



HEALTH CARE AND HUMAN SERVICES POLICY, RESEARCH, AND CONSULTING—WITH REAL-WORLD PERSPECTIVE.

Study of Health Outcomes in Children with Autism and their Families

Task B: Health Conditions

Final Report

Prepared for: National Institute of Mental Health

Submitted by: The Lewin Group, Inc.

September 6, 2012

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Executive Summary

Introduction and Study Objectives

The National Institute of Mental Health (NIMH) contracted with The Lewin Group to conduct a two-year study from September 2010 to September 2012 entitled “The Study of Health Outcomes in Children with Autism and their Families.” This study seeks to address a significant gap in the empirical knowledge base about the trajectories of health conditions, health outcomes and utilization of health care services among children with autism spectrum disorders (ASD), their siblings, and their parents. The ability to study a very large and heterogeneous group of children with ASD using claims data and the ability to link to information about family members is unprecedented and holds promise to advance clinical and health services knowledge about ASD substantially.

The overall purpose of Task B was to compare the health conditions of children with ASD and their siblings and parents to children without ASD and their siblings and parents. This study first examined the occurrence of a broad set of groups of health conditions and then addressed targeted research questions for three specific conditions. The goals of the three specific subtasks were to:

- Compare the prevalence of gastrointestinal conditions in children with ASD to children without ASD;
- Compare the rates of injury in children with ASD to children without ASD; and
- Compare the prevalence of stress-related conditions in parents of children with ASD to parents of children without ASD.

Thus the overall goals of the Task B of the Health Outcomes Study are to:

- Report the proportions and the associated odds ratios of the samples with evidence of eight groups of health conditions and overall comorbidity controlling only for length of continuous enrollment to examine the broad association between ASD and the co-occurring health conditions.
- Calculate odds ratios for gastrointestinal conditions among children with and without ASD; hazard ratios for injuries among children with and without ASD; and the odds ratios for stress-related conditions among parents of children with and without ASD.

Study Design and Analytic Strategy

This retrospective claims data study used medical data, pharmacy data, and enrollment information from the OptumInsight research database containing claims from the large health plan affiliated with OptumInsight. Claims data for the period 01 January 2001 to 31 December 2009 were linked to a consumer database for select socioeconomic information. All study subjects were identified among commercial enrollees who have medical, pharmacy, and behavioral health coverage. Six main samples were selected: children with ASD, a comparison group of children without ASD, parents of children with and without ASD, and siblings of children with and without ASD.

Based on the results of the Task A: Chart Study, children with at least 2 ASD claims were defined as having ASD and were included in the Task B study. In the chart study, the positive predictive value increased from 74.2% to 87.4% when children with only 1 ASD claim were excluded from the case definition, increasing our confidence that the children with ASD in Task B are true cases. However, exclusion of children with only 1 ASD claim from both the case and control groups likely increases the differences between children with ASD and their family members when compared to controls. Also, two additional sample subgroups were identified for select analyses to address the research questions identified for Task B. The first was a subset of children with ASD for whom we estimated their initial diagnosis occurred during the study observation period. The second was the parents of these children initially diagnosed with ASD during the enrollment period.

To address the research questions concerning the associations between ASD and selected groups of co-occurring health conditions, we adjusted for enrollment time and demographic variables. Specifically, for binary dependent variables indicating whether a study subject had evidence of a particular group of conditions (e.g., infectious diseases, autoimmune conditions), we utilized logistic regression to produce enrollment-adjusted proportions and odds ratios (OR) for the outcomes of interest. Logistic regression models were fitted including the primary independent dichotomous variable capturing the samples of interest (e.g., subjects with ASD vs. comparison group) and the total enrollment time. The odds ratios were produced comparing the two samples of interest.

In addition to using a binary indicator for injuries, we measured the count of injury episodes. For these count measures, enrollment-adjusted rates were calculated as the count of episodes across a sample divided by the total person-time for that sample. Rate ratios (RR) comparing the rates between the ASD and non-ASD samples along with the associated p-values were then generated.

Results

Among 33,565 children with ASD and their 99,970 family members, we found the following results about health outcomes:

- After controlling for varying enrollment time during study, a higher proportion of children with ASD than children without ASD have all eight groups of health conditions examined, including neurological/neurodevelopmental disorders, mental health conditions, gastrointestinal/nutritional conditions, autoimmune conditions, congenital/genetic disorders, and metabolic dysfunction and common childhood conditions including infectious diseases and injuries.
- Specifically, 70.8% of children with ASD had evidence of co-occurring neurological/neurodevelopmental disorders; 70.1% had evidence of mental health conditions; and 19.5% had evidence of gastrointestinal/nutritional conditions. Substantially fewer children without ASD had evidence of these conditions (9.2%, 8.7%, and 5.1%, respectively).
- Siblings of children with ASD also experience higher rates of all eight groups of physical and mental health conditions. For example, more siblings of children with ASD had evidence of neurological/neurodevelopmental disorders (17.3% vs. 9.0%), mental health

conditions (17.9% vs. 8.6%), and gastrointestinal/ nutritional conditions (7.4% vs. 4.2%) than siblings of children without ASD.

- The unadjusted results showed children with ASD to be at a slightly greater risk for injuries overall, but this increase in risk diminished (and actually reversed) after controlling for demographic, socioeconomic variables and co-occurring conditions. However, analyses exploring injury risk separately by age period indicated that during younger ages (<6 years old), those with ASD were at increased risk for injury compared to those without ASD, while during older ages (>10 years old) those with ASD were at decreased risk of injury compared to those without ASD.
- Interactions between sample group (with ASD vs. not) and gender and co-occurring conditions were also modeled to examine whether the effect of ASD differs across subgroups defined by these variables. While these interaction terms (with the exception of seizures) were statistically significant at conventional alpha error tolerance ($p < 0.05$), the statistical significance was driven by the large sample size. The heterogeneity of the ASD effects across subgroups, unlike in the case of age, was not large.
- Children with ASD had substantially higher odds of a GI condition than children without ASD (OR=3.94, $p < 0.001$). Our attempts to control for surveillance bias did not change the effect estimates at all. Stronger ASD effects on GI occurrence were seen in subjects without seizure or autoimmune disease, respectively, (OR=4.01 and 4.12) compared to subjects with seizure or autoimmune disease (OR=1.83 and OR=3.07, respectively).
- Among children with ASD, girls, younger children, and children with seizures or an autoimmune condition had increased odds of a GI condition.
- The odds of having a GI condition were 40% higher in the 12 month period following, compared to the 12 month period before, a child's initial ASD diagnosis (OR = 1.397, $p < 0.001$).
- Parents of children with ASD had higher odds of a stress-related condition than parents of children without ASD (OR=1.48, $p < 0.001$). Controlling for surveillance bias in the model did not alter the ASD effect on having a stress-related condition (ASD OR=1.50, $p < 0.001$), meaning that the observed increase in stress-related conditions was not due to greater exposure to the health care system among parents of children with ASD.
- Both the odds of a stress-related condition and costs associated with stress-related conditions were higher in the 12 month period following, compared to the 12 month period before, their child's initial ASD diagnosis (OR = 1.322, $p < 0.001$; Cost ratio = 1.246, $p < 0.001$).

Implications and Recommendations

In summary, we found that children with ASD and their families were at greater risk for many different types of health conditions than were children without ASD and their families. Specifically, our results lead to the following implications:

- Overall injury risk associated with ASD appeared to be age dependent. We saw approximately 30% higher injury rates in ASD than in the comparison groups at younger

ages (<6 years) - but that effect reversed at higher ages (>10 years) where the children with ASD had injury rates approximately 35% lower than comparably aged children without ASD after adjusting for socio-demographic variables and co-occurring conditions. In the U.S., the distribution of injury type (particularly nonfatal injury) is known to vary greatly by age. Consequently, further investigation of injury risk in children with ASD should focus on distinct age subgroups and consider the varying determinants of different injury types.

- Our findings indicate that, in the community, children with ASD are more frequently recognized with, and presumably treated for, GI conditions. This strongly supports the need for further research into the relationship between ASD and the gastrointestinal system.
- Our finding that parents of children with ASD were more likely to experience a stress-related condition than parents of children without ASD demonstrate that support for both parents as well as children is essential to caring for children with ASD and helping families live a high quality life.

Because we have the ability to include a large and heterogeneous group of children with ASD and to compare to children and families without ASD, our estimates of risk may be more precise and objective than previously available. These findings, along with our results concerning the poorer physical and mental health among parents and siblings, demonstrate that the health of the child both reflects and impacts the health of the whole family, which may potentially threaten family resources and points to a need for supportive interventions for the family as a whole rather than each individual separately in order to most improve the health and quality of life of children with ASD and their families. The family associations also raise questions about potentially shared etiologic pathways that could be the grounds for future research.

I. Introduction and Background

A. Overview of Study

The National Institute of Mental Health (NIMH) contracted with The Lewin Group to conduct a two-year study from September 2010 to September 2012 entitled “The Study of Health Outcomes in Children with Autism and their Families.” The Lewin Group’s study team is a collaboration of organizations reflecting expertise in the epidemiology of autism spectrum disorders (ASD), health services research, and the clinical care of children and families. An External Advisory Committee comprised of experts in ASD research as well as stakeholders from parent advocacy groups and treatment providers was also convened to provide consultation and guidance to the project team. This study sought to address a significant gap in the empirical knowledge base about health conditions and health care service utilization among children with ASD, their siblings, and their parents. The project employed large administrative health care claims databases to fulfill four distinct aims:

- Task A: Identify a large and diverse number of children with ASD and a general population comparison group, along with their family members, and describe these samples in terms of age and gender, geographic distribution, and socioeconomic characteristics.
- Task B: Describe and compare the health conditions of children with ASD and their family members to family members of children without ASD.
- Task C: Describe and compare the use of health care services by children with ASD and their family members to family members of children without ASD.
- Task D: Propose an approach for using administrative data to identify potential risk factors for ASD for future research.

Task A, conducted between September 2010 and March 2012, was comprised of two subtasks: 1) baseline claims analyses to identify and describe children with ASD, their siblings and parents, and their respective comparison groups, from the large administrative dataset; and 2) a medical chart review to validate the claims-based identification of children with ASD in the study population, or the “chart study.” The purpose of the chart study was to evaluate the ability to identify children with ASD within research claims databases by comparing claims-based ASD case identification to ASD status as documented in clinical (medical) charts.

The focus of this report is to present the methodology and results of the Task B Health Conditions Study. The methodology and results of the Task A: Baseline Claims Analyses and Task A: Chart Study that informed our approach for Task B are detailed in companion reports that were submitted to NIMH on October 17, 2011 and March 2, 2012, respectively.

While much research is underway to examine the prevalence and consequences of ASD, to identify the risk factors and potential causes of ASD, and to explore potential treatments, fewer efforts have been directed toward understanding the overall health status of a large

heterogeneous group of children with ASD and of members of their families.¹ To date, few studies have used large administrative claims databases to examine health conditions in children with ASD, especially over an extended period of time.² In addition, as most studies are clinical studies with small sample sizes that are not representative of the US population of children or children with ASD generally, a larger, more representative study drawn from existing electronic datasets can help advance the research for children with ASD and their families without the additional burden to individuals, families, clinicians or researchers of prospective data collection. Finally, longitudinal data for family members of children with ASD will inform research on how ASD impacts families in addition to its effects on the individual with ASD over time.

B. ASD Diagnosis and Treatment

ASD includes Autism, Asperger's Syndrome, and Pervasive Developmental Disorder not otherwise specified (PDD-NOS). Although Rett Syndrome and Childhood Disintegrative Disorder are also considered Pervasive Developmental Disorders, and thus belong on the autism spectrum, they are not included in the focus of this study.

ASD is a group of developmental disorders that have significant and life-long impacts on affected individuals and their families. The key features of ASD are sustained impairments in communication and social interaction, restricted interests, and repetitive behaviors. Common ASD-associated and co-occurring conditions include anxiety, depression, epilepsy or other seizure activity, learning disabilities, obsessive-compulsive disorders and attention deficit disorder.¹

The diagnosis of ASD has been increasing in recent years, and the Centers for Disease Control and Prevention now estimate that 1 in 88 children are diagnosed with an autism spectrum disorder.² Whether this change can be fully explained by improved awareness and by the greater availability of services or, instead, is related to an as-yet unknown environmental exposure is still to be determined. As ASD is heterogeneous in its characteristics and presentation, the meaning of the diagnosis itself is unclear, often raising more questions than it answers regarding risk factors, heritability, health trajectories, promising treatments, and outcomes.

Since ASD also manifests along a spectrum of severity, its prognosis is also highly variable, and ranges from very poor quality of life with only minimal ability to function independently to relatively normal social and vocational functioning or even superlative skills in a focused area. While the causes of ASD are not known, both genetics and environment are believed to be etiologic factors.

Currently, the disorder does not have a cure but treatment for ASD, especially when implemented early, can help children advance social and language skills, address behavioral and learning problems and improve functioning and quality of life.³ Common therapies include educational

¹ See the National Institute of Mental Health web page on autism: <http://www.nimh.nih.gov/health/topics/autism-spectrum-disorders-pervasive-developmental-disorders/index.shtml#>, the link there to clinical trials regarding autism, and also the research summary by the Interagency Autism Coordinating Committee at <http://iacc.hhs.gov/summary-advances/2010/>.

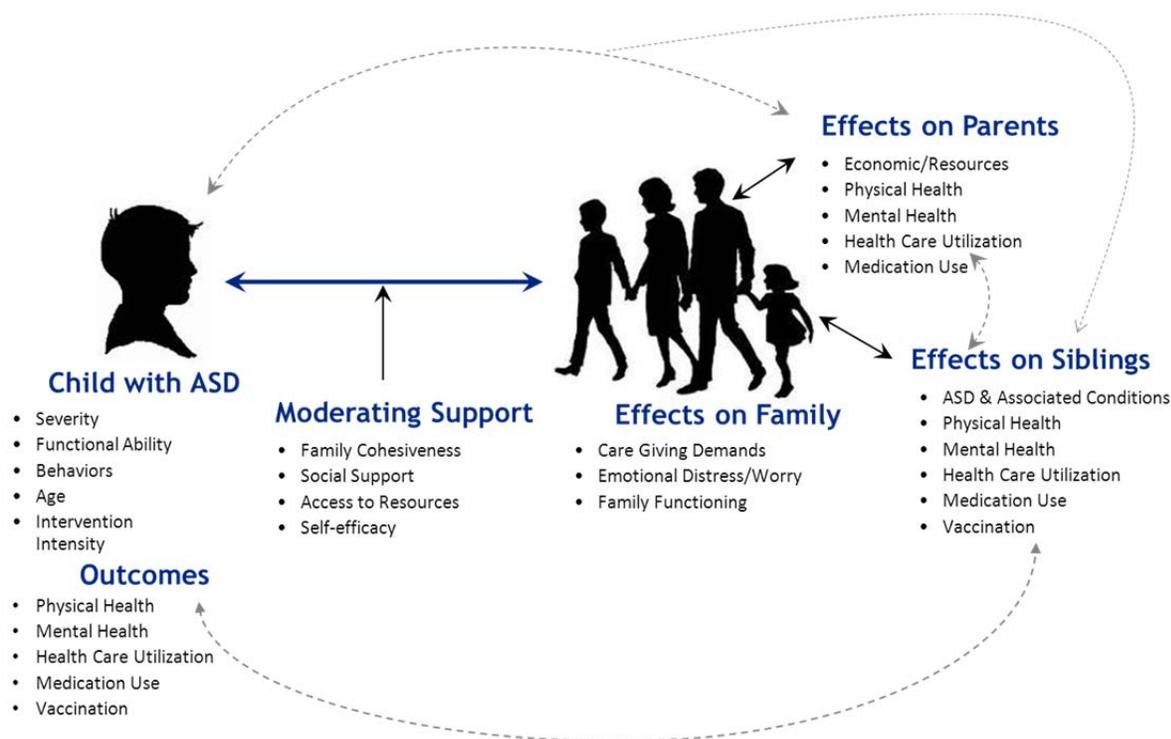
² The Request for Proposal for this study, HHS-NIH-MH-2010-018 at Attachment 3 page 2 of 12 references the "significant gaps" in this area.

and behavioral interventions (e.g., applied behavioral analysis, speech therapy, and occupational therapy) and medications that ameliorate associated symptoms and conditions. Such medications include antidepressants, anti-anxiety medications (anxiolytics), stimulants, anticonvulsants (for seizures), and antipsychotic medications (for impulsivity or other behavioral symptoms). Alternative therapeutic approaches (e.g., dietary interventions) are also used.

C. ASD, Co-occurring Health Conditions and the Family

There is evidence that members of families having a child with ASD, like members of all families, share certain common biologic characteristics and environmental influences.^{4,5} There is also considerable literature^{6,7,8} supporting the potentially profound effects on the family of having a child with ASD. These conditions fall into several realms of “family health” including parental health, sibling health, family functioning as a whole as well as the consequences of the practical and economic burdens of caring for a child with disabilities. One framework for considering the effects and important variables that moderate family health conditions is presented below.

Figure 1. Conceptual Model of Family Health Conditions



The conceptual model above shows that the child affects the family (and vice versa) through several mechanisms: First, in families where there is a child with ASD, there is a higher risk of ASD and of many of the co-occurring conditions in both parents and siblings. Secondly, the caregiving demands of having a family member with ASD affects the resources (time, financial and emotional) available to the other members of the family which can, in turn, also impact parent and sibling physical and mental health. For example, studies^{9,10} have found that mothers of children with disabilities are less likely to be employed outside the home, with often detrimental effects on the mother’s emotional health as well as on income. Siblings of children

with a chronic illness or disability have been found to have increased levels of anxiety, depression, peer problems and behavioral difficulties.¹¹ Siblings of children with high-functioning autism in particular were found to have an elevated level of internalizing behaviors including anxiety, phobias, and depression.¹² Lastly, a child with ASD has an impact on family functioning as a whole which can be both positive and/or negative in terms of cohesiveness, strength of marriage, relationships with siblings, etc.

Characteristics of the child are important mediating variables in assessing family conditions. These include, for example, the severity and degree of functional disability in the child with ASD, the presence of troublesome behaviors and symptoms, the child's age, and the intensity of their interventions or treatment program. Other variables moderate the effects on the family including the presence and number of other affected and unaffected children, the level of social, external and within-family support and functioning, availability of child care and respite, financial resources, spirituality, perception of stigma and parental self-efficacy.

Claims data can be useful to assess some of these family effects, specifically those medical conditions that require accessing the health care system and thus generating a claim with a physical or mental health diagnosis in the child with ASD or in a parent or sibling. To date, there is a lack of studies that take advantage of administrative data to investigate co-occurring conditions and health concerns associated with children with ASD and members of their families. In this report, we sought to examine physical and mental health – the two major domains of health – of children with ASD and of their family members using a large, national commercial plan claims research database. It is anticipated that the use of a large-scale claims database, which represents a reasonable segment of the actual U.S. population of families with children with ASD, will provide a foundation for scientific work that will contribute significantly to our understanding of the diagnosis, course, and impacts of ASD, and may help inform future research on the causes of ASD. In evaluating health conditions of children with ASD, the large sample sizes and rich diagnosis information inherent to our research databases (described below) will provide the opportunity to shed insight on some of the high priority co-occurring conditions as well as some of the less frequently occurring and previously unexamined conditions. Our ability to study a very large and heterogeneous group of children with ASD using claims data and the ability to link to information about family members is unprecedented and holds promise to advance clinical and health services knowledge about ASD substantially.

We hypothesized that there would be an increased occurrence of a broad set of physical and mental health conditions in children with ASD and their family members as compared to children without ASD and their family members. However, because of the dynamic nature of the complex relationships (sometimes unobservable due to lack of data) among multiple variables influencing family and child health and the often unclear clinical pathways, our investigations were intended to establish relationships (or the lack of thereof) rather than causal inferences.

Of particular interest were three health conditions: injuries, gastrointestinal conditions, and parental stress. These three areas were chosen as they represent areas that are currently of great interest and which lack research using population-based, nationally diverse data. Additionally, these conditions are potentially preventable or treatable, and could have great impact on the quality of life of children with ASD and their families. Injury is one of the leading causes of morbidity and mortality among children; it has been suggested that children with ASD might be at increased risk for injury,

particularly certain types of injury.⁵³ Gastrointestinal conditions are relatively common childhood conditions, and have been reported to occur more frequently among children with ASD, although based on evidence that has limited generalizability.^{70,71,72,74} Several studies have previously examined parental stress in relation to ASD, but they have used very small or self-selected samples and mostly relied on self-report.^{97, 103, 105} Furthermore, the presence of psychological conditions (e.g., anxiety and depression) and physical conditions (e.g., chronic pain and sleep disorders) that may be triggered by chronic stress have not been sufficiently examined previously, especially in the context of ASD. Cognizant of the interest in these areas, and in consultation with NIMH and our External Advisory Committee, we chose to conduct more in-depth analysis for these three conditions.

II. Study Objectives and Research Questions

The overall purpose of Task B of this project was to compare the health conditions of children with ASD and their family members to children without ASD and their family members. This study first generally examined the occurrence of a broad set of health conditions and then addressed targeted research questions for a smaller set of specific conditions.

The overarching research questions for this task were:

1. Compared to **children** without ASD, do more **children** with ASD have evidence of the following conditions:
 - infectious diseases;
 - neurological and neurodevelopmental disorders;
 - mental health conditions;
 - metabolic dysfunction;
 - autoimmune conditions;
 - genetic disorders;
 - gastrointestinal/nutritional conditions;
 - injuries; and
 - overall morbidity.
2. How do **siblings** of children with ASD and **siblings** of children without ASD compare in terms of the above seven conditions and overall morbidity?
3. Compared to **parents** of children without ASD, do more **parents** of children with ASD have evidence of mental health conditions and stress-related conditions? How do parents of children with and without ASD compare in terms of overall morbidity?

In addition to the above broad research questions, we targeted three specific health conditions for additional analysis: injuries and gastrointestinal conditions among children with and without ASD and stress-related conditions among parents. The research questions were:

Injuries:

1. Compared to **children** without ASD, do **children** with ASD have higher rates of injury adjusting for potential covariates?
2. Does the rate of injuries differ between children with and without ASD by age?
3. Does the rate of injuries vary among key subgroups of children with ASD?

Gastrointestinal Conditions:

1. Compared to **children** without ASD, do **children** with ASD have higher odds of having a gastrointestinal condition adjusting for potential covariates?
2. Do the odds of having a gastrointestinal condition vary among key subgroups of children with ASD?

3. Among children with ASD, are the odds of having a gastrointestinal condition different one year after his/her initial ASD diagnosis compared to one year before the initial diagnosis?

Stress-Related Conditions:

1. Compared to **parents** of children without ASD, do **parents** of children with ASD have higher odds of having a stress-related condition adjusting for potential covariates?
2. Do the odds of having a stress-related condition vary among key subgroups of parents of children with ASD?
3. Among parents of children with ASD, are the odds of having a stress-related condition different one year following his/her child's initial ASD diagnosis compared to one year before the initial diagnosis? Does the extent of stress-related conditions, as measured by stress-related health care costs, change following his/her child's initial ASD diagnosis?

The remainder of this report describes the data and methods used in addressing these research questions and the results and implications of our analyses. Section III describes the overall study design, including study data sources, study eligibility criteria and sample identification, and key variable definitions that were used throughout the study. Section IV presents data on sample identification and summarizes the demographic and enrollment characteristics of study samples. Section V presents the results and discussion of the general health conditions. Sections VI, VII, and VIII are organized by each of the three targeted sets of research questions pertaining to injuries and gastrointestinal conditions in children and stress-related conditions in parents. Each of these sections provides background on the topic, presents the methods used and analytic results, and offers a discussion of findings. Finally, Section IX concludes the report with a summary of key implications from our findings and the study limitations. Additional information is included in the Appendices referenced throughout the report.

III. Study Design

This retrospective claims data study used medical data, pharmacy data, and enrollment information from the OptumInsight research database containing claims from the large health plan affiliated with OptumInsight. Claims data for the period 01 January 2001 to 31 December 2009 were linked to a consumer database for select socioeconomic information. All study subjects were identified among commercial enrollees who have medical, pharmacy, and behavioral health coverage. Six main samples were selected: children with ASD, a comparison group of children without ASD, parents of children with and without ASD, and siblings of children with and without ASD.

This section outlines the details of our study design including a) an overview of the database that was the source for study sample selection and the claims-based analyses; b) the study reviews that were required for study approval; c) a description of the sample design, including subject eligibility criteria, sampling strategy, observation periods, and analytical subgroups of interest; and d) descriptions of select variables constructed for analysis.

A. Data Sources

The data sources for the Task B study included both claims data and a linked database containing socioeconomic data for study subjects.

1. Claims Data Source

OptumInsight has access to a proprietary research database (“OptumInsight Research Database”) containing medical (including behavioral health) and pharmacy claims with linked enrollment information covering the period from 1993 to 2010. For 2009, data relating to approximately 13.3 million individuals with both medical and pharmacy benefit coverage are available. The underlying population is geographically diverse across the US and reasonably representative of the privately insured US population.

- Medical Claims

Medical claims or encounter data are collected from all available health care sites (inpatient hospital, outpatient hospital, emergency room, outpatient office, surgery center, etc.) for all types of covered services, including specialty, preventive and office-based treatments. Medical claims and coding conform to insurance industry standards. Claims for ambulatory services submitted by individual providers (e.g., physicians) use the HCFA-1500 or CMS-1500 format.¹³ Claims for facility services submitted by institutions (e.g., hospitals) use the UB-82, or UB-92, or UB-04 format.^{14,15} Medical claims include: diagnosis codes recorded with the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis codes; procedures recorded with ICD-9-CM procedure codes, Current Procedural Terminology (CPT), or Health care Common Procedure Coding System (HCPCS) codes; site of service codes; provider specialty codes; revenue codes (for facilities); paid amounts; and other information. Typically, facility claims do not include complete information about drugs administered within a hospital. Approximately 6 months following the delivery of services is required for complete medical data due to lags in claims submissions and final claims processing. In this report, the term “medical claims” is used to refer to both claims for both physical health care and

behavioral health care submitted and processed for reimbursement. Health care not processed as a medical claim (e.g., care provided as part of a wellness program or as an Employee Assistance Program - EAP) is not included.

- Pharmacy Claims

Claims for pharmacy services are typically submitted electronically by the pharmacy at the time prescriptions are filled. The pharmacy claims history is a profile of all outpatient prescription pharmacy services provided and covered by the health plan. Pharmacy claims data include drug name, dosage form, drug strength, fill date, days of supply, financial information, and de-identified subject and prescriber codes, allowing for longitudinal tracking of medication refill patterns and changes in medications. Pharmacy claims are typically added to the research database within 6 weeks of medication dispensing.

The OptumInsight Research Database is a unique data source for autism research, affording rich, longitudinal data on disease and comorbidity and health care utilization and costs for large samples of study subjects. Nonetheless, claims data have inherent limitations given that they are generated for payment, not research, purposes. For example, a pharmacy claim is for a filled prescription that may or may not be consumed by a patient as prescribed. Over-the-counter medications or medications provided as samples by a physician are not included in the data and therefore could not be measured. Information on diagnosis may also be inaccurate. For example, a diagnosis submitted on a claim may be an interim or transient diagnosis, while the patient is undergoing tests until a definitive diagnosis is established. Thus, in order to enhance accuracy in claims analysis, researchers frequently apply inclusion and exclusion criteria as appropriate - for example, requiring multiple appearances of a diagnosis code over time -- before considering a particular condition to be present. Similarly, diagnoses that do not impact payment or that could negatively impact payment may be under-reported. Finally, minor conditions that did not result in medical treatment at a health care setting and diagnoses made outside the health care setting are not captured.¹⁶ For example, diagnoses, evaluations and treatments made within the educational system are not included.

2. Socioeconomic Data

Many aspects of health care utilization and cost, including treatment selection, therapy patterns, and health conditions, may be associated with factors not directly measured in administrative claims data. For example, a vast literature has demonstrated differences in a variety of health-related conditions for patients of differing educational attainment, income, net worth, race/ethnicity, and family composition.^{17, 18} To allow for more powerful insight into the prevalence and burden of illness, OptumInsight has linked a unique source of patient-level data to the OptumInsight administrative claims data that allows for analysis of socioeconomic characteristics. The socioeconomic data are derived through a match done by the health plan with a marketing database maintained for a large segment of the US population. Specifically, these data elements include race, ethnicity, homeowner status, occupation type (e.g., blue collar, white collar, self-employed), household income category, and household net worth category. The data populating these socioeconomic elements are generated by a combination of self-report, modeling, census data, and a variety of other individual-level and population-level data sources. Approximately 30% of the race/ethnicity data are collected directly from public records (e.g. driver's license records), while the remaining data are imputed based on sophisticated algorithms

using enhanced geocoding (e.g. address and census block data enhanced by onomastic rules). Household income and net worth are populated either by self-report or through predictive modeling. Sources for the self-reported economic measures include national surveys and consumer product registrations. Predicted household income and net worth are generated by modeling a variety of factors including age, occupation, home ownership, and median income from the Block Group Census data. While these data have application to health economics and outcomes research, certain limitations are associated with these data, including potential inaccuracies in the assignment of socioeconomic status, missing data, and pre-defined categorizations (e.g., income level). Rates of missing data vary, depending on the specific study population and the specific data elements used. The socioeconomic variables used in this study were household income, race/ethnicity, and household size (number of adults and children within the household). Generally, these variables are populated for 60-70%, 65-75%, and 30-55% of the claims population, respectively.

The socioeconomic database is refreshed on a quarterly basis. Data used for this study were based on the most recent refresh available to OptumInsight, which varied from September 2007 through June 2011 for individual subjects. Depending on whether a subject's information changed between refreshes, the effective dates for the socioeconomic information used in this study may have been earlier than the latest refresh date and varied by subject.

A. Study Reviews

1. Institutional Review Board (IRB) Review

OptumInsight submitted the Task B study protocol and a request for exemption review to the New England Institutional Review Board (NEIRB). In December 2011, NEIRB exempted the study from IRB review. The study was eligible for exemption under Category E (research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available OR if the information is recorded by the Investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects).

2. OptumInsight Disclosure Limitation Program

OptumInsight has implemented a Disclosure Limitation Process as part of its overall privacy initiative, in order to comply with applicable privacy laws and best business practices in protecting sensitive data in OptumInsight custody. Specifically, OptumInsight's Disclosure Limitation Program allows OptumInsight to comply with the Privacy Rule adopted by the U.S. Department of Health and Human Services under the Health Insurance Portability and Accountability Act (HIPAA). In situations where the Privacy Rule does not allow use of protected health information (PHI), the Privacy Rule does allow de-identification of the PHI. Once de-identified, PHI is no longer subject to the Privacy Rule, and can be used or disclosed without limitation (as long as it is not re-identified). OptumInsight has worked with recognized industry experts on de-identification methodology to comply with HIPAA Privacy requirements and developed a "Statistical Alternative Methodology" for de-identification of data. In December 2011, disclosure analysis of Task B study data was completed under OptumInsight's Disclosure Limitation Program, and it was determined that the data has been de-identified as required under applicable law and that there is a minimal risk of re-identification.

B. Study Sample

The base samples for this study were the subjects identified within the OptumInsight Research Database for Task A: Baseline Claims Analyses. Specifically, the OptumInsight samples of children with ASD, the comparison group of children without ASD, and the parent and sibling samples identified were used. Task A also used data from the Impact National Benchmark Database™. However, given that the family plan members (and therefore parent and sibling samples) were only identifiable within the OptumInsight data and that the socioeconomic data was only linkable to the OptumInsight data, study analyses under Task B focused on subjects from the OptumInsight data only.

1. Subject Eligibility Criteria

This study included commercial health plan members in the OptumInsight Research Database. To be included in the sample, individuals met the following inclusion criteria.

■ Children with ASD

Inclusion criteria:

- Commercial health plan enrolled individual with medical, pharmacy, and behavioral health coverage with at least 6 months of continuous enrollment between 01 January 2001 and 31 December 2009; the first day of the individual's first period of enrollment with all three types of coverage was set as the index date³
- Aged ≤ 20 years as of the index date
- At least 1 claim with an ASD diagnosis code, including Autistic Disorder, other specified PDD (including Asperger's Disorder) or unspecified PDD (ICD-9-CM 299.0x, 299.8x, 299.9x), in any position (i.e., primary or secondary position)⁴ during enrollment between 01 January 2001 and 31 December 2009

Exclusion criteria:

- At least one claim with a diagnosis of Rett syndrome (ICD-9-CM 330.8x) in any position or childhood disintegrative disorder (CDD, ICD-9-CM 299.1x) in any position during enrollment between 01 January 2001 and 31 December 2009.⁵

■ Comparison Group: Children without ASD

A general comparison group including individuals aged ≤ 20 years who did not have evidence of ASD, Rett syndrome or CDD (see diagnosis codes above) was selected.⁶

³ Continuous enrollment was based on simultaneous medical, pharmacy, and behavioral health coverage. Gaps in enrollment of ≤ 32 days were bridged and included in calculation of continuous enrollment duration. Note: if a subject had more than one enrollment period with all three types of coverage, the index date was set as the first day of their first day of enrollment with all three types of coverage during the study period.

⁴ Up to 4 diagnosis codes are recorded on physician claims and up to 9 diagnosis codes are recorded on facility claims. Primary position refers to the first diagnosis code listed; secondary position refers to any diagnosis after the first diagnosis.

⁵ While Rett syndrome and CDD are also considered types of pervasive development disorders similar to ASD, subjects with evidence of these disorders were excluded because these two disorders have different etiologies, disease progression and prognoses than Autistic Disorder, other specified PDD and unspecified PDD.

The inclusion criteria for the **comparison group** were:

- Commercial health plan enrolled individual with medical, pharmacy, and behavioral health coverage with at least 6 months of continuous enrollment between 01 January 2001 and 31 December 2009; the first day of the individual's first period of enrollment with all three types of coverage was set as the index date⁷
- Aged ≤ 20 years as of the index date
- No evidence of ASD during enrollment between 01 January 2001 and 31 December 2009
- No evidence of Rett syndrome or CDD during enrollment between 01 January 2001 and 31 December 2009
- Not a family member of a subject with ASD

Once these individuals were identified, a random sample was selected for inclusion in the study comparison group. A sampling ratio of approximately 3 comparison subjects to 1 subject with ASD was used.

