



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 C: Health Care Utilization and Costs

Final Report

Prepared for: National Institute of Mental Health

Submitted by: The Lewin Group, Inc.

Revised December 20, 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 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 objective of Task C was to describe the use of health care services by children with ASD and their families and compare their use to children without ASD and their families. To meet this overarching objective, Task C was designed to have two components. This study first examined the use and costs of a broad set of health care services and then addressed two areas of particular interest in the literature and to NIMH and our External Advisory Committee (EAC) – psychotropic polypharmacy and adherence to MMR vaccination.

The goals of the psychotropic polypharmacy and MMR vaccination analyses were to:

- Measure the prevalence and extent of polypharmacy among children with ASD;
- Determine the individual and provider characteristics related to psychotropic medication use and psychotropic polypharmacy among children with ASD;
- Compare the rates of MMR vaccination among children with ASD and their siblings relative to children without ASD and their siblings;
- Compare the rates of MMR vaccination among children with ASD vs. children without ASD and ASD younger siblings vs. comparison younger siblings; and
- Determine if there was a difference in MMR vaccination rates between children with ASD and their younger siblings and between children without ASD and their younger siblings.

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 C 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 C are true cases. However, exclusion of children with only 1 ASD claim from both the case and comparison groups likely increases the differences between children with ASD and their family members when compared to controls.

To address the research questions concerning the use and costs of health care services by children with ASD and their family members relative to children without ASD and their family members, descriptive techniques that account for length of enrollment time were used; annualized health care visits, counts of medications and medication dispensings and per member per month (PMPM) health care costs were calculated. Additionally, for the binary variable indicating whether a study subject had evidence of psychotropic medication use, we utilized logistic regression to produce enrollment-adjusted proportions and odds ratios. The odds of having a psychotropic medication fill for each medication class of interest at any point during enrollment were estimated. All results are stratified by case sample (children with ASD, parents of children with ASD, and siblings of children with ASD) and the respective comparison group. Further, select results were produced for each sample by gender and age groups at index date (See Appendix C).

Psychotropic Polypharmacy

The analytic approach to measuring psychotropic polypharmacy included a clear definition of polypharmacy and appropriate modeling techniques. Measures of psychotropic polypharmacy variables were determined for children with ASD based on pharmacy claims for prescriptions filled during the child's total enrollment time during the study. An episode of single-class psychotropic polypharmacy was defined as overlapping fills of two or more psychotropic medications within the same class for at least 30 days. Two definitions were created – one that captured episodes of *specific* within-class medication combinations lasting 30 days or more and a broader definition that captured episodes of *any* within-class combination(s) lasting 30 days or more. An episode of multi-class psychotropic polypharmacy was defined as overlapping fills of medications across two or more classes for at least 30 days. As with single-class polypharmacy, two definitions were created – one that captured episodes of *specific* class combinations lasting 30 days or more and an overall definition that captured episodes of *any* multi-class combination(s) lasting 30 days or more. In measuring multi-class polypharmacy, no single medication within a class needed to overlap by 30 days with a particular medication in another class. We were only interested in unique combinations of *classes* of at least 30 days.

Descriptive analyses were conducted to examine the prevalence and extent of psychotropic polypharmacy among children with ASD and summarize the characteristics of their psychotropic polypharmacy episodes. To determine the individual and provider characteristics related to psychotropic use and psychotropic polypharmacy, four multivariate models were run based on the sample of children with ASD. In the first two analyses, binary measures of any psychotropic use and any combination-specific multi-class polypharmacy, respectively, were modeled using a logistic regression model. The third model, a multinomial logistic regression, modeled psychotropic use and combination-specific multi-class polypharmacy. The dependent variable for this model categorized children with ASD into five mutually-exclusive groups: 0) no psychotropic use, 1) at least one psychotropic medication without multi-class polypharmacy, 2) multi-class polypharmacy with a maximum of 2 classes, 3) multi-class polypharmacy with a maximum of 3 classes, and 4) multi-class polypharmacy with a maximum of 4 or more classes.

Finally, a generalized linear model with gamma distribution and log link was used to model length of polypharmacy among the subset of children with ASD with evidence of combination-specific multi-class polypharmacy.

Adherence to MMR Vaccination

Adherence to recommended MMR vaccinations was determined for children with and without ASD and their siblings. Specifically, whether or not a child had a claim for MMR between the ages of 12 and 24 months and between the ages of 4 and 6 years was determined.

To compare how children with ASD and their siblings compare to children without ASD and their siblings in terms of recommended MMR vaccination, the proportion of children with evidence of MMR vaccination between the age periods of 12 and 24 months and 4 and 6 years was calculated. To compare whether having a child with ASD is related to adherence to recommended MMR vaccinations among younger siblings, logistic regression analyses modeling vaccination were conducted, one model for the period of 12 to 24 months of age and another for the period of 4 to 6 years of age. The analyses were based on a matched pair sample, including children with and without ASD with enrollment during the entire age period who also had a *younger* sibling with enrollment during the entire same age period. Comparisons examined within the models were children with ASD vs. children without ASD and ASD younger siblings vs. comparison younger siblings. We also tested whether there was a difference between children with ASD and their younger siblings and between children without ASD and their younger siblings.

