative exposure amounts.

Exhibit 14.6.
Cumulative Exposure Birth to 7 Months:
F-test for Variation Among Participant Cases, Non-participant Cases, Participant Controls, and Non-Participant Controls

Source	DF	Type III SS	Mean Square	F Value	Pr > F
Group	3	1087.6	362.5	0.54	0.658

Exhibit 14.7
Cumulative Exposure Birth to 7 Months:
Contrasts of Non-Participant to Participant Cases and Non-Participant to Participant Controls and

Contrast	Estimate	Standard Error	t Value	Pr > |t|
NonPar.Case - *Par .Case*	0.07	2.09	0.03	0.975
NonPar.Cntrl - *Par.Cntrl*	-1.26	1.18	-1.07	0.283

Exhibit 14.8.
Cumulative Exposure Birth to One Month:
F-test for Variation Among Participant Cases, Non-participant Cases, Participant Controls, and Non-Participant Controls

Source	DF	Type III SS	Mean Square	F Value	Pr > F
Group	3	135.1	45.0	1.54	0.201

Exhibit 14.9.
Cumulative Exposure Birth to One Month:
Contrasts of Non-Participant to Participant Cases and Non-Participant to Participant Controls and

Contrast	Estimate	Standard Error	t Value	Pr > |t|
NonPar.Case - Par .Case	0.56	0.43	1.3	0.194
NonPar.Cntrl - Par.Cntrl	-0.22	0.24	-0.91	0.365

Exhibit 14.10
Cumulative Exposure Birth to 20 Months:
F-test for Variation Among Participant Cases, Non-participant Cases, Participant Controls, and Non-Participant Controls

Source	DF	Type III SS	Mean Square	F Value	Pr > F
Group	3	2406.335	802.112	0.97	0.4059

Exhibit 14.11
Cumulative Exposure Birth to 20 Months:
Contrasts of Non-Participant to Participant Cases and Non-Participant to Participant Controls and

Contrast	Estimate	Standard Error	t Value	Pr > |t|
NonPar.Case - Par .Case	-0.99	2.31	-0.43	0.669
NonPar.Cntrl - Par.Cntrl	-1.87	1.30	-1.43	0.152

15. Effects of Having an Older Autistic Sibling

15.1. Introduction

The results in Chapter 9 indicated that for some of the exposure measures, higher exposure was associated with decreased risk of ASD outcomes. This means that on average, the covariate adjusted mean exposure levels for the AD and ASD cases were lower than the covariate adjusted mean exposure levels of their matched control counterparts. This finding motivates the question as to why controls would have higher exposure levels than cases. In this chapter, we present the results of analyses 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.

To explore this hypothesis as a potential explanation for the observed (slightly) lower exposure levels in cases, relative to controls, we conducted the following steps:

- We used parent interview data to identify cases and controls that had older siblings that had ever been diagnosed with autism;
- We looked at the relationship between having an older autistic sibling and measures of postnatal exposure;
- Since there was some weak evidence that children with autistic older siblings had lower average exposure on some of the exposure measures, we made two modifications of the analysis models used to estimate the associations between exposure and autism risk: In the first, we added an indicator variable for whether the child had an older sibling with autism; In the second, we omitted from the analysis all all cases and controls that had an autisitic older sibling.

15.1.1. Summary of Results

The results of analyses presented in this section can be summarized as follows:

- Although for each exposure measure, the mean levels were slightly lower for children with autistic older siblings than for children that did not have autistic older siblings, the differences did not meet the study criterion for statistical significance ($p<0.05$) for any of the measures.
- The addition of a covariate indicator for having an older autistic sibling to the models used to estimate the relationships of exposure measures to autism risk had very little effect on the estimates.
- The exclusion of cases and controls that had an older autistic sibling from models used to estimate the relationships of exposure measures to autism risk had very little effect on the estimates.

The sections that follow describe the analyses and the results in detail.

15.2. Cases and Controls with Autistic Older Siblings

We first needed to identify cases and controls that had older siblings with autism. Two sets of questions in parent interview were used. In the parent interview, the respondents were asked about whether any of their children (other than the focus child) had ever been diagnosed with autism. The interview started from the oldest child, followed by the next oldest child, and so on, skipping the focus child. Answers to this set of questions revealed that 59 focus children (including both cases and controls) had autistic siblings, either older or younger.

Next we compared the birth order of each focus child to that of his/her autistic sibling(s) to determine whether the focus child was younger than his/her autistic sibling(s). At the beginning of the parent interview, the respondents were asked about the names of their children, from the oldest to the youngest, and where the focus child fell in this list. We compared the birth order of the focus child to that of his/her autistic sibling(s).

The comparison indicated that 39 focus children had autistic older siblings, among them 17 were controls, and 22 were cases (15 were cases who met the criteria of ASD classification, and 7 were cases who did not meet the criteria for ASD classification). Thus, as expected, a higher proportion of cases than controls had autistic older siblings (22 out of 321 cases, or 6.9%, vs. 17 out of 762 controls or 2.2 percent).

Next, we explored the relationship between having an older autistic sibling and measures of postnatal exposure.

15.3. Relationship of Exposure Amount to Indicator of Autistic Older Siblings

Models were fit to the data to address the following research questions: Did children with an older autistic sibling have lower postnatal exposure than those who had no older autistic siblings? Did the relationship between exposure and having an older autistic sibling differ for cases and controls?

In these models, the dependent variables were *Amt01mos, Amt07mos, Amt17mos,* and *Amt020mos*, instead of *Exp01mos*, *Exp07mos*, etc., that include child's weight as the time of vaccine receipt as part of the measures, because decisions about when and if to have a child vaccinated, and what type of vaccine to use have a direct effect on the "*Amt*" variables, but has a less direct effect on the "*Exp*" variables. For definations of these exposure variables, see Section 7.3.2. We define the independent variable *older_aut_sib*

as an indicator of whether or not the focus child had an autistic older sibling (1=yes; 0=no).

In order to understand the relationship of having an older autistic sibling to exposure amounts, and whether the relationship differs for cases and controls, we fit five models to each exposure amount variable. Model 1 was used to estimate the average difference in exposure amount between ASD cases and controls. Model 2 estimates the difference in exposure amounts between the focus children who had older autistic siblings and those that did not. Model 3 estimates the case-control exposure difference in a model that has a term to adjust for having an older autistic sibling. Model 4 includes an interaction term to test for whether the effect of having an older autistic sibling on cumulative exposure amount differs for cases and controls. And finally, Model 5 is exactly like Model 1, except that all children that had autistic older siblings are omitted from the analysis. Thus, Model 5 produces an estimate of the case control exposure difference among cases and controls that do not have an autistic older sibling.

Model specifications follow. Each was an ordinary least square regression model with dummy variables to represent matching strata, such that the model produces estimates of exposure amount differences, where the differences are agregated across the matching strata. Models 1-4 were fit to the same n=1,008 records for ASD cases and their matched controls that were used in the analyses reported in Chapter 9. Model 5 was fit to the subset of ASD cases and matched controls that did not have older autistic siblings (n=977).

Model 1:

$$Amt07mos = \beta_0 + \beta_1(ASD\_Outc) + \sum_{m}^{M-1} \beta_{1+m}(MatchingStratum_m) + \varepsilon$$

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

where

$Amt07mos$ [10]= cumulative amount of ethylmercury from vaccines and immune globulins received during the age range spanning birth to seven months (1 – 214 days), calculated using VSD data.

ASD_Outc = an indicator of case control status, $ASD = 1$ if confirmed case, and =0 if matched control.

$MatchingStratum_m$ = 1 if individual belongs to m^{th} matching stratum, =0 else. Matching strata are defined by birth year, sex, and HMO.

[10] *Amt07mos* is shown as an example dependent variable in the model specification. Models were also fit to the data where dependent variables were the meaures *Amt01mos, Amt17mos,* and *Amt020mos*.

$\hat{\beta}_1$ = the OLS estimate of the difference between ASD case and control childen in exposure amount, controlling for matching strata.

Model 2:

$$Amt07mos = \beta_0 + \beta_1(older\_aut\_sib) + \sum_m^{M-1} \beta_{1+m}(MatchingStratum_m) + \varepsilon$$

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

where,

older_aut_sib = an indicator of whether or not the focus child had an autistic older sibling (1=yes; 0=no).

$\hat{\beta}_1$ = the OLS estimate of the difference between childen that did and did not have an older autistic sibiling in exposure amount, controlling for matching strata.

Model 3:

$$Amt07mos = \beta_0 + \beta_1(ASD\_Outc) + \beta_2(older\_aut\_sib) + \sum_m^{M-1} \beta_{2+m}(MatchingStratum_m) + \varepsilon$$

$$H_0 : \beta_1 = 0 \quad vs \quad H_a : \beta_1 \neq 0$$
$$H_0 : \beta_2 = 0 \quad vs \quad H_a : \beta_2 \neq 0$$

$\hat{\beta}_1$ = the OLS estimate of the difference between ASD case and control childen in exposure amount, controlling for whether child had an older autistic sibling, and conrolling matching strata.

$\hat{\beta}_2$ = the OLS estimate of the difference between childen that did and did not have an older autistic sibiling in exposure amount, controlling for ASD case/control status, and matching strata.

Model 4:

To determine whether the relationship between exposure and having an older autistic sibling was different for cases and controls, we fit models of the form shown below:

$$Amt01mos = \beta_0 + \beta_1(older\_aut\_sib) + \beta_2(ASD\_Outc)$$
$$+ \beta_3(older\_aut\_sib * ASD\_Outc) + \sum_m^{M-1} \beta_{3+m}(MatchingStratum_m) + \varepsilon$$

$$H_0 : \beta_3 = 0 \quad vs \quad H_a : \beta_3 \neq 0$$

where,

$\hat{\beta}_3$ = an interaction term that is equal to the case-control difference in the effect of having an older autistic sibling on mean exposure amount.

Model 5:
Model 5 is exactly the same as Model 1, except that the model is fit to the subset of n=977 ASD case and control that did not have an older autistic sibling.

15.3.1. Model Results

The results of the five models described above, fit to data for each exposure variable, are summarized in Exhibit 15.3.1. Although the estimated effects of having an autistic older sibling were in the hypothesized direction for each of the exposure measures, none were statistically significant. That is, the estimates were in the direction of lower exposure for children with autistic older siblings (Model 2), and the effect of having autistic older siblings was in the direction of being a larger effect for ASD cases than for controls (Model 4), but none of the effects reached the 0.05 alpha criterion level for statistical significance. For cumulative exposure birth to 20 months, Model 2 results showed that children with autistic older siblings were estimated to have mean exposure levels that were 8.6 micrograms lower than those that did not have an older autistic sibling, but this p-value for this estimated difference was just above the study's 0.05 alpha level criterion (p=0.083).

Across exposure measures, the results of Model 1 show that, although ASD cases had lower estimated mean cumulative exposure amounts for all of the exposure amount measures, the case - control difference was not significantly different from zero for any of the measures. Comparing results of Models 3 and 5 to Model 1 suggests that controlling for having an older autistic sibling, or omitting records of children that had autistic older siblings, pushed the estimates of the case-control difference in exposure amounts closer to zero.

Exhibit 15.3.1. Model Summary: Autistic Older Siblings and Exposure Amount

Exposure Amount	Parameter	Estimate	S.E.	T	Pr>|t|
Amt01mos					
Model 1 (n=1,008)	ASD_Outc	-0.224	0.411	-0.55	0.586
Model 2 (n=1,008)	older_aut_sib	-1.702	1.038	-1.64	0.101
Model 3 (n=1,008)	ASD_Outc	-0.164	0.412	-0.40	0.691
	older_aut_sib	-1.664	1.043	-1.60	0.111
Model 4 (n=1,008)	ASD_Outc	-0.111	0.421	-0.26	0.791
	older_aut_sib	-1.063	1.434	-0.74	0.459
	older_aut_sib *ASD_Outc	-1.276	2.090	-0.61	0.542

Exhibit 15.3.1. Model Summary: Autistic Older Siblings and Exposure Amount

Exposure Amount	Parameter	Estimate	S.E.	T	Pr>|t|	
Model 5 (n=977) focus w/ older autistic sib omitted	ASD_Outc	-0.118	0.421	-0.28	0.7798	
Amt17mos						
Model 1 (n=1,008)	ASD_Outc	-2.200	1.731	-1.27	0.204	
Model 2 (n=1,008)	older_aut_sib	-3.980	4.378	-0.91	0.364	
Model 3 (n=1,008)	ASD_Outc	-2.074	1.738	-1.19	0.233	
	older_aut_sib	-3.502	4.396	-0.80	0.426	
Model 4 (n=1,008)	ASD_Outc	-1.774	1.776	-1.00	0.318	
	older_aut_sib	-0.080	6.045	-0.01	0.989	
	older_aut_sib *ASD_Outc	-7.267	8.812	-0.82	0.410	
Model 5 (n=977) focus w/ older autistic sib omitted	ASD_Outc	-1.786	1.783	-1.00	0.317	
Amt07mos						
Model 1 (n=1,008)	ASD_Outc	-2.424	1.790	-1.35	0.176	
Model 2 (n=1,008)	older_aut_sib	-5.682	4.527	-1.26	0.210	
Model 3 (n=1,008)	ASD_Outc	-2.238	1.797	-1.25	0.213	
	older_aut_sib	-5.166	4.545	-1.14	0.256	
Model 4 (n=1,008)	ASD_Outc	-1.885	1.836	-1.03	0.305	
	older_aut_sib	-1.144	6.249	-0.18	0.855	
	older_aut_sib *ASD_Outc	-8.543	9.109	-0.94	0.349	
Model 5 (n=977) focus w/ older autistic sib omitted	ASD_Outc	-1.904	1.843	-1.03	0.302	
Amt020mos						
Model 1 (n=1,008)	ASD_Outc	-2.456	1.973	-1.25	0.213	
Model 2 (n=1,008)	older_aut_sib	-8.639	4.984	-1.73	0.083	~
Model 3 (n=1,008)	ASD_Outc	-2.162	1.979	-1.09	0.275	
	older_aut_sib	-8.141	5.005	-1.63	0.104	
Model 4 (n=1,008)	ASD_Outc	-1.982	2.023	-0.98	0.327	
	older_aut_sib	-6.081	6.884	-0.88	0.377	
	older_aut_sib *ASD_Outc	-4.374	10.035	-0.44	0.663	
Model 5 (n=977) focus w/ older autistic sib omitted	ASD_Outc	-2.003	2.036	-0.98	0.326	

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

15.4. Estimates of Relationships of Exposure Measures to Case-Control Outcomes, Controlling for Older Autistic Siblings

Results presented in Chapter 9 show estimates of relationships of exposure measures to autism outcomes, controlling for matching strata and child and family characteristics. To find out whether having older autistic siblings has an effect on the estimated relationships between exposure and autism risk, we modified the models used in Chapter 9 by adding one more covariate: the indicator for older autistic siblings. The model results presented in this section have the same model specifications and used the same covariate sets as those used to produce results in Chapter 9 Exhibits 9.4.1, 9.4.2, and 9.4.3, the only difference being that in current section, the older autistic sibling indicator was added to the model as a covariate.

Comparison of Exhibits 15.4.1, 15.4.2 and 15.4.3 to Exhibits 9.4.1, 9.4.2, and 9.4.3, respectively, indicates that controlling for whether child has an older sibling with autism does not substantially affect the estimated associations between exposure measures and autism risk.

Exhibit 15.4.1. Model Summary: *PreNatThimer* and *Exp07mos* Exposure Models, Controlling for Older Autistic Sibling Variable

Outcome	N	Exposure Measure	Estimate	Stderr	Prob ChiSq		One Unit Chg. OR[a]	Lower 95% CL	Upper 95% CL	1/OR	2 SD Unit Chg. OR[b]	1/OR
ASD_Outc	1008	PreNatThimer	0.0067	0.0096	0.488		1.007	0.988	1.026	0.993	1.11	
ASD_Outc	1008	Exp07mos	-0.0324	0.0166	0.051	~	0.968	0.937	1.000	1.033	0.60	1.66
AD_Outc	911	PreNatThimer	0.0107	0.0108	0.322		1.011	0.990	1.032	0.989	1.19	
AD_Outc	911	Exp07mos	-0.0422	0.0189	0.025	*	0.959	0.924	0.995	1.043	0.52	1.93
ASD_Only	773	PreNatThimer	-0.0017	0.0200	0.934		0.998	0.960	1.038	1.002	0.97	1.03
ASD_Only	773	Exp07mos	-0.0247	0.0295	0.404		0.976	0.921	1.034	1.025	0.68	1.47
ASD_Regr	701	PreNatThimer	0.0401	0.0214	0.061	~	1.041	0.998	1.085	0.961	1.92	
ASD_Regr	701	Exp07mos	-0.1023	0.0343	0.003	**	0.903	0.844	0.966	1.108	0.20	4.92
AD_ExLoIQ	884	PreNatThimer	0.0152	0.0108	0.157		1.015	0.994	1.037	0.985	1.28	
AD_ExLoIQ	884	Exp07mos	-0.0544	0.0205	0.008	**	0.947	0.910	0.986	1.056	0.43	2.33
ASD_Scr	821	PreNatThimer	0.0049	0.0101	0.624		1.005	0.985	1.025	0.995	1.08	
ASD_Scr	821	Exp07mos	-0.0433	0.0187	0.021	*	0.958	0.923	0.993	1.044	0.51	1.96
AD_Scr	728	PreNatThimer	0.0128	0.0120	0.284		1.013	0.989	1.037	0.987	1.23	
AD_Scr	728	Exp07mos	-0.0599	0.0225	0.008	**	0.942	0.901	0.984	1.062	0.39	2.54

~ 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 15.4.2. Model Summary: *PreNatThimer* , *Exp01mos, Exp17mos* Exposure Models, Controlling for Older Autistic Sibling Variable

Outcome	N	Exposure Measure	Estimate	Stderr	Prob ChiSq		One Unit Chg. OR[a]	Lower 95% CL	Upper 95% CL	1/OR	2 SD Unit Chg. OR[b]	1/OR
ASD_Outc	1008	PreNatThimer	0.0067	0.0096	0.488		1.007	0.988	1.026	0.993	1.11	
ASD_Outc	1008	Exp01mos	-0.0271	0.0449	0.546		0.973	0.891	1.063	1.027	0.90	1.12
ASD_Outc	1008	Exp17mos	-0.0334	0.0182	0.067	~	0.967	0.933	1.002	1.034	0.62	1.63
AD_Outc	911	PreNatThimer	0.0103	0.0109	0.343		1.010	0.989	1.032	0.990	1.18	
AD_Outc	911	Exp01mos	0.0304	0.0491	0.536		1.031	0.936	1.135	0.970	1.13	
AD_Outc	911	Exp17mos	-0.0559	0.0211	0.008	**	0.946	0.907	0.986	1.058	0.44	2.26
ASD_Only	773	PreNatThimer	-0.0037	0.0197	0.850		0.996	0.959	1.036	1.004	0.94	1.06
ASD_Only	773	Exp01mos	-0.2136	0.0948	0.024	*	0.808	0.671	0.973	1.238	0.42	2.39
ASD_Only	773	Exp17mos	0.0010	0.0308	0.974		1.001	0.942	1.063	0.999	1.01	
ASD_Regr	701	PreNatThimer	0.0400	0.0214	0.061	~	1.041	0.998	1.085	0.961	1.92	
ASD_Regr	701	Exp01mos	-0.1123	0.0877	0.200		0.894	0.753	1.061	1.119	0.63	1.58
ASD_Regr	701	Exp17mos	-0.1003	0.0381	0.009	**	0.905	0.839	0.975	1.105	0.23	4.30
AD_ExLoIQ	884	PreNatThimer	0.0151	0.0108	0.161		1.015	0.994	1.037	0.985	1.28	
AD_ExLoIQ	884	Exp01mos	-0.0097	0.0536	0.856		0.990	0.892	1.100	1.010	0.96	1.04
AD_ExLoIQ	884	Exp17mos	-0.0631	0.0229	0.006	**	0.939	0.898	0.982	1.065	0.40	2.50
ASD_Scr	821	PreNatThimer	0.0049	0.0101	0.626		1.005	0.985	1.025	0.995	1.08	
ASD_Scr	821	Exp01mos	-0.0619	0.0474	0.192		0.940	0.857	1.031	1.064	0.78	1.29
ASD_Scr	821	Exp17mos	-0.0398	0.0203	0.051	~	0.961	0.923	1.000	1.041	0.56	1.78
AD_Scr	728	PreNatThimer	0.0122	0.0121	0.313		1.012	0.989	1.036	0.988	1.22	
AD_Scr	728	Exp01mos	-0.0020	0.0541	0.971		0.998	0.898	1.110	1.002	0.99	1.01
AD_Scr	728	Exp17mos	-0.0717	0.0249	0.004	**	0.931	0.886	0.977	1.074	0.35	2.84

~ 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 15.4.3. Model Summary: *PreNatThimer* and *Exp020mos* Exposure Models, Controlling for Older Autistic Sibling Variable

Outcome	N	Exposure Measure	Estimate	Stderr	Prob ChiSq		One Unit Chg. OR[a]	Lower 95% CL	Upper 95% CL	1/OR	2 SD Unit Chg. OR[b]	1/OR
ASD_Outc	1008	PreNatThimer	0.0065	0.0096	0.497		1.007	0.988	1.026	0.993	1.11	
ASD_Outc	1008	Exp020mos	-0.0322	0.0161	0.045	*	0.968	0.938	0.999	1.033	0.56	1.78
AD_Outc	911	PreNatThimer	0.0102	0.0108	0.348		1.010	0.989	1.032	0.990	1.18	
AD_Outc	911	Exp020mos	-0.0385	0.0181	0.034	*	0.962	0.929	0.997	1.039	0.50	1.98
ASD_Only	773	PreNatThimer	-0.0014	0.0200	0.944		0.999	0.960	1.039	1.001	0.98	1.02
ASD_Only	773	Exp020mos	-0.0268	0.0279	0.336		0.974	0.922	1.028	1.027	0.62	1.61
ASD_Regr	701	PreNatThimer	0.0382	0.0209	0.068	~	1.039	0.997	1.082	0.963	1.87	
ASD_Regr	701	Exp020mos	-0.0791	0.0325	0.015	*	0.924	0.867	0.985	1.082	0.24	4.10
AD_ExLoIQ	884	PreNatThimer	0.0146	0.0108	0.175		1.015	0.994	1.036	0.985	1.27	
AD_ExLoIQ	884	Exp020mos	-0.0487	0.0197	0.013	*	0.952	0.916	0.990	1.050	0.42	2.38
ASD_Scr	821	PreNatThimer	0.0048	0.0101	0.636		1.005	0.985	1.025	0.995	1.08	
ASD_Scr	821	Exp020mos	-0.0377	0.0178	0.034	*	0.963	0.930	0.997	1.038	0.51	1.96
AD_Scr	728	PreNatThimer	0.0122	0.0120	0.310		1.012	0.989	1.036	0.988	1.22	
AD_Scr	728	Exp020mos	-0.0492	0.0213	0.021	*	0.952	0.913	0.993	1.050	0.42	2.40

~ 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.

15.5. Estimates of Relationships of Exposure Measures to Case-Control Outcomes, where Cases and Controls with Older Autistic Siblings are Omitted

In this section we present results of analyses conducted to determine if the estimated relationships of exposure to autism risk are sensitive to the inclusion or exclusion of children that had older siblings with autism. The results presented in this section are from models of the same form as those used to produce Chapter 9 Exhibits 9.4.1, 9.4.2, and 9.4.3, the only difference being that in the current section, cases and controls that had autistic older siblings were excluded from the analysis.

Comparison of Exhibits 15.5.1, 15.5.2 and 15.5.3 to Exhibits 9.4.1, 9.4.2, and 9.4.3, respectively, indicates that excluding cases and controls that had an older sibling with autism does not substantially affect the estimated associations between exposure measures and autism risk.

