Environmental Risk Factors for Autistic Disorder

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SAN DIEGO STATE UNIVERSITY

Environmental Risk Factors for Autistic Disorder

A dissertation submitted in partial satisfaction of the requirements for the degree of Doctor of Philosophy in Public Health (Epidemiology)

by

Stephen T. Schultz

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San Diego State University

Professor Ming Ji
Professor Caroline A. Macera

2006
The dissertation of Stephen T. Schultz is approved, and is acceptable in quality and form for publication on microfilm:

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________________________________________ Chair

University of California, San Diego
San Diego State University
2006
DEDICATION

This dissertation is lovingly dedicated to my son Nathan who inspired me to return to school and investigate the risk factors for autistic disorder, and to my son Matthew who encouraged me to continue.
# TABLE OF CONTENTS

Signature Page ................................................................. iii

Dedication ................................................................. iv

Table of Contents ............................................................ v

List of Figures ................................................................. vi

List of Tables ................................................................. vii

Acknowledgements ........................................................... viii

Vita ................................................................. ix

Abstract ................................................................. x

I. Introduction ................................................................. 1

II. Breastfeeding, Infant Formula Supplementation, and Autistic Disorder: the Results of a Parent Survey ................................................................. 5

III. National Acetaminophen Sales and Autistic Disorder in California: An Ecological Association ................................................................. 26

IV. Acetaminophen after Measles-Mumps-Rubella Vaccination and Autistic Disorder: the Results of a Parent Survey ................................................................. 46

V. Conclusion ................................................................. 75

Appendices (Survey Instruments) ................................................................. 84
LIST OF FIGURES

Chapter III, Figure 1: National purchases of children’s aspirin and acetaminophen products by year, 1979-1985………………………………………40

Chapter III, Figure 2: Number of enrolled persons with autistic disorder in California with addition of historical events………………………………..41
LIST OF TABLES

Chapter II, Table 1: Characteristics of participants in the Autism Internet Research Survey 2005.................................................................20

Chapter II, Table 2: Age-adjusted associations of breastfeeding and autistic disorder for children aged 2-18.........................................................21

Chapter II, Table 3: Age-adjusted association of infant formula use with autistic disorder for children aged 2-4.........................................................22

Chapter III, Table 1: Linear regression models with the number of eligible persons with autistic disorder in California by birth year.............39

Chapter IV, Table 1: Characteristics of participants in the autistic disorder survey, 2005-2006.................................................................66

Chapter IV, Table 2: Crude associations with autistic disorder, 2005-2006.................................................................................................67

Chapter IV, Table 3: Adjusted associations of analgesic use age 12-18 months with autistic disorder, 2005-2006.................................68

Chapter IV, Table 4: Adjusted associations of illness concurrent with measles-mumps-rubella vaccination and autistic disorder, 2005-2006......69

Chapter IV, Table 5: Adjusted associations of analgesic use after measles-mumps-rubella vaccination with autistic disorder, 2005-2006......70
ACKNOWLEDGEMENTS

I would like to thank the members of my committee for their efforts to assist me with this research and dissertation. I appreciate the assistance of Christopher Bacher in providing one of the datasets and also the keywords for the online surveys. I am grateful to Valerie's List and the Schafer Autism Report for publishing my request for participation in the online surveys.

This dissertation was funded in part by the US Navy. The views expressed are those of the authors and do not reflect the official policy or position of the Department of the Navy, the Department of Defense, or the US Government.

The texts of Chapters II, III, and IV are reprints of material that have been submitted for publication. The dissertation author was the primary researcher and author, and the co-authors listed in these publications directed and supervised the research which forms the basis for those chapters. The submitted publications are:


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ABSTRACT OF THE DISSERTATION

Environmental Risk Factors for Autistic Disorder

by

Stephen T. Schultz

Doctor of Philosophy in Public Health (Epidemiology)

University of California, San Diego, 2006

San Diego State University, 2006

Professor Hillary S. Klonoff-Cohen, Chair

This dissertation consists of three studies which investigated environmental risk factors for autistic disorder. The first was a case-control study (861 cases, 123 controls identified February-April, 2005) which suggested that children with autistic disorder compared to those without were more likely to have been breastfed less than six months (OR 2.48, 95% CI 1.42, 4.35). Limiting the cases to children with regression in development found similar results (OR 1.95, 95% CI 1.01, 3.78). Children with autistic disorder were more likely to have used infant formula without docosahexaenoic acid and arachidonic acid supplementation than to have been exclusively breastfed (OR 4.41, 95% CI 1.24, 15.7), and the result appeared stronger after limiting cases to children with regression in development (OR 12.96, 95% CI 1.27, 132).
Second, an ecological study showed significant positive associations between annual sales (1979-1985) of children's acetaminophen tablets and liquid and the number of autistic disorder cases in California who had the same birth years (p<0.05). Sales of children's aspirin products showed a significant negative association (p<0.01).

Third, a case-control study (83 cases, 80 controls identified July 2005-January 2006) indicated that children with autistic disorder were more likely than those without autistic disorder to have used acetaminophen after measles-mumps-rubella vaccination when considering children 1 to 5 years of age (OR 6.11, 95% CI 1.42-26.3), children 1 to 18 years with regression in development (OR 3.97, 95% CI 1.11-14.3), and children 1 to 18 years with post-vaccination sequelae (OR 8.23, 95% CI 1.56-43.3), all adjusted for age, gender, mother's ethnicity, and the presence of illness concurrent with measles-mumps-rubella vaccination. Children with autistic disorder were more likely to have had illness concurrent with the measles-mumps-rubella vaccination when all cases were considered (OR 8.81, 95% CI 2.29-33.9) and after limiting cases to children with regression in development (OR 17.2, 95% CI 3.51-84.5), adjusting for age, gender, mother's ethnicity, and acetaminophen use after measles-mumps-rubella vaccination.

These studies suggest that lack of breastfeeding, unsupplemented infant formula use, acetaminophen use, and illness concurrent with the measles-
mumps-rubella vaccination may be risk factors for autistic disorder. Further investigation is required to confirm these preliminary findings.
I. Introduction
Autistic disorder (AD) is a severe developmental disorder defined by social and communication deficits and ritualistic-repetitive behaviors that are seen in early childhood. A small percentage of cases of AD are associated with several known congenital conditions such as fragile X syndrome, Angelman syndrome, tuberous sclerosis, congenital rubella syndrome, neurofibromatosis, phenylketonuria, and Rett syndrome. Most cases of AD, however, have an unknown etiology. Genes involved in neurodevelopment have been investigated in relation to AD, and recently the genes with systemic impact and involved with environmental responsiveness have come under increased scrutiny.

For some children, environmental factors may contribute to an increased risk for AD. Theories regarding potential environmental risk factors need to take into consideration the interaction with genetic susceptibility and stage of development. In other words, environmental factors may only increase the risk for individuals who are genetically susceptible to AD and in a susceptible stage of development.

Possible environmental factors for AD include childhood vaccinations, environmental exposures, and viral infections. In addition, small clinical studies have suggested a link between measles-mumps-rubella (MMR) vaccination and AD, but epidemiological studies have not supported this relationship.
The research studies for this dissertation were performed to investigate three risk factors: #1 lack of breastfeeding, #2 infant formula use without docosahexaenoic acid and arachidonic acid (DHA/ARA) supplementation, #3 the presence of illness concurrent with the MMR vaccination and #4 childhood analgesic use, which resulted in three papers.

The first investigation consisted of a case-control study to examine whether the length of breastfeeding and use of infant formula without DHA/ARA supplementation was associated with AD. One previous study has shown a positive association of breastfeeding and AD, although the current study is the first to examine length of breastfeeding and AD. No previous studies have explored the use of infant formula without DHA/ARA and AD; however, DHA and ARA have been shown to be important for brain development.

The second study was an ecological study to determine if sales of children's acetaminophen and aspirin products could be correlated with the number of children with AD in California. No previous studies have investigated the possible association of children's analgesics and AD. One previous study, however, has shown that some children with AD do not process acetaminophen as efficiently as control children. This could in theory increase the production of a toxic by-product of acetaminophen metabolism, which could lead to AD. The trend in sales of children's acetaminophen products increased markedly in 1980 after a Reye's Syndrome—aspirin link was published. This was also the same time that the AD trend in California
made a marked increase. The current study was performed to determine if these two trends could be statistically correlated.

The third study was a case-control study examining the association of AD with the use of acetaminophen after MMR vaccination. No previous studies have investigated this association, but many have examined the MMR vaccination in relation to AD. Small clinical studies have shown an association of the MMR vaccination and AD; however, none of the large epidemiological studies have shown an association of the MMR vaccination and AD. This study was initiated to determine if some factor associated with the MMR vaccination, such as acetaminophen use or the presence of concurrent illness, could be associated with AD.
II. Breastfeeding, Infant Formula Supplementation, and Autistic Disorder: the

Results of a Parent Survey
Abstract

The present study was performed to determine whether less breastfeeding or the use of infant formula without docosahexaenoic acid and arachidonic acid supplementation increase the likelihood of autistic disorder. Absence of breastfeeding when compared to breastfeeding for more than six months was significantly associated with an increase in the odds of having autistic disorder when all cases were considered (OR 2.48, 95% CI 1.42, 4.35) and after limiting cases to children with regression in development (OR 1.95, 95% CI 1.01, 3.78). Use of infant formula without docosahexaenoic acid and arachidonic acid supplementation versus exclusive breastfeeding was associated with a significant increase in the odds of autistic disorder when all cases were considered (OR 4.41, 95% CI 1.24, 15.7) and after limiting cases to children with regression in development (OR 12.96, 95% CI 1.27, 132). The results of this preliminary study indicate that children who were not breastfed or were fed infant formula without docosahexaenoic acid/arachidonic acid supplementation were significantly more likely to have autistic disorder.
Introduction

Autistic disorder (AD), also called autism, is a severe developmental disorder defined by deficits in reciprocal social interaction and communication, and the presence of repetitive and ritualistic behaviors that emerge before three years of age (American Psychiatric Association, 1994). Some parents report regression in their children or a loss of previously acquired skills with the subsequent development of AD (Lord et al., 2004). Parental report of regression in children with AD is estimated to occur in approximately 22% of cases (Siperstein and Volkmar, 2004). Recently, parental report of regression has been validated with the use of videotape of children’s first and second birthdays (Werner and Dawson, 2005). In most cases the cause of AD is unknown (Fombonne, 2003).

A report by the California Department of Developmental Services (2003) shows a noted increase in individuals with a diagnosis of AD receiving services. The proportion (and number) of eligible individuals with AD in their client population of special needs children rose from 3.5% (2,778/80,389) to 12.4% (20,377/163,792) between 1987 and 2002. Changes in case definitions, administrative and diagnostic procedures, and service-related issues have had an effect on the number of eligible individuals with AD in California (Lawler et al., 2004). The increase in eligible individuals with AD in California may also be due to widening of the case definition to include
children with normal or above-normal intelligence (Eagle, 2004) or due to diagnostic substitution of children with mental retardation (Croen et al., 2002).

A world-wide review by Fombonne (2003) of autism epidemiological surveys concluded that changes in case definition and improved awareness account for much of the recent increases in autism. A more recent study reported a stable incidence in Midlands, UK over 15 years when study design features were held constant (Chakrabarti and Fombonne, 2005). It is not known whether AD incidence is increasing or whether increases in prevalence are the result of changing diagnostic criteria and better case ascertainment.

The prevalence of breastfeeding in the US increased during the 1970s, decreased during the 1980s, and rose again during the 1990s (Abbott Laboratories, 2002). For 2002, breastfeeding in the hospital and at six months of age reached an all-time high of 70.1% and 33.2% respectively (Abbott Laboratories, 2002). Breastfeeding is the recommended method for infant feeding, and increasing the number of mothers who breastfeed their children to six months of age is a goal of Healthy People 2010 (US Department of Health and Human Services, 2000). Breastfeeding has been associated with increases in cognitive ability and academic performance (Horwood and Fergusson, 1998; Jain et al., 2002).

Breastfeeding may also be important for the cognitive ability of children at risk for AD. In a study of 145 autistic and 224 normal children, a significantly higher proportion of autistic children (24.8%) compared to control children
(7.5%) were weaned by the end of the first week of life (Tanoue and Oda, 1989).

A related study examined the broader category of pervasive developmental disorder and breastfeeding. This study found no significant difference in breastfeeding rates between 50 children with pervasive developmental disorder and 50 control children, although both groups reported significantly less breastfeeding than the national average (Burd et al., 1988). Further, the normal siblings of the children with pervasive developmental disorder had breastfeeding rates almost identical to the national average (Burd et al., 1988). This study may have been overmatched since cases and controls were matched on IQ which has been linked to breastfeeding and AD (Horwood and Fergusson, 1998; Jain et al., 2002; Fombonne, 2003).

In 1994, the World Health Organization published a report recommending that infants should be fed breast milk if at all possible, but if fed formula, it should be supplemented with the polyunsaturated fatty acids, docosahexaenoic acid (DHA) and arachidonic acid (ARA). In January 2002, the first infant formulas supplemented with DHA and ARA were offered for sale in the US, although the older versions of formula without supplementation also continue to be sold (US Food and Drug Administration, 2005).

DHA/ARA supplemented formula enhances weight gain in premature infants (Innis et al., 2002) and raises the plasma and red blood cell concentrations of DHA and ARA in full-term infants to levels comparable to
breastfed infants (Koo, 2003). DHA and ARA are considered conditionally essential substrates during early life and are related to the quality of growth and development (Larque et al., 2002). A search of the literature revealed no published studies that have investigated infant formula use in relation to AD.

One study found decreased DHA in the composition of plasma total phospholipids which resulted in significantly lower levels of total omega-3 polyunsaturated fatty acids for autistic compared to mentally retarded subjects (Vancassel et al., 2001). Another study found a significant decrease in the ARA composition of red blood cell polar lipids for children with regressive autism compared to control children (Bell et al., 2004). These decreases could be due to decreased availability of DHA and ARA in the diets of these children.

The present study was undertaken for the purpose of determining whether breastfeeding or the use of infant formula (with or without DHA/ARA supplementation) is associated with AD. The hypothesis is that less breastfeeding and use of infant formula without DHA/ARA supplementation increase the likelihood of AD.

Materials and Methods

The Autism Internet Research Survey was created by the parent of a child with autism hoping to identify possible causes for the rise in autism. The survey did not state whether the rise in autism was due to a rise in incidence or in the number of individuals registered for special education programs;
however, parents who believe there is an increase in autism incidence may have been more inclined to take the survey. In order to quickly obtain the number of cases required for this analysis, the internet was used to solicit participants. Subsequently, this developed into a New Jersey-based nonprofit organization, Autism Internet Research Survey. Neither the organization nor the survey is related to any commercial entity.

The Autism Internet Research Survey invited parents to complete surveys for their children with or without AD. Whether a child had AD was self-reported by clicking on one of two links: “For those with autistic children who want to take the survey click here.” or “For those who want to take the control survey (you have children, but not with any autism spectrum disorder) click here.”

Ads for the surveys were placed online using Google and restricted to the United States. Individuals who performed online searches containing keywords (autistic, autism research, autism, MMR, autism education, etc.) were shown an ad requesting their participation in a research survey. The total number of keywords used was 306, and they were grouped into the following categories: autism and autistic features 262, treatment for autism 24, prominent people involved in autism 13, and possible causes of autism 7. Participants completed the surveys February-April, 2005. The surveys included 91 questions on breastfeeding, infant formula use, date of birth, and the nature of their child’s development. Limiting the age range to children two
to 18 years and the respondents to parents yielded 861 case and 123 control children.

Breastfeeding data was recorded from a drop-down menu with nine choices of duration of breastfeeding. This variable was recoded into five categories: none, less than 2 months, 2-6 months, more than 6 months, and unknown. These breastfeeding categories were tested for association with autism using logistic regression.

Infant formula use data was recorded from a drop-down menu with 39 brand-name choices as well as “Other”, “None”, and “I don’t know”. This variable was recoded into three categories: None, Formula without DHA/ARA, and Formula with DHA/ARA. Information regarding DHA/ARA supplementation was ascertained from the manufacturers websites. If parents chose the category “Other” or “I don’t know”, no determination could be made regarding DHA/ARA supplementation, and the data was excluded from further analysis (n=38). The remaining three infant formula categories were tested for association with autism using logistic regression.