Results

We found the following results about health care utilization and costs, psychotropic polypharmacy, and adherence to recommended MMR vaccinations:

- Overall, children with ASD had higher utilization than children without ASD. Children with ASD had more inpatient and emergency department visits, total office visits, total outpatient facility visits, behavioral health care visits, preventive care visits, ancillary therapy visits, and medication dispensings than children without ASD. In addition, children with ASD were more likely to have psychotropic medication fills.
- Similarly, with the exception of parent use of inpatient services, family members of children with ASD had higher health care utilization than their comparison groups. For example, parents of children with ASD had a median of 6.2 ambulatory visits per year, compared to 4.5 for comparison parents. Siblings of children with ASD had a median of 4.6 total ambulatory visits per year, compared to 3.0 for comparison siblings. The median number of medication dispensings was 6.3 and 4.0 for ASD and comparison parents respectively, and 2.2 and 1.4 for and ASD and comparison siblings, respectively.
- Greater utilization of health care services translated into higher health care costs for children with ASD as well as for their family members. For example, median monthly costs for children with ASD exceeded those for children without ASD for total medical care (\$202.28 vs. \$39.53), behavioral health care (\$72.26 vs. \$0.00), and medications (\$46.22 vs. \$3.86).
- Just under 40% of all children with ASD had either single-class or multi-class polypharmacy. Approximately 20% of the 33,565 children with ASD had evidence of

single-class polypharmacy, and 35% of the sample had evidence of multi-class polypharmacy. The most common type of single-class polypharmacy was among ADD medications (11.6%).

- The mean number of multi-class episodes per child was 5.6, totaling a median of approximately 346 days of polypharmacy. Approximately 38% of the children with multiclass polypharmacy had at least one episode involving an antidepressant and ADD medication, and just over a quarter had at least one episode with an antipsychotic and ADD medication. About 20% of the children with multi-class polypharmacy had at least one episode with an antipsychotic and antidepressant or an antipsychotic, antidepressant and ADD medication.
- Our results suggest that seizures, ADD, bipolar disorder, and anxiety are all significant predictors of psychotropic use and, along with depression, of multi-class polypharmacy among children with ASD. Furthermore, children with ASD who also had seizures, ADD, or bipolar disorder had the highest odds of more complicated multi-class polypharmacy (as measured by a higher number of medication classes involved). Additionally, among children with multi-class polypharmacy, these three conditions were associated with a 15%-30% longer duration on polypharmacy.
- Older age at index and having had a psychiatrist visit were consistently related to higher odds across all psychotropic medication use outcomes (psychotropic use, polypharmacy and polypharmacy use involving many classes of medications) relative to no psychotropic use. Additionally, among children with multi-class polypharmacy, older age at index and having had a psychiatrist visit were associated with longer duration on polypharmacy.
- After controlling for demographic characteristics and the presence of allergies or seizures, we found that children with ASD were just as likely as comparison children to be vaccinated with MMR between the ages of 12 and 24 months and between the ages of 4 and 6 years. In contrast, younger siblings of children with ASD were less likely to have received the MMR vaccination than younger siblings of comparison children during both age periods. Most importantly, we found that between 12 and 24 months of age, while younger siblings of the comparison sample did not differ from their older sibling without ASD, younger siblings of children with ASD were less likely to be vaccinated than the child with ASD. Our interpretation of this finding is that in spite of an increase in the rate of vaccination over time, parents of children with ASD may continue to harbor some apprehension about a potential causal link between the MMR vaccine and ASD and, as a result, fewer younger siblings of children with ASD were vaccinated.

Implications and Recommendations

In summary, we found that children with ASD and their families used more health care services than children without ASD and their families. Our psychotropic polypharmacy analysis found that 40% of children with ASD had psychotropic polypharmacy and the presence of co-occurring conditions was associated with more complicated psychotropic polypharmacy use. We also found that younger siblings of children with ASD were less likely to have received the MMR

vaccination than their older sibling with ASD between 12 and 24 months of age. Specifically, our results lead to the following implications:

- Considering the morbidity of ASD itself and the high rates of co-occurring conditions, it is somewhat reassuring to see that these children are making use of health care services substantially more than comparison children without ASD. Still unanswered, however, are questions regarding whether they are receiving appropriate or enough care for ASD and co-occurring conditions as well child care that all children should receive.
- Our findings demonstrate that the medical use and cost patterns of the entire family may be influenced by having a child with ASD. Supportive interventions for the family as a whole rather than each individual separately are therefore necessary in order to improve the health care experience and quality of life of children with ASD and their families.
- When comparing our psychotropic medication use results to results in the literature for children with ASD covered by Medicaid, our results suggest more unity than discord. Both populations have a prevalent use of psychotropic medications, a high rate of polypharmacy, and age, race, and co-occurring conditions are all statistically significant on psychotropic use.
- The high use of concomitant pharmacotherapy with powerful psychotropic medications merits concern and further investigation about the safety and effectiveness of such practices on developing children. Our estimates of the prevalence of polypharmacy among children with ASD emphasize the need for additional evidence on the appropriateness, effectiveness and safety of psychotropic medications in this population. Moreover, further research into the sociodemographic and geographic variation in the practice of polypharmacy and whether the variation is driven by clinical need or other factors may provide a better understanding of differences in treatment patterns across the country.
- Our finding that younger siblings of children with ASD are less likely to have received the MMR vaccination than the child with ASD, underscores the need for continued public education on the topic of vaccination safety, especially among families caring for children with ASD.

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 may be more precise and objective than previously available. Our findings on general utilization are in line with previous studies but are based on a larger and likely more heterogeneous population of privately insured children with ASD with great ability to conduct in-depth analysis of important variables and subgroups in the future. Our analyses of polypharmacy and MMR vaccinations provide new insights about challenges in care for children with ASD and their siblings.

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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 (EAC) 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 children without ASD and their family members.
- Task C: Describe and compare the use of health care services by children with ASD and their family members to children without ASD and their family members.
- Task D: To explore the utility of claims data in investigating potential risk factors for ASD.

Task A, conducted between September 2010 and March 2012, was comprised of two subtasks: 1) a 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 C: Health Care Utilization Study. The methodology and results of the Task A: Baseline Claims Analysis and Task A: Chart Study that informed our approach for Task C 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 and health care needs of a large heterogeneous group of children with ASD and of members of their families. 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. 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 (ADD).^{1,1}

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 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.

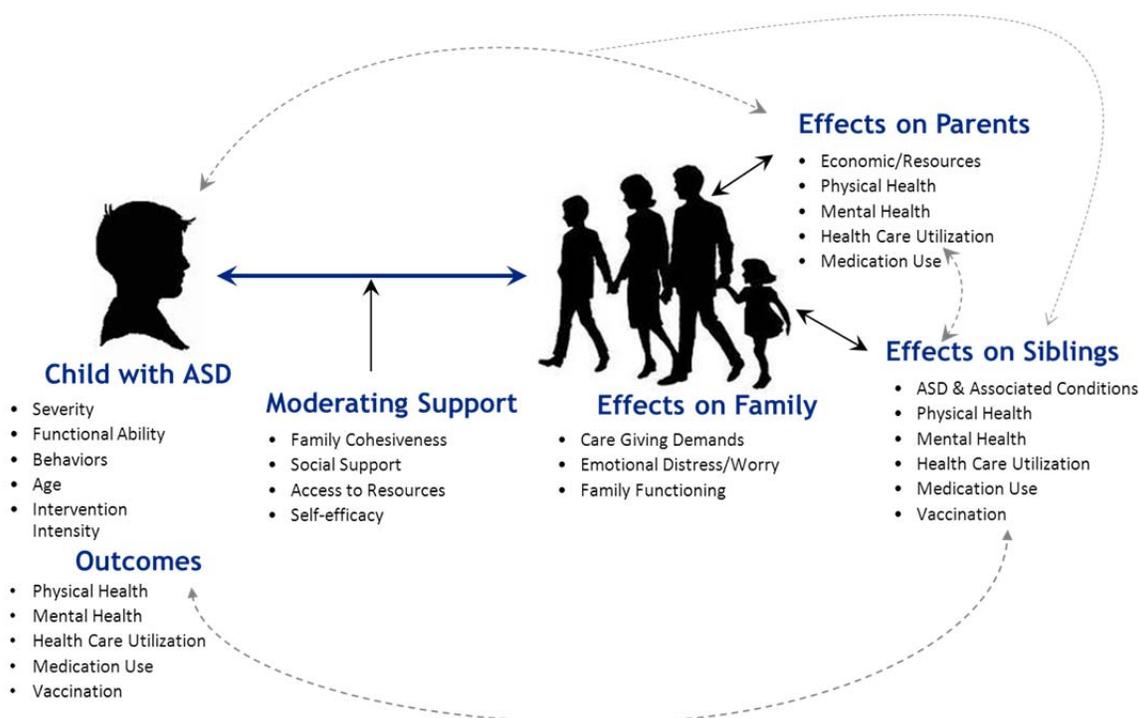
C. ASD, Health Care Utilization, and the Family

Members of families having a child with ASD, like members of all families, share certain common biologic characteristics and environmental influences. There is also considerable literature,

¹ 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.

supporting the potentially profound family effects of having a child with ASD. These effects fall into several realms of “family health” including parental health, sibling health, and 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 and health care utilization is presented below.