Exhibit 15.5.1. Model Summary: *PreNatThimer* and *Exp07mos* Exposure Models, Where Cases and Controls with Older Autistic Siblings were Omitted

Outcome	N	Exposure Measure	Estimate	Stderr	Prob ChiSq	One Unit Chg. OR[a]	Lower 95% CL	Upper 95% CL	1/OR	2 SD Unit Chg. OR[b]	1/OR
ASD_Outc	977	PreNatThimer	0.0055	0.0100	0.5848	1.006	0.986	1.025	0.995	1.09	0.91
ASD_Outc	977	Exp07mos	-0.0288	0.0168	0.0863	0.972	0.940	1.004	1.029	0.64	1.57
AD_Outc	884	PreNatThimer	0.0104	0.0113	0.3587	1.010	0.988	1.033	0.990	1.18	0.84
AD_Outc	884	Exp07mos	-0.0394	0.0190	0.0383	0.961	0.926	0.998	1.040	0.54	1.85
ASD_Only	753	PreNatThimer	-0.0033	0.0201	0.8703	0.997	0.958	1.037	1.003	0.95	1.06
ASD_Only	753	Exp07mos	-0.0137	0.0294	0.6419	0.986	0.931	1.045	1.014	0.81	1.24
ASD_Regr	682	PreNatThimer	0.0404	0.0213	0.0584	1.041	0.999	1.086	0.960	1.93	0.52
ASD_Regr	682	Exp07mos	-0.1006	0.0346	0.0036	0.904	0.845	0.968	1.106	0.21	4.79
AD_ExLoIQ	858	PreNatThimer	0.0146	0.0113	0.1950	1.015	0.993	1.037	0.986	1.27	0.79
AD_ExLoIQ	858	Exp07mos	-0.0522	0.0207	0.0118	0.949	0.911	0.988	1.054	0.44	2.25
ASD_Scr	796	PreNatThimer	0.0038	0.0103	0.7137	1.004	0.984	1.024	0.996	1.06	0.94
ASD_Scr	796	Exp07mos	-0.0394	0.0189	0.0371	0.961	0.926	0.998	1.040	0.54	1.85
AD_Scr	707	PreNatThimer	0.0112	0.0122	0.3609	1.011	0.987	1.036	0.989	1.20	0.83
AD_Scr	707	Exp07mos	-0.0569	0.0227	0.0122	0.945	0.904	0.988	1.059	0.41	2.42

~ 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 15.5.2. Model Summary: *PreNatThimer* , *Exp01mos, Exp17mos* Exposure Models, Where Cases and Controls with Older Autistic Siblings were Omitted

Outcome	N	Exposure Measure	Estimate	Stderr	Prob ChiSq	One Unit Chg. OR[a]	Lower 95% CL	Upper 95% CL	1/OR	2 SD Unit Chg. OR[b]	1/OR
ASD_Outc	977	PreNatThimer	0.0055	0.0101	0.5837	1.006	0.986	1.026	0.995	1.09	0.91
ASD_Outc	977	Exp01mos	-0.0138	0.0454	0.7611	0.986	0.902	1.078	1.014	0.95	1.06
ASD_Outc	977	Exp17mos	-0.0315	0.0185	0.0880	0.969	0.935	1.005	1.032	0.63	1.58
AD_Outc	884	PreNatThimer	0.0100	0.0114	0.3823	1.010	0.988	1.033	0.990	1.18	0.85
AD_Outc	884	Exp01mos	0.0380	0.0497	0.4448	1.039	0.942	1.145	0.963	1.17	0.86
AD_Outc	884	Exp17mos	-0.0540	0.0213	0.0114	0.947	0.909	0.988	1.055	0.46	2.19
ASD_Only	753	PreNatThimer	-0.0050	0.0199	0.8033	0.995	0.957	1.035	1.005	0.92	1.08
ASD_Only	753	Exp01mos	-0.1805	0.1006	0.0729	0.835	0.685	1.017	1.198	0.48	2.09
ASD_Only	753	Exp17mos	0.0090	0.0316	0.7747	1.009	0.949	1.073	0.991	1.14	0.88
ASD_Regr	682	PreNatThimer	0.0403	0.0213	0.0588	1.041	0.999	1.086	0.960	1.93	0.52
ASD_Regr	682	Exp01mos	-0.1109	0.0888	0.2115	0.895	0.752	1.065	1.117	0.64	1.57
ASD_Regr	682	Exp17mos	-0.0985	0.0383	0.0102	0.906	0.841	0.977	1.103	0.24	4.19
AD_ExLoIQ	858	PreNatThimer	0.0145	0.0113	0.1978	1.015	0.992	1.037	0.986	1.27	0.79
AD_ExLoIQ	858	Exp01mos	-0.0086	0.0544	0.8744	0.991	0.891	1.103	1.009	0.97	1.04
AD_ExLoIQ	858	Exp17mos	-0.0606	0.0231	0.0089	0.941	0.899	0.985	1.062	0.41	2.41
ASD_Scr	796	PreNatThimer	0.0038	0.0103	0.7162	1.004	0.984	1.024	0.996	1.06	0.94
ASD_Scr	796	Exp01mos	-0.0500	0.0479	0.2969	0.951	0.866	1.045	1.051	0.82	1.23
ASD_Scr	796	Exp17mos	-0.0374	0.0206	0.0691	0.963	0.925	1.003	1.038	0.58	1.72
AD_Scr	707	PreNatThimer	0.0105	0.0124	0.3957	1.011	0.986	1.035	0.990	1.19	0.84
AD_Scr	707	Exp01mos	0.0076	0.0545	0.8899	1.008	0.905	1.121	0.992	1.03	0.97
AD_Scr	707	Exp17mos	-0.0701	0.0252	0.0054	0.932	0.887	0.980	1.073	0.36	2.77

~ 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 15.5.3. Model Summary: *PreNatThimer* and *Exp020mos* Exposure Models, Where Cases and Controls with Older Autistic Siblings were Omitted

Outcome	N	Exposure Measure	Estimate	Stderr	Prob ChiSq	One Unit Chg. OR[a]	Lower 95% CL	Upper 95% CL	1/OR	2 SD Unit Chg. OR[b]	1/OR
ASD_Outc	977	PreNatThimer	0.0055	0.0100	0.5807	1.006	0.986	1.026	0.994	1.09	0.91
ASD_Outc	977	Exp020mos	-0.0309	0.0163	0.0575	0.970	0.939	1.001	1.031	0.58	1.73
AD_Outc	884	PreNatThimer	0.0100	0.0113	0.3763	1.010	0.988	1.033	0.990	1.18	0.85
AD_Outc	884	Exp020mos	-0.0382	0.0184	0.0377	0.963	0.929	0.998	1.039	0.51	1.97
ASD_Only	753	PreNatThimer	-0.0029	0.0201	0.8849	0.997	0.959	1.037	1.003	0.95	1.05
ASD_Only	753	Exp020mos	-0.0191	0.0275	0.4883	0.981	0.930	1.036	1.019	0.71	1.41
ASD_Regr	682	PreNatThimer	0.0386	0.0209	0.0649	1.039	0.998	1.083	0.962	1.88	0.53
ASD_Regr	682	Exp020mos	-0.0766	0.0326	0.0189	0.926	0.869	0.987	1.080	0.26	3.92
AD_ExLoIQ	858	PreNatThimer	0.0142	0.0113	0.2063	1.014	0.992	1.037	0.986	1.26	0.79
AD_ExLoIQ	858	Exp020mos	-0.0496	0.0200	0.0131	0.952	0.915	0.990	1.051	0.41	2.42
ASD_Scr	796	PreNatThimer	0.0037	0.0103	0.7172	1.004	0.984	1.024	0.996	1.06	0.94
ASD_Scr	796	Exp020mos	-0.0362	0.0181	0.0451	0.964	0.931	0.999	1.037	0.52	1.91
AD_Scr	707	PreNatThimer	0.0108	0.0122	0.3789	1.011	0.987	1.035	0.989	1.19	0.84
AD_Scr	707	Exp020mos	-0.0484	0.0217	0.0253	0.953	0.913	0.994	1.050	0.42	2.37

~ 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.

16. Why Were Exposure Levels Higher in Controls? Was it Higher Number of Vaccines Received, or Equal Number but Higher Thimerosal Content?

In this chapter we present results of analyses designed to answer the question of whether controls had slightly[11] higher cumulative postnatal exposure because they received greater numbers of vaccines, or because they received comparable numbers of vaccines but where less likely to have received thimerosal-free preparations or combination vaccines (e.g., combined DTaP-Hib instead of separate DTaP and Hib vaccines). We also present results of analyses designed to determine whether case-control differences in exposure amounts were due to incorrect mercury amount assignments when lot numbers were unknown. Since the primary research questions that motivated the study focus on ASD cases versus matched controls, and AD cases versus matched controls, and since the estimated exposure effects were larger for the latter, we focused our analyses using data from AD cases and matched controls.

A summary of results is as follows:

- The number of vaccines received by AD 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 slightly lower cumulative exposure levels.
    - HepB Receipts – cases were more likely to have thimerosal-free HepB vaccines than controls, resulting in slightly lower cumulative exposure levels.
- It is very unlikely that differences between AD cases and controls on cumulative exposure levels were due to incorrect assignment of mercury amounts when lot numbers were unknown.

16.1. Motivation for Analysis

The results in Chapter 9 indicated that for some of the exposure measures, higher exposure was associated with decreased risk of autism outcomes. This means that on average, the covariate adjusted mean exposure levels for the autistic cases were lower than the covariate adjusted mean exposure levels of their matched control counterparts. Examination of Exhibits 9.3.1 – 9.3.7 indicates that the cumulative exposure amounts for autism cases tended to be slightly lower than

[11] We use the term "slightly" throughout this chapter to underscore the fact that there was not a statistically significant difference between cases and controls on cumulative exposure amounts, and the differences between the to groups were small when expressed as a proportion of a standard deviation unit of exposure, or when expressed as a proportion of a single 12.5 microgram vaccine receipt.

for their matched control counterparts. For example, in each of the exhibits (9.3.1-9.3.7) the mean of the measure of cumulative exposure for the period spanning birth to seven months (i.e., the variable *Amt07mos*, where mercury amount was not divided by weight at time of vaccine receipt) is higher for controls than for cases. In each of the exhibits the size of the difference between the mean exposure for cases and controls appears to be small. For example, the means of *Amt07mos* for AD cases and their matched controls were 101.4 and 105.0, respectively. This average difference of 3.6 micrograms of cumulative exposure from birth to seven months appears small relative to the range of the measure (0, 190.8), or relative to a standard deviation unit (42.2), or even relative to the mercury amounts that were typical of a single thimerosal-containing vaccine in use in the 1990s, (12.5 and 25 were typical mercury amounts in a single thimerosal-containing vaccine in use at that time).

Nonetheless, in a model that controlled only for matching strata, the statistical significance of the estimated decrease in autism risk associated with the exposure measure *Amt07mos*, was 0.08, which is just above the traditional p-value criterion of 0.05. Thus what appears to be a small difference in average exposure can correspond to an estimated risk effect that is close to the traditional level of statistical significance. And for other outcomes, i.e., ASD with Regression, ASD vs screened control group, and AD vs screened control group, that had similarly small differences in mean exposure levels for case and control groups, the estimated risk effects were statistically significant at a $p<0.05$ criterion.

The difference in mean exposure level between cases and controls is a critical force in the estimate that says that increased exposure, birth to seven months, is associated with decreased risk of autism outcomes. The analysis results presented in the current chapter represent one approach among several that are reported in this volume, that attempt to answer the question, "why did the controls in our sample have slightly greater exposure levels than the cases?" In particular, this chapter is focused on the following statement and questions.

16.2. Research Questions

We have observed that controls had slightly higher mean exposure in the age range from birth to seven months than cases. Is that because:

A) Controls received a greater number of vaccines?
B) Controls received similar numbers of vaccines, but were less likely to have thimerosal-free vaccines, or combination vaccines (e.g. combined DTaP-Hib)[12]?

16.3. Analysis Approach

A set of data plots were created to address this question. They show for AD cases and matched controls, across the age range spanning birth to two years (1 to 730 days) three types of cumulated measures:

- the cumulative number of vaccines received
  - (labeled "Count" on y-axis)
- the cumulative amount of ethylmercury received
  - (labeled "Amt" on y-axis)

[12] Receipt of a combination vaccine can result in a lower exposure amount than receipt of two separate vaccines (e.g. separate DTaP, separate Hib).

- the cumulative exposure, where exposure is measured as ethylmercury amount divided by weight in kilograms at the time of vaccine receipt
    - (labeled "Exp" on y-axis).

The types of vaccines included in the count of number of vaccines received include only the types of vaccines the ever contained thimerosal. For example, some HepB vaccines contained thimerosal, others did not. All HepB receipts were counted. Some Hibs contained thimerosal, others did not. All Hibs were counted. MMR, Measles, Mumps, Rubella, Polio, varicella, RSV, Rota, Typhoid and Yellow fever vaccines never contained thimerosal[13], and were not counted.

We created plots of cumulative counts amounts for all vaccine types combined, and individual vaccine types (e.g., HepBs, Hibs, etc.). The plot heading "All" indicates that it is a cumulative count of *all types of vaccines that ever contained thimerosal*. For the purpose of counting the number of "All" vaccines received, combined vaccines such as DTP-Hibs, were counted as one receipt. For the purpose counting receipts of specific vaccine types, e.g., Hib receipts, a combined vaccine such as a DTP-Hib would be counted as one Hib Receipt. In a separate plot, the same receipt would also be counted as one DTP receipt.

For the purpose of cumulating the amount of ethylmercury received for a specific vaccine type (e.g. Hib) the amount of mercury in combined vaccines (e.g., DTP-Hib) was equally divided among the two types of vaccines. For example, if a child received a DTP-Hib that contained 25 micrograms of ethlymercury, then 12.5 micrograms was counted towards the Hib receipt, and 12.5 micrograms was counted towards the DTP receipt.

In the analysis models in the main report, matching within matching strata adjusts for any imbalance in the case/control ratio across matching strata. In order to mimimic that adjustment in the caluculation of cumulative mean counts and amounts, we weighted the controls within each stratum such that the weights summed to three times the number of cases in the stratum[14]. For example, suppose in Stratum A there were 2 cases and 4 controls. The controls would each be assigned a weight of 1.5, so that the sum of the control weights would be three times the number of cases (6). Suppose that in Stratum B there were 10 cases and 40 controls. Then each control would be assigned a weight of 0.75, so that their weights would sum to 30. Mean counts and amounts were calculated as weighted means.

16.4. Results

The plot in the upper left-hand panel of Exhibit 16.1 shows the mean cumulative number of vaccine receipts for AD cases and matched controls for the age range spanning birth to two years (1 to 730 days). The plot indicates that the mean cumulative number of vaccine receipts was very similar for AD cases and matched controls. The mean cumulative

[13] For more details on the mercury amounts in each vaccine type, see Exhibit 7.3.4.1.
[14] Our target case/control ratio was 3 cases to one controls

number of vaccine receipts for AD cases and matched controls at ages 1, 28, 214, and 609 days (birth, one month, 7 months, 20 months) was 0.43 and 0.44; 0.75 and 0.74; 6.57 and 6.66; and 9.10 and 9.07, respectively[15].

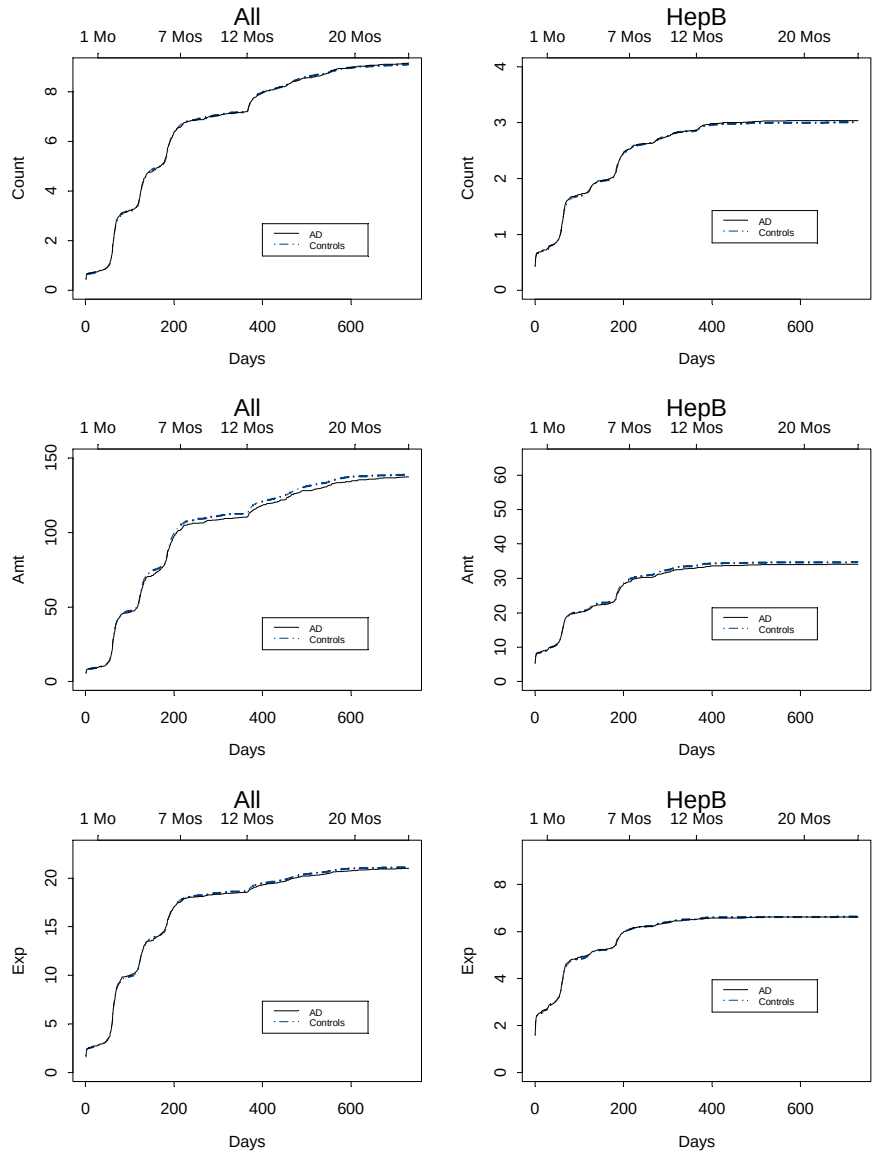
The plot in the middle row of the left-hand panel of Exhibit 16.1 shows the mean cumulative amount of mercury from vaccines and immune globulins by received AD cases and matched controls. By around 7 months (214 days) the plot indicates that the average cumulative exposure for controls is slightly higher than for cases. Since the number of vaccines received was virtually identical for AD cases and controls, these plots suggest that controls might have had more thimerosal-containing vaccine preparations, compared to cases, while the cases might have had more thimerosal-free receipts. The bottom panel shows that there was less difference between cases and controls when mercury amount was divided by the child's weight at the time of vaccine receipt.

In order to better understand what specific types of vaccines contributed to the greater exposure amounts for controls, we made similar sets of plot corresponding to vaccine types. The plots on the right-hand side of Exhibit 16.1 correspond to receipts of HepB vaccines. Exhibit 16.2 and 16.3 have plots corresponding to DTP, Hib, Flu, and other types of vaccine or immune globulins receipts (see exhibits for specific types of vaccines included in each cumulative measure

Examination of the plots suggests that for each vaccine type, the numbers of vaccines received by AD cases and controls were very similar, but that the cumulative mercury amounts (labeled "Amt" on plots) received from HepB and Hib receipts were slightly higher for controls than cases. In the sections that follow, we examine the case-control differences in Hib and HepB amounts in more detail.

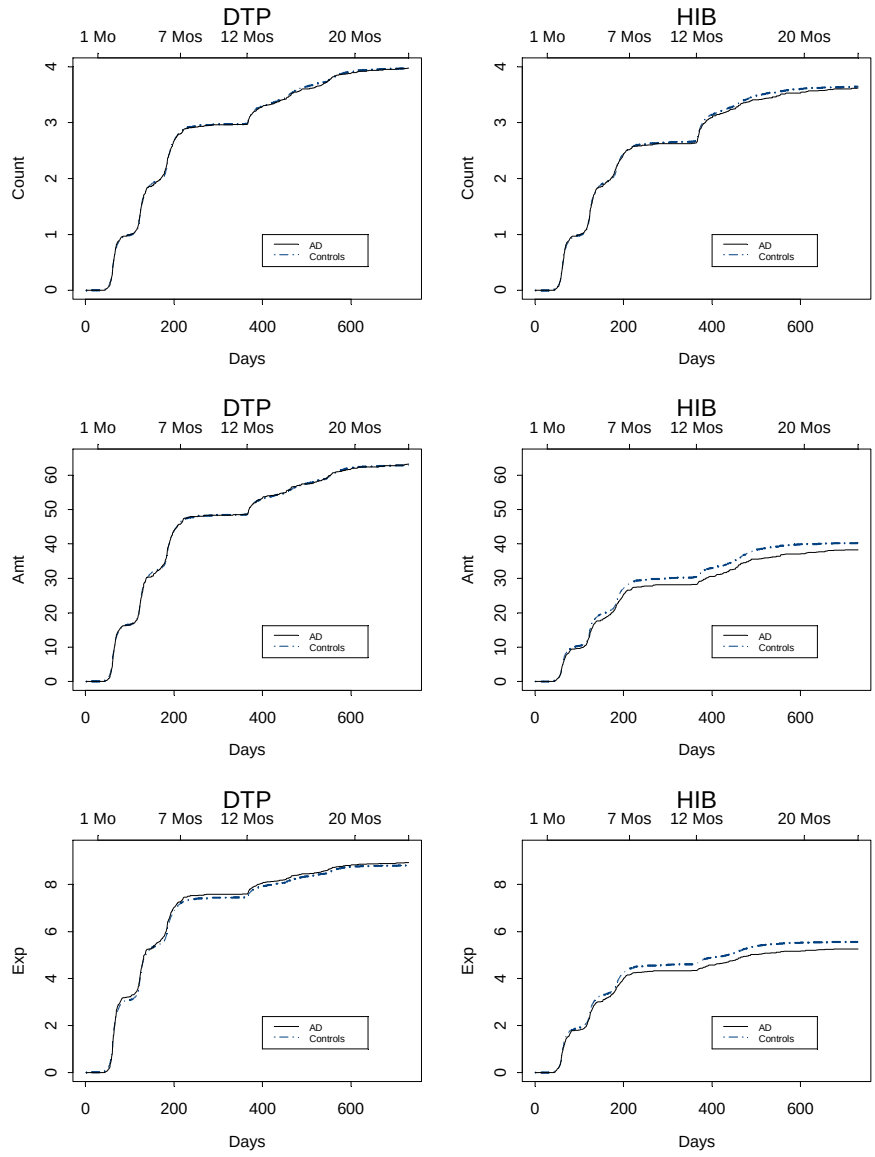
[15] There were no statistically significant differences between AD cases and controls in cumulative number of vaccines received at ages 28, 214, or 609 days. Nor were there significant differences in cumulative number of vaccines received at these age ranges between controls and any of the other classifcations of cases (ASD, ASD with Regression, ASD-not-AD, AD with Low Cognitive Function Excluded, ASD with screened control group, and AD with screened control group).

Exhibit 16.1. AD Cases vs Controls: Average Cumulative Numbers of Vaccines Received, and Average Cumulative Exposure – All Vaccine Types, and HepB Receipts



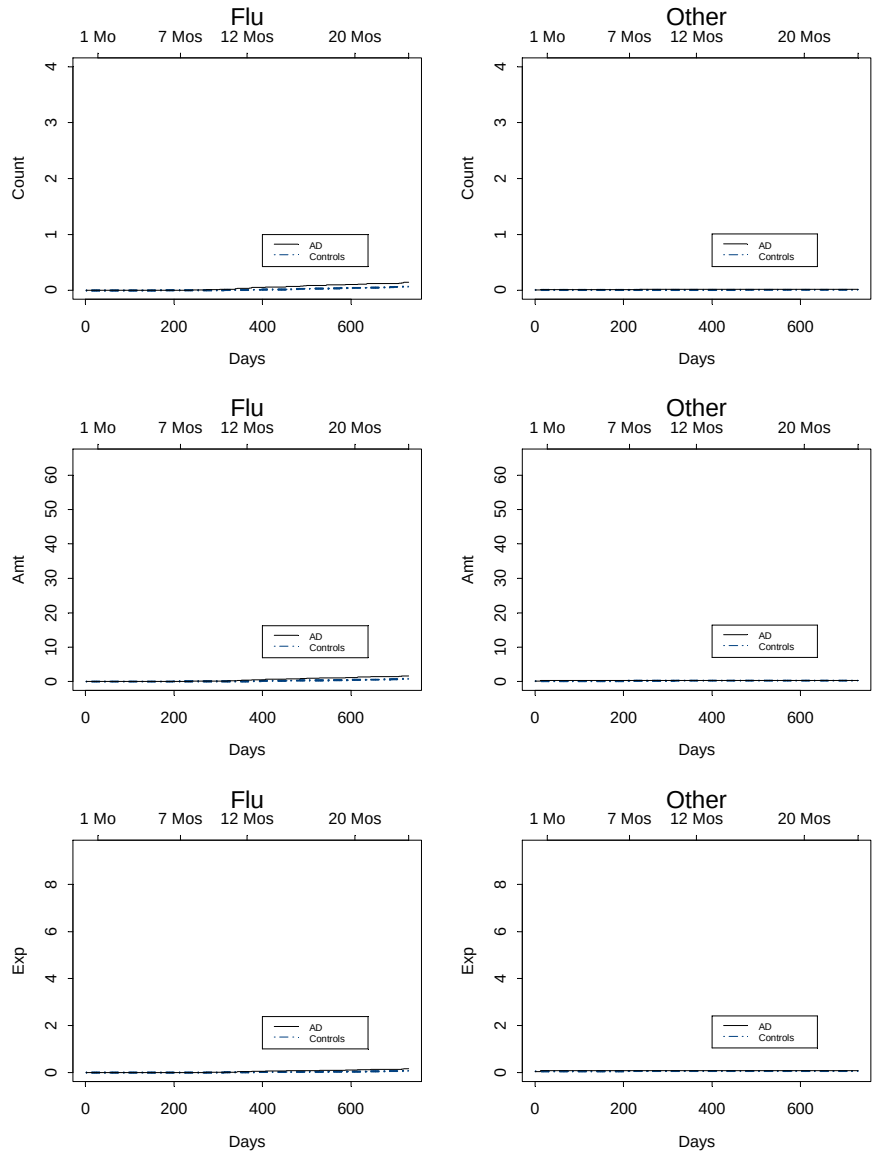
"All Vaccine types" includes HepB, DT TD, DTP, DTaP, Flu, Hib, HBIG, IG GG, Rabies, Vari-IG, DTaPHepB,HepB-Hib, DTP-Hib, Pneumo
"HepB Receipts" include HepB, HepB-Hib, DTaP-HepB. Exposure amounts for combined vaccines are divided by 2.

Exhibit 16.2. AD Cases vs Controls: Average Cumulative Numbers of Vaccines Received, and Average Cumulative Exposure – DTP and Hib Receipts



"DTP Receipts" include DT TD, DTP, DTP-Hib, DTaP, DTaP-HepB.
"Hib Receipts" include DTP-Hib, Hib, HepB-Hib. Exposure amounts for combined vaccines are divided by 2.