Family Members

To identify subjects for the parent and sibling samples, family health plan members of both children with and without ASD were identified within the OptumInsight Research Database using a unique system-generated family identifier variable. We determined whether each sampled subject with ASD or comparison group member had at least one family identification (ID) value. If a subject with or without ASD had more than one family ID, we used all family IDs associated with the subject to identify family members.

It is important to note that the eligibility criteria for the samples of children with and without ASD were such that these samples themselves could include family members (e.g., two children with ASD within the same family could be in the sample of children with ASD).⁸ For the family member analysis, the study included family plan members assumed to be a parent, stepparent or adult domestic partner of a parent as well as family members assumed to be a sibling, step-sibling or other like child relevant to a subject with or without ASD. The family member samples did *not*

⁶ An unmatched, as opposed to a matched, comparison group was selected as we felt that the large size of this unmatched comparison group would allow us to effectively employ statistical adjustment as needed for a variety of outcomes when important confounders might vary. Matching is a potentially more efficient, not a more valid, means of controlling for confounding than post hoc adjustment. The efficiency difference between matching and adjustment diminishes as available sample size increases and is greatest when there are strong confounders in play. The lack of a priori data on strong confounders for our Task B analyses coupled with the large size of the comparison group supported our decision to draw an unmatched comparison cohort.

⁷ Continuous enrollment was based on simultaneous medical, pharmacy, and behavioral health coverage. Gaps in enrollment of ≤ 32 days were bridged and included in calculation of continuous enrollment duration. Note: if a patient had more than one enrollment period with all three types of coverage, the index date was set as the first day of their first day of enrollment with all three types of coverage during the study period.

⁸ The occurrence of multiple family members within the samples of children with and without ASD was relatively rare: about 8.4% of the members of the ASD sample had another family member and about 2.0% of the members of the comparison sample had another family member.

include family plan members already included in the sample of children with ASD or already included in the comparison group.

In order to identify potential parents and siblings of children with ASD and of children without ASD, the *difference* between the subject's age at index date and that of his/her family members as of the subject's index date was used.⁹ The final algorithm used to assign relationships is summarized in Table 1. Family plan members whose relative age did not meet the criteria for parent and siblings were excluded from the analysis.

Table 1. Algorithm for Identifying Parents and Siblings

Age Difference	Family Member Sample Assignment
Family member is 1-17 years younger than child with or without ASD	Sibling
Family member is 0-17 years older	Sibling
Family member is 18-49 years older	Parent
Family member is 50 or more years older	Not applicable (assumed grandparent)
Family member is 18 or more years younger	Not applicable (assumed offspring)

The final inclusion criteria for family plan members were:

- Member of the same family health plan as one of the sampled children with or without ASD
- Not a member of the sample of children with ASD or the comparison group of children without ASD
- Met the age criteria for parent or sibling relative to a sampled subject with or without ASD (see Table 1 above)
- Commercial health enrollee with medical, pharmacy, and behavioral health coverage with at least 6 months of continuous enrollment between 01 January 2001 and 31 December 2009; the first day of the family member's first period of enrollment with all three types of coverage was set as the index date¹⁰

⁹ Other information within the claims data was also considered in the selection of parent and sibling samples. Relationship/dependent information (relative to the health plan subscriber) was available for many individuals with and without ASD and their family members. In a few cases, this information was detailed ("sibling," "niece/nephew," "grandchild," "stepchild"). However, the information was ultimately not used in determining the parent and sibling samples because the overwhelming majority of individuals with and without ASD were simply noted to be "child," and for the majority of family members, the available relationship/dependent information was simply another "child," "subscriber/employee," "spouse" or "domestic partner." Because detailed relationship status could not be ascertained relative to the case/comparison group member, the final algorithm for the family member samples used the difference in age between the family member and case/comparison group member to determine whether a family member was assumed to be a parent or sibling relevant to the child with ASD or child without ASD.

¹⁰ Continuous enrollment was based on simultaneous medical, pharmacy, and behavioral health coverage. Gaps in enrollment of ≤ 32 days were bridged and included in calculation of continuous enrollment duration. Note: if a patient had more than one enrollment period with all three types of coverage, the index date was set as the first day of their first day of enrollment with all three types of coverage during the study period.

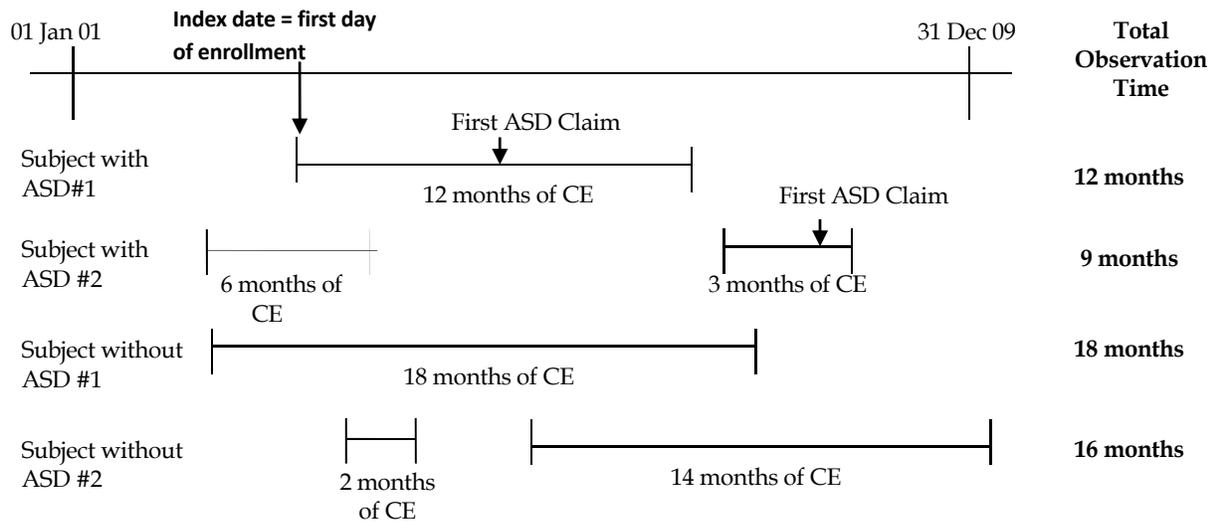
It is possible that a sampled family member could have met the sibling criteria for one study subject and the parent criteria for another. In these cases, the family member was assigned to both family member samples.

A significant strength of our study is the ability to identify family plan members as described above. However, based on the data available regarding family plan member relationships, we were unable to directly identify blood relationships (e.g., blood family members vs. step family members) for all cases, and we were also unable to explicitly identify parent and sibling relationships. It is important to note that a family member who was classified as a sibling or parent could have been a spouse instead, that a family member classified as a parent could have been a sibling, that a family member classified as a grandparent could have been a parent, etc. We also cannot rule out the presence of other family members in the household who are not covered under the insurance plan with which our database is associated. These family members are not included in our study.

2. Time Windows for Sample Identification and Observation

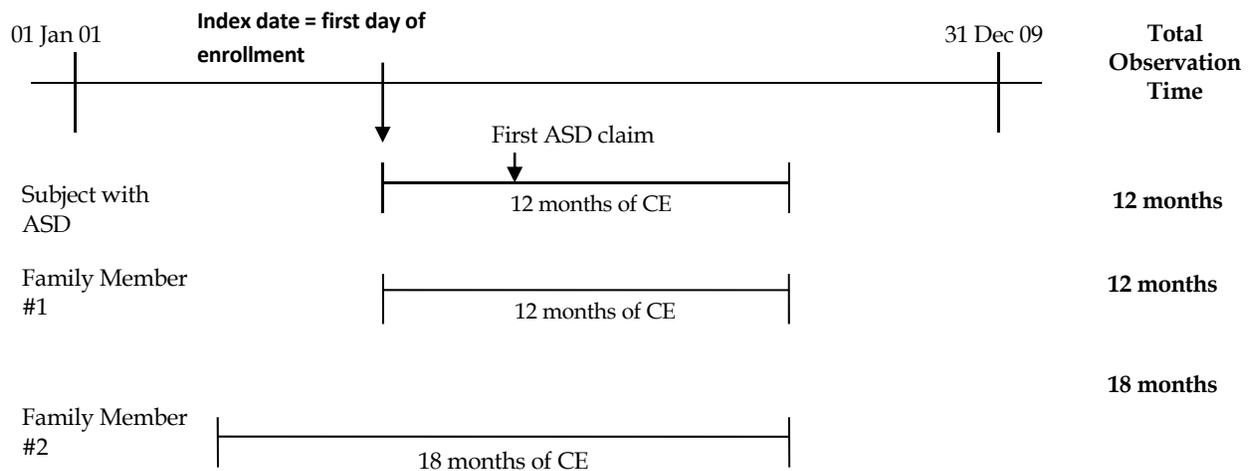
The figures below illustrate the identification and observation periods for children with and without ASD (Figure 2) and their family members (Figure 3). As indicated above, children with and without ASD were identified between January 2001 and December 2009. To capture the individuals' complete claims experience during the study period, the start of the individual's first day of enrollment with simultaneous medical, pharmacy and behavioral health coverage during this time window was set as the index date. Subjects were required to have 1 period of at least 6 months of continuous enrollment during the identification window but may have had more enrollment time with all three types of coverage during the study period. Subjects with at least the minimum 6 months of continuous enrollment were studied during the time between January 2001 and December 2009. If subjects had more than 6 months of continuous enrollment *or* more than one enrollment period with simultaneous medical, pharmacy, and behavioral health coverage during the study time frame, they were studied during that additional enrollment time as well. Each subject's total study observation time is the sum of all enrollment time during the study time frame during which the subject had all three types of coverage. Figure 2 includes examples of the distribution of observation time for four hypothetical ASD and comparison group subjects.

Figure 2. Study Observation Time - Children with and without ASD



Family plan members who met the inclusion criteria were also required to have 1 period of at least 6 months of continuous enrollment between January 2001 and December 2009 and also may have had more enrollment time with simultaneous medical, pharmacy and behavioral health coverage. As with the children with and without ASD, each family member’s total study observation time was the sum of all enrollment time during the study period during which the family plan member had all three types of coverage. It is important to note that the observation time for a sampled family member could be the same as or different than that of the subject(s) with whom that family member is affiliated. As a result, it is possible that observation time for a sampled family member may include time *before* the family member became a parent or sibling of the sampled child with or without ASD. Figure 3 includes an example of observation time for a hypothetical child with ASD and two hypothetical family members.

Figure 3. Study Observation Time - Family Plan Members



3. Refinement of ASD Sample within Task B

In Task A, eligible ASD subjects were classified into two groups: “Likely ASD” and “Possible ASD.” The Likely ASD group included subjects with 2 or more medical claims with an ASD diagnosis code in any position or 1 claim with an ASD diagnosis code in a position and 1 pharmacy claim for risperidone. The Possible ASD group was defined as those children with just 1 claim with an ASD diagnosis code in any position. In the Task A: Chart Study, we conducted a medical chart review to assess the claims-based diagnoses against “gold standard” criteria. Based on the results of the chart study, we made two significant revisions to the ASD sample in Task B. First, we revised the Likely ASD criteria to include only children with 2 or more claims with an ASD diagnosis code in any position. The chart study found that a higher proportion of false positives had a prescription for risperidone than the true positives (14.3% vs. 4.4%), suggesting that risperidone may have been prescribed for conditions other than ASD. For that reason, we dropped the criteria of 1 claim with an ASD diagnosis code and 1 prescription for risperidone from the Likely ASD group definition.

Second, we dropped the Possible ASD group from the ASD sample, focusing Task B analyses on the revised definition of the Likely ASD group. In the chart study, the positive predictive value increased from 74.2% to 87.4% when the Possible ASD group was excluded from the case definition. Therefore, we have greater confidence that children in the Likely ASD group represent true ASD cases, and we focused on this ASD group in Task B. The sampling process and study subject characteristics are presented in Section IV: Sample Identification and Demographic Characteristics.

4. Analytic Subgroups

In addition to the overall samples described above, two sample subgroups were identified for select analyses to address the research questions identified for Task B. The first was a subset of children with ASD for whom we estimated their initial diagnosis occurred during the study. The second was parents of these children initially diagnosed with ASD.

a. Children Initially Diagnosed with ASD

In identifying subjects initially diagnosed with ASD during our study, the first ASD claim in our database was not assumed to be the initial diagnosis for all subjects with ASD because for many subjects we did not have complete health plan enrollment since birth, and even for those enrolled in the health plan since birth, we did not necessarily have long enough enrollment to identify initial diagnosis as diagnosis of ASD is usually not considered reliable until approximately the age of 2 years and initial diagnosis often occurs as late as school age.

For these reasons, we used a combination of child’s age at first ASD claim, his/her continuous health plan enrollment prior to this first claim, and other relevant information. Specifically, subjects meeting the criteria outlined in Table 2 were considered to be initially diagnosed during their study observation time. Their date of initial ASD diagnosis was set as indicated in the table below.

Table 2. Criteria for Children with Initial Diagnosis of ASD During Study

Scenario	Age at First ASD Claim	Continuous Enrollment (CE) Prior to First ASD Claim	Other	Date of Initial ASD Diagnosis
1	0	n/a	Another claim for ASD at age 2 or later and CE until second claim	Date of second claim for ASD
2	1	n/a	Another claim for ASD at age 2 or later and CE until second claim	Date of second claim for ASD
3	2-9 years	Enrolled since age 0	n/a	Date of first claim for ASD
4	2-8 years	12 months	An evaluation/diagnosis/assessment CPT code or service/care within 3 months of the ASD diagnosis (pre or post). This does not include developmental or other screening tests that may have taken place within the context of a well-child visit. The list of codes is provided in Appendix A.)	Date of first claim for ASD
5	9 to 16 years	CE since age 7	Same CPT codes as above.	Date of first claim for ASD

It is important to note that the algorithms identified in the table above may have incorrectly identified subjects as initially diagnosed during our study. For example, our approach includes subjects for whom their first ASD claim occurred between the ages of 2-9 as long as the subject had continuous enrollment for a year before the first claim and had evaluation, diagnostic or assessment procedure code. It is possible that the older subjects identified were actually initially diagnosed earlier than 12 months before their first claim during our study. It is also possible that younger children identified were not formally diagnosed until later. It is difficult to assess the impact of this error on the results of the study but it is important to also note that our approach may have also excluded subjects who in fact were initially diagnosed during our study.

b. Parents of Children Initially Diagnosed with ASD

Parents of children with an initial diagnosis of ASD (see above) were also identified for some analyses.

C. Variable Definitions

The variables described below include basic subject enrollment and demographic characteristics. Unless otherwise indicated, variables were measured for all study subjects (i.e., children with ASD, comparison children without ASD, as well as family members of both groups of children).

Some of the independent variables and outcome variables associated with specific research questions are discussed below in Sections V: General health conditions analysis; VI: Injury among the child samples; VII: Gastrointestinal conditions among the child samples; and VIII: Stress-related conditions among the parent samples.

1. Subject Enrollment Characteristics

- **Index year:** The year of the subject's index date—i.e., the subject's first day of enrollment with medical, pharmacy, and behavioral health coverage between 01 January 2001 and 31 December 2009.
- **Continuous enrollment periods:** A count of separate enrollment periods with simultaneous medical, pharmacy, and behavioral health coverage during the study time frame for each subject. Continuous enrollment was defined as enrollment up until disenrollment or a gap in enrollment of more than 32 days. If an enrollment period began prior to 01 January 2001 it was truncated at 01 January 2001. Similarly, if an enrollment period extended beyond 31 December 2009, it was truncated to 31 December 2009.
- **Continuous enrollment at index:** Starting with their index date, subjects' length of continuous enrollment in days. If a subject had multiple continuous enrollment periods, this measured only the length of the first continuous enrollment period.
- **Additional continuous enrollment:** Whether a subject had more than one continuous enrollment period with medical, pharmacy and behavioral health coverage before 31 December 2009. The number of separate periods and the length of the additional enrollment in days were calculated.
- **Total enrollment time during study.** The sum of the number of days of enrollment during the index continuous enrollment period and additional continuous enrollment periods. For subjects with multiple enrollment periods, one or more gaps in enrollment were present during this time. The length of these gaps was not included in the calculation of total enrollment time (unless the gap was less than 33 days and was thus included as part of the continuous enrollment period).

2. Subject Demographic Characteristics

- **Gender.** Gender from enrollment data.
- **Age at index year.** Using subjects' date of birth, subjects' age in years as of the year of the index date – i.e., the start of study enrollment. The definition of this variable was revised from that used in Task A: Baseline Claims Analysis, for which age at index year was determined based on the subjects' year of birth as opposed to actual date of birth. For this reason, results presented in this report differ somewhat from results presented in the report for Task A.
- **Age group at index year.** Children with and without ASD were categorized <2, 2-10, 11-17, and 18-20 years at index. Siblings were classified as <2, 2-10, 11-17, 18-20, and 21+ years at index. Parents were categorized as <18, 18-21, 22-29, 30-49, 50-64, and 65+ years at index.
- **Age at initial ASD diagnosis.** For the subset of children initially diagnosed with ASD only. Age at initial ASD diagnosis was calculated as the date of birth subtracted from the date of initial diagnosis (see Table 2).

- **Race/ethnicity.** Available categories included: White, African-American/Black, Native Hawaiian or Pacific Islander, American Indian or Alaskan Native, Asian, Hispanic or other. Because of smaller sample sizes, Native Hawaiian or Pacific Islander and American Indian or Alaskan Native were combined with the other category to form a combined “other” category. This variable depended on the successful linkage with and the availability of information within the socioeconomic database. Data were therefore missing for some study subjects. Subjects with missing data were categorized as “unknown.”
- **Household income.** Modeled household income from the linked socioeconomic data. Available categories included: Under \$15,000 , \$15,000 - \$19,999, \$20,000 - \$29,999, \$30,000 - \$39,999, \$40,000 - \$49,999, \$50,000 - \$59,999, \$60,000 - \$74,999, \$75,000 - \$99,999, \$100,000 - \$124,999, \$125,000 - \$149,999, \$150,000 - \$249,999, and \$250,000+. For our analyses, these groups were further collapsed into a smaller set of categories: <\$50,000, \$50,000 – \$74,999, \$75,000 - \$99,999, \$100,000 - \$124,999, and \$125,000+. This variable depended on the successful linkage with and the availability of information within the socioeconomic database. Data were therefore missing for some study subjects. Subjects with missing data were categorized as “unknown.”
- **Geographic location.** The United States region in which the study subject was enrolled in a health plan as of the index date. States were categorized into geographic regions in accordance with the U.S. Census Bureau’s region designations. The regions are presented below in Table 3.

Table 3. Geographic Regions

Census Region	Census Division	State
Northeast	New England	CT MA ME NH RI VT
	Mid Atlantic	NJ NY PA
Midwest	East North Central	IL IN MI OH WI
	West North Central	IA KS MN MO ND NE SD
South	South Atlantic	DC DE FL GA MD NC SC VA WV
	East South Central	AL KY MS TN
	West South Central	AR LA OK TX
West	Mountain	AZ CO ID MT NM NV UT WY
	Pacific	AK CA HI OR WA

IV. Sample Identification and Demographic Characteristics

A. Sample Identification

Figure 4 below summarizes the identification of children with and without ASD. A more detailed description of sample selection process, implemented as part of the Task A: Baseline Claims Analysis and results can be found in Appendix B.

1. Children with and without ASD

To select eligible subjects for the study, first all commercial health plan enrollees with at least some type of health plan coverage between January 2001 and December 2009 were searched. Over 62 million enrollees in the OptumInsight database were identified. From these, a little over 30 million enrollees with at least 6 months of continuous enrollment with simultaneous medical, pharmacy and behavior health coverage at some point during the identification window were identified.¹¹ Enrollees' age as of the first day of enrollment (with all three types of coverage) during the study period was calculated (based on year of birth).

Among the 30 million enrollees meeting the above criteria, individuals whose age was 20 years or younger were retained. Individuals with evidence of Rett or CDD were then excluded.¹² The resulting 9.5 million children comprised the sampling frame from which children with and without ASD were identified for the study. Ultimately, the sample selection process as implemented in Task A: Baseline Claims Analysis resulted in 46,236 children with ASD and 138,876 children without ASD (selected using an approximate sampling ratio of 3:1) identified within the OptumInsight database.

2. Family Members

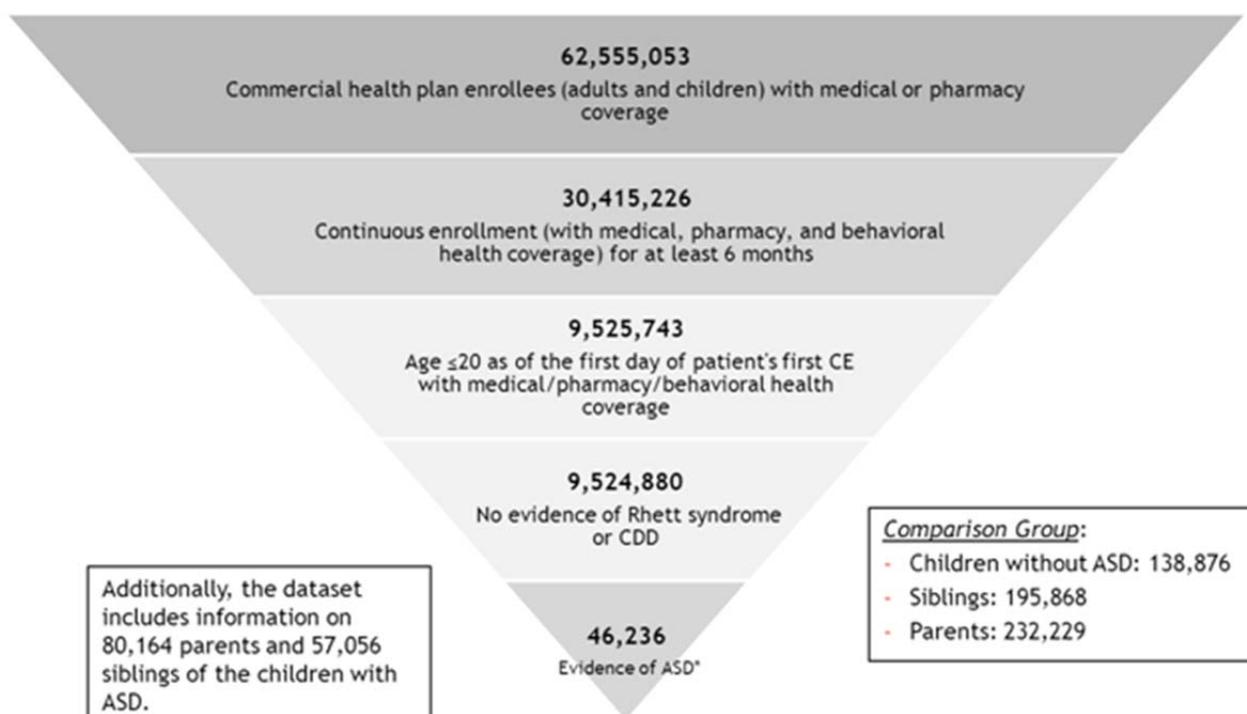
As shown in Tables B-2 and B-3 of Appendix B, approximately 99% of the children with and without ASD had evidence of being in a family health plan, and for all but approximately 2% of these subjects, at least one family plan member was identified within the database. The number of unique family plan members identified among all children with and without ASD was over 614,000. Specifically, 147,083 family plan members were identified for children with ASD (an average of 3.18 per subject), and 467,764 were identified for the comparison group (an average of 3.37 per subject).

¹¹ While all subjects sampled for the study were required to have at least 6 months continuous enrollment, sample members were not required to have medical claims during their study enrollment time, with the exception of children with ASD (whose ASD diagnosis necessitated at least 1 medical claim). It is important to note that a subset of comparison subjects (12.4%) and a subset of members of the parent samples (10.1% of comparison parents, 4.0% of ASD parents) and sibling samples (14.2% of comparison siblings, 5.0% of ASD siblings) had no medical claims during their study observation time. Basic demographic information was available for these subjects, but, by definition, these subjects lack evidence of any of the analyzed outcomes as well as have no utilization and health care costs during the study period. Therefore, while the children with ASD sampled inherently were "health care users," the other samples, including both the comparison group and family cohorts, included some "non-users."

¹² Of the 1,432 patients with at least one claim for Rett or CDD, approximately 60% had a claim for Rett, and approximately 40% had a claim for CDD. Very few (<1.0%) had claims for both.

To select family plan members eligible for the study, family plan members with at least 6 months of continuous enrollment with simultaneous medical, pharmacy and behavior health coverage during the identification window of 2001 through 2009 were flagged. Family plan members who met this requirement (n=568,198) represented 92% of all family members identified. From these, a tiny subset of family plan members who were linked (through system-generated family plan identification numbers) back to both children with and without ASD (n=78) were omitted.¹³ Finally, the age criteria outlined in Table 1 were applied to identify assumed “parents” and “siblings” of children with and without ASD. A total of 312,393 family plan members were designated as parents (80,164 for children with ASD and 232,229 for the comparison group), and a total of 252,924 were designated as siblings (57,056 for children with ASD and 195,868 for the comparison group).

Figure 4: Sampling Process as in Task A: Claims Based Analysis



*presence of one or more claims with an ICD-9 for Asperger's, Autism, or PDD-NOS

3. Refinement of ASD-Related Samples in Task B

In Task A: Baseline Claims Analysis, eligible ASD subjects were classified into two groups: “Likely ASD” and “Possible ASD.” The Likely ASD group included subjects with 2 or more medical claims with an ASD diagnosis code in any position or 1 claim with an ASD diagnosis code in any position and 1 claim for risperidone. The Possible ASD group included those children with just 1 claim with an ASD diagnosis code in any position.

¹³ While comparison group members could not be a family member of an individual with ASD, 78 family members identified had family IDs that linked back to a member of both samples and were thus excluded from the study.

As described above, the sample for Task B used a revised definition of the Likely ASD sample (limiting this group to only those with two ASD claims), and the Possible ASD group was excluded from not only the ASD samples but also the comparison groups in Task B. **Table 4** shows the impact of these changes on the sample of children with ASD as well as affiliated parents and siblings. The final ASD-related samples used in Task B were 33,565 children with ASD, 58,757 parents of children with ASD, and 41,213 siblings of children with ASD.

It is important to note that because of these sample changes, results presented for the ASD-related samples in this report differ from related results presented in the final report for Task A: Baseline Claims Analysis. Additionally, in Task A: Baseline Claims Analysis, we found that subjects with one ASD claim tended to fall in between the subjects with 2 or more ASD claims and children without ASD on a number of indicators. For example, subjects with one ASD claim had lower health care utilization and costs compared to children with two ASD claims but nonetheless significantly higher utilization and costs than children without ASD. Differences observed in Task B between ASD-related samples and the comparison groups may be wider than what they would have been had the group of children with one ASD claim (and their family members) had not been excluded.

Table 4. Likely vs. Possible ASD Subjects and Affiliated Parents and Siblings

	Total ASD		Parents of ASD Group		Siblings of ASD Group	
	n	%	n	%	n	%
Total Number of Subjects in Sample	46,236	100.00	80,164	100.00	57,056	100.00
Likely ASD Subject	33,565	72.59	58,757	73.30	41,213	72.23
Possible ASD Subject	12,671	27.41	21,407	26.70	15,843	27.77
Final Sample Used in Analysis	33,565	72.59	58,757	73.30	41,213	72.23

Note: Likely ASD subjects include children with 2 or more claims with ASD diagnosis in any position. Possible ASD subjects include children with only one claim with ASD diagnosis in any position.

4. Children Initially Diagnosed with ASD

Table 5 presents the analytic subgroup of children determined to be initially diagnosed with ASD during the study based on the algorithms outlined earlier in Table 2. As is shown, the number of subjects identified was 5,932 or 17.7% of the total 33,565 sample of children with ASD. The majority (74.5%) of the children determined to be initially diagnosed met the criteria for Scenario 4. This scenario required the child to be 2-8 years of age at the first ASD claim, have 12 months of continuous health plan enrollment prior to the first ASD claim, and a relevant evaluation/diagnosis/assessment code within three months before or after the first ASD diagnosis.

Table 5. Children Initially Diagnosed with ASD during Study

	Patients with ASD (N=33,565)	
	n	%
Initially Diagnosed	5,932	17.67
Scenario 1	10	0.17
Scenario 2	518	8.73
Scenario 3	1,304	21.98
Scenario 4	4,656	78.49
Scenario 5	468	7.89
Age at Diagnosis among All Initially Diagnosed		
2 years	1,720	29.00
3-8 years	3,744	63.12
9-16 years	468	7.89

Note: See page 17 for algorithms for identifying initially diagnosed subjects among ASD group. Scenarios are not necessarily mutually exclusive. A subject may have met the criteria for more than one scenario.

5. Children with Observation Time at Select Ages

Below in **Table 6** we present the sample sizes available for children with ASD and the comparison group during each of the age periods examined: 0-2 years, 3-5 years, 6-10 years, 11-20 years, and 21+ years. Subjects who had at least one day of enrollment with simultaneous medical, pharmacy, and behavioral health coverage during the ages comprising an age period were included in the analysis for that age period. The age period with the smallest sample size was 21+ (1,198 and 11,902 children with and without ASD, respectively); the largest age period samples were observed for the 6-10 and 11-20 age periods. Over 60% of all study subjects had enrollment during only 1 age period (data not shown in table).

Table 6. Sample Sizes for ASD and Comparison Groups by Age Period

Sample Size	Total ASD (N=35,565)	Comparison (N=138,876)
Age Period		
0-2 years	8,060	31,975
3-5 years	14,736	35,450
6-10 years	19,652	48,867
11-20 years	15,856	75,449
21+ years	1,198	11,902

B. Demographic and Enrollment Characteristics

1. Children with and without ASD

Table 7 summarizes the demographic and enrollment characteristics of both the sample of children with ASD and the comparison group of children without ASD. Whereas children without ASD were nearly equally split between males and females (50.6% and 49.4%,

respectively), just over 80% of the sample of children with ASD were male. This result was expected as ASD disproportionately affects boys, with boys 4 times more likely than girls to be diagnosed with autism.^{1,19}

The mean age at index date (first day of enrollment during study) was 8.7 years for comparison group members and 6.7 years for children with ASD. In general, a larger percentage of children with ASD were aged 2-10 years at index, whereas more children without ASD were aged 11 years and older. Nearly 9.7% of the comparison group were between the ages of 18-20 years, compared to only 2.1% of children with ASD. Given, on average, children are diagnosed with ASD before the age of 8^{20,21} we expected more children with ASD than children without ASD to be in the younger age groups. Nonetheless, while we refer to both samples as “children,” it is important to note that both groups include adults as of the index date and that subjects younger than 18 years at index may have transitioned into adulthood during the study.

Geographic differences are also observed between the two samples of children. More children with ASD were in the Northeast (15.7% vs. 10.5%) and Midwest (34.4% vs. 30.3%) regions, whereas more comparison subjects were in the Southern region (44.3% vs. 36.0%). These differences may point to state and regional differences in health plan coverage for ASD, differences in ASD diagnostic practices, or other factors.

Information about race/ethnicity was only available for a subset of subjects (61.6% of children with ASD and 51.5% of comparison group members). Among these subjects, the majority of both groups was white, with fewer African American/Black, Hispanic, Asian members in both samples. More children with ASD were white (86.1% vs. 78.7%), and slightly more comparison group members are African American/Black (6.8% vs. 3.3%) and Hispanic (10.4% vs. 6.6%). Fewer than 2% of both samples were Native Hawaiian or other Pacific Islander and American Indian or Alaskan Native or of and other race/ethnicity.

As with race/ethnicity, data on household income was only available for a subset of subjects (58.4% of children with ASD and 45.4% of comparison group members). Among these subjects, the summary income distribution was as follows: < \$50,000 (15.8% children with ASD, 24.1% children without ASD); \$50,00-74,999 (26.3% children with ASD, 28.9% children without ASD); \$75,000-99,999 (24.6% children with ASD, 21.9% children without ASD); \$100,000-124,999 (18.3% children with ASD, 14.3% children without ASD); and \$125,000 and above (14.9% children with ASD, 10.9% children without ASD). Slightly higher percentages of children without ASD fell into the income groups lower than and up to \$75,000, and slightly higher percentages of children with ASD fell into the income groups \$75,000 and higher.

Finally, **Table 7** also summarizes the distribution of index dates and enrollment characteristics for children with ASD and the comparison group without ASD. A detailed description of subject enrollment characteristics can be found in Appendix B.

As mentioned in the Sample Identification section, all sample members selected for the study were required to have a minimum of at least one period of 6 months of continuous enrollment with simultaneous medical, pharmacy, and behavior health coverage between 2001 and 2009. The first day of each subject’s enrollment with all three types of coverage during this time frame was set as his/her index date. Subjects were observed for their entire duration of continuous enrollment between 2001 and 2009. If a subject had more than 6 months of continuous enrollment

or had more than one enrollment period with medical, pharmacy, and behavioral health coverage during this time frame, subjects were observed during the additional time and period(s) as well. Therefore, observation time varied by subject.