Figure 1. Conceptual Model of Family Health Conditions and Health Care Utilization for Families who have a Child with ASD



The conceptual model above shows that the child affects the family (and vice versa) through several potential mechanisms. First, in families in which there is a child with ASD, there is a higher risk of ASD and of many of the common 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 in both positive and negative ways. For example, studies have found that mothers of children with disabilities are less likely to be employed outside the home, with effects that are often detrimental to the mother’s emotional health as well as on family income. Lastly, a child with ASD has an impact on family functioning as a whole which can also be positive and/or negative in terms of cohesiveness, strength of marriage, relationships with siblings, etc.

The characteristics of the child with ASD can be important mediating variables in assessing family health conditions and family use of health care services. These include, for example, the severity and degree of functional disability in the child with ASD, the presence of troublesome behaviors and symptoms, the existence of co-occurring conditions, the child’s age, and the intensity of interventions or treatment program received by the child. 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 family functioning, availability of child care and respite, access to health care, family 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 lead to 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 claims data to investigate health concerns and the use of health care services associated with children with ASD and with the members of their families. In this report, we sought to examine the use of health care services of children with ASD and of their family members using a large, national commercial health plan claims research database. It is our hope that our use of the large-scale claims database 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. The large sample sizes and rich diagnostic information inherent to our research databases (described below) provide the opportunity to shed insight on some of the most commonly used health care services as well as on some previously unexamined variables of interest.

The objective of Task C was to add to existing literature by describing the use of health care services by children with ASD and their families and comparing their use to use by children without ASD and their families. To meet this overarching objective, Task C was designed to have two components. The first component focused on general health care utilization and costs. We hypothesized that we would find higher health care utilization and costs among children with ASD and their families compared to our comparison group of children without ASD and their families. However, because of the dynamic nature of the complex relationships (sometimes unobservable due to lack of data) among the multiple variables influencing family and child health (sometimes unobservable due to lack of data) and the often unclear clinical pathways, our investigations were intended to establish correlations (or the lack of thereof) rather than causal inferences.

The second component delved more deeply into two areas of particular interest in the literature and to NIMH and our EAC: psychotropic polypharmacy use among children with ASD and measles, mumps, and rubella (MMR) vaccination adherence. These issues reflect health decisions by providers and parents that may have an important impact on a child's health and quality of life and, ultimately, on public health. Current research about polypharmacy (the concurrent use of multiple medications) lacks detail on the prescription patterns among children diagnosed with ASD. Our Task A: Baseline Claims Analysis report highlighted the use of psychotropic medications among children with ASD: 59% of children with ASD had at least one prescription for a psychotropic medication during their study observation time compared with only 11% of children without ASD. The rise in polypharmacy treatment and the safety concerns associated with concomitant use of these medications have prompted experts to note the need to monitor rates of medication use among children in general, particularly those with psychological conditions. Vaccination adherence among children with ASD and among their siblings is also an area of interest given the varying rates of vaccine refusal due to parental worries about their safety in general and related to autism in particular. Because parental attitudes toward vaccinations can have strong ramifications for public health, our analysis focused on whether our data demonstrate that children with ASD and their siblings were less likely to be vaccinated than children without ASD and their siblings.

II. Study Objectives and Research Questions

The overall purpose of Task C was to compare the health care utilization and costs of children with ASD and their family members to children without ASD and their family members. This study first examined overall health care utilization and costs across a range of health care service categories and then specifically focused on psychotropic medication use among children with ASD and adherence to recommended measles, mumps, and rubella (MMR) vaccination among children with and without ASD and their siblings. We list the specific research questions below.

A. General Health Care Utilization and Costs

1. How do children with and without ASD, parents of children with and without ASD, and siblings of children with and without ASD compare in terms of ambulatory (office and outpatient), emergency department, inpatient, behavioral, preventive and ancillary therapy health care services utilization as well as in terms of prescription medication?
2. How do children with and without ASD, parents of children with and without ASD, and siblings of children with and without ASD compare in terms of ambulatory (office and outpatient), emergency department, inpatient, behavioral, pharmacy, ambulatory sensitive condition-related, and total health care costs?

B. Psychotropic Polypharmacy

1. Among children with ASD, how common is psychotropic polypharmacy (within and across medication classes)?
 - How many unique overlapping psychotropic medications are observed for children with ASD?
 - What types of health care providers have children with psychotropic polypharmacy seen?
 - Among children with ASD with evidence of multi-class psychotropic polypharmacy, what are the most common combinations of medication classes used?
2. What individual and provider characteristics are related to psychotropic medication use, including psychotropic polypharmacy, among children with ASD?

C. Adherence to MMR Vaccination

1. Overall, how do children with ASD and their siblings compare to children without ASD and their siblings in terms of adherence to recommended MMR vaccination?
2. Is having a child with ASD related to adherence to recommended MMR vaccinations among younger siblings?