Exhibit 16.3. AD Cases vs Controls: Average Cumulative Numbers of Vaccines Received, and Average Cumulative Exposure – Flu and Other Receipts



"Flu Receipts" include Flu.
"Other Receipts" include HBIG,IG GG,Rabies,Vari-IG.

16.4.1. Focus on Hib Receipts

During the time frame when the study participants were in the age range spanning birth to seven months, a receipt of a Hib vaccination could result in exposure to zero, 12.5, or 25 micrograms of ethylmercury. For the current analysis, when children received a DTP-Hib vaccine that contained 25 micrograms of ethylmercury, we counted 12.5 micrograms toward the Hib total amount, and 12.5 toward the DTP total amount.

The cumulative *Amt* of ethylmercury received from Hib vaccinations by age 7 months (214 days) for AD cases and controls was 26.5 and 28.6 micrograms, respectively. This average difference of 2.1 micrograms is equivalent to a difference of about one sixth (or 17 percent) of a single 12.5 microgram-containing Hib receipt, or about one twelfth of a single 25 microgram-containing Hib receipt. The mean numbers of Hib receipts for cases and controls were 2.56 and 2.59, respectively, or a difference of three one-hundredths of a single receipt. The difference in the number of Hib receipts does not fully account for the difference in the Hib *Amt* measure. Therefore, we looked at the mean numbers of Hib receipts that contained 0, 12.5, and 25 micrograms of ethylmercury.

The mean counts of each type of Hib receipt, aggregated over all of the matching strata, are shown at the top of Exhibit 16.4. The results show that the controls had slightly greater average numbers of 12.5 and 25 microgram-containing receipts, (4 one-hundredths, and 7 one-hundredths greater, respectively), while AD cases had a slightly greater average number of thimerosal-free Hib receipts (an average difference of 8 one-hundredths of a single receipt). These differences in the average numbers of thimerosal-containing receipts roughly account for the average difference between AD cases and controls in the *Amt* measure. Specifically, (0.03 * 12.5) + (0.07 * 25) = 2.1, which is equal to the average difference of 2.1 micrograms of ethylmercury calculated for the *Amt* measure. The mean counts of each type of Hib receipt are shown for each of the matching strata in Exhibit 16.4 There are only a few matching strata where the average numbers of receipts of any of the types of Hibs differ by as much as one half of one receipt.

Exhibit 16.4.
Mean Counts of Mercury-free and Mercury-containing Hib Receipts, by Stratum
(Counts are for the period spanning birth to 7 months)

		# of Cases and Controls	Mean Count of Hib Any	Hib 0 μg	Hib 12.5 μg	Hib 25 μg	Comments
Overall (all strata	Control	724	2.54	0.78	1.24	0.53	
combined)	AD Case	187	2.52	0.86	1.20	0.46	
Matching Stratum							
2=HMO-A1994M	Control	5	2.8	0	0	2.8	
2=HMO-A1994M	AD Case	1	3	0	0	3	
3=HMO-A1995F	Control	3	2.67	0	0	2.67	
3=HMO-A1995F	AD Case	1	3	0	0	3	
5=HMO-A1996F	Control	4	3	0	0	3	
5=HMO-A1996F	AD Case	1	3	0	0	3	
7=HMO-A1997F	Control	2	3	0	0	3	
7=HMO-A1997F	AD Case	1	3	0	0	3	
9=HMO-A1998F	Control	2	3	0	0	3	
9=HMO-A1998F	AD Case	1	3	0	0	3	
10=HMO-A1998M	Control	4	2.75	0	0	2.75	
10=HMO-A1998M	AD Case	1	3	0	0	3	
12=HMO-A1999M	Control	4	3	0	0	3	
12=HMO-A1999M	AD Case	1	3	0	0	3	
13=HMO-B1994F	Control	16	3	0	3	0	
13=HMO-B1994F	AD Case	3	3	0	3	0	
14=HMO-B1994M	Control	69	2.78	0.04	2.70	0.04	
14=HMO-B1994M	AD Case	15	2.93	0.13	2.80	0	
15=HMO-B1995F	Control	17	2.94	0	2.94	0	
15=HMO-B1995F	AD Case	5	2.80	0	2.60	0.2	
16=HMO-B1995M	Control	52	2.88	0	2.88	0	
16=HMO-B1995M	AD Case	10	2.80	0	2.70	0.1	
17=HMO-B1996F	Control	6	2.83	0	2.83	0	
17=HMO-B1996F	AD Case	1	3	0	3	0	
18=HMO-B1996M	Control	49	2.94	0	2.90	0.04	
18=HMO-B1996M	AD Case	9	2.67	0	2.67	0	
19=HMO-B1997F	Control	13	2.54	0	1.23	1.31	← Controls have more 25 μg Hibs
19=HMO-B1997F	AD Case	3	3	0	3	0	← Cases have more 12.5 μg Hibs
20=HMO-B1997M	Control	55	2.89	0	1.33	1.56	
20=HMO-B1997M	AD Case	12	2.92	0	1.67	1.25	
21=HMO-B1998F	Control	5	3	0	0.00	3	← Controls have more 25 μg Hibs
21=HMO-B1998F	AD Case	1	2	0	0	2	
22=HMO-B1998M	Control	44	2.86	0	0.50	2.36	
22=HMO-B1998M	AD Case	17	2.82	0	0.29	2.53	
24=HMO-B1999M	Control	17	2.76	1	0.18	1.59	← Controls have more 25 μg Hibs
24=HMO-B1999M	AD Case	7	3	2.57	0	0.43	← Cases have more 0 μg Hibs

Exhibit 16.4.
Mean Counts of Mercury-free and Mercury-containing Hib Receipts, by Stratum
(Counts are for the period spanning birth to 7 months)

		# of Cases and Controls	Mean Count of Hib Any	Hib 0 μg	Hib 12.5 μg	Hib 25 μg	Comments
25=oHMO-C1994F	Control	7	2.29	0	2.29	0	
25=oHMO-C1994F	AD Case	2	2	0	2	0	
26=oHMO-C1994M	Control	12	2.50	0	2.50	0	
26=oHMO-C1994M	AD Case	2	2.50	0	2.50	0	
28=oHMO-C1995M	Control	18	2.78	0	2.78	0	
28=oHMO-C1995M	AD Case	4	2.75	0	2.75	0	
29=oHMO-C1996F	Control	11	2.73	1	1.73	0	← Controls have more 12.5 μg Hibs
29=oHMO-C1996F	AD Case	1	2	2	0	0	← Cases have more 0 μg Hibs
30=oHMO-C1996M	Control	42	2.62	0.79	1.83	0	
30=oHMO-C1996M	AD Case	10	2.50	0.60	1.90	0	
32=oHMO-C1997M	Control	36	2.06	2.06	0	0	
32=oHMO-C1997M	AD Case	10	2.1	2.1	0	0	
33=oHMO-C1998F	Control	5	2	2	0	0	
33=oHMO-C1998F	AD Case	2	2	2	0	0	
34=oHMO-C1998M	Control	49	1.98	1.98	0	0	
34=oHMO-C1998M	AD Case	12	1.83	1.83	0	0	
36=oHMO-C1999M	Control	38	2.11	2.11	0	0	
36=oHMO-C1999M	AD Case	10	2.10	2.10	0	0	
38=eHMO-C1994M	Control	10	2.10	0	2.10	0	
38=eHMO-C1994M	AD Case	4	2	0	2	0	
40=eHMO-C1995M	Control	18	2.56	0.33	2.22	0	
40=eHMO-C1995M	AD Case	8	2.63	0.38	2.25	0	
42=eHMO-C1996M	Control	25	2.60	0.80	1.80	0	← Controls have more 12.5 μg Hibs
42=eHMO-C1996M	AD Case	7	2.43	1.29	1.14	0	← Cases have more 0 μg Hibs
43=eHMO-C1997F	Control	3	2	2	0	0	
43=eHMO-C1997F	AD Case	1	2	2	0	0	
44=eHMO-C1997M	Control	35	2.20	2.17	0.03	0	
44=eHMO-C1997M	AD Case	12	2.08	2.08	0	0	
46=eHMO-C1998M	Control	20	2.05	2.05	0	0	
46=eHMO-C1998M	AD Case	4	2	2	0	0	
48=eHMO-C1999M	Control	28	2	2	0	0	
48=eHMO-C1999M	AD Case	8	2.13	2.13	0	0	

"μg"= micrograms.

Read table: For the age range spanning birth to 7 months, (1 to 214 days), the mean number of Hib receipts for Controls in stratum 44 was 2.20. For this group the mean number of Hib receipts where the Hib contained 0 micrograms of ethylmercury was 2.17, and the mean number of receipts where the Hib contained 12.5 micrograms of ethylmercury was 0.03.

16.4.1.1. Hib Receipts When Lot Number was Unknown

In order to assign mercury amounts to each vaccine receipt, we used information about the vaccine type (e.g., Hib, HepB, DTaP, etc.), the manufacturer, and the lot number. When the lot number was unknown, but manufacturer was known, we assigned the most commonly occurring amount for the particular vaccine type, manufacturer, year of receipt, and HMO. For example, a child had a record of having received a Hib vaccine in 1994, at HMO-C original sample, and where the manufacturer was MSD, and where the lot number was not recorded. Since all other Hib receipts in 1994 (and 1995) where the manufacturer was MSD, and the lot number was known had contained 12.5 micrograms of ethylmercury, we assigned a mercury amount of 12.5 micrograms for this Hib receipt. In this example, even though the lot number was not recorded, we have a high degree of confidence that we have made the correct mercury amount assignment.

As a second example, consider a Hib vaccine received in 1997, at HMO-C original sample, where the manufacturer was MSD, and the lot number was unknown. Among Hib receipts in 1997 where the manufacturer was MSD and the lot number was known, 352 were thimerosal-free preparations, and 11 were thimerosal-containing preparations where the mercury amount for a single receipt was 12.5 micrograms. At HMO-C original sample, when the lot number was known, 188 Hibs where thimerosal-free and 10 contained 12.5 micrograms. So, for the receipt with the unknown lot number, our best guess was that it was a thimerosal-free preparation, and hence we assigned a mercury amount equal to zero for this receipt. But, this is an example where we cannot be fully confident that we have assigned the correct mercury amount.

In this section we consider the question of whether the mercury amount assignment for receipts with unknown lot numbers could explain the difference between AD cases and controls in the cumulative amount of ethylmercury exposure, birth to seven months, from Hib receipts.

Study participants received Hib vaccinations during the age range spanning birth to seven months either as a combined DTP-Hib, a combined HepB-Hib, or a singular Hib vaccine. Even when lot numbers were unknown, we are highly confident that all DTP-Hib receipts contained 25 micrograms of ethylmercury, and all HepB-Hib receipts contained zero micrograms of ethylmercury[16]. We therefore focus our attention on the singular Hib receipts that had potential mercury amounts equal to zero, 12.5, and 25 micrograms.

[16] The HepB-Hibs with unknown lot numbers were received in 1999 and 2000, and we are confident that these would have been thimerosal-free.

Exhibit 16.5 shows the frequency of singular Hib vaccination receipts (birth to seven months) where the lot number and manufacturer were known and unknown for AD cases and controls. We note that analysts were blinded to case-control status at the time that mercury amount assignments were made. The data in the table indicates where we made guesses at the mercury amount due to unknown lot numbers, controls were more likely to receive guess values that were 0 micrograms than were AD cases, and AD cases were more likely to receive guess values that were 12.5 or 25 micrograms. A summary of the data in the table is a follows.

- Guess assignments where assigned amount was 0 micrograms
    - 2.29 percent of Hibs received by controls were guess assignments of 0 micrograms (2.17 + 0.12 = 2.29)
    - 0.86 percent of Hibs received by AD Cases were guess assignments of 0 micrograms

- Guess assignments where assigned amount was 12.5 micrograms
    - 0.60 percent of Hibs received by controls were guess assignments of 12.5 micrograms (0.48 + 0.12 = 0.60)
    - 0.86 percent of Hibs received by AD Cases were guess assignments of 12.5 micrograms

- Guess assignments where assigned amount was 25 micrograms
    - 0 percent of Hibs received by controls were guess assignments of 25 micrograms
    - 0.43 percent of Hibs received by AD Cases were guess assignments of 25 micrograms

Recall that the puzzling finding was that controls had, on average, slightly higher ethylmercury exposure from Hib vaccines than AD cases. The results above and in Exhibit 16.5 indicate that when lot numbers were unknown, our guesses at mercury amounts tended to result in lower assumed amounts for controls than cases. (We stress again that we were blinded to case-control status when making the mercury amount assignments). Thus, the current analysis suggests that the higher ethylmercury exposure from Hib receipts for controls was very unlikely to be due to incorrect guesses when lot numbers were unknown. Indeed, when individuals with unknown lot numbers are omitted, and cumulative ethylmercury exposure from Hib vaccines received birth to seven months are recalculated, the mean amount rises for controls from 28.6 micrograms in the full sample, to 29.1 when individuals with unknown lot numbers are omitted, and falls for cases from 26.6 (full sample) to 26.5 (with individuals omitted).

In Exhibit 16.6, we show the records where Hib receipts had unknown lot numbers (left-hand panel), and the corresponding data from Hib receipts with known lot numbers where the vaccines were received in the same year and HMO, and, if known, the same manufacturer. For example, the record indicated in Row 1 of the exhibit was for a Hib vaccine received by an AD case in 1997 in HMO-C expanded sample, and where the lot

number and manufacturer were unknown. The information in the right-hand panel of the exhibit shows that in 1997, among receipts of singular Hib vaccines when the lot number was known, 99.4 percent where thimerosal-free preparations, and 0.6 percent were thimerosal-containing Hib vaccines. Thus, for the record in Row 1, we assigned the most common ethylmercury amount for this year and HMO, which was 0 micrograms.

Exhibit 16.5. Frequency of Hib Receipts (Birth to Seven Months) Where Lot Number and Manufacturer are Unknown or Known

AD Cases						Cumulative	Cumulative
AD_Outc	HaveLot	HaveMFR	MercAmt	Frequency	Percent	Frequency	Percent
1	No	Unk	0	2	0.86	2	0.86
1	No	Unk	25	1	0.43	3	1.29
1	No	Yes	12.5	2	0.86	5	2.16
1	Yes	Yes	0	129	55.6	134	57.76
1	Yes	Yes	12.5	13	5.6	147	63.36
1	Yes	Yes	25	85	36.64	232	100
Controls						**Cumulative**	**Cumulative**
AD_Outc	**HaveLot**	**HaveMFR**	**MercAmt**	**Frequency**	**Percent**	**Frequency**	**Percent**
0	No	Unk	0	18	2.17	18	2.17
0	No	Unk	12.5	4	0.48	22	2.65
0	No	Yes	0	1	0.12	23	2.77
0	No	Yes	12.5	1	0.12	24	2.89
0	Yes	Yes	0	434	52.29	458	55.18
0	Yes	Yes	12.5	49	5.9	507	61.08
0	Yes	Yes	25	323	38.92	830	100

Counts of Hib receipts in age range spanning birth to seven months.
AD_Outc = 1 if AD case, 0 if control.
HaveLot = “Yes” if lot number was recorded in record, =”No” else.
HaveMFR = “Yes” if vaccine manufacturer was listed in record, = “Unknown” else.

Read table: Among the 232 Hib vaccines received by AD cases in the age range spanning birth to seven months (not counting DTP-Hib and HepB-Hib receipts), there were two receipts of Hib vaccines where the lot number and manufacturer were unknown, and where the mercury amount assignment was set to zero micrograms.

Exhibit 16.6. Hib Receipts with Unknown Lot Numbers and Assigned Mercury Amount Compared to Mercury Amounts from Receipts with Known Lot Numbers

Records of Receipts with Unknown Lot Numbers									Data from Receipts with Known Lot Numbers					
									0 μg		12.5 μg		25 μg	
Row	AD_Outc	Have Lot	MFR	Merc Amt (μg)	Fake ID	HMO	Matching Stratum	Year of Receipt	Freq	%	Freq	%	Freq	%
1	1	No	Unk	0	983	eHMO-C	44	1997	164	99.4	1	0.6	0	0
2	1	No	Unk	0	912	oHMO-C	32	1998	228	100	0	0	0	0
3	1	No	Unk	25	69	HMO-A	10	1998	0	0	0	0	36	100
4	1	No	MSD	12.5	390	oHMO-C	26	1994	0	0	43	100	0	0
5	1	No	MSD	12.5	144	oHMO-C	30	1996	0	0	2	100	0	0
6	0	No	Unk	0	132	oHMO-C	30	1996	3	100	0	0	0	0
7	0	No	Unk	0	132	oHMO-C	30	1996	3	100	0	0	0	0
8	0	No	Unk	0	132	oHMO-C	30	1996	3	100	0	0	0	0
9	0	No	Unk	0	1007	eHMO-C	42	1997	164	99.4	1	0.6	0	0
10	0	No	Unk	0	1041	eHMO-C	44	1997	164	99.4	1	0.6	0	0
11	0	No	Unk	0	812	eHMO-C	43	1997	164	99.4	1	0.6	0	0
12	0	No	Unk	0	693	oHMO-C	30	1997	195	95.1	10	4.9	0	0
13	0	No	Unk	0	693	oHMO-C	30	1997	195	95.1	10	4.9	0	0
14	0	No	Unk	0	869	oHMO-C	30	1997	195	95.1	10	4.9	0	0
15	0	No	Unk	0	168	oHMO-C	32	1998	228	100	0	0	0	0
16	0	No	Unk	0	868	oHMO-C	34	1998	228	100	0	0	0	0
17	0	No	Unk	0	393	oHMO-C	32	1998	228	100	0	0	0	0
18	0	No	Unk	0	747	oHMO-C	34	1998	228	100	0	0	0	0
19	0	No	Unk	0	1061	eHMO-C	46	1999	87	100	0	0	0	0
20	0	No	Unk	0	1069	eHMO-C	48	1999	87	100	0	0	0	0
21	0	No	Unk	0	889	oHMO-C	36	1999	177	100	0	0	0	0
22	0	No	Unk	0	889	oHMO-C	36	1999	177	100	0	0	0	0
23	0	No	Unk	0	921	oHMO-C	36	1999	177	100	0	0	0	0
24	0	No	Unk	12.5	792	eHMO-C	40	1995	3	30	7	70	0	0
25	0	No	Unk	12.5	792	eHMO-C	40	1995	3	30	7	70	0	0
26	0	No	Unk	12.5	792	eHMO-C	40	1995	3	30	7	70	0	0
27	0	No	Unk	12.5	138	oHMO-C	25	1995	1	9.1	10	90.9	0	0
28	0	No	MSD	0	864	oHMO-C	32	1997	188	94.9	10	5.1	0	0
29	0	No	MSD	12.5	915	oHMO-C	25	1994	0	0	43	100	0	0

AD_Outc =1 if AD Case, =0 if Control
MFR = Manufacturer; MSD = Merck, Sharp, Dohme
MercAmt = The mercury amount assigned to the receipt
HMO: oHMO-C = HMO-C original sample, eHMO-C = HMO-C expanded sample
Data from receipts with know lot numbers: This gives the frequency and percent of Hib receipts where the lot number was known.

16.4.2. Focus on HepB Receipts

We note that, up until the late 1990s, all HepBs contained 12.5 micrograms of ethlymercury, then starting in 1999, some HepBs contained 0 micrograms of ethylmercury. We also note, however, that combined HepB-Hib vaccines that were received by some study participants as early as 1995, contained zero micrograms of ethlymercury.

At age 7 months (214 days) the means of HepB *Amt* for AD cases and controls were 28.9 and 29.8, respectively, or a difference of 0.9 micrograms of ethylmercury. We can think of this mean difference as being equivalent to a difference of less than one tenth of a single receipt of a 12.5 microgram of ethylmercury-containing HepB vaccine. In fact, 0.9 divided by 12.5 comes out to 7.2 one-hundredths, or 7.2 percent of a 12.5 microgram-containing receipt. The mean numbers of HepB receipts for cases and controls were 2.52 and 2.54, respectively, or a difference of two one-hundredths of a single receipt. The difference in the number of HepB receipts does not fully account for the difference in the HepB *Amt* measure. Therefore we looked at the mean number of HepB receipts that contained 12.5, or 0 micrograms of ethylmercury.

The mean numbers of 12.5 microgram-containing HepB receipts for cases and controls were 2.32 and 2.39, respectively, or a difference of seven one-hundredths of a single receipt. And, mean numbers of 0 microgram-containing HepB receipts for cases and controls were 0.21 and 0.15, respectively, or a difference of six one-hundredths of a single receipt. Thus, allowing for some rounding error from aggregating means across matching strata, we conclude that at seven months, although the mean number of HepB receipts for AD cases and controls differed by only two one-hundreds of a single receipt, the mean difference between AD cases and controls of seven one-hundreds of a single 12.5 microgram-containing HepB receipt was due to controls having received, on average, slightly more thimerosal-containing HepBs, while AD cases, on average, received slightly more thimerosal-free HepBs.

In order to delve even deeper, we calculated the mean numbers of thimerosal-containing and thimerosal-free HepBs received by AD cases and controls in each of the matching strata. The results are displayed in Exhibit 16.7. We have highlighted in the exhibit, the matching strata where the mean number of thimerosal-containing HepB receipts differ by one-half of a receipt or more. For example, in Matching Stratum 9 (females from HMO-A, born in 1998), controls had an average of 0.5 more thimerosal-containing HepB receipts than their AD counterparts. Conversely, in Matching Stratum 7 (females from HMO-A, born in 1997), it is the AD cases who had, on average, a greater number of thimerosal-containing HepB receipts.

Matching Strata 12, 24, 36, and 48 correspond to males born in 1999, at HMO-A, HMO-B, original-sample-HMO-C, and expanded-sample-HMO-C, respectively. The results in Exhibit 16.7, show that in three out of four of these strata, controls received slightly higher mean numbers of thimerosal-containing HepBs, while in two out of three of those

strata, the AD cases received slightly higher mean numbers of thimerosal-free HepBs. In the fourth stratum, the opposite pattern occurred. That is, the controls received more thimerosal-free HepBs and the AD cases received more thimerosal-containing HepBs. Of the 34 matching strata, there are 11 where the AD cases had greater mean numbers of thimerosal-containing HepBs, 20 where controls had the greater number of thimerosal-containing HepBs, and 3 where the mean numbers were the same in the two groups.

Exhibit 16.7.
Mean Counts of Mercury-free and Mercury-containing HepB Receipts, by Stratum
(Counts are for the period spanning birth to 7 months)

		# of	Mean Count For Stratum			
		Cases and Controls	HepB Any	HepB 0 μg	HepB 12.5 μg	Comments
Overall (all strata	Control	724	2.54	0.15	2.39	
combined)	AD Case	187	2.52	0.21	2.32	
Matching Stratum						
2= HMO-A1994M	Control	5	2.20	0	2.20	
2=HMO-A1994M	AD Case	1	2	0	2	
3=HMO-A1995F	Control	3	2	0	2	
3=HMO-A1995F	AD Case	1	2	0	2	
5=HMO-A1996F	Control	4	2	0	2	
5=HMO-A1996F	AD Case	1	2	0	2	
7=HMO-A1997F	Control	2	2	0	2	
7=HMO-A1997F	AD Case	1	3	0	3	
9=HMO-A1998F	Control	2	2.50	0.00	2.50	← Controls have more 12.5 μg HepBs
9=HMO-A1998F	AD Case	1	2	0	2	
10=HMO-A1998M	Control	4	2.75	0	2.75	
10=HMO-A1998M	AD Case	1	2	0	2	
12=HMO-A1999M	Control	4	2	0	2	← Controls have more 12.5 μg HepBs
12=HMO-A1999M	AD Case	1	1	0	1	← Cases have more 0 μg HepBs
13=HMO-B1994F	Control	16	2.44	0	2.44	
13=HMO-B1994F	AD Case	3	2.33	0	2.33	
14=HMO-B1994M	Control	69	2.13	0.04	2.09	← Controls have ***fewer*** 12.5 μg HepBs
14=HMO-B1994M	AD Case	15	2.53	0	2.53	
15=HMO-B1995F	Control	17	2.35	0	2.35	
15=HMO-B1995F	AD Case	5	2.40	0	2.40	
16=HMO-B1995M	Control	52	2.35	0	2.35	
16=HMO-B1995M	AD Case	10	2.40	0	2.40	
17=HMO-B1996F	Control	6	2.33	0	2.33	
17=HMO-B1996F	AD Case	1	2	0	2	
18=HMO-B1996M	Control	49	2.41	0	2.41	
18=HMO-B1996M	AD Case	9	2.22	0	2.22	
19=HMO-B1997F	Control	13	2	0	2	
19=HMO-B1997F	AD Case	3	2.33	0	2.33	
20=HMO-B1997M	Control	55	2.53	0	2.53	
20=HMO-B1997M	AD Case	12	2.58	0	2.58	
21=HMO-B1998F	Control	5	2.60	0	2.60	← Controls have more 12.5 μg HepBs
21=HMO-B1998F	AD Case	1	2	0	2	
22=HMO-B1998M	Control	44	2.48	0	2.48	
22=HMO-B1998M	AD Case	17	2.59	0	2.59	
24=HMO-B1999M	Control	17	2.35	0.94	1.41	← Controls have more 12.5 μg HepBs

Exhibit 16.7.
Mean Counts of Mercury-free and Mercury-containing HepB Receipts, by Stratum
(Counts are for the period spanning birth to 7 months)

		# of	Mean Count For Stratum			
		Cases and Controls	HepB Any	HepB 0 μg	HepB 12.5 μg	Comments
24=HMO-B1999M	AD Case	7	2.29	1.43	0.86	← Cases have more 0 μg HepBs
25=oHMO-C1994F	Control	7	2.86	0	2.86	
25=oHMO-C1994F	AD Case	2	2.50	0	2.50	
26=oHMO-C1994M	Control	12	2.83	0	2.83	← Controls have more 12.5 μg HepBs
26=oHMO-C1994M	AD Case	2	2	0	2	
28=oHMO-C1995M	Control	18	2.83	0	2.83	
28=oHMO-C1995M	AD Case	4	3.00	0	3	
29=oHMO-C1996F	Control	11	2.73	0	2.73	
29=oHMO-C1996F	AD Case	1	3	0	3	
30=oHMO-C1996M	Control	42	2.76	0	2.76	
30=oHMO-C1996M	AD Case	10	2.60	0	2.6	
32=oHMO-C1997M	Control	36	2.83	0.03	2.81	
32=oHMO-C1997M	AD Case	10	2.70	0	2.70	
33=oHMO-C1998F	Control	5	2.80	0	2.80	
33=oHMO-C1998F	AD Case	2	2.50	0	2.50	
34=oHMO-C1998M	Control	49	2.88	0	2.88	
34=oHMO-C1998M	AD Case	12	2.50	0	2.50	
36=oHMO-C1999M	Control	38	2.68	0.97	1.71	← Controls have more 12.5 μg HepBs
36=oHMO-C1999M	AD Case	10	2.50	1.90	0.60	← Cases have more 0 μg HepBs
38=eHMO-C1994M	Control	10	2.70	0	2.70	
38=eHMO-C1994M	AD Case	4	2.25	0	2.25	
40=eHMO-C1995M	Control	18	2.72	0.17	2.56	
40=eHMO-C1995M	AD Case	8	2.75	0.38	2.38	
42=eHMO-C1996M	Control	25	2.84	0	2.84	
42=eHMO-C1996M	AD Case	7	2.57	0	2.57	
43=eHMO-C1997F	Control	3	2.67	0	2.67	
43=eHMO-C1997F	AD Case	1	3	0	3	
44=eHMO-C1997M	Control	35	2.66	0	2.66	
44=eHMO-C1997M	AD Case	12	2.92	0	2.92	
46=eHMO-C1998M	Control	20	2.75	0	2.75	
46=eHMO-C1998M	AD Case	4	2.75	0	2.75	
48=eHMO-C1999M	Control	28	2.18	1.29	0.89	← Controls have ***fewer*** 12.5 μg HepBs
48=eHMO-C1999M	AD Case	8	2.50	0.88	1.63	← Cases have ***fewer*** 0 μg HepBs

" μg "= micrograms.