Most subjects (over 80%) had only one period of continuous enrollment during the study period. Of those who had more than one period of enrollment, the overwhelming majority (over 90%) had only one additional period of enrollment. Overall, children with ASD had an average of 39 months of continuous enrollment from their index date as opposed to an average continuous enrollment of 27 months for children without ASD. Subjects with more than one enrollment period during the study had an average of 3 to 5 months of enrollment from these additional enrollment periods. Children with ASD had an average of 43.5 months (over 3 years) of total enrollment during the study, and children without ASD had an average of 30.5 months (roughly 2 and a half years). Only 5.7% of the children with ASD had less than a year of enrollment, and just over half had three years or more. Seventy-five percent of children with ASD and 52% of children without ASD had 2 or more years of enrollment during the study period.¹⁴ That the ASD sample had longer enrollment time was anticipated as families with ASD or any other chronic health condition may be more likely to seek, stay with, or return to health insurance coverage to the extent possible.²²

Table 7. Demographic and Enrollment Characteristics of ASD and Comparison Groups

Demographic and Enrollment Characteristics	ASD (N=33,565)		Comparison (N=138,876)		p-value
	n	%	n	%	
Gender					
Male	27,479	81.87	70,321	50.64	<0.001
Female	6,086	18.13	68,555	49.36	<0.001
Geographic Region					
Northeast	5,271	15.70	14,537	10.47	<0.001
Midwest	11,561	34.44	42,064	30.29	<0.001
South	12,090	36.02	61,497	44.28	<0.001
West	4,643	13.83	20,778	14.96	<0.001
Race/Ethnicity*					
White	17,796	53.02	56,286	40.53	<0.001
African American/Black	691	2.06	4,883	3.52	<0.001
Asian	466	1.39	1,899	1.37	0.767
Hispanic	1,366	4.07	7,434	5.35	<0.001
Other	339	1.01	1,001	0.72	<0.001
Unknown	12,907	38.45	67,373	48.51	<0.001

¹⁴ Given that over 80% of the OptumInsight sample had one enrollment period, the distributions of observation time in the study samples based on just the single longest continuous enrollment period (data not shown) are similar to those seen for total enrollment time.

Demographic and Enrollment Characteristics	ASD (N=33,565)		Comparison (N=138,876)		p-value
	n	%	n	%	
Household Income*					
<\$50,000	3,090	9.21	15,193	10.94	<0.001
\$50,000 - \$74,999	5,149	15.34	18,226	13.12	<0.001
\$75,000 - \$99,999	4,838	14.41	13,789	9.93	<0.001
\$100,000 - \$124,999	3,596	10.71	9,030	6.50	<0.001
\$125,000 +	2,915	8.68	6,854	4.94	<0.001
Unknown	13,977	41.64	75,784	54.57	<0.001
Age Group at Index Date					
0-1 years	5,609	16.71	25,534	18.39	<0.001
2-10 years	19,987	59.55	56,305	40.54	<0.001
11-17 years	7,277	21.68	43,584	31.38	<0.001
18-20 years	692	2.06	13,453	9.69	<0.001
	mean	SD	mean	SD	
Age at Index Date (continuous)	6.73	4.93	8.66	6.20	<0.001
Continuous Enrollment (CE) from Index Date (months)	38.78	26.82	27.48	21.84	<0.001
Additional Enrollment during Study (months)**	4.68	13.13	3.00	9.87	<0.001
Total Enrollment during Study (months)**	43.46	26.32	30.47	22.58	<0.001
	n	%	n	%	
Total Enrollment during Study (categories)**					
6 months	1,928	5.74	23,672	17.05	<0.001
12 months	6,563	19.55	43,361	31.22	<0.001
24 months	6,426	19.14	26,808	19.30	0.509
36 months	5,533	16.48	17,307	12.46	<0.001
≥48 months	13,115	39.07	27,728	19.97	<0.001

*From merged socioeconomic data.

**Based on simultaneous medical, pharmacy and behavioral health coverage. Subjects may have had gap(s) in enrollment during this time.

In Task A: Baseline Claims Analysis, we conducted analyses to assess the representativeness of the comparison group of children without ASD within the OptumInsight Research Database relative to the general US population and the commercially insured US population aged 0-20 years. These analyses focused on key demographic variables, including age, gender and region. With the exception of region, we found that the comparison sample in this study is similar to the privately insured population in the US. We also examined our sample of children with ASD relative to a national sample of children with ASD available through the National Survey of Children's Health (NSCH) and the findings were similar. However, it is also likely that our privately insured study samples (with and without ASD) are not representative of the entire US population in that the privately insured population is generally healthier, has better access to care, has higher income, and is less racially and ethnically diverse than the US population as a whole.²³ See Task A: Baseline Claims Analyses Report submitted to NIMH on October 17, 2011 for more information.

2. Family Members

Table 8 summarizes the same demographic and enrollment characteristics of the family member samples (i.e., family members of children with ASD and family members of comparison group members without ASD). For both groups, 51% of the parents were female. Not surprisingly, very few parents in either cohort were younger than 18 years (<1%) or 65 years and older (<1%) as of their first day of enrollment during the study. The majority of both parent samples were 30-49 years in age (over three-fourths of both sets of parents); smaller proportions were aged 22-29 and 50-64 years. The mean age at index was approximately 38 years for both parents of children with ASD and parents of children without ASD.

Among siblings, a slightly higher percentage of ASD siblings were female compared to the comparison siblings (52.0% vs. 49.4%), but the split between male and female siblings remained nearly equal for both groups. The mean age at first day of enrollment during the study was 7.7 years among ASD siblings, lower than the mean (9.4 years) for comparison siblings. Over 40% of siblings in both groups were 2-10 years of age and a quarter or more were 11-17 years of age at study start. While relatively few siblings were older than 17 years of age in either group (6.7% for ASD siblings, 11.3% for comparison siblings), it is important to note that both sibling samples included young and older adults as of the index date and that siblings younger than 18 years at index may have transitioned into adulthood during the study.

Not surprisingly, the regional distribution of family members resembles that of children with and without ASD within the OptumInsight database. Most parents and siblings in both cohorts live in either the South (approximately 36% for ASD parents and siblings and 43% of comparison parents and siblings) or Midwest regions (approximately 35% of ASD parents and siblings and 31% of comparison parents and siblings). More family members of children with ASD live in the Northeast and more family members of children without ASD live in the South.

Race/ethnicity data were available for a subset of parents and siblings (64.4% to 53.4%, respectively). As with children with and without ASD, the overwhelming majority (approximately 80% or more) of parents and siblings were white, 3-4% of ASD parents and siblings and over 5% of comparison parents and siblings were African American/black, under 3% of ASD and comparison parents and siblings were Asian, and approximately 6% of ASD parents and siblings and 10% of comparison parents and siblings were Hispanic. Fewer than 2% of either group were Native American or other Pacific Islander or American Indian or Alaska Native or of another race/ethnicity.

Income data were also available for a subset of parents and siblings (62.6% to 47.7%). The results are similar to those presented earlier for children with and without ASD. Slightly higher percentages of family members of children without ASD fell into the income groups lower than and up to \$75,000, and slightly higher percentages of family members of children with ASD fell into the income groups \$75,000 and higher.

As was also seen with children with ASD, family members of children with ASD had, on average, longer total enrollment lengths than family members of children without ASD (45.6 months vs. 35.8 months for parents; 41.1 months compared to 32.1 months for siblings). Approximately 15% of comparison siblings, 12% of comparison parents, 8% of ASD siblings, and 6% of ASD parents had less than 1 year of enrollment during the study. Three-fourths of ASD parents, 67% of ASD

siblings, 60% of comparison parents, and 55% of comparison siblings had total study enrollment of 2 years or more. Overall, as expected, parents had more enrollment time than other members of their family.

Table 8. Demographic and Enrollment Characteristics of ASD and Comparison Group Family Members

Demographic & Enrollment Characteristics	Parents (N=290,986)				Siblings (N=237,081)				ASD vs Comparison Parents p-value	ASD vs Comparison Siblings p-value
	ASD (N=58,757)		Comparison (N=232,229)		ASD (N=41,213)		Comparison (N=195,868)			
	n	%	N	%	n	%	n	%		
Gender										
Male	28,824	49.06	114,456	49.29	19,794	48.03	99,143	50.62	0.320	<0.001
Female	29,933	50.94	117,773	50.71	21,419	51.97	96,725	49.38	0.320	<0.001
Geographic Region										
Northeast	9,439	16.06	25,544	11.00	5,750	13.95	19,099	9.75	<0.001	<0.001
Midwest	20,189	34.36	71,787	30.91	14,994	36.38	61,654	31.48	<0.001	<0.001
South	20,986	35.72	100,374	43.22	14,702	35.67	85,053	43.42	<0.001	<0.001
West	8,143	13.86	34,524	14.87	5,767	13.99	30,062	15.35	<0.001	<0.001
Race/Ethnicity*										
White	35,679	60.72	117,150	50.45	21,135	51.28	80,546	41.12	<0.001	<0.001
African American/Black	1,234	2.10	7,498	3.23	1,023	2.48	6,742	3.44	<0.001	<0.001
Asian	1,046	1.78	4,239	1.83	487	1.18	2,654	1.35	0.464	0.005
Hispanic	2,734	4.65	14,665	6.31	1,533	3.72	10,948	5.59	<0.001	<0.001
Other	725	1.23	2,372	1.02	318	0.77	1,207	0.62	<0.001	<0.001
Unknown	17,339	29.51	86,305	37.16	16,717	40.56	93,771	47.87	<0.001	<0.001
Household Income*										
<\$50,000	6,451	10.98	31,775	13.68	3,619	8.78	21,479	10.97	<0.001	<0.001
\$50,000 - \$74,999	10,814	18.40	40,562	17.47	5,991	14.54	25,813	13.18	<0.001	<0.001
\$75,000 - \$99,999	10,019	17.05	31,546	13.58	5,607	13.60	19,757	10.09	<0.001	<0.001
\$100,000 - \$124,999	7,787	13.25	21,097	9.08	4,229	10.26	13,231	6.76	<0.001	<0.001
\$125,000 +	6,219	10.58	15,926	6.86	3,409	8.27	9,991	5.10	<0.001	<0.001
Unknown	17,467	29.73	91,323	39.32	18,358	44.54	105,597	53.91	<0.001	<0.001
Age Group at Index Date										
0-1 years					8,535	20.71	27,875	14.23		<0.001
2-10 years					19,575	47.50	83,951	42.86		<0.001
11-17 years					10,329	25.06	61,972	31.64		<0.001
18-20 years					1,800	4.37	12,669	6.47		<0.001
21+ years					974	2.36	9,401	4.80		<0.001
<18 years	31	0.05	383	0.16					<0.001	
18-21 years	353	0.60	2,633	1.13					<0.001	
22-29 years	6,817	11.60	33,038	14.23					<0.001	
30-49 years	47,658	81.11	180,293	77.64					<0.001	
50-64 years	3,892	6.62	15,836	6.82					0.093	
65+ years	6	0.01	46	0.02					0.120	

Demographic & Enrollment Characteristics	Parents (N=290,986)				Siblings (N=237,081)				ASD vs Comparison Parents p-value	ASD vs Comparison Siblings p-value
	ASD (N=58,757)		Comparison (N=232,229)		ASD (N=41,213)		Comparison (N=195,868)			
	mean	SD	mean	SD	mean	SD	mean	SD		
Age at Index Date (continuous)	38.04	7.36	37.71	7.85	7.65	6.14	9.43	6.67	<0.001	<0.001
Continuous Enrollment (CE) from Index Date (months)	39.73	28.25	31.32	24.67	36.63	26.22	28.62	22.49	<0.001	<0.001
Additional Enrollment during Study (months)**	5.84	14.83	4.45	12.42	4.44	12.69	3.48	10.67	<0.001	<0.001
Total Enrollment during Study (months)**	45.57	27.66	35.78	25.31	41.06	26.12	32.10	23.24	<0.001	<0.001
Total Enrollment during Study (categories)**	n	%	n	%	n	%	n	%		
6 months	3,308	5.63	28,452	12.25	3,154	7.65	29,588	15.11	<0.001	<0.001
12 months	10,861	18.48	62,450	26.89	9,002	21.84	58,263	29.75	<0.001	<0.001
24 months	10,604	18.05	45,023	19.39	8,049	19.53	38,740	19.78	<0.001	0.250
36 months	9,251	15.74	32,417	13.96	6,488	15.74	25,643	13.09	<0.001	<0.001
≥48 months	24,733	42.09	63,887	27.51	14,520	35.23	43,634	22.28	<0.001	<0.001

*From merged socioeconomic data.

**Based on simultaneous medical, pharmacy and behavioral health coverage. Subjects may have had gap(s) in enrollment during this time.

V. General Health Conditions Analysis

A. Background

Existing evidence suggests that children with ASD have a high rate of co-occurring conditions, many of which can be as disabling as ASD itself.^{24,25} These conditions include intellectual disability, anxiety and other psychiatric or behavioral conditions, sensory sensitivities, seizures and tics, as well as gastrointestinal and sleep conditions. Although the risk of occurrence of ASD in the sibling of a child with ASD is known to be increased, information about other health conditions, whether associated with ASD or not, in siblings and parents of children with ASD is not well understood.²⁶ Without a doubt, ASD affects the whole family.²⁷ Parents of children with ASD exhibit a high degree of emotional distress,²⁸ likely related to both biological and environmental factors. Poor health overall has also been described for parents of children with ASD, especially among mothers.^{29,30,31} Despite this early evidence, more research is needed to examine the presence of mental and physical conditions among family members of children with ASD.

The objective of our first set of research questions was to report the prevalence of our samples with nine specific health conditions controlling only for length of continuous enrollment and to examine the broad association between ASD and the co-occurring health conditions, without adjustment for any potential covariates (i.e., confounders or moderating and mediating variables).

1. Compared to children without ASD, do more children with ASD have evidence of the following conditions: **infectious diseases; neurological and neurodevelopmental disorders; mental health conditions; metabolic dysfunction; autoimmune conditions; genetic disorders; gastrointestinal/nutritional conditions; and injuries**? How do children with and without ASD compare in terms of overall morbidity?
2. Compared to siblings of children without ASD, do more siblings of children with ASD have evidence of the same conditions? How do siblings of children with ASD and siblings of children without ASD compare in terms of overall morbidity?
3. Compared to parents of children without ASD, do more parents of children with ASD have evidence of **mental health conditions** and **stress-related conditions** including reactive mental health conditions¹⁵ (i.e., mood/anxiety disorders; sleep disorders; somatoform and psychological pain syndromes; substance-related disorders; physical conditions with stress-related triggers; and other stress-related conditions)? How do parents of children with and without ASD compare in terms of overall morbidity?

B. Methods

1. Variable Definitions

The following variables were created for the children and parent samples. Variables were based on subjects' total enrollment time during study.

¹⁵ All future uses of the term "stress-related conditions" also include reactive mental health conditions.

- **Select infectious diseases.** Whether a subject had at least 1 medical claim with a diagnosis code for an infectious disease of interest. To qualify, the diagnosis code could be in any position. One overall dichotomous variable (0/1) was created with subjects with evidence of one or more of these diseases coded as 1, otherwise 0. This outcome was measured for children only, including subjects with and without ASD and siblings. See Appendix A for conditions included and corresponding ICD-9-CM codes.
- **Neurological/neurodevelopmental disorders.** Whether a subject had at least 2 medical claims with a diagnosis code for a neurological or neurodevelopmental disorder of interest. To qualify, the diagnosis code could be in any position but the 2 claims for the same disorder had to be 30 or more days apart.¹⁶ One overall dichotomous variable (0/1) was created; subjects with evidence of one or more of these conditions were coded as 1, otherwise 0. This outcome was measured for children only, including subjects with and without ASD and siblings. See Appendix A for conditions included and corresponding ICD-9-CM codes.
- **Mental health conditions.** Whether a subject had at least 2 medical claims with a diagnosis code for a mental health condition of interest. To qualify, the diagnosis code could be in any position but the 2 claims for the same condition had to be 30 or more days apart.¹⁷ One overall dichotomous variable (0/1) was created; subjects with evidence of one or more of these conditions were coded as 1, otherwise 0. This outcome was measured for both children and parent samples. See Appendix A for conditions included and corresponding ICD-9-CM codes.
- **Metabolic dysfunction.** Whether a subject had at least 2 medical claims with a diagnosis code for a metabolic condition of interest. To qualify, the diagnosis code could be in any position but the 2 claims for the same condition had to be 30 or more days apart.¹⁸ One overall dichotomous variable (0/1) was created; patients with evidence of one or more of these conditions were coded as 1, otherwise 0. This outcome was measured for children only, including subjects with and without ASD and their siblings. See Appendix A for conditions included and corresponding ICD-9-CM codes.
- **Autoimmune conditions.** Whether a subject had at least 2 medical claims with a diagnosis code for an autoimmune condition of interest. To qualify, the diagnosis code could be in any position but the 2 claims for the same condition had to be 30 or more days apart. One overall dichotomous variable (0/1) was created; subjects with evidence of one or more of these conditions were coded as 1, otherwise 0. This outcome was measured for children

¹⁶ For migraine, epilepsy and ADD, relevant medications were also used to identify subjects with these conditions. For all three, one claim with a relevant diagnosis plus one relevant medication claim counted as evidence. See Appendix A for list of medications.

¹⁷ For sleep disorders, one of the mental health conditions included, two claims for select insomnia medications 30 days apart or one claim with a relevant diagnosis code and one claim for an insomnia medication also counted as evidence. See Appendix A for list of medications.

¹⁸ For diabetes, one of the metabolic disorders included, two claims for select oral medications or insulin 30 days apart or one claim with a relevant diagnosis code and one claim for an oral hypoglycemic agent or insulin medication also counted as evidence. See Appendix A for list of select medications. Also, for overweight and obesity, only 1 medical claim with diagnosis code in any position was considered evidence of this condition as it is typically infrequently coded in claims even when present and diagnosed (Bleich SN et al, 2010).

only, including subjects with and without ASD and their siblings. See Appendix A for conditions included and corresponding ICD-9-CM codes.

- **Congenital/genetic disorders.** Whether a subject had at least 2 medical claims with a diagnosis code for a congenital or genetic disorder of interest. To qualify, the diagnosis code could be in any position but the 2 claims for the same disorder had to be 30 or more days apart. One overall dichotomous variable (0/1) was created; subjects with evidence of one or more of these conditions were coded as 1, otherwise 0. This outcome was measured for children only, including subjects with and without ASD and their siblings. See Appendix A for conditions included and corresponding ICD-9-CM codes.
- **Gastrointestinal and nutrition conditions.** Whether a subject had at least 2 medical claims with a diagnosis code for a gastrointestinal and nutrition condition of interest. To qualify, the diagnosis code could be in any position but the 2 claims for the same condition had to be 30 or more days apart. There was one exception: GI hemorrhage only required 1 medical claim with diagnosis in any position. One overall dichotomous variable (0/1) was created; subjects with evidence of one or more of these conditions was coded as 1, otherwise 0. This outcome was measured for children only, including subjects with and without ASD and siblings. See Appendix A for conditions included and corresponding ICD-9-CM codes.
- **Injuries.** Whether a subject had an injury episode (yes/no) and the count of injury episodes observed for each subject using the Episode Treatment Groups (ETG) methodology and software. ETGs were developed in the mid-1990's to group claims data into episodes of care for a clinical condition and are widely used for this purpose. Detail on the logic, such as the linkage of specific diagnosis and treatment codes from claims into episodes, and the time windows used for doing so, is publically available.¹⁹ For purposes of this study, we identified four subtypes of injury episodes: trauma, burns, poisonings, and environmental injuries (e.g., drowning) (defined in Appendix A). A child may have had multiple injuries during the study time period, and a single incident could have resulted in more than one injury episode: for example, a car accident could have given rise to a trauma episode for bone fractures as well as a burn episode, both with the same episode start date. An indicator variable (yes/no) and episode count variable were created for each type of injury. These conditions were measured for children only, including subjects with and without ASD and siblings.
- **Stress-related conditions.** Whether a subject had at least 2 or more medical claims with a diagnosis code for a mood/anxiety condition; sleep disorder; somatoform and psychological pain syndromes; substance-related disorder; physical condition with stress-related triggers; and other stress-related conditions. To qualify, the diagnosis code could be in any position but the 2 claims for the same condition had to be 30 or more days apart.²⁰ For each of these categories, a dichotomous variable (0/1) was created; subjects

¹⁹ <http://www.optuminsight.com/transparency/etg-links/>. A set of white papers on the site describes the method.

²⁰ For sleep disorders, asthma, hypertension, irritable bowel syndrome, and migraine/headaches, one claim with a relevant diagnosis code and one claim for a medication (See Appendix A) also counted as evidence. For sleep disorders, 2 claims for insomnia medication 30 days apart also counted for this type of stress-related condition. For constipation, only 1 dx in any position counted as evidence of this condition.

with evidence of one or more of the relevant conditions were coded as 1, otherwise 0. Additionally, one overall dichotomous variable was created to summarize across subtypes whether a subject had evidence of a stress-related condition. This outcome was measured only for parents of children with and without ASD. See Appendix A for conditions included and affiliated ICD-9-CM codes.

- **Quan-Charlson comorbidity score for parents.** A comorbidity score calculated based on the presence of diagnosis codes on medical claims (see Quan et al, 2005 32). Scores ranged from 0 (no comorbidity) to 29 (high comorbidity). Given that this measure was developed with adults in mind, this score was calculated only for the parent samples.
- Overall comorbidity score for children. There is currently no comorbidity measure for claims analysis that is universally recognized or used for children. To capture overall comorbidity for the child samples in our study, we calculated a comorbidity score modeled after Feudtner et al. 2000,³³ a comorbidity score based on the presence of diagnosis codes on medical claims for the child samples (children with and without ASD and siblings). For each subject, a dichotomous flag (0/1) was created for each of 9 categories of chronic conditions: 1) neuromuscular, 2) cardiovascular, 3) respiratory, 4) renal, 5) gastrointestinal, 6) hematologic or immunologic, 7) metabolic, 8) other congenital or genetic defect, and 9) malignant neoplasms. For each category, a subject was coded 1 if he or she had at least one claim for a diagnosis in any position for a condition within the category. These flags were then summed, which resulted in a possible score ranging from 0 to 9. While the results of this score were in line with expectations, it is important to acknowledge that the measure has not been formally validated for claims analysis.

2. Analytic Approach

To address the research questions concerning the general association between ASD and the selected co-occurring health conditions, we used several methods adjusting for enrollment time depending on the condition of interest. Specifically, for binary variables indicating whether a study subject had evidence of a particular condition (e.g., infectious disease, autoimmune condition, injury), we utilized logistic regression to produce enrollment-adjusted proportions and odds ratios. Logistic regression models (LOGISTIC procedure, SAS 9.2, SAS Institute Inc.) were fitted including the primary independent dichotomous variable capturing the samples of interest (e.g., children with ASD vs. comparison group) and the total enrollment time. Enrollment time was included as five categorical variables representing the distribution of enrollment time in quintiles. The adjusted proportion of each sample with the condition of interest was calculated using the predicted probabilities from the model. The third quintile enrollment category (including the median) was used in the prediction. The odds ratios were produced comparing the two samples of interest.

In addition to a binary indicator for injuries, we examined the count of injury episodes. For these count measures, enrollment-adjusted rates were calculated as the count of episodes across a sample divided by the total person time for that sample. Rate ratios (RR) comparing the rates between the ASD and non-ASD samples along with the associated p-value were then generated.

Finally, we analyzed the Quan-Charlson comorbidity score for parents and a separate comorbidity score for the child samples based on the presence of diagnosis codes on medical claims (see above). Based on the distribution of these comorbidity scores, these scores were

modeled as count variables, and negative binomial models were used to compare overall morbidity between children with and without ASD, siblings of children with and without ASD, and parents of children with and without ASD, adjusting for total enrollment time. The rate ratio (RR) for children with ASD (and their parents and siblings) compared to children without ASD (and their parents and siblings) were obtained from the model. The GENMOD procedure in SAS 9.2 (SAS Institute Inc., Cary, NC, USA) was used to fit the negative binomial regression models.

Note that with large sample sizes (such as those of our study samples), tests of association tend to be statistically significant; therefore, confidence intervals were also calculated.

C. Results

Table 9 presents enrollment-adjusted proportions of conditions for children with and without ASD. After adjusting for differences in study enrollment between the two study groups, a higher proportion is observed for children with ASD across all eight health conditions: infectious disease, neurological/neurodevelopmental disorders, mental health conditions, autoimmune conditions, congenital/genetic disorders, gastrointestinal/nutritional conditions, metabolic dysfunction, and injuries. Particularly noticeable is the proportion of children with ASD with evidence of neurological/neurodevelopmental disorders (70.8%), mental health conditions (70.1%), infectious diseases (50.0%), injuries (35.9%, especially trauma) and gastrointestinal/nutritional conditions (19.5%). With the exception of infectious diseases and injuries, of which a noteworthy proportion of children without ASD also had evidence (34.8% and 31.3%, respectively), significantly fewer children without ASD had evidence of the conditions examined. Children with ASD also had a higher comorbidity score overall compared to children without ASD with a rate ratio of 2.3, $p < 0.001$.

**Table 9. Select Health Conditions among ASD and Comparison Groups:
Enrollment-Adjusted Proportions**

	ASD (N=33,565)	Comparison (N=138,876)	Odds Ratio	Lower 95% CI	Upper 95% CI	p-value
	%	%				
Infectious diseases	50.00	34.80	1.877	1.830	1.925	<0.001
Neurological/ neurodevelopmental disorders	70.80	9.20	24.062	23.321	24.827	<0.001
Mental health conditions	70.10	8.70	24.676	23.917	25.459	<0.001
Metabolic dysfunction	4.70	1.10	4.375	4.095	4.675	<0.001
Autoimmune conditions	6.60	3.90	1.746	1.670	1.825	<0.001
Congenital/genetic disorders	5.10	1.50	3.525	3.319	3.744	<0.001
Gastrointestinal/ nutritional conditions	19.50	5.10	4.449	4.296	4.607	<0.001
Injuries	35.90	31.30	1.229	1.197	1.262	<0.001
Trauma	32.50	29.50	1.150	1.120	1.181	<0.001
Burn	0.90	0.70	1.379	1.233	1.542	<0.001
Poison	2.40	1.00	2.545	2.345	2.762	<0.001
Environment	2.70	1.50	1.799	1.676	1.930	<0.001
	Rate	Rate	Rate Ratio	Upper 95% CI	Lower 95% CI	p-value
Comorbidity Score	0.191	0.082	2.340	2.294	2.387	<0.001

Note: Proportions adjusted for enrollment time. Median enrollment category used in prediction.

Table 10 provides additional data on injuries for children with and without ASD. This table presents the rates of injury episodes per enrollment time (years). Similar to the results in Table 9 above, higher rates of injuries are observed for children with ASD compared to children without ASD. This is true overall (0.2414 vs. 0.2185, RR= 1.11, $p<0.001$) as well as by injury subtype. While the rate of poison-related injuries is relatively small for both children with and without ASD, the difference between the two samples is highest for this type of injury (RR=2.52, $p<0.001$).

Table 10. Rates of Injuries among ASD and Comparison Groups

Health Condition	Rates per Enrollment Time (Year)										Rate Ratio	
	ASD (N=33,565)					Comparison (N=138,876)					ASD vs Comparison	
	Events	Person-time	Rate	Lower 95% CI	Upper 95% CI	Events	Person-time	Rate	Lower 95% CI	Upper 95% CI	Ratio	p-value
Injuries (count of episodes)	29,349	121,561	0.2414	0.2387	0.2442	77,058	352,682	0.2185	0.2170	0.2200	1.1050	<0.001
Trauma (count of episodes)	25,970	121,561	0.2136	0.2111	0.2163	71,910	352,682	0.2039	0.2024	0.2054	1.0478	<0.001
Burn (count of episodes)	490	121,561	0.0040	0.0037	0.0044	1,063	352,682	0.0030	0.0028	0.0032	1.3374	<0.001
Poison (count of episodes)	1,272	121,561	0.0105	0.0099	0.0111	1,462	352,682	0.0041	0.0039	0.0044	2.5242	<0.001
Environment (count of episodes)	1,617	121,561	0.0133	0.0127	0.0140	2,623	352,682	0.0074	0.0072	0.0077	1.7885	<0.001

Separate tables will be generated to look at gender/age group comparisons and gender/ethnicity comparisons.

Tables 11 and 12 present the same information as Tables 9 and 10 for siblings of children with and without ASD, with higher proportions and rates observed across the eight health conditions for siblings of children with ASD. After controlling for differences in enrollment time, more siblings of children with ASD than siblings of children without ASD had evidence of neurological/neurodevelopmental disorders (17.3% vs. 9.0%), mental health conditions (17.9% vs. 8.6%), gastrointestinal/nutritional conditions (7.4% vs. 4.2%), and the other conditions. Infectious diseases and injuries, however, were fairly common for both sets of siblings. Just over 40% of siblings of children with ASD and 30% of siblings of children without ASD had evidence of an infectious disease, and just about a third of both samples had evidence of an injury. While the rates of injury were all higher for siblings of children with ASD, the rate ratios were no larger than 1.2 (Table 12). Siblings of children with ASD also had higher comorbidity scores compared to siblings of children without ASD (RR=1.202, $p<0.001$).

**Table 11. Select Health Conditions among ASD and Comparison Group Siblings:
Enrollment-Adjusted Proportions**

	ASD Siblings (N=41,213)	Comparison Siblings (N=195,868)	Odds Ratio	Lower 95% CI	Upper 95% CI	p-value
	%	%				
Infectious diseases	41.60	31.50	1.550	1.515	1.585	<0.001
Neurological/ neurodevelopmental disorders	17.30	9.00	2.104	2.045	2.165	<0.001
Mental health conditions	17.90	8.60	2.321	2.255	2.389	<0.001
Metabolic dysfunction	1.30	1.10	1.231	1.137	1.333	<0.001
Autoimmune conditions	4.50	3.30	1.365	1.305	1.429	<0.001
Congenital/genetic disorders	2.10	1.40	1.515	1.415	1.622	<0.001
Gastrointestinal/nutritional conditions	7.40	4.20	1.797	1.728	1.869	<0.001
Injuries	34.30	30.60	1.186	1.159	1.214	<0.001
Trauma	32.20	28.90	1.165	1.138	1.193	<0.001
Burn	0.80	0.60	1.253	1.124	1.397	<0.001
Poison	1.20	0.90	1.262	1.152	1.383	<0.001
Environment	1.80	1.40	1.251	1.163	1.345	<0.001
	Rate	Rate	Rate Ratio	Upper 95% CI	Lower 95% CI	p-value
Comorbidity Score	0.091	0.075	1.202	1.176	1.228	<0.001

Note: Proportions adjusted for enrollment time. Median enrollment category used in prediction.

Table 12. Rates of Injuries among ASD and Comparison Group Siblings

Health Condition	Rates per Enrollment Time (Year)										Rate Ratio	
	ASD Siblings (N=41,213)					Comparison Siblings (N=195,868)					ASD vs Comparison Siblings	
	Events	Person-time	Rate	Lower 95% CI	Upper 95% CI	Events	Person-time	Rate	Lower 95% CI	Upper 95% CI	Ratio	p-value
Injuries (count of episodes)	33,595	141,033	0.2382	0.2357	0.2408	110,509	523,983	0.2109	0.2097	0.2121	1.1295	<0.001
Trauma (count of episodes)	31,300	141,033	0.2219	0.2195	0.2244	103,549	523,983	0.1976	0.1964	0.1988	1.1230	<0.001
Burn (count of episodes)	459	141,033	0.0033	0.0030	0.0036	1,398	523,983	0.0027	0.0025	0.0028	1.2198	<0.001
Poison (count of episodes)	669	141,033	0.0047	0.0044	0.0051	2,027	523,983	0.0039	0.0037	0.0040	1.2262	<0.001
Environment (count of episodes)	1,167	141,033	0.0083	0.0078	0.0088	3,535	523,983	0.0067	0.0065	0.0070	1.2265	<0.001

Separate tables will be generated to look at gender/age group comparisons and gender/ethnicity comparisons.

Table 13 presents enrollment-adjusted proportions for parents of children with and without ASD across several mental health and stress-related conditions. Across the board, more parents of children with ASD had evidence of these conditions compared to parents of children without ASD. Whereas 30.6% and 54.5% of parents of children with ASD had claims for mental health and stress-related conditions, respectively, these proportions were 18.4% and 43.1% for parents of children without ASD. Among stress-related conditions, mood/anxiety disorders, somatoform and psychological pain syndromes, and physical conditions with stress-related triggers were most common in both parent samples. The Quan-Charlson comorbidity score shows that parents of children with ASD had slightly higher overall comorbidity burden compared to parents of children without ASD (RR=1.100, p<0.001).

Table 13. Select Health Conditions among ASD and Comparison Group Parents: Enrollment-Adjusted Proportions

	ASD Parents (N=58,757)	Comparison Parents (N=232,229)	Odds Ratio	Lower 95% CI	Upper 95% CI	p-value
	%	%				
Mental health conditions	30.60	18.40	1.966	1.925	2.007	<0.001
Stress-related conditions	54.50	43.10	1.579	1.549	1.610	<0.001
Mood/anxiety disorders	23.50	12.70	2.114	2.066	2.162	<0.001
Sleep disorders	10.20	7.00	1.499	1.455	1.544	<0.001
Somatoform and psychological pain syndromes	28.20	23.20	1.303	1.277	1.331	<0.001
Substance-related disorders	1.00	0.80	1.200	1.095	1.315	<0.001
Physical conditions with stress-related triggers	24.60	20.80	1.241	1.215	1.267	<0.001
Other stress-related conditions	1.90	1.10	1.656	1.555	1.764	<0.001
	Rate	Rate	Rate Ratio	Upper 95% CI	Lower 95% CI	p-value
Quan-Charlson Comorbidity Score	0.146	0.133	1.100	1.079	1.122	<0.001

Note: Proportions adjusted for enrollment time. Median enrollment category used in prediction.

D. Discussion

1. Mental and physical health of children with ASD

Children with ASD experience high rates of many psychiatric, neurological, and physical health conditions. Since the etiology of ASD is likely related to both biological and environmental variables, some of these co-occurring conditions may point to shared etiologic mechanisms or common environmental factors or triggers. In this study, we examined diagnoses for conditions which children with ASD are already known to have increased rates, such as epilepsy and mental health conditions, as well as other types of conditions for which associations with ASD have been suggested but are less clear. In addition, we examined diagnoses for common childhood conditions such as infectious diseases and injuries to better understand the overall illness. Finally, we assessed medical complexity by adapting a validated child comorbidity index for our study and assessing this metric for all children samples in our study.