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 sample-related variable definitions. Section IV presents data on sample identification and

summarizes the demographic characteristics of study samples. Sections V, VI, and VII are organized by each of the three sets of research questions: general health care utilization and cost measures, psychotropic polypharmacy, and MMR vaccination adherence. Each of these sections includes background on the topic, variable definitions, methods, results, and discussion. Finally, Section VIII concludes the report with a summary of key findings and a discussion of implications and recommendations. Additional information is included in the Appendices, which are 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, and observation periods; and d) descriptions of select analytical variables constructed for the study analysis.

A. Data Sources

The data sources for the Task C 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.⁴ Claims for facility services submitted by institutions (e.g., hospitals) use the UB-82, or UB-92, or UB-04 format.^{5,6} 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 six 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 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 six 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.⁷ 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.^{8, 9} 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.

B. Study Reviews

1. Institutional Review Board (IRB) Review

OptumInsight submitted the Task C 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 C 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.

C. Study Sample

The base samples for this study were the subjects identified within the OptumInsight Research Database for Task A: Baseline Claims Analysis. 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 C 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 six 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 date^{II}
- Aged ≤ 20 years as of the index date
- At least one 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)^{III} 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.^{IV}

- 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.^V

^{II} 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.

^{III} Up to four diagnosis codes are recorded on physician claims and up to nine 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.

^{IV} 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 six 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 date^{vi}
- 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 three comparison subjects to one 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).^{vii} 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* include family plan members already included in the sample of children with ASD or already included in the comparison group.

^v 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 C analyses coupled with the large size of the comparison group supported our decision to draw an unmatched comparison cohort.

^{vi} 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.

^{vii} 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.

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.^{viii} 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 six 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 date^{ix}

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

^{viii} 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.

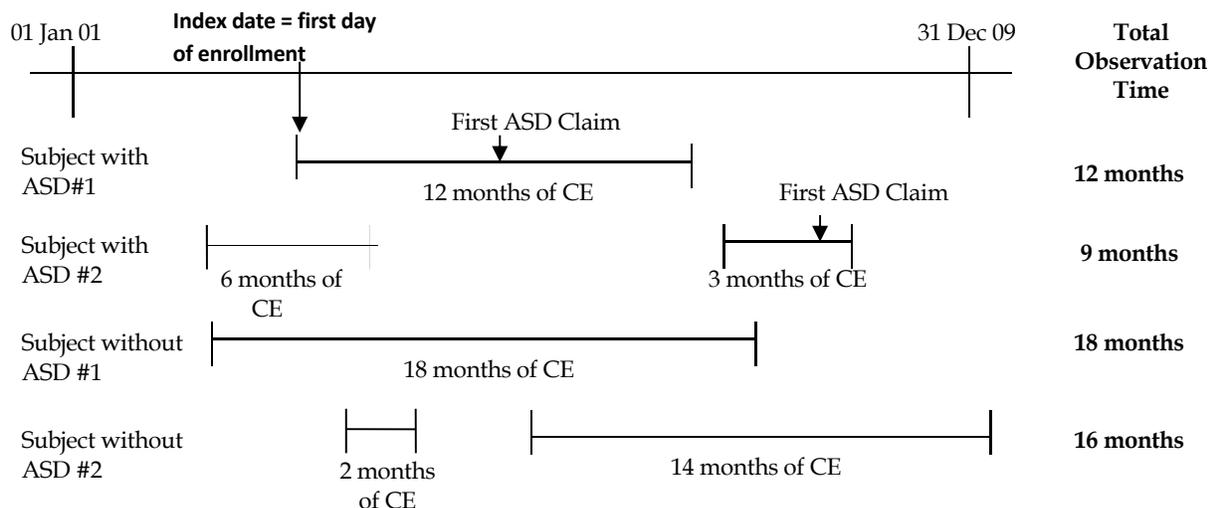
^{ix} Continuous enrollment was based on simultaneous medical, pharmacy, and behavioral health coverage. Gaps in enrollment of ≤ 32 days were bridged and included in calculation of continuous enrollment duration. Note: if a patient had more than one enrollment period with all three types of coverage, 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.

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 one period of at least six 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 six months of continuous enrollment were studied during the time between January 2001 and December 2009. If subjects had more than six 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.