Read table: For the age range spanning birth to seven months, (1 to 214 days), the mean number of HepB receipts for Controls in stratum 48 was 2.18. For this group the mean number of HepB receipts where the HepB contained 12.5 micrograms of ethylmercury was 1.29, and the mean number of receipts where the HepB contained 0 micrograms of ethylmercury was 0.89.

16.4.2.1. HepB Receipts When Lot Number was Unknown

In this section we consider the question of whether the mercury amount assignment for receipts with unknown lot numbers could explain the difference between AD cases and controls in the cumulative amount of ethylmercury exposure, birth to seven months, from HepB receipts. Study participants received HepB vaccinations during the age range spanning birth to seven months either as a combined DTaP-HepB, a combined HepB-Hib, or a singular HepB vaccine. There were no receipts of combined DTaP-HepB vaccines where the lot number was unknown. For HepB-Hib vaccines, when lot numbers were unknown, we are highly confident that all contained zero micrograms of ethylmercury[17]. We therefore focus our attention on the singular HepB receipts that had potential mercury amounts equal to 0 or 12.5 micrograms. We note, however, that we can be confident that all singular HepB vaccines received in 1994-1998 would have contained 12.5 micrograms of ethylmercury. Therefore, an unknown lot number for a HepB received in those years does not present a problem for assignment of mercury amount. We therefore focus our attention on the HepB vaccines that had unknown lot numbers, and that were received in the years 1999 and 2000, when both thimerosal-containing and thimerosal-free preparations were in use.

For AD cases, among the 443 receipts of HepB vaccines in the age range spanning birth to seven months, 2 had unknown lot numbers and were received in 1999 or 2000. This comes out to 0.4 percent of HepB receipts in the age range birth to seven months. For both of these receipts, we assigned mercury amounts of 12.5 micrograms because the thimerosal-containing vaccines were much more prevalent in those years. In particular, the two receipts with unknown lot numbers were from HMO-C original sample and HMO-C expanded sample, where 100 percent of 1999 and 2000 HepB receipts where thimerosal-containing preparations.

Controls received 1,754 of HepB vaccines in the age range spanning birth to seven months, which included 7 that were received in 1999 or 2000 and had unknown lot numbers. This comes out to 0.4 percent of HepB receipts in the age range birth to seven months. Again, we assumed that these were thimerosal-containing vaccines and assigned ethymercury amounts of 12.5 micrograms. Two of the seven with unknown lot numbers were received at HMO-A where 83 percent of HepB receipts in those years were thimerosal-containing preparations, and the remaining five with unknown lot numbers were from HMO-C original sample and HMO-C expanded sample, where 100 percent of 1999 and 2000 HepB receipts where thimerosal-containing preparations.

Thus, for both cases and controls, 0.4 percent of all HepB receipts in the age range spanning birth to seven months had mercury amount assignments that were based on the

[17] The HepB-Hibs with unknown lot numbers were received n 1999 and 2000, and we are confident that these would have been thimerosal-free. There were six HepB-Hibs received in 1995 that had lot numbers, but where the manufacturer did not recognize the lot numbers. We are currently in the process of checking our assumption that these were thimerosal-free preparations.

assumption that, because most HepB vaccines received in 1999 and 2000 that had known lot numbers contained 12.5 micrograms of ethylmercury, those with unknown lot number should be assigned amounts equal to 12.5 micrograms also. With such a small number of HepB receipts where unknown lot numbers could potentially have resulted in incorrect mercury amount assignments, the idea that amount assignments for the receipts with unknown lot numbers could explain the difference between AD cases and controls in exposure amount from HepB receipts does not appear to be plausible.

As a check, we recalculated the mean mercury exposure amounts from HepBs received birth to seven months, but where individuals were omitted if they had any HepB receipts in 1999 or 2000 with unknown lot numbers. The omission of those individuals changed the means by only one tenth of a microgram for both cases and controls. The mean amount rose for controls from 29.8 micrograms in the full sample, to 29.9 when individuals with unknown lot numbers were omitted, and rose for cases from 28.9 (full sample) to 29.0 (with individuals omitted).

Thus, the current analysis suggests incorrect guesses when lot numbers were unknown is a very unlikely explanation for the finding that ethylmercury exposure from HepB receipts was slightly higher for controls than for AD cases.

16.5. Conclusions

In summary, we focused this chapter on results of analysis on a comparison of AD cases to matched control because our primary research questions concerned comparisons of ASD cases to controls and AD cases to controls, and the differences between cumulative exposures were greater for the latter pair. Results for other outcome contrasts (e.g. AD cases versus Screened Controls) were similar. The results indicated that while the average number of vaccinations received by AD cases and their matched control counterparts were very similar, that the cumulative amount received by each group differed slightly. The differences in cumulative amounts of ethylmercury received appeared to be driven primarily by differences in ethylmercury amounts received in HepB and Hib vaccinations, and these differences were explained by controls receiving slightly greater numbers of thimerosal-containing versions of these vaccines, while AD cases received slightly greater numbers of thimerosal-free preparations. It is very unlikely that incorrect mercury amount assignment when lot numbers were missing is the reason for differences between AD cases and controls on cumulative exposure amounts.

17. 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. If the mothers of children with autism were more likely to remember exposure events than the mothers of controls, the result could be spurious associations between measures of prenatal and early childhood exposures and autism outcomes.

For our 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. (See Chapter 7 for explanation of creation of measures).

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. We conducted each of the analyses that were specified in the analysis plan even though in some cases the data were too sparse to draw conclusions about differential recall. For example, the analysis plan specified a comparison between chart and maternal report of valproic acid during pregnancy. According to either source, only one case mother and four control mothers used valproic acid during pregnancy. These data are clearly too sparse to draw inferences about whether there is differential recall between case and control mothers.

One of the planned analyses was a comparison of maternal recall of their child's receipt of a hepatitis B vaccine at birth, to medical record data obtained from chart abstraction and computer automated (VSD) records. Although this analysis did not indicate any significant differences between the recall of case and control mothers, it did show that there were a substantial number of mothers who reported that their child had received a HepB at birth, while the medical record data indicated that the child did not receive a HepB at bith. We investigated these discrepancies and present the results in this chapter. Since the results indicate that the relevant information was obtained from children's birth hospitalization we conclude that the discrepancies are more likely due to maternal recall error than missed vaccines in the records, and we assume that the medical record data are correct. We present analyses conducted to determine whether the overall model results are sensitive to that assumption, and conclude that they are not.

In summary, there are no results presented in this chapter 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 children's early infancy. All analyses in this chapter are based on the analysis sample of 256 ASD cases and 752 matched controls.

17.1. Maternal and Chart Reported Receipts of Immune Globulins Received during Pregnancy

Exhibit 7.4.3.1, in Chapter 7, shows the amount of agreement between chart data and maternal report of immune globulin receipt during pregnancy with the focus child. In that exhibit, the decision codes 1.01 – 1.04, 1.07, 2.01- 2.04, and 3.00 indicate records where the chart abstraction data unambiguously indicated that the mother had received an immune globulin during her pregnancy with the focus child. For the mothers with those codes, we ask, were the mothers of cases more likely to have remembered that they received an immune globulin during pregnancy?

There were 19 cases and 57 control mothers that had any of the decision codes listed above. Among the 19 cases, 11 (58 percent) reported that they had received an immune globulin during pregnancy. Among the 57 controls, 39 (68 percent) reported having received an immune globulin during pregnancy[18]. A chi-square test of independence failed to reject the null hypothesis of no difference between cases and controls in the proportion that correctly reported having received an immune globulin (p=0.40).

The results of this analysis do not support the hypothesis that mothers of ASD cases were more likely to recall having received an immune globulin during pregnancy with the focus child.

We can also ask whether the mothers of cases were more likely to have reported having received an immune globulin during pregnancy, when the information in the chart indicated that no immune globulin was received during pregnancy. These types of reports correspond to the decision codes 4.04, 4.05, 4.07[19], and 4.09 in Exhibit 7.4.3.1.

Among the 236 case mothers whose charts said they did not receive an immune globulin during pregnancy, 4 (1.7 percent) reported that they had received one. Among the 690 corresponding control mothers, 13 (1.8 percent) reported having received one. There was not a statistically significant difference between these two proportions (Fisher's exact test, p=0.99).

[18] Mothers who reported having received an immune globulin during pregnancy or during both pregnancy and breastfeeding were counted having remembered the receipt. Mothers who said they had not received an immune globulin, had only received an immune globulin during the breastfeeding period, had received an immune globulin during pregnancy or breastfeeding but didn't know which, or did not know if they had received an immune globulin during pregnancy or breastfeeding were counted as having not remembered.
[19] One mother with decision code 4.07, but who said she had received an immune globulin during breastfeeding but not during pregnancy is excluded from this group.

These results do not indicate that case mothers were more likely to report having received an immune globulin during pregnancy when their medical charts indicated that they did not.

17.2. Maternal and Chart Reported Receipts Vaccines Received during Pregnancy

Data on receipt of influenza vaccine during pregnancy were obtained primarily from maternal report as part of the parent interview. Chart abstractors checked maternal charts for records of flu receipts, but found few because flu vaccines are often administered outside of the HMO system (e.g., flu shots at work, at shopping malls, and grocery stores), and even when administered within the HMOs, were rarely recorded in the maternal charts. Of the 38 recorded flu receipts among the 256 case and 752 control mothers, only two (both for controls) were recorded in the maternal medical charts.

Of the 256 ASD case mothers, 12 (4.7 percent) reported receiving a flu vaccine during pregnancy, and of the 752 control mothers, 26 (3.5 percent) reported receiving a flu vaccine during pregnancy. There was not a statistically significant difference between these two proportions (Fisher's exact test, p=0.35).

These results do not indicate that case mothers had a higher probability of recall flu vaccines during pregnancy, but the chart abstraction data cannot be used to verify the receipts. Therefore, these results are inconclusive.

Data on receipts of other vaccines during pregnancy (tetanus, diptheria-tetatanus, and rubella vaccines) came from medical chart abstraction. There were no questions in the parent interview about prenatal receipts of vaccines other than influenza.

17.3. Maternal and Chart Reported Use of Folic Acid Supplements during Pregnancy

Data on use of folic acid during pregnancy was obtained primarily from maternal report as part of the parent interview. Chart abstractors checked maternal charts for records of folic acid use, but few were recorded in the maternal medical charts. Maternal use of multivitamins during pregnancy was counted as use of folic acid, and it is not surprising that routine of multivitamins would not be recorded in charts.

Among the 256 case mothers 246 (96 percent) recorded having used folic acid supplements during pregnancy. Among those, 2 (0.8 percent) had their folic acid use confirmed by data in the medical charts. Among the 752 control mothers 686 (91 percent) reported use of folic acid, of which 19 (2.5 percent) had confirming records in their medical charts. Two control mothers had folic acid use listed in their charts, but did not self-report use. Although a significantly greater proportion of case than control mothers reported use of folic acid during pregnancy (chi-square test of independence, p=0.011),

these data do not help answer the question of whether case or control mothers are better able to accurately recall events during pregnancy.

17.4. Maternal and Chart Reported Use of Valproic Acid during Pregnancy

According to both maternal report and chart abstraction data, few mothers used valproic acid during pregnancy. One case mother had a record of valproic acid use in her chart, but she did not report in the parent interview having used valproic acid during pregnancy. Four control mothers used valproic acid during pregnancy. Among those four, one self-reported use and had use recorded in her chart, two self-reported use but did not have a record of use in her chart, and one had a record of use in her chart but did not self-report use during the parent interview. Again, these data are too sparse to help answer the question of whether there is differential recall between case and control mothers.

17.5. Maternal and Chart Reported Use of Alcohol during Pregnancy

Only 5 case mothers (2 percent) reported occasional alcohol use during pregnancy, while 27 (3.6 percent) of control mothers reported occasional, light, or moderate use of alcohol during pregnancy. The difference in proportions reporting at least occasional use was not statistically significant (chi-square test of independence, p=0.197).

There were no significant differences between cases and controls in the proportions whose self-reported alcohol use were confirmed by medical chart abstraction. Among the 5 case mothers who reported alcohol use, 2 (40 percent) had use confirmed in their medical charts. Among the 27 controls who reported alcohol use, 8 (30 percent) had use confirmed in their medical charts.

Nor were there significant differences between proportions who said they did not use alcohol, but whose charts indicated they did. Among case mothers who reported no alcohol use, 6 percent had had an indication of alcohol use in their medical chart, while among control mothers who reported no alcohol use during pregnancy, 4 percent had an indication of alcohol use in their medical chart.

17.6. Maternal and Chart Reported Use of Tobacco during Pregnancy

There were no significant differences between case and control mothers regarding self-report of tobacco use during pregnancy. Three percent of case mothers and three percent of control mothers reported having used tobacco during their pregnancies. Seventy one and 58 percent of self-reported use was confirmed by chart abstraction data for case and control mothers, respectively. Among those who reported that they did not use tobacco during pregnancy, 2 percent of case mothers and 2 percent of control mothers had tobacco use during pregnancy recorded in their charts.

17.7. Maternal and Chart Reported Childhood Lead Exposure

Of the 256 case mothers, 22 (8.6 percent) reported childhood lead exposure, and of 752 control mothers 18 (2.4 percent) reported childhood lead exposure. This difference in proportions was statistically significant (chi-square test of independence, $p<0.001$). Only one of the reported exposures of cases, and one of the reported exposures of controls were confirmed by the chart abstraction data. Thus, although childhood lead exposure was significantly higher in cases than controls, the available data are not able to confirm or refute that possibility that the result is influenced by recall bias.

For additional detail on childhood lead exposure data, see Section 9.3.1. As noted in that section, there was a high degree of overlap between measures of child lead exposure and child pica. As with the child lead exposure, the maternal reports of pica were confirmed by medical chart records for only one case and one control.

17.8. Maternal and Chart Reported Date of Initiation of Prenatal Care

Twelve case mothers (4.7 percent) and 18 control mothers (2.4 percent) had Kotelchuck initiation of prenatal care index scores in the "inadequate" range (chi-square test of independence $p=0.062$). The index score was primarily created from first date of prenatal care indicated on the maternal medical chart. Among the cases with an "inadequate" score, one mother's self-reported a date of initiation was in a range that that would have resulted in an "inadequate" score, and two did not report an initiation date. Among controls in the inadequate range, four reported a date of initiation was in a range that that would have resulted in an "inadequate" score. As with other measures described in this chapter, the data are too sparse on this measure to make conclusions about differential recall.

17.9. Maternal and Chart Reported Receipt of Hepatitis B Vaccine at Birth

As described in Chapter 7, neonatal receipt of hepatitis B vaccine at birth was ascertained from medical records data (i.e., from medical chart abstraction and computer automated (VSD) records). Additionally, as part of the parent interview, mothers were asked whether their child had received a hepatitis B vaccine at birth. In order to assess whether there is evidence of differential recall on the part of case and control mothers, we compared the parent interview responses to the medical records data. For these analyses, we treat the medical records data on neonatal receipt of HepB vaccines as the "gold standard" for accuracy and assess whether case and control mothers had differential recall of HepB receipts against the gold standard. We subsequently describe why we treat the medical records data as the gold standard and why we assume discrepancies are due to error in maternal recall. We also subsequently provide results of analyses to assess whether the overall study results are sensitive to the assumption that discrepancies are due to error in maternal recall.

For the current analysis we categorized the parent interview responses into 5 categories that describe whether the mother's recall agrees or disagrees with the verified medical records data, or if she reported that she did not know whether her child had received a hepatitis B vaccine at birth. Within the five categories there are two types of agreement, two types of disagreement, and one category for mothers who did not know. The five categories and the number and percentages of case and control mothers in each category are shown in Exhibit 17.1.

Overall, over half of mothers either did not know if their child had received a HepB vaccine at birth (34.3 percent), or gave responses that were discrepant with the information obtained from the child's medical records (17.6 percent). There were no significant differences between the percentages of case and control mothers whose parent interview response agreed with the medical records data (43 vs. 50%, p=0.056), whose parent interview disagreed with medical records data (20 vs 17%, p=0.18), or who did not know if their child had received a hepatitis B vaccination at birth (37 vs 34%, p=0.350). These results do not support the hypothesis that case mothers would have better recall of early childhood health events or exposures.

Exhibit 17.1. Comparison of Maternal Recall of Child Receipt of Hepatitis-B Vaccine at Birth to Medical Record Data (Chart and VSD data)

	HepB Received in 1st 28 Days?		Cases		Controls		Total	
Maternal Recall	**Medical Records**	**Maternal Report**	**n**	**%**	**n**	**%**	**n**	**%**
Agreement: Mother report agrees w/ medical records	Yes	Yes	106	41.4	343	45.6	449	44.5
	No	No	4	1.6	32	4.3	36	3.6
Discrepancy: Mother report disagrees w/medical records	No	Yes	41	16.0	101	13.4	142	14.1
	Yes	No	11	4.3	24	3.2	35	3.5
Mother could not recall	Y or N	DK	94	36.7	252	33.5	346	34.3
		Total:	**256**	**100**	**752**	**100**	**1008**	**100**

Chi-square test of independence between maternal recall (5 rows) and case-control status (2 columns): χ^2 =6.79, df = 4, p = 0.148

17.9.1. Additional Analyses of Discrepancies

There are two kinds of discrepant responses shown in Exhibit 17.1. One kind is where medical record showed that the child received a birth dose of hepatitis B, but where the mother said the child did not. There were 35 mothers who provided this kind of discrepant response. For these 35 the medical records clearly indicate receipt of HepBs in the first month of life and we can be confident that these discrepancies represent inaccuracies on the part of mothers who were reporting on an event that would have occurred six to 13 years prior to the parent interview. Since some of the 35 children received these HepB vaccinations a day or two after they were born, and five received them between ages 7 and 20 days, it is possible that that some of these mothers interpreted the question "did your child receive a hepatitis B vaccine at birth?" as only warranting a "yes" response if the child received the vaccine the day he or she was born. Either way there is nothing particularly troubling about this type of discrepancy, and it was not significantly more likely to occur in one group, cases or controls, than the other.

The other type of discrepancy was where the medical records indicated no birth dose of HepB, but where the mother said a HepB was received at birth. There were 142 such discrepancies. This type of discrepancy is cause for greater concern because it suggests that some vaccines could have been missed in the medical records. Since it is plausible that some of the birth dose vaccines may have been missed in the medical records, we present information in this section that describes the completeness of the medical records for the 142 discrepancies.

Of the 142 mothers with this type discrepant response all but one said that the child had not received any vaccinations, flu shots, or other types of injections outside of the HMO during his or her first year of life. And the one that said that shots had been received outside the HMO, listed a clinic that was actually part of the same HMO, and thus part of the same records system from which chart abstractions and VSD data were obtained. Thus, there is no reason to think that these represent missed birth doses that were received outside of the HMO system.

All 142 children with the discrepant records were born in hospitals that were part of their HMO system and all children's chart abstraction data included information that was recorded during the birth hospitilization. For example, all had complete records of their 1 minute and 5 minute APGAR scores, and all had birth weight and gestational age recorded. Thirty one of the children spent time in the neonatal intensive care unit. And 23 children had records of having received antibiotics at ages one or two days.

Thus, while it is plausible that some of these children had actually received HepB vaccines at birth, but that these receipts were not recorded in their medical charts, it does appear that each child had relevant medical records abstracted from the birth hospitalization. Given the finding that many mothers had trouble with recalling whether their child received a HepB at birth i.e., 34 percent of mothers said they did not know, and 3.5 percent provided the previously described type of discrepant response, it is likely that a large number or all of these discrepant responses are due to maternal recall error. Almost all children get a vitamin K injection on the day they were born. Some of the mothers who reported that their child received a HepB at birth may have been remembering the vitamin K injection.

We note that included in the 142 with discrepant responses were 12 whose responses to other questions on the parent interview indicated that, in fact, a HepB was not received a birth. Mothers were asked if their child missed or was late on any vaccines during the first year of life, and if so, why. All twelve of these mothers said their children had missed or were late on vaccines. Four said their child did not receive HepB at birth because their children were low birth weight, and seven gave specific information that indicated that their child did not receive a birth dose. Examples include a mother who said that "HepB was not right at birth, a little while after", two who gave the date of the child's first HepB, both of which were when the children were older than one and half months, one who said her doctor had said that her child was to receive his first HepB at his two month check up, another that said he did not receive a HepB at birth because he

was in intensive care, and one that said he received his first HepB at age three months. These reports contradicted the first statement that a HepB had been received and each appeared to be in alignment with the medical records data. These 12 included 4 cases and 8 controls.

17.9.2. Sensitivity of Model Results to Inclusion of Records Where Mother Said a HepB was Received, but Medical Records Did Not

The results in the previous section suggest that the discrepancies between mother report and medical record data on receipt of HepB at birth are more likely to be due to inaccurate recall on the part of mothers than to inaccuracies in the medical records. Nonetheless, we cannot be certain that none of the children in this group received a HepB vaccine at birth. In the main analyses, presented in Chapter 9 and elsewhere, we have assumed that the medical record data are correct. This means that we have assumed that the 142 children described previously did not receive a HepB at birth. In this section we present results of analyses conducted to determine whether the overall study results are sensitive to that assumption. Since it is clear that 12 of the 142 previously described did not receive HepB vaccines at birth, we focus our sensitivity analyses on the remaining 130.

We conducted two sets of sensitivity analyses. In the first, we omitted the records of the n=130 children with the previously described discrepancies between mother report and medical record data, and re-ran the main analysis models. In the second set of sensitivity analyses, we made the opposite assumption to what we had assumed for the main analyses. In these analyses we assumed that the mother was correct and the medical records were incorrect and assigned each of the 130 children a HepB receipt on the day of birth with an exposure amount equal to 12.5 micrograms of ethylmercury. This amount was divided by the child's birth weight to obtain the measure of exposure divided by child's weight in kilograms at the time of vaccine receipt. This resulted in each of the 130 children having increases to their exposure measures *Exp01mos*, *Exp07mos*, and *Exp020mos* (see Chapter 7 for additional details on exposure measures). The two sets of results are summarized in Exhibits 17.2 – 17.4 and 17.5-17.7, respectively. These results can be compared to the original results displayed in Chapter 9, Exhibits 9.4.1 – 9.4.3.

The sensitivity analyses indicate that the model results are not particularly sensitive to the inclusion or exclusion of the 130 children with discrepant records. For most models omission of the 130 children from the analysis resulted in exposure estimates that were slightly closer to zero, and the loss of sample size resulted in slightly larger standard errors of the estimates, such that the p-values on most tests were increased slightly. Some of the estimated exposure effects that were below the $p<0.05$ criterion in the full data set moved above that criterion in the reduced data set. And all exposure effects that that had been non-significant full data set remained non-significant after omission of the 130 children with discrepancies.

Results were also generally insensitive to an alternative assumption that all 130 children received thimerosal-containing HepB vaccinations at birth. Compared to the result based on original assumptions, the estimates based on alternative assumptions were often slightly attenuated (closer to zero) such that a few of the exposure effects that were below the $p<0.05$ criterion in the full data set moved above that criterion in the reduced data set. And all exposure effects that that had been non-significant full data set remained non-significant using the alternative HepB assumption for the 130 children with discrepancies.