Our results indicate that after controlling for varying enrollment time during study, a higher proportion of children with ASD than children without ASD have the eight groups of health conditions, and children with ASD have a higher overall comorbidity score. Specifically, we found that over 70% of children with ASD had a neurological/ neurodevelopmental disorder or mental health condition, 50% had an infectious disease, 36% had an injury, about 20% had a gastrointestinal/ nutritional condition, 7% had an autoimmune condition, 5% had a congenital/ genetic disorder, and 5% had a metabolic dysfunction. However, the analysis in this section was meant to provide a crude estimate of the relative risk associated with ASD. Therefore caution needs to be taken in interpreting these results as they were calculated without adjusting for other potential covariates (e.g. age, gender, region, income, etc.) beyond the enrollment time which was a significant confounder even in calculating crude relative risks.

Although not directly comparable due to different study designs, definition of variables, etc., our findings are similar to those of other studies that have reported rates of co-occurring psychiatric, neurological and physical health conditions among children with ASD, compared to children without ASD.^{24,34,35} Most of the other studies, however, are small clinical studies unlikely to represent children with ASD more generally. These studies suggest a wide range of possible prevalence. Furthermore, most published studies relied on parental report and recall or were unable to compare to children without ASD.^{24, 35}

Table 14: Prevalence of Co-occurring Health Conditions In the Literature

Condition	Range of Prevalence
Neurological/Neurodevelopmental Disorders^{1,36,37}	
Cognitive, intellectual disability	40-80%
Language deficits	50-63%
Attention problem, impulsivity, or hyperactivity	59%
Motor delay	9-19%
Hypotonia	50%
Tactile	80-90%
Auditory sensitivity	5-47%
Seizures and epilepsy	5-49%
Tics	8-10%

Condition	Range of Prevalence
Mental Health Conditions^{38,39,34}	
Anxiety	43-84%
Depression	2-30%
Obsessive compulsive disorder or interfering repetitive behavior	37%
Oppositional defiant disorder	7%
Behavioral problems	3%
Disruptive, irritable, or aggressive behavior	8-32%
Self-injurious behavior	34%
Psychiatric^{24, 34}	
Schizophrenia	2%
Sleep disruption/disorders	52-73%
Gastrointestinal^{40, 34}	
Food selectivity	30-90%
Bowel disorders (including IBD)	12%
Gastro-esophageal reflux, constipation	8-59%
Congenital/Genetic³⁴	
Cranial anomalies	13%
Muscular dystrophy	.5%
Metabolic³⁴	
Diabetes (Type 1)	1%
Autoimmune Disorders³⁴	
Autoimmune Disorders	0.5%

To our knowledge, there has been only one recent study that was, like ours, based on a large sample measuring rates of diagnoses of mental and physical health conditions. This study, however, used electronic health record diagnoses rather than claims and was based on a sample of individuals under age 35 with ASD and children and young adults without ASD receiving inpatient and outpatient care at 4 hospitals in the Boston, Massachusetts area.³⁴ It described a higher rate of epilepsy, schizophrenia, bowel disorders, cranial anomalies, diabetes, muscular dystrophy, and sleep disorders among the sample with ASD compared to the sample without ASD. These authors reported proportions among 0-17 year olds as well as among the 18-34 year olds compared to other users of the hospital systems. The rates among 0-17 year olds are included in Table 14 above to allow comparison to our results. However, because of the differences in the way conditions were grouped and defined – some narrowly and some broadly – as well as differences in the characteristics of the populations included, the rates reported in this study are also not directly comparable to our results.

2. Sibling and parental health

Our study found that siblings of children with ASD had higher proportions and rates across the 8 health conditions relative to siblings of children without ASD. This is similar to existing literature in which siblings of children with a chronic illness or disability have been found to have increased levels of anxiety, depression, peer problems and behavioral difficulties.^{11, 41} Specifically, siblings of children with autism have been reported to have increased levels of psychiatric and behavioral

conditions (including anxiety, phobias, and depression),¹² although the literature is somewhat inconsistent and often unable to compare to a group of siblings of typically developing children.

Similarly, more parents of children with ASD exhibited physical health and mental health conditions in our study. A more in-depth discussion of the literature and findings for this research question can be found in the multivariate results about stress-related conditions in parents in Section VIII: Parental Stress. Similar to findings in children with ASD as well as their siblings, parents of children with ASD had higher rates of stress-related conditions and overall comorbidity than parents of children without ASD.

In contrast to most previous studies where sibling health was reported by parents or siblings themselves, our results for siblings are based on actual medical claims among a very large and representative sample of siblings of children with ASD. Furthermore, we are able to compare to an even larger group of siblings of children without ASD (three comparison children were chosen for each child with ASD). We found that siblings do indeed experience higher rates of many mental and physical health conditions, even for conditions that are not known to be associated with ASD. These findings, along with the poorer physical and mental health among parents of children with ASD, raise questions about potentially shared etiologic pathways that could include both biological and environmental factors that could be amenable to intervention. More immediately, these findings indicate that the health of the child encompasses the whole family and can affect overall family functioning and resources, pointing to a need for supportive interventions for the family as a whole rather than each individual separately in order to improve the health and quality of life of children with ASD and their families.

VI. Injuries

A. Background

Injuries in children are the leading cause of preventable death. In 2004, unintentional injury was the leading cause of death in children aged 1–4 years⁴², and annually, an estimated 9.2 million children have emergency department visits for unintentional injury.⁴³ Risk of injury and the types of injuries children experience differ by age group with younger children being at highest risk. In addition to age, risk factors for accidents or unintentional injuries among children include male gender, larger family size, and white race.^{44, 45, 46, 47} The literature was more divided on the impact of socio-economic status (SES) as a risk factor for injury. Some articles found that higher SES, as measured by income and insurance coverage, was associated with a greater risk of injury.^{45,46} In contrast, others found that lower SES was associated with a higher risk for some types of injuries.^{44,47} It is possible that this discrepancy is partially caused by the differing methods the studies used to measure SES and injury. It has also been shown that poor parental supervision is associated with childhood injuries among children overall as well as among children with mental health conditions.⁴⁸

Numerous studies have reported that children with developmental disabilities or chronic medical conditions are at higher risk for injury compared to children without these conditions possibly related to the physical, mental, and social impairments that are features of their disabilities or medical conditions.^{44, 49, 50, 51,52} Sherrard and colleagues assessed medically attended injury rates (injuries that resulted in medical care) in young people with intellectual disability relative to the general population and found a higher rate of injury (aspirations, poisoning, immersion, and other severe traumatic injury) among children with intellectual disability.⁵² Lee and colleagues reported that children with ADD²¹, as well as other psychological conditions, were about two to three times more likely to experience an injury that warranted or resulted in medical attention than unaffected comparison children.⁵³

Very few studies have examined whether there is increased risk of injury associated with ASD. Using Medicaid claims data, a study by McDermott found a relative risk of 7.62 for the emergency/hospital treatment of self-inflicted injury or suicide attempt among children with autism and PDD compared to children without disabilities.⁵⁴ This same study also reported that children with autism or PDD had significantly higher rates of head, face, and neck injuries (RR = 1.47) and poisoning (RR = 7.6) but significantly lower rates of sprains and strains (RR = 0.54) than children without disability. Lee and colleagues used results from the National Survey of Children's Health to examine risk of injury among children ages 3 – 5 years with autism or with other mental health conditions such as ADD, depression, or anxiety.⁵³ This study found that, based on parent-reported outcomes, children with autism were 2.15 times more likely to experience an injury that required medical attention than unaffected controls after adjusting for sex, age, number of children in the family, race, and poverty level.

Despite these studies linking injury with ASD, it is unclear whether there are specific patterns in terms of frequency of injury among children with ASD in general or among key subgroups of

²¹ While some literature makes a distinction between ADD and ADHD, we did not in either our data or analysis. We shall use "ADD" to refer to both.

children with ASD. Using a large population of subjects diagnosed with ASD identified from a large, national commercial health plan claims database, we sought to answer the following specific research questions:

1. Compared to children without ASD, do children with ASD have higher rates of injury adjusting for potential covariates?
2. Does the risk of injuries differ between children with and without ASD by age?
3. Does the risk of injuries vary among key subgroups of children with ASD?

B. Methods

1. Variable Definition

The common outcome variable of interest for all three injury-specific research questions is the overall injury variable described in Section V: General Health Conditions and reiterated here.

- **Injuries.** Whether a subject had an injury episode (yes/no) and the count of episodes observed for each subject using the ETG methodology and software. Additionally, an indicator variable (yes/no) and episode count variable were created for four subtypes of injuries: trauma, burns, poisonings, and environmental injuries (e.g., drowning). A child may have had multiple injuries during the study time period, and a single incident could have resulted in more than one injury episode: for example, a car accident could have given rise to a trauma episode for bone fractures as well as a burn episode, both with the same episode start date. An indicator variable (yes/no) and episode count variable were created for each type of injury. These conditions were measured for children only, including subjects with and without ASD and siblings.

It is worth noting that in the General Conditions section, the descriptive statistics (Tables 9 & 10) indicated that among children (with or without ASD) who had at least one episode of injury, the vast majority (90-94%) of children had a traumatic injury (fractures, dislocations, sprains, etc. See Tables A-13 and A-14 in the Appendix A for the full list of the ICD-9 and ETG codes used to define injuries). Burns, poisonings, or environmental injuries were less common among our sample. It is unclear whether this is due to true differences in risk of different kinds of injuries or if the minor cases of these three types of injuries are less likely to result in a medical encounter that would lead to a claim being filed. Due to the very low prevalence of these specific injury subtypes, we did not examine them as separate independent variables.

Our multivariate analyses of injury included several covariates. In addition to the demographic, enrollment, and socio-economic variables as described earlier in the report (Section III.D: Variable Definitions) we also created additional variables for six distinct behavioral health conditions that often co-occur with ASD and may be related to injury to be controlled for in the injury models.⁵³ These variables are described below:

- **Attention deficit disorders (ADD).** Whether or not a subject had evidence of an attention deficit disorder during their total enrollment during the study. To qualify, a subject must have had at least 2 medical claims with a relevant diagnosis code in any position at least 30 days apart OR a subject must have had 1 claim with a diagnosis code in any position and 1 claim for an ADD medication. One binary indicator variable (0/1) was created for

children only, including subjects with and without ASD. This variable definition differs from the definition used in Task A: Baseline Claims Analysis. For this reason, results presented in this report differ somewhat from results presented in the report for Task A. See Appendix A for conditions included and corresponding ICD-9-CM diagnosis codes.

- **Anxiety.** Whether or not a subject had evidence of anxiety during their total enrollment during the study. To qualify, a subject must have had at least 2 medical claims with a relevant diagnosis code in any position at least 30 days apart. One binary indicator variable (0/1) was created for children only, including subjects with and without ASD. This variable definition differs from the definition used in Task A: Baseline Claims Analysis. For this reason, results presented in this report differ somewhat from results presented in the report for Task A. See Appendix A for conditions included and corresponding ICD-9-CM diagnosis codes.
- **Depression.** Whether a subject had evidence of depression during their total enrollment during the study. To qualify, a subject must have had at least 2 medical claims with a relevant diagnosis code in any position at least 30 days apart. One binary indicator variable (0/1) was created for children only, including subjects with and without ASD. This variable definition differs from the definition used in Task A: Baseline Claims Analysis. For this reason, results presented in this report differ somewhat from results presented in the report for Task A. See Appendix A for conditions included and corresponding ICD-9-CM diagnosis codes.
- **Learning/intellectual disability.** Whether a subject had evidence of a learning/intellectual disability during their total enrollment during the study. To qualify, a subject must have had at least 2 medical claims with a relevant diagnosis code in any position at least 30 days apart. One binary indicator variable (0/1) was created for children only, including subjects with and without ASD. This variable definition differs from the definition used in Task A: Baseline Claims Analysis. For this reason, results presented in this report differ somewhat from results presented in the report for Task A. See Appendix A for conditions included and corresponding ICD-9-CM diagnosis codes.
- **Visual impairment.** Whether a subject had evidence of visual impairment during their total enrollment during the study. To qualify, a subject must have had at least 1 medical claim with a relevant diagnosis code in any position. One binary indicator variable (0/1) was created for children only, including subjects with and without ASD. See Appendix A for conditions included and corresponding ICD-9-CM diagnosis codes.
- **Seizure disorder/epilepsy (Seizures).** Whether a subject had evidence of seizures. To qualify, a subject must have had at least 2 medical claims with a relevant diagnosis code in any position at least 30 days apart OR a subject must have had 1 medical claim with a diagnosis code in any position and 1 claim for a medication for seizures. One binary indicator variable (0/1) was created for children only, including subjects with and without ASD. This variable definition differs from the definition used in Task A: Baseline Claims Analysis. For this reason, results presented in this report differ somewhat from results presented in the report for Task A. See Appendix A for conditions included and corresponding ICD-9-CM diagnosis codes.

As ASD is heterogeneous in its manifestations, most experts recognize that ASD severity, particularly functional severity, is an important variable in determining outcomes. Administrative claims data in general, including the OptumInsight Research Database, are limited in their ability to adequately capture functional severity, as relevant variables are not comprehensively coded in claims. ASD severity may, however, be related to certain diagnoses or co-occurring conditions that are associated with ASD. For example, the absence or presence of a seizure disorder is correlated with ASD severity and level of functioning⁵⁵ as well as being an injury risk factor.^{56, 57} Thus, we included seizure disorders as an important covariate in our multivariate models. Though the a priori justification is perhaps not as strong for conditions other than seizures, following this same general rationale we also considered adjustment for other co-occurring conditions that have been previously linked to increased injury risk (ADD, anxiety, depression, learning/intellectual disability, and visual impairments) as additional control for possible case complexity.

2. Analytical Approach

To address the research questions specific to injuries, multivariate regression analyses were conducted using counting process models. The counting process model is an extension of the Cox proportional hazards model applied to recurrent count data where a subject contributes to the risk set for an event as long as the subject is under observation at the time the event occurs. Counting process models can also be applied when subjects are observed for discontinuous risk intervals. For example, if a subject has two separate periods of enrollment meeting inclusion criteria (greater than 6 months), both risk intervals can be included.⁵⁸ A sandwich estimate of the covariance matrix was utilized to account for intra-subject correlation of risk intervals.²² The Cox Model-based counting process model requires a proportionality assumption – i.e., it assumes that the relative risk for an independent variable is constant over time. We examined the proportionality assumption with respect to the principal variable of interest (ASD vs. comparison group). Graphical checks (specifically a plot of survival function across time and a plot of log negative log of the survival function across time by sample) yielded no obvious departures from the assumption. The counting process model requires few other assumptions because of its semi-parametric nature, unlike, for example, a GEE Poisson model which is fully parametric and requires specifying the working correlation matrix to derive the robust estimator of variance. The counting process model is robust in that it estimates valid effects under a variety of baseline hazard function assumptions⁵⁸, is resistant to over-dispersion, and can handle time-dependent covariates.⁵⁹ The counting process model yields effect estimates that are interpreted as log relative risks of the occurrence of an injury event.

²² If a patient has one enrollment period and no events (Injuries) during that enrollment period, he will contribute one row to the dataset used in the counting process analysis. The start date of this record will be the index enrollment date and the end date will be the end of the enrollment period. The event count will be set to zero which will tell SAS that the record was 'right censored'. If a patient has two enrollment periods and one event in each enrollment period (total of 2 events), then he will contribute 4 rows to the dataset. The first row would be from the start of the first enrollment period to the date of the first event. The second row would be from the end of the first event episode plus one day (at risk concept) to the end of the first enrollment period. The third and fourth rows would follow but would be from the second enrollment period.

Two sets of models were run. The first set of models included both the samples of children with and without ASD so that the risk of injury could be compared between the two samples while controlling for other variables. The second set of models focused only on children with ASD to identify which subgroups of children with ASD have higher risk of injury.

For each model, the covariates defined above were included based upon clinical rationale, descriptive analyses, and/or statistical significance. The covariates retained in the full models were: gender, income, race, region, age at index, as well as binary indicators of a number of behavioral co-occurring conditions including ADD, anxiety, depression, learning/intellectual disability, visual impairment, and seizures. For each model, the Wald test of global fit was examined to assess model fit. The results of the diagnostics are provided with the model results.

One concern of our project team was the treatment of age within our models. In the models described above, age at index date (first day of enrollment during study) was included. While this approach is commonly used in claims-based analyses, the longer study enrollment time and the differences in study enrollment time among subjects, made it difficult to interpret the age effects. To address the second research question above – whether the risk of injuries differs between children with and without ASD by age – we also ran the injury models limiting observation time to select age periods: 0-2, 3-5, 6-10, 11-20, and 21+ years (see Table 6).

To detect multicollinearity we examined correlations among the variables included in the models as well as variance inflation factors (VIF), an indicator of how much variance there would be if there was no multicollinearity among explanatory variables. Generally, correlations of .80 and more signal a strong linear relationship between two variables.^{60, 61} While there is no one agreed-upon criterion for what level of VIF indicates multicollinearity, some believe VIF values exceeding 10 should warrant concern.⁶² All of the correlations and VIF values observed fell below these thresholds, indicating little need to be concerned about multicollinearity among our model variables.

C. Results

Table 15 first shows the unadjusted descriptive results for the dependent and independent variables included in the multivariate models analyzing the relative risk of injury for samples of children with and without ASD. Specifically, the table presents the mean count of injury episodes and the proportion of children who had evidence of the co-occurring conditions included as covariates. (For descriptive analyses of the demographic variables included in the models, refer back to Table 7 in Section IV.B.1.) As shown, the mean number of injury episodes was less than 1.00 for both groups (0.87 for children with ASD and 0.55 for children without ASD). For both samples, the median number of episodes was 0 and the 75th percentile was 1.00, with the maximum number of episodes observed totaling 25 and 20 for children with and children without ASD, respectively (data not shown). The most common conditions for children with ASD were attention deficit disorder (38.8%), anxiety (16.4%), and depression (12.1%). Fewer children with ASD (4-8%) had evidence of a learning/intellectual disability, seizures, or visual impairment. Among children without ASD, all of the conditions were relatively rare, with 4.3% or fewer of this sample having evidence of one of these conditions.

Table 15. Descriptive Analyses of Clinical Covariates for ASD and Comparison Groups

	ASD (N=33,565)		Comparison (N=138,876)	
	Mean	SD	Mean	SD
Unadjusted Outcome				
Count of Injury Episodes*	0.87	1.41	0.55	1.10
Independent Variables	N	%	N	%
Anxiety	5,507	16.41	2,973	2.14
Attention deficit disorders	13,018	38.78	5,987	4.31
Depression	4,065	12.11	4,149	2.99
Learning/intellectual disability	1,433	4.27	46	0.03
Seizures	2,554	7.61	522	0.38
Visual impairment	1,617	4.82	1,540	1.11

Note: Results are not adjusted for enrollment time.

Table 16 presents the modeling results addressing the first injury-specific research question above: after controlling for possible confounders, do children with ASD have higher rates of injury than children without ASD? The unadjusted model is presented in the first column, followed by a model controlling for demographic characteristics in the second column, and the full model including the behavioral co-occurring conditions in the far right column. In the unadjusted base model, the hazard ratio observed for children with ASD is 1.119 ($p < 0.001$), suggesting that children with ASD had a 12% greater injury risk than children without ASD.

With the inclusion of demographic variables, the magnitude of the hazard ratio decreased to 1.03. Because of the large sample size, the effect remained statistically significant at a conventional alpha error tolerance but the clinical importance of just a 3% increased risk is less striking and, further, an effect this small is less robust to uncontrolled issues of bias or confounding (e.g., unmeasured confounders or measurement error). When the variables for co-occurring conditions were incorporated into the model, the relative risk estimate moved below 1.0, down to 0.889 ($p < 0.001$), suggesting that after this additional adjustment children with ASD were actually 11% *less likely* to experience an injury than children without ASD. Interpretation of this result is challenging because it is unclear whether adjustment for these co-occurring conditions is isolating the true independent effect of ASD on injury risk (where the results suggest that there is injury risk protection associated with ASD) or whether it is introducing over-adjustment where the appearance of claim codes for these conditions are direct consequences of ASD. If the latter is true, the effect of these intermediate variables should not be adjusted away. However, as will be discussed below, further modeling suggested that the ASD injury effect is modified by the age of the child and, consequently, the results that should be the major focus of interpretation should therefore be the age-stratified findings.

Table 16. Counting Process Regression of Injuries among ASD and Comparison Groups

Independent Variables	Hazard Ratio for Recurrent Injuries		
	Model1: Un-adjusted	Model2: Demographics added	Model3: Demographics and co- occurring conditions added
Sample			
Comparison	ref.	ref.	ref.
ASD	1.119*	1.029*	0.889*
Gender			
Female		ref.	ref.
Male		1.230*	1.235*
Household Income*			
<\$50,000		ref.	ref.
\$50,000 - \$74,999		0.994	0.992
\$75,000 - \$99,999		1.01	1.004
\$100,000 - \$124,999		1.038*	1.031
\$125,000 +		1.108*	1.097*
Unknown		0.979	0.98
Race/Ethnicity*			
White		ref.	ref.
African American/Black		0.727*	0.737*
Asian		0.687*	0.706*
Hispanic		0.817*	0.826*
Other		0.889*	0.908*
Unknown		0.949*	0.958*
Geographic Region			
South		ref.	ref.
Northeast		1.095*	1.101*
Midwest		1.077*	1.070*
West		0.989	0.999
Age at Index Date (continuous)		1.002*	0.998*
Attention deficit disorders			1.133*
Anxiety			1.069*
Depression			1.298*
Learning/intellectual disability			1.088*
Visual impairment			1.197*
Seizures			1.433*

Observations read = 302,263, Observations used= 302,046 (217 observations removed because event occurred at the start of an enrollment period)

*Statistically significant at 0.05 confidence level

Model 1: (217 observations removed because event occurred on start of an enrollment period); Wald (Sandwich) Test of Global Model Fit: chi-square=141.563 DF=1, p-value=<0.001

Model2: (102 observations removed); Wald (Sandwich) Test of Global Model Fit: chi-square=1305.784, DF=16, p-value=<0.001

Model 3: (217 observations removed); Wald (Sandwich) Test of Global Model Fit: chi-square=2201.710, DF=22, p-value=<0.001

Additional models were fit to examine possible interactions between sample group (with ASD vs. not) and gender, age, and co-occurring conditions to examine whether the effect of ASD on injury risk differs across subgroups defined by these variables (data not shown). All interaction terms were statistically significant at conventional alpha error tolerance ($p < 0.05$) except for the interaction with the seizure variable. However, with the exception of age, which will be discussed further below, the heterogeneity of the ASD effects across subgroups was not that large and the statistical significance was driven by the large sample size. For example, among males the ASD HR was 1.05 whereas among females the ASD HR was 1.04. So, while this interaction is statistically significant, there is no readily apparent clinical significance. The relationship between ASD and injury varied by whether a child had an attention deficit disorder and depression. Among children with an attention deficit disorder, children with ASD were slightly more likely to have an injury (HR = 1.031), whereas among children without an attention deficit disorder, the risk for injury was lower for children with ASD (HR=0.942). Likewise, among children with depression, children with ASD had a higher risk for injury (HR = 1.104), whereas among children without depression, the risk was lower among our ASD sample (HR=0.927). This suggests that any excess injury risk, though small, may be a function of certain aspects of ASD phenotypic complexity rather than core symptomology. However, as mentioned, this heterogeneity of effect was not seen across all co-occurring conditions. For both children with anxiety and without anxiety, the risk for injury was lower for children with ASD compared to children without ASD but the risk was slightly higher for those with anxiety (HR= 0.977 vs. 0.917).

To address our second injury-related research question- whether the risk of injury differs between children with and without ASD by age - Table 17 presents the results of the full model (Model 3 in Table 16 above) for each of the five age periods introduced earlier in Table 6. To be included in the age period model, subjects had to have at least one day of enrollment with simultaneous medical, pharmacy, and behavioral health coverage during the ages comprising an age period. These models resulted in a key finding: after controlling for socio-demographic characteristics and select co-occurring conditions, the risk of injury among children with and without ASD varied by age. Whereas among older children (during the ages of 11-20 years and 21+ years), children with ASD had *lower* risk of injury compared to children without ASD (as was found above in the overall model), among younger children (during the ages of 0-5), children with ASD instead had *higher* risk of injury. No statistically significant difference was observed in the risk of injury between children with and without ASD during the middle age period - i.e., between the ages of 6 and 10 years.

Table 17. Counting Process Regression of Injuries among ASD and Comparison Groups by Age Periods

Independent Variables	Age Period				
	0-2 Years	3-5 Years	6-10 Years	11-20 Years	21+ Years
Sample					
Comparison	ref.	ref.	ref.	ref.	ref.
ASD	1.141*	1.282*	1.001	0.634*	0.580*
Gender					
Female	ref.	ref.	ref.	ref.	ref.
Male	1.158*	1.187*	1.141*	1.313*	1.223*

Independent Variables	Age Period				
	0-2 Years	3-5 Years	6-10 Years	11-20 Years	21+ Years
Household Income*					
<\$50,000	ref.	ref.	ref.	ref.	ref.
\$50,000 - \$74,999	1.040	0.955	0.925*	1.014	1.128
\$75,000 - \$99,999	1.019	1.038	0.995	0.989	1.098
\$100,000 - \$124,999	1.045	1.048	0.984	1.051	1.011
\$125,000 +	1.094	1.159*	1.092*	1.092*	1.094
Unknown	1.028	1.051	0.946	0.956	1.048
Race/Ethnicity*					
White	ref.	ref.	ref.	ref.	ref.
African American/Black	0.913	0.666*	0.763*	0.703*	0.763*
Asian	0.909	0.800*	0.703*	0.596*	0.743
Hispanic	0.936	0.904*	0.836*	0.770*	0.862
Other	0.921	0.926	1.046	0.831*	0.593
Unknown	0.954	0.951	0.981	0.952*	0.898
Geographic Region					
South	ref.	ref.	ref.	ref.	ref.
Northeast	1.085*	1.084*	1.054*	1.136*	1.136
Midwest	0.977	0.980	1.041*	1.146*	1.157*
West	0.933*	0.967	0.942*	1.059*	1.146*
Attention deficit disorders	1.148*	1.069*	1.124	1.243*	1.137
Anxiety	1.104	1.090	1.096*	1.086*	1.551*
Depression	1.266*	1.112	1.157*	1.359*	1.421*
Learning/intellectual disability	0.824	1.121	1.154*	1.174*	2.035*
Visual impairment	1.150*	1.145*	1.187*	1.307*	0.678
Seizures	1.466*	1.460*	1.519*	1.394*	2.007*
Observations Used	54,228	67,317	96,362	147,744	17,571

*Statistically significant at 0.05 confidence level

0-2 Model: Wald (Sandwich) Test of Global Model Fit: chi-square=327.1453, DF=21, p-value=<0.001

3-5 Model: Wald (Sandwich) Test of Global Model Fit: chi-square=848.4970, DF=21, p-value=<0.001

6-10 Model: Wald (Sandwich) Test of Global Model Fit: chi-square=842.2948, DF=21, p-value=<0.001

11-20 Model: Wald (Sandwich) Test of Global Model Fit: chi-square=2978.0830, DF=21, p-value=<0.001

21+ Model: Wald (Sandwich) Test of Global Model Fit: chi-square=373.0873, DF=21, p-value=<0.001

Table 18 presents the results addressing our third injury-specific research question, whether key demographic and clinical subgroups of children with ASD are at higher risk of injury. The results of two models are shown, one with just the demographic covariates included and the other including the co-occurring conditions. Statistically significant predictors of injuries among children with ASD include age at index, where older children were at lower risk of injuries (HR=0.97, $p>0.001$), and, generally consistent with the findings reported above, the presence of co-occurring behavioral health conditions. Regional differences in injury rates were seen, with children with ASD living in the Northeast region of the country had higher injury risk compared to those living in the Southern region (HR=1.08, $p=0.002$), as were differences associated with race: African-American, Asian and Hispanic children with ASD were at lower risk compared to White children with ASD (HR=0.686, HR=0.833, and HR=0.881, respectively). Among children with ASD, gender and household income were not related to injury risk.

Table 18. Counting Process Regression of Injuries among Children with ASD

Independent Variables	Injuries			
	hazard ratio	lower 95% CI	upper 95% CI	p-value
Gender				
Female	ref.	–	–	–
Male	1.027	0.984	1.071	0.218
Household Income*				
<\$50,000	ref.	–	–	–
\$50,000 - \$74,999	0.932	0.873	0.995	0.034
\$75,000 - \$99,999	0.953	0.892	1.019	0.158
\$100,000 - \$124,999	0.968	0.902	1.039	0.370
\$125,000 +	1.016	0.946	1.090	0.668
Unknown	1.021	0.952	1.095	0.553
Race/Ethnicity*				
White	ref.	–	–	–
African American/Black	0.686	0.604	0.779	<0.001
Asian	0.835	0.734	0.949	0.006
Hispanic	0.881	0.812	0.956	0.003
Other	0.877	0.743	1.035	0.121
Unknown	0.963	0.915	1.015	0.157
Geographic Region				
South	ref.	–	–	–
Northeast	1.077	1.028	1.129	0.002
Midwest	1.034	0.996	1.073	0.084
West	1.000	0.950	1.052	1.000
Age at Index Date (continuous)	0.973	0.970	0.977	<0.001
Attention deficit disorders	1.097	1.061	1.134	<0.001
Anxiety	1.051	1.005	1.098	0.028
Depression	1.234	1.173	1.298	<0.001
Learning/intellectual disability	1.153	1.072	1.240	0.000
Visual impairment	1.157	1.085	1.233	<0.001
Seizures	1.437	1.364	1.515	<0.001

Observations read = 68,256, Observations used = 68,210 (46 observations removed because event occurred on start of an enrollment period)

Wald (Sandwich) Test of Global Model Fit: chi-square=603.156, DF=21, p-value=<0.001

D. Discussion

To our knowledge, this study was the first to use claims data for a large sample of the privately insured US population to compare the occurrence of injuries overall among children with ASD relative to children without ASD. Similar to studies using other data sources, we estimated a higher risk of injury among children with ASD compared to children without ASD before adjusting for covariates beyond the enrollment time. However, this increase in risk diminished after controlling for demographic and socioeconomic variables. While adjustment for some co-occurring conditions showed that children with ASD in general are at less risk of injury when the effects of these conditions are controlled, it is difficult to know whether or not this step could represent over-adjustment in the model. A number of behavioral and mental health conditions are known to predispose children to injuries^{44, 63, 64, 65, 66} and whether the codes capturing these conditions represent independent effects that should be adjusted for or are causal manifestations of the overall ASD effect is unclear.

The relationship between ASD and injury risk varied substantially by age, however, with younger children with ASD at increased risk of injuries compared to children without ASD, after controlling for socio-demographic variables and co-occurring conditions, and older children with ASD being somewhat protected. As the predominant types and mechanisms of injury vary greatly by age for children^{67 68 69} – with motor vehicle accidents the leading cause of injury-related deaths overall but suffocation and falls causing more injuries among younger children, it is not surprising that age is also an important determinant for risk of injury among children with or without ASD. Although we examined a common endpoint of “injury”, some of the observed differences in risk by age period may be a result of different types and mechanisms leading to “injury” at different age periods. Considering that age is typically correlated with level of autonomy, it is not surprising that older children with ASD have fewer injuries than their peers without ASD who may be more autonomous and independent. This could, for example, be related to older children with ASD tending to have fewer motor vehicle accidents compared to their peers as they may be less likely to drive.

The risk attributable to the co-occurring conditions and the way these also vary by the age of the child may also be revealing. For example, having a seizure disorder is an important risk factor for injury at every age, whereas learning or intellectual disability does not impact injury risk at the younger ages but is highly predictive in adolescence. Injuries in children overall have decreased during the time period of our study,⁶⁷ but poisoning in teens has increased, which is thought to be largely related to the increased use of prescription medications. Older children with ASD who have co-occurring conditions are often treated with psychoactive medications and would thus be at increased risk for such injuries; they are likely a group for whom injury prevention interventions should be particularly focused.

We also considered the potential for surveillance bias in the multivariate results. Children with ASD may have greater exposure to the health care system than children without ASD, making the comparison between the two groups difficult. One could argue, however, that this surveillance bias effect may be less pronounced with an acute outcome like injury than with a chronic medical condition. However, to address this potential concern, we included a measure of preventive health care utilization as a proxy measure of surveillance in the overall injury multivariate analyses (results not shown).²³ While preventive health care utilization was statistically significant, the hazard ratio associated with the sample remained the same after adjustment (for example in the models adjusting for demographic characteristics and co-occurring conditions, the ASD HR after addition of the preventive health care term was 0.865 compared to 0.889 prior to adjustment).

Among the few studies that have previously examined the association of injury with ASD, the study by McDermott and colleagues is perhaps the most comparable to ours in terms of study design, data source, study population, and large sample size. In this study examining the risk of injury among children covered by the South Carolina Medicaid program, the authors identified 138,111 children in the year 2003, including 1,610 children with a diagnosis for autism or pervasive developmental disorders (PDD).⁵⁴ Poisson regression was used to model the rate of

²³ Children with ASD had a median of 1.04 annualized preventive health care visits during the study, compared to 0.71 for children without ASD. See the final report for Task C: Health Care Utilization and Costs for more information.

injuries receiving emergency room or hospital treatment as well as to model each specific type or location of injury while adjusting for age and gender. The authors found that the rate of receiving emergency room or hospital treatment for an injury was significantly higher in children with autism or PDD than in children without autism or PDD (rate ratio (RR) =1.20). The rate of receiving emergency or inpatient care for head, face, and neck injuries was even higher (RR=1.47). Children with autism or PDD had a rate of poisoning and self-inflicted injury that was 7.6 times higher and a rate of sprains and strains that was lower (RR=0.54) than those observed for children without autism.