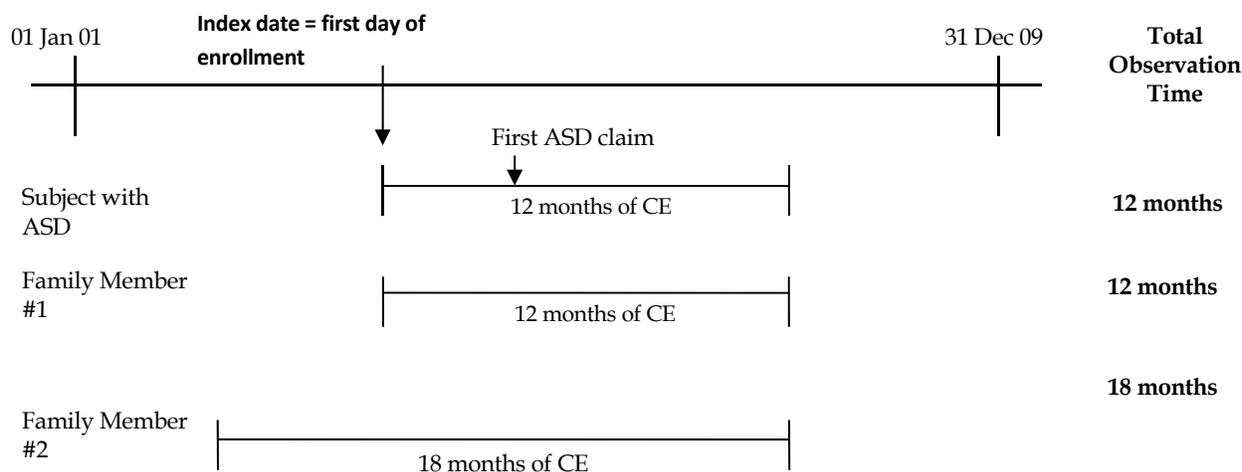
Figure 2. Study Observation Time - Children with and without ASD



Family plan members who met the inclusion criteria were also required to have one period of at least six 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 C

In Task A, eligible ASD subjects were classified into two groups: “Likely ASD” and “Possible ASD.” The Likely ASD group included subjects with two or more medical claims with an ASD diagnosis code in any position or one claim with an ASD diagnosis code in a position and one pharmacy claim for risperidone. The Possible ASD group was defined as those children with just one 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 C. First, we revised the Likely ASD criteria to include only children with two 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 one claim with an ASD diagnosis code and one prescription for risperidone from the Likely ASD group definition.

Second, we dropped the Possible ASD group from the ASD sample, focusing Task C 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 C. The sampling process and study subject characteristics are presented in Section IV: Sample Identification and Demographic Characteristics.

D. Variable Definitions

The variables described below focus on 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).

Additional analytic variables are described later in Sections V: General Health Care Utilization Measures; VI: Polypharmacy; and VII: Vaccination.

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 period 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.

- **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, \$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 2**.

Table 2. 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 3 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 six months of continuous enrollment with simultaneous medical, pharmacy and behavior health coverage at some point during the identification window were identified.^x 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.^{xi} 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).

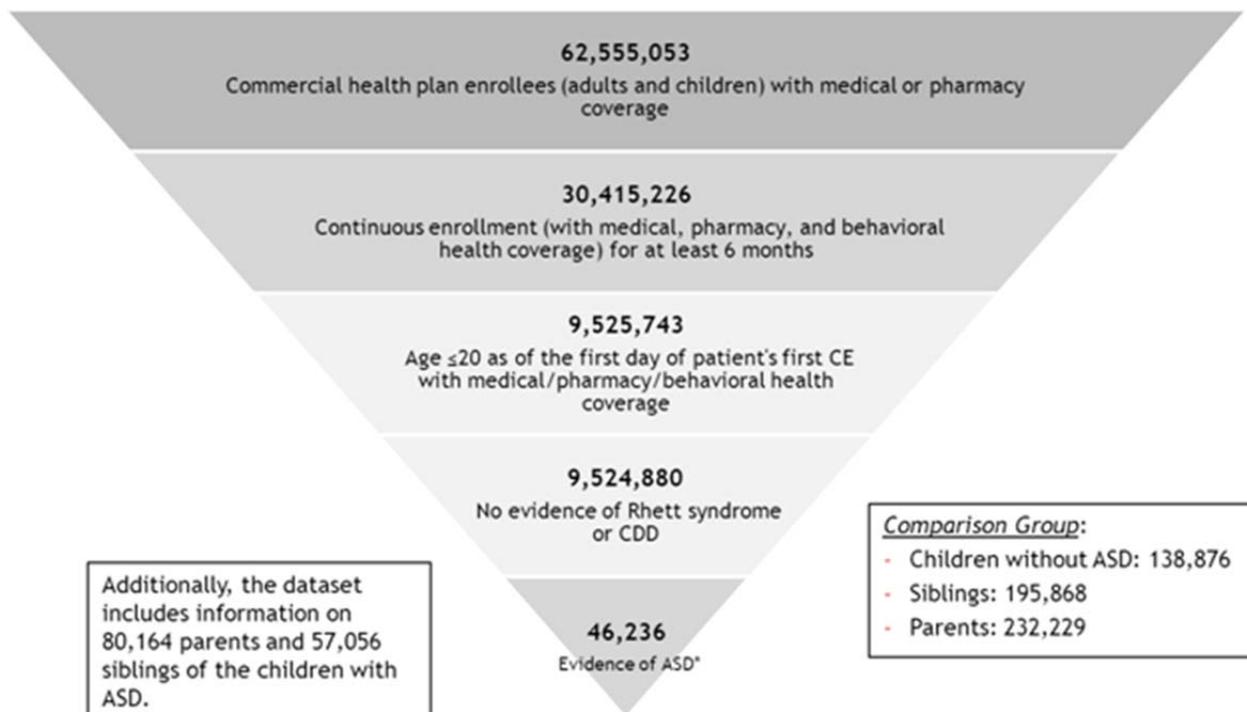
To select family plan members eligible for the study, family plan members with at least six months of continuous enrollment with simultaneous medical, pharmacy and behavior health coverage during the identification window of 2001 through 2009 were flagged. Family plan

^x While all subjects sampled for the study were required to have at least six 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 one 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."