Exhibit 17.2. Model Summary: *PreNatThimer* and *Exp07mos* Exposure Models
Records Omitted if Mother Said Child Received a HepB at Birth, but Medical Records Indicated No HepB at Birth (n=130 omitted)

Outcome	N	Exposure Measure	Estimate	Stderr	Prob ChiSq		One Unit Chg. OR[a]	Lower 95% CL	Upper 95% CL	1/OR	2 SD Unit Chg. OR[b]	1/OR
ASD_Outc	878	PreNatThimer	0.0073	0.0096	0.448		1.007	0.989	1.027		1.13	
ASD_Outc	878	Exp07mos	-0.0329	0.0183	0.072	~	0.968	0.934	1.003	1.033	0.60	1.67
AD_Outc	796	PreNatThimer	0.0107	0.0108	0.325		1.011	0.990	1.032		1.19	
AD_Outc	796	Exp07mos	-0.0414	0.0205	0.043	*	0.959	0.922	0.999	1.042	0.52	1.91
ASD_Only	673	PreNatThimer	0.0079	0.0216	0.715		1.008	0.966	1.051		1.14	
ASD_Only	673	Exp07mos	-0.0096	0.0362	0.792		0.990	0.923	1.063	1.010	0.86	1.16
ASD_Regr	609	PreNatThimer	0.0343	0.0226	0.130		1.035	0.990	1.082		1.75	
ASD_Regr	609	Exp07mos	-0.1104	0.0367	0.003	**	0.895	0.833	0.962	1.117	0.18	5.58
AD_ExLoCF	770	PreNatThimer	0.0166	0.0108	0.123		1.017	0.996	1.039		1.31	
AD_ExLoCF	770	Exp07mos	-0.0494	0.0224	0.027	*	0.952	0.911	0.995	1.051	0.46	2.16
ASD_Scr	725	PreNatThimer	0.0078	0.0099	0.428		1.008	0.989	1.028		1.14	
ASD_Scr	725	Exp07mos	-0.0447	0.0205	0.029	*	0.956	0.919	0.996	1.046	0.50	2.01
AD_Scr	646	PreNatThimer	0.0140	0.0116	0.229		1.014	0.991	1.038		1.26	
AD_Scr	646	Exp07mos	-0.0548	0.0245	0.025	*	0.947	0.902	0.993	1.056	0.43	2.34

~ 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 17.3. Model Summary: *PreNatThimer* , *Exp01mos, Exp17mos* Exposure Models Records Omitted if Mother Said Child Received a HepB at Birth, but Medical Records Indicated No HepB at Birth (n=130 omitted)

Outcome	N	Exposure Measure	Estimate	Stderr	Prob ChiSq		One Unit Chg. OR[a]	Lower 95% CL	Upper 95% CL	1/OR	2 SD Unit Chg. OR[b]	1/OR
ASD_Outc	878	PreNatThimer	0.0075	0.0097	0.437		1.008	0.989	1.027		1.13	
ASD_Outc	878	Exp01mos	0.0070	0.0500	0.888		1.007	0.913	1.111		1.03	
ASD_Outc	878	Exp17mos	-0.0400	0.0203	0.048	*	0.961	0.923	1.000	1.041	0.56	1.79
AD_Outc	796	PreNatThimer	0.0108	0.0110	0.323		1.011	0.989	1.033		1.19	
AD_Outc	796	Exp01mos	0.0500	0.0549	0.362		1.051	0.944	1.171		1.23	
AD_Outc	796	Exp17mos	-0.0582	0.0230	0.011	*	0.943	0.902	0.987	1.060	0.43	2.33
ASD_Only	673	PreNatThimer	0.0049	0.0213	0.820		1.005	0.964	1.048		1.08	
ASD_Only	673	Exp01mos	-0.1505	0.1092	0.168		0.860	0.695	1.066	1.162	0.54	1.85
ASD_Only	673	Exp17mos	0.0218	0.0420	0.603		1.022	0.941	1.110		1.37	
ASD_Regr	609	PreNatThimer	0.0359	0.0228	0.116		1.037	0.991	1.084		1.80	
ASD_Regr	609	Exp01mos	-0.0005	0.0942	0.996		0.999	0.831	1.202	1.001	1.00	1.00
ASD_Regr	609	Exp17mos	-0.1385	0.0447	0.002	**	0.871	0.798	0.950	1.149	0.13	7.50
AD_ExLoCF	770	PreNatThimer	0.0169	0.0109	0.119		1.017	0.996	1.039		1.32	
AD_ExLoCF	770	Exp01mos	0.0181	0.0605	0.765		1.018	0.904	1.146		1.08	
AD_ExLoCF	770	Exp17mos	-0.0621	0.0252	0.014	*	0.940	0.895	0.987	1.064	0.41	2.47
ASD_Scr	725	PreNatThimer	0.0079	0.0099	0.426		1.008	0.989	1.028		1.14	
ASD_Scr	725	Exp01mos	-0.0294	0.0526	0.576		0.971	0.876	1.076	1.030	0.89	1.13
ASD_Scr	725	Exp17mos	-0.0475	0.0224	0.034	*	0.954	0.913	0.996	1.049	0.50	2.00
AD_Scr	646	PreNatThimer	0.0138	0.0118	0.243		1.014	0.991	1.038		1.25	
AD_Scr	646	Exp01mos	0.0282	0.0612	0.645		1.029	0.912	1.160		1.12	
AD_Scr	646	Exp17mos	-0.0700	0.0270	0.010	*	0.932	0.884	0.983	1.072	0.36	2.77

~ 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 17.4. Model Summary: *PreNatThimer* and *Exp07mos* Exposure Models Records Omitted if Mother Said Child Received a HepB at Birth, but Medical Records Indicated No HepB at Birth (n=130 omitted)

Outcome	N	Exposure Measure	Estimate	Stderr	Prob ChiSq		One Unit Chg. OR[a]	Lower 95% CL	Upper 95% CL	1/OR	2 SD Unit Chg. OR[b]	1/OR
ASD_Outc	878	PreNatThimer	0.0071	0.0096	0.460		1.007	0.988	1.026		1.12	
ASD_Outc	878	Exp020mos	-0.0328	0.0177	0.064	~	0.968	0.935	1.002	1.033	0.56	1.79
AD_Outc	796	PreNatThimer	0.0101	0.0109	0.354		1.010	0.989	1.032		1.18	
AD_Outc	796	Exp020mos	-0.0371	0.0197	0.059	~	0.964	0.927	1.001	1.038	0.52	1.94
ASD_Only	673	PreNatThimer	0.0078	0.0216	0.718		1.008	0.966	1.052		1.14	
ASD_Only	673	Exp020mos	-0.0144	0.0345	0.678		0.986	0.921	1.055	1.014	0.77	1.29
ASD_Regr	609	PreNatThimer	0.0329	0.0224	0.142		1.033	0.989	1.080		1.71	
ASD_Regr	609	Exp020mos	-0.1040	0.0360	0.004	**	0.901	0.840	0.967	1.110	0.16	6.39
AD_ExLoCF	770	PreNatThimer	0.0160	0.0108	0.138		1.016	0.995	1.038		1.30	
AD_ExLoCF	770	Exp020mos	-0.0425	0.0216	0.049	*	0.958	0.919	1.000	1.043	0.47	2.13
ASD_Scr	725	PreNatThimer	0.0076	0.0099	0.444		1.008	0.988	1.027		1.13	
ASD_Scr	725	Exp020mos	-0.0375	0.0197	0.057	~	0.963	0.927	1.001	1.038	0.51	1.95
AD_Scr	646	PreNatThimer	0.0135	0.0117	0.248		1.014	0.991	1.037		1.25	
AD_Scr	646	Exp020mos	-0.0420	0.0233	0.072	~	0.959	0.916	1.004	1.043	0.47	2.11

~ 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 17.5. Model Summary: *PreNatThimer* and *Exp07mos* Exposure Models Records Where Mother Said Child Received a HepB at Birth, and Medical Records Indicated No HepB Was Received Were Recoded to Assume HepB Was Received (n=130 recoded)

Outcome	N	Exposure Measure	Estimate	Stderr	Prob ChiSq		One Unit Chg. OR[a]	Lower 95% CL	Upper 95% CL	1/OR	2 SD Unit Chg. OR[b]	1/OR
ASD_Outc	1008	PreNatThimer	0.0065	0.0094	0.489		1.007	0.988	1.025		1.11	
ASD_Outc	1008	Exp07mos	-0.0255	0.0163	0.117		0.975	0.944	1.006	1.026	0.67	1.49
AD_Outc	911	PreNatThimer	0.0106	0.0105	0.313		1.011	0.990	1.032		1.19	
AD_Outc	911	Exp07mos	-0.0390	0.0186	0.036	*	0.962	0.927	0.998	1.040	0.55	1.83
ASD_Only	773	PreNatThimer	-0.0027	0.0200	0.893		0.997	0.959	1.037	1.003	0.96	1.05
ASD_Only	773	Exp07mos	-0.0119	0.0293	0.685		0.988	0.933	1.047	1.012	0.83	1.20
ASD_Regr	701	PreNatThimer	0.0365	0.0209	0.080	~	1.037	0.996	1.080		1.82	
ASD_Regr	701	Exp07mos	-0.0783	0.0328	0.017	*	0.925	0.867	0.986	1.081	0.30	3.39
AD_ExLoCF	884	PreNatThimer	0.0152	0.0105	0.147		1.015	0.995	1.036		1.28	
AD_ExLoCF	884	Exp07mos	-0.0486	0.0202	0.016	*	0.953	0.916	0.991	1.050	0.47	2.13
ASD_Scr	821	PreNatThimer	0.0045	0.0098	0.649		1.004	0.985	1.024		1.08	
ASD_Scr	821	Exp07mos	-0.0344	0.0182	0.059	~	0.966	0.932	1.001	1.035	0.59	1.71
AD_Scr	728	PreNatThimer	0.0118	0.0115	0.303		1.012	0.989	1.035		1.21	
AD_Scr	728	Exp07mos	-0.0526	0.0221	0.018	*	0.949	0.908	0.991	1.054	0.44	2.27

~ 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 17.6. Model Summary: *PreNatThimer* , *Exp01mos, Exp17mos* Exposure Models Records Where Mother Said Child Received a HepB at Birth, and Medical Records Indicated No HepB Was Received Were Recoded to Assume HepB Was Received (n=130 recoded)

Outcome	N	Exposure Measure	Estimate	Stderr	Prob ChiSq		One Unit Chg. OR[a]	Lower 95% CL	Upper 95% CL	1/OR	2 SD Unit Chg. OR[b]	1/OR
ASD_Outc	1008	PreNatThimer	0.0068	0.0095	0.472		1.007	0.988	1.026		1.12	
ASD_Outc	1008	Exp01mos	0.0221	0.0435	0.612		1.022	0.939	1.113		1.09	
ASD_Outc	1008	Exp17mos	-0.0349	0.0182	0.055	~	0.966	0.932	1.001	1.036	0.60	1.66
AD_Outc	911	PreNatThimer	0.0108	0.0106	0.311		1.011	0.990	1.032		1.19	
AD_Outc	911	Exp01mos	0.0488	0.0483	0.312		1.050	0.955	1.154		1.22	
AD_Outc	911	Exp17mos	-0.0572	0.0211	0.007	**	0.944	0.906	0.984	1.059	0.44	2.30
ASD_Only	773	PreNatThimer	-0.0043	0.0198	0.829		0.996	0.958	1.035	1.004	0.93	1.07
ASD_Only	773	Exp01mos	-0.0973	0.0914	0.287		0.907	0.758	1.085	1.102	0.67	1.49
ASD_Only	773	Exp17mos	-0.0007	0.0309	0.983		0.999	0.941	1.062	1.001	0.99	1.01
ASD_Regr	701	PreNatThimer	0.0384	0.0210	0.067	~	1.039	0.997	1.083		1.87	
ASD_Regr	701	Exp01mos	0.0254	0.0838	0.762		1.026	0.870	1.209		1.11	
ASD_Regr	701	Exp17mos	-0.1025	0.0388	0.008	**	0.903	0.837	0.974	1.108	0.23	4.44
AD_ExLoCF	884	PreNatThimer	0.0155	0.0105	0.143		1.016	0.995	1.037		1.29	
AD_ExLoCF	884	Exp01mos	0.0261	0.0522	0.616		1.026	0.927	1.137		1.11	
AD_ExLoCF	884	Exp17mos	-0.0646	0.0229	0.005	**	0.937	0.896	0.981	1.067	0.39	2.56
ASD_Scr	821	PreNatThimer	0.0046	0.0098	0.642		1.005	0.985	1.024		1.08	
ASD_Scr	821	Exp01mos	-0.0077	0.0474	0.871		0.992	0.904	1.089	1.008	0.97	1.03
ASD_Scr	821	Exp17mos	-0.0398	0.0203	0.050	~	0.961	0.924	1.000	1.041	0.56	1.78
AD_Scr	728	PreNatThimer	0.0117	0.0116	0.317		1.012	0.989	1.035		1.21	
AD_Scr	728	Exp01mos	0.0379	0.0548	0.489		1.039	0.933	1.156		1.17	
AD_Scr	728	Exp17mos	-0.0720	0.0249	0.004	**	0.931	0.886	0.977	1.075	0.35	2.85

~ 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 17.7. Model Summary: *PreNatThimer* and *Exp07mos* Exposure Models Records Where Mother Said Child Received a HepB at Birth, and Medical Records Indicated No HepB Was Received Were Recoded to Assume HepB Was Received (n=130 recoded)

Outcome	N	Exposure Measure	Estimate	Stderr	Prob ChiSq		One Unit Chg. OR[a]	Lower 95% CL	Upper 95% CL	1/OR	2 SD Unit Chg. OR[b]	1/OR
ASD_Outc	1008	PreNatThimer	0.0064	0.0094	0.496		1.006	0.988	1.025		1.11	
ASD_Outc	1008	Exp020mos	-0.0256	0.0156	0.102	~	0.975	0.945	1.005	1.026	0.63	1.58
AD_Outc	911	PreNatThimer	0.0101	0.0105	0.336		1.010	0.990	1.031		1.18	
AD_Outc	911	Exp020mos	-0.0355	0.0178	0.046	*	0.965	0.932	0.999	1.036	0.53	1.88
ASD_Only	773	PreNatThimer	-0.0025	0.0200	0.901		0.998	0.959	1.037	1.003	0.96	1.04
ASD_Only	773	Exp020mos	-0.0156	0.0274	0.571		0.985	0.933	1.039	1.016	0.76	1.32
ASD_Regr	701	PreNatThimer	0.0353	0.0206	0.086		1.036	0.995	1.079		1.78	
ASD_Regr	701	Exp020mos	-0.0590	0.0309	0.056	~	0.943	0.887	1.002	1.061	0.35	2.86
AD_ExLoCF	884	PreNatThimer	0.0147	0.0105	0.161		1.015	0.994	1.036		1.27	
AD_ExLoCF	884	Exp020mos	-0.0435	0.0193	0.024	*	0.957	0.922	0.994	1.044	0.46	2.17
ASD_Scr	821	PreNatThimer	0.0043	0.0098	0.662		1.004	0.985	1.024		1.07	
ASD_Scr	821	Exp020mos	-0.0291	0.0172	0.090	~	0.971	0.939	1.005	1.030	0.60	1.68
AD_Scr	728	PreNatThimer	0.0113	0.0115	0.325		1.011	0.989	1.035		1.20	
AD_Scr	728	Exp020mos	-0.0421	0.0207	0.042	*	0.959	0.921	0.998	1.043	0.47	2.12

~ 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.

18. Additional Detail on Weight at Time of Vaccine Receipt

The exposure variables used in the main models shown in Chapter 9 of Volume I (*Exp01mos, Exp17mos, Exp07mos,* and *Exp020mos*) were calculated as the amount of ethlylmercury (in micrograms) in each vaccine or immune globulin received by a child, divided by the child's weight (in kilograms) at the time of the receipt, and summed over the relevant age range, i.e., birth to one month, one to seven months, birth to seven months, and birth to 20 months. (See Chapter 7 for additional details on the creation of these variables). For most vaccine receipts, the child's weight was obtained on the same day that the vaccine was received and recorded in the child's medical records. In instances when a vaccine or immune globulin was received, but the child's weight was not recorded, we replaced the missing value for the child's weight at time of receipt with an imputed weight. Either of two methods was used to obtain an imputed weight: interpolation, or extrapolation. The purpose of the current chapter is to provide details on:

- The interpolation method
- The extrapolation method
- The frequency that interpolation and extrapolation were used to obtain imputed values
- The number of days between observed weights (i.e., weights that were recorded in the child's medical chart), and the imputed weights

We note that since similar results were obtained from models that used the exposure measures that divided by weight at time of receipt (*Exp01mos, Exp17mos, Exp07mos,* and *Exp020mos*) and from models that used the exposure measures that were not divided by weight at the time of vaccine receipt (*Amt01mos, Amt17mos, Amt07mos,* and *Amt 020mos*), we conclude that the results could not have been sensitive to the imputation of weights when weights were not recorded on the same day as vaccine receipt.

18.1. The Interpolation Method

When there was no weight recorded for a child on the day the he or she received a vaccine or immune globulin, but the child had a recorded weights both prior to and after the day of the receipt, linear interpolation was used. We explain the method via the following hypothetical example.

Suppose that:

- a child's weight at birth (age = 1 day) was 3,884 grams
- his weight at age 15 days was 4,082 grams
- he received a vaccination on day 4, but no weight was recorded.

For the method of linear interpolation, we calculate that the child gained 4,082 – 3,884 = 198 grams, over 14 days, or an average of 198/14 = 14.1 grams per day. We obtain the interpolated weight as the weight on day 1, plus three days of growth at 14.14 grams per

day, which equals 3884 + (3*14.14) = 3,926.4 grams. In the data set, we replace the missing weight at day 4 with the imputed value 3,926.4.

We note that in this example, the number of days from the imputed weight (day 4) to the closest observed weight (day 1) was 3.

18.2. The Extrapolation Method

All children had recorded birth weights. When a child's records indicted receipt of a thimerosal-containing vaccine or immune globulin, and there was no recorded weight from the same day and no recorded weights on any subsequent days, the weight was extrapolated using a prediction model based on the child's birth weight and sex. The prediction model produced a predicted value for the child's weight for a particular age. We developed the prediction model from the observed data and checked the predictions from the model against the CDC growth charts[20] and found close agreement. For each child where extrapolation was used, the agreement between predicted and observed weights appeared to be close (example plots are shown subsequently). We used the following prediction models to obtain a predicted value ($\hat{Y}_{wgt}$) of a child's unknown weight at a given age given the child's birth weight and sex:

$$\hat{Y}_{wgt} = \hat{\beta}_0 + \hat{\beta}_1(BirthWt) + \hat{\beta}_2(Age) + \hat{\beta}_3(Age^2) + \hat{\beta}_4(Age^3) + \hat{\beta}_5(Age^4)$$
$$+ \hat{\beta}_6(BirthWt * Age) + \hat{\beta}_7(BirthWt * Age^2) + \hat{\beta}_8(BirthWt * Age^3) + \hat{\beta}_9(BirthWt * Age^4)$$
$$+ \hat{\beta}_{10}(BirthWt^2 * Age) + \hat{\beta}_{11}(BirthWt^2 * Age^2) + \hat{\beta}_{12}(BirthWt^2 * Age^3) + \hat{\beta}_{13}(BirthWt^2 * Age^4)$$

where
BirthWt was the child's weight at birth in kilograms, and
Age was child's age in days – 1, at time of vaccine receipt. On the day of birth, this age measure took the value of zero.

The values of the beta-hats used were as follows:

	If female	If male
$\hat{\beta}_0$	-0.01075	0.03011
$\hat{\beta}_1$	1.0066	0.9975
$\hat{\beta}_2$	27.9254	48.2572
$\hat{\beta}_3$	-31.0399	-98.7214
$\hat{\beta}_4$	22.1590	94.4414
$\hat{\beta}_5$	-5.4832	-31.6001
$\hat{\beta}_6$	-6.3240	-15.1316
$\hat{\beta}_7$	7.0345	38.1719
$\hat{\beta}_8$	-7.3054	-39.9481
$\hat{\beta}_9$	2.1121	13.8173

[20] *2000 CDC Growth Charts for the United States: Methods and Developments*.

$\hat{\beta}_{10}$	1.7201	2.9066
$\hat{\beta}_{11}$	-2.3570	-6.5567
$\hat{\beta}_{12}$	2.3927	6.5596
$\hat{\beta}_{13}$	-0.7460	-2.1961

18.3. The Frequency of Interpolated and Extrapolated Weights

In the process of creating an analysis data set, we replaced all missing weights for any vaccine or immune globulin receipts with imputed values. However, the use of imputed weights, rather than having actual observed weights, has the potential to affect the results of the study only when the imputed weight corresponds to a receipt of a thimerosal-containing vaccine or immune globulin. Therefore, in this section we provide frequencies of observed and imputed weights corresponding to the receipt of thimerosal-containing vaccines, within the age range spanning birth to 20 months. These data correspond to the n=1,008 participants in the analyses of ASD cases to matched controls.

Exhibit 18.1 shows that the child's weight was recorded on the day of receipt for 80 percent of the receipts of thimerosal-containing vaccines and immune globulins received in the age range spanning birth to 20 months. Thirteen percent of the receipts had interpolated weights where the number of days from the interpolated weight to the closest observed weight was in the range of 1 to 30 days. Four percent were interpolated where the closest observed weight was 31 to 182 days away. When the number of days from the imputed weight to the closest observed date is small, there is little potential for the imputed value to be far from what would have been obtained had the child been weighed on the day of vaccine receipt. Few interpolated values were more than six months from an observed value. Three percent of weights were extrapolated.

Exhibit 18.2 is similar to the previous exhibit but is split out by case-control status. Among ASD cases, 78 percent of weights were recorded on the same day as vaccine receipts, while for controls 80 percent were recorded on the same day.

Exhibits 18.3 – 18.6 show observed and imputed weights for some randomly chosen individuals that had imputed weights. The plots show child's age in months along the x-axis plotted against child's weight in grams on the Y-axis. Observed weights are indicated by the plotting symbol "o", while imputed weights are shown with the symbol "+". Exhibits 18.3 and 18.4 show interpolated and extrapolated weights, respectively, where the closest observed weight was less than six months from the imputed weight. Exhibits 18.5 and 18.6 are similar, but correspond to individuals that had at least one imputed weight, where imputed weight was more than six months from the closest observed weight.