Children under two years old were excluded since AD is rarely diagnosed before age two. For analysis of breastfeeding, the age range was limited to 2-18 years. Eighteen years was chosen as the upper age for the range in an attempt to minimize recall bias from the parents.

For analysis of infant formula, 2-4 years was chosen as the age range. Four years was chosen as the upper age for this portion of the study since
supplementation with DHA/ARA has only been available in the US since 2002. Children older than four would not have had the opportunity to use DHA/ARA supplemented formulas during the first year of life.

Parents of autistic children were also questioned about the nature of their child’s development. Three choices were given in a drop-down menu: 1) My child developed normally, then regressed (lost skills). 2) My child developed normally, then stopped. 3) My child never developed in a normal way. For the purposes of this study, if response number 1 was chosen, the child was assumed to have a regression in development, i.e. lost skills that had previously been acquired.

In order to remove the effects of congenital conditions associated with autism from the odds ratios seen in this study, breastfeeding and infant formula use were also tested for association with autism for the subset of children with reported regression in development.

All analyses, including characterization of the population and logistic regression, were performed using SAS version 9.1 for Windows (SAS Institute Inc., Cary, North Carolina). This study was approved by the University of California, San Diego Human Research Protections Program and the Institutional Review Board at San Diego State University.
Results

Table 1 presents the characteristics of children in the Autism Internet Research Survey. For those aged 2-18 years, there were 861 cases and 123 controls, and for those aged 2-4 years, there were 150 cases and 38 controls. Parental report of regression in development for these two age groups was 25% and 23% respectively.

For children aged 2-18 years, the mean age of cases and controls was similar at 7.8 and 7.4, respectively. Breastfeeding varied by group, with no breastfeeding being reported more frequently for cases (28%) than controls (16%) and breastfeeding for greater than six months being reported more frequently for controls (36%) than cases (25%).

For children aged 2-4 years, the mean age of cases was 3.2 and of controls was 3.0. Infant formula use varied by group with exclusive breastfeeding (no formula use) being reported more often for controls (16%) than cases (8%). Use of infant formula containing DHA/ARA was also reported more frequently for controls (58%) than cases (26%) while use of infant formula without DHA/ARA was reported more frequently for cases (43%) than controls (18%). Breastfeeding for greater than six months was reported for all children with no formula use and 23% of children with formula use (data not shown).

Age-adjusted associations of breastfeeding and AD are presented in Table 2 for children aged 2-18. Decreased breastfeeding was significantly
associated with increased likelihood of having a child with AD. No breastfeeding versus breastfeeding for more than six months was significantly associated with an increase in the odds of having AD when all cases were considered (OR 2.48, 95% CI 1.42, 4.35) and after limiting cases to children with regression in development (OR 1.95, 95% CI 1.01, 3.78). Duration of breastfeeding showed a dose-response relationship with AD before and after limiting cases to children with regression in development (chi square test for trend, p=.0007 and p=.031 respectively).

Age-adjusted associations of infant formula use with AD are presented in Table 3 for children 2-4 years old. Use of infant formula without DHA/ARA supplementation versus exclusive breastfeeding was associated with a significant increase in the odds of AD when all cases were considered (OR 4.41, 95% CI 1.24, 15.7) and after limiting cases to children with regression in development (OR 12.96, 95% CI 1.27, 132). Use of unsupplemented versus supplemented infant formula was also associated with a significant increase in the odds of AD (OR 4.33, 95% CI 1.65, 11.4) when all children were considered and after excluding children who were breastfed for more than six months (OR 4.78, 95% CI 1.57, 14.6) (data not shown in table). Use of infant formula with DHA/ARA compared to exclusive breastfeeding was not significantly associated with an increase in the odds of AD.
Discussion

The children with AD in this survey were significantly less likely to have been breastfed and were significantly less likely to have been fed infant formula with DHA/ARA than typically developing children. A possible mechanism for these associations is immune system dysfunction. Without breast milk or infant formula supplemented with DHA/ARA, some children’s immune systems could be compromised which could in theory lead to AD. Breast milk provides the infant IgA and other humoral components from the mother which are important for the immune protection of the infant. Also, use of formula with DHA/ARA supplementation could be beneficial to the infant immune system. DHA and ARA are discussed in a review by Yaqoob (2004) as important for proper immune system functioning.

The results of this study are from an online internet survey and should be viewed with caution. This survey was not a random sampling of the population and has the attendant problem of ascertainment bias. Only individuals who had computers and were interested in taking an online survey were participants. Also, the survey could have biased participant responses by telling them the purpose was to find reasons for the rise in autism.

The present study relied on self-reported data regarding the diagnosis of AD and therefore the accuracy of diagnosis was not confirmed. However, parental report of the proportion of cases with regression in development in this study (23% for children aged 2-4 and 25% for children aged 2-18) was similar to that
seen in a study by Siperstein and Volkmar (2004) in which 22% of parents reported regression in their children diagnosed with AD using DSM-IV criteria. However, the present study did not use the same question regarding regression, and the similarities in the proportion with reported regression may be due to other reasons.

The exposure data of breastfeeding and infant formula use were of necessity also self-reported. Reliance on self-report leads to misclassification bias; however, there is no reason to believe that this bias is differential, especially in terms of formula use with and without supplementation, and is therefore assumed to be random. Non-differential misclassification would bias the results toward the null, indicating the odds ratios seen in this study could be higher in a more rigorous study.

The internet survey was a parent-based effort and did not include all of the demographic questions normally found in epidemiologic surveys. The analyses in this study were only adjusted for age. Information on gender and socioeconomic status (SES) was not obtained. SES has been shown to not be associated with AD; however, gender is associated with AD—approximately 76% of those with AD are male (Larsson et al., 2005). Gender could confound the association of breastfeeding and AD if mothers are more likely to breastfeed due to the child’s gender, but child’s gender has been shown to not be associated with duration of breastfeeding (Vogel et al., 1999). The health status of the controls is unknown, other than the parents indicating
that their children had no autism spectrum disorder. These questions will need to be addressed in future studies.

The survey used for this study also did not address the reason why some mothers stopped or did not initiate breastfeeding. If there is a problem breastfeeding infants due to AD, then this is a source of possible confounding; however, this would not be an issue for the infant formula analysis. Also, the infant formula information used in this study did not categorize the amounts of partial infant formula use. These questions will need to be addressed in a future study.

One advantage of using this internet survey was the speed at which the survey was administered and the results received. This survey was completed in less than three months. Also this survey had a large number of participants, 861 cases and 123 controls, which gives the study sufficient power to detect differences in breastfeeding and infant formula use. This was an innovative study produced by concerned parents who want to find answers to the question of what causes AD.

Another advantage is the large number of infant formula choices in the survey’s drop-down menu—39 brand name choices were available along with “none”, “other”, and “I don’t know”. Having this number of infant formula choices allowed this variable to be accurately recoded into categories with and without DHA/ARA supplementation. Interestingly, 17% of case parents chose the “other” category compared to 3% of control parents. The reason for this
difference is unknown; however, if all of the children in the “other” category used supplemented formula, then control children still used more supplemented formula than cases, and the association between lack of supplementation and autistic disorder remains significant (OR 4.39, 95% CI 1.23, 15.7). Alternatively, if all of those in the “other” category used formula not supplemented with DHA/ARA, then the association between autistic disorder and lack of supplementation is even greater (OR 5.64).

While Tanoue and Oda (1989) found a significantly higher number of children with autism compared to control children had already stopped breastfeeding when assessed at the end of the first week of life, the present study is the first to show that increased duration of breastfeeding is associated with a decreased likelihood of AD. This is also the first study to suggest a possible link between the use of infant formula without DHA/ARA supplementation and AD. However, this study was based on a small group and should be followed by a larger more rigorous study to confirm the results.

Acknowledgements

The text of Chapter II in full is a reprint of the material that has been submitted for publication. The dissertation author was the primary researcher and author, and the co-authors listed in this publication directed and supervised the research which forms the basis for this chapter:

Chapter II, Table 1. Characteristics of participants in the Autism Internet Research Survey 2005.

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### Chapter II, Table 2. Age-adjusted associations of breastfeeding and autistic disorder for children aged 2-18.

<table>
<thead>
<tr>
<th>Variable</th>
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<th>(95% Confidence Interval)</th>
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<td>2.48</td>
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<td>Breastfeeding &lt;2 months</td>
<td>1.70</td>
<td>(1.00 - 2.88)</td>
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<td>Breastfeeding 2-6 months</td>
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<td>(0.75 - 2.14)</td>
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Limited to cases with reported regression in development

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<th>p value</th>
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<td>Breastfeeding 2-6 months</td>
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Chapter II, Table 3. Age-adjusted association of infant formula use with autistic disorder for children aged 2-4.

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<td>Formula with DHA/ARA</td>
<td>1.02</td>
<td>(0.33 - 3.18)</td>
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<td>Exclusive breastfeeding (no formula use)</td>
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Limited to cases with reported regression in development

<table>
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<td>Formula without DHA/ARA</td>
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<td>Formula with DHA/ARA</td>
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References


Mothers Survey, Ross Products Division, Abbott Laboratories (2002).


III. National Acetaminophen Sales and Autistic Disorder in California:

An Ecological Association
Abstract

This study examined whether trends in national sales of children’s acetaminophen products were associated with trends in reported cases of autistic disorder. This is an ecologic study using published data of annual national sales of children’s acetaminophen and aspirin products between 1979 and 1985, and published data on the number of children with autistic disorder eligible for services from the California Department of Developmental Services. Linear regression analyses showed significant positive associations of annual sales of children’s acetaminophen tablets and liquid with cases of autistic disorder by year of birth (p<0.05), while sales of children’s aspirin products showed a significant negative association (p<0.01). These data suggest a possible link between acetaminophen sales and reported cases of autistic disorder in California.
**Introduction**

Autistic disorder (AD) is a severe developmental disorder defined by social and communication deficits and ritualistic-repetitive behaviors that appear in early childhood (American Psychiatric Association [APA], 1994). There is a strong genetic component to AD with a reported rate of 60 percent concordance in monozygotic twins (Bailey *et al.*, 1995). AD can be comorbid with tuberous sclerosis (1.2%), fragile X syndrome (0.3%), and congenital rubella syndrome (0.3%), although the attributable proportion of all medical disorders is less than 10% (Fombonne, 2003). In most cases the cause of AD is unknown (Fombonne, 2003).

A report from the California Department of Developmental Services (DDS) (2003) shows a marked increase in the number of individuals with AD who are eligible for services. This report shows the number of persons with AD increased in their client population from 2,778 to 20,377 for the years 1987 to 2002. As a percent of their total client population, AD increased from 3.5 percent to 12.4 percent during this period. The reason for this increase is unknown and may not indicate an increase in AD incidence since changing case definitions, administrative procedures, and service issues have had an effect on the number of individuals with AD eligible for services in California and nationwide (Croen *et al.*, 2002; Lawler *et al.*, 2004; Mandell and Palmer, 2005; Eagle, 2004).
There are several theories about possible environmental triggers for AD including childhood vaccinations, mercury exposure, and viral infections. Small descriptive clinical studies have suggested a link between measles-mumps-rubella (MMR) vaccination and AD/pervasive developmental disorder (Furlano et al., 2001; Kawashima et al., 2000; Singh et al., 2002; Singh and Jensen, 2003; Torrente et al., 2002; Uhlmann et al., 2002; Wakefield et al., 1998; Wakefield et al., 2000, but see Horton, 2004; Murch et al., 2004; Taylor et al., 2002). Epidemiological studies have not supported the relationship between prevalence of autism and the MMR vaccine (Fombonne & Chakrabarti, 2001; Institute of Medicine, 2001). A 14-year prospective study of children from Finland showed no association between the MMR vaccination and AD (Peltola et al., 1998). Two large population studies from Denmark and England also showed no epidemiological evidence for association (Taylor et al., 1999; Madsen et al., 2002). An ecological study from England found no significant increase in AD following the introduction of the MMR vaccination (Chen et al., 2004), and comparison of MMR vaccination coverage in California with the increasing autism trend from the California DDS also showed no association (Dales et al., 2001).

While there has been no scientific evidence supporting the link between the MMR vaccine and an elevated risk of AD, it is possible that some factor temporally related to the MMR vaccination increases the risk for AD in some children. Children are often given acetaminophen if they have symptoms such
as fever or irritability, and the MMR vaccination can cause these symptoms. Perhaps the administration of acetaminophen is associated with the development of AD in these children.

A search of the literature revealed no studies investigating a link between acetaminophen and AD. However, a pilot study of low functioning children with AD indicated that some children had a sulfation deficit which causes them to process acetaminophen differently from the control group (Alberti et al., 1999). There are three pathways for the metabolism of acetaminophen: glucuronidation, sulfation, and the cytochrome P-450 system. In children, sulfation is the primary pathway for acetaminophen metabolism until age 10-12 years (Tucker, 2003). With a sulfation deficit, more acetaminophen could be metabolized by the cytochrome P-450 system which would increase production of the metabolite N-acetyl-p-benzoquinone imine (NAPQI), a known cytotoxic/genotoxic agent (Bender et al., 2004). Normally, when NAPQI is produced, it is conjugated with glutathione and excreted as non-toxic conjugates. One study found that children with AD had significantly lower plasma levels of glutathione than the control group (James et al., 2004). The possible model for the relationship of acetaminophen to AD is this difficulty detoxifying NAPQI which in theory could be an environmental trigger for AD.

As a first step, the present study was performed to determine if national sales patterns of acetaminophen could be associated with the number of individuals with AD who were eligible for services from the California DDS.
Methods

An internet search revealed four historical events in the history of acetaminophen. These events were compared with the number of eligible persons with AD from a 1999 report to the legislature by the California DDS. This data was collected by 21 regional centers that provide services to children with developmental disabilities. Because this report only contains information on children whose parents had registered for assistance, it is not a complete ascertainment of all cases. However, it is estimated that 75-80% of parents have registered based on electronic linkage of California’s DDS database with the Department of Education, special education databases (Croen et al., 2002).

The number of eligible persons with AD by year of birth was abstracted from Figure 1 in the California report (DDS, 1999). This information was used to perform the first analysis consisting of two linear regressions to determine if there was a change in the AD trend before and after the publication of a link to Reye Syndrome from aspirin use (Starko et al., 1980). The first linear regression included individuals born from 1961-1980 and the second linear regression included individuals born in 1980-1990. The slopes of the two lines were compared to indicate whether a significant change occurred in the AD trend after the sales of children’s aspirin decreased and the sales of children’s acetaminophen products increased in 1980 (Arrowsmith et al., 1987).
For the second analysis, information on analgesic sales was abstracted from the graph in a published manuscript by Arrowsmith and colleagues (1987). (Original data was unavailable.) This yielded the number of children’s aspirin tablets, acetaminophen tablets, and cubic centimeters of acetaminophen liquid sold in the US for the years 1979-1985. Linear regression models were developed to determine if annual sales of children’s aspirin or acetaminophen products were associated with year of birth for eligible individuals with AD in California.

**Results**

Figure 1 presents national sales for children’s aspirin and children’s acetaminophen products for the years 1979-1985 (Arrowsmith et al., 1987). In 1980 the use of aspirin in children with viral infection was linked to the development of Reye Syndrome (Starko et al., 1980). The figure shows a marked decline in children’s aspirin sales and concomitant rise in sales of children’s acetaminophen products beginning in 1980.

Figure 2 shows the number of eligible persons with AD by year of birth adapted from the 1999 report to the legislature by the California DDS. The figure shows a notable increase in the number of eligible persons with AD born after 1980. Superimposed on the figure are events in the history of acetaminophen. In 1977 a Food and Drug Administration (FDA) panel recommended a warning label be placed on acetaminophen products due to the association of acetaminophen use and liver damage (FDA, 2002). This
corresponds to a drop in the number of eligible individuals with AD for a birth year of 1977. As previously detailed, there was an increase in acetaminophen sales in 1980, which corresponds to an increasing trend in the number of eligible individuals with AD born after 1980. In 1982 and again in 1986, acetaminophen capsules were tampered with by replacing the contents with cyanide. Seven people were killed in Chicago when they ingested the cyanide-laced acetaminophen capsules in 1982 (Beck et al., 1982). One woman was killed in New York when she ingested cyanide-laced acetaminophen capsules in 1986 (Koepp, 1986). Both of these events precipitated sharp declines in acetaminophen sales. Correspondingly, there are inflections in the increasing AD trend in the number of eligible individuals for the years 1982-1984 and 1986-1987.