^{xi} 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.

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.^{xii} 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 3. 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 C

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 two or more medical claims with an ASD diagnosis code in any position or one claim with an ASD diagnosis code in any position and one claim for risperidone. The Possible ASD group included those children with just one claim with an ASD diagnosis code in any position.

As described above, the sample for Task C 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 C. **Table 3** shows the impact of these changes on the sample of children with ASD as well as affiliated

^{xii} 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.

parents and siblings. The final ASD-related samples used in Task C 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 two 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 C 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 3. 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 two or more claims with ASD diagnosis in any position. Possible ASD subjects include children with only one claim with ASD diagnosis in any position.

B. Demographic and Enrollment Characteristics

1. Children with and without ASD

Table 4 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 four times more likely than girls to be diagnosed with autism.^{1,10}

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 was between the ages of 18-20 years at index, compared to only 2.1% of children with ASD. Given, on average, children are diagnosed with ASD before the age of 8^{11,12} 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 4** 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 six 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 six 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 three to five months of enrollment from these additional enrollment periods. Children with ASD had an average of 43.5 months (over three years) of total enrollment during the study, and children without ASD had an average of 30.5 months (roughly two 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 two or more years of enrollment during the study period.^{XIII} 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.¹³

Table 4. 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
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

^{XIII} 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
	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.¹⁴ See Task A: Baseline Claims Analysis Report submitted to NIMH on October 17, 2011 for more information.

2. Family Members

Table 5 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 one 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 two years or more. Overall, as expected, parents had more enrollment time than other members of their family.

Table 5. Demographic and Enrollment Characteristics of ASD and Comparison Group Family Members

Demographic and 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 and 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
	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

*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 Care Utilization and Costs

A. Background

ASD are complex conditions which are often accompanied by other health conditions in addition to its hallmark social impairments.¹⁵ Given this level of complexity and morbidity, one would expect more interactions with the health care system and different utilization patterns for children with ASD than a group of peers without ASD, as has been found in previous studies.^{16,17,18,19, 20, 22, 25} What is less well known are if there are any differences in utilization patterns and costs of health care among parents and siblings of children with ASD relative to parents and siblings of children without ASD. In this study, we examined a number of measures of health care utilization and costs, such as preventive care visits and costs, and behavioral health care visits and costs among our sample of children with ASD, their family members, and the comparison groups. Our objective in measuring health care costs (health plan costs plus patient out-of-pocket costs) was two-fold. First, it provides a proxy for total utilization as obviously we are unable to add utilization across service types, such as the number of outpatient visits and inpatient admissions. Second, it is a measure of intensity of health care use for a particular type of health care service. For example, the count of inpatient admissions does not take into account length of stay or intensity of services received, which can be captured in health care costs. The objective of our first set of research questions was to examine health care utilization and costs controlling only for length of continuous enrollment. The corresponding research questions, first introduced in Section II, are repeated below:

1. How do children with and without ASD, parents of children with and without ASD, and siblings of children with and without ASD compare in terms of ambulatory (office and outpatient), emergency department, inpatient, behavioral, preventive and ancillary therapy health care services utilization as well as in terms of prescription medication?
2. How do children with and without ASD, parents of children with and without ASD, and siblings of children with and without ASD compare in terms of ambulatory (office and outpatient), emergency department, inpatient, behavioral, pharmacy, ambulatory sensitive condition-related, and total health care costs?

B. Methods

1. Variable Definitions

Unless otherwise indicated, health care utilization and costs were measured for all study subjects – children with ASD, children without ASD, as well as family members – and for subjects' total enrollment time during the study.

- **All-cause health care utilization.** A count of a subject's office visits (e.g., physician offices, health clinics), outpatient facility visits (e.g., outpatient hospital clinics or surgical centers), ambulatory visits (office and outpatient combined), emergency department visits, and inpatient stays regardless of the primary reason for the visit. A separate measure for each type of visit was created. Office and outpatient facility visits were calculated as one per provider per day, and emergency department visits were calculated as one per day.