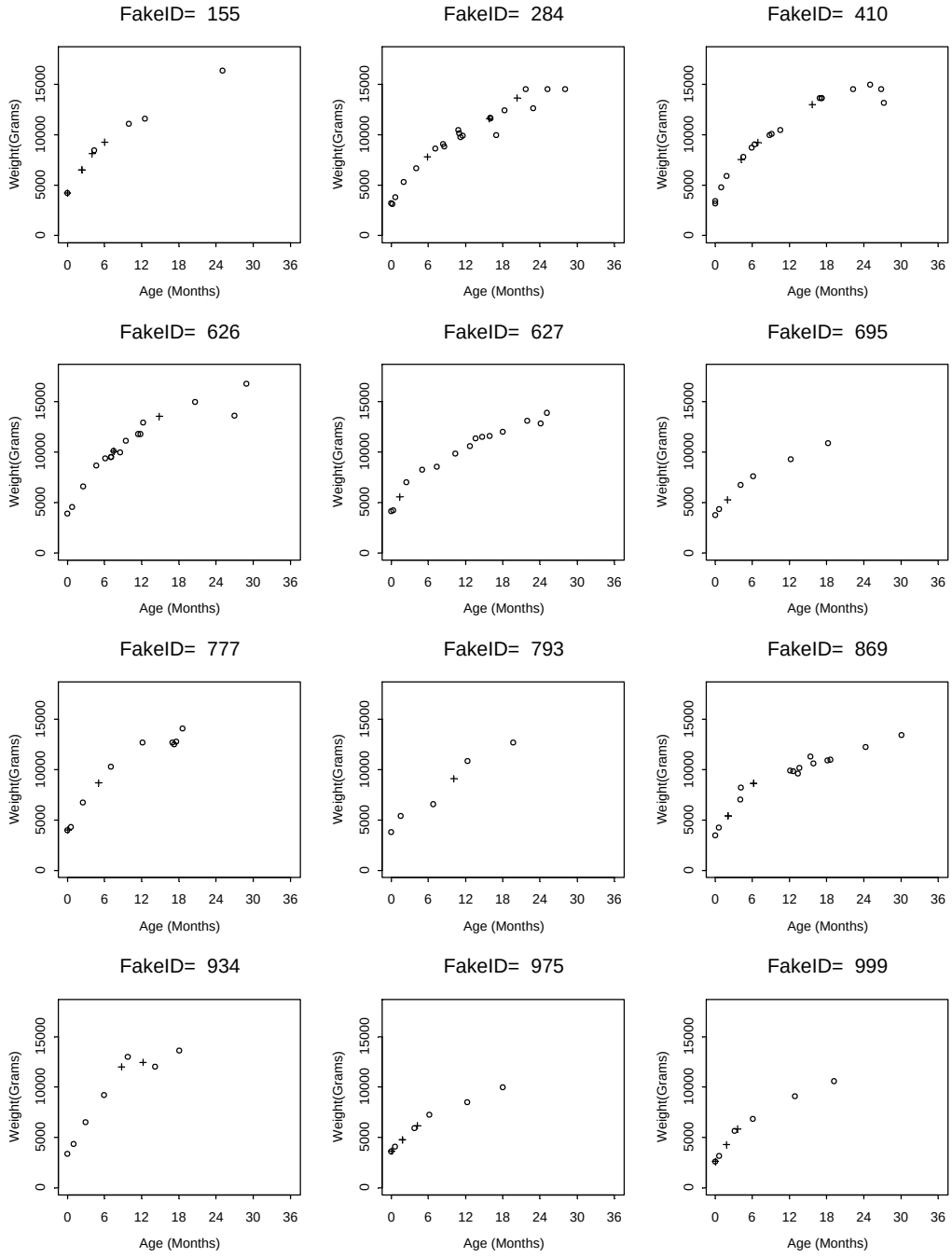
Exhibit 18.1. Frequency and Percent of Interpolations and Extrapolations For Weights At Time of Receipt of Thimerosal-Containing Vaccines and Immune Globulins (Data from n=1,008 ASD Cases and Matched Controls)

Type of Weight Measure	Days to Closest Observed Weight	Frequency	Percent	Frequency	Percent
Observed	0	5,663	79.63	5,663	79.63
Interpolated	1-30 days	912	12.82		
Interpolated	31-182 days	292	4.11	1,224	17.21
Interpolated	>6 months	20	0.28		
Extrapolated	1-30 days	27	0.38		
Extrapolated	31-182 days	112	1.57	225	3.16
Extrapolated	>6 months	86	1.21		
Total # of Receipts of Thimerosal-containing Vaccines or Immune Globulins		7,112	100	7,112	100

Exhibit 18.2. Case / Control Comparison of Frequency and Percent of Interpolations and Extrapolations For Weights At Time of Receipt of Thimerosal-Containing Vaccines and Immune Globulins (Data from n=1,008 ASD Cases and Matched Controls)

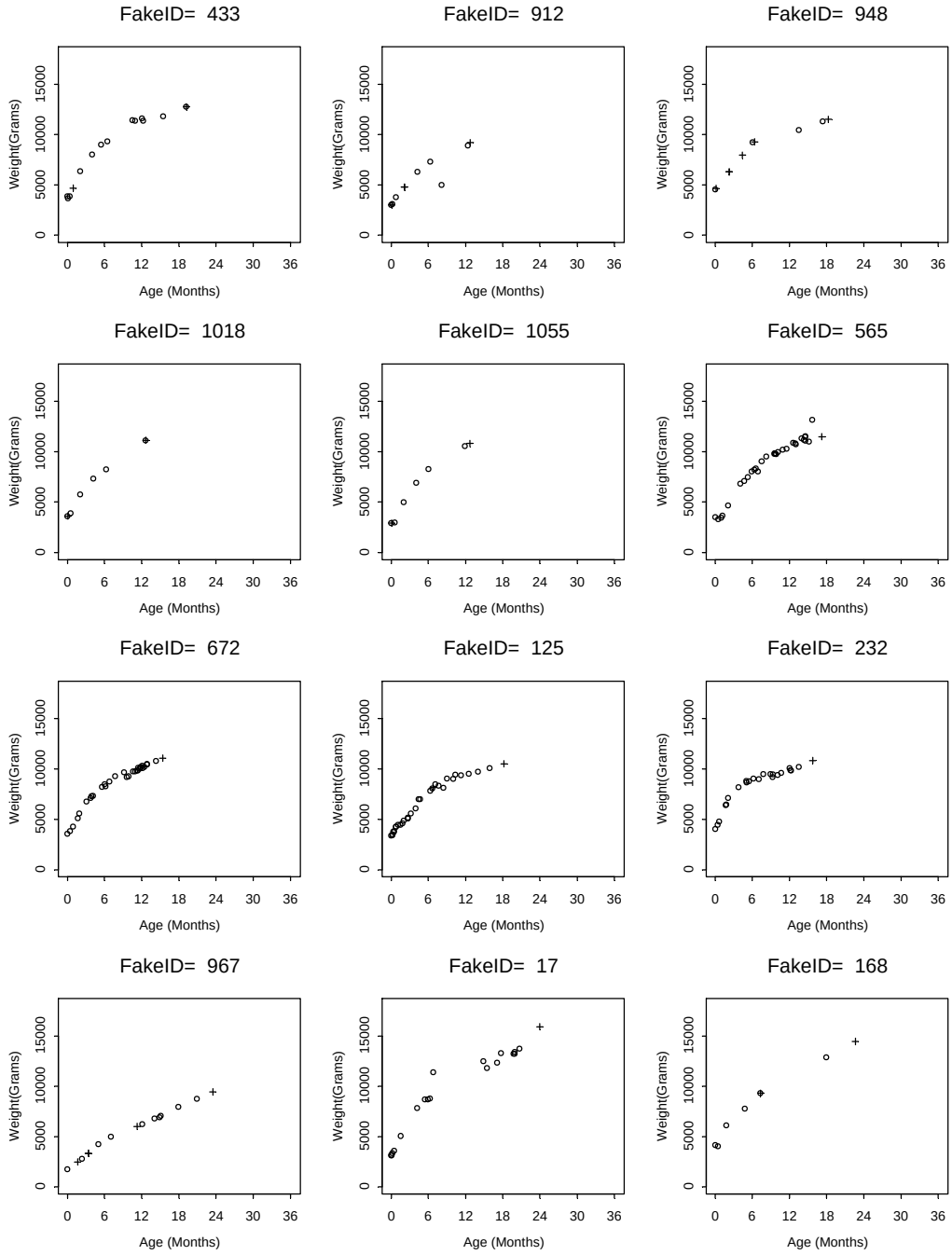
Type of	Days to Closest	ASD Cases		Controls	
Weight Measure	Observed Weight	Frequency	Percent	Frequency	Percent
Observed	0	1379	78.04	4284	80.15
Interpolated	1-30 days	227	12.85	685	12.82
Interpolated	31-182 days	79	4.47	213	3.99
Interpolated	>6 months	10	0.57	10	0.19
Extrapolated	1-30 days	9	0.51	18	0.34
Extrapolated	31-182 days	36	2.04	76	1.42
Extrapolated	>6 months	27	1.53	59	1.1
Total # of Receipts of Thimerosal-containing Vaccines or Immune Globulins		1767	100	5345	100

Exhibit 18.3. Examples of Interpolations Where Closest Observed Value is Less than 6 Months From the Imputed Value



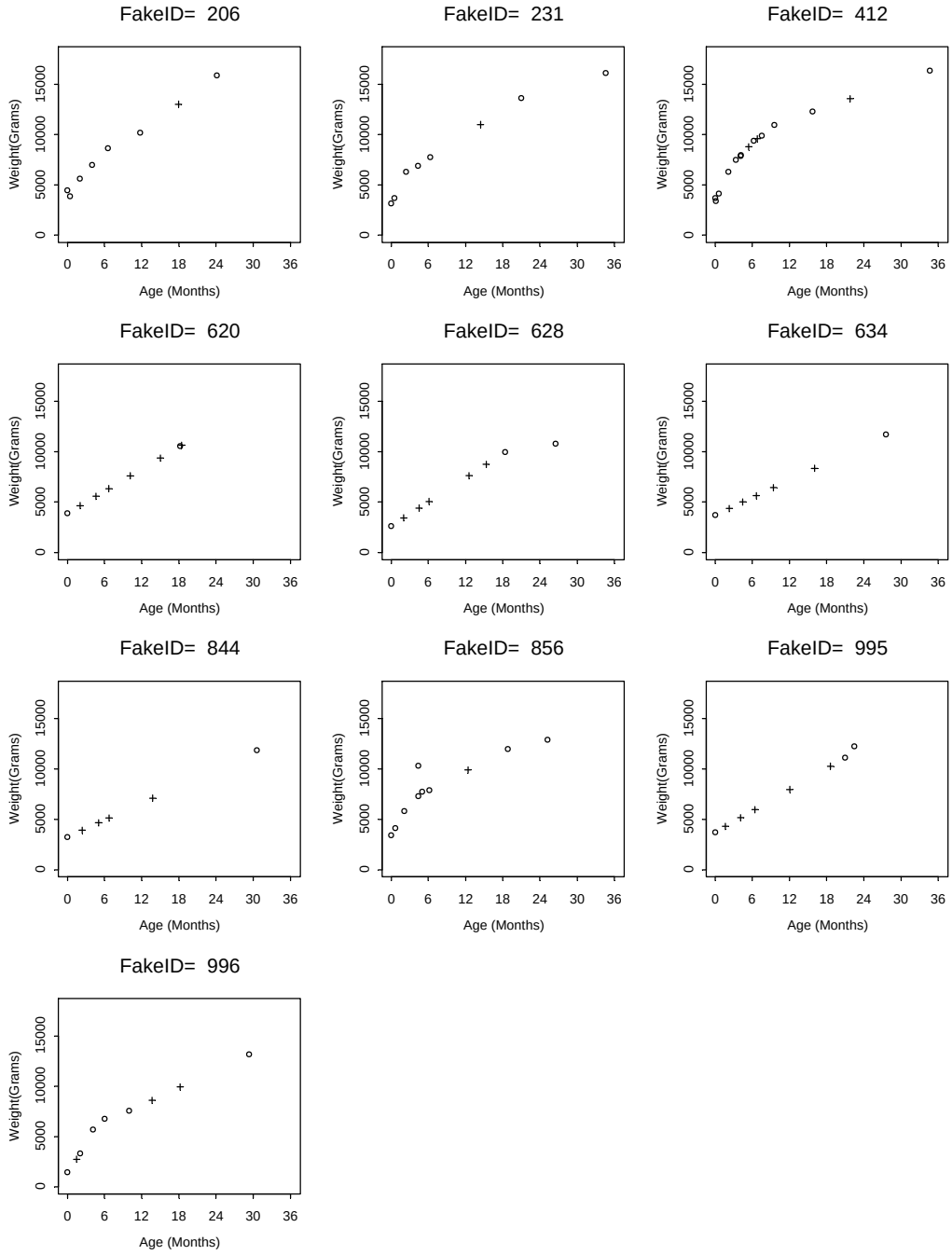
"FakeID" is an identification number corresponding to individual study participants.
"0" indicates observed weights.
"+" indicates imputed weights

Exhibit 18.4. Examples of Extrapolations Where Closest Observed Value is Less than 6 Months From the Imputed Value



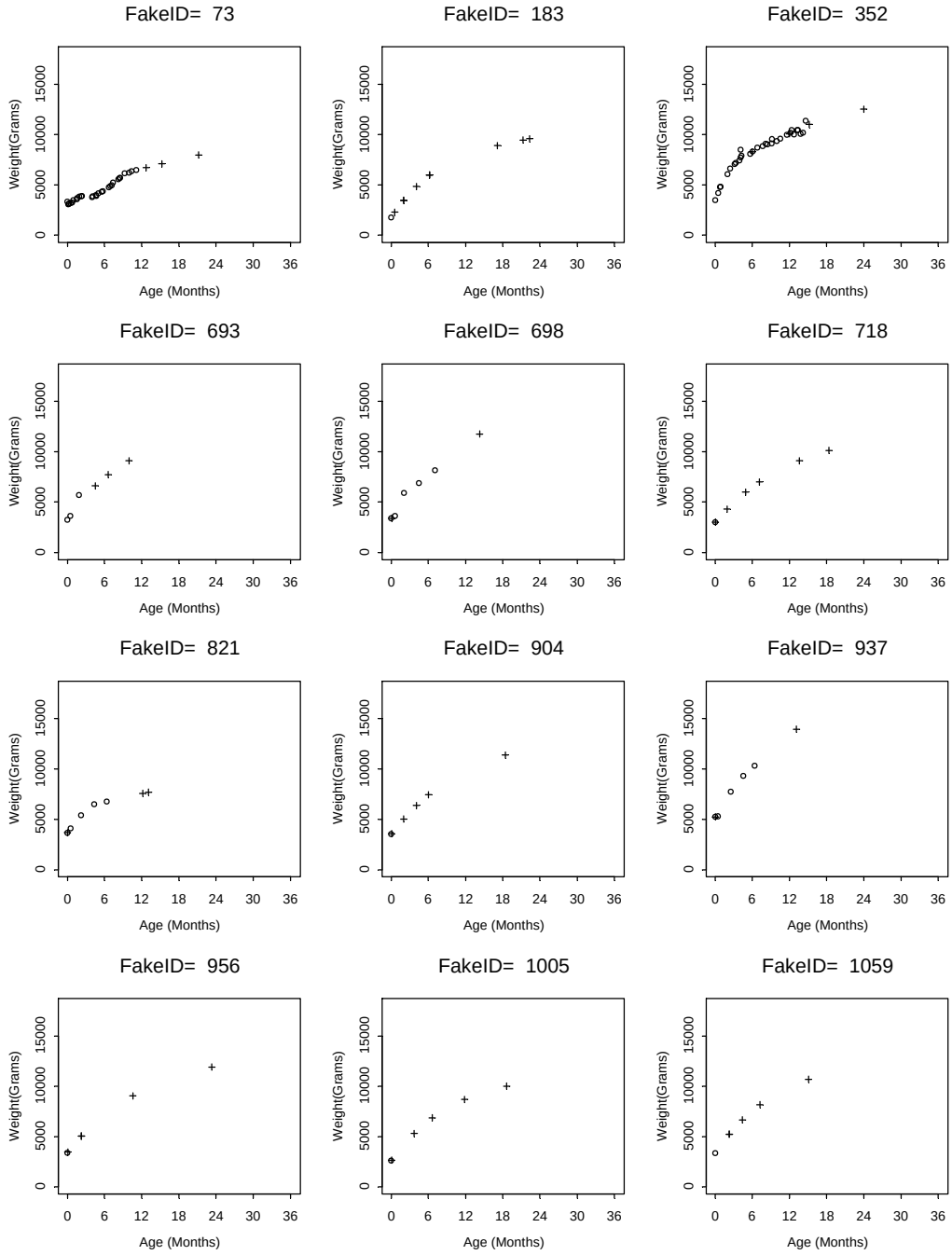
"FakeID" is an identification number corresponding to individual study participants.
"0" indicates observed weights.
"+" indicates imputed weights

Exhibit 18.5. Examples of Interpolations Where Closest Observed Value is 6 Months or More From the Imputed Value



There were only 10 individuals with interpolated values that were more than six months from an observed value.
"0" indicates observed weights.
"+" indicates imputed weights

Exhibit 18.6. Examples of Extrapolations Where Closest Observed Value is 6 Months or More From the Imputed Value



"FakeID" is an identification number corresponding to individual study participants.
"0" indicates observed weights.
"+" indicates imputed weights

19. Detail of Model Results

This appendix shows the detail of model results for two outcomes (ASD, and AD) for the model with exposure measures *PreNatThimer*, *Exp01mos*, and *Exp17mos*.

Exhibit 19.1. ASD Outcome: Detail of Model Results

The PHREG Procedure

Model Information

Data Set	WORK.BASE2	
Dependent Variable	ASD_time	=1 if ASD/AD, =2 Cntr, .=exclude
Censoring Variable	ASD_Outc	=1 if ASD/AD, =0 Cntr, .=exclude
Censoring Value(s)	0	
Ties Handling	DISCRETE	

Number of Observations Read	1008
Number of Observations Used	1008

Summary of the Number of Event and Censored Values

Stratum	Match Strat	Total	Event	Censored	Percent Censored
1	2	6	1	5	83.33
2	3	4	1	3	75.00
3	4	7	1	6	85.71
4	5	5	1	4	80.00
5	7	3	1	2	66.67
6	8	3	1	2	66.67
7	9	3	1	2	66.67
8	10	5	1	4	80.00
9	12	5	1	4	80.00
10	13	19	3	16	84.21
11	14	89	20	69	77.53
12	15	24	7	17	70.83
13	16	66	14	52	78.79
14	17	8	2	6	75.00
15	18	62	13	49	79.03
16	19	17	4	13	76.47
17	20	73	18	55	75.34
18	21	6	1	5	83.33
19	22	63	19	44	69.84
20	23	7	1	6	85.71
21	24	25	8	17	68.00
22	25	10	3	7	70.00
23	26	15	3	12	80.00
24	28	25	7	18	72.00
25	29	13	2	11	84.62
26	30	56	14	42	75.00
27	32	50	14	36	72.00
28	33	8	3	5	62.50
29	34	67	18	49	73.13
30	35	10	1	9	90.00
31	36	51	13	38	74.51
32	38	15	5	10	66.67
33	40	27	9	18	66.67
34	42	35	10	25	71.43
35	43	4	1	3	75.00
36	44	51	16	35	68.63
37	46	25	5	20	80.00
38	47	6	1	5	83.33
39	48	40	12	28	70.00
Total		1008	256	752	74.60

Exhibit 19.1. ASD Outcome: Detail of Model Results

Convergence Status

Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics

Criterion	Without Covariates	With Covariates
-2 LOG L	1014.335	932.907
AIC	1014.335	986.907
SBC	1014.335	1082.627

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	81.4277	27	<.0001
Score	78.9093	27	<.0001
Wald	69.2152	27	<.0001

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
PreNatThimer	1	0.00687	0.00942	0.5314	0.4660	1.007
Exp01mos	1	-0.03042	0.04474	0.4622	0.4966	0.970
Exp17mos	1	-0.03359	0.01816	3.4203	0.0644	0.967
BW1_1p5k	1	-3.09721	1.54387	4.0246	0.0448	0.045
BW1p5_2p5k	1	-2.03395	1.19236	2.9098	0.0880	0.131
BW2p5_4k	1	-2.22305	1.18387	3.5260	0.0604	0.108
BW4kup	1	-2.16804	1.20730	3.2248	0.0725	0.114
Mom20_24	1	-0.44952	0.69003	0.4244	0.5148	0.638
Mom25_29	1	0.27659	0.64295	0.1851	0.6671	1.319
Mom30_34	1	0.59281	0.64454	0.8459	0.3577	1.809
MomGE35	1	0.70536	0.64870	1.1823	0.2769	2.025
BirthOrder2_1	1	-0.13951	0.17471	0.6376	0.4246	0.870
BirthOrderGE3_1	1	-0.75300	0.22999	10.7194	0.0011	0.471
BF1_6mos	1	-0.28450	0.20513	1.9236	0.1655	0.752
BFgt6mos	1	-0.33430	0.20169	2.7473	0.0974	0.716
PovertyRatio1	1	-0.10636	0.02953	12.9748	0.0003	0.899
PreNatAlcohol_1	1	0.29948	0.24175	1.5347	0.2154	1.349
Folic_PNVit_Multi	1	0.83485	0.36509	5.2291	0.0222	2.304
Anemia	1	-0.57294	0.57274	1.0007	0.3171	0.564
ChildPica	1	1.51903	0.35474	18.3364	<.0001	4.568
HC_InitInad_1	1	0.69973	0.44317	2.4930	0.1144	2.013
HC_Cholest_1	1	-0.13966	0.32182	0.1883	0.6643	0.870
HC_Cholest_2	1	0.47178	0.23738	3.9499	0.0469	1.603
HC_PAP_1	1	0.36955	1.23456	0.0896	0.7647	1.447
HC_PAP_2	1	-0.25276	1.20965	0.0437	0.8345	0.777
PreNatLead_1	1	-0.18887	0.18213	1.0754	0.2997	0.828
PreNatViralInf	1	0.31347	0.32144	0.9510	0.3295	1.368

Exhibit 19.2. AD Outcome: Detail of Model Results

The PHREG Procedure

Model Information

Data Set	WORK.BASE2	
Dependent Variable	AD_time	=1 if AD, =2 Cntr, .=exclude
Censoring Variable	AD_Outc	=1 if AD, =0 Cntr, .=exclude
Censoring Value(s)	0	
Ties Handling	DISCRETE	

Number of Observations Read 911
Number of Observations Used 911

Convergence Status

Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics

Criterion	Without Covariates	With Covariates
-2 LOG L	813.650	731.754
AIC	813.650	779.754
SBC	813.650	857.300

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	81.8959	24	<.0001
Score	78.5266	24	<.0001
Wald	65.8955	24	<.0001

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
PreNatThimer	1	0.01057	0.01059	0.9956	0.3184	1.011
Exp01mos	1	0.02837	0.04888	0.3370	0.5616	1.029
Exp17mos	1	-0.05599	0.02106	7.0687	0.0078	0.946
BW1_1p5k	1	-3.84962	1.60444	5.7569	0.0164	0.021
BW1p5_2p5k	1	-3.44192	1.30484	6.9581	0.0083	0.032
BW2p5_4k	1	-3.67264	1.30456	7.9255	0.0049	0.025
BW4kup	1	-3.70067	1.33253	7.7127	0.0055	0.025
Mom20_24	1	-0.80647	0.71106	1.2864	0.2567	0.446
Mom25_29	1	-0.20454	0.65807	0.0966	0.7559	0.815
Mom30_34	1	0.14847	0.65834	0.0509	0.8216	1.160
MomGE35	1	0.27381	0.66186	0.1711	0.6791	1.315
BirthOrder2_1	1	-0.07301	0.19767	0.1364	0.7119	0.930
BirthOrderGE3_1	1	-0.79786	0.26608	8.9914	0.0027	0.450
BF1_6mos	1	-0.27192	0.23410	1.3492	0.2454	0.762
BFgt6mos	1	-0.22584	0.22866	0.9755	0.3233	0.798
PovertyRatio1	1	-0.13267	0.03542	14.0292	0.0002	0.876
Folic_PNVit_Multi	1	0.89237	0.43124	4.2820	0.0385	2.441
Anemia	1	-1.88940	1.05583	3.2023	0.0735	0.151
ChildPica	1	1.61779	0.38955	17.2469	<.0001	5.042
HC_InitInad_1	1	0.27165	0.53891	0.2541	0.6142	1.312
HC_Cholest_1	1	-0.39450	0.37707	1.0946	0.2955	0.674
HC_Cholest_2	1	0.47071	0.26714	3.1049	0.0781	1.601
HC_PAP_1	1	0.15643	1.27236	0.0151	0.9022	1.169
HC_PAP_2	1	-0.61175	1.24166	0.2427	0.6222	0.542

20. Power Analyses

This appendix is intended to 1) document the reasons for differences between the numbers of cases that the study was expected to have, as envisioned in the design phase of the project, and the actual number of cases obtained; and 2) provide power calculations showing the minimum detectable effect sizes (MDEs) from the obtained sample, and how those MDEs compare what had been envisioned during the design phase.

20.1. Comparison of Expected to Obtained Sample Sizes

Exhibit 20.1 shows our design phase assumptions about the numbers of cases that would be identified as having previously been diagnosed with ASD within the three participating HMOs (n=877), the steps in the recruitment and assessment processes, and the proportions of cases that would be lost at each step, and finally, the numbers of confirmed ASD and AD cases that would be available in the analysis data set (n=320 and n=200, respectively). One of the assumptions implicit in the diagram was that 62.5 percent of the confirmed ASD cases would be confirmed AD cases. Thus, 320 confirmed ASD cases would yield an analysis sample of 200 confirmed AD cases. The power calculations presented in the analysis plan were based on assumptions of analysis samples with n=320 ASD cases and n=200 AD cases, and a ratio of three controls per case. Note that at one point in the design phase, we had increased the target size of cases that had previously been diagnosed with ASD from n=877 to n=1,095. We had set this higher target number based on revised assumption that only 50 percent of ASD cases would also meet criteria for AD. This meant that to get 200 confirmed AD cases we would need to identify the 400 confirmed ASD cases. This assumption led to an increase in the target number of previously diagnosed cases (shown at the top of Exhibit 1) from n=877 to n=1,095[21]. However, that assumption was later determined to be too conservative. We eventually returned to the original assumption that roughly 62 percent of confirmed ASD cases would be confirmed for AD, which returned us to the original target number of n=877. As explained below, the actual proportion of confirmed ASD cases that also met criteria for AD was even higher (73 percent).

Exhibit 20.2 shows the actual numbers of cases obtained. In the text that follows, we discuss the actual and the expected numbers and proportions at each stage of the process. The discussion follows the ordering of the diagrams from top to bottom.

Previously diagnosed with ASD: We had expected that within the three participating HMOs, we could identify 877 cases previously diagnosed with ASD that met the

[21] Using the same assumptions regarding the proportions of cases lost at each step as shown in Exhibit 1, we had assumed that if we started with 1,095 at the top of the diagram, we would obtain n=400 ASD cases for use in the analyses. This later scenario, however, assumed that only 50 percent of ASD cases would meet criteria for AD, so this scenario resulted in the same projected number of AD cases in the analysis sample as had the original projection, i.e., n=200 AD cases.

eligibility criteria shown in the diagrams. As we developed the sampling frames from the three HMOs, it was discovered that there were fewer eligible cases at the three HMOs than had been originally expected. To respond to this problem, we opened up a new geographic area from HMO-C to the eligibility criteria, which made an additional population of cases eligible for the study. After adding this new geographic area and an assessment clinic for that area, the number of cases previously diagnosed with ASD was n=810. While this number was still short of the 877 originally envisioned, it was decided that the costs of adding yet another clinic and population to the study were prohibitive.

Physician Letter: Letters went to the primary care physicians of the sample of n=810 cases.

Physician Refusal: We had originally expected that physicians would refuse participation for only 1 percent of cases. The actual refusal rate was higher (4 percent). Additionally, 1 percent were determined to be ineligible at this phase. The refusal rate was considerably higher at one HMO (10 %) where the IRB required written permission from each child's primary care physician before the child's mother could be invited to participate in the study. At the other two HMOs, the child's primary care physician had to be notified, but written permission was not required (less than 1 % refusal rate).

HMO Recruitment Letter and Opt-out Card: The way that recruitment and eligibility outcome data were reported does not allow us to identify the proportion that opted-out via the opt-out card. Therefore, in Exhibit 20.2, we have entered question marks ("?") for that point in the process.