As shown in Table 1, regression coefficients for the number of eligible individuals with AD were significantly different for those born between 1961-1980 and 1980-1990 (t test, p<.0001). In other words, there is a significant difference in the slope of the AD trend in California before and after 1980.

Linear regression was also performed to determine if sales of children’s analgesics were related to the number of enrolled individuals with AD in California by birth year. These analyses were not adjusted for potential confounders. The sales of children’s aspirin products showed a significant negative association with the number of individuals with AD (p<0.01). Both sales of children’s acetaminophen tablets and liquid showed significant
positive associations with AD (p<0.05). The results of these linear regressions are shown in Table 1.

Discussion

The sales of children's aspirin products declined and the sales of children's acetaminophen products rose after an aspirin-Reye Syndrome link was reported in 1980 (Starko et al., 1980). Using data abstracted from the report by the California DDS (1999), the increasing trend of AD cases for the period after 1980 was significantly greater than for the period before 1980. This significant difference could be due to increasing sales of children's acetaminophen products which would presumably lead to more use by young children. However, the changing trend in AD registration in California may be due to many other factors and does not necessarily indicate an increase in AD incidence. Better diagnosing of AD or the increased availability of services may have caused an increase in registration.

The diagnosis of AD has changed over time. The third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM), published in 1980, separated the diagnosis of autism from childhood schizophrenia and placed it under a new category of pervasive developmental disorders (APA, 1980). DSM III criteria included onset before 30 months of age, lack of responsiveness to other people, gross impairments in communication and language, and bizarre responses to the environment. DSM IV, published in 1994, defines autism as part of a spectrum of disorders with variations in
severity (APA, 1994). Communication difficulties are the primary differences in the criteria for the autistic spectrum disorders, which include autistic disorder, Asperger's disorder, and pervasive developmental disorder-not otherwise specified (APA, 1994).

Lawler and colleagues (2004) have suggested that changes in case definitions, administrative and diagnostic procedures, and service-related incentives or impediments have had an effect on the number of eligible individuals with AD in California. It has also been suggested that the increase in eligible individuals with AD in California is due to widening of the case definition to include children with normal or above-normal intelligence (Eagle, 2004) or due to diagnostic substitution of children with mental retardation (Croen et al., 2002).

A world-wide review by Fombonne (2003) of autism epidemiological surveys concluded that changes in case definition and improved awareness account for much of the increased autism trend in recent decades. A further report by Chakrabarti and Fombonne (2005) reported a stable incidence in Midlands, UK over 15 years when study design features were held constant. Further study is needed to establish whether there has been a true increase in autism incidence world-wide and/or in California.

In 1969, the Lanterman Mental Retardation Services Act established regional centers of care in California for persons with mental retardation. In 1973 this act was amended to include persons with autism and other
developmental disabilities, and in 1976 this act was again amended to establish a right to treatment and habilitation services for children and adults with developmental disabilities (DDS, 2006). The availability of these services may have contributed to the increasing trend in the number of eligible individuals with AD who were registered in California.

Linear regression of national sales of children’s aspirin tablets, acetaminophen tablets, and acetaminophen liquid with the number of eligible individuals with AD in California yielded significant associations. Sales of children’s aspirin decreased and sales of children’s acetaminophen increased as AD increased. The increasing AD trend in California may be related to increasing use of children’s acetaminophen or decreasing use of children’s aspirin. Although these events may be related, it is also possible that these are coincidental findings and that AD has no relation to changing analgesic sales.

The linear regression analysis of analgesic sales with AD cases is problematic. National children’s analgesic sales were abstracted from a graph in a published study (Arrowsmith et al., 1987). Although the principal investigator of this study was contacted, the raw data for this graph was no longer available. No national figures for the numbers of individuals with AD were available for the study years, and this study relied on the number of individuals with AD abstracted from a California report (DDS, 1999). Further, although sales of children’s analgesics vary from year to year, the
observations are not independent, and sales from any given year will be correlated with sales from the previous year. This correlation could lead to errors in a linear regression analysis but should have been suitable for this preliminary study.

For each of four historical events related to acetaminophen, there is a corresponding inflection in the number of eligible individuals with AD in California as shown in figure 2. These inflections would be expected if acetaminophen exposure is related to development of AD. However, the drop in the number of individuals with a birth year of 1977 could be an artifact since it occurred in only one year. Also, the increase in the trend for AD that began in 1980 could be due to other factors as previously detailed. More interesting are the apparent effects of historical events in 1982 and 1986 when eight people were murdered with cyanide-laced acetaminophen capsules. The apparent effects from both of these events (from the graph in Figure 2) continued for more than one year and precipitated declines in an AD trend that had been increasing and which afterwards continued increasing after 1987 through 2002 (DDS, 2003). Of course, other events could be responsible for the decreases in the number of eligible individuals with those birth years.

Other environmental factors may also be involved in the apparent increase in AD seen in this study. For example, low levels of breastfeeding could decrease immune protection in infants by decreasing mother to child transfer of IgA. Decreased immune protection could make a child more vulnerable to
viral infection which in theory could lead to AD. The prevalence of breastfeeding in the US increased during the 1970s and decreased during the 1980s. (Abbott Laboratories, 2002). This pattern does not correlate well to the reported cases of AD seen in the present study but has in the authors’ previous work (submitted for publication).

The significant differences seen in this study should be viewed with caution, as this is an ecological study with no measured acetaminophen exposures in any of the individuals with AD. Ecologic studies of this type are useful to generate hypotheses but cannot establish a cause and effect relationship. The purpose of this study was to explore a possible correlation between acetaminophen sales and AD. It is hoped that this possible association might generate new thinking about potential environmental triggers for AD. The authors hope that this report is followed by case-control and cohort studies where exposures can be measured for individuals with and without AD.

Acknowledgement

The text of Chapter III in full is a reprint of the material that has been submitted for publication. The dissertation author was the primary researcher and author, and the co-authors listed in this publication directed and supervised the research which forms the basis for this chapter:

Chapter III, Table 1. Linear regression models with the number of eligible persons with autistic disorder in California by birth year.

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<tr>
<td>1961-1980</td>
<td>2.4</td>
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<td>1980-1990</td>
<td>33.3</td>
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<table>
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<td>Millions of children's aspirin tablets</td>
<td>- 0.34</td>
<td>0.81</td>
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</tr>
<tr>
<td>Millions of children's acetaminophen tablets</td>
<td>0.44</td>
<td>0.71</td>
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<tr>
<td>Millions of cc's of children's acetaminophen liquid</td>
<td>0.29</td>
<td>0.76</td>
<td>0.010</td>
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* The slopes of the regression lines for the two periods are significantly different from each other, 2 sample t test (p<0.0001).
Chapter III, Figure 2. Number of enrolled persons with autistic disorder in California by year of birth with addition of events in the history of acetaminophen and autism. Adapted from "Changes in the population of persons with autism and pervasive developmental disorders in California's developmental services system: 1987 through 1998, a report to the legislature" (DDS, 1999).

1 1976—Lanterman act amended in California to establish right to treatment and habilitation services for children and adults with developmental disabilities.
2 1980—Diagnostic and Statistical Manual of Mental Disorders (3rd edition) published which separated the diagnosis of autism from childhood schizophrenia.
References

Abbott Laboratories (2002). Ross Products Division, Mother’s Survey.


IV. Acetaminophen after Measles-Mumps-Rubella Vaccination and Autistic Disorder: The Results of a Parent Survey
Abstract

The present study was performed to determine whether acetaminophen use after the measles-mumps-rubella vaccination was associated with autistic disorder. Case-control study using the results of an online parental survey conducted from July 16, 2005 to January 30, 2006, consisting of 83 children with autistic disorder and 80 control children aged 1 to 18 years. Acetaminophen use after measles-mumps-rubella vaccination was significantly associated with autistic disorder when considering children 1 to 5 years of age (OR 6.11, 95% CI 1.42-26.3), limiting cases to children 1 to 18 years with regression in development (OR 3.97, 95% CI 1.11-14.3), and when considering only children 1 to 18 years who had post-vaccination sequelae (OR 8.23, 95% CI 1.56-43.3), adjusting for age, gender, mother's ethnicity, and the presence of illness concurrent with measles-mumps-rubella vaccination. Presence of concurrent illness with the measles-mumps-rubella vaccination was significantly associated with autistic disorder when all cases were considered (OR 8.81, 95% CI 2.29-33.9) and after limiting cases to children with regression in development (OR 17.2, 95% CI 3.51-84.5), adjusting for age, gender, mother's ethnicity, and acetaminophen use after measles-mumps-rubella vaccination. This preliminary study found that acetaminophen use after measles-mumps-rubella vaccination and the presence of illness concurrent with measles-mumps-rubella vaccination were
independently associated with autistic disorder. Future studies are required to confirm these results.
Introduction

Autistic disorder (AD) is a severe developmental disorder defined by social and communication deficits and ritualistic-repetitive behaviors that are seen in early childhood (American Psychiatric Association, 1994). A small percentage of cases of AD are associated with several known congenital conditions such as fragile X syndrome, Angelman syndrome, tuberous sclerosis, congenital rubella syndrome, neurofibromatosis, phenylketonuria, and Rett syndrome. Approximately 94% of AD cases are not associated with a congenital condition and have an unknown etiology (Fombonne, 1999). AD is a neurobiological disorder with genetic underpinnings (Muhle et al., 2004), and recent evidence suggests that brain growth abnormalities and symptoms may occur during the first year of life (Courchesne, Carper, & Akshoomoff, 2003).

For some children, environmental factors may contribute to an increased risk of AD (Lawler et al., 2004). Theories about possible environmental triggers for AD include childhood vaccinations, environmental exposures, and viral infections. Our previous ecological study suggested a link between acetaminophen use and AD (Schultz et al., submitted). Small clinical studies have suggested a link between measles-mumps-rubella (MMR) vaccination and AD (Furlano et al., 2001; Singh et al., 2002; Singh and Jensen, 2003; Torrente et al., 2002; Uhlmann et al., 2002; Wakefield et al, 1998; Wakefield et al., 2000, but see Horton, 2004; Murch et al., 2004; Taylor et al., 2002). However, epidemiological studies have not supported the relationship between
prevalence of AD and the MMR vaccine (Fombonne & Chakrabarti, 2001; Institute of Medicine, 2001). A prospective study from Finland showed no association between the MMR vaccination and AD (Peltola et al., 1998), and two large population studies from Denmark and England also showed no evidence for this association (Taylor et al., 1999; Madsen et al., 2002). A further study from England found no significant increase in AD following the introduction of the MMR vaccination (Chen et al., 2004), and comparison of MMR vaccination coverage in California with AD also showed no association (Dales et al., 2001).

Reported adverse reactions in children to the MMR vaccination are fever (5-15%) and rash (5%), although other complications are rare (Centers for Disease Control and Prevention [CDC], 2006). Some other factor related to the MMR vaccination or the timing of the MMR vaccination may be related to AD. Acetaminophen is often given to prevent or treat a reaction to the MMR vaccination. Some low functioning children with AD have been shown to have a sulfation deficit which causes them to process acetaminophen differently from control children (Alberti et al., 1999). Acetaminophen use may increase the risk for AD in some children. A search of the literature revealed no studies investigating a link between acetaminophen use and AD, other than our ecological study (Schultz et al., submitted). The present study was initiated to assess whether acetaminophen use after MMR vaccination could be associated with AD.
Materials and Methods

Parents of children with and without AD were recruited via the internet to take an internet-based survey. Participants were invited to complete either 36-question version for children with AD (case children) or a 22-question version for children without AD (control children). Two autism listserv publications, Valerie’s List and the Schafer Autism Report, published links to the online surveys. Ads were also placed online using Google™, and individuals who performed online searches containing keywords (autistic, autism, etc.) were shown ads requesting their participation in a research survey. The number of keywords used was 306, and they can be grouped into the following categories: autism and autistic features (262), treatment for autism (24), prominent people involved in autism (13), and possible causes of autism (7).

Cases were obtained by sending requests for participation to Valerie’s List and the Schafer Autism Report beginning on July 16, 2005. This was followed by Google™ advertising beginning on September 22, 2005. One hundred ninety case surveys were completed by October 16, 2005. This study was approved by the University of California, San Diego Human Research Protections Program and the Institutional Review Board at San Diego State University.

The controls were obtained in four separate groups. The parents of children with AD who took the survey between July 16, 2005 and September 21, 2005 were asked to provide a control for their survey. Nine control
surveys were obtained in this way. From September 22, 2005 to October 16, 2005, parents for the control survey were solicited using Google™ advertising which yielded an additional 41 control surveys. On November 30, 2005 an additional appeal was made via Valerie’s List to parents who had taken the case survey to find parents to take the control survey. This resulted in an additional 23 control surveys. On January 7, 2006, another appeal was made via Valerie’s List and ads were again placed on Google™. By January 30, 2006, 50 additional control surveys had been obtained for a total of 123.

Parents taking the case survey were asked to select the diagnosis for their child from the following choices: Autism or Autistic Disorder, Pervasive Developmental Disorder—Not Otherwise Specified (PDD-NOS), Asperger's Disorder, or Other. Limiting the age of children in both groups to less than 18 years, the case diagnosis to Autism or Autistic Disorder, and the respondents to parents, yielded 114 case and 113 control surveys. All of the parents of case children reported that their child was diagnosed by at least one medical professional, most commonly a clinical psychologist (n=61), while others reported a diagnosis from a neurologist (n=33), pediatrician (n=33), child psychiatrist (n=18), or developmental pediatrician (n=11).

The MMR vaccination is recommended for children aged 12 to 15 months. Since children less than one year old would not have had the opportunity to have this vaccination, the study was further limited to children older than one year at the time of the study. This yielded 113 case and 109 control surveys.
The main question of interest in this study was whether children had been given acetaminophen after the MMR vaccination. After restricting the study to those who answered this question, 83 case and 80 control children were available for study. Compared to those retained in the study, those dropped were slightly older (8.2 vs. 7.5 years) and more likely to be male (81% vs. 68%). Caucasian ethnicity of the mothers and fathers for those dropped was 85% and 83%, respectively, which was similar to the mothers and the fathers of those retained, 85% and 84%, respectively. Analysis with 113 case and 109 control surveys did not significantly change the findings of the study.

Three cases reported first diagnosis before the age of 20 months. A total of 12 cases were first diagnosed before the age of 24 months, fifty-two cases were diagnosed from 24 through 36 months of age, and 19 between ages 3 and 18 years. Fifty-four cases reported that their child had been given one or more standardized diagnostic tests (Autism Diagnostic Interview—Revised, Autism Diagnostic Observation Schedule, Childhood Autism Rating Scale, etc.) while 20 cases reported that they didn't know what specific test had been used as part of a clinical evaluation, and nine cases did not respond to the question.

The surveys included questions on the child's gender, ethnicity and education of each respondent parent (five choices each), date of the child's birth, and the nature of the child's development. On the survey, parents were also asked whether their child was given an analgesic to prevent or treat a
reaction to the MMR vaccination. Parents could check yes or no to the use of aspirin, acetaminophen, or ibuprofen, in that order. No parents reported using aspirin and this variable was dropped from further analysis. Parents were also asked in a separate question whether their child was given aspirin (yes, no) acetaminophen (yes, no) or ibuprofen (yes, no) during the ages of 12 to 18 months. For this question as well, no parents reported using aspirin; only use of acetaminophen and ibuprofen were explored.

The survey asked parents if their child appeared sick (yes, no) at the time he/she was given the MMR vaccination. The survey also included a question asking whether their child had any of the following reactions to the MMR vaccination: fever, rash, diarrhea, irritability, and/or seizures. The total number of reactions to the MMR vaccination was recoded into a new variable.

Parents of autistic children were questioned about the nature of their child’s development to determine if the child had a regression in development. Autistic regression indicates that a child goes through a normal period of development followed by a regression in development and subsequent development of AD. For the purpose of this study, regression was defined as a child’s attainment and loss of at least three words, using the definition of Lord, Shulman, and DiLavore (2004).