Despite some similarities, our study is different than the McDermott study in several key ways. First, our study focused on episodes of injury care in any care setting (i.e., inpatient, emergency room, or outpatient), likely capturing less severe injuries than the McDermott study, which only focused on injuries requiring emergency department or hospital admission. In addition, while our study excluded children who had childhood disintegrative disorder or Rett disorder, these were included in the McDermott study within the PDD group (though these probably represent a very small portion of subjects). The McDermott study also excluded from their comparison group children who had a diagnosis code for developmental disability (DD) or mental retardation (MR) while our comparison group represented a random sample of children without ASD in our health plan. Although rates of intellectual disability were low in both samples of children with and without ASD in our study, these conditions were likely underreported in both groups as they relied on clinical data without information from other sources such as schools. Lastly, the McDermott study was able to separate unintentional from intentional injuries – which we did not distinguish from the claims data. Thus, it is unknown whether our findings would differ for self-injury and accidental injuries when considered separately. Finally, the McDermott study only adjusted for age and gender while our study adjusted for, not only subjects' demographic and socioeconomic characteristics, but also some of the key co-occurring behavioral conditions that may be important risk factors of injuries among children. Neither our study nor McDermott's study were able to assess whether certain types of injuries or mechanisms such as injuries resulting from wandering are increased among children with ASD. Furthermore, ASD severity – particularly functional severity – is likely an important determinant of injuries, a variable that was not available in our data.

Overall, injury risk associated with ASD appeared to be age dependent. Analyses exploring injury risk separately by age period indicated that during younger ages (<6 years old), those with ASD were at increased risk for injury compared to those without ASD, while during older ages (>10 years old) those with ASD were at decreased risk of injury compared to those without ASD. We saw approximately 30% higher injury rates in ASD than in the comparison groups at younger ages (<6 years) - but that effect reversed at higher ages (>10 years) where the children with ASD had injury rates approximately 35% lower than comparably aged children without ASD after adjusting for socio-demographic variables and co-occurring conditions. In the U.S., the distribution of injury type (particularly nonfatal injury) is known to vary greatly by age.⁶⁷ Consequently, further investigation of injury risk in children with ASD should focus on distinct age subgroups and consider the varying determinants of different injury types.

VII. Gastrointestinal and Nutritional Conditions

A. Background

Gastrointestinal (GI) and nutritional conditions – broadly defined as including a range of conditions and symptoms such as inflammatory bowel disease, appendicitis, food allergies, heart burn and abdominal pain – are commonly reported in children and can be major causes of morbidity and hospitalization. For instance, in the United States, acute diarrhea alone accounts for more than 1.5 million outpatient visits in children, 200,000 hospitalizations, and approximately 300 deaths per year.⁷⁰ GI conditions and symptoms substantially affect the quality of life of children who experience them^{71,72} and increase the level of parental stress, especially that of maternal caregivers.⁷³ The management of GI conditions and their sequelae usually requires a particular understanding of symptoms in the context of daily life since feeding or eating and bowel and bladder excretion are a part of every child's day and impacts one's ability to function in learning and social environments, independently or with assistance. Caring for a child with a GI or nutritional condition similarly adds to the already substantial effort involved in taking care of a child with ASD.⁷⁴

Clinically, the relationship between GI conditions and ASD is complex and unclear. Many have also speculated that particular foods or gastrointestinal factors may play a role in the etiology or treatment of autism. One study suggested that more frequent GI symptoms in children with autism may have resulted from deficiencies in the enzymatic activity of disaccharides and hexose transporters,⁷⁵ another that the presence of *Sutterella* 16S rNA gene sequences,⁷⁵ and a third that underlying dysregulated innate immune defenses may be the cause.⁷⁶ With few definitive treatments for ASD, the use of alternative diets is a common strategy employed to treat ASD, with anecdotal reports of success, especially among children who exhibit gastrointestinal symptoms but even in those without any clear gastrointestinal manifestations.^{77,83} It has also been reported that intestinal permeability (43% in subjects with ASD vs. 0% in controls) and resulting digestive and immune system-related complications are major contributors of GI problems in autistic patients.⁷⁸ One small study, for example, collected stool samples from 58 children with ASD and 39 healthy children aged 2.5 to 18 years of age.⁷⁹ These authors found that, in terms of beneficial bacteria, children with ASD had 45% lower levels of *Bifidobacterium*, 16% lower levels of *Enterococcus*, and 100% higher levels of *Lactobacillus*. The ASD group was also more likely to have *Bacillus* spp, a commensal or symbiotic bacteria; lower levels of lysozyme, a possible marker of inflammation; and lower total amounts of short chain fatty acids.

Large epidemiologic samples have yet to conclusively demonstrate differences in prevalence of GI conditions between children with and without ASD but smaller observational studies and clinical case series suggest strongly that the management of GI conditions is an important clinical concern in children with ASD.⁸⁰ Several, generally smaller, studies have found significantly higher rates of GI conditions in children with ASD^{81,82} but the prevalence of GI conditions reported in children with ASD has varied greatly among studies (from 17% to 85% in one review),⁸³ partially because the definition of a GI condition has also ranged from broad to specific depending on the study and population of interest. For instance, Ibrahim and colleagues found significant differences between ASD cases and comparison cases when looking at constipation alone (33.9% vs. 17.6%) and food selectivity (24.5% vs. 16.1%).⁸⁴ However, there were no significant differences between the two groups in overall incidence of GI symptoms. Several other studies^{83,85,86,87} similarly found no

association between an ASD diagnosis and GI conditions. Fundamental differences in study design, study setting, study sample, definition of GI conditions and ASD case definitions, and small, non-representative sample sizes may have contributed to the discrepant results in the existing literature.

A study drawing from a large sample of children with ASD from a large medical claims database can contribute significantly to the body of conflicting literature on this topic. To our knowledge, there has not been a large, population-based study using medical claims to study GI conditions among children with ASD. Additionally, we did not locate any studies that sought to determine the occurrence of GI conditions relative to the time of first ASD diagnosis for a child. We sought to answer the following research questions:

1. Compared to children without ASD, do children with ASD have higher odds of having a gastrointestinal condition adjusting for potential covariates?
2. Do the odds of having a gastrointestinal condition vary among key subgroups of children with ASD?
3. Among children with ASD, are the odds of having a gastrointestinal condition different one year after his/her initial ASD diagnosis compared to one year before the initial diagnosis?

B. Methods

1. Variable Definitions

The common outcome variable of interest for all three GI-specific research questions is the overall GI condition variable described in Section V: General Health Conditions and reiterated here.

Gastrointestinal and nutrition conditions. Whether a subject had at least 2 medical claims with a diagnosis code for a gastrointestinal and nutrition condition of interest. To qualify, the diagnosis code could be in any position but the 2 claims for the same condition had to be 30 or more days apart. There was one exception: GI hemorrhage, which as an acute condition, only required 1 medical claim with a diagnosis in any position. One overall dichotomous variable (0/1) was created; patients with evidence of one or more of these conditions were coded as 1, otherwise 0. This variable was calculated for children only, including subjects with and without ASD. In addition to being created for subjects' total enrollment during the study, the variable was created for the period of 12 months continuous enrollment prior to the initial diagnosis of ASD and the period of 12 months continuous enrollment after (and including) the initial diagnosis of ASD for the smaller sample of children with ASD for whom initial ASD diagnosis was been determined. See Appendix A for conditions included and corresponding ICD-9-CM codes.

Our multivariate analyses of GI conditions included a number of covariates. In addition to the demographic, enrollment, and socio-economic variables as described earlier in the report (Section III.D: Variable Definitions) we included autoimmune conditions and seizure disorder in the models (defined in Sections III and VI respectively) as covariates. Seizure was included as one well-reported (in claims data) marker of ASD complexity and autoimmune conditions were considered as a potential confounder between ASD and GI outcomes because they might be etiologically related to both ASD and gastrointestinal conditions and symptoms.

2. Analytical Approach

To address our research questions specific to GI, multivariate analyses were conducted using logistic regression. Three main models were run. The first model included both the samples of children with and without ASD in order to estimate the relative odds of the effect of ASD on GI outcomes while controlling for other variables. The second model included only children with ASD to identify the subgroups with higher odds of GI conditions. The first two models included enrollment time as a covariate to account for the influence varying lengths of enrollment may have on the detection of a GI condition. The third model was fit to the subgroup of children with ASD who met criteria developed to identify those who were initially diagnosed with ASD during the study time frame (see Section III.C.4) and who also had 12 months of continuous enrollment before and after that initial ASD diagnosis (n= 3,772). This model used a generalized estimating equation (GEE) to examine evidence of GI conditions from the 12 months prior to first ASD diagnosis to the 12 months following first ASD diagnosis.

For each model, covariates were included based upon clinical rationale, descriptive analyses, and/or statistical significance. The covariates included in all models were: gender, income, race, region, age at index, seizure condition status, and autoimmune condition status. For each model, regression diagnostics (Likelihood ratio, Hosmer and Lemeshow, and c statistic) were examined to assess goodness-of-fit. The results of these diagnostics are provided with the model results.

As with the injury models, to detect multicollinearity in the GI models, we examined correlations among the variables included in the models as well as variance inflation factors (VIF). All of the correlations and VIF values observed fell below the desired thresholds, indicating little need to be concerned about multicollinearity among our model variables.

C. Results

Table 19 first shows the unadjusted descriptive results for the dependent and independent variables included in the multivariate models for the samples of children with and without ASD. Specifically, the table presents the unadjusted proportion of children who had evidence of a GI condition and of the co-occurring conditions included as covariates. (For descriptive analyses of the demographic variables included in the models, refer back to Table 7 in Section IV.B.1.) As was shown earlier, children with ASD were more likely to have a GI condition and have evidence of seizures during the study time period. A higher proportion of children with ASD also had evidence of an autoimmune condition compared to the sample of children without ASD (10.5% vs. 4.5%).

Table 19. Descriptive Analyses of Model Variables for ASD and Comparison Groups

	ASD (N=33,565)		Comparison (N=138,876)	
	N	%	N	%
Unadjusted Outcome				
GI condition	8,414	25.07	7,599	5.47
Independent Variables				
Autoimmune disorder	3,507	10.45	6,290	4.53
Seizures	2,554	7.61	522	0.38

Note: Results are not adjusted for enrollment time.

To address question #1 above, **Table 20** presents the results of the logistic regression analysis modeling GI conditions among children with and without ASD. After controlling for enrollment time and the other variables included in the model, children with ASD had higher odds of a GI condition than children without ASD (OR=3.94, $p<0.001$).

Separate models were fit including interaction terms between the ASD indicator and each of the following covariates: gender, age, seizure disorder, and autoimmune condition (data not shown). The p-value on the coefficient for each of these terms can be used to test the null hypothesis that the ASD affect is similar across subgroups defined by each of the variables. The p-value on each interaction, except gender, was below 0.05. Consequently, at this sample size where relatively small effects achieve statistical significance fairly easily, the evidence suggests strongly that effect of ASD on GI odds is similar in boys and girls. Stronger ASD effects were seen in subjects without seizure or autoimmune disease, respectively, (OR=4.01 and 4.12) compared to subjects with seizure or autoimmune disease (OR=1.83 and OR=3.07, respectively). Children with ASD had higher odds of a GI condition in all age groups but the odds were highest among children aged 2-10 years at index date (OR= 5.43).

**Table 20. Logistic Regression of Gastrointestinal/
Nutritional Conditions among ASD and Comparison Groups**

Independent Variables	Gastrointestinal/Nutritional Conditions			
	Odds ratio	Lower 95% CI	Upper 95% CI	p-value
Sample				
Comparison	ref.	–	–	–
ASD	3.939	3.788	4.096	<0.001
Gender				
Female	ref.	–	–	–
Male	0.860	0.828	0.894	<0.001
Household Income*				
<\$50,000	ref.	–	–	–
\$50,000 - \$74,999	0.942	0.878	1.011	0.100
\$75,000 - \$99,999	0.985	0.916	1.060	0.684
\$100,000 - \$124,999	0.939	0.867	1.017	0.124
\$125,000 +	0.939	0.862	1.023	0.152
Unknown	0.936	0.870	1.007	0.077
Race/Ethnicity*				
White	ref.	–	–	–
African American/Black	0.739	0.657	0.832	<0.001
Asian	0.801	0.688	0.932	0.004
Hispanic	1.008	0.929	1.095	0.840
Other	1.168	0.982	1.390	0.079
Unknown	0.931	0.880	0.985	0.013
Geographic Region				
South	ref.	–	–	–
Northeast	0.871	0.822	0.922	<0.001
Midwest	0.925	0.887	0.964	<0.001
West	0.931	0.881	0.983	0.011
Age at Index Date (continuous)	0.943	0.940	0.946	<0.001

Independent Variables	Gastrointestinal/Nutritional Conditions			
	Odds ratio	Lower 95% CI	Upper 95% CI	p-value
Seizures	2.170	1.994	2.361	<0.001
Autoimmune Conditions	2.750	2.611	2.896	<0.001
Total Enrollment during Study (quintiles)**				
Lowest quintile	ref.	–	–	–
2nd quintile	1.685	1.546	1.837	<0.001
3rd quintile	2.673	2.469	2.894	<0.001
4th quintile	3.830	3.547	4.135	<0.001
Highest quintile	5.522	5.122	5.953	<0.001

Observations read = 172,441, Observations used= 172,441

Likelihood ratio: chi-square=17964.666, DF=22, p-value=<0.001

Hosmer and Lemeshow: chi-square=117.174, DF=8, p-value=<0.001

c statistic = 0.795

*From merged socioeconomic data.

** Subjects may have had gap(s) in enrollment during this time. Quintiles calculated among combined ASD and comparison groups.

Table 21 presents the results of the logistic regression analysis modeling evidence of GI conditions among children with ASD. The purpose of this analysis was to examine whether the odds of having a GI condition varies among key subgroups of children with ASD (see question #2). After controlling for enrollment time, all of the covariates included in the model were significantly related to having a GI condition among children with ASD. Specifically, girls, younger children, and children with seizures or an autoimmune condition had higher odds of a GI condition. African-American children with ASD were less likely to have evidence of a GI condition than white children with ASD (OR=0.663, p<0.001). Additionally children with ASD living in the Northeast region of the country were less likely to have a GI condition than children with ASD living in the Southern region (OR=0.888, p=0.004).

Table 21. Logistic Regression of Gastrointestinal/ Nutritional Conditions among Children with ASD

Independent Variables	Gastrointestinal/Nutritional Conditions			
	Odds ratio	Lower 95% CI	Upper 95% CI	p-value
Gender				
Female	ref.	–	–	–
Male	0.882	0.826	0.942	<0.001
Household Income*				
<\$50,000	ref.	–	–	–
\$50,000 - \$74,999	0.896	0.804	0.999	0.048
\$75,000 - \$99,999	0.967	0.867	1.079	0.551
\$100,000 - \$124,999	0.978	0.871	1.098	0.711
\$125,000 +	0.949	0.839	1.074	0.408
Unknown	1.016	0.908	1.136	0.781
Race/Ethnicity*				
White	ref.	–	–	–
African American/Black	0.663	0.542	0.812	<0.001
Asian	0.808	0.647	1.009	0.060
Hispanic	0.909	0.795	1.038	0.157
Other	1.045	0.813	1.343	0.731
Unknown	0.877	0.809	0.951	0.002

Independent Variables	Gastrointestinal/Nutritional Conditions			
	Odds ratio	Lower 95% CI	Upper 95% CI	p-value
Geographic Region				
South	ref.	–	–	–
Northeast	0.888	0.820	0.962	0.004
Midwest	1.001	0.941	1.065	0.974
West	1.031	0.950	1.120	0.465
Age at Index Date (continuous)	0.951	0.946	0.956	<0.001
Seizures	1.958	1.791	2.140	<0.001
Autoimmune Conditions	2.465	2.287	2.657	<0.001
Total Enrollment during Study (quintiles)**				
Lowest quintile	ref.	–	–	–
2nd quintile	1.617	1.468	1.782	<0.001
3rd quintile	2.190	1.993	2.405	<0.001
4th quintile	2.780	2.534	3.049	<0.001
Highest quintile	3.368	3.071	3.694	<0.001

Observations read = 33,565, Observations used= 33,565

Likelihood ratio: chi-square=2712.191, DF=21, p-value=<0.001

Hosmer and Lemeshow: chi-square=17.047, DF=8, p-value=0.030

c statistic = 0.681

*From merged socioeconomic data.

**Subjects may have had gap(s) in enrollment during this time. Quintiles calculated among combined ASD group.

The last set of results presented in this section pertains to our third research question: among children initially diagnosed with ASD, are the odds of having a GI condition different before and after diagnosis? As mentioned above, these analyses were restricted to the 3,772 ASD group children meeting our criteria for being initially diagnosed with ASD during our study time frame (see Table 2 in Section III.C.4) and who also had continuous enrollment both 12 months prior to and 12 months following their initial ASD diagnosis.

Table 22 provides the unadjusted descriptive results for the dependent and independent variables included in the multivariate analysis for this subgroup. Specifically, the table presents the unadjusted proportion of children who had evidence of a GI condition before and after their initial diagnosis and the distributions of demographic variables included as covariates.

Table 22. Descriptive Analyses of Model Variables for Initially Diagnosed ASD Children

Characteristic	Initially Diagnosed ASD Children* (N=3,772)	
	n	%
GI Condition		
Before Initial Diagnosis	831	22.03
After Initial Diagnosis	1,064	28.21
Gender		
Male	3,098	82.13
Female	674	17.87
Geographic Region		
Northeast	563	14.93
Midwest	1,220	32.34
South	1,449	38.41
West	540	14.32
Race/Ethnicity**		
White	1,957	51.88
African American/Black	75	1.99
Asian	75	1.99
Hispanic	155	4.11
Other	44	1.17
Unknown	1,466	38.87
Household Income**		
<\$50,000	304	8.06
\$50,000 - \$74,999	512	13.57
\$75,000 - \$99,999	606	16.07
\$100,000 - \$124,999	460	12.20
\$125,000 +	389	10.31
Unknown	1,501	39.79
Age Group at Index Date		
0-1 years	2,204	58.43
2-10 years	1,568	41.57
11-17 years	0	0.00
18-20 years	0	0.00
	mean	SD
Age at Index Date (continuous)	1.73	2.05

*Must have continuous enrollment 12 months prior to and after diagnosis date.

Based on simultaneous medical, pharmacy and behavioral health coverage.

**From merged socioeconomic data.

Table 23 presents the results for the logistic model generalized estimated equation (GEE). After controlling for the various covariates, and accounting for the non-independence of the paired observations when estimating standard errors, the odds of having a GI condition were 40% higher in the 12 month period following, compared to the 12 month period before, a child's initial ASD diagnosis (OR = 1.397, $p < 0.001$).

**Table 23. Logistic GEE of Gastrointestinal/
Nutritional Conditions among Children Initially Diagnosed with ASD**

Independent Variables	Gastrointestinal/Nutritional Conditions			
	Odds ratio	Lower 95% CI	Upper 95% CI	p-value
Gender				
Female	ref.	–	–	–
Male	0.884	0.756	1.033	0.120
Household Income*				
<\$50,000	ref.	–	–	–
\$50,000 - \$74,999	1.039	0.789	1.369	0.785
\$75,000 - \$99,999	1.031	0.789	1.349	0.821
\$100,000 - \$124,999	1.098	0.832	1.450	0.508
\$125,000 +	1.084	0.810	1.451	0.587
Unknown	1.046	0.791	1.383	0.752
Race/Ethnicity*				
White	ref.	–	–	–
African American/Black	0.451	0.248	0.820	0.009
Asian	0.953	0.636	1.428	0.815
Hispanic	0.787	0.585	1.060	0.115
Other	1.584	0.937	2.676	0.086
Unknown	1.054	0.869	1.278	0.594
Geographic Region				
South	ref.	–	–	–
Northeast	0.822	0.681	0.992	0.041
Midwest	0.980	0.850	1.128	0.774
West	0.991	0.828	1.186	0.924
Age at Index Date (continuous)	0.905	0.880	0.930	<0.001
Window of Observation				
12 months prior to initial ASD diagnosis	ref.	–	–	–
12 months following initial ASD diagnosis	1.397	1.275	1.531	<0.001

Observations read = 7,544, Observations used= 7,544. Two observations per subject (one for the pre-diagnosis period, another for the post diagnosis period) were included in the analysis.

*From merged socioeconomic data.

D. Discussion

We set out to answer three research questions about the association of ASD and GI conditions: first, we compared the odds of having a GI condition between children with ASD and children without ASD controlling for demographic and socio-economic characteristics; second, we examined whether the odds of having a GI condition varied among key subgroups of children with ASD; and finally, we examined whether the odds of having a GI condition differed prior to vs. following an initial diagnosis of ASD. Taking advantage of detailed diagnosis information contained in medical claims data, we were able to consider a wide range of GI conditions (see Appendix A for a complete list of these conditions) including conditions beyond those typically included in previous studies.^{81,84} Considering the great deal of interest in, and confusion about, the relationship between GI and nutritional conditions and ASD, our study sought to build on past studies.

In our analysis, we found that, after controlling for enrollment time and other potential confounders, children with ASD had substantially higher odds of a GI condition than children without ASD (OR=3.94, $p<0.001$). GI conditions, especially since the range here unlike in other studies include a number of more common, symptom-defined conditions (such as, for example, constipation and diarrhea), could be vulnerable to surveillance bias associated with the increased health system contact frequency seen among children with ASD diagnoses. However, after further adjustment for a variable that tallied the number of preventive health care visits as a proxy measure for extent of medical surveillance (data not shown) the ASD affect estimate, at OR= 3.74, was virtually unchanged.

The effect of ASD on the odds of having a GI condition was modified by age. The presence of either a seizure or autoimmune condition reduced the ASD effect, although the ORs were still above 1.0 in the groups with seizure or autoimmune condition. This suggests that ASD's effect on GI is not strictly limited to children with autoimmune or seizure conditions. Among children with ASD, girls, younger children, and children with seizures or an autoimmune condition had increased odds of a GI condition, findings potentially of interest to clinicians following children with ASD.

We also found that the odds of a GI condition were higher following, compared to the 12 months before, the child's initial ASD diagnosis (OR = 1.40, $p<0.001$). This odds ratio is smaller than what we found when comparing children with ASD to those without ASD, suggesting that the GI involvement may occur simultaneously with, as opposed to following, the emergence of ASD symptoms.

A study by Smith found that the rate of treatment for bowel symptoms was 24% among children with ASD and only 5% among typically developing children.⁸⁷ Valicenti-McDermott conducted health interviews in 2006 comparing 50 children with ASD with a control group of 50 typically developing children and with another control group of 50 children with other developmental disabilities.⁸² This study found that the adjusted odds ratio of having GI symptoms associated with ASD was 3.8 (95% confidence interval 1.7 - 11.2) relative to the typically developing reference group and 1.3 (0.5 - 3.6) relative to children with other developmental disabilities. In addition, abnormal stool pattern was found to be more common among children with ASD as compared to the control group (18% vs. 4%). Using information from medical records, a study by Ibrahim reported significant differences between autism case and control subjects in the cumulative incidence of constipation (33.9% vs. 17.6%) and feeding issues/food selectivity (24.5% vs. 16.1%).⁸⁴ These estimates are comparable to other literature, as shown in Table 14 in Section V.E.1., that found the prevalence of food selectivity, bowel disorders, and constipation could be found in as many as 90%, 12%, and 59% of children with ASD, respectively.

Another study based on the National Survey for Children's Health found that autism and food allergies had the strongest association (OR= 4.5).³⁵ An earlier study by Horvath reported higher prevalence of reflux esophagitis, chronic inflammation of the gastric mucosa, and chronic nonspecific duodenal inflammation; decreased activity of one or more disaccharides or glucoamylase; and low lactase level, loose stools and/or gaseousness among 36 autistic children aged 3-7 as compared to 22 control children.⁸¹ In addition to the overall association between autism and GI symptoms, there is also some evidence that GI symptoms correlate strongly with the severity of autism.^{79, 88} Specifically, Wang showed that having "Full Autism" (OR: 14.28) or

“Almost Autism” (OR: 5.16) was most highly associated with experiencing GI problems after adjusting for confounders in a conditional logistic regression.⁸⁸

While there is some evidence that ASD may be associated with higher risk of having certain types of GI symptoms, other studies did not find a positive association between GI conditions and ASD. The Ibrahim study, for instance, did not find significant associations between autism case status and overall incidence of gastrointestinal symptoms or any other gastrointestinal symptom category beyond constipation and feeding issues/food selectivity.⁸⁴ The study by Adams and colleagues reported that the overall intestinal health (indicated by the presence of red blood cells or occult blood, fecal pH) was not different between children with ASD and a control group of healthy children.⁷⁹ Furthermore, a longitudinal study in Denmark found no evidence that patients with infantile autism were more likely than control persons without autism to have defined GI diseases (e.g. heartburn; gastritis; abdominal pain; bloating; food intolerance; chronic constipation; diarrhea, reflux esophagitis, etc.) during a 30.3- year observation.⁸⁶

Only a few studies examined the timing of GI problems among children with ASD. One study by Black and colleagues concluded that children with autism were no more likely than children without autism to have had gastrointestinal conditions at any time before the diagnosis, although this study did not investigate the presence of GI conditions post diagnosis.⁸⁷

Using claims data for a very large cohort of US children with ASD, we find evidence that children with ASD are more likely to have a GI condition compared to children without ASD. Our attempts to control for surveillance bias did not change the effect estimates at all. While our data suggested higher frequency of evidence of GI after an initial ASD diagnosis was recorded, this may be a byproduct of increased surveillance post ASD recognition. Our findings underscore the notion that, in the community, children with ASD are more frequently recognized with, and presumably treated for, GI conditions. This strongly supports the need for further research into the relationship between ASD and the gastrointestinal system. Since children with ASD are such a heterogeneous group, clarifying unique risk factors for GI sequale among children with ASD could be a fruitful further line of research. We note, for example, that while girls with ASD had greater odds of GI conditions, gender did not modify the ASD effect, suggesting that the ASD has the same relative effect on the odds of having GI in girls (who begin with higher baseline risk of GI conditions in the population) than boys. The co-occurring conditions we explored (seizures and autoimmune conditions) were not synergistic with ASD on GI occurrence odds (in fact the ASD effect was lower in these groups). Finding co-occurring conditions or other phenotypic or behavioral markers that identify ASD cases at especially high risk for GI condition should remain a research priority.

VIII. Parental Stress

A. Background

Parents and caregivers of children with developmental disorders and/or intellectual disabilities such as developmental delays, Down syndrome, autism, and cerebral palsy have been found to be at increased risk for stress and stress-related conditions.^{89,90} In particular, being the parent or caregiver of someone with behavioral problems, low cognitive functioning, and/or learning disabilities has been shown to be very stressful.⁹¹

As stress is often subjective and its expression takes many forms, the accurate evaluation and classification of the health effects of stress can be challenging for physicians. However, there is evidence that chronic stress results in psychological impairment over time and can result in greater severity of mental health conditions such as anxiety and depression.⁹² Such psychological conditions have, in turn, been found to contribute to a weakened immune system,⁹³ which is itself associated with physical symptoms such as chronic pain and sleep disorders.^{94,95} Despite the studies that suggest various relationships and mechanisms, there has been little certainty about the ways that stress, the timing of stress, and the different types of stress impact mental and physical health among parents and caregivers of children with developmental disabilities such as ASD.

Several studies^{100,101,102} reported higher levels of stress-related conditions (depression, anxiety, psychological stress) and lower overall mental well-being among parents (particularly among mothers) of children with ASD based on standardized instruments such as The Parenting Stress Index Short Form (PSI/SF) and the Center for Epidemiologic Studies Depression Inventory (CES-D). While few studies have examined stress levels among fathers of children with ASD, an Italian study showed that mothers and fathers of children with PDD had statistically significantly lower mean scores in the domains of social relationships and mental health, indicating a poorer quality of life than a comparison group without affected children.⁹⁶ Another study assessing frequency of depressed moods and feelings based on the CES-D instrument found that the mean score for mothers of children newly diagnosed with autism or PDD NOS (n=54) was higher (13.4) than the mean score (10.1) for fathers of these children, indicating poorer well-being among mothers compared to fathers.⁹⁷

Except for a few studies that examined stress levels following a new ASD diagnosis^{97,98} the literature does not assess changes – increases or decreases – in stress among parents of children diagnosed with ASD. Having a child diagnosed with a developmental disorder is certainly stressful. However, compared to the stress of an uncertain diagnosis and without the opportunity for improvement from interventions targeted toward a particular diagnosis, we wondered if and how parental stress and stress-related conditions might change with diagnostic confirmation. Therefore, in addition to investigating the general association of ASD and stress-related conditions among parents, we sought to answer the following specific research questions:

1. Compared to parents of children without ASD, do parents of children with ASD have higher odds of having a stress-related condition adjusting for potential covariates?
2. Do the odds of having a stress-related condition vary among key subgroups of parents of children with ASD?

3. Among parents of children with ASD, are the odds of having a stress-related condition different one year following his/her child's initial ASD diagnosis compared to one year before the initial diagnosis? Does the extent of stress-related conditions, as measured by stress-related health care costs, change following his/her child's initial ASD diagnosis?

B. Methods

3. Variable Definitions

The common outcome variable of interest for all three research questions is our overall measure of stress-related conditions described earlier in Section V: General Health Conditions and reiterated here. Stress-related costs were also examined to address our third research question.

- **Stress-related conditions.** Whether a subject had at least 2 or more medical claims with a diagnosis code for a mood/anxiety disorder; sleep disorder; somatoform and psychological pain syndromes; substance-related disorder; physical condition with stress-related triggers; and other stress-related conditions. To qualify, the diagnosis code could be in any position but the 2 claims for the same condition had to be 30 or more days apart.²⁴ For each of these categories, a dichotomous variable (0/1) was created; individuals with evidence of one or more of the relevant conditions were coded as 1, otherwise 0. Additionally, one overall dichotomous variable was created to summarize across subtypes as to whether a subject had evidence of any stress-related condition. This outcome was measured only for parents of children with and without ASD. For parents of children with ASD, indicator variables for stress conditions were created for the period of 12 months continuous enrollment prior to his/her child's initial diagnosis of ASD and the period of 12 months continuous enrollment after (and including) his/her child's initial diagnosis of ASD. See Appendix A for conditions included and corresponding ICD-9-CM codes.
- **Costs of stress-related conditions.** For parents of children with ASD, stress disorder-related costs were totaled for the period of 12 months continuous enrollment prior to his/her child's initial diagnosis of ASD and the period of 12 months continuous enrollment after (and including) his/her child's initial diagnosis of ASD. Calculated costs included combined health plan and patient paid amounts for all claims with a diagnosis code for stress-related conditions in any position²⁵ (see Appendix A). All costs were adjusted using the annual medical care component of the Consumer Price Index (CPI) to reflect inflation between 2001 and 2009.⁹⁹ Additionally, costs were calculated for each of the stress condition subtype categories (e.g., mood/anxiety disorder; sleep disorder).

In addition to the demographic, enrollment, and socio-economic covariates described earlier in the report (Section III.D Variable Definitions), in the multivariate analysis for stress-related conditions,

²⁴ For sleep disorders, asthma, hypertension, irritable bowel syndrome, and migraine/headaches, one claim with a relevant diagnosis code and one claim for a medication (see separate file of select medications) will also count as evidence. For sleep disorders, 2 claims for insomnia medication 30 days apart will also count for this type of stress related condition. The medications to be considered are being compiled in a separate file. Also note other exception for stress-related conditions: For constipation, only 1 dx in any position will count as evidence of this condition.

²⁵ Claims for medications used to identify sleep disorders (and any other condition within this category) were also included in the calculation. The medications to be considered are compiled in Appendix A.

we also included parent and child comorbidity scores as covariates as child comorbidity may be associated with stress levels among parents of children both with and without ASD.

4. Analytical Approach

To address our stress-related research questions, multivariate analyses were conducted using logistic regression (binary indicator of stress-related conditions) and a generalized linear model with a log link and gamma distribution (stress-related costs). Three main models were run. The first model, a logistic regression, included both the samples of parents of children with ASD and parents of children without ASD so that the odds of a stress-related condition could be compared between the two parent samples while controlling for other variables. The second model, also a logistic regression, focused only on parents of children with ASD to identify subgroups of these parents who have higher odds of stress-related conditions. These logistic regression models included enrollment time as a covariate to account for varying lengths of enrollment. Effect estimates are odds ratios estimating the relative difference in odds of stress outcomes. Finally, a third set of models used a generalized estimating equation (GEE) approach to examine stress-related conditions and stress-related costs in the 12 months prior to and 12 months following initial diagnosis among parents of children identified to be initially diagnosed with ASD during the study (see Section III.C.4). The cost model technically estimated the difference in logged total costs between samples. Therefore, for ease of interpretation, all coefficients were exponentiated and model coefficients were converted to ratios, which we refer to as “cost ratios.” Because the statistical software used in the analysis (SAS) drops subjects with \$0.00 costs in the GEE cost model, subjects with a total of \$0.00 stress-related costs were recoded to \$0.01 so that they were retained in the model.²⁶

For each model, specific independent variables were finalized based upon clinical rationale, descriptive analyses, and/or statistical significance. Both parent-specific and child-related variables were considered in the models. Specifically, parent gender, age, household income, race/ethnicity, region, number of children²⁷, and comorbidity score were included; also included were the age of the youngest child and the highest comorbidity score among the sampled parent’s children with ASD for ASD parents and among the sampled parents’ children without ASD for the comparison parents. The models also controlled for parents’ length of enrollment time in the study. For each logistic model, regression diagnostics (Likelihood ratio, Hosmer and Lemeshow, and c statistic) were examined to assess goodness-of-fit. The results of these diagnostics are provided with the model results.

As with the earlier multivariate models, to detect multicollinearity in the GI models, we examined correlations among the variables included in the models as well as variance inflation factors (VIF). All of the correlations and VIF values observed fell below the desired thresholds, indicating little need to be concerned about multicollinearity among our model variables.

²⁶ The model was also run in a parameterization that included \$0.00. The results from that model were consistent with the results presented in this report.

²⁷ The number of children associated with a parent included the number of child(ren) with or without ASD as well as siblings of that/those child(ren).

C. Results

Table 24 first shows the unadjusted descriptive results for the dependent and independent variables included in the multivariate models for the parent samples. In particular, the table presents the unadjusted proportion of parents who had evidence of a stress-related condition during the study and their mean stress-related health care costs. As was shown earlier in Section V: General Health Conditions, the proportion of parents of children with ASD with a stress-related condition was higher than that observed for parents of children without ASD, and this result is reiterated by stress-related costs as well. Table 24 also presents parents' mean number of children, a covariate included in the models. For descriptive analyses of the other demographic variables included in the models, refer back to Table 8 in Section IV: Sample Identification and Demographic Results.