Additionally, unlike the depiction in the original diagram (Exhibit 1), "refusals", "unlocated / passive refusals[22]", and "ineligibles" were identified during both recruitment and eligibility calls. Therefore, the diagram for the actual number of cases obtain diverges in form from the original diagram at this point.

HMO Recruitment Call / Sent to Recruitment: The originally envisioned scenario planned for n=868 cases going to recruitment after removal of physician opt-out cases. The actual number going to recruitment was smaller, (n=771 cases going to recruitment). The assumption was that 20 percent of cases would refuse participation at this point in the process. The actual number was higher: 28 percent of cases refused participation at this point, an additional 3 percent could not be located or passively refused, plus 11 percent were discovered to be ineligible. Thus, only 59 percent of the cases that went to recruitment actually made it to the eligibility screening call, compared with the 80 percent in the design assumptions.

Eligibility Screening Call: The design assumed that 20 percent of cases screened for eligibility would be found ineligible. In fact, only 4 percent were determined to be ineligible at this stage, with another 5 percent of cases refusing, and 1 percent that were unlocated/ passive refusers. Whereas we had assumed that 80 percent of the cases that made it to the eligibility call would continue to the parent interview, the actual proportion

[22] Passive refusals include repeated attempts at phone contact with no answer or no returned calls.

going to the parent interview was higher (90 percent). Since we had assumed that a sample of n=625 cases would make it to the eligibility screening call and 80 percent would be found eligible, the expected sample for the parent interview was 500. The actual number of cases for the parent interview was 90 percent of the sample of n=452, or n=409 cases.

Parent Interview: We had expected that 20 percent of parents would refuse or fail to complete the parent interview, with the remaining 80 percent (n = 400) going to the clinical assessment. The actual proportion that completed the parent interview and continued on to the clinical assessment was higher--94 percent, (for a sample of 386).

Clinical Assessment: Once cases went to clinical assessment, it was assumed that 16 percent would fail to meet study criteria for classification as ASD; the actual proportion was 17 percent. However, the original assumptions were that only 4 percent of cases would fail to ***complete*** the assessment, while the actual proportion was 17 percent. Thus, while the original assumptions led to an expected completion rate of 80 percent of cases that being assessed and meeting criteria for ASD, the actual proportion was lower—only 66 percent.

ASD Case: The combined assumptions about sample flow resulted in an estimated n=320 cases in the analysis data set whereas the actual number of cases in the analysis data set was n=256.

AD Case: The original assumptions were that 63 percent of ASD cases would meet criteria for AD, resulting in n=200 cases in the analysis data set. The actual results had 73 percent of ASD cases meeting criteria for AD, resulting in n=187 cases in the analysis data set.

Controls: The originally envisioned scenario had a control to case ratio of 3 to 1. The actual ratios of ASD to matched controls, and AD to matched controls were 2.9 to 1, and 3.9 to 1, respectively.

20.2. Comparison of Expected to Obtained Power to Detect Effects

Relationships with ASD

The power calculations were based on the exposure effect sizes associated with each increase in 12.5 micrograms of ethylmercury from thimerosal-containing vaccines and immune globulins. During the design phase of the study, we had estimated that with samples of 320 ASD cases and 960 matched controls (3:1 controls to cases), the study would have approximately 80 percent power to detect exposure effects of the following sizes:

For prenatal exposure, power to detect an odds ratio of 1.80 associated with each increase in 12.5 micrograms of exposure.

For exposure in the first month of life, power to detect an odds ratio of 1.90 associated with each increase in exposure of 12. 5 micrograms.
For cumulative exposure during the age range one to seven months, power to detect an odds ratio of 1.11 associated with each increase of 12.5 micrograms of exposure, or equivalently, to detect an odds ratio of 1.53 associated with each increase of 50 micrograms of exposure to ethylmercury from vaccines.

The actual minimum detectable effects (MDEs) that could be detected with 80 percent power from the realized study sample was influenced by the sample size, the type of analysis model used, the distributions of exposure variables, and the correlation between covariate and exposure measures. Those factors all influence the standard errors of the exposure effect estimates, which are used in the power calculations, as described below.

Our calculations of actual MDEs are based on the estimates of standard errors of exposure as reported in Volume I, Exhibit 9.4.2. Let $\hat{\beta}$ be the estimate of an exposure effect (e.g., the effect of the exposure measure *PreNatThimer*) obtained from the conditional logistic regression model (with covariates) fit to the data from 256 ASD cases and 752 matched controls, and let $s.e.(\hat{\beta})$ be the estimate of the standard error of the parameter obtained from the same model. The MDE, expressed in the original metric of the exposure variable, can be obtained as $MDE = (t_{\alpha/2} + t_{\theta})s.e.(\hat{\beta})$, where "t" refers to the quantiles of a t-distribution and the subscripts α and θ correspond to alpha levels, and power, which are set to 0.05 and 80 percent, respectively. Substituting in the appropriate quantiles of the t-distribution we obtain $MDE = (1.96 + 0.8416)s.e.(\hat{\beta}) = (2.8016)s.e.(\hat{\beta})$.

The results from the model

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

produced the following standard error estimates:

For *PreNatThimer*: $s.e.(\hat{\beta}_1)$ =0.0094
For *Exp01mos*: $s.e.(\hat{\beta}_2)$ =0.0447
For *Exp17mos*: $s.e.(\hat{\beta}_3)$ =0.0182

Thus, the MDE for *PreNatThimer* is $(2.8016)s.e.(\hat{\beta}) = 2.8016*0.0094 = 0.02633$. If we take the exponent, we get the MDE expressed as an odds ratio for a one unit change in *PreNatThimer*, which is exp(2.8016*0.0094) =1.027. To make the estimate comparable to the estimate obtained from the design phase, we seek the MDE for the odds ratio for a 12.5 unit change in *PreNatThimer* which is obtained as exp(2.8016*0.0094 * 12.5) =

1.39. Comparing to the expected MDE calculated during the design phase, we see that even though the sample was smaller than expected, the standard error of the *PreNatThimer* effect was smaller than expected, therefore the study is powered to detect smaller *PreNatThimer* effects than expected. The results of the simulations in the analysis plan indicate that we expected the standard error of the *PreNatThimer* exposure effect to be larger (0.017) than was actually obtained (0.0094).

We perform similar calculations to get the actual MDE expressed as an odds ratio for a one-unit change *Exp01mos* as exp(2.8016*0.0447) = 1.133. To make an estimate that is comparable to the estimate obtained during the design phase, we need to determine the number of units if *Exp01mos* that are roughly comparable to a 12.5 unit increase in micrograms of ethylmercury. Noting that the correlation between *Exp01mos* (which is exposure divided by weight in kilograms at the time of exposure) and *Amt01mos* (which is exposure expressed as micrograms of ethylmercury, not divided by weight at time of exposure) is 0.95, and that a 1.94 standard deviation difference in *Amt01mos* is equal to a difference of 12.5 micrograms, we can reason that a 1.94 standard deviation increase in *Exp01mos*, divided by the correlation coefficient, is roughly comparable to a 12.5 microgram increase. The standard deviation of *Exp01mos* is 2.04. Thus, the quantity exp(2.8016*0.0447 * 1.94 * 2.04/.95) = 1.68 is roughly comparable to the MDE estimated during the design phase. In other words, the study has 80 percent power to detect an odds ratio of 1.68 for a 1.94/.95 standard deviation increase in *Exp01mos*, and a 1.94/.95 standard deviation increase in *Exp01mos* roughly corresponds to a difference of 12.5 micrograms of ethylmercury exposure in the period spanning birth to one month.

As an alternative approach, we fit a model identical to the one described above, but replaced the terms *Exp01mos* and *Exp17mos* with the terms for *Amt01mos* and *Amt17mos*. Using the standard error of estimate for *Amt01mos* (0.01358), and multiplying by 12.5, results in the quantity exp(2.8016*0.01358 * 12.5) = 1.609, which is very similar to the result above. This result indicates that the study had 80 percent power to detect an odds ratio of 1.609 for a difference of 12.5 micrograms of exposure to ethylmercury during the age range from birth to one month.

Using similar logic for *Exp17mos*, which has a correlation with *Amt17mos* of 0.90, and noting that 1.22 standard deviations units of *Amt17mos* is equal to a difference of 50 micrograms of ethylmercury exposure, and noting that the standard deviation of *Exp17mos* is 7.27, we obtain exp(2.8016*0.0182 * 1.22 * 7.27/.90) = 1.65. This indicates that the study has 80 percent power to detect an odds ratio of 1.65 for an increase of approximately 50 micrograms of exposure in the age range spanning 1 to 7 months. This estimate is in close alignment with what was envisioned during the design phase. As a check, we also present the estimated MDE using the standard error of the estimate for *Amt17mos* (0.00317), multiplied by 50, which is exp(2.8016*0.00317 * 50) = 1.559, which is similar to the estimate obtained above.

Relationships with AD

The power calculations were based on the exposure effect sizes associated with each increase in 12.5 micrograms of ethylmercury from thimerosal-containing vaccines and immune globulins. During the design phase of the study, we had estimated that with samples of 200 ASD cases and 600 matched controls (3:1 controls to cases), the study would have approximately 80 percent power to detect exposure effects of the following sizes:
For prenatal exposure, power to detect an odds ratio of 2.10 associated with each increase in 12.5 micrograms of exposure.
For exposure in the first month of life, power to detect an odds ratio of 2.19 associated with each increase in exposure of 12. 5 micrograms.
For cumulative exposure during the age range one to seven months, power to detect an odds ratio of 1.14 associated with each increase of 12.5 micrograms of exposure, or equivalently and to detect an odds ratio of 1.73 associated with each increase of 50 micrograms of exposure to ethylmercury from vaccines.

The results from the model for the comparison of AD cases to matched controls

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

produced the following standard error estimates:

For *PreNatThimer*: $s.e.(\hat{\beta}_1)$ =0.0106
For *Exp01mos*: $s.e.(\hat{\beta}_2)$ =0.0489
For *Exp17mos*: $s.e.(\hat{\beta}_3)$ =0.0211.

Using the same logic as describe above, we obtain the following MDEs:

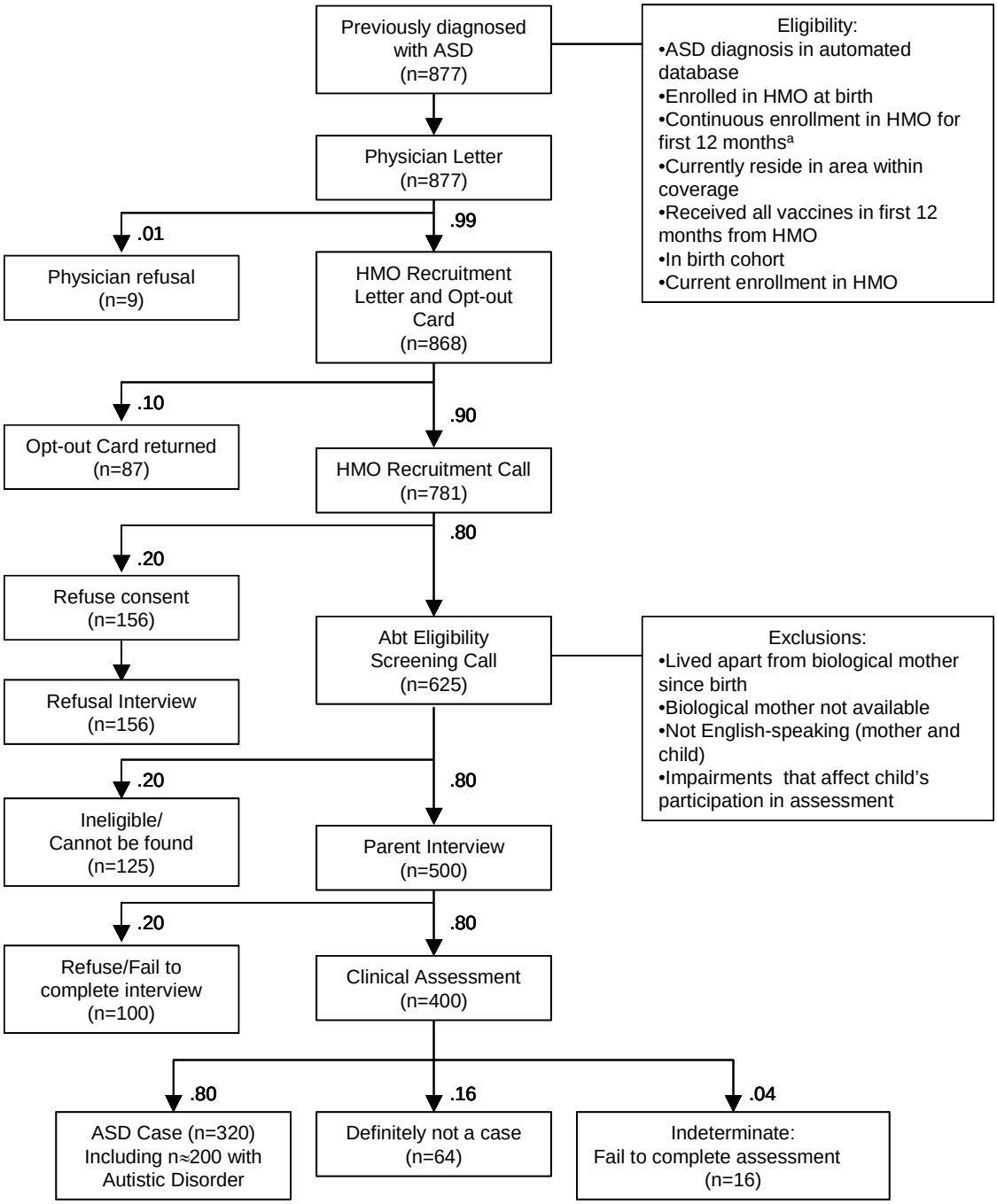
We seek the MDE for the odds ratio for a 12.5 unit change in *PreNatThimer* which is obtained as exp(2.8016*0.0106 * 12.5) = 1.449. Thus, the study was powered to detect smaller effects for this analysis that originally expected.
We seek the MDE for the odds ratio for a 12.5 unit change in *Exp01mos* which is obtained as exp(2.8016*0.0489 * 1.94 * 2.04/.95) = 1.77. This estimate is somewhat smaller than the MDE estimated during the design phase. This estimate indicates that the study has 80 percent power to detect an odds ratio of 1.77 for a 1.94/.95 standard deviation increase in *Exp01mos,* and a 1.94/.95 standard deviation increase in *Exp01mos* roughly corresponds to a difference of 12.5 micrograms of ethylmercury exposure in the period spanning birth to one month. The corresponding estimate obtained by modeling *Amt01mos* in place of *Exp01mos* is exp((2.8016*0.01509*12.5)=1.696.
For *Exp17mos,* we obtain exp(2.8016*0.0211 * 1.22 * 7.27/.90) = 1.79. This estimate is very close to the MDE estimated during the design phase. This indicates that the study

has 80 percent power to detect an odds ratio of 1.79 for an increase of approximately 50 micrograms of exposure in the age range spanning 1 to 7 months. The corresponding estimate obtained by modeling *Amt17mos* in place of *Exp17mos* is exp((2.8016*0.00363*50)=1.663.

In summary, even though the sample size was smaller than expected, the study was powered to detect smaller effects than expected for *PreNatThimer* and *Exp01mos* effects, and was powered to detect effects for *Exp17mos* that were very close to the original expectations.

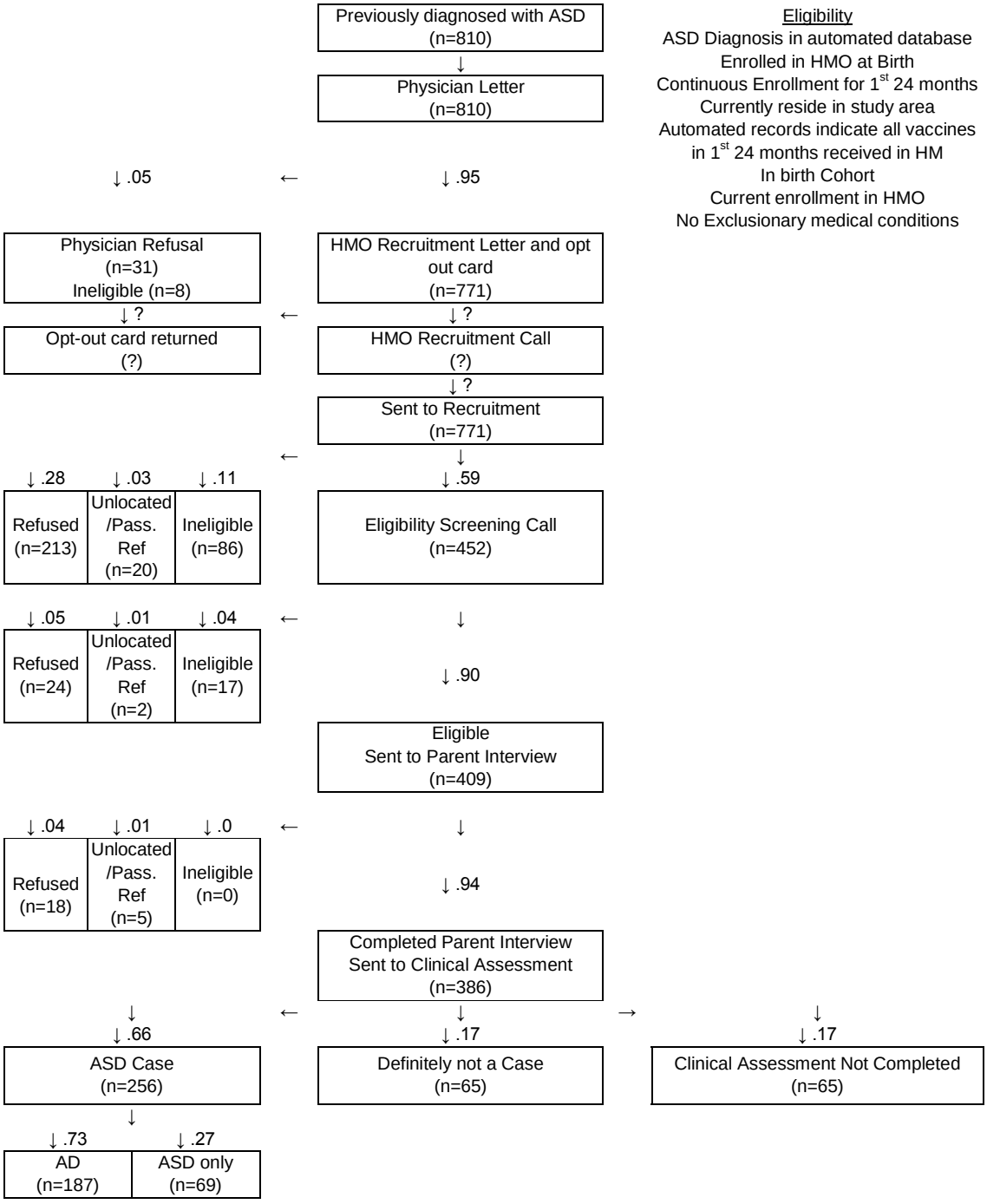
Exhibit 20.1

Design Phase Expectation of Number of Cases That Would be Obtained



a "Continuous" defined as no gaps in coverage from birth to age 24 months.

Exhibit 20.2
Actual Number of Cases Obtained



21. Other Analyses

21.1. Summary of Refusal Interview Responses

At two of the three HMOs that participated in the study refusal interviews were administered to a small sample of families that were contacted, but who refused to participate. The sampling procedure was such that the target number of refusal interview to be obtained was equal to be 10 percent of the total number of active refusals. Prior to recruitment we estimated the number of case and control families that would actively refuse to participate at each HMO, calculated 10 percent of those numbers. Recruiters then administered refusal interviews to active refusers, starting with the first active refuser encountered, and stopping when the target 10 percent was reached.

At HMO-A there were a total of 50 active refusers, from which 10 refusal interviews were obtained (20 percent). At HMO-C, refusal interview were obtained from 98 of the 967 active refusers (10 percent). See Exhibit 21.1.1. Unfortunately, we did not receive full information from recruiters on the number of families that refused to participate in the refusal interview. Thus we do not know the extent to which the respondents to the refusal interview are representative of the full set of active refusers.

Exhibit 21.1.1. Number of Refusal Interviews Obtained

Refusal Interview Completed:	HMO-A		HMO-C	
	Case n (%)	Control n (%)	Case n (%)	Control n (%)
Yes	2 (18)	8 (20)	12 (8)	86 (11)
No	9 (82)	31 (80)	147 (92)	722 (89)
Total[a]:	11 (100)	39 (100)	159 (100)	808 (100)

[a] Total is the total number of families that recruiters successfully contacted, but who refused to participate in the study. For further details on recruitment outcomes, see Exhibit 5.3.1.

The refusal interview included an open-ended item that asked "why did you decide not to participate in the study?" We have grouped the open ended responses into seven categories, and tabulated them as shown in Exhibit 21.1.2. For both cases and controls, half or more of the reasons given for non-participation were time constraints. The overall distribution of reasons for non-participation, however, was significantly different for cases and controls (chi-square test of independence, p=0.03). 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.

Examples of open-ended responses that were coded into the "Time" category include "because I don't have the time", "no time, too busy", "survey takes too long", "my schedule is crazy", "distance, clinic is too far away", and "time". Three responses were coded into the coded into the "did not want to subject child to testing" category. Evidently, some control refusers did not understand that their child would not be subject

to any form of testing, as they gave reasons for refusal such as “don’t want to expose child to that”, and “thought it would not be okay for child”.

Several of the responses that were coded into the “Distrustful, negative, or ambivalent attitude towards research” mentioned the word guinea pig, as in “don’t want my son to be used as a guinea pig”. Other responses in this category included “afraid to do a health study”, “the studies out there are not reliable”, and “I don’t feel like I get any benefit out of it”. One case refuser indicated that that she did not want her child being labeled as having autism.

Several control mothers said they refused because their child’s health issues. Evidently they did not fully understand that control children would not be assessed or interviewed. Some refusers said that they thought they were not eligible for the study for reasons such as “not with [HMO] anymore”, “thought it was just for kids with autism”, and for cases, responses indicated that they did not think their child had autism. The responses that were coded as “Maternal Health” indicate that the mother was depressed, or that discussing the child would make her sad. The “No reason given” category included responses such as “don’t really know”, “just don’t want to”, and refusal to give any reason for non-participation.

Exhibit 21.1.2. Summary of Reasons for Refusal to Participate

Reason for Non-participation	Controls n (percent)	Cases n (percent)	Total n (percent)
Time	58 (62)	7 (50)	65 (60)
Did not want to subject child to testing	2 (2)	1 (7)	3 (3)
Distrustful, negative, or ambivalent attitude toward research	22 (23)	1 (7)	23 (21)
Child health problems	3 (3)	0 (0)	3 (3)
Belief that child is ineligible for study	4 (4)	2 (14)	6 (6)
Maternal health	0 (0)	2 (14)	2 (2)
No reason given	5 (5)	1 (7)	6 (6)
Total:	94 (100)	14 (100)	108 (100)

21.2. Health Care Seaking Behavior

In the design phase of the study, in meetings that included the study's Principal Investigators and the panel of External Expert Consultants the issue of health care seeking bias was discussed. 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. If the expectations described above were true, it would lead to health care seeking bias in that, health care seeking behavior would create a spurious association between higher exposure and higher likelihood of autism outcomes.

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 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.

As specified in the analysis plan, those measures were tested for inclusion as covariates in the models used to estimate the relationship between exposure and autism risk (see Section 8.2 for details).

In this chapter we show descriptive data on the measures of health care seeking behavior for cases and controls. We then address the question of:

> *Are higher levels of health care seeking behavior, as measured by our three proxy variables, related to higher amounts of exposure to mercury from thimerosal-containing vaccines and immune globulins?*

21.2.1. Measures of Health Care Seeking for Cases And Controls

Implicit in the use of the three measures chosen for this study as proxies for health care seeking is an assumption that health care seeking is a stable trait that would not be expected to change drastically over the span of several years. The initiation of prenatal care variable (*HC_InitInad*) is a measure that corresponds to the time when the mother was pregnant with the focus child. The variables *HC_Cholest* and *HC_Pap* are used as proxies for health care seeking behavior that corresponds to a time that is 6 to 13 years after pregnancy with the focus child. If health care seeking is not a stable trait, than a person could be a non-health care seeker during pregnancy and during her child's infancy, and could later become a health care seeker.

Comparisons of cases to controls on each of the three health care seeking proxies are shown in Exhibits 21.2.1 – 21.2.3. The results indicate most of the mothers of both case and control children had adequate initiation of prenatal care, (95-98%), but that proportion of health care seekers, i.e., those with adequate initiation of prenatal care, was slightly greater in the control group. The results for most recent cholesterol tests (i.e., the variable *HC_Cholest*), suggests the opposite. That is, the results for this proxy measure of health care seeking behavior suggest that there was a higher proportion of health care seekers in the case group. Exhibit 21.2.2 shows that a greater proportion of cases reported have had a cholesterol test in the prior three years, and a lower proportion reported having never received a cholesterol test. As shown in Exhibit 21.2.3, cases and controls did not differ on the measure of most recent pap smear.

In summary, one of the three measures of health care seeking behavior suggested that there was a slightly greater proportion of health care seekers in the control group (initiation of prenatal care, but where p-value was just ***above*** the commonly used $p<0.05$ criterion), results for one measure suggested that there was a slightly greater proportion of health care seekers in the case group (most recent cholesterol tests, but where p-value was just ***below*** the commonly used $p<0.05$ criterion), and one measure indicated that there was no difference between cases and controls. Taken collectively, these results suggest that neither the case nor the control group had a radically greater proportion of health care seekers. The results also suggest that the three of these variables may not be measuring the same underlying, stable person-characteristic or trait. If all three were very good measures of the same stable construct, then the results of case/control comparisons across the three measures should have been consistent.