SAS for Windows version 9.1 was used for all statistical analyses. Logistic regression analysis and 2x2 contingency tables were used to test the univariate association of AD with acetaminophen or ibuprofen use after MMR
vaccination, acetaminophen or ibuprofen use at age 12 to 18 months, age, gender, education of the parents, ethnicity of the parents, whether the child appeared sick concurrent to the MMR vaccination (i.e., illness apparent prior to the vaccination), and the number of sequelae to the MMR vaccination.

Adjusted logistic regression analysis was used to produce models of AD with acetaminophen use, ibuprofen use, and the presence of illness concurrent with the MMR vaccination adjusting for variables found to be associated with AD (p<.05) in univariate analyses if they produced a 10% change in the odds ratio. Additional logistic regression models were developed for subgroups of the sample. One subgroup was limited to children 1 to 5 years old in order to minimize the effect of recall bias. An additional subgroup included only case children with regression because these children may be more likely to have been affected by environmental influences. A further subgroup was limited to children who had sequelae to the MMR vaccination in order to test whether acetaminophen use after MMR vaccination was a surrogate measure for post-vaccination sequelae. Since children with post-vaccination sequelae are more likely to be given acetaminophen, this analysis was included to test whether acetaminophen use was associated with AD while holding the variable for post-vaccination sequelae constant.

Interaction analyses were also performed to determine if the association of AD with acetaminophen use after MMR vaccination, acetaminophen use age
12 to 18 months, and illness concurrent with the MMR vaccination varied by the levels of the adjustment variables.

**Results**

Table 1 presents the characteristics of children in the AD research survey. The mean age of cases (n=83) and controls (n=80) was similar at 7.7 years and 7.3 years, respectively (p=0.53). Gender varied by group; 86% of the cases were male versus 50% of the controls (p<0.01). There were no apparent differences between the two groups in terms of parent education or ethnicity of the fathers, but more mothers of controls were Caucasian (92% vs. 78%, p=0.01).

Presence of illness concurrent with MMR vaccination varied by group (cases 31%, controls 4%, p<0.01). Sequelae to the MMR vaccination were reported more frequently for the cases than controls: fever (53% vs. 21%, p<0.01), rash (11% vs. 4%, p=0.09), diarrhea (24% vs. 1%, p<0.01), irritability (40% vs. 12%, p<0.01), and seizures (1% vs. 0%, p=0.52). Overall, 59% of the cases compared with 28% of the controls experienced at least one of these sequelae (p<0.01).

Acetaminophen use after MMR vaccination (n=163) varied by group, with significantly more cases than controls reporting its use (75% vs. 55%, p<0.01). Acetaminophen use at age 12 to 18 months (n=137) also varied significantly by group, with more cases than controls reporting its use (94% vs. 75%, p<0.01). More cases than controls reported using ibuprofen after MMR
vaccination (n=111, 15% vs. 9%) and at age 12 to 18 months (n=103, 61% vs. 52%), although these differences were not significant. Analgesic use for acetaminophen and ibuprofen was recorded as yes/no and includes overlap for individuals taking both drugs (n=6 for individuals using both analgesics after MMR vaccination and n=55 for individuals using both analgesics at age 12 to 18 months).

The analyses were limited to those parents who answered the question on acetaminophen use after MMR vaccination (n=163 surveys). Since responses to the other questions varied, the number answering each question are shown in parentheses. Assuming non-responses were "No" changed the significance level of acetaminophen use at 12 to 18 months from p<0.01 to p<0.05, but did not alter the lack of significance for ibuprofen use after the MMR vaccination or at age 12 to 18 months.

Table 2 shows the crude associations of potential risk factors with AD. Males were significantly more likely to have AD (n=163, OR 5.92, 95% CI 2.79-12.6). Parents’ education, fathers’ ethnicity, and children’s age were not significantly associated with AD. Mothers with Caucasian versus other ethnicity were significantly less likely to have a child with AD (n=162, OR 0.30, 95% CI 0.11-0.79). Children with illness concurrent with measles-mumps-rubella vaccination were more than 11 times as likely to have AD (n=161, OR 11.5, 95% CI 3.30-39.8). For each sequela to the MMR vaccination, children were twice as likely to have AD (n=155, OR 2.36, 95% CI 1.64-3.42). Use of
acetaminophen after MMR vaccination (n=163, OR 2.42, 95% CI 1.25-4.69) and at age 12 to 18 months (n=137, OR 5.42, 95% CI 1.72-17.1) significantly increased the likelihood of being in the AD group by two and five times, respectively. Ibuprofen use after MMR vaccination and at age 12 to 18 months were not significantly associated with AD.

Table 3 presents the associations of analgesic use between 12 and 18 months of age with autistic disorder adjusted for age, gender, and mother’s ethnicity. Although age was not a confounder of the associations, it was included in the final models for completeness. Children who used acetaminophen at age 12 to 18 months were more than eight times as likely to be in the AD group when all children were considered (n=137, OR 8.37, 95% CI 2.08-33.7) and more than 20 times as likely to be in the AD group when limiting cases to children with regression (n=93, OR 20.9, 95% CI 1.33-329). Limiting the analysis to all children from one to five years produced a marginally significant association of acetaminophen use at 12 to 18 months with AD (n=46, p=0.052). Ibuprofen use at age 12 to 18 months was not significantly associated with AD when all children were considered (n=102), when considering children 1 to 5 years (n=35), or when limiting cases to children with regression (n=73). The lack of an association remained when limiting the analysis of ibuprofen use to all children who did not report taking acetaminophen (n=67, OR=1.84, 95% CI 0.55-6.15) (data not shown in submitted publication).
Table 4 shows the association of presence of illness concurrent with MMR vaccination and AD, adjusted for age, gender, mother’s ethnicity, and acetaminophen use after measles-mumps-rubella vaccination. Children with illness concurrent with the MMR vaccination were more than eight times as likely to be in the AD group when all children were considered (n=160, OR 8.81, 95% CI 2.29-33.9), and more than 17 times as likely to be in the AD group when cases were limited to children with regression in development (n=108, OR 17.2, 95% CI 3.51-84.5). There was no significant association between illness concurrent with the MMR vaccination and AD when considering children 1 to 5 years old (n=52).

Table 5 presents the association of analgesic use after MMR vaccination with AD, adjusted for age, gender, mother’s ethnicity, and the presence of illness concurrent with the MMR vaccination. Acetaminophen use after MMR vaccination increased by six fold the likelihood of AD when considering only children 1 to 5 years (n=52, OR 6.11, 95% CI 1.42-26.3), by four fold after limiting cases to children with regression in development (n=108, OR 3.97, 95% CI 1.11-14.3), and by eight fold when considering only children who had post-vaccination sequelae (n=67, OR 8.23, 95% CI 1.56-43.3). The association of acetaminophen use after MMR vaccination with AD was marginally significant when considering all children 1 to 18 years (n=180, p=0.059). Ibuprofen use after MMR vaccination was not significantly associated with AD for children 1 to 18 years (n=108), for children 1 to 5 years
(n=39), when cases were limited to children with regression (n=76), or for children with post-vaccination sequelae (n=40).

Acetaminophen use after MMR vaccination was tested for interaction with the number of post-vaccination sequelae and with the presence of concurrent illness at the time of the MMR vaccination. No significant interactions were found in these analyses (p>0.05).

**Discussion**

The present study found that acetaminophen use after the MMR vaccination was associated with AD when considering children 1 to 5 years, after limiting cases to children with regression in development, and when considering only children who had post-vaccination sequelae. This finding could explain the inconsistency of the previous studies of MMR and AD since acetaminophen use was not considered.

Acetaminophen use at age 12 to 18 months was also significantly associated with AD. Since MMR vaccination is usually given at age 12 to 15 months, this finding would be expected if the combination of MMR vaccination and acetaminophen use is a risk factor for AD. Ibuprofen use at age 12 to 18 months was not associated with AD. This indicates that the use of analgesic after MMR vaccination associated with AD may be specific for acetaminophen. However, fewer parents reported ibuprofen use and this study should be repeated with larger numbers of ibuprofen users.
The analysis of acetaminophen use after MMR vaccination included limiting cases to children with regression in development since it was thought that these children may develop normally until their MMR vaccination. The odds ratio for acetaminophen use (versus none) after MMR vaccination attained significance after limiting cases to children with regression (OR 3.97, 95% CI 1.11-14.3). This result is consistent with the possibility that regression (and subsequent AD) is due to the administration of acetaminophen after MMR vaccination.

This study found that illness concurrent with the MMR vaccination was significantly associated with AD when considering all children 1 to 18 years old and after limiting cases to children with regression in development. The odds ratio of the association was higher when considering only children with regression in development (OR 17.2 vs. 8.81). It is possible that children with illness concurrent with the MMR vaccination would have a weakened immune system due to the presence of illness, and this could have predisposed them to developing AD. However, it is also possible that more children with AD were reported to be ill at the time of their MMR vaccination because symptoms of AD could have been interpreted as illness, or parents could have reported post-vaccination sequelae as concurrent illness. Illness at the time of the MMR vaccination should be investigated further as a risk factor for AD.

The presence of illness concurrent with the MMR vaccination and AD were not significantly associated when limiting the analysis to children 1 to 5 years
old. This may be due to the small number of children in this subset, or it could be due to recall bias in that parents of older children are less accurate in their recollections. It is also possible that parents of the younger children are more accurate in their recollections, and there is no real effect.

In children, sulfation is the primary pathway for acetaminophen metabolism until age 10 to 12 years (Tucker, 2003). One pilot study reported a sulfation deficit in a small group of low functioning children with AD which may cause them to process acetaminophen differently from control children (Alberti et al., 1999). This difference in processing acetaminophen could lead to increased production of NAPQI which could have interfered with the typical immune response to the MMR vaccination and precipitated AD in susceptible children. However, other models for the association of acetaminophen and AD are also possible, including direct neurotoxic effects of acetaminophen or NAPQI.

A potential concern in this study is that acetaminophen use after MMR vaccination was acting as a surrogate for sequelae to the MMR vaccination, i.e. it is really only the sequelae that are important. However, the use of acetaminophen after MMR vaccination produced a significant odds ratio (OR 8.23) after limiting the analysis to children who had post-vaccination sequelae. This is consistent with the idea that acetaminophen use after MMR vaccination is a risk factor for AD and not a surrogate measure for sequelae. The model would not converge when limited to children who did not have post-vaccination sequelae, and this analysis was not possible. Testing the interaction of
acetaminophen use after MMR vaccination with the number of sequelae produced no significant results (p>.05).

One problem with this study is the reliance on self-report from the parents in reporting the exposures and the outcome of AD. Reliance on self-report can lead to misclassification bias. If the child’s medical records were available, the problem of recording exposures would still exist since acetaminophen is available without a prescription and its use not often recorded. Having medical records available would be beneficial to reducing AD misclassification since the diagnostic procedures could be verified. However, all of the parents of case children reported that their child was diagnosed by at least one medical professional.

Age in this study was limited to 1 to 18 years in an attempt to minimize recall bias in the parental responses. In a further attempt to minimize recall bias, a subgroup of children 1 to 5 years was also analyzed. However, it is possible that parents of children with AD may be more likely to remember and report acetaminophen use. It is also possible that children with AD are generally less healthy than their peers and are therefore more likely to be given acetaminophen.

Since participants were recruited over the internet and took the survey on a website, there is a possibility of ascertainment bias. Controls may not be representative of all non-cases in that they may have known a case or were searching the internet for topics on autism. This difference is illustrated by the
higher percent of controls reporting fever after the MMR vaccination versus the percent reported by the CDC (2006) for the general population (21% vs. 5 to 15%). Both cases and controls may differ from the general population in that they have access to computers and are willing to take an online survey. Participants in this study most likely differed from the population in other ways as well, as this study was not a random sample.

There is a problem of missing data in this study as seen in the varying numbers of cases and controls in the analyses. Only surveys with responses to the question regarding acetaminophen use after MMR vaccination were included in this study; however, other questions suffered from non-response. The answers to questions on ibuprofen use were especially lacking, making the finding of no association of ibuprofen use with AD questionable.

It would have been interesting to have information on breastfeeding and infant formula use in this sample. Our previous research has shown a significant association with infant feeding method (Schultz et al., submitted). Mothers of children with AD were less likely to have breastfed their children.

This is the first case-control study to show a possible association of acetaminophen use with AD, and is consistent with our ecological study (Schultz et al., submitted). The findings may be coincidental. More research needs to be completed to confirm the results of this preliminary study.
Acknowledgments

Valerie’s List and the Schafer Autism Report were instrumental in recruiting parents to take the case and control surveys. We would also like to acknowledge the assistance of Christopher Bacher in providing the keywords for the Google™ ads.

The text of Chapter IV in full is a reprint of the material that has been submitted for publication. The dissertation author was the primary researcher and author, and the co-authors listed in this publication directed and supervised the research which forms the basis for this chapter:

Chapter IV, Table 1. Characteristics of participants in the autistic disorder survey, 2005-2006.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases (n=83)</th>
<th>Controls (n=80)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = Cases, Controls</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age (years) (n = 83, 80)</strong></td>
<td>7.7 (4.1)</td>
<td>7.3 (3.9)</td>
<td>0.527(^1)</td>
</tr>
<tr>
<td><strong>Number of sequelae to the measles-mumps-rubella vaccination (n = 80, 75)</strong></td>
<td>1.3 (1.3)</td>
<td>0.4 (0.7)</td>
<td>&lt; 0.001(^1)</td>
</tr>
<tr>
<td><strong>Gender (male) (n= 83, 80)</strong></td>
<td>86 (71)</td>
<td>50 (40)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Mother’s ethnicity (Caucasian) (n= 83, 79)</strong></td>
<td>78 (65)</td>
<td>92 (73)</td>
<td>0.012</td>
</tr>
<tr>
<td><strong>Father’s ethnicity (Caucasian) (n= 83, 80)</strong></td>
<td>87 (72)</td>
<td>81 (65)</td>
<td>0.338</td>
</tr>
<tr>
<td><strong>Mother’s education (college graduate or higher) (n = 82, 79)</strong></td>
<td>61 (50)</td>
<td>65 (51)</td>
<td>0.639</td>
</tr>
<tr>
<td><strong>Father’s education (college graduate or higher) (n = 81, 79)</strong></td>
<td>53 (43)</td>
<td>61 (48)</td>
<td>0.278</td>
</tr>
<tr>
<td><strong>Regression (loss of words) (n = 81, --)</strong></td>
<td>38 (31)</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td><strong>Cases having a sibling with autism (n = 83, --)</strong></td>
<td>12 (10)</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td><strong>Received measles-mumps-rubella vaccination (n = 83, 80)</strong></td>
<td>100 (83)</td>
<td>99 (79)</td>
<td>0.491(^2)</td>
</tr>
<tr>
<td><strong>Illness concurrent with measles-mumps-rubella vaccination (n = 81, 80)</strong></td>
<td>31 (25)</td>
<td>4 (3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Reported sequelae to measles-mumps-rubella vaccination (n = 80, 75)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>53 (42)</td>
<td>21 (16)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Rash</td>
<td>11 (9)</td>
<td>4 (3)</td>
<td>0.091</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>24 (19)</td>
<td>1 (1)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Irritability</td>
<td>40 (32)</td>
<td>12 (9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Seizures</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>0.516(^2)</td>
</tr>
<tr>
<td>Any of above</td>
<td>59 (47)</td>
<td>28 (21)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Acetaminophen use after measles-mumps-rubella vaccination (n = 83, 80)</td>
<td>75 (62)</td>
<td>55 (44)</td>
<td>0.008</td>
</tr>
<tr>
<td>Ibuprofen use after measles-mumps-rubella vaccination (n = 53, 58)</td>
<td>15 (8)</td>
<td>9 (5)</td>
<td>0.379(^2)</td>
</tr>
<tr>
<td>Acetaminophen use age 12-18 months (n = 69, 68)</td>
<td>94 (65)</td>
<td>75 (51)</td>
<td>0.002</td>
</tr>
<tr>
<td>Ibuprofen use age 12-18 months (n = 49, 54)</td>
<td>61 (30)</td>
<td>52 (28)</td>
<td>0.338</td>
</tr>
</tbody>
</table>

* All p values by chi square unless otherwise noted. \(^1\) Logistic regression p value. \(^2\) Fisher’s exact test p value, two sided.
Chapter IV, Table 2. Crude Associations with autistic disorder, 2005-2006.