Table 24. Descriptive Analyses of Model Variables for ASD and Comparison Group Parents

Unadjusted Outcomes	ASD Parents (N=58,757)		Comparison Parents (N=232,229)	
	N	%	N	%
Stress-related conditions*	34,181	58.17	97,594	42.02
	Mean	SD	Mean	SD
Stress-related health care costs (\$)	89.84	328.94	57.85	319.44
Independent Variables	Mean	SD	Mean	SD
Number of children	2.39	1.14	2.51	1.22

*Results are not adjusted for enrollment time.

To address question #1 above, **Table 25** presents the results of the logistic regression modeling the occurrence of any stress-related conditions among ASD and comparison group parents. After controlling for parent enrollment time and the other variables included in the model, parents of children with ASD had higher odds of a stress-related condition than parents of children without ASD (OR=1.48, $p<0.001$). A separate model was generated to examine a possible interaction between the ASD effect and parent gender (data not shown). This interaction term was found to be statistically significant at the conventional alpha error threshold ($p<0.001$) and the gender-specific ASD effect estimates derived from this model were 1.65 for mothers and 1.32 for fathers.

Table 25. Logistic Regression of Stress-related Conditions among ASD and Comparison Group Parents

Independent Variables	Stress-related Conditions			
	Odds ratio	Lower 95% CI	Upper 95% CI	p-value
Parent Sample				
Comparison	ref.	–	–	–
ASD	1.482	1.451	1.515	<0.001
Parent Gender				
Female	ref.	–	–	–
Male	0.646	0.635	0.657	<0.001

Independent Variables	Stress-related Conditions			
	Odds ratio	Lower 95% CI	Upper 95% CI	p-value
Parent Household Income*				
<\$50,000	ref.	–	–	–
\$50,000 - \$74,999	1.003	0.973	1.034	0.847
\$75,000 - \$99,999	0.938	0.908	0.969	<0.001
\$100,000 - \$124,999	0.908	0.876	0.940	<0.001
\$125,000 +	0.874	0.841	0.909	<0.001
Unknown	0.931	0.899	0.963	<0.001
Parent Race/Ethnicity*				
White	ref.	–	–	–
African American/Black	0.889	0.845	0.935	<0.001
Asian	0.595	0.559	0.635	<0.001
Hispanic	0.793	0.764	0.822	<0.001
Other	0.718	0.662	0.780	<0.001
Unknown	0.847	0.824	0.871	<0.001
Parent Geographic Region				
South	ref.	–	–	–
Northeast	0.888	0.864	0.913	<0.001
Midwest	0.923	0.905	0.941	<0.001
West	0.963	0.939	0.988	0.004
Parent Quan-Charlson Comorbidity Score (categorical)				
0	ref.	–	–	–
1	4.842	4.728	4.958	<0.001
2	5.031	4.822	5.249	<0.001
3+	9.632	9.020	10.286	<0.001
Parent Age at Index Date (continuous)	1.019	1.017	1.020	<0.001
Number of Children (continuous)***	0.989	0.982	0.996	0.001
Child's Age at Index**	1.012	1.010	1.014	<0.001
Child's Comorbidity Score (categorical)****				
0	ref.	–	–	–
1	1.250	1.223	1.277	<0.001
2	1.279	1.230	1.331	<0.001
Parent Total Enrollment during Study (quintiles)*****				
Lowest quintile	ref.	–	–	–
2nd quintile	1.722	1.675	1.769	<0.001
3rd quintile	2.515	2.446	2.586	<0.001
4th quintile	3.552	3.455	3.653	<0.001
Highest quintile	5.663	5.500	5.831	<0.001

Observations read = 290,986, Observations used= 290,986

Likelihood ratio: chi-square=70758.848, DF=27, p-value=<0.001

Hosmer and Lemeshow: chi-square=117.711, DF=8, p-value=<0.001

c statistic = 0.772

*From merged socioeconomic data.

**The youngest child's age was retained where multiple related children exist.

***Includes both index children and siblings of index children

****The largest score was retained where multiple related children exist.

***** Subjects may have had gap(s) in enrollment during this time. Quintiles calculated among combined ASD and comparison groups.

Table 26 presents the results of the logistic regression modeling stress-related conditions among the parents with ASD. The purpose of this analysis was to examine whether the odds of stress-related conditions varies among key subgroups of parents of children with ASD (see question #2). After controlling for parents' enrollment time, parent gender, parent race/ethnicity, parent age and parent comorbidity were all significantly related to having a stress-related condition among parents with children with ASD. Specifically, mothers (compared to fathers), white parents, older parents, and parents with more comorbidity themselves had higher odds of a stress-related condition. Additionally, child age at index and child comorbidity score were significantly related to the presence of a stress-related condition among parents of children with ASD; parents of older children and parents of children with higher comorbidity had higher odds of a stress-related condition. The size of the gender effect was quite large, as were comorbidity effects. Parent and child age each was associated with increased odds of parent stress outcomes – a 5-year age increase in either parent or child age corresponding approximately to 10% increased odds.

For parents of children with ASD, separate logistic regression models were also run on two subtypes of stress-related conditions: mood/anxiety disorders and sleep disorders (Results shown in Appendix C). The purpose of this analysis was to examine whether the odds of these particular subtypes of stress-related conditions vary among key subgroups of parents of children with ASD and whether the results for the stress subtypes differ from stress-related conditions overall. Despite a few differences, the results proved to be similar to the overall model for stress-related conditions. After controlling for parents' enrollment time, parent gender, parent race/ethnicity, and parent comorbidity were all significantly related to having a mood/anxiety and sleep disorder among parents with children with ASD. Specifically, mothers (compared to fathers), white parents, and parents with more comorbidity had higher odds of both stress-related conditions. Additionally, child age at index and child comorbidity score were significantly related to these two subtypes of stress-related conditions among parents of children with ASD: parents of older children and parents of children with the highest comorbidity score were more likely to have a mood/anxiety disorder or sleep disorder. While parent and child comorbidity were still significant predictors for these subtypes of stress conditions, the effects were not as dramatic as those observed in the overall stress model (Table 26). There may be other specific stress conditions for which comorbidity effects are particularly high, suggesting that more analysis on subtypes of stress-related conditions may be helpful.

Table 26. Logistic Regression of Stress-related Conditions among ASD Parents

Independent Variables	Stress-related Conditions			
	Odds ratio	Lower 95% CI	Upper 95% CI	p-value
Parent Gender				
Female	ref.	–	–	–
Male	0.549	0.528	0.569	<0.001
Parent Household Income*				
<\$50,000	ref.	–	–	–
\$50,000 - \$74,999	0.969	0.902	1.040	0.383
\$75,000 - \$99,999	0.955	0.888	1.027	0.211
\$100,000 - \$124,999	0.924	0.856	0.998	0.044
\$125,000 +	0.880	0.810	0.956	0.002
Unknown	0.876	0.810	0.948	<0.001

Independent Variables	Stress-related Conditions			
	Odds ratio	Lower 95% CI	Upper 95% CI	p-value
Parent Race/Ethnicity*				
White	ref.	–	–	–
African American/Black	0.827	0.726	0.942	0.004
Asian	0.625	0.544	0.718	<0.001
Hispanic	0.783	0.716	0.856	<0.001
Other	0.712	0.605	0.839	<0.001
Unknown	0.896	0.844	0.950	<0.001
Parent Geographic Region				
South	ref.	–	–	–
Northeast	0.933	0.882	0.987	0.015
Midwest	1.003	0.959	1.048	0.908
West	1.032	0.973	1.094	0.295
Parent Quan-Charlson Comorbidity Score (categorical)				
0	ref.	–	–	–
1	4.406	4.180	4.645	<0.001
2	4.865	4.434	5.338	<0.001
3+	9.074	7.865	10.469	<0.001
Parent Age at Index Date (continuous)	1.019	1.016	1.022	<0.001
Number of Children (continuous)***	0.999	0.983	1.016	0.918
Child's Age at Index**	1.016	1.012	1.021	<0.001
Child's Comorbidity Score (categorical)****				
0	ref.	–	–	–
1	1.138	1.091	1.187	<0.001
2	1.214	1.150	1.281	<0.001
Parent Total Enrollment during Study (quintiles)*****				
Lowest quintile	ref.	–	–	–
2nd quintile	1.727	1.613	1.850	<0.001
3rd quintile	2.500	2.334	2.676	<0.001
4th quintile	3.389	3.169	3.624	<0.001
Highest quintile	5.362	5.007	5.743	<0.001

Observations read = 58,757, Observations used= 58,757

Likelihood ratio: chi-square=12527.393, DF=26, p-value=<0.001

Hosmer and Lemeshow: chi-square=5.121, DF=8, p-value=0.745

c statistic = 0.758

*From merged socioeconomic data.

**The youngest child's age was retained where multiple related children exist.

***Includes both index children and siblings of index children

****The largest score was retained where multiple related children exist.

*****Subjects may have had gap(s) in enrollment during this time. Quintiles calculated among combined ASD and comparison groups.

The remaining results presented in this section pertain to our third research question, whether, among parents of children with ASD, the odds of having a stress-related condition and health care costs associated with stress-related conditions are different after their child's ASD diagnosis compared to before. To conduct these analyses, we focused on the parents of the children we

identified as being initially diagnosed with ASD during our study (see description in Section III.C) and further limited the analyses to parents and children in this subgroup who had continuous health plan enrollment 12 months prior to their initial diagnosis and 12 months following diagnosis. Of the 5,932 children within the subgroup of children initially diagnosed with ASD, 3,772 children and 6,488 parents met these enrollment requirements. **Table 27** provides the unadjusted descriptive results for the dependent and independent variables included in the multivariate analysis for this subgroup of parents. Specifically, the table presents the unadjusted proportion of parents who had evidence of a stress-related condition as well as the mean stress-related health care costs before and after their child's initial diagnosis. The table also provides the distribution of demographic variables included as covariates. Overall, a higher proportion of parents had a stress-related condition following their child's initial ASD diagnosis (28.2% vs. 22.0%), and likewise, their mean stress-related costs were higher after diagnosis (\$3,188 vs. \$2,613). Median stress-related costs among parents were \$309.94 and \$511.67 pre- and post-diagnosis, respectively (data not shown).

Table 27. Descriptive Analyses of Model Variables for Parents of Initially Diagnosed ASD Children

	Parents* of Initially Diagnosed ASD Children (N=6,488)	
	n	%
Stress-Related Condition		
Before Initial Diagnosis	831	22.03
After Initial Diagnosis	1,064	28.21
	Mean	SD
Stress-Related Costs (\$)		
Before Initial Diagnosis	2613.36	10801.35
After Initial Diagnosis	3187.67	9343.20
	N	%
Parent Gender		
Female	3,289	50.69
Male	3,199	49.31
Parent Household Income**		
<\$50,000	635	9.79
\$50,000 - \$74,999	1,187	18.30
\$75,000 - \$99,999	1,315	20.27
\$100,000 - \$124,999	1,041	16.05
\$125,000 +	881	13.58
Unknown	1,429	22.03
Parent Race/Ethnicity**		
White	4,220	65.04
African American/Black	149	2.30
Asian	180	2.77
Hispanic	347	5.35
Other	128	1.97
Unknown	1,464	22.56

	Parents* of Initially Diagnosed ASD Children (N=6,488)	
Parent Geographic Region		
South	2,450	37.76
Northeast	1,024	15.78
Midwest	2,093	32.26
West	921	14.20
Parent Quan-Charlson Comorbidity Score (categorical)		
0	4,120	63.50
1	1,535	23.66
2	506	7.80
3+	327	5.04
Child's Comorbidity Score (categorical)*****		
0	2,843	43.82
1	1,998	30.80
2	1,647	25.39
Child's Gender		
All Males	5,308	81.81
All Females	1,065	16.41
At Least One Male and At Least One Female	115	1.77
Child's Age Group at Index Date***		
0-1 years	0	0.00
2-10 years	6,368	98.15
11-17 years	120	1.85
18-20 years	0	0.00
Parent Age Group at Index Date		
<18 years	8	0.12
18-21 years	66	1.02
22-29 years	1,382	21.30
30-49 years	4,987	76.86
50-64 years	45	0.69
65+ years	0	0.00
	mean	SD
Parent Age at Index Date (continuous)	33.99	5.84
Number of Children (continuous)****	2.33	1.08
Child's Age at Index***	4.46	2.46

*Must have continuous enrollment 12 months prior to and after diagnosis date.

Based on simultaneous medical, pharmacy and behavioral health coverage.

**From merged socioeconomic data.

***The youngest child's age was retained where multiple related children exist.

****Includes both index children and siblings of index children.

*****The largest score was retained where multiple related children exist.

To examine whether the odds of stress-related conditions were different for parents before or after a child's initial ASD diagnosis, **Tables 28 and 29** present the results for parents of children initially diagnosed with ASD using data from 12 months prior to the child's initial diagnosis to 12 months following this diagnosis. Table 28 is based on the binary outcome of evidence of stress-

related conditions, and Table 29 is based on stress-related costs. After controlling for the same parent and child variables included in the models above, both the odds of a stress-related condition and costs associated with stress-related conditions were higher following diagnosis compared to prior to their child's initial ASD diagnosis (OR = 1.322, $p < 0.001$; Cost ratio = 1.246, $p < 0.001$, respectively).

Table 28. Logistic GEE of Stress-related Conditions among Parents of Children Initially Diagnosed with ASD

Independent Variables	Stress-related Conditions			
	Odds ratio	Lower 95% CI	Upper 95% CI	p-value
Parent Gender				
Female	ref.	–	–	–
Male	0.589	0.541	0.642	<0.001
Parent Household Income*				
<\$50,000	ref.	–	–	–
\$50,000 - \$74,999	0.950	0.804	1.123	0.549
\$75,000 - \$99,999	0.990	0.837	1.169	0.902
\$100,000 - \$124,999	0.941	0.790	1.121	0.497
\$125,000 +	0.902	0.748	1.087	0.277
Unknown	0.877	0.729	1.056	0.166
Parent Race/Ethnicity*				
White	ref.	–	–	–
African American/Black	0.668	0.500	0.892	0.006
Asian	0.724	0.552	0.950	0.020
Hispanic	0.778	0.644	0.941	0.010
Other	0.934	0.677	1.288	0.676
Unknown	0.858	0.753	0.979	0.023
Parent Geographic Region				
South	ref.	–	–	–
Northeast	0.983	0.863	1.120	0.799
Midwest	0.988	0.892	1.094	0.815
West	1.013	0.884	1.161	0.849
Parent Age at Index Date (continuous)	1.013	1.005	1.022	0.001
Parent Quan-Charlson Comorbidity Score (categorical)				
0	ref.	–	–	–
1	4.190	3.767	4.660	<0.001
2	5.094	4.153	6.249	<0.001
3+	6.210	4.603	8.378	<0.001
Number of Children (continuous)***	0.963	0.927	1.001	0.059
Child's age at index**	1.037	1.018	1.056	<0.001
Child's Comorbidity Score (categorical)****	1.255	1.152	1.368	<0.001
0	ref.	–	–	–
1	1.255	1.152	1.368	<0.001
2	1.392	1.246	1.555	<0.001
Window of Observation				
12 months prior to initial ASD diagnosis	ref.	–	–	–
12 months following initial ASD diagnosis	1.322	1.245	1.403	<0.001

Observations read = 12,976, Observations used= 12,976. Two observations per subject (one for the pre-diagnosis period, another for the post diagnosis period) were included in the analysis.

*From merged socioeconomic data.

**The youngest child's age was retained where multiple related children exist.

***Includes both index children and siblings of index children.

****The largest score was retained where multiple related children exist..

Table 29. GLM (Gamma Family, Log Link) GEE of Stress-related Costs among Parents of Children Initially Diagnosed with ASD

Independent Variables	Stress-related Costs			
	Cost ratio	Lower 95% CI	Upper 95% CI	p-value
Parent Gender				
Female	ref.	–	–	–
Male	0.551	0.495	0.613	<0.001
Parent Household Income*				
<\$50,000	ref.	–	–	–
\$50,000 - \$74,999	0.764	0.619	0.944	0.013
\$75,000 - \$99,999	0.869	0.696	1.086	0.218
\$100,000 - \$124,999	0.982	0.759	1.270	0.888
\$125,000 +	0.965	0.763	1.220	0.767
Unknown	0.899	0.706	1.144	0.385
Parent Race/Ethnicity*				
White	ref.	–	–	–
African American/Black	0.606	0.431	0.853	0.004
Asian	0.878	0.679	1.135	0.320
Hispanic	0.647	0.530	0.789	<0.001
Other	0.726	0.518	1.018	0.063
Unknown	0.842	0.717	0.990	0.037
Parent Geographic Region				
South	ref.	–	–	–
Northeast	0.997	0.853	1.166	0.974
Midwest	1.117	0.980	1.274	0.098
West	1.018	0.868	1.193	0.830
Parent Age at Index Date (continuous)	1.007	0.997	1.017	0.187
Parent Quan-Charlson Comorbidity Score (categorical)				
0	ref.	–	–	–
1	2.619	2.338	2.934	<0.001
2	5.020	4.174	6.038	<0.001
3+	8.378	6.023	11.653	<0.001
Number of Children (continuous)***	0.963	0.920	1.008	0.108
Child's age at index**	1.050	1.028	1.071	<0.001
Child's Comorbidity Score (categorical)****				
0	ref.	–	–	–
1	1.364	1.196	1.556	<0.001
2	1.305	1.154	1.477	<0.001
Window of Observation				
12 months prior to initial ASD diagnosis	ref.	–	–	–
12 months following initial ASD diagnosis	1.246	1.141	1.362	<0.001

Observations read = 12,976, Observations used= 12,976. Two observations per subject (one for the pre-diagnosis period, another for the post diagnosis period) were included in the analysis.

*From merged socioeconomic data.

**The youngest child's age was retained where multiple related children exist.

***Includes both index children and siblings of index children.

****The largest score was retained where multiple related children exist.

D. Discussion

To our knowledge, this study was the first to use claims data for a large sample of the privately insured US population to measure the occurrence of stress-related conditions among parents of children with ASD. Also, this is the first study to look at the occurrence and cost of stress-related conditions among parents of children with ASD as they relate to the child's initial diagnosis of ASD. Similarly to studies using other data, we found that parents of children with ASD are more likely to have stress-related conditions, compared to parents of children without ASD. We hypothesized that surveillance bias could play a role in observed differences in parental stress between parents of children with ASD compared to parents of children without ASD given that parents of children with ASD would be frequenting sites of medical care with their child with ASD more so than parents of children without ASD, and thus possibly more likely to access care for their own health issues. In parents without frequent exposure to health professionals, stress may still be experienced similarly but not result in health care visits. To test this, we used parent utilization of preventive care services as a proxy for surveillance bias. Perhaps surprisingly, we found that including preventive health care utilization as a proxy measure for surveillance bias in the model did not alter the ASD effect on having a stress-related condition: the ASD OR after addition of the preventive health care term was 1.50 compared to 1.48 prior to adjustment. It seems that surveillance bias when measured this way does not play a substantial role in the measured differences in occurrence of stress.

Among parents of children with ASD, mothers, White parents, and parents with higher comorbidity scores were more likely have a stress-related condition. Characteristics of the child with ASD also play a role in parental stress - a higher child medical co-morbidity score and older child age were associated with having a stress-related condition among parents. These results were true for stress-related conditions overall as well as for mood and anxiety and sleep disorders in particular. Furthermore, our results shed light on the effect of an initial ASD diagnosis on the presence of stress-related conditions among parents - the odds of stress-related conditions among parents of children with ASD were higher during the 12 months after their child's ASD diagnosis compared to the 12 months prior to diagnosis.

These results are consistent with the findings of several other studies that examined stress in parents of children with ASD relative to parents of children without ASD. Montes and colleagues, while controlling for similar confounders, found that mothers of a child with autism were more than twice as likely to report poor or fair mental/emotional health as compared to mothers in the general population (odds ratio: 2.42).¹⁰⁰ Similarly, other studies found that parents of children with ASD scored higher (worse health) on the questionnaire instruments noted above than the comparison parents.^{89, 96, 101, 102} In contrast, one Swedish study did not find increased stress among parents of children with Asperger's compared to parents of other children. However, it is likely that many or most of the children with ASD in our sample have more complex cases of ASD than the relatively high-functioning children with Asperger's in this study.¹⁰³

The effect of confounding variables on parental stress varied across the studies. One study found that less maternal employment was associated with higher stress (relative to higher employment),¹⁰¹ whereas another found that less maternal education and lower family income were associated with higher stress.⁸⁹ Maternal employment as a variable may be both a marker of socioeconomic status (SES) as well as indicate a greater degree of maternal well-being, and, possibly, a child that requires less care (enabling the mother to be able to work outside the home).

Our study did not include this covariate. Our study used family income as a marker of socioeconomic status and found analogous results – that lower SES was associated with higher odds of a stress-related condition. Many other studies did not find a significant association between demographic variables such as maternal education, income, or age and stress.^{96, 100, 103, 104, 105} However, these also did not control for parent and child comorbidity scores or study enrollment time, so our results cannot be easily compared to these results. Also consistent with the literature, we found that mothers of children with ASD were more likely to have a stress-related condition than fathers.⁹⁷ This may be related to mothers typically having greater involvement in their child’s care than fathers.¹⁰⁶

In our review of the literature, only two studies focused on stress-related conditions among parents with children newly diagnosed with ASD. Neither study, however, collected data on parents prior to the ASD diagnosis nor examined the costs of the stress-related conditions making a comparison to our results difficult. A study by Davis examined families in which the child had been diagnosed three months prior to the start of the study, and a study by Smith compared the well-being of parents of toddlers versus the parents of adolescents with ASD.^{97, 98} These studies found maternal anger and behavior disengagement levels are higher years after the initial diagnosis, and parental stress immediately following the diagnosis may not be as high as expected.

Despite similarities, our study differs from the prior studies in the literature in a few key ways. First, most studies relied on survey instruments of stress and depression (such as The Parenting Stress Index Short Form (PSI/SF) and the Center for Epidemiologic Studies Depression Inventory (CES-D) to assess mental well-being of parents.^{89, 96, 97, 104} While self-reports and surveys using validated instruments such as these used may capture a greater range of severity of stress-related conditions than was possible in our study – which required two medical claims with a stress-related diagnosis – surveys are also more subject to recall bias, especially over the lengthy time periods included in our data.¹⁰⁷ Furthermore, previous studies were limited by small sample sizes (ranging from 14 to 459 children) and often characterized by low statistical power, low response rates and possible selection bias. Generalizability from these studies was uncertain because samples were typically drawn from clinical settings, schools, or parent organizations rather than a more representative group. Finally, we were unable to measure a child’s behavioral characteristics or ASD severity nor the parents’ belief systems, coping styles, and personality characteristics, all of which may impact parental mental health and the experience of stress.^{108, 109} We were, however, able to assess SES in our study, as well as examine the impact of race/ethnicity for the majority of the sample, which has not been examined in other studies. Although race/ethnicity and income were missing for a sizable subset (ranging from 38% to 55%) of our study samples, we believe that they are missing at random and should not alter the generalizability of our results.

Studying stress among parents of children with ASD can contribute to a better understanding of the clinical circumstances leading to high stress, which can then assist providers in identifying parents at risk as well as treating and ameliorating stress-related conditions, ultimately benefiting both the parents and their children. Our results reinforce previous findings that parents of children with ASD were more likely to suffer from a stress-related condition than parents of children without ASD. Our work also provides results not yet reported in the literature that sheds light on the effect of an initial ASD diagnosis on parents - the odds of having a stress-related condition were

higher (OR=1.32) 12 months following the initial diagnosis of ASD compared to the 12 months prior to the diagnosis. Due to a higher prevalence of stress after the initial diagnosis, it is not surprising that we also found parents had higher costs associated with stress-related conditions following diagnosis compared to prior to their child's initial ASD diagnosis (Cost ratio = 1.25). The results demonstrate that support for parents is essential to helping families with a child with ASD live a high quality life.

IX. Conclusion

A. Summary of Results and Implications

1. General Health Conditions

Our results indicate that children with ASD have a higher proportion of each of the eight groups of health conditions that we studied as compared to children without ASD. Specifically, we found that over 70% of children with ASD had neurological/neurodevelopmental disorders or mental health conditions, 50% had infectious diseases, 36% had injuries, approximately 20% had gastrointestinal/nutritional conditions, 7% had autoimmune conditions, 5% had congenital/genetic disorders, and another 5% had evidence of metabolic dysfunction. Relatively high proportions of the comparison children also had evidence of infectious diseases (35%) and injuries (31%).

Our study also found that siblings of children with ASD had higher proportions and rates across the same health conditions relative to siblings of children without ASD. These findings, along with the poorer physical and mental health among parents of children with ASD, raise questions about potentially shared etiologic pathways that could include both biological and environmental factors and be amenable to intervention. More immediately, these findings indicate that the health of the child encompasses the whole family and may affect overall family functioning and resources, pointing to a need for supportive interventions for the family as a whole rather than each individual separately in order to improve the health and quality of life of children with ASD and their families.

2. Injuries

Without adjustment, we estimated a higher risk of injury among children with ASD compared to children without ASD. However, this increase in risk diminished after controlling for demographic and socioeconomic variables. While additional adjustment for some co-occurring conditions suggested that children with ASD might be at lower risk of injury when the effects of these conditions are controlled, it is difficult to know whether or not this step represents over-adjustment. In other words, it is unclear if the codes capturing these conditions represent independent effects that should be adjusted for or are causal manifestations of ASD that are really part of the overall ASD effect. The fact that ASD hazard ratios were larger in subgroups defined by co-occurring conditions suggests that children with more medically complex ASD could be at higher injury risk (an effect seen in the analyses restricted to the ASD group) but these interactions were not consistent across all subgroups of children with co-occurring conditions. The ASD hazard ratios remained the same after adjustment for surveillance bias (as measured by the annual count of preventive care visits), suggesting greater exposure to the health care system for children with ASD did not markedly influence the unadjusted results.

Overall, injury risk associated with ASD appeared to be age dependent. Analyses exploring injury risk separately by age period indicated that during younger ages (<6 years old), those with ASD were at increased risk for injury compared to those without ASD, while during older ages (>10 years old) those with ASD were at decreased risk of injury compared to those without ASD. We saw approximately 30% higher injury rates in ASD than in the comparison groups at younger ages (<6 years) - but that effect reversed at higher ages (>10 years) where the children with ASD had injury rates approximately 35% lower than comparably aged children without ASD after

adjusting for socio-demographic variables and co-occurring conditions. In the U.S., the distribution of injury type (particularly nonfatal injury) is known to vary greatly by age. Consequently, further investigation of injury risk in children with ASD should focus on distinct age subgroups and consider the varying determinants of different injury types.

3. Gastrointestinal and Nutritional Conditions

In our analysis, we found that, after controlling for enrollment time and other potential confounders, children with ASD had substantially higher odds of a GI condition than children without ASD (OR=3.94, $p<0.001$). Our study, unlike others, looked at a broad range of GI conditions, including more common, symptom-defined conditions (such as, for example, constipation and diarrhea). Consequently, our study could be vulnerable to surveillance bias associated with the increased health system contact frequency seen among children with ASD diagnoses. However, after further adjustment for a variable that tallied the number of preventive health care visits as a proxy measure for extent of medical surveillance (data not shown), the ASD effect estimate, at OR= 3.74, was virtually unchanged. Stronger ASD effects were seen in subjects without seizure or autoimmune disease, respectively, (OR=4.01 and 4.12) compared to subjects with seizure or autoimmune disease (OR=1.83 and OR=3.07, respectively). This suggests that ASD's effect on GI conditions is not strictly limited to children with autoimmune or seizure conditions. Among children with ASD, girls, younger children, and children with seizures or an autoimmune condition had increased odds of a GI condition, findings potentially of interest to clinicians who care for children with ASD. We also found that the odds of a GI condition were higher following, compared to the 12 months before, the child's initial ASD diagnosis (OR = 1.40, $p<0.001$). While this could suggest a higher frequency of evidence of GI conditions after an initial ASD diagnosis was recorded, this could also be a byproduct of increased surveillance post ASD diagnosis.

Our findings underscore the notion that, in the community, children with ASD are more frequently recognized with, and presumably treated for, GI conditions and strongly support the need for further research into the relationship between ASD and the gastrointestinal system. Since children with ASD are such a heterogeneous group, clarifying unique risk factors for GI sequelae among children with ASD might be a fruitful further line of research. Finding co-occurring conditions or other phenotypic or behavioral markers that identify ASD cases at especially high risk for GI conditions should remain a research priority.

4. Parental Stress

Our study found that parents of children with ASD had higher odds of having a stress-related condition than parents of children without ASD (OR=1.48, $p<0.001$). We also found that including preventive health care utilization as a proxy measure for surveillance bias in the model did not alter the ASD effect on having a stress-related condition (OR=1.50). Therefore, it does not appear that surveillance bias plays a substantial role in the measured differences in occurrence of stress. We also found that the odds of having a stress-related condition were higher among both mothers and fathers of children with ASD compared to mothers and fathers of children without ASD, the odds ratio was higher among mothers (OR=1.647) than fathers (OR= 1.332). Furthermore, our results shed light on the effect of an initial ASD diagnosis on the presence of stress-related conditions among parents - the odds of stress-related conditions and costs associated with stress-related conditions among parents of children with ASD were higher during the 12 months after their

child's ASD diagnosis compared to the 12 months prior to diagnosis (OR = 1.322; Cost ratio = 1.246).

Studying stress among parents of children with ASD can contribute to a better understanding of the clinical circumstances leading to high stress which can then assist providers in identifying parents at risk as well as treating and ameliorating stress-related conditions, ultimately benefiting both the parents and their children. Our results reinforce previous findings that parents of children with ASD were more likely to suffer from a stress-related condition than parents of children without ASD. Our results also provide results not yet reported in the literature that sheds light on the effect of an initial ASD diagnosis on parents - the odds of having a stress-related condition were higher 12 months following the initial diagnosis of ASD compared to the 12 months prior to the diagnosis. The results demonstrate that support for both parents as well as children is essential to caring for children with ASD and helping families live healthier, and presumably, higher quality lives.

B. Strengths of the Study

The strengths of our study include: first, using claims data from a large, private insurance plan over a ten-year period, we identified a total of 33,565 children with ASD and 138,876 comparison children without ASD who represent heterogeneous and geographically diverse children with or without ASD who are covered by private insurance in the U.S. Our study sample sizes are significantly larger than any of the studies that we found in the literature for ASD. We were also able to link our large sample of children to their family members that are covered under the same health plans to examine the potential impact of ASD on parental and sibling health. Secondly, the claims-based case identification algorithms we used to identify the 33,565 children with ASD were the result of a medical chart validation study that was specifically conducted under this research effort. Therefore, although not all of our cases were verified based on clinical assessment, these children are very likely to be true positive cases based on the positive predictive value from our chart study (87.4% for the algorithm that was used to identify the 33,565 children with ASD). Finally, in addition to including variables that are traditionally seen among studies using health care claims data, our analysis linked enrollment history, medical information as reflected in their medical and pharmacy claims, and socioeconomic data such as family income and race/ethnicity that were captured from a unique database that was accompanying our claims database. Although a portion of our study subjects had missing values on both socioeconomic variables, the missing patterns seem to be random.

C. Study Limitations

As we have noted throughout this report, claims data have inherent limitations given that they are generated for payment, not research, purposes. For example, it is possible that some of the data related to medical diagnoses is inaccurate. It is also possible that diagnoses that do not impact payment or that could negatively impact payment were under-reported. Claims data also would not capture minor conditions that did not result in medical treatment at a health care setting, nor would they capture diagnoses made outside the health care setting (in a school, for instance). Other limitations include the possibility of surveillance bias affecting our results, although our attempts to control for this suggested that this was not a significant factor. Finally, claims data do not capture a child's behavior or the severity of their ASD, nor could we measure

similar characteristics in family members. Such contextual information may prove to be important in better understanding the health conditions we studied.

D. Implications and Recommendations for Future Research

We have spent two years conducting detailed and extensive research on children with autism and their families, resulting in five reports summarizing our extensive analyses. Nevertheless, there are substantial further important research opportunities that can be pursued.

In the preceding sections of this report, we have discussed both findings and limitations. Perhaps, for future researchers, it is worth emphasizing strengths of claims data that our work exhibits for ASD research. Using claims data, we have been able to:

- Construct a large cohort of children highly probable to have ASD
- Link siblings and parents to the children with ASD
- Construct a large cohort of comparison children and families without ASD
- Link socio-demographic detail
- Link detail about characteristics of treating health care providers²⁸
- Portray co-occurring conditions with a strategy for confirming diagnoses²⁹
- Identify and conduct more detailed and in-depth analyses of important and treatable conditions likely to be observable in medical claims, such as significant acute events (injuries) and conditions that are chronic in nature (stress and GI)
- Portray the experience of children with ASD, siblings and parents over time, with extended continuous periods of observation

To us, our analyses and results demonstrate the value of claims data both for description and analyses but, perhaps equally important, for the generation of new insights and hypotheses for investigation.

More specific implications arise as well. We are acutely aware that while we have reported on the elevated prevalence of several medical conditions in children with ASD, parents of children with ASD and siblings of children with ASD, we have not examined family patterns -- we have not yet determined the extent to which elevated risk is a common factor within families. For example, is the increased risk for GI conditions in a child with ASD associated with elevated risk for GI conditions among his/her siblings? We believe there is much more that can be studied and determined with claims data to identify family patterns. Such analyses could further inform research on etiology as well as research about family-based strategies for interventions.

²⁸ In this study, we have made use of information on provider specialty. Other provider characteristics are available in the database which could be mined for deeper understanding of the experience of children with ASD and their families.

²⁹ The Task A: Chart Study examined chart-based evidence on selected co-occurring conditions.