Exhibit 21.2.1.
Measure of Health Care Seeking Behavior: Initiation of Prenatal Care

Measure: *HC_InitInad* **Category**	**Controls n (%)**	**ASD Cases n (%)**	**Total**
0 = Adequate	734 (97.6%)	244 (95.3%)	978
1 = Inadequate initiation of prenatal care	18 (2.4)	12 (4.7)	30
Total	752	256	1008

Chi-square test of independence:

Statistic	DF	Value	Prob
Chi-Square	1	3.5	0.062

Exhibit 21.2.2.
Measure of Health Care Seeking Behavior: Most Recent Cholesterol Test

Measure: *HC_Cholest* **Category**	**Controls n (%)**	**ASD Cases n (%)**	**Total**
0 = Never	126 (16.8%)	33 (12.9%)	159
1 = >3 years	106 (14.1)	24 (9.4)	130
2 = within 3 years	520 (69.1)	199 (77.7)	719
Total	752	256	1008

Chi-square test of independence:

Statistic	DF	Value	Prob
Chi-Square	2	7.1	0.029

Exhibit 21.2.3.
Measure of Health Care Seeking Behavior: Most Recent Pap Smear

Measure: *HC_Pap* **Category**	**Controls n (%)**	**ASD Cases n (%)**	**Total**
0 = Never	3 (0.4%)	1 (0.4%)	4
1 = >3 years	46 (6.1)	23 (9.0)	69
2 = within 3 years	703 (93.5)	232 (90.6)	935
Total	752	256	1008

Chi-square test of independence:

Statistic	DF	Value	Prob
Chi-Square	2	2.46	0.29

21.2.2. Models of Health Care Behavior as Predictors of Exposure Measures

21.2.2.1. Introduction

The models summarized in this section were motivated by the following research 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, the models were used to examine the association between measures of mothers' health care 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.

21.2.2.2. Models: Predicting Exposure by Health Care Behavior

We fit models to estimate the relationships between measures of mothers' health care behavior (*HC_Cholest, HC_Pap, and HC_InitInad_1*) and measures of prenatal and postnatal cumulative exposure to ethylmercury from thimerosal-containing vaccines and immune globulins (*PreNatThimer, Amt01mos, Amt07mos, and Amt020mos*)[23]. Since average cumulative exposure amounts vary by birth year and HMO, we included terms in the models to adjust for those factors in the models when estimating the relationships between health care seeking and exposure.

Ordinary least squares regression models of the form shown below were used to address the question:

$$ExposureVar = \beta_0 + \beta_1(HC\_Cholest[=0]) + \beta_2(HC\_Cholest[=1]) + \sum_{m=1}^{23} \beta_{2+m}(I_{BirthYear*HMO,m}) + \varepsilon$$

where,

ExposureVar	is *PreNatThimer, Amt01mos, Amt07mos,* or *Amt020mos*
HC_Cholest[=0]	=1 if never had a cholesterol test, =0 else
HC_Cholest[=1]	=1 if had a cholesterol test more than three years prior =0 else
HC_Cholest[=2]	=1 if had a cholesterol test within three years, =0 else Note: this was the omitted category in the models.
$I_{BirthYear*HMO,m}$	is the m^{th} (m=1,…,23) indicator variables for birth year by HMO classes
$I_{BirthYear*HMO,1}$	=1 if birth year = 1994 and HMO-A, =0 else

[23] For definitions of these exposure variables, see Section 7.3.2.

...

$I_{BirthYear*HMO,2}$ =1 if birth year = 1999 and HMO-A, =0 else

...

$I_{BirthYear*HMO,23}$ =1 if birth year = 1998 and HMO-Ce, =0 else

$I_{BirthYear*HMO,24}$ =1 if birth year = 1999 and HMO-Ce, =0 else

Note: this was the omitted category in the models.

From this model we present results of a two degree of freedom F-test for the null hypothesis of zero variation of mean exposure among the three groups defined by the *HC_Cholest* variable. That is, a test of the question, "is there a difference among the three groups in exposure?" The test is of the form:

$$H_0 : \begin{bmatrix} \beta_1 \\ \beta_2 \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \end{bmatrix} \quad vs \quad H_a : \begin{bmatrix} \beta_1 \\ \beta_2 \end{bmatrix} \neq \begin{bmatrix} 0 \\ 0 \end{bmatrix}$$

In the summary table of results, the F-statistic and the p-value from the test are in the columns labeled "F" and "Pr>F"

We also present results of tests of whether the difference in mean exposure between never tested and tested within the past three years is zero,

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

and tests of whether the difference in mean exposure between tested more than three years prior and tested within the past three years is zero

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

The p-values corresponding to these tests are found in a column labeled "Pr>|T|" in the summary table of results.

We also fit models of the same form, except where the health care seeking variables used on the right hand side of the equation were *HC_Pap* and *HC_InitInad*.

Model results are summarized in Exhibit 21.2.4. The results indicate that there were no statistically significant associations between any of the three measures of health care seeking and any of the four measures of prenatal or postnatal exposure to ethylmercury from thimerosal-containing vaccines and immune globulins. Although not statistically significant, the estimated relationships of two of the health care seeking measures to the the measure of neonatal exposure (exposures birth to one month) were in the hypothesized direction. Children of mothers with inadequate prenatal care had lower mean exposure (p=0.076), and children of mothers that had never had a pap smear had lower exposure than children whose mothers had had the test, but not within the prior three years, who in turn, had lower exposure than children whose mothers had had the test within the three years preceding the parent interview (p=0.12).

We also fit a set of models (not shown) where we added terms for mother' age, mother's education, and family income (expressed as percent of the poverty line) as covariates. The addition of these additional control variables had little effect on the estimates of the relationships between there health care seeking measures and the exposure measure. There were no significant relationships found in these models.

The results presented in this section 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.

Exhibit 21.2.4. Model Summary: Health Care Behavior and Exposure Models

Exposure Measure	Health Care Behavior	Level	Est.	S.E.	T	Pr>|t|	F	Pr>F
PreNatThimer	*HC_Cholest*	0=never tested	0.290	0.680	0.43	0.669	0.15	0.862
	HC_Cholest	1=tested 3+ years	-0.184	0.722	-0.25	0.799		
	HC_pap	0=never tested	-1.875	3.973	-0.47	0.637	0.14	0.246
	HC_pap	1=tested 3+ years	1.509	0.935	1.61	0.107		
	HC_InitInad	1=inadequate	-0.176	1.407	-0.12	0.901	0.02	0.900
Amt01mos	*HC_Cholest*	0=never tested	-0.101	0.490	-0.21	0.837	0.04	0.964
	HC_Cholest	1=tested 3+ years	-0.109	0.521	-0.21	0.834		
	HC_pap	0=never tested	-3.173	2.864	-1.11	0.268	2.06	0.128
	HC_pap	1=tested 3+ years	-1.160	0.674	-1.72	0.086		
	HC_InitInad	1=inadequate	-1.801	1.014	-1.78	0.076	3.16	0.076
Amt07mos	*HC_Cholest*	0=never tested	-1.514	2.103	-0.72	0.472	0.43	0.649
	HC_Cholest	1=tested 3+ years	1.001	2.235	0.45	0.654		
	HC_pap	0=never tested	5.822	12.312	0.47	0.636	0.18	0.835
	HC_pap	1=tested 3+ years	-1.048	2.898	-0.36	0.718		
	HC_InitInad	1=inadequate	-5.075	4.353	-1.17	0.244	1.36	0.244
Amt020mos	*HC_Cholest*	0=never tested	1.624	2.315	0.70	0.483	0.32	0.729
	HC_Cholest	1=tested 3+ years	1.218	2.461	0.49	0.621		
	HC_pap	0=never tested	8.352	13.554	0.62	0.538	0.30	0.740
	HC_pap	1=tested 3+ years	-1.474	3.190	-0.46	0.644		
	HC_InitInad	1=inadequate	3.831	4.794	0.80	0.425	0.64	0.425

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

Read Table: The covariate adjusted mean difference in prenatal exposure (*PreNatThimer)* between mothers that never had a cholesterol test, and those that had a test within three years prior to the interview, was 0.290 microgram units. This difference was not significantly different than zero (p=0.669). Prenatal exposure was 0.184 lower, on average, for mothers that had had a cholesterol test more than three years prior to the interview, than for mothers that had a test within the three years prior to the interview. This difference was not significantly different than zero (p=0.799). There was no significant variation among the three cholesterol testing groups (never tested, tested more than three years prior, and tested within the prior three years) on prenatal exposure to ethylmercury from thimerosal-containing vaccines and immune globulins (p=0.862)

21.3. Exploratory Analysis of co-morbid conditions

The data presented in this section are not relevant to the question of whether exposure to ethylmercury from thimerosal-containing vaccines and immune globulins is related to autism risk. However, during the design phase of the study, in meetings of the Principal Investigators and External Expert Consultants it was suggested that the study could provide useful data to the field of autism research concerning the frequencies that AD and ASD cases have a range of co-morbid conditions. Therefore, as specified in the analysis plan, we abstracted each participant child's medical chart in order to identify diagnoses of the following conditions:

- Epilepsy
- Cerebral palsy
- Hearing disorder
- Vision impairment
- Downs' syndrome
- Neurofibromatosis
- Phenylketonuria (PKU)
- Cytomegalovirus CMV
- Developmental delay
- GI disorders
    - Chronic abdominal pain/cramps before age 3
    - Chronic bloating before age 3
    - Chronic celiac disease before age 3
    - Chronic constipation before age 3
    - Chronic food intolerance before age 3
    - Chronic gastroenteritis before age 3
    - Chronic malabsorption before age 3
    - Chronic/recurrent diarrhea before age 3
    - Chronic regional enteritis before age 3
    - Chronic vomiting/colic before age 3

The medical chart abstraction data included codes for each of the conditions listed above, and for each indicated whether the diagnosis was "definite", "possible/probable/ruleout", or "unknown". In the results that follow, we counted the condition as present only when the diagnosis code was "definite". An item on the parent interview asked whether the child had ever had a diagnosis of developmental delay. For that condition, we present results from both the medical chart abstraction data and from the parent interview data.

Exhibit 21.3.1. shows the frequencies of each diagnosis among cases, and for comparison, the frequency of each diagnosis among controls. The percentages shown are the percents of the n=187 AD cases, the n=256 ASD cases, and the n=752 controls.

Exhibit 21.3.1. Frequency and Percent of Conditions in AD and ASD Cases, and Controls

	AD Cases n=187		ASD Cases n=256		Controls n=752	
	Freq.	Percent	Freq.	Percent	Freq.	Percent
Epilepsy	10	5.35	11	4.30	12	1.60
Cerebral palsy	1	0.53	1	0.39	5	0.66
Hearing disorder	7	3.74	8	3.13	13	1.73
Vision impairment	4	2.14	4	1.56	1	0.13
Downs' syndrome	1	0.53	1	0.39	0	0.00
Neurofibromatosis	1	0.53	1	0.39	1	0.13
Phenylketonuria (PKU)	0	0.00	0	0.00	0	0.00
Cytomegalovirus CMV	0	0.00	0	0.00	0	0.00
Developmental delay (Chart)	24	12.83	30	11.72	10	1.33
Developmental delay (Parent Interview)	35	18.72	45	17.58	5	0.66
GI disorders						
Chronic abdominal pain/cramps before age 3	0	0.00	0	0.00	0	0.00
Chronic bloating before age 3	0	0.00	0	0.00	0	0.00
Chronic celiac disease before age 3	0	0.00	0	0.00	0	0.00
Chronic constipation before age 3	2	1.07	2	0.78	4	0.53
Chronic food intolerance before age 3	0	0.00	0	0.00	7	0.93
Chronic gastroenteritis before age 3	1	0.53	1	0.39	4	0.53
Chronic malabsorption before age 3	0	0.00	0	0.00	0	0.00
Chronic/recurrent diarrhea before age 3	0	0.00	0	0.00	3	0.40
Chronic regional enteritis before age 3	0	0.00	0	0.00	0	0.00
Chronic vomiting/colic before age 3	1	0.53	1	0.39	1	0.13

22. Additional Details about Sampling Frame

This section responds to some questions for about the sampling frame that arose after the presentation of preliminary results to the study's Principal Investigators from the HMOs and the CDC, and to the External Expert Consultants. The questions were:

a. By birth year, HMO and ASD case-control status, how many children that were born into the HMO remained in the HMO at time of sample frame creation (i.e. are still enrolled 6 to 13 years after birth)?

b. How many were removed from the sampling frame due to receipts of experimental vaccines with unknown mercury content?

c. Are the families that leave the HMO the same or different than families that stay?

d. Are families with ASD more likely to drop out of HMO?

e. What is the rate of children with ASD diagnoses in the sampling frame at each of the HMOs (e.g. 9 per 1000 children in the sampling frame had ASD diagnoses)
    i. Compare to national and regional rates
    ii. Show prevalence for each of the six birth years according to complete HMO records.

f. How many children were dropped from sampling frame due to continuous enrollment criteria?

g. Were some birth years (e.g., more recent ones) more likely to be included in the final sample?

a. By birth year, HMO and ASD case-control status, how many children that were born into the HMO remained in the HMO at time of sample frame creation (i.e. are still enrolled 6 to 13 years after birth)?

The study did not collect data that would be required to fully respond to Question a. We do have some information, however, that will provide a partial response. At the phase of the project when sampling frame was created, the study team (i.e., the study PI's, from the HMOs and the CDC, the data managers from the HMOs, Abt staff) had made specifications for what records should be included in the sampling frame. Those specifications are described in Section 5.1 of Volume I of this report. Those specifications include that the child had to be a current member of the HMO, had to have been born between Jan 1, 1994 and Dec 31, 1999, must have been enrolled in the HMO at birth, etc. (See Section 5.1 for additional detail).

Each HMO sent a preliminary sampling frame made to those specifications to Abt Associates. Two of the three HMOs also sent a listing of the number of records that were retained / omitted after applying each of those specifications. Exhibit 22.1 shows the listing from HMO-B. While this listing does not indicate by birth year, how many were enrolled and how many remained after applying these criteria, the numbers in the exhibit are relevant to answering at least part of Question a. After applying criterion #5, 164,232 records remained in the data set. We see that application of criterion #6 (i.e., current members as of third quarter of 2004), that the number remaining drops to 98,726. **Thus, about 60 percent of those born in HMO-B hospitals between 1994 and 1999 were still enrolled in 3rd quarter of 2004.**

Exhibit 22.2 shows a similar list from HMO-A. Start with the 23,003 that were born in HMO-A Hospitals between 1994 and 1999. Of those 23,003, we see that 5,948 were still enrolled as of the 3rd quarter of 2004. **Thus, about 26 percent of those born in HMO-A hospitals between 1994 and 1999 were still enrolled in 3rd quarter of 2004.**

Exhibit 22.1. **HMO-B Listing of Records Retained/Omitted After At Each Step of Application of Specification for Creation of Preliminary Sampling Frame**	
1. In VSD 2003 / Youth/Constant file	1,851,533
2. Keeping only births between 1994-1999	421,317
3. Keeping only births into HMO-B	180,957
4. Keeping only if all vaccines in first two years received in HMO-B	165,374
5. Dropping if received vaccine with unknown mercury amount (experimentals X04 or X08)	164,232
6. Keeping only current members (as of 3rd quarter of 2004)	98,726
7. Keeping if live within 60 miles of assessment site	43,937
8. Keeping if maternal MRN not missing	43,871
9. Keeping if child DOB matches IC	43,850
10. Keeiping if maternal DOB matches PatDem	43,703
11. Dropping if mom or child in No Contact List	43,511
12. Dropping if out of area patient	43,459
13. Dropping if birth hospital is "xxx" because of unreliable immunization data	43,449
Size of Preliminary Sampling Frame:	**43,449**

Exhibit 22.2. **HMO-A Listing of Records Retained/Omitted After At Each Step of Application of Specification for Creation of Preliminary Sampling Frame**	
1. In VSD 2003 / Youth/Constant file	191,662
2. Keeping only births between 1994-1999	36,416
3. Keeping only births into HMO-A	23,003
4. Keeping only current members (as of Dec 2004)	5,948
5. Keeping only 14 HVMA sites and removing restrict members	4,121
6. Keeping only if all vaccines in first 3 years from HMO-A	**3,775**
Size of Preliminary Sampling Frame:	**3,775**

b. How many were removed from the sampling frame due to receipts of experimental vaccines with unknown mercury content?

Exhibit 22.2 indicates that at HMO-A, none were removed due to receipt of experimental vaccines with unknown mercury content. At HMO-B, Exhibit 22.1 shows that difference between steps 4 and 5 of the process was 1,142 children that were removed from the sampling frame due to receipt of experimental vaccines with unknown mercury content. We do not have relevant data from HMO-C to answer this question.

a. Are the families that leave the HMO the same or different than families that stay?
b. Are families with ASD more likely to drop out of HMO?

This study did not collect the relevant data that would be needed to answer these questions. A new study would need to be designed that would use VSD data to address these questions.

c. What is the rate of children with ASD diagnoses in the sampling frame at each of the HMOs (e.g. 9 per 1000 children in the sampling frame had ASD diagnoses)
    i. Compare to national and regional rates
    ii. Show prevalence for each of the six birth years according to complete HMO records.

Rates by HMO are shown in Exhibit 22.3.

Using data from the from the 2007 National Survey of Children's Health Kogan et. al (2009) estimated the national prevalence of parent reported diagnosis of ASD among children aged 3 to 17 years at 11 per 1,000. Estimates from the same survey conducted in 2003-2004 resulted in estimates at 5.5 per 1,000 (MMWR, 2006).

Exhibit 22.3. Rates of ASD Diagnoses per 1,000 in Preliminary Sampling Frame, by HMO and Birth Year

	Rates of ASD Diagnoses per 1,000			
Birth Year	HMO-A	HMO-B	HMO-C	All Combined
1994	7.7	11.9	9.2	10.5
1995	10.0	9.1	9.3	9.2
1996	3.0	8.1	13.3	10.3
1997	9.2	9.2	14.8	11.9
1998	8.1	9.1	14.0	11.4
1999	10.0	5.9	15.8	10.9
All Birth Years Combined	7.9	8.8	12.9	10.7

d. How many children were dropped from sampling frame due to continuous enrollment criteria?

The continuous enrollment criterion specified that the **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.

- HMO-A: of 3,775 records in preliminary sampling frame, 278 records were omitted due to the enrollment gap criterion: 278 / 3775 = 7 %.

- HMO-B: of 43,449 records in preliminary sampling frame, 9,888 records were omitted due to the enrollment gap criterion: 9,888 / 43,449 = 23 %.

- HMO-C: of 42,238 records in preliminary sampling frame, 7,606 records were omitted due to the enrollment gap criterion: 7,606 / 42,238 = 18 %.

e. Were some birth years (e.g., more recent ones) more likely to be included in the final sample?

Exhibit 9.1.1 shows the proportions of analysis sample that were from each birth year. The analysis sample is comprised of the the n=256 cases and n=752 matched controls that were used in the main analyses.

The proportions of the phase II sample (i.e. the sample that was released to recruitment), that were from each birth year are shown in the exhibit below.

Exhibit 22.4. Percentage of Phase II Sample from Each Birth Year

	% From Each Birth Year		
Birth Year	Case	Control	Total (Cases & Controls)
1994	12%	14%	13%
1994	14	13	14
1996	16	16	16
1996	22	20	21
1998	19	17	18
1999	18	19	18
	100	100	100
Phase II sample included 771 cases and 2,760 controls.			

23. Comparison of "Regression" Criteria Used in Current Study to Criteria Used in Other Studies

The purpose of the current section is to respond to a question regarding a comparison of rates of regression found in the current study to rates reported from other studies. The question was as follows:

> In the latest IAN study (see http://www.autismspeaks.org/inthenews/ian_findings_regression.php) based on parental report, about 39% of ASD children had regression (percents depended on ASD subtype), and in other studies, 46% (Richler 2006) and 41% (Hanson 2008) are regressive. In our study, 49 of 256 or 19% had regression. Can the differences be explained, and does the lower percentage in this study reflect a low participation rate among regressive cases more often linked to vaccine-injury by parents?

We visited the web site listed above on 8/14/08 and printed the relevant pages. We also obtained copies of the reports referenced therein. They were Richler et. al, (2006), Hanson et. al., (2008), and Siperstein & Volkmar (2004). Below, we provide a summary of the IAN findings, and the findings from the three papers referenced above, and suggest explanations for why the regression rates vary so widely across the various studies.

Thimerosal and Autism Study (Price et. al, 2009)

Our definition of regression was made in consultation with Dr. Cathy Lord (co-developer of ADI-R). Our definition required:

- The response to ADI-R 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 early language skills listed in ADI-R Regression Item 12b that a child had before 24 months, were lost for a month or more before 36 months.

We reported that of the 256 cases that met criteria for ASD, 19 percent met our study criteria for regression.

(For additional details, see Section 7.1.2 of Volume I Technical Report)

IAN Findings (from web link shown above)

The IAN findings were based on information obtained via the internet from families of children with ASD living in the United States. The number of families was reported to be "in the thousands".

They report that the following questions were asked:

> 1. Did your child lose words, daily living skills, motor abilities, or social skills that he/she previously had?
> 2. How significant was your child's loss of skills?
> 3. Which type of skill was affected most (speech and language, motor abilities, social skills, or daily living skills)?
> 4. What age was your child when you first noticed this loss of skills?

5. Did your child's development plateau or halt such that he/she stopped gaining new skills but retained previously acquired skills?
6. What age was your child when you first noticed this plateau or halt in his/her development?

They don't report how those survey items were used to define regression, but they do state that they "began by looking at children who had been reported to lose skills". They reported that the percentage of children who lost skills in the age range from 0 to 36 months was 39%.

The authors reported that their definition was likely to include some types of skill loses that were unrelated to autism-related regression, such as skill loss after emotional trauma.

Possible reasons for differences between rates reported by Price et. al, (2009), and IAN findings:

- The IAN findings were based on a definition of regression that included a broad array of skills, whereas the definition used by Price et.. al, (2009) was specific to loss of early language skills.
    - We would have to expect that the broader definition used by IAN would result in higher rates.
- The data collection modes were different for the two studies. The survey items used in the study by Price et.. al, (2009) were administered in a face-to-face clinical setting with by a trained, research reliable administrator, whereas the IAN findings are based on data from an internet survey.
    - Data collection modes can affect the rates estimated from surveys.

Richler et. al (2006)

They defined "word loss regression" and "no-word loss regression". Their reported rate of 46% with regression among study children with ASD and PDD-NOS (Pervasive developmental disorders not otherwise specified) included both "word loss regression" and "no-word loss regression".

Possible reasons for differences between rates reported by Price et. al, (2009), and Richler et. al (2006):

- The inclusion of "no-word loss regression" in the definition used by Richler et. al (2006) would be expected to produce higher rates, relative to the definition used by Price et. al, (2009).
- Note also that the definition of "word loss regression" used by Richler et. al (2006) was not identical to the definition of regression used by Price et. al, (2009).
    - Richler et. al's "word loss" required that children had used at least 3 meaningful words before loss, whereas Price et. al, (2009) required that children had used least 5 meaningful words before loss.

Hansen et. al (2008)

- Their definition of regression included loss of language and/or loss of social skills.
- Their definition of loss of language was based on ADI-R question 11, but used "probable loss" as a criterion
- They reported that 41% of children with ASD had regression.

Possible reasons for differences between rates reported by Price et. al, (2009), and Hansen et. al (2008):

- The inclusion of both language loss and social skill loss in the definition used by Hansen et. al (2008) would be expected to produce higher rates, relative to the definition used by Price et. al, (2009).
- Hansen's use of "probable loss" as a criterion for language loss would be expected to produce higher rates, relative to the definition used by Price et. al, (2009), which required "definite loss"
- Hansen's definition of language loss was based on ADI-R items 11 and 25, whereas the definition used by Price et. al, (2009) was based on ADI-R items 11 and 12b.

Siperstein & Volkmar (2004)

In their study parents were asked, "did the child seem to develop normally for a time and then lose skills? If yes, please describe." Responses were grouped into one of the four following categories:

1) clear loss group (parents report clear loss of skills in any domain other than some nonspecific behavioral change);
2) possible loss group (either the parents were not sure, the loss was not dramatic or reflected a general parental concern rather than loss of specific skills);
3) stagnation group (parents reported a stagnation in development);
4) no reported loss group (no loss of specific skills or no loss at all).

They reported that 11.8% were placed in the clear or possible loss categories, and 9.3% were placed in the stagnation group.

Possible reasons for differences between rates reported by Price et. al, (2009), and Siperstein & Volkmar (2004):

- Siperstein & Volkmar (2004) used post-coded responses from an open-ended survey item to create their measure. Price et. al, (2009) used items from the ADI-R in their definition.
- Siperstein & Volkmar (2004) definition was not specific to language loss.

Conclusions

Among the five studies reviewed here no two used the same definition of regression. Three studies (Price et. al, 2009; and Hansen et. al, 2008, Richler et. al, 2006), used items from the ADI-R in their definitions but no two used the exact same items and criteria. Price et. al, (2009) defined regression entirely in terms of language loss, whereas the other four studies included the loss of other skills in their definitions. Substantial differences between the rates of regression reported Price et. al, (2009) and each of the other studies are to be expected given the variation in definitions and assessment instruments across the studies.

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