<table>
<thead>
<tr>
<th>Variable*</th>
<th>Odds Ratio</th>
<th>(95% Confidence Interval)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per year, n=163)</td>
<td>1.03</td>
<td>(0.95-1.11)</td>
<td>0.527</td>
</tr>
<tr>
<td>Gender (male/female, n=163)</td>
<td>5.92</td>
<td>(2.79-12.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mother's ethnicity (Caucasian/other, n=162)</td>
<td>0.30</td>
<td>(0.11-0.79)</td>
<td>0.015</td>
</tr>
<tr>
<td>Father's ethnicity (Caucasian/other, n=163)</td>
<td>1.51</td>
<td>(0.65-3.52)</td>
<td>0.340</td>
</tr>
<tr>
<td>Mother's education (college graduate or higher/other, n=161)</td>
<td>0.86</td>
<td>(0.45-1.63)</td>
<td>0.639</td>
</tr>
<tr>
<td>Father's education (college graduate or higher/other, n=160)</td>
<td>0.73</td>
<td>(0.39-1.37)</td>
<td>0.328</td>
</tr>
<tr>
<td>Presence of illness concurrent with measles-mumps-rubella vaccination (yes/no, n=161)</td>
<td>11.5</td>
<td>(3.30-39.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Number of sequelae to measles-mumps-rubella vaccination (per sequelae, n=155)</td>
<td>2.36</td>
<td>(1.64-3.42)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Acetaminophen use after measles-mumps-rubella vaccination (yes/no, n=163)</td>
<td>2.42</td>
<td>(1.25-4.69)</td>
<td>0.009</td>
</tr>
<tr>
<td>Ibuprofen use after measles-mumps-rubella vaccination (yes/no, n=111)</td>
<td>1.88</td>
<td>(0.58-6.17)</td>
<td>0.295</td>
</tr>
<tr>
<td>Acetaminophen use age 12-18 months (yes/no, n=137)</td>
<td>5.42</td>
<td>(1.72-17.1)</td>
<td>0.004</td>
</tr>
<tr>
<td>Ibuprofen use age 12-18 months (yes/no, n=103)</td>
<td>1.47</td>
<td>(0.67-3.21)</td>
<td>0.339</td>
</tr>
</tbody>
</table>

*n is the number of respondents to the question out of a possible 163.
Chapter IV, Table 3. Adjusted* associations of analgesic use age 12-18 months with autistic disorder, 2005-2006.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>(95% Confidence Interval)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Children 1-18 years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetaminophen (70 cases, 67 controls)</td>
<td>8.37</td>
<td>(2.08-33.7)</td>
<td><strong>0.003</strong></td>
</tr>
<tr>
<td>Ibuprofen (49 cases, 53 controls)</td>
<td>2.17</td>
<td>(0.82-5.72)</td>
<td>0.119</td>
</tr>
<tr>
<td><strong>Children 1-5 years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetaminophen (23 cases, 23 controls)</td>
<td>5.29</td>
<td>(0.99-28.3)</td>
<td>0.052</td>
</tr>
<tr>
<td>Ibuprofen (16 cases, 19 controls)</td>
<td>1.23</td>
<td>(0.22-6.85)</td>
<td>0.810</td>
</tr>
<tr>
<td><strong>Children 18 years or less, cases limited to children with regression</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetaminophen (26 cases, 67 controls)</td>
<td>20.9</td>
<td>(1.33-329)</td>
<td><strong>0.031</strong></td>
</tr>
<tr>
<td>Ibuprofen (20 cases, 53 controls)</td>
<td>2.44</td>
<td>(0.63-9.54)</td>
<td>0.199</td>
</tr>
</tbody>
</table>

*Adjusted for age, gender, and mother's ethnicity.
Chapter IV, Table 4. Adjusted* associations for the presence of illness concurrent with measles-mumps-rubella vaccination and autistic disorder, 2005-2006.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>(95% Confidence interval)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children 1-18 years (81 cases, 79 controls)</td>
<td>8.81</td>
<td>(2.29-33.9)</td>
<td>0.002</td>
</tr>
<tr>
<td>Children 1-5 years (26 cases, 26 controls)</td>
<td>3.35</td>
<td>(0.40-28.0)</td>
<td>0.265</td>
</tr>
<tr>
<td>Children 1-18 years, cases limited to children with regression (29 cases, 79 controls)</td>
<td>17.2</td>
<td>(3.51-84.5)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Adjusted for age, gender, mother’s ethnicity, and acetaminophen use after measles-mumps-rubella vaccination.
Chapter IV, Table 5. Adjusted* associations of analgesic use after measles-mumps-rubella vaccination with autistic disorder, 2005-2006.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>(95% Confidence Interval)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Children 1-18 years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetaminophen (81 cases, 79 controls)</td>
<td>2.13</td>
<td>(0.97-4.66)</td>
<td>0.059</td>
</tr>
<tr>
<td>Ibuprofen (51 cases, 57 controls)</td>
<td>1.62</td>
<td>(0.34-7.73)</td>
<td>0.544</td>
</tr>
<tr>
<td><strong>Children 1-5 years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetaminophen (26 cases, 26 controls)</td>
<td>6.11</td>
<td>(1.42-26.3)</td>
<td>0.015</td>
</tr>
<tr>
<td>Ibuprofen (18 cases, 21 controls)</td>
<td>3.60</td>
<td>(0.45-28.7)</td>
<td>0.226</td>
</tr>
<tr>
<td><strong>Children 1-18 years, cases limited to children with regression</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetaminophen (29 cases, 79 controls)</td>
<td>3.97</td>
<td>(1.11-14.3)</td>
<td>0.035</td>
</tr>
<tr>
<td>Ibuprofen (19 cases, 57 controls)</td>
<td>1.72</td>
<td>(0.21-14.5)</td>
<td>0.615</td>
</tr>
<tr>
<td><strong>Children 1-18 years with post-vaccination sequelae</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetaminophen (46 cases, 21 controls)</td>
<td>8.23</td>
<td>(1.56-43.3)</td>
<td>0.013</td>
</tr>
<tr>
<td>Ibuprofen (26 cases, 14 controls)</td>
<td>0.89</td>
<td>(0.10-8.30)</td>
<td>0.918</td>
</tr>
</tbody>
</table>

*Adjusted for age, gender, mother's ethnicity, and presence of illness concurrent with measles-mumps-rubella vaccination.
References


V. Conclusion
Autistic Disorder (AD) is a mysterious disorder and the etiology is unknown. Some children have a regression in development whereby they appear to develop normally for a period of time, lose some of their communication and social skills, and begin to develop the symptoms of AD. The three studies presented have identified environmental factors that may be associated with AD, some of which have not previously been considered.

The first study investigated length of breastfeeding and the use of infant formula supplemented with docosahexaenoic acid (DHA) and arachidonic acid (ARA) with AD. The children with AD in this survey were significantly less likely to have been breastfed and further were significantly less likely to have been fed infant formula with DHA/ARA than typically developing children. DHA and ARA are present in high amounts in breast milk and are considered conditionally essential nutrients. Developing infants who are not breastfed may not be able to produce enough of these fatty acids and may require supplementation. It has been shown that a lack of these fatty acids can slow development and it is conceivable that this could influence the development of AD.

It was determined that children with AD compared to those without were more likely to have been breastfed less than six months (OR 2.48, 95% CI 1.42, 4.35). Limiting the cases to children with regression in development found similar results (OR 1.95, 95% CI 1.01, 3.78). Children with autistic disorder were more likely to have used infant formula without
docosahexaenoic acid and arachidonic acid supplementation than to have been exclusively breastfed (OR 4.41, 95% CI 1.24, 15.7), and the result appeared stronger after limiting cases to children with regression in development (OR 12.96, 95% CI 1.27, 132).

Although these results were statistically significant, there are several limitations that should be addressed in the first study. Data was used from an online survey, and it did not include any demographic variables except for age. This was a problem given that male gender is highly associated with increased likelihood for AD. Other demographic variables that should have been included are the education level and ethnicity of the parents, although these factors have not been relevant in other studies. Also, the survey did not have information on timing and duration of partial breastfeeding, so that the breastfeeding information was incomplete. The survey relied on self-report for the diagnosis of AD, which means there is likely misclassification, which could have produced erroneous results. For example, parents of control children may have come upon this online survey because they were interested in AD topics. This could indicate that some of the control children may have had some symptoms of AD. Parents of AD children could have remembered details more accurately than the parents of control children because of guilt, thereby resulting in a differential bias.

Recall bias could also be a problem in this study as parents were asked to remember breastfeeding and infant formula use for their children, which would
especially be a problem for the data on the older children. If parents of children with AD reported less breastfeeding than actually occurred, then the odds ratios seen in this study would be erroneously high. Conversely, if parents of children with AD reported more breastfeeding than actually occurred, then the odds ratios seen would be erroneously low. Difficulties in measuring exposure based on parental recall are especially problematic when the parents have prior beliefs about causation or believe that they understand the purpose of the study. If parents thought they knew the purpose of the study, they may have answered the questions to give what they thought would be the acceptable responses or responses in line with their own beliefs. While this may have been a problem for the breastfeeding analysis, it is unlikely for the infant formula supplementation analysis, as brands were chosen by name recognition from a drop-down menu with thirty-nine choices.

The second study investigated whether children's aspirin sales and children's acetaminophen sales could be correlated with the AD trend in California. Linear regression of national sales of children's aspirin tablets, acetaminophen tablets, and acetaminophen liquid with the number of eligible individuals with AD in California by birth year yielded significant associations. Sales of children's aspirin decreased and sales of children's acetaminophen increased as AD increased. It appears that the increasing AD trend in California may be related to increasing use of children's acetaminophen
and/or decreasing use of children’s aspirin, but these results require confirmation in future studies.

There are also several limitations for the second study. The diagnosis of AD has changed over time, contributing to the increased AD trend in California. There is no consensus about whether there has been a true increase in AD incidence in California or whether apparent increases are due to changes in the diagnostic criteria that led to inclusion of a wider variety of cases, greater public awareness of AD, and/or the increased availability of services.

Next, the data for this study was abstracted from previously published papers, which could have led to estimation errors. This may have influenced the accuracy of the linear regression analyses. Also, the reported linear regressions were time series, which means that the data points were not independent observations. Finally, this was an ecological study with no direct information on individual analgesic use for the children with AD.

The third study was developed to look more directly at the results from the second study regarding the possibility that acetaminophen use might be a risk factor for AD. This study found that acetaminophen use after the MMR vaccination was associated with AD when considering children 1 to 5 years old (OR 6.11, 95% CI 1.42-26.3), after limiting cases to children with regression in development (OR 3.97, 95% CI 1.11-14.3), and when considering only children who had post-vaccination sequelae (OR 8.23, 95%
This finding could explain the inconsistency of the previous studies of MMR and AD because acetaminophen use was not considered. Acetaminophen use at age 12 to 18 months was significantly associated with AD (OR 8.37, 95% CI 2.08-33.7). Given that the MMR vaccination is recommended for ages 12 to 15 months, this finding would be expected if the combination of MMR vaccination and acetaminophen use is a risk factor for AD. This study also found that illness concurrent with the MMR vaccination was significantly associated with AD when considering all children 1 to 18 years old (OR 8.81, 95% CI 2.29-33.9) and after limiting cases to children with regression in development (OR 17.2, 95% CI 3.51-84.5). This association has never been reported and the explanation for it is unknown. If replicated repeatedly, this does raise the question whether children should be healthy prior to receiving the MMR vaccination.

One problem with this study is the reliance on self-report from the parents in reporting the exposures and the outcome of AD. Reliance on self-report can lead to misclassification bias. If the child’s medical records were available, the problem of recording exposures could still exist since acetaminophen is available without a prescription and its use not often recorded. Utilizing medical records would be beneficial to reducing AD misclassification since the diagnostic procedures could be verified. However, all of the parents of case children reported that their child was diagnosed by at least one medical professional.
Age in this study was limited to 1 to 18 years in an attempt to minimize recall bias in the parental responses. In a further attempt to minimize recall bias, a subgroup of children 1 to 5 years was also analyzed. Children 1 to 5 years old with AD were more likely than children 1 to 18 years old to have used acetaminophen after the MMR vaccination. This result could be due to a more accurate recall of acetaminophen use by the parents of the younger children. However, this result could also be due to other factors, such as an increased likelihood of younger parents to use acetaminophen.

Because this was an online survey, there may have been ascertainment bias, as only individuals with access to computers and willing to take an online survey were participants. Participants in this study most likely differed from the population in other ways as well, as this study was not a random sample. Controls may not be representative of all non-cases in that they may have known a case or were searching the internet for topics on AD. This difference is illustrated by the higher percent of controls reporting fever after the MMR vaccination compared to the percent reported by the CDC for the general population.

The survey did not include questions regarding breastfeeding and infant formula use, so it was not possible to see how that information would have changed the results. There was variable response to the questions in that not all parents answered every question. Missing information could have had an effect on the results, especially the finding of no effect for ibuprofen use, as
responses to questions on ibuprofen use were especially lacking. Other explanations for the results may include a particular bias of the parents who responded to these surveys who believe vaccines, formula use, or other environmental factors are largely (or entirely) responsible for their child’s AD. There may also be a larger proportion of respondents than expected who believe that their child suffered a regression in development, furthering biasing the results.

The subgroup analyses for the first and third studies limited the number of cases and controls that were available for study. The wide confidence intervals for the odds ratios observed in Table 3 of paper 1 and Tables 3-5 of paper 3 may be artifacts in the data due to small sample sizes and an imbalance of the number of cases and controls.

These are the first studies to suggest that acetaminophen use and use of infant formula without DHA/ARA supplementation may be associated with AD. This is also the first time that the presence of illness concurrent with the MMR vaccination has been shown to be associated with AD. Only one previous study has shown an increased likelihood for AD with shortened period of breastfeeding.

Other explanations are possible for the findings in these studies. It is possible that children with AD are more difficult to breastfeed and that this is reason for the apparent association with breastfeeding. Infant formula with DHA/ARA is more expensive than unsupplemented infant formula, and this
may have influenced some parents' decision regarding formula use. For acetaminophen use, it is possible that parents of children with AD overestimated their use of this analgesic. It may also be that illness or pain symptoms are more common in infants who develop AD, resulting in increased analgesic use. The studies presented here need to be repeated and verified before any conclusions can be drawn regarding the observed associations.

A future case-control study is being planned in an attempt to confirm the findings of these preliminary studies. In this future study, parents will be personally interviewed by a blinded interviewer to obtain more complete and unbiased answers to the questions. Also, the diagnosis of AD in the cases and the health of the controls will be confirmed by a medical professional. It is also anticipated that younger children will be enrolled in an effort to reduce recall bias in the parental responses. Additional questions will also be included in this study to determine if other factors, such as genetics, mercury exposure, and other unidentified factors may be involved in the development of AD. This new study should help to confirm or refute the findings of the current studies. The ultimate goal is to generate new thinking about the cause of AD and open new treatment and prevention possibilities.
VI. Appendices
Survey for Parents of a Child with Autism or Autistic Disorder

I would greatly appreciate it if you would participate in this survey. I am Dr. Stephen Schultz, the father of a child with autism, and I am conducting this study as part of my dissertation research in the Joint Doctoral Program in Epidemiology of the University of California San Diego and San Diego State University. I have decided to return to school and dedicate the rest of my life researching the cause of autism. This survey tests the association of medical history and autism, and it should take about 20 minutes to complete. Please have your child’s vaccination and medical records available.

Participation in this study is voluntary. If you decide to participate, you are free to withdraw your consent and to stop your participation at any time. There will be no direct benefit to you for participating in this research study, but it could help all of us unravel the mystery of autism. The only risk that you could have for participating in this study would be the loss of confidentiality, and this risk is minimal because the only personal identifying information collected is your child’s birth date.