With the exception of the selected deeper analysis we have conducted for a few topics, such as the analyses regarding the age patterns of injuries among children with ASD, we have not established the temporal patterns of incidence for most conditions – for example, to what degree are there common patterns of co-occurring conditions over time among children with ASD, their siblings or among important subgroups of these children? Our data would support further such analyses, and could yield highly valuable information for designing interventions during childhood or adulthood. In particular, our data could also be used to conduct focused analysis of transition periods from young childhood to adolescence and from adolescence to early adulthood. This could lead to insights for better understanding of the natural course of ASD, optimal timing of treatment interventions and highlighting of opportunities to impact future productivity as these children reach adulthood.

We have only been able to conduct high level, descriptive analysis for most of the health conditions we selected for this study. While we report on the elevated prevalence of infectious diseases, metabolic problems, autoimmune disorders and various mental health conditions (beyond stress-related conditions in parents), we have not delved into them further, regarding issues of timing, repeat occurrences, family patterns, correlations with other conditions, etc. Much valuable work remains to be done. Further, results of our Task A: Baseline Claims Analysis identified a number of medical conditions with increased prevalence among children with ASD and their family members compared to other families that are worthy of further analysis. These include respiratory problems, musculoskeletal issues, and ear and eye disorders.

While we have investigated several selected conditions in greater depth, even within these topics important research questions remain. For example, we have not distinguished accidental injuries from self-inflicted or intentional injuries, nor have we isolated iatrogenic injuries (e.g., poisonings related to medications). These are areas of further analysis our data may be well positioned to support.

Our study demonstrates the power of claims data to understand the health experience of children with ASD and their families. Our study contributes substantively to the knowledge of factors impacting child and family health outcomes. We hope our work provides a platform for continuing research in these areas, so that children with ASD, their parents and siblings may benefit from better health care and enjoy healthier lives.

References

- 1 Newschaffer C, Croen LA, Daniels J, Giarelli E, et al. The Epidemiology of Autism Spectrum Disorders. *Annu. Rev. Public Health.* 2007;28:21.1–21.24.
- 2 Centers for Disease Control and Prevention. “Prevalence of Autism Spectrum Disorders --- Autism and Developmental Disabilities Monitoring Network, 14 Sites, United States, 2008.” Available at: <http://www.cdc.gov/mmwr/pdf/ss/ss6103.pdf>. Accessed March 30, 2012.
- 3 Warren Z, McPheeters ML, Sathe N, Foss-Feig JH, Glasser A, Veenstra-Vanderweele J. A systematic review of early intensive intervention for autism spectrum disorders. *Pediatrics.* 2011;127:e1303-e1311.
- 4 Rai D, Lewis G, Lundberg M, Araya R, Svensson A, Dalman C, Carpenter P, Magnusson C. Parental socioeconomic status and risk of offspring autism spectrum disorders in a Swedish population-based study. *J Am Acad Child Adolesc Psychiatry.* 2012;51(5): 467-476.
- 5 Constantino JN, Zhang Y, Frazier T, Abbacchi AM, Law P. Sibling recurrence and the genetic epidemiology of autism. *Am J Psychiatry.* 2010;167:1349-1356.
- 6 Anderson D, Dumont S, Jacobs P, Azzaria L. The personal costs of caring for a child with a disability: a review of the literature. *Public Health Rep.* 2007;122:3-16.
- 7 Kogan MD, Strickland BB, Blumberg SJ, Singh GK, Perrin JM, van Dyck PC. A national profile of the health care experiences and family impact of autism spectrum disorder among children in the United States, 2005-2006. *Pediatrics.* 2008;122(6):e1149-58.
- 8 Curran AL, Sharples PM, White C, Knapp M. Time costs of caring for children with severe disabilities compared with caring for children without disabilities. *Dev Med Child Neurol.* 2001;43(8):529-33.
- 9 Thyen U, Kuhlthau K, Perrin JM. Employment, child care, and mental health of mothers caring for children assisted by technology. *Pediatrics.* 1999;103:1235-42.
- 10 Laurvick CL, Msall ME, Silburn S, Bower C, de Klerk N, Leonard H. Physical and mental health of mothers caring for a child with Rett syndrome. *Pediatrics.* 2006;118:e1152-e1164.
- 11 O'Brien I, Duffy A, Nicholl H. Impact of childhood chronic illnesses on siblings: a literature review. *Br J Nurs.* 2009;18(22):1358,1360-5.
- 12 Rao PA, Beidel DC. The impact of children with high-functioning autism on parental stress, sibling adjustment, and family functioning. *Behav Modif.* 2009;33(4):437-51..
- 13 Centers for Medicare & Medicaid Services. “Medicare Claims Processing Manual, Chapter 26: Completing and Processing Form CMS-1500 Data Set.” Available at: <https://www.cms.gov/manuals/downloads/clm104c26.pdf>. Accessed September 7, 2011.
- 14 Cecil G. Sheps Center for Health Services Research. “Implementation of the UB-04.” Available at: http://www.shepscenter.unc.edu/research_programs/hosp_discharge/links/ub04_fact_sheet.pdf. Accessed September 7, 2011.
- 15 National Uniform Billing Committee. “History of the NUBC.” Available at: <http://www.nubc.org/history.html>. Accessed September 7, 2011.
- 16 Shimabukuro, T, Grosse, S, Rice, C. Medical Expenditures for Children with an Autism Spectrum Disorder in a Privately Insured Population. *J. Autism Dev Dis.* 2007:546-552.

- 17 Commission to Build a Healthier America. "Education Matters for Health." Available at:<http://www.commissiononhealth.org/PDF/c270deb3-ba42-4fbd-baeb-2cd65956f00e/Issue%20Brief%206%20Sept%2009%20-%20Education%20and%20Health.pdf>. Accessed July 10, 2012.
- 18 Ettner SL. New evidence on the relationship between income and health. *J Health Econ.* 1996;15:67-85.
- 19 National Institute of Neurological Disorders and Stroke. "Autism Fact Sheet." Available at: http://www.ninds.nih.gov/disorders/autism/detail_autism.htm. Accessed July 10, 2012.
- 20 Shattuck PT, Durkin M, Maenner M, Newschaffer C, Mandell DS, Wiggins L, Lee LC, Rice C, Giarelli E, Kirby R, Baio J, Pinto-Martin J, Cuniff C. Timing of identification among children with an autism spectrum disorder: findings from a population-based surveillance study. *J Am Acad Child Adolesc Psychiatry.* 2009;48:474-483.
- 21 Mandell DS, Novak MM, Zubritsky CD. Factors associated with age of diagnosis among children with autism spectrum disorders. *Pediatrics.* 2005;116:1480-86.
- 22 Stroupe KT, Kinney ED, Kniesner JJ. Chronic illness and health insurance-related job lock. *J Policy Anal Manage.* 2001;20:525-544.
- 23 DeNavas-Walt C, Proctor BD, Lee, CH. "Income, Poverty and Health Insurance Coverage in the United States, 2005," United States Census Bureau. 2006. Available at <http://www.census.gov/prod/2006pubs/p60-231.pdf>. Accessed September 2, 2011.
- 24 Levy SE, Mandell DS, Schultz RT. Autism. *Lancet.* 2009;374(9701):1627-38.
- 25 Matson JL, Nebel-Schwalm MS. Comorbid psychopathology with autism spectrum disorder in children: an overview. *Res Dev Disabil.* 2007;28(4):341-52.
- 26 Ritvo ER, Jorde LB, Mason-Brothers A, et al. The UCLA-University of Utah epidemiologic survey of autism: recurrence risk estimates and genetic counseling. *Am J Psychiatry.* 1989;146(8):1032-6.
- 27 Montalbano R, Roccella M. The quality of life of children with pervasive developmental disorders. *Minerva Pediatr.* 2009;61(4):361-70.
- 28 Yamada A, Suzuki M, Kato M, et al. Emotional distress and its correlates among parents of children with pervasive developmental disorders. *Psychiatry Clin Neurosci.* 2007;61(6):651-7.
- 29 Allik H, Larsson JO, Smedje H. Health-related quality of life in parents of school-age children with Asperger Syndrome or High-Functioning Autism. *Health Qual Life Outcomes.* 2006;4:1.
- 30 Herring S, Gray K, Taffe J, Tonge B, Sweeney D, Einfeld S. Behaviour and emotional problems in toddlers with pervasive developmental disorders and developmental delay: associations with parental mental health and family functioning. *J Intellect Disabil Res.* 2006;50(Pt 12):874-82.
- 31 Mugno D, Ruta L, D'Arrigo VG, Mazzone L. Impairment of quality of life in parents of children and adolescents with pervasive developmental disorder. *Health Qual Life Outcomes.* 2007;5:22.
- 32 Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, Saunders LD, Beck CA, Feasby TE, Ghali WA. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care.* 2005;43:1130-1139.
- 33 Feudtner C, Christakis DA, Connell FA. Pediatric deaths attributable to complex chronic conditions: a population-based study of Washington State, 1980-1997. *Pediatrics.* 2000;106:205-209.

- 34 Kohane IS, McMurry A, Weber G, MacFadden D, Rappaport L, et al. The Comorbidity Burden of Children and Young Adults with Autism Spectrum Disorders. *PLoS ONE*. 2012;7(4): e33224.
- 35 Gurney JG, McPheeters ML, Davis MM. Parental report of health conditions and health care use among children with and without autism: National Survey of Children's Health. *Arch Pediatr Adolesc Med*. 2006;160:825-830.
- 36 Rogers SJ, Hepburn S, Wehner E. Parent reports of sensory symptoms in toddlers with autism and those with other developmental disorders. *J Autism Dev Disord*. 2003;33:631-642.
- 37 Rapin I, Tuchman R. Autism: definition, neurobiology, screening, diagnosis. *Pediatr Clin North Am* 2008;55:1129-1146.
- 38 Simonoff E, Pickles A, Charman T, Chandler S, Loucas T, Baird G. Psychiatric disorders in children with autism spectrum disorders: prevalence, comorbidity, and associated factors in a population-derived sample. *J Am Acad Child Adolesc Psychiatry*. 2008;47:921-929.
- 39 Hartley SL, Sikora DM, McCoy R. Prevalence and risk factors of maladaptive behaviour in young children with autistic disorder. *J Intellect Disabil Res*. 2008;52:819-829.
- 40 Nikolov RN, Bearss KE, Lettinga J, et al. Gastrointestinal symptoms in a sample of children with pervasive developmental disorders. *J Autism Dev Disord*. 2008;39:405-413.
- 41 Sharpe, D, Rossiter, L. Siblings of children with a chronic illness: A meta-analysis. *Journal of Pediatric Psychology*. 2002;27, 699-710.
- 42 Centers for Disease Control and Prevention. "Deaths: Final Data 2009." Available at: http://www.cdc.gov/nchs/data/dvs/deaths_2009_release.pdf. Accessed July 10, 2012.
- 43 Centers for Disease Control and Prevention. "Patterns of Unintentional Injuries among 0-19 year olds in the United States, 2000-2006." Available at: <http://www.cdc.gov/safecild/images/CDC-ChildhoodInjury.pdf>. Accessed July 10, 2012.
- 44 Rowe R, Maughan B, Goodman R. Childhood psychiatric disorder and unintentional injury: findings from a national cohort study. *J Pediatr Psychol*. 2004;29:119-130.
- 45 Scheidt PC, Harel Y, Trumble AC, Jones DH, Overpeck MD, Bijur PE. The epidemiology of nonfatal injuries among US children and youth. *Am J Public Health*. 1995;85:932-938.
- 46 Pastor PN, Reuben CA. Identified attention-deficit/hyperactivity disorder and medically attended, nonfatal injuries: US school-age children, 1997-2002. *Ambul Pediatr*. 2006;6:38-44.
- 47 Soubhi H, Raina P, Kohen D. Neighborhood, family, and child predictors of childhood injury in Canada. *Am J Health Behav*. 2004;28:397-409.
- 48 Schwebel DC, Hodgins JB, Sterling S. How mothers parent their children with behavior disorders: implications for unintentional injury risk. *J Safety Res*. 2006;37:167-173.
- 49 Xiang H, Stallones L, Chen G, Hostetler SG, Kelleher K. Nonfatal injuries among US children with disabling conditions. *Am J Public Health*. 2005;95:1970-1975.
- 50 Leland NL, Garrard J, Smith DK. Comparison of injuries to children with and without disabilities in a day-care center. *J Dev Behav Pediatr*. 1994;15:402-408.
- 51 Slayter EM, Garnick DW, Kubisiak JM, Bishop CE, Gilden DM, Hakim RB. Injury prevalence among children and adolescents with mental retardation. *Ment Retard*. 2006;44:212-223.

- 52 Sherrard J, Tonge BJ, Ozanne-Smith J. Injury in young people with intellectual disability: descriptive epidemiology. *Inj Prev*. 2001;7:56-61.
- 53 Lee LC, Harrington RA, Chang JJ, Connors SL. Increased risk of injury in children with developmental disabilities. *Res Dev Disabil*. 2008;29:247-255.
- 54 McDermott S, Zhou L, Mann J. Injury Treatment among Children with Autism or Pervasive Developmental Disorder. *J Autism Dev Disord*. 2007;38:626-633.
- 55 Bolton PF, Carcani-Rathwell I, Hutton J, Goode S, Howlin P, Rutter M. Epilepsy in autism: features and correlates. *Br J Psychiatry*. 2011 Apr;198(4):289-94.
- 56 Tomson T, Beghi E, Sundqvist A, Johannessen SI. Medical risks in epilepsy: a review with focus on physical injuries, mortality, traffic accidents and their prevention. *Epilepsy Res*. 2004 Jun;60(1):1-16.
- 57 Téllez-Zenteno JF, Nguyen R, Hernández-Ronquillo L. Injuries, accidents and mortality in epilepsy: a review of its prevalence risk factors and prevention. *Rev Invest Clin*. 2010 Sep-Oct;62(5):466-79.
- 58 Guo Z, Gill TM, Allore HG. Modeling repeated time-to-event health conditions with discontinuous risk intervals. An example of a longitudinal study of functional disability among older persons. *Methods Inf Med*. 2008;47:107-116.
- 59 Andersen, PK, Gill, RD. Cox's regression model for counting processes: a large sample study. *The Annals of Statistics*. 1982; 10(4): 1100-1120.
- 60 Stevens, J. Applied Multivariate statistics for the social sciences. 1992. Hillsdale, NJ: Lawrence Erlbaum Associates.
- 61 Tabachnick, B. and Fidell, LS. Using multivariate statistics. 1989. New York, NY: Harper & Row.
- 62 Freund RJ, Littell RC. SAS System for Regression. 2nd Edition. 1991. Cary, NC: SAS Institute
- 63 Xiang H, Stallones L, Chen G, Hostetler SG, Kelleher K. Nonfatal injuries among US children with disabling conditions. *Am J Public Health*. 2005;95:1970-1975.
- 64 Leland NL, Garrard J, Smith DK. Comparison of injuries to children with and without disabilities in a day-care center. *J Dev Behav Pediatr*. 1994;15:402-408.
- 65 Slayter EM, Garnick DW, Kubisiak JM, Bishop CE, Gilden DM, Hakim RB. Injury prevalence among children and adolescents with mental retardation. *Ment Retard*. 2006;44:212-223.
- 66 Sherrard J, Tonge BJ, Ozanne-Smith J. Injury in young people with intellectual disability: descriptive epidemiology. *Inj Prev*. 2001;7:56-61.
- 67 Centers for Disease Control and Prevention. "Vital signs: unintentional deaths among persons aged 0-19 years - United States, 2000-2009." *MMWR Morb Mortal Wkly Rep*. 2012 Apr 20;61:270-6.
- 68 Agran PF, Anderson C, Winn D, Trent R, Walton-Haynes L, Thayer S. Rates of pediatric injuries by 3-month intervals for children 0 to 3 years of age. *Pediatrics*. 2003 Jun;111(6 Pt 1):e683-92.
- 69 Agran PF, Anderson C, Winn D, Trent R, Walton-Haynes L, Thayer S. Rates of pediatric and adolescent injuries by year of age. *Pediatrics*. 2001 Sep;108(3):e45.
- 70 King CK, Glass R, Bresee JS, Duggan C. Managing acute gastroenteritis among children: oral rehydration, maintenance, and nutritional therapy. *MMWR Recomm Rep*. 2003;52(RR-16):1-16.

- 71 Youssef, NN, Murphy T, Langseder AL, Rosh JR. Quality of Life for Children With Functional Abdominal Pain: A Comparison Study of Patients' and Parents' Perceptions. *Pediatrics*. 2006; 117(1):54-59.
- 72 Youssef NN, Langseder AL, Verga BJ, Mones RL, Rosh JR. Chronic Childhood Constipation Is Associated with Impaired Quality of Life: A Case-Controlled Study. *Journal of Pediatric Gastroenterology and Nutrition*. 2005; 41:56-60.
- 73 Taft TH, Ballou S, Keefer L. Preliminary evaluation of maternal caregiver stress in pediatric eosinophilic gastrointestinal disorders. *J Pediatr Psychol*. 2012;37:523-532.
- 74 Drossman DA. "Gastroenterology: The focus on mind and body." Inside the Minds: The Art and Science of Gastroenterology. Aspatore Books; 2007: 23-43.
- 75 Williams BL, Hornig H, Parekh T, Lipkin WI. Application of novel PCR-based methods for detection, quantitation, and phylogenetic characterization of *Sutterella* species in intestinal biopsy samples from children with autism and gastrointestinal disturbances. *mBio*. 2012;(1):e00261-11.
- 76 Jyonouchi H, Geng L, Streck DL, Toruner GA. Children with autism spectrum disorders (ASD) who exhibit chronic gastrointestinal (GI) symptoms and marked fluctuation of behavioral symptoms exhibit distinct innate immune abnormalities and transcriptional profiles of peripheral blood (PB) monocytes. *Journal of Neuroimmunology*. 2011;238: 73-80.
- 77 Levy SE, Hyman SL. Complementary and alternative medicine treatments for children with autism spectrum disorders. *Child Adolesc Psychiatr Clin N Am*. 2008;17:803-20.
- 78 D'Eufemia P, Celli M, Finocchiaro R, Pacifico L, Viozzi L, Zaccagnini M, Cardi E, Giardini O. Abnormal intestinal permeability in children with autism. *Acta Paediatr*. 1996;85:1076-1079.
- 79 Adams JB, Johansen LJ, Powell LD, Quig D, Rubin RA. Gastrointestinal flora and gastrointestinal status in children with autism--comparisons to typical children and correlation with autism severity. *BMC Gastroenterol*. 2011;11:22.
- 80 Buie T, et al. Evaluation, diagnosis, and treatment of gastrointestinal disorders in individuals with ASDs: a consensus report. *Pediatrics*. 2010; 125(Suppl. 1):S1-S18.
- 81 Horvath K, Papadimitriou JC, Rabsztyn A, Drachenberg C, Tildon JT. Gastrointestinal abnormalities in children with autistic disorder. *J Pediatr*. 1999;135:559-563.
- 82 Valicenti-McDermott M, McVicar K, Rapin I, Wershil BK, Cohen H, Shinnar S. Frequency of gastrointestinal symptoms in children with autistic spectrum disorders and association with family history of autoimmune disease. *J Dev Behav Pediatr*. 2006;27:S128-S136.
- 83 Coury D. Medical treatment of autism spectrum disorders. *Curr Opin Neurol*. 2010;23:131-136.
- 84 Ibrahim SH, Voigt RG, Katusic SK, Weaver AL, Barbaresi WJ. Incidence of gastrointestinal symptoms in children with autism: a population-based study. *Pediatrics*. 2009;124:680-686.
- 85 Whitehouse AJ, Maybery M, Wray JA, Hickey M. No association between early gastrointestinal problems and autistic-like traits in the general population. *Dev Med Child Neurol*. 2011;53:457-462.
- 86 Mouridsen SE, Rich B, Isager T. A longitudinal study of gastrointestinal diseases in individuals diagnosed with infantile autism as children. *Child Care Health Dev*. 2010;36:437-443.
- 87 Black C, Kaye JA, Jick H. Relation of childhood gastrointestinal disorders to autism: nested case-control study using data from the UK General Practice Research Database. *BMJ*. 2002;325:419-421.

- 88 Wang LW, Tancredi DJ, Thomas DW. The prevalence of gastrointestinal problems in children across the United States with autism spectrum disorders from families with multiple affected members. *J Dev Behav Pediatr.* 2011;32:351-360.
- 89 Eisenhower AS, Baker BL, Blacher J. Preschool children with intellectual disability: syndrome specificity, behaviour problems, and maternal well-being. *J Intellect Disabil Res.* 2005;49:657-671.
- 90 Hauser-Cram P, Warfield ME, Shonkoff JP, Krauss MW, Sayer A, Upshur CC. Children with disabilities: a longitudinal study of child development and parent well-being. *Monogr Soc Res Child Dev.* 2001;66:i-114.
- 91 Mobarak R, Khan NZ, Munir S, Zaman SS, McConachie H. Predictors of stress in mothers of children with cerebral palsy in Bangladesh. *J Pediatr Psychol.* 2000;25:427-433.
- 92 Kim KS, Han PL. Optimization of chronic stress paradigms using anxiety- and depression-like behavioral parameters. *J Neurosci Res.* 2006;83:497-507.
- 93 Kiecolt-Glaser JK, Glaser R, Shuttleworth EC, Dyer CS, Ogrocki P, Speicher CE. Chronic stress and immunity in family caregivers of Alzheimer's disease victims. *Psychosom Med.* 1987;49:523-535.
- 94 Romano JM, Turner JA. Chronic pain and depression: does the evidence support a relationship? *Psychol Bull.* 1985;97:18-34
- 95 Song C, Lin A, Bonaccorso S, Heide C, Verkerk R, Kenis G, Bosmans E, Scharpe S, Whelan A, Cosyns P, de JR, Maes M. The inflammatory response system and the availability of plasma tryptophan in patients with primary sleep disorders and major depression. *J Affect Disord.* 1998;49:211-219.
- 96 Mugno D, Ruta L, D'Arrigo VG, Mazzone L. Impairment of quality of life in parents of children and adolescents with pervasive developmental disorder. *Health Qual Life Outcomes.* 2007;5:22.
- 97 Davis NO, Carter AS. Parenting stress in mothers and fathers of toddlers with autism spectrum disorders: associations with child characteristics. *J Autism Dev Disord.* 2008;38:1278-1291.
- 98 Smith L, Seltzer M, Tager-Flusberg H, Greenberg J, Carter A. A comparative analysis of well-being and coping among mothers of toddlers and mothers of adolescents with ASD. *J Autism Dev Disord.* 2008;38:876-889.
- 99 U.S. Department of Labor, Bureau of Labor Statistics. "Consumer Price Index. Chained Consumer Price Index for all urban consumers (C-CPI-U) 1999-2008, Medical Care". Series ID: SUUR0000SAM. Available at: <http://data.bls.gov/cgi-bin/surveymost?su>. Accessed June 15, 2012.
- 100 Montes G, Halterman JS. Psychological functioning and coping among mothers of children with autism: a population-based study. *Pediatrics.* 2007;119:e1040-e1046.
- 101 Quintero N, McIntyre LL. Sibling adjustment and maternal well-being: An examination of families with and without a child with an autism spectrum disorder. *Focus on Autism and Other Developmental Disabilities.* 2010;25:37-46
- 102 Schieve LA, Blumberg SJ, Rice C, Visser SN, Boyle C. The relationship between autism and parenting stress. *Pediatrics.* 2007;119 (suppl 1):S114- S121
- 103 Allik H, Larsson JO, Smedje H. Health-related quality of life in parents of school-age children with Asperger Syndrome or High-Functioning Autism. *Health Qual Life Outcomes.* 2006;4:1.
- 104 Lecavalier L, Leone S, Wiltz J. The impact of behaviour problems on caregiver stress in young people with autism spectrum disorders. *J Intellect Disabil Res.* 2006;50:172-183.

- ¹⁰⁵ Yamada A, Suzuki M, Kato M, Suzuki M, Tanaka S, Shindo T, Taketani K, Akechi T, Furukawa TA. Emotional distress and its correlates among parents of children with pervasive developmental disorders. *Psychiatry Clin Neurosci*. 2007;61:651-657.
- ¹⁰⁶ Konstantareas, MM, Homatidis, S. Mothers' and fathers' self-report of involvement with autistic, mentally delayed, and normal children. *J. Marriage Fam*. 1992; 54:153-164.
- ¹⁰⁷ Bauhoff, S. Systematic Self-Report Bias in Health Data: Impact on Estimating Cross-Sectional and Treatment Effects. *Health Serv Outcomes Res Methodol*. 2011;11: 44-53.
- ¹⁰⁸ Konstantareas, M. Autistic, developmentally disabled and delayed children's impact on their parents. *Canadian Journal of Behavioural Science*. 1991;23(3), 358-375.
- ¹⁰⁹ Hill, R. Generic features of families under stress. *Social Casework*. 1958;39, 139-150.

Appendix A: Variable Definitions

Table A-1. Evaluation/Diagnosis/Assessment CPT Codes used to Identify Children with an Initial Diagnosis with ASD

Evaluation/Diagnosis/Assessment CPT Codes
90801
90802
92506
96100
96111
96115
96117
96150
96101
96102
96103
96116
96118
96119
96120
96125
96151

An evaluation/diagnosis/assessment CPT code or service/care within 3 months of the ASD diagnosis (pre or post). This does not include developmental or other screening tests that may take place within the context of a well-child visit.

Table A-2. Diagnosis Codes for Identifying Clinical Characteristics Variables

Co-Morbidity	ICD-9-CM Diagnosis Codes	Description
Anxiety	293.84	Anxiety disorder in conditions classified elsewhere
	300.0x	Anxiety states
	300.2x	Phobic disorders
	300.6	Depersonalization disorder
	309.24	Adjustment disorder with anxiety
	309.28	Adjustment disorder with mixed anxiety and depressed mood
	313	Overanxious disorder specific to childhood and adolescence
Attention Deficit Disorder	314.x	Attention deficit disorder of childhood
Bipolar Disorder	296.0x	Bipolar I disorder, single manic episode
	296.1x	Manic disorder, recurrent episode
	296.4x	Bipolar I disorder, most recent episode (or current) manic
	296.5x	Bipolar I disorder, most recent episode (or current), depressed
	296.6x	Bipolar I disorder, most recent episode (or current), mixed
	296.7	Bipolar I disorder, most recent episode (or current) unspecified
	296.8x	Other and unspecified bipolar disorders
	296.9x	Other and unspecified episodic mood disorder
Depression	296.2x	Major depressive disorder, single episode
	296.3x	Major depressive disorder, recurrent episode
	296.82	Atypical depressive disorder
	298	Depressive type psychosis
	309	Adjustment disorder with depressed mood
	309.1	Prolonged depressive reaction as adjustment reaction
	309.28	Adjustment disorder with mixed anxiety and depressed mood
	311	Depressive disorder, not elsewhere classified
	E939.0	Antidepressants causing adverse effect in therapeutic use
	300.4	Dysthymic disorder
Epilepsy and Seizure Disorders	345.xx	Epilepsy and recurrent seizures
Intellectual Disability	317	Mild mental retardation
	318	Moderate mental retardation
	318.1	Severe mental retardation
	318.2	Profound mental retardation
	319	Unspecified mental retardation

Table A-2. Diagnosis Codes for Identifying Clinical Characteristic Variables (continued)

Co-Morbidity	ICD-9-CM Diagnosis Codes	Description
Visual Impairment	367.51	Paresis of accommodation
	367.52	Total or complete internal ophthalmoplegia
	367.53	Spasm of accommodation
	368.00-368.03	Amblyopia
	368.11	Sudden visual loss
	368.2	Diplopia
	368.30	Unspecified binocular vision disorder
	368.31	Suppression of binocular vision
	369.01-369.08; 369.10-369.18; 369.20-369.25	Better eye vision impairment
	369.61-369.76	One eye vision impairment
	743.42	Congenital corneal opacity

Table A-3. Drug Names for Identifying Attention Deficit Disorder

Drug Name
amphetamine/dextroamphetamine
atomoxetine
dexmethylphenidate
dextroamphetamine
lisdexamfetamine
methamphetamine
methylphenidate
modafinil
pemoline

Table A-4. Diagnosis Codes for Identifying Chronic Conditions Used for Comorbidity Score

ICD-9-CM Diagnosis	Description	ICD-9-CM Diagnosis	Description
Neuromuscular		Hematologic or Immunologic	
740.0x - 742.9x	Brain and spinal cord malformations	282.5x - 282.6x	Sickle cell disease
318.0x - 318.2x	Intellectual disability	282.0x - 282.4x	Hereditary anemias
330.0x - 330.9x	Central nervous system degeneration and disease	279.00 - 279.9x	Hereditary immunodeficiency
334.0x - 334.2x			
335.0x - 335.9x			
343.0x - 343.9x	Infantile cerebral palsy	446.1x	Acquired immunodeficiency
359.0x - 359.3x	Muscular dystrophies and myopathies	042.0x - 042.1x	
345.0x - 345.9x	Epilepsy and seizure disorders	Metabolic	
Cardiovascular		270.0x - 270.9x	Amino acid metabolism
745.0x - 747.0x	Heart and great vessel malformations	271.0x - 271.9x	Carbohydrate metabolism
425.0x - 425.4x	Cardiomyopathies	272.0x - 272.9x	Lipid metabolism
429.1x			
426.0x - 427.4x	Conduction disorders	277.3x	Storage disorders
427.6x - 427.9x	Dysrhythmias	277.5x	
Respiratory		275.0x - 275.3x	Other metabolic disorders
748.0x - 748.9x	Respiratory malformations	277.2x	
770.7x	Chronic respiratory disease	277.4x	
277.0x	Cystic fibrosis	277.6x	
493.0x - 493.9x	Asthma	277.8x - 277.9x	
Renal		249.xx	Diabetes
753.0x	Congenital anomalies	250.xx	
585.xx	Chronic renal failure	Other Congenital or Genetic Defect	
Gastrointestinal		758.0x - 758.9x	Chromosomal anomalies
750.3x	Congenital anomalies	259.4x	Bone and joint anomalies
751.1x-751.3x			
751.6x - 751.9x			
571.4x - 571.9x	Chronic liver disease and cirrhosis	737.3x	Diaphragm and abdominal wall
555.0x - 556.9x	Inflammatory bowel disease	756.0x - 756.5x	
		555.3x	Other congenital anomalies
		756.6x - 756.7x	
		759.7x - 759.9x	
		Malignant Neoplasms	
		140.0x - 208.9x	Malignant neoplasms
		235.0x - 239.9x	

Table A-5. Prescriptions for Identifying Asthma

Subclass
Inhaled corticosteroids (ICS)
Long-acting b-agonists (LABA)
ICS/LABA combination
Mast cell stabilizers
Leukotriene modifiers
Methylxanthines
Short-acting b-agonists (SABA)
b-agonist/ACH
Systemic corticosteroids
Anticholinergics

Table A-6. Prescriptions for Identifying Diabetes

Major Class	Subclass
Oral Hypoglycemic Agents	Sulfonylureas
	Biguanide
	Thiazolidinediones (TZD)
	α-glucosidase inhibitors
	Meglitinide derivatives
	Dipeptidyl peptidase-4 (DPP-4) inhibitor*
	SU/metformin
	SU/TZD
	TZD/metformin
	Meglitinide/metformin
	DPP-4/metformin
	DPP-4/statin
	Insulin
Short-acting insulins	
Intermediate-acting Insulins	
Long-Acting Insulins	
Mixed Insulins	
Inhaled Insulins	
Animal Source Insulins	

Table A-7. Diagnosis Codes for Identifying Infectious Disease

ICD-9-CM Diagnosis Codes	Description
<i>Vaccine preventable infectious diseases in children</i>	
055.xx	Measles, includes morbilli, rubeola, keratoconjunctivitis, post measles encephalitis, pneumonia, otitis media, with complications, without complications, measles without complication
072.xx	
056.xx	Mumps, includes orchitis, parotitis, with and without complications Rubella includes German measles, excludes congenital rubella, with neurological complications, without complications.
052.xx	Varicella/chicken pox, includes postvaricella encephalitis, pneumonitis
036.xx	Meningococcal infections/meningitis
032.xx	Diphtheria
033.xx	Pertussis/whooping cough
037.xx	Tetanus-excludes neonatal tetanus as this occurs before vaccine given and occurs in babies born to unimmunized mothers
070.xx	Viral Hepatitis A, B, C included with specific codes for each, no vaccine for hepatitis c currently
045.xx	Poliomyelitis
487.xx - 488.xx	Influenza
320.1x	Pneumococcal pneumonia meningitis/septicemia
567.1x	
038.2x	
481.xx	
041.2x	
008.61	Rotaviral diarrhea
482.2x	Hemophilis influenza type B
038.41	
041.5x	
320.0x	

ICD-9-CM Diagnosis Codes	Description
<i>Other vaccine preventable infectious diseases where organism is often unknown</i>	
038.xx	Septicemia/bacteremia
790.7x	
790.8	
381.00-381.52	Otitis media (nonsuppurative and suppurative)
382.xx	
480.xx-486.xx	Pneumonia
320.xx-322.xx	Meningitis
009.2x - 009.3x	Diarrhea (infectious or presumed infectious)
464.00-465.0x	Acute laryngitis/pharyngitis
711.0x	Pyogenic arthritis

Table A-8. Diagnosis Codes for Identifying Neurological/Neurodevelopmental Disorders

ICD-9-CM Diagnosis Codes	Description
Neurological disorders	
003.21, 013.xx, 036.xx, 047.xx, 049.xx, 052., 053.0, 054.3, 055.0, 053.0,	Meningoencephalitides (infectious/inflammatory conditions of the brain and neurological system)
321.2x	
322.0x - 323.9x	
348.3x - 348.4x	
349.82	
349.89	
781.6x	
331.3x – 331.5x	
331.81	
331.89	
331.9x	
742.3	
741.xx	Spina bifida
740.xx	Other congenital anomalies of the nervous system
742.3	
332.0-332.1	Movement disorders (tics, stereotypic movements, tremor, myoclonus)
333.xx	
781.0x	
781.2x	
781.3x-781.4	
307.20 - 307.23	
307.3x	
346.xx	
339.xx	Other Headache Syndromes
343.xx	Cerebral palsy, infantile or congenital paralytic syndromes
345.0x - 345.9x	Epilepsy & convulsions
780.3x	