My telephone number is (760) 744-1731, and I would be glad to answer any of your questions regarding this study or to verify my identity. If you would like to have documentation linking your participation with this research, please email me at stschultz@ucsd.edu. For questions about your rights as a research participant or to report research-related problems you may contact the Institutional Review Board at San Diego State University at (619) 594-6622, irb@mail.sdsu.edu or the University of California, San Diego Human Research Protections Program at (858) 455-5050. At the end of this survey is the “Experimental Subject’s Bill of Rights” which is required to be given to you and is for your information.

Thank you kindly if you agree to participate in this survey! If you know another parent who has a child with autism, please ask them to participate as well. Together we can make a difference!

Sincerely,
Dr. Stephen Schultz

Instructions: To check a box, please click on it with your mouse—clicking a box a second time will uncheck it. Items with drop-down boxes can be selected with a mouse click. For questions that require a written entry, please click on the box and type in your response.
1. Who is filling out this survey? Please check the box.
   - [ ] Father
   - [ ] Mother
   - [ ] Other

2. Please enter the birth date of your child in the box using the form mm/dd/yyyy:  

3. In what city and state (or country if not US) was your child born?  

4. In what city and state (or country if not US) was your child diagnosed with autism?  

5. In what city and state (or country if not US) was your child first treated for autism?  

6. Please check the box for the gender of your child. [ ] Male [ ] Female

7. What is the ethnicity of your child’s father?
   - [ ] Hispanic
   - [ ] African-American
   - [ ] Asian
   - [ ] Native American
   - [ ] Caucasian/White
   - [ ] Other If Other, please list:
8. **What is the ethnicity of your child’s mother?**

- [ ] Hispanic
- [ ] African-American
- [ ] Asian
- [ ] Native American
- [ ] Caucasian/White
- [ ] Other If Other, please list: __________

9. **What is the occupation of your child’s parents? Please type a response in the box for father and mother.**

Father’s Occupation __________

Mother’s Occupation __________

10. **What is the education level for your child’s parents? Please choose one response for each parent.**

Father’s education level __________

Mother’s education level __________

**Child’s Disease History**

11. **Has your child been diagnosed with any of the following medical conditions?**

- [ ] Fragile X syndrome
- [ ] Angelman’s syndrome
- [ ] Tuberous Sclerosis
- [ ] Congenital Rubella Syndrome
- [ ] Neurofibromatosis
- [ ] Phenylketonuria (PKU)
- [ ] Rett Syndrome
Childhood Disintegrative Disorder
None

12. Please write the age in months when you first became concerned that your child might have

a developmental problem: [ ] months

13. Please check the box that most closely matches the diagnosis for your child.

☐ Autism or Autistic Disorder
☐ Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS)
☐ Asperger’s Disorder
☐ Other - If Other please click the box and enter the diagnosis:

14. Please check the box for the type of medical professional(s) that diagnosed your child.

☐ Clinical Psychologist
☐ Pediatrician
☐ Child Psychiatrist
☐ Neurologist
☐ Family Practice Physician
☐ Other - If Other, please write the type in the box:

Please write your child’s age in months at first diagnosis: [ ] months
15. **Please check the boxes and enter the date (if known) for all of the tests that were used to help make a diagnosis/assess your child.**

- [ ] Autism Diagnostic Interview—Revised (ADI-R) (mm/dd/yyyy): 
- [ ] Autism Diagnostic Observation Schedule (ADOS) (mm/dd/yyyy): 
- [ ] Childhood Autism Rating Scale (CARS) (mm/dd/yyyy): 
- [ ] Checklist for Autism in Toddlers (CHAT) (mm/dd/yyyy): 
- [ ] Autism Screening Questionnaire (mm/dd/yyyy): 
- [ ] Screening Test for Autism in Two-Year Olds (STAT) (mm/dd/yyyy): 
- [ ] Gilliam Autism Rating Scale (GARS) (mm/dd/yyyy): 
- [ ] Differential Ability Scales (mm/dd/yyyy): 
- [ ] Mullen Scales of Early Learning (mm/dd/yyyy): 
- [ ] Bayley Scales of Infant Development (mm/dd/yyyy): 
- [ ] Vineland Adaptive Behavior Scales (mm/dd/yyyy): 
- [ ] None
- [ ] Other Please list: ____________________________ (mm/dd/yyyy): 
- [ ] I don’t know

16. **Did your child seem to develop normally for a time and then lose skills?**

- [ ] Yes  -  [ ] No

If No, please skip to question 18.
If Yes, please check yes or no for each skill loss and fill out the rest of the line if yes:

<table>
<thead>
<tr>
<th>Skill Loss</th>
<th>Yes</th>
<th>No</th>
<th>Age in months when skill loss occurred</th>
<th>Age in months when the skill was first acquired</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lost eye contact or interest in social games or in other people</td>
<td>☐</td>
<td>☐</td>
<td>months</td>
<td>months</td>
</tr>
<tr>
<td>Word loss or stopped talking</td>
<td>☐</td>
<td>☐</td>
<td>months</td>
<td>months</td>
</tr>
<tr>
<td>Began stereotyped behavior</td>
<td>☐</td>
<td>☐</td>
<td>months</td>
<td>months</td>
</tr>
<tr>
<td>Became irritable, anxious, tactilely defensive, or sensitive to noise or texture</td>
<td>☐</td>
<td>☐</td>
<td>months</td>
<td>months</td>
</tr>
<tr>
<td>Lost ability to walk or climb stairs</td>
<td>☐</td>
<td>☐</td>
<td>months</td>
<td>months</td>
</tr>
<tr>
<td>Other skill loss</td>
<td>☐</td>
<td>☐</td>
<td>months</td>
<td>months</td>
</tr>
</tbody>
</table>

If Other skill loss, please list:

17. If your child did have a loss of skills, was it after one of the following events?

Please check yes or no and fill in the rest of the line if yes.

<table>
<thead>
<tr>
<th>Event</th>
<th>Yes</th>
<th>No</th>
<th>Age in months that the event happened</th>
<th>Age in months that the skill loss occurred</th>
</tr>
</thead>
<tbody>
<tr>
<td>Illness</td>
<td>☐</td>
<td>☐</td>
<td>months</td>
<td>months</td>
</tr>
<tr>
<td>Traumatic Injury</td>
<td>☐</td>
<td>☐</td>
<td>months</td>
<td>months</td>
</tr>
<tr>
<td>MMR vaccination</td>
<td>☐</td>
<td>☐</td>
<td>months</td>
<td>months</td>
</tr>
<tr>
<td>DTP or DTaP vaccination</td>
<td>☐</td>
<td>☐</td>
<td>months</td>
<td>months</td>
</tr>
<tr>
<td>Other vaccination</td>
<td>☐</td>
<td>☐</td>
<td>months</td>
<td>months</td>
</tr>
<tr>
<td>Other event</td>
<td>☐</td>
<td>☐</td>
<td>months</td>
<td>months</td>
</tr>
</tbody>
</table>
If you checked Other vaccination, please enter the vaccination in the box:

If you checked Other event, please enter the other event in the box:

18. Did your child ever have a period where he/she used at least three meaningful words (not including mama or dada) on a daily basis for at least a month followed by a period of at least a month where he/she used no recognizable words?

☐ Yes  ☐ No

If No, please skip to question 19.

If Yes, please write the number of words your child could say before the period when he/she used no recognizable words.

Please write the words (no more than 5) in the boxes and the ages (in months) when the events occurred:

<table>
<thead>
<tr>
<th>Word</th>
<th>Age in months when your child first used the word</th>
<th>Age in months when your child stopped using the word</th>
<th>If your child started using the word again, please list the age in months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tr>
</tbody>
</table>
19. Have you ever noticed an improvement in your child’s autistic symptoms when he/she had a fever?

☐ Yes ☐ No

20. Please write in the boxes the number of brothers and sisters (blood relatives) your child has.

☐ Brothers ☐ Sisters

If any brothers or sisters has autism, please specify. Number of brothers with autism: [Blank]

Number of sisters with autism: [Blank]

21. Is your child receiving special services for children with autism?

☐ Yes ☐ No

If Yes, please write the type of services your child receives.

[Blank]

22. Did your child receive the Measles-Mumps-Rubella (MMR) vaccination?

☐ Yes ☐ No ☐ I don’t know

If Yes, please enter the age in months that your child first received the Measles-Mumps-Rubella (MMR) Vaccination: [Blank] months

If No or I don’t know, please skip to question 28.
23. Were any other vaccinations given at the same time or within 2 months of your child’s first Measles-Mumps-Rubella (MMR) vaccination? Please check all that apply.

☐ DTaP (Diphtheria-Tetanus-acellular Pertusis)
☐ DTP (Diphtheria-Tetanus-Pertusis)
☐ Hepatitis B
☐ Influenza
☐ HiB (H. influenzae type B)
☐ Oral Poliovirus (OPV)
☐ Inactivated Poliovirus (IPV)
☐ Varicella
☐ Rotavirus
☐ None
☐ I don’t know
☐ Other - If Other, please enter the name in the box.

24. For questions 22-23, did you refer to a vaccination card?

☒ Yes ☐ No

If No, please check the box of the method that was used:

☐ Memory ☐ Medical Record

25. Did your child appear sick at the same time when he/she was given the Measles-Mumps- Rubella vaccination?

☒ Yes ☐ No

If Yes, please describe the sickness in the box.

If Yes, please list the medications your child took for this sickness.
26. Did your child have any of the following reactions to his/her first Measles-Mumps-Rubella (MMR) vaccination? Please check yes or no and fill in the rest of the line if yes.

<table>
<thead>
<tr>
<th>Type of Reaction</th>
<th>Yes</th>
<th>No</th>
<th>Number of days after MMR vaccination</th>
<th>Number of days reaction lasted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irritability</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seizures</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other Reaction</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

27. If Other Reaction, please write the reaction in the box.

28. Regarding your child’s first Measles-Mumps-Rubella (MMR) vaccination, was he/she given any of the following pain medicines to prevent a reaction or to treat a reaction? Please check yes or no and fill in the rest of the line if yes.

<table>
<thead>
<tr>
<th>Pain Medicine</th>
<th>Yes</th>
<th>No</th>
<th>Amount of each dose</th>
<th>Frequency each dose was given</th>
<th>Duration-days the pain medicine was given</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td></td>
<td></td>
<td></td>
<td>please select</td>
<td></td>
</tr>
<tr>
<td>Tylenol (or acetaminophen)</td>
<td></td>
<td></td>
<td></td>
<td>please select</td>
<td></td>
</tr>
<tr>
<td>Motrin (or Advil or ibuprofen)</td>
<td></td>
<td></td>
<td></td>
<td>please select</td>
<td></td>
</tr>
<tr>
<td>Other Medication</td>
<td></td>
<td></td>
<td></td>
<td>please select</td>
<td></td>
</tr>
</tbody>
</table>

29. If Other Medication, please click on the box and enter the name of the medicine.
Pregnancy

30. Please tell me about pain medication use by your child’s mother (or you if you are the child’s mother) during each trimester of pregnancy with this child. If yes is checked, please fill in the rest of the line.

First Trimester

<table>
<thead>
<tr>
<th>Pain Medicine</th>
<th>Yes</th>
<th>No</th>
<th>Amount of each dose</th>
<th>Frequency each dose was given</th>
<th>Duration-days the pain medicine was given</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>please select</td>
<td>☐</td>
</tr>
<tr>
<td>Tylenol (or acetaminophen)</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>please select</td>
<td>☐</td>
</tr>
<tr>
<td>Motrin (or Advil or ibuprofen)</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>please select</td>
<td>☐</td>
</tr>
<tr>
<td>Other Medication</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>please select</td>
<td>☐</td>
</tr>
</tbody>
</table>

If Other Medication, please click on the box and enter the name of the medicine.
### Second Trimester

<table>
<thead>
<tr>
<th>Pain Medicine</th>
<th>Yes</th>
<th>No</th>
<th>Amount of each dose</th>
<th>Frequency each dose was given</th>
<th>Duration - days the pain medicine was given</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
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<td></td>
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<tr>
<td>Tylenol (or acetaminophen)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motrin (or Advil or ibuprofen)</td>
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<td></td>
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<tr>
<td>Other Medication</td>
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</table>

If Other Medication, please click on the box and enter the name of the medicine.


### Third Trimester

<table>
<thead>
<tr>
<th>Pain Medicine</th>
<th>Yes</th>
<th>No</th>
<th>Amount of each dose</th>
<th>Frequency each dose was given</th>
<th>Duration - days the pain medicine was given</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Tylenol (or acetaminophen)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motrin (or Advil or ibuprofen)</td>
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<tr>
<td>Other Medication</td>
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</table>

If Other Medication, please click on the box and enter the name of the medicine.


31. **What type of pain medicines did you give your child between 0-3 years old? Please check all that apply.**

- [ ] Aspirin
- [ ] Tylenol (or acetaminophen) tablets
- [ ] Tylenol (or acetaminophen) liquid
- [ ] Motrin or Advil (or ibuprofen) tablets
- [ ] Motrin or Advil (or ibuprofen) liquid
- [ ] None
- [ ] Other

**If Other, please click on this box and enter the name of the medicine:**

32. **Please tell me about the sicknesses your child had in the first year of life. For each time your child was sick, please choose the type of sickness from the drop-down menu and complete the rest of the line.**

<table>
<thead>
<tr>
<th>Type of Illness</th>
<th>Age (months)</th>
<th>Duration (days)</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>please select</td>
<td>months</td>
<td>days</td>
<td></td>
</tr>
<tr>
<td>please select</td>
<td>months</td>
<td>days</td>
<td></td>
</tr>
<tr>
<td>please select</td>
<td>months</td>
<td>days</td>
<td></td>
</tr>
<tr>
<td>please select</td>
<td>months</td>
<td>days</td>
<td></td>
</tr>
<tr>
<td>please select</td>
<td>months</td>
<td>days</td>
<td></td>
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<tr>
<td>please select</td>
<td>months</td>
<td>days</td>
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<tr>
<td>please select</td>
<td>months</td>
<td>days</td>
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<tr>
<td>please select</td>
<td>months</td>
<td>days</td>
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<td>please select</td>
<td>months</td>
<td>days</td>
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<tr>
<td>please select</td>
<td>months</td>
<td>days</td>
<td></td>
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<tr>
<td>please select</td>
<td>months</td>
<td>days</td>
<td></td>
</tr>
<tr>
<td>please select</td>
<td>months</td>
<td>days</td>
<td></td>
</tr>
</tbody>
</table>
33. Please tell me if your child was given pain medications for each of the three age levels. If yes is checked, please fill in the rest of the line.

**Age 0-6 Months**

<table>
<thead>
<tr>
<th>Pain Medicine</th>
<th>Yes</th>
<th>No</th>
<th>Amount of each dose</th>
<th>Frequency each dose was given</th>
<th>Duration-days the pain medicine was given</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>☐</td>
<td>☑</td>
<td></td>
<td>please select</td>
<td></td>
</tr>
<tr>
<td>Tylenol (or acetaminophen)</td>
<td>☐</td>
<td>☑</td>
<td></td>
<td>please select</td>
<td></td>
</tr>
<tr>
<td>Motrin (or Advil or ibuprofen)</td>
<td>☐</td>
<td>☑</td>
<td></td>
<td>please select</td>
<td></td>
</tr>
<tr>
<td><strong>Other Medication</strong></td>
<td>☐</td>
<td>☑</td>
<td></td>
<td>please select</td>
<td></td>
</tr>
</tbody>
</table>

If Other Medication, please click on the box and enter the name of the medicine.

[Enter name of medicine]

**Age 7-12 Months**

<table>
<thead>
<tr>
<th>Pain Medicine</th>
<th>Yes</th>
<th>No</th>
<th>Amount of each dose</th>
<th>Frequency each dose was given</th>
<th>Duration-days the pain medicine was given</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>☐</td>
<td>☑</td>
<td></td>
<td>please select</td>
<td></td>
</tr>
<tr>
<td>Tylenol (or acetaminophen)</td>
<td>☐</td>
<td>☑</td>
<td></td>
<td>please select</td>
<td></td>
</tr>
<tr>
<td>Motrin (or Advil or ibuprofen)</td>
<td>☐</td>
<td>☑</td>
<td></td>
<td>please select</td>
<td></td>
</tr>
<tr>
<td><strong>Other Medication</strong></td>
<td>☐</td>
<td>☑</td>
<td></td>
<td>please select</td>
<td></td>
</tr>
</tbody>
</table>
If Other Medication, please click on the box and enter the name of the medicine.

Age 12-18 Months

<table>
<thead>
<tr>
<th>Pain Medicine</th>
<th>Yes</th>
<th>No</th>
<th>Amount of each dose</th>
<th>Frequency each dose was given</th>
<th>Duration-days the pain medicine was given</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>☐</td>
<td>☐</td>
<td></td>
<td>please select</td>
<td></td>
</tr>
<tr>
<td>Tylenol (or acetaminophen)</td>
<td>☐</td>
<td>☐</td>
<td></td>
<td>please select</td>
<td></td>
</tr>
<tr>
<td>Motrin (or Advil or ibuprofen)</td>
<td>☐</td>
<td>☐</td>
<td></td>
<td>please select</td>
<td></td>
</tr>
<tr>
<td>Other Medication</td>
<td>☐</td>
<td>☐</td>
<td></td>
<td>please select</td>
<td></td>
</tr>
</tbody>
</table>

If Other Medication, please click on the box and enter the name of the medicine.

Family History

34. Is there a medical history of hay fever (or seasonal allergies) in your child or any of his/her blood relatives?

Please check all that apply.

- ☐ Your child
- ☐ Father
- ☐ Mother
- ☐ Brother(s) How many with hay fever?: ☐
- ☐ Sister(s) How many with hay fever?: ☐
- ☐ Aunt(s) How many with hay fever?: ☐
35. **Is there a medical history of asthma (narrowing of the airways in the lungs resulting in symptoms of wheezing, coughing, chest tightness, and shortness of breath) in your child or any of his/her blood relatives?**

Please check all that apply.

- [ ] Your child
- [ ] Father
- [ ] Mother
- [ ] Brother(s) How many with asthma?: [ ]
- [ ] Sister(s) How many with asthma?: [ ]
- [ ] Aunt(s) How many with asthma?: [ ]
- [ ] Uncle(s) How many with asthma?: [ ]
- [ ] Cousin(s) How many with asthma?: [ ]
- [ ] Grandparent(s) How many with asthma?: [ ]
- [ ] None known

36. **If there is anything else you would like to add regarding your child, please click on the box and enter the information:**


Thank you kindly and sincerely for your participation.

Please click the Submit button.
 EXPERIMENTAL SUBJECT’S BILL OF RIGHTS

The faculty and staff of the University of California, San Diego and the Veteran’s Affairs San Diego Healthcare System wish you to know:

Any person who is requested to consent to participate as a subject in a research study involving a medical experiment, or who is requested to consent on behalf of another, has the right to:

1. Be informed of the nature and purpose of the experiment.
2. Be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be used.
3. Be given a description of any attendant discomforts and risks reasonably to be expected from the experiment.
4. Be given an explanation of any benefits to the subject reasonably to be expected from the experiment, if applicable.
5. Be given a disclosure of any appropriate alternative procedures, drugs, or devices that might be advantageous to the subject, and their relative risks and benefits.
6. Be informed of the avenues of medical treatment, if any, available to the subject after the experiment if complications should arise.
7. Be given an opportunity to ask any questions concerning the experiment or the procedures involved.
8. Be instructed that consent to participate in the medical experiment may be withdrawn at any time, and the subject may discontinue participation in the medical experiment without prejudice.
9. Be given a copy of a signed and dated written consent form when one is required.
10. Be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion, or undue influence on the subject’s decision.

If you have questions regarding a research study, the researcher or his/her assistant will be glad to answer them. You may seek information from the Human Research Protections Program - established for the protection of volunteers in research projects - by calling (858) 455-5050 from 8:00 a.m. to 4:30 p.m., Monday through Friday, or by writing to the above address.
Survey for Parents of a Child Without Autism or Autistic Disorder

The purpose of this survey is to test the association of medical history and autism. Answers on this survey will provide a comparison group of children without autism or autistic disorder. Please have your child’s vaccination and medical records available.

I am Dr. Stephen Schultz, the father of a child with autism, and I will be conducting this study as part of my dissertation research in the Joint Doctoral Program in Epidemiology of the University of California San Diego and San Diego State University. Because my son is autistic, I have decided to return to school and dedicate the rest of my life researching the cause of autism. I would greatly appreciate it if you would participate in this survey. This survey should take approximately 20 minutes to complete.

Participation in this study is voluntary. If you decide to participate, you are free to withdraw your consent and to stop your participation at any time. There will be no direct benefit to you for participating in this research study, but it could help all of us unravel the mystery of autism. The only risk that you could have for participating in this study would be the loss of confidentiality. This risk is minimal, however, because the only personal identifying information collected is your child’s birth date.

My telephone number is (760) 744-1731, and I would be glad to answer any of your questions regarding this study or to verify my identity. If you would like to have documentation linking your participation with this research, please email me at stschultz@ucsd.edu. For questions about your rights as a research participant or to report research-related problems you may contact the Institutional Review Board at San Diego State University at (619) 594-6622, irb@mail.sdsu.edu or the University of California, San Diego Human Research Protections Program at (858) 455-5050. At the end of this survey is the “Experimental Subject’s Bill of Rights” which is required to be given to you and is for your information.

Thank you kindly if you agree to participate in this survey! Together we can make a difference!

Sincerely,
Dr. Stephen Schultz

Please answer questions 1-21 for your child without autism or developmental problems.

Instructions: To check a box, please click on it with your mouse—clicking a box a second time will uncheck it. Items with drop-down boxes can be selected with a mouse click. For questions that require a written entry, please click on the box and type in your response.
1. Who is filling out this survey? Please check the box. □ Father □ Mother □ Other

2. Please enter the birth date of your child in the box using the form mm/dd/yyyy:

3. In what city and state (or country if not US) was your child born?

4. Please check the box for the gender of your child. □ Male □ Female

5. What is the ethnicity of your child’s father?

   □ Hispanic
   □ African-American
   □ Asian
   □ Native American
   □ Caucasian/White
   □ Other If Other, please list:

6. What is the ethnicity of your child’s mother?

   □ Hispanic
   □ African-American
   □ Asian
   □ Native American
   □ Caucasian/White
   □ Other If Other, please list:

7. What is the occupation of your child’s parents?

   Please type a response in the box for father and mother.

   Father’s Occupation
   Mother’s Occupation
8. What is the education level for your child’s parents?

    Please choose one response for each parent.

    Father’s education level [please select]
    Mother’s education level [please select]

**Child’s Vaccines**

9. Did your child receive the Measles-Mumps-Rubella (MMR) vaccination?

    ☐ Yes
    ☐ No
    ☐ I don’t know

    If Yes, please enter the age in months that your child first received the Measles-Mumps-Rubella (MMR) Vaccination: [__] months

    If No or I don’t know, please skip to question 15.

10. Were any other vaccinations given at the same time or within 2 months of your child’s first Measles-Mumps-Rubella (MMR) vaccination?

    Please check all that apply.

    ☐ DTaP (Diphtheria-Tetanus-acellular Pertusis)
    ☐ DTP (Diphtheria-Tetanus-Pertusis)
    ☐ Hepatitis B
    ☐ Influenza
    ☐ HiB (H. influenzae type B)
    ☐ Oral Poliovirus (OPV)
    ☐ Inactivated Poliovirus (IPV)
    ☐ Varicella
    ☐ Rotavirus
None
☐ I don’t know
☐ Other If Other, please enter the name in the box.

11. For questions 9-10, did you refer to a vaccination card?

☐ Yes
☐ No

If No, please check the box of the method that was used: ☐ Memory
☐ Medical Record

12. Did your child appear sick at the same time when he/she was given the Measles-Mumps-Rubella vaccination?

☐ Yes
☐ No

If Yes, please describe the sickness in the box.

If Yes, please list the medications your child took for this sickness.
13. Did your child have any of the following reactions to his/her first Measles-Mumps-Rubella (MMR) vaccination?

Please check yes or no and fill in the rest of the line if yes.

<table>
<thead>
<tr>
<th>Type of Reaction</th>
<th>Yes</th>
<th>No</th>
<th>Number of days after MMR vaccination</th>
<th>Number of days reaction lasted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>☐</td>
<td>☐</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>☐</td>
<td>☐</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>☐</td>
<td>☐</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irritability</td>
<td>☐</td>
<td>☐</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seizures</td>
<td>☐</td>
<td>☐</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other Reaction</td>
<td>☐</td>
<td>☐</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If Other Reaction, please write the reaction in the box.

If Other Reaction, please write the reaction in the box.

14. Regarding your child’s first Measles-Mumps-Rubella (MMR) vaccination, was he/she given any of the following pain medicines to prevent a reaction or to treat a reaction?

Please check yes or no and fill in the rest of the line if yes.

<table>
<thead>
<tr>
<th>Pain Medicine</th>
<th>Yes</th>
<th>No</th>
<th>Amount of each dose</th>
<th>Frequency each dose was given</th>
<th>Duration-days the pain medicine was given</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>☐</td>
<td>☐</td>
<td></td>
<td>please select</td>
<td></td>
</tr>
<tr>
<td>Tylenol (or acetaminophen)</td>
<td>☐</td>
<td>☐</td>
<td></td>
<td>please select</td>
<td></td>
</tr>
<tr>
<td>Motrin (or Advil or ibuprofen)</td>
<td>☐</td>
<td>☐</td>
<td></td>
<td>please select</td>
<td></td>
</tr>
<tr>
<td>Other Medication</td>
<td>☐</td>
<td>☐</td>
<td></td>
<td>please select</td>
<td></td>
</tr>
</tbody>
</table>
If Other Medication, please click on the box and enter the name of the medicine.

**Pregnancy**

15. Please tell me about pain medication use by your child’s mother (or you if you are the child’s mother) during each trimester of pregnancy with this child.

If yes is checked, please fill in the rest of the line.

**First Trimester**

<table>
<thead>
<tr>
<th>Pain Medicine</th>
<th>Yes</th>
<th>No</th>
<th>Amount of each dose</th>
<th>Frequency each dose was given</th>
<th>Duration-days the pain medicine was given</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>☐</td>
<td>☐</td>
<td></td>
<td>please select</td>
<td></td>
</tr>
<tr>
<td>Tylenol (or acetaminophen)</td>
<td>☐</td>
<td>☐</td>
<td></td>
<td>please select</td>
<td></td>
</tr>
<tr>
<td>Motrin (or Advil or ibuprofen)</td>
<td>☐</td>
<td>☐</td>
<td></td>
<td>please select</td>
<td></td>
</tr>
<tr>
<td>Other Medication</td>
<td>☐</td>
<td>☐</td>
<td></td>
<td>please select</td>
<td></td>
</tr>
</tbody>
</table>

If Other Medication, please click on the box and enter the name of the medicine.
Second Trimester

<table>
<thead>
<tr>
<th>Pain Medicine</th>
<th>Yes</th>
<th>No</th>
<th>Amount of each dose</th>
<th>Frequency each dose was given</th>
<th>Duration-days the pain medicine was given</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>☐</td>
<td>☐</td>
<td></td>
<td>please select</td>
<td></td>
</tr>
<tr>
<td>Tylenol (or acetaminophen)</td>
<td>☐</td>
<td>☐</td>
<td></td>
<td>please select</td>
<td></td>
</tr>
<tr>
<td>Motrin (or Advil or ibuprofen)</td>
<td>☐</td>
<td>☐</td>
<td></td>
<td>please select</td>
<td></td>
</tr>
<tr>
<td>Other Medication</td>
<td>☐</td>
<td>☐</td>
<td></td>
<td>please select</td>
<td></td>
</tr>
</tbody>
</table>

If Other Medication, please click on the box and enter the name of the medicine.

Third Trimester

<table>
<thead>
<tr>
<th>Pain Medicine</th>
<th>Yes</th>
<th>No</th>
<th>Amount of each dose</th>
<th>Frequency each dose was given</th>
<th>Duration-days the pain medicine was given</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>☐</td>
<td>☐</td>
<td></td>
<td>please select</td>
<td></td>
</tr>
<tr>
<td>Tylenol (or acetaminophen)</td>
<td>☐</td>
<td>☐</td>
<td></td>
<td>please select</td>
<td></td>
</tr>
<tr>
<td>Motrin (or Advil or ibuprofen)</td>
<td>☐</td>
<td>☐</td>
<td></td>
<td>please select</td>
<td></td>
</tr>
<tr>
<td>Other Medication</td>
<td>☐</td>
<td>☐</td>
<td></td>
<td>please select</td>
<td></td>
</tr>
</tbody>
</table>

If Other Medication, please click on the box and enter the name of the medicine.
Child Medications

16. What type of pain medicines did you give your child between 0-3 years old

Please check all that apply.

☐ Aspirin
☐ Tylenol (or acetaminophen) tablets
☐ Tylenol (or acetaminophen) liquid
☐ Motrin or Advil (or ibuprofen) tablets
☐ Motrin or Advil (or ibuprofen) liquid
☐ None
☐ Other
If Other, please click on this box and enter the name of the medicine:

17. Please tell me about the sicknesses your child had in the first year of life

For each time your child was sick, please choose the type of illness from the drop-down menu and complete the rest of the line.

<table>
<thead>
<tr>
<th>Type of Illness</th>
<th>Age (months)</th>
<th>Duration (days)</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>please select</td>
<td>months</td>
<td>days</td>
<td></td>
</tr>
<tr>
<td>please select</td>
<td>months</td>
<td>days</td>
<td></td>
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<tr>
<td>please select</td>
<td>months</td>
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<td>please select</td>
<td>months</td>
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<td>days</td>
<td></td>
</tr>
<tr>
<td>please select</td>
<td>months</td>
<td>days</td>
<td></td>
</tr>
</tbody>
</table>
18. Please tell me if your child was given pain medications for each of the three age levels.

If yes is checked, please fill in the rest of the line.

**Age 0-6 Months**

<table>
<thead>
<tr>
<th>Pain Medicine</th>
<th>Yes</th>
<th>No</th>
<th>Amount of each dose</th>
<th>Frequency each dose was given</th>
<th>Duration-days the pain medicine was given</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>☐</td>
<td>☐</td>
<td></td>
<td>please select</td>
<td></td>
</tr>
<tr>
<td>Tylenol (or acetaminophen)</td>
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<td></td>
<td>please select</td>
<td></td>
</tr>
<tr>
<td>Other Medication</td>
<td>☐</td>
<td>☐</td>
<td></td>
<td>please select</td>
<td></td>
</tr>
</tbody>
</table>

If Other Medication, please click on the box and enter the name of the medicine.

**Age 7-12 Months**

<table>
<thead>
<tr>
<th>Pain Medicine</th>
<th>Yes</th>
<th>No</th>
<th>Amount of each dose</th>
<th>Frequency each dose was given</th>
<th>Duration-days the pain medicine was given</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>☐</td>
<td>☐</td>
<td></td>
<td>please select</td>
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</tr>
<tr>
<td>Tylenol (or acetaminophen)</td>
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<td>☐</td>
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<td>please select</td>
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</tr>
<tr>
<td>Motrin (or Advil or ibuprofen)</td>
<td>☐</td>
<td>☐</td>
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</tr>
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<td>Other Medication</td>
<td>☐</td>
<td>☐</td>
<td></td>
<td>please select</td>
<td></td>
</tr>
</tbody>
</table>

If Other Medication, please click on the box and enter the name of the medicine.
### Age 12-18 Months

<table>
<thead>
<tr>
<th>Pain Medicine</th>
<th>Yes</th>
<th>No</th>
<th>Amount of each dose</th>
<th>Frequency each dose was given</th>
<th>Duration - days the pain medicine was given</th>
</tr>
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<tbody>
<tr>
<td>Aspirin</td>
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<tr>
<td>Tylenol (or acetaminophen)</td>
<td>☐</td>
<td>☐</td>
<td></td>
<td>please select</td>
<td>☐</td>
</tr>
<tr>
<td>Motrin (or Advil or ibuprofen)</td>
<td>☐</td>
<td>☐</td>
<td></td>
<td>please select</td>
<td>☐</td>
</tr>
<tr>
<td>Other Medication</td>
<td>☐</td>
<td>☐</td>
<td></td>
<td>please select</td>
<td>☐</td>
</tr>
</tbody>
</table>

If Other Medication, please click on the box and enter the name of the medicine.

### Family History

19. Is there a medical history of hay fever (or seasonal allergies) in your child or any of his/her blood relatives?

Please check all that apply.