ICD-9-CM Diagnosis Codes	Description
360.xx - 368.xx	Disorders of the eye
369.xx	Blindness and low vision
378.xx	Strabismus and other disorders of eye movement
379.5x	Nystagmus and other irregular eye movements
348.xx	Other conditions of the brain (anoxic brain damage, benign intracranial hypertension)
350.xx - 352.xx	Cranial nerve disorders
359.xx	Muscular dystrophies and myopathies
376.82	
Neurodevelopmental disorders	
314.00 - 314.01	Attention deficit hyperactivity disorder, Hyperkinetic syndrome of childhood (ADD/ADHD)
314.1x - 314.2x	
314.8x - 314.9x	
784.3x	Aphasia
783.42	Delayed milestones
788.3x	Urinary incontinence
307.6x	
315.xx	Specific delays in development
783.40	Lack of expected normal physiological development in childhood (includes short stature, and unspecified delays)
783.43	
307.23	Tourette syndrome
317.xx - 319.xx	Intellectual disability
799.52	
315.5x	Mixed developmental syndrome
315.9x	Developmental disorder/Learning disorder—not otherwise specified
330.0x - 330.9x	Central nervous system degeneration and disease
334.0x - 334.2x	
335.0x - 335.9x	
333.4	
336.1 - 336.9	
359.0x - 359.9x	

Table A-9. Diagnosis Codes for Identifying Mental Health Conditions

ICD-9-CM Diagnosis Code	Description
309.XX	Adjustment disorders
300.XX	Anxiety disorders
309.8X	
313.0X	
309.21	
312.XX - 315.XX	Disorders usually diagnosed in infancy, childhood or adolescence
317.XX - 319.XX	
758.3X	
787.6X	
V40.XX	
300.1X	Dissociative disorders
300.6X	Eating disorders
307.1	
307.5X	
300.16	
300.19	
300.16	Factitious disorders
300.19	
301.51	Impulse control disorders, not elsewhere classified
312.3X	
293.8x	Mental disorders due to general medical conditions not elsewhere classified
293.9X	
294.1X	
294.8	
310.1	
V67.3X	Miscellaneous mental disorders
293.83	Mood disorders
296.XX	
300.4X	
301.13	
311.XX	

ICD-9-CM Diagnosis Code	Description
307.XX	Other conditions that may be a focus of clinical attention & additional codes
313.1X	
313.3X	
313.83	
316.XX	
332.1X	
333.1X	
333.7X	
333.82	
333.90 - 333.99	
357.5X	
425.5X	
535.3X	
571.0X - 571.3X	
648.40 - 648.44	
779.5X	
780.09	
780.1X	
780.50	
780.55 - 780.56	
780.58	
780.9X	
790.3X	
799.2X	
995.5X	
995.80 - 995.85	
V11.XX	
V15.4X	
V15.81 - V15.82	
V61.0X - V61.9X	
V62.0X - V62.6X	
V62.8X - V62.9X	
V65.2X	
V66.3X	
V70.1X - V70.2X	
V71.0X	
V79.XX	

Table A-9. Diagnosis Codes for Identifying Mental Health Conditions (continued)

ICD-9-CM Diagnosis Code	Description
301.XX	Personality disorders
306.0X - 306.4X	Psychogenic disorders
306.50	
306.51	
306.52	
306.53	
306.59	
306.6X - 306.9X	
293.8X	Schizophrenia and other psychotic disorders
295.XX	
297.XX - 298.XX	
302.7x	Psychosexual dysfunctions
307.4X	Sleep disorders
780.5X	
347.XX	
300.7X - 300.8X	Somatoform disorders
307.8X	
see codes in Tables A-11	Substance abuse disorders

Table A-10. Prescriptions for Identifying Epilepsy

Drug Subclass	Drug Name
Anticonvulsants	carbamazepine
	divalproex (also referred to as valproate or valproic acid)
	gabapentin
	lamotrigine
	levetiracetam
	oxcarbazepine
	tiagabine
	topiramate
	zonisamide
	Anticonvulsants: Other Antiepileptic Drugs (AEDs)
phenobarbital sodium	
Phenobarbital	
phenytoin sodium extended	
phenytoin sodium	
Phenytoin	
Ethotoin	
Mephenytoin	
Primidone	
Trimethadione	
Paramethadione	
Phensuximide	
Methsuximide	
Ethosuximide	
Phenacemide	
Clonazepam	
Diazepam	
Mephobarbital	
Felbamate	
fosphenytoin sodium	
rufinamide	
Pregabalin	
Vigabatrin	
Lacosamide	

Table A-11. Drug Names for Identifying Insomnia

Drug Name
Zolpidem
Eszopiclone
Ramelteon
Zaleplon
Triazolam (oral)
Temazepam

Table A-12. Diagnosis Codes for Identifying Metabolic Dysfunction

ICD-9-CM Diagnosis Codes	Description
249.xx	Diabetes Mellitus
250.xx	
270.xx - 274.xx	Other metabolic and immunity disorders (includes disorders of amino acid transport, carbohydrate transport and metabolism, lipid metabolism, protein metabolism, mineral metabolism— includes phenylketonuria, Other unspecified disorders of metabolism (cystic fibrosis, amyloidosis, Adenylosuccinate lyase deficiency)
275.xx	
277.xx	
277.87	Mitochondrial disorders
278.xx	Overweight and obesity
V85.30-V85.45	
V85.54	

Table A-13. Diagnosis Codes for Identifying Injuries

ICD-9-CM Diagnosis Codes	Description
800.xx - 829.xx	Fractures
830.xx - 839.xx	Dislocations
840.xx - 848.xx	Sprains and strains
850.xx - 854.xx	Intracranial injuries
860.xx - 869.xx	Internal injuries Thorax, Abdomen, Pelvis
870.xx - 897.xx	Open wounds (head, neck, trunk, upper and lower limbs)
900.xx - 904.xx	Injuries to blood vessels
910.xx - 924.xx	Superficial injuries and contusions
925.xx - 929.xx	Crushing injuries
930.xx - 939.xx	Foreign bodies through orifices
940.xx - 949.xx	Burns
950.xx - 957.xx	Injuries to nerves/spinal cord
958.xx - 959.xx	Traumatic unspecified
960.xx - 979.xx	Poisoning due to medications
980.xx - 989.xx	Poisoning non-medication
990.xx - 994.xx	Other (external causes such as exposure, lighting, drowning)
995.xx	Other adverse effects (includes child maltreatment)
996.xx - 999.xx	Complications of care

Table A-14. Episode Treatment Groups used to identify Injuries

Episode Treatment Groups	Description
316300, 316500, 318100, 318300, 351900, 388600, 402400, 405100, 440400, 440600, 474400, 475800, 478200, 478300, 523000, 589000, 668901, 668902, 668903, 668904, 668905, 668906, 668907, 668909, 668912, 669001, 669002, 669003, 669004, 669005, 669006, 669007, 669009, 669010, 669012, 712901, 712902, 712903, 712904, 712905, 712906, 712907, 712909, 713101, 713102, 713103, 713104, 713105, 713106, 713107, 713109, 714501, 714502, 714503, 714504, 714505, 714506, 714509, 714512, 714601, 714602, 714603, 714604, 714605, 714606, 714607, 714608, 714609, 714611, 714612	Trauma
668700	Burns
821100	Environmental trauma
821200	Poisoning and toxic effects of drugs

Table A-15. Diagnosis Codes for Identifying Autoimmune Disorders

ICD-9-CM Diagnosis Codes	Description
279.xx	Disorders involving the immune mechanism, autoimmune disease not otherwise classified (279.4)
283.0x	Autoimmune hemolytic anemias
284.xx	Aplastic anemia and other bone marrow failure syndromes
287.0x	Allergic purpura
287.3x	Primary thrombocytopenia
691.xx	Atopic dermatitis and related conditions
692.xx	Contact dermatitis and other eczema
696.xx	Autoimmune-psoriasis (per EAC)
695.4x	Autoimmune-lupus (per EAC)
710.0x	
583.81	
708.xx	Urticaria
714.xx	Rheumatoid arthritis and other inflammatory polyarthropathies
720.xx	Ankylosing spondylitis and other inflammatory spondylopathies
140.xx - 209.xx	Cancer/neoplasms (excludes benign neoplasms 210-229), (includes unspecified, carcinoma in situ,
230.xx - 239.xx	

Table A-16. Diagnosis Codes for Identifying Congenital/Genetic Disorders

ICD-9-CM Diagnosis Codes	Description
758.xx	Chromosomal anomalies include: syndromes associated with anomalies in the number and form of chromosomes (includes down syndrome, trisomy 13, trisomy 18, angelman syndrome, cri du chat and other autosomal deletion syndromes, klinefelter's (XYY), turner (XXX) and other sex-linked syndromes, velocardiofacial syndrome, Williams syndrome
271.1x	Galactosaemia
759.8x	Other specified anomalies (includes prader willi, marfan syndrome, fragile x, laurence-moon-biedl)
759.9x	Congenital anomaly unspecified
759.89	Noonan syndrome, rubinstein-taybi syndrome, smith-lempitz syndrome, cornelia de Lange syndrome
759.5x	Tuberous sclerosis
330.8x	Rett syndrome**
277.5x	San Filipo syndrome
750.5x	Pyloric stenosis
237.70 - 237.72	Neurofibromatosis
259.4x	Bone and joint anomalies
737.3x	
754.0x-755.9x	
756.0x - 756.5x	
555.3x	Diaphragm and abdominal wall
550.0x-553.9x	
756.6x - 756.7x	
756.6x - 757.9	Other congenital anomalies
759.7x - 759.9x	

Table A-17. Diagnosis Codes for Identifying Gastrointestinal and Nutrition Disorders

ICD-9-CM Diagnosis Codes	Description
531.xx - 534.xx	Gastric, duodenal, peptic, jejunal ulcers
536.xx - 537.xx	Disorders of stomach function and other disorders of upper intestine
535.xx	Gastritis and duodenitis appendicitis Non-infectious enteritis and colitis (includes crohn's disease, ulcerative colitis)
540.xx - 543.xx	Appendicitis
555.xx - 556.xx	Non-infectious enteritis and colitis (includes crohn's disease, ulcerative colitis)
578.xx	Gastrointestinal hemorrhage
579.xx	Intestinal malabsorption (includes celiac disease, and unspecified)
783.0x - 783.3x	Symptoms concerning nutrition, metabolism and development (includes anorexia, abnormal weight gain, feeding problems), unspecified nutritional deficiency
296.9x	
783.41	Failure to thrive
783.6x	Polyphagia
564.xx	Functional digestive disorders NOS (includes constipation, irritable bowel, functional diarrhea)
787.0x - 787.1x	Nausea and vomiting
787.2x - 787.91	Heart burn Dysphagia, flatulence, abnormal bowel sounds, feces, encopresis
558.3x-558.4x	
477.1x	
693.1x	Food allergies
995.6x-995.7x	
V15.01 - V15.05	
271.3x	Lactose intolerance
V15.02	Milk protein allergy

Table A-18. Drug Names for Identifying Irritable Bowel Syndrome

Drug Name
alosetron
tegaserod
Amitiza

Table A-19. Diagnosis Codes for Identifying Stress-Related Conditions Including Reactive Mental Health Conditions

ICD-9-CM Diagnosis Codes	Description
Mood/Anxiety disorders	
309.XX	Other mood/anxiety disorders
293.84	Anxiety disorders
300.0x	
300.2x-6x	
300.9x	
308.XX	
309.8X	
293.83	
296.XX	
300.4X	
301.13	
311.XX	
300.1X	Dissociative disorders
300.6X	
Other	
307.1	Eating disorders
307.5x	
307.52 - 307.53	
300.16	Factitious disorders
300.19	
301.51	
312.3x	Impulse control disorders, not elsewhere classified

ICD-9-CM Diagnosis Codes	Description
Other (cont'd)	
316	Other conditions that may be a focus of clinical attention & additional codes
333.1X	
780.9X	
995.80 - 995.85	
V15.41 - V15.42	
V15.49	
V15.81 - V15.82	
V61.01	
V61.03 - V61.05	
V61.08 - V61.09	
V61.1X	
V61.20 - V61.22	
V61.24	
V61.83	
V62.1X	
V62.20 - V62.22	
V62.3X	
V62.4X	
V62.81	
V62.89	
V71.0X	
V79.X	
302.7x	Psychosexual dysfunctions
Physical condition with stress-related triggers	
493.XX	Asthma
564.0X	Constipation
401.XX	Hypertension
564.1X	Irritable bowel syndrome

Table A-19. Diagnosis Codes for Identifying Stress-Related Conditions Including Reactive Mental Health Conditions (continued)

ICD-9-CM Diagnosis Codes	Description
<i>Somatoform and psychological pain syndromes</i>	
307.81	Headache/migraine
339.xx	
784.0	
346.XX	
780.7X	Malaise/fatigue/chronic fatigue
307.8X	Pain disorders with psychological cause
306.0	Psychogenic disorders
306.1	
306.2X - 306.4X	
306.50	
306.51	
306.52 - 306.53	
306.59	
306.6X - 306.9X	
300.7	Somatoform disorders
300.8X	
307.80	
307.89	
338.2	Fibromyalgia, chronic back pain, chronic pain, abdominal pain
338.4	
723.1	
724.2	
724.5	
789.0	

ICD-9-CM Diagnosis Codes			
<i>Substance-related disorders</i>			
291.0	304.00		305.42
291.1	304.01	304.62	305.43
291.2	304.02	304.63	305.50
291.3	304.03	304.70	305.51
291.5	304.10	304.71	305.52
291.81	304.11	304.72	305.53
291.82	304.12	304.73	305.60
291.89	304.13	304.80	305.61
291.9	304.20	304.81	305.62
303.00	304.21	304.82	305.63
303.01	304.22	304.83	305.70
303.02	304.23	304.90	305.71
303.03	304.30	304.91	305.72
303.90	304.31	304.92	305.73
303.91	304.32	304.93	305.80
303.92	304.33	305.20	305.81
303.93	304.40	305.21	305.82
305.00	304.41	305.22	305.83
305.01	304.42	305.23	305.90
305.02	304.43	305.30	305.91
305.03	304.50	305.31	305.92
V65.42	304.51	305.32	305.93
292.0	304.52	305.33	V61.42
292.89	304.53	305.40	
292.9	304.60	305.41	

Table A-20. Prescriptions for Identifying Hypertension

Major Class	Subclass
Oral Hypoglycemic Agents	non-selective b-blockers
	cardioselective b-blockers
	a/b-blockers
Calcium channel blockers (CCB)	non-dihydropyridine CCB
	dihydropyridine CCB
Agents affecting the renin-angiotensin-aldosterone system (RAAS)	ACE inhibitors
	Angiotensin receptor blockers (ARB)
	Aldosterone antagonist
	Renin inhibitor
Adrenolytics	Central
	Peripheral
a-blockers	
Reserpine	
Vasodilators	
Diuretics	thiazides and thiazide-like
	loop diuretics
	potassium-sparing
Combination antihypertensives	b-blocker + thiazide
	ACE inhibitor + CCB
	ACE inhibitor + thiazide
	Renin inhibitor + thiazide
	Renin inhibitor + ARB
	Renin inhibitor + CCB
	Renin inhibitor + CCB + thiazide
	ARB + CCB
	ARB + thiazide
	ARB + CCB + thiazide
	potassium-sparing + thiazide
	a-blocker + thiazide
	adrenolytic + thiazide
	reserpine + thiazide
	reserpine + vasodilator + thiazide
vasodilator + thiazide	
vasodilator + other	

Table A-21. Drug Names for Identifying Migraines

Drug Name
Almotriptan
Eletriptan
Frovatriptan
Naratriptan
Rizatriptan
SUMATRIPTAN
SUMATRIPTAN SC
SUMATRIPTAN/NAPROXEN
Zolmitriptan

APPENDIX B: Sample Identification and Study Observation Time

A. Sample Identification

1. Children with and without ASD

Table B-1 below summarizes the identification of children with and without ASD. Ultimately, the sample selection process, implemented as part of Task A: Baseline Claims Analysis, resulted in 46,236 children with ASD and 138,876 children without ASD identified within the OptumInsight database.

Table B-1. ASD and Comparison Group Sample Selection

Sample Criterion	Patients Excluded		Patients Remaining	
	n	%	n	%
Commercial health plan enrollee with medical or pharmacy coverage between 01 Jan 2001 and 31 Dec 2009	0	100.00	62,555,053	100.00
Continuous enrollment (with behavioral health coverage) for at least 1 period of at least 6 months between 01 Jan 2001 and 31 Dec 2009	32,139,827	51.38	30,415,226	48.62
Age ≤20 as of the first day of subject's continuous enrollment with medical/pharmacy/behavioral health coverage between 01 Jan 2001 and 31 Dec 2009	20,889,483	68.68	9,525,743	31.32
No evidence of Rett syndrome or CDD between 01 Jan 2001 and 31 Dec 2009	863	0.01	9,524,880	99.99
Children with ASD				
Evidence of ASD between 01 Jan 2001 and 31 Dec 2009 using enrollment claims	9,478,588	99.51	46,292	0.49
Evidence of ASD between 01 Jan 2001 and 31 Dec 2009 using member claims	56	0.12	46,236	99.88
Children without ASD				
Eligible patients who are not related to Patients with ASD	55,589	0.58	9,422,999	98.93
Random selection for study	9,284,123	98.53	138,876	1.47

2. Family Members

Tables B-2 and B-3 summarize the identification of family health plan members for the ASD and comparison group samples. As shown in Table 5, approximately 99% of the children with and without ASD had evidence of being in a family health plan, and for all but approximately 2% of these subjects, at least one family plan member was identified within the database. After all exclusion and inclusion criteria were applied, a total of 312,393 family plan members were designated as parents (80,164 for children with ASD and 232,229 for the comparison group), and a total of 252,924 were designated as siblings (57,056 for children with ASD and 195,868 for the comparison group).

Table B-2. ASD and Comparison Group Subjects with Family Plan Member(s)

Sample Criteria	Subjects Excluded						Subjects Remaining					
	ASD (N = 46,236)		Comparison (N = 138,876)		Total (N = 185,112)		ASD (N = 46,236)		Comparison (N = 138,876)		Total (N = 185,112)	
	n	%	n	%	n	%	n	%	n	%	n	%
Number of subjects with at least one family ID	556	1.20	1,529	1.10	2,085	1.13	45,680	98.80	137,347	98.90	183,027	98.87
Number of subjects with at least one family member	272	0.60	2,963	2.16	3,235	1.77	45,408	99.40	134,384	97.84	179,792	98.23

Table B-3. ASD and Comparison Group Family Sample Selection

Sample Criteria	Patients Excluded						Patients Remaining					
	ASD (N = 46,236)		Comparison (N = 138,876)		Total (N = 185,112)		ASD (N = 46,236)		Comparison (N = 138,876)		Total (N = 185,112)	
	n	%	n	%	n	%	n	%	n	%	n	%
Number of unique family members							147,083	100.00	467,764	100.00	614,847	100.00
Number of unique family members with continuous enrollment (with behavioral health coverage) for at least 1 period of at least 6 months between 01 Jan 2001 and 31 Dec 2009	9,239	6.28	37,410	8.00	46,649	7.59	137,844	93.72	430,354	92.00	568,198	92.41
Number of unique family members who are not linked to both an ASD case and comparison patient	78	0.06	78	0.02	156	0.03	137,766	99.94	430,276	99.98	568,042	99.97
Number of unique family members who are not also ASD case patients	0	0.00	0	0.00	0	0.00	137,766	100.00	430,276	100.00	568,042	100.00
Parent subjects							80,164	58.19	232,229	53.97	312,393	54.99
Sibling subjects							57,056	41.42	195,868	45.52	252,924	44.53

B. Study Observation Time

All sample members selected for the study were required to have a minimum of 6 months of continuous enrollment with simultaneous medical, pharmacy, and behavior health coverage between 2001 and 2009. The first day of each subject's enrollment with all three types of coverage during this time frame was set as his/her index date. Subjects were observed for their entire duration of continuous enrollment between 2001 and 2009. If a subject had more than 6 months of continuous enrollment or had more than one enrollment period with medical, pharmacy, and behavioral health coverage during this time frame, subjects were observed during the additional time and period(s) as well; therefore, observation time varied by subject.

1. Children with and without ASD

Table B-4 summarizes the distribution of index dates and enrollment characteristics for children with ASD and the comparison group without ASD. Generally speaking, the distribution of index year (2001-2009) is similar between children with and without ASD, with a higher percentage of subjects with study enrollment starting in 2001 and a lower percentage in 2009. The former is a function of a large increase in health plan enrollees within the OptumInsight Research Database in 2001 as well as that the initial study year of 2001 captures both individuals whose enrollment actually started in 2001 and those who had enrollment prior to and into 2001, thereby representing some individuals from earlier years as well. The latter (the lower proportion in 2009) is a function of study eligibility criteria, which required subjects to have at least 6 months of enrollment, therefore limiting index dates to just the first half of 2009.

Most subjects (over 80%) had only one period of continuous enrollment during the study period time frame. Of those who had more than one period of enrollment, the overwhelming majority (over 90%) had only one additional period of enrollment. Only 645 of the sample of children with ASD and 2,104 of the comparison sample of children without ASD had 3 or more enrollment periods during the study representing no more than 2.0% of either group.

Table B-4 also presents the *length* of enrollment time available from the index date as well as subject's total enrollment time during the study, both of which are expressed in terms of months. Overall, study subjects had a noteworthy amount of enrollment time during the study. Children with ASD had an average of 43.5 months (over 3 years) of enrollment during the study, and children without ASD had an average of 30.5 months (roughly 2 and a half years). Only 5.7% of the children with ASD had less than a year of enrollment and just over half had three years or more. Just over 50% of the children without ASD had 2 or more years of enrollment during the study period.¹ That the ASD sample had longer enrollment time was anticipated as families with ASD or any other chronic health condition may be more likely to seek, stay with, or return to health insurance coverage to the extent possible.¹ For subjects with more than one enrollment period, the additional enrollment time was on average shorter than the average continuous enrollment time starting from subjects' index date. Overall, subjects with more than one enrollment period during the study had an average of 3 to 5 months of enrollment from these additional enrollment periods.

¹ Given that over 80% of the OptumInsight sample had one enrollment period, the distributions of observation time in the study samples based on just the single longest continuous enrollment period (data not shown) are similar to those seen for total enrollment time.

Table B-4. Enrollment Characteristics* of ASD and Comparison Groups

Enrollment Characteristic	ASD (N=33,565)		Comparison (N=138,876)		p-value
	n	%	n	%	
Index Year					
2001	8,532	25.42	40,266	28.99	<0.001
2002	3,272	9.75	14,118	10.17	0.023
2003	3,304	9.84	13,367	9.63	0.224
2004	3,457	10.30	12,701	9.15	<0.001
2005	3,873	11.54	13,491	9.71	<0.001
2006	3,665	10.92	12,941	9.32	<0.001
2007	3,735	11.13	13,783	9.92	<0.001
2008	2,470	7.36	11,151	8.03	<0.001
2009	1,257	3.74	7,058	5.08	<0.001
Number of Enrollment Periods during Study	n	%	n	%	
Subjects with multiple enrollment periods	5,670	16.89	19,420	13.98	<0.001
1	27,895	83.11	119,456	86.02	<0.001
2	5,025	14.97	17,316	12.47	<0.001
3	599	1.78	1,910	1.38	<0.001
≥4	46	0.14	194	0.14	0.907
	mean	SD	mean	SD	
Continuous Enrollment (CE) from Index Date (months)	38.78	26.82	27.48	21.84	<0.001
Additional Enrollment during Study (months)**	4.68	13.13	3.00	9.87	<0.001
Total Enrollment during Study (months)**	43.46	26.32	30.47	22.58	<0.001
Total Enrollment during Study (categories)**	n	%	n	%	
6 months	1,928	5.74	23,672	17.05	<0.001
12 months	6,563	19.55	43,361	31.22	<0.001
24 months	6,426	19.14	26,808	19.30	0.509
36 months	5,533	16.48	17,307	12.46	<0.001
≥48 months	13,115	39.07	27,728	19.97	<0.001

*Based on simultaneous medical, pharmacy and behavioral health coverage.

**Subjects may have had gap(s) in enrollment during this time.

2. Family Members

Table B-5 summarizes the distribution of index dates and enrollment characteristics for members of the parent and sibling samples within the OptumInsight database. Very similar to the enrollment patterns observed for children with and without ASD, the highest percentage of family plan members had enrollment starting in 2001 and the lowest percentage in 2009.

As was also seen with children with ASD, family members of children with ASD had, on average, longer enrollment lengths than family members of children without ASD (45.6 months vs. 35.8

months for parents; 41.1 months compared to 32.1 months for siblings). Approximately 15% of comparison siblings, 12% of comparison parents, 8% of ASD siblings, and 6% of ASD parents had less than 1 year of enrollment during the study. Three-fourths of ASD parents, 67% of ASD siblings, 60% of comparison parents, and 55% of comparison siblings had total study enrollment of 2 years or more. Overall, as expected, parents had more enrollment time than other members of their family.

Table B-5. Enrollment Characteristics* of ASD and Comparison Group Family Members

Characteristic	Parents (N=290,986)				Siblings (N=237,081)				ASD vs Comparison Parents p-value	ASD vs Comparison Siblings p-value
	ASD (N=58,757)		Comparison (N=232,229)		ASD (N=41,213)		Comparison (N=195,868)			
	n	%	n	%	n	%	n	%		
Index Year										
2001	18,206	30.99	80,584	34.70	10,529	25.55	61,240	31.27	<0.001	<0.001
2002	5,941	10.11	24,777	10.67	3,974	9.64	20,385	10.41	<0.001	<0.001
2003	5,636	9.59	22,619	9.74	3,903	9.47	19,117	9.76	0.279	0.071
2004	5,696	9.69	20,936	9.02	4,156	10.08	18,284	9.33	<0.001	<0.001
2005	6,275	10.68	21,521	9.27	4,757	11.54	18,873	9.64	<0.001	<0.001
2006	5,719	9.73	19,368	8.34	4,434	10.76	17,549	8.96	<0.001	<0.001
2007	5,664	9.64	19,808	8.53	4,615	11.20	18,169	9.28	<0.001	<0.001
2008	3,701	6.30	13,897	5.98	3,204	7.77	13,773	7.03	0.004	<0.001
2009	1,919	3.27	8,719	3.75	1,641	3.98	8,478	4.33	<0.001	0.002
Number of Enrollment Periods during Study										
Subjects with multiple enrollment periods	11,668	19.86	42,063	18.11	6,848	16.62	30,526	15.58	<0.001	<0.001
1	47,089	80.14	190,166	81.89	34,365	83.38	165,342	84.42	<0.001	<0.001
2	10,144	17.26	36,686	15.80	6,074	14.74	26,984	13.78	<0.001	<0.001
3	1,375	2.34	4,812	2.07	705	1.71	3,210	1.64	<0.001	0.299
≥4	149	0.25	565	0.24	69	0.17	332	0.17	0.652	0.926
	mean	SD	mean	SD	mean	SD	mean	SD		
Continuous Enrollment (CE) from Index Date (months)	39.73	28.25	31.32	24.67	36.63	26.22	28.62	22.49	<0.001	<0.001
Additional Enrollment during Study (months)**	5.84	14.83	4.45	12.42	4.44	12.69	3.48	10.67	<0.001	<0.001
Total Enrollment during Study (months)**	45.57	27.66	35.78	25.31	41.06	26.12	32.10	23.24	<0.001	<0.001

Characteristic	Parents (N=290,986)				Siblings (N=237,081)				ASD vs Comparison Parents p-value	ASD vs Comparison Siblings p-value
	ASD (N=58,757)		Comparison (N=232,229)		ASD (N=41,213)		Comparison (N=195,868)			
	n	%	n	%	n	%	n	%		
Total Enrollment during Study (categories)**										
6 months	3,308	5.63	28,452	12.25	3,154	7.65	29,588	15.11	<0.001	<0.001
12 months	10,861	18.48	62,450	26.89	9,002	21.84	58,263	29.75	<0.001	<0.001
24 months	10,604	18.05	45,023	19.39	8,049	19.53	38,740	19.78	<0.001	0.250
36 months	9,251	15.74	32,417	13.96	6,488	15.74	25,643	13.09	<0.001	<0.001
≥48 months	24,733	42.09	63,887	27.51	14,520	35.23	43,634	22.28	<0.001	<0.001

*Based on simultaneous medical, pharmacy and behavioral health coverage.

**Subjects may have had gap(s) in enrollment during this time.

ⁱ Stroupe KT, Kinney ED, Kniesner JJ. Chronic Illness and health insurance-related job lock. *J Policy Anal Manage.* 2001;20:525-544.

Appendix C: Stress Subtype Results

Table C-1. Logistic Regression of Mood/Anxiety Disorders among ASD Parents

Independent Variables	Stress-related Conditions			
	Odds ratio	Lower 95% CI	Upper 95% CI	p-value
Parent Gender				
Female	ref.	–	–	–
Male	0.468	0.450	0.487	<0.001
Parent Household Income*				
<\$50,000	ref.	–	–	–
\$50,000 - \$74,999	0.962	0.893	1.035	0.295
\$75,000 - \$99,999	0.993	0.921	1.070	0.855
\$100,000 - \$124,999	0.964	0.890	1.043	0.359
\$125,000 +	0.944	0.867	1.028	0.182
Unknown	0.915	0.842	0.994	0.036
Parent Race/Ethnicity*				
White	ref.	–	–	–
African American/Black	0.509	0.435	0.595	<0.001
Asian	0.367	0.305	0.441	<0.001
Hispanic	0.643	0.581	0.711	<0.001
Other	0.468	0.379	0.577	<0.001
Unknown	0.882	0.828	0.938	<0.001
Parent Geographic Region				
South	ref.	–	–	–
Northeast	1.136	1.071	1.205	<0.001
Midwest	1.274	1.216	1.335	<0.001
West	1.202	1.129	1.280	<0.001
Parent Quan-Charlson Comorbidity Score (categorical)				
0	ref.	–	–	–
1	1.534	1.463	1.608	<0.001
2	1.721	1.600	1.852	<0.001
3+	1.927	1.770	2.098	<0.001
Parent Age at Index Date (continuous)	1.002	0.999	1.006	0.188
Number of Children (continuous)***	1.010	0.993	1.027	0.253
Child's Age at Index**	1.011	1.006	1.017	<0.001
Child's Comorbidity Score (categorical)****				
0	ref.	–	–	–
1	1.076	1.030	1.125	0.001
2	1.087	1.030	1.148	0.003

Independent Variables	Stress-related Conditions			
	Odds ratio	Lower 95% CI	Upper 95% CI	p-value
Parent Total Enrollment during Study (quintiles)*****				
Lowest quintile	ref.	–	–	–
2nd quintile	1.638	1.499	1.791	<0.001
3rd quintile	2.136	1.958	2.329	<0.001
4th quintile	2.596	2.387	2.823	<0.001
Highest quintile	3.408	3.135	3.704	<0.001

Observations read = 58,757, Observations used= 58,757

Likelihood ratio: chi-square=4438.869, DF=26, p-value=<0.001

Hosmer and Lemeshow: chi-square=7.156, DF=8, p-value=0.520

c statistic = 0.677

*From merged socioeconomic data.

**The youngest child's age was retained where multiple related children exist.

***Includes both index children and siblings of index children

****The largest score was retained where multiple related children exist.

***** Subjects may have had gap(s) in enrollment during this time. Quintiles calculated among combined ASD and comparison groups.

Table C-2. Logistic Regression of Sleep Disorders among ASD Parents

Independent Variables	Stress-related Conditions			
	Odds ratio	Lower 95% CI	Upper 95% CI	p-value
Parent Gender				
Female	ref.	–	–	–
Male	0.875	0.831	0.922	<0.001
Parent Household Income*				
<\$50,000	ref.	–	–	–
\$50,000 - \$74,999	1.034	0.939	1.139	0.499
\$75,000 - \$99,999	1.029	0.933	1.136	0.567
\$100,000 - \$124,999	1.015	0.914	1.127	0.779
\$125,000 +	1.119	1.003	1.248	0.044
Unknown	1.017	0.910	1.135	0.771
Parent Race/Ethnicity*				
White	ref.	–	–	–
African American/Black	0.709	0.583	0.862	<0.001
Asian	0.474	0.373	0.602	<0.001
Hispanic	0.724	0.636	0.824	<0.001
Other	0.551	0.413	0.734	<0.001
Unknown	0.834	0.768	0.907	<0.001
Parent Geographic Region				
South	ref.	–	–	–
Northeast	0.675	0.623	0.731	<0.001
Midwest	0.791	0.744	0.841	<0.001
West	1.036	0.957	1.122	0.377
Parent Quan-Charlson Comorbidity Score (categorical)				
0	ref.	–	–	–
1	1.844	1.735	1.961	<0.001
2	2.428	2.229	2.646	<0.001
3+	3.566	3.250	3.912	<0.001
Parent Age at Index Date (continuous)	1.019	1.014	1.023	<0.001
Number of Children (continuous)***	1.011	0.989	1.033	0.332
Child's Age at Index**	1.022	1.015	1.028	<0.001
Child's Comorbidity Score (categorical)****				
0	ref.	–	–	–
1	1.058	0.998	1.122	0.059
2	1.113	1.038	1.193	0.003

Independent Variables	Stress-related Conditions			
	Odds ratio	Lower 95% CI	Upper 95% CI	p-value
Parent Total Enrollment during Study (quintiles)*****				
Lowest quintile	ref.	–	–	–
2nd quintile	1.528	1.336	1.747	<0.001
3rd quintile	2.159	1.899	2.454	<0.001
4th quintile	2.732	2.414	3.091	<0.001
Highest quintile	3.582	3.170	4.046	<0.001

Observations read = 58,757, Observations used= 58,757

Likelihood ratio: chi-square=3047.151, DF=26, p-value=<0.001

Hosmer and Lemeshow: chi-square=15.260, DF=8, p-value=0.054

c statistic = 0.693

*From merged socioeconomic data.

**The youngest child's age was retained where multiple related children exist.

***Includes both index children and siblings of index children

****The largest score was retained where multiple related children exist.

***** Subjects may have had gap(s) in enrollment during this time. Quintiles calculated among combined ASD and comparison groups.