- [ ] Your child
- [ ] Father
- [ ] Mother
- [ ] Brother(s) How many with hay fever?: ☐
- [ ] Sister(s) How many with hay fever?: ☐
- [ ] Aunt(s) How many with hay fever?: ☐
- [ ] Uncle(s) How many with hay fever?: ☐
- [ ] Grandparent(s) How many with hay fever?: ☐
- [ ] Cousin(s) How many with hay fever?: ☐
- [ ] None known
20. Is there a medical history of asthma (narrowing of the airways in the lungs resulting in symptoms of wheezing, coughing, chest tightness, and shortness of breath) in your child or any of his/her blood relatives?

Please check all that apply.

- Your child
- Father
- Mother
- Brother(s) How many with asthma?: [ ]
- Sister(s) How many with asthma?: [ ]
- Aunt(s) How many with asthma?: [ ]
- Uncle(s) How many with asthma?: [ ]
- Cousin(s) How many with asthma?: [ ]
- Grandparent(s) How many with asthma?: [ ]
- None known

21. If there is anything else you would like to add regarding your child, please click on the box and enter the information:

__________________________

Thank you kindly and sincerely for your participation! Please click the Submit button.
EXPERIMENTAL SUBJECT’S BILL OF RIGHTS

The faculty and staff of the University of California, San Diego and the Veteran’s Affairs San Diego Healthcare System wish you to know:

Any person who is requested to consent to participate as a subject in a research study involving a medical experiment, or who is requested to consent on behalf of another, has the right to:

1. Be informed of the nature and purpose of the experiment.
2. Be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be used.
3. Be given a description of any attendant discomforts and risks reasonably to be expected from the experiment.
4. Be given an explanation of any benefits to the subject reasonably to be expected from the experiment, if applicable.
5. Be given a disclosure of any appropriate alternative procedures, drugs, or devices that might be advantageous to the subject, and their relative risks and benefits.
6. Be informed of the avenues of medical treatment, if any, available to the subject after the experiment if complications should arise.
7. Be given an opportunity to ask any questions concerning the experiment or the procedures involved.
8. Be instructed that consent to participate in the medical experiment may be withdrawn at any time, and the subject may discontinue participation in the medical experiment without prejudice.
9. Be given a copy of a signed and dated written consent form when one is required.
10. Be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion, or undue influence on the subject’s decision.

If you have questions regarding a research study, the researcher or his/her assistant will be glad to answer them. You may seek information from the Human Research Protections Program - established for the protection of volunteers in research projects - by calling (858) 455-5050 from 8:00 a.m. to 4:30 p.m., Monday through Friday, or by writing to the above address.
Autism Internet Research Survey - Cases

Please answer only the questions that are relevant to you. If you do not remember a product, you can just leave the question alone or select "I Don't Know". If the product you used is not listed in the dropdown list, you can add it to the textbox in the final question. If you utilized more than one product in the list, then select the one that you used more frequently. Thank you for helping.

1. Please enter your relationship to the child (or children):

2. Please enter the number of children you have with Autism Spectrum Disorder (Autism, Aspergers, Pervasive Developmental Disorder or Pervasive Developmental Disorder Not Otherwise Specified)

3. Does the child's mother have any close relatives with Autism, Aspergers, PDD, PDD-NOS, or any other autism spectrum disorder?

4. Does the child's father have any close relatives with Autism, Aspergers, PDD, PDD-NOS, or any other autism spectrum disorder?

5. Please select the nature of your child's development from the list below:

6. Please select the option best describes your child's condition:

7. Please enter the date of birth of your first child with autistic spectrum disorder. (MM/DD/YYYY)
8. Enter your age at this child's birth:

9. Please indicate the type of delivery you had with your autistic child.

10. Please indicate any procedures or medications that were used during your delivery of the above-mentioned child.

11. Please indicate any conditions or problems you may have had during your pregnancy and delivery (please check all that apply):

12. Please enter the zip code for the town/city in which you lived for most of your pregnancy:

13. Please enter the APGAR score your child had after birth if you remember.

14. If you used a shampoo/conditioner combination during pregnancy, please select it from the list.

15. What shampoo did you most use during your pregnancy?

16. What was your favored conditioner during your pregnancy?

17. Please select the dandruff shampoo/product (if any) you used during pregnancy:
18. Please indicate any mousse or styling gel you used while pregnant:

19. Please indicate the hairspray you used while you were pregnant:

20. Please choose the bar soap you used during pregnancy:

21. Select the body wash you used during pregnancy:

22. Please indicate the body/hand moisturizer or lotion that you favored during your pregnancy:

23. Please select your favored facial moisturizer that you used during pregnancy:

24. Please select your preferred deodorant/antiperspirant during pregnancy:

25. Please select the foundation/concealer makeup you most often used during pregnancy (if any):

26. Please select the lip color you most often used during your pregnancy:

27. Please indicate the fragrance you most often used pregnancy (if any)
28. Please indicate the type of eye shadow you favored during pregnancy (if any):

29. Please enter the mascara your preferred while pregnant (if any):

30. Please select the make-up remover you preferred during your pregnancy:

31. Please enter the toothpaste you used most often during your pregnancy:

32. Please indicate your preferred mouthwash during pregnancy:

33. Please indicate the pain reliever you used most often during your pregnancy:

34. Please indicate the cough and cold medication you used most frequently (if any) during your pregnancy:

35. Please indicate the antacid you used most during pregnancy (if any):

36. Please enter the laxative you used most often during pregnancy (if any):

37. Please indicate the liquid hand soap you used most often during your pregnancy (if any):

38. Please indicate the nail polish you used most often during your pregnancy (if any):
39. Please indicate the nail polish remover you used during your pregnancy (if any):

40. Please indicate the sunscreen or sun-related product you used most often during your pregnancy (if any):

41. Please select prenatal or multivitamin you took during your pregnancy:

42. Please enter the blush you used most often during pregnancy:

43. Please indicate the optical solution you used most frequently during pregnancy (if any):

44. Please enter the types of protein you ate frequently during pregnancy with this child:

45. Please enter the type of beverages you drank frequently during your pregnancy with this child:

46. Please enter the types of fast food you ate the most of (if any) during your pregnancy with this child:

47. Please enter the type of fillings you have of in your teeth:

48. Please enter the approximate number of fillings you had in your teeth during pregnancy:
49. Please enter the Baby Bath you used most frequently when your child was a baby:

50. Please enter the baby shampoo you used most frequently on your child when he/she was a baby:

51. Please enter the wipes you used most often with this child:

52. Please enter the baby lotion/oil you used most frequently with this child:

53. Please enter the baby powder you used most frequently with this child:

54. Please indicate the baby/diaper rash ointment you used most frequently with this child:

55. Please indicate the period of time you breast feed your child:

56. Please indicate the type of diapers you used most frequently with this child:

57. Please select the type of baby formula you used most frequently with this child.

58. Please indicate the sunscreen/sunblock you used most frequently with this child:

59. Approximately how many times did your child swim in a chlorinated pool or hot tub during his/her first two years of life?
60. Please select the pain reliever you used most often with your child:

61. Please indicate select ALL of the pain relievers you used with your child:

62. Please indicate the cough and cold remedy your child used most often:

63. Please indicate the laxative you used most often with this child:

64. Please indicate the pediatric diarrhea related product your child used most frequently.

65. Please indicate the gas-relief product you used most frequently with this child:

66. Please select the topical teething pain relief product your child used most often:

67. Did your child have abnormal digestive problems during the first two years? (orange, oily and/or smelly stools, stomach pain etc.)

68. Please indicate the type of pacifier your child used most often:

69. Please indicate the approximate number of ear infections your child had before age 2:

70. Please enter the antibiotic your child took most frequent from birth to age 2.
71. Please enter how far your affected child progressed with the CDC recommended immunization (vaccine) schedule:

72. Did your child have a cold, fever, ear infection or any other illness during any of his/her vaccinations?

73. Please enter the type of laundry detergent you used most frequently both during your pregnancy and during your child's first two years:

74. Please select the bleach you used most frequently during pregnancy and the child's first two years:

75. Please select the fabric softener you used most often during pregnancy and the first two years of your child's life:

76. Please enter the type of hand dishwashing liquid you used most frequently during your pregnancy and the first two years of your child's life:

77. Please enter the dishwasher detergent you used most frequently during pregnancy and the first two years of your child's life:

78. Please enter the automatic dishwasher rinse agent you used most frequently during pregnancy and the child's first two years:

79. Please indicate the type of air freshener you used most frequently during your pregnancy and your child's first two years:
80. Please enter the surface/counter/all-purpose cleaner you used most frequently during pregnancy and the child's first two years:

81. Please select the disinfectant cleaner you used most often during pregnancy and the child's first two years:

82. Please enter the name of the bathroom cleaner you used most frequently during pregnancy and the child's first two years:

83. Please select the floor cleaner you used most frequently during pregnancy and the child's first two years:

84. Please enter the type of carpeting that you have most of in your home:

85. Please enter the type of other flooring (if any) you had in your home during your pregnancy and the child's first two years:

86. Please enter the type of paint that covered the most wall space in your home during your pregnancy and the child's first two years:

87. Please indicate the pesticides/insecticide you used most frequently during pregnancy and the baby's first year. If you used more than one, please enter it in the answer box that appears with the last question:

88. Please enter the Lawn Product you used most frequently during your pregnancy and the child's first two years. If you used more than one, please enter it in the text box that appears with the last question:
Autism Internet Research Survey - Controls

Please answer only the questions that are relevant to you. If you do not remember a product, you can just leave the question alone or select "I Don't Know". If the product you used is not listed in the dropdown list, you can add it to the textbox in the final question. If you utilized more than one product in the list, then select the one that you used more frequently. Thank you for helping.

1. Please enter your relationship to your child (or children):

2. Does the child's mother have any close relatives with Autism, Aspergers, PDD, PDD-NOS, or any other autism spectrum disorder?

3. Does the child's father have any close relatives with Autism, Aspergers, PDD, PDD-NOS, or any other autism spectrum disorder?

4. Please enter the date of birth of your first child. (MM/DD/YYYY)

5. Enter your age at this child's birth:

6. Please indicate the type of delivery you had with your first child.

7. Please indicate any procedures or medications that were used during your delivery of the above-mentioned child.
8. Please indicate any conditions or problems you may have had during your pregnancy and delivery (please check all that apply):

9. Please enter the zip code for the town/city in which you lived for most of your pregnancy:

10. Please enter the APGAR score your child had after birth if you remember.

11. If you used a shampoo/conditioner combination during pregnancy, please select it from the list.

12. What shampoo did you most use during your pregnancy?

13. What was your favored conditioner during your pregnancy?

14. Please select the dandruff shampoo/product (if any) you used during pregnancy:

15. Please indicate any mousse or styling gel you used while pregnant:

16. Please indicate the hairspray you used while you were pregnant:

17. Please choose the bar soap you used during pregnancy:
18. Select the body wash you used during pregnancy:

19. Please indicate the body/hand moisturizer or lotion that you favored during your pregnancy:

20. Please select your favored facial moisturizer that you used during pregnancy:

21. Please select your preferred deodorant/antiperspirant during pregnancy:

22. Please select the foundation/concealer makeup you most often used during pregnancy (if any):

23. Please select the lip color you most often used during your pregnancy:

24. Please indicate the fragrance you most often used during your pregnancy (if any)

25. Please indicate the type of eye shadow you favored during pregnancy (if any):

26. Please enter the mascara your preferred while pregnant (if any):

27. Please select the make-up remover you preferred during your pregnancy:

28. Please enter the toothpaste you used most often during your pregnancy:
29. Please indicate your preferred mouthwash during pregnancy:

30. Please indicate the pain reliever you used most often during your pregnancy:

31. Please indicate the cough and cold medication you used most frequently (if any) during your pregnancy:

32. Please indicate the antacid you used most during pregnancy (if any):

33. Please enter the laxative you used most often during pregnancy (if any):

34. Please indicate the liquid hand soap you used most often during your pregnancy (if any):

35. Please indicate the nail polish you used most often during your pregnancy (if any):

36. Please indicate the nail polish remover you used during your pregnancy (if any):

37. Please indicate the sunscreen or sun-related product you used most often during your pregnancy (if any):

38. Please select prenatal or multivitamin you took during your pregnancy:
39. Please enter the blush you used most often during pregnancy:

40. Please indicate the optical solution you used most frequently during pregnancy (if any):

41. Please enter the type of pots and pans you used most frequently with during pregnancy and with this child during the first two years (check all that apply):

42. Please enter the types of protein you ate frequently during pregnancy with this child:

43. Please enter the type of beverages you drank frequently during your pregnancy with this child:

44. Please enter the types of fast food you ate the most of (if any) during your pregnancy with this child:

45. Please enter the type of fillings you have of in your teeth:

46. Please enter the approximate number of fillings you had in your teeth during pregnancy:

47. Please enter the Baby Bath you used most frequently when your child was a baby:

48. Please enter the baby shampoo you used most frequently on your child when he/she was a baby:
49. Please enter the wipes you used most often with this child:

50. Please enter the baby lotion/oil you used most frequently with this child:

51. Please enter the baby powder you used most frequently with this child:

52. Please indicate the baby/diaper rash ointment you used most frequently with this child:

53. Please indicate the period of time you breast feed your child:

54. Please indicate the type of diapers you used most frequently with this child:

55. Please select the type of baby formula you used most frequently with this child:

56. Please indicate the sunscreen/sunblock you used most frequently with this child:

57. Approximately how many times did your child swim in a chlorinated pool or hot tub during his/her first two years of life?

58. Please select the pain reliever you used most often with your child:
59. Please indicate select ALL of the pain relievers you used with your child:

60. Please indicate the cough and cold remedy your child used most often:

61. Please indicate the laxative you used most often with this child:

62. Please indicate the pediatric diarrhea related product your child used most frequently.

63. Please indicate the gas-relief product you used most frequently with this child:

64. Please select the topical teething pain relief product your child used most often:

65. Did your child have abnormal digestive problems during the first two years? (orange, oily and/or smelly stools, stomach pain etc.)

66. Please indicate the type of pacifier your child used most often:

67. Please indicate the approximate number of ear infections your child had before age 2:

68. Please enter the antibiotic your child took most frequent from birth to age 2.
69. Please enter how far your affected child progressed with the CDC recommended immunization (vaccine) schedule:

70. Did your child have a cold, fever, ear infection or any other illness during any of his/her vaccinations?

71. Please enter the type of laundry detergent you used most frequently both during your pregnancy and during your child's first two years:

72. Please select the bleach you used most frequently during pregnancy and the child's first two years:

73. Please select the fabric softener you used most often during pregnancy and the first two years of your child's life:

74. Please enter the type of hand dishwashing liquid you used most frequently during your pregnancy and the first two years of your child's life:

75. Please enter the dishwasher detergent you used most frequently during pregnancy and the first two years of your child's life:

76. Please enter the automatic dishwasher rinse agent you used most frequently during pregnancy and the child's first two years:

77. Please indicate the type of air freshener you used most frequently during your pregnancy and your child's first two years:
78. Please enter the surface/counter/all-purpose cleaner you used most frequently during pregnancy and the child's first two years:

79. Please select the disinfectant cleaner you used most often during pregnancy and the child's first two years:

80. Please enter the name of the bathroom cleaner you used most frequently during pregnancy and the child's first two years:

81. Please select the floor cleaner you used most frequently during pregnancy and the child's first two years:

82. Please enter the type of carpeting that you have most of in your home:

83. Please enter the type of other flooring (if any) you had in your home during your pregnancy and the child's first two years:

84. Please enter the type of paint that covered the most wall space in your home during your pregnancy and the child's first two years:

85. Please indicate the type(s) of furniture covering that was in your home during pregnancy and during the child's first two years:

86. Please indicate the pesticides/insecticide you used most frequently during pregnancy and the baby's first year. If you used more than one, please enter it in the answer box that appears with the last question:
87. Please enter the Lawn Product you used most frequently during your pregnancy and the child's first two years. If you used more than one, please enter it in the text box that appears with the last question:

88. If you remember, please enter the names of any specific products that you can recall that did not appear in the lists. Also, if you feel a product category is missing, please let us know here. If you wish to provide feedback, you can also use this area to do that. Thanks.