- **Preventive care visits.** A count of subjects' preventive care visits. Claims for select CPT codes and ICD-9-CM diagnosis (in any position) and procedure codes were included. The count was calculated as one per provider per day. See Appendix A Table A-1 for the relevant diagnosis and procedure codes.
- **Behavioral health care visits.** A count of subjects' visits for behavioral health care in the medical or specialty behavioral sector. Behavioral health care claims were identified based on an algorithm prepared by OptumHealth Behavioral Solutions. The algorithm includes a list of selected diagnosis codes as well as two CPT procedure codes (90870 or 90871 for electroconvulsive therapy). To be included in the calculation, the behavioral health diagnosis had to be in the primary position for inpatient claims and could be in any position for other types of medical claims (e.g., office visits). Inpatient stays, emergency department, and office/outpatient visits were calculated separately per the specifications above. Behavioral health care visits thus potentially overlap with one or more of the other medical utilization categories (e.g., office visits, outpatient facility visits, emergency visits, inpatient stays). See Appendix A Table A-2 for the relevant diagnosis and procedure codes.
- **Ancillary therapy visits.** A count of subjects' ancillary therapy visits (e.g., speech therapy visits). Claims for select CPT codes and ICD-9-CM diagnosis (in any position) and procedures codes were included. The count was calculated one per provider per day. See Appendix A Table A-3 for the relevant diagnosis and procedure codes.
- **Unique medications.** A total count of unique medications filled based on medication codes.
- **Total medication dispensings.** A total count of all pharmacy claims, or prescription fills.
- **Psychotropic medications.** Whether a subject had at least one claim for an anticonvulsant/antiepileptic, antidepressant, lithium, antipsychotic, anxiolytic, ADD, or anticholinergic/antiparkinson's medication. Measurement was based on pharmacy claims for prescriptions filled. A flag was created overall and by class (see Appendix A Table A-4) for the children samples. Additionally, a total count of prescription fills overall and for each class and subclass was calculated. The definition of these variables was revised from that used in Task A: Baseline Claims Analysis.^{xiv} For this reason, results presented in this report differ somewhat from results presented in the report for Task A.
- **All-cause health care costs.**^{xv} The combined health plan and patient paid amounts for all claims. Costs calculated included overall costs, pharmacy costs, and medical costs. Medical costs were further broken down by office costs, outpatient facility costs, ambulatory costs (office and outpatient combined), emergency department costs, inpatient costs, and other costs. All costs have been adjusted to reflect 2009 dollar values

^{xiv} Medical claims for medications (i.e., J codes) were not included in the Task C measurement. Both pharmacy claims and medical claims were used to identify psychotropic and other select medication use in Task A: Baseline Claims Analysis. Among the 46,236 children with ASD identified within the OptumInsight database, 27,287 had evidence of a psychotropic, ADD medication, hormone or mood stabilizing medication. Of these, only 246 or 0.01% had one or more medical claims for these medications.

^{xv} All cost variables and results will be omitted from the NDAR deliverable.

using the annual medical care component of the Consumer Price Index (CPI) to reflect inflation between 2001 and 2009.^{xvi}

- **Behavioral health care costs.** The combined health plan and patient paid amounts for behavioral health care services in the medical or specialty behavioral sector. Behavioral health care claims were identified based on an algorithm prepared by OptumHealth Behavioral Solutions. The algorithm includes a list of selected diagnosis codes as well as two CPT procedure codes (90870 or 90871 for electroconvulsive therapy). To be included in the calculation, the behavioral health diagnosis had to be in the primary position for inpatient claims and could be in any position for other types of medical claims (e.g., office visits). As with the other cost variables, behavioral health care costs were CPI adjusted. Behavioral health care costs potentially overlap with one or more of the other medical cost categories (e.g., office costs, outpatient facility costs, emergency costs, inpatient costs, and other costs). See Appendix A Table A-2 for the relevant diagnosis and procedure codes.
- **Costs for ambulatory-sensitive conditions.** The combined health plan and patient paid amounts for inpatient and emergency department claims for ambulatory-sensitive conditions, including asthma, dehydration/gastroenteritis, pneumonia, seizure, skin infection, and urinary tract infection/pyelonephritis. An inpatient and emergency department claim with a relevant diagnosis code in the primary position was included in the calculation. The purpose for calculating these costs was to track conditions that are treatable in an outpatient setting but if not effectively managed can result in the need for emergency and inpatient care. We created this variable after consultation with our EAC, with whom we discussed the hypothesized possibility that children with ASD may be more difficult to treat in an outpatient setting due to manifestations of their ASD condition, may be more likely to develop severe cases of these outpatient manageable conditions, and thus may be more likely to have high costs for these conditions, due to higher use of emergency and inpatient care. See Appendix A Table A-5 for the relevant diagnosis codes.

2. Analytical Approach

To examine health care utilization and costs, descriptive techniques that account for length of enrollment time were used; annualized health care visits, counts of medications and medication dispensings and per member per month (PMPM) health care costs were calculated. Means, medians, and standard deviations are provided for these variables.

Additionally, for the binary variable indicating whether a study subject had evidence of psychotropic medication use, we utilized logistic regression to produce enrollment-adjusted proportions and odds ratios. The odds of having used a medication type at any point during enrollment were estimated. 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 created as five categorical variables representing the distribution of enrollment time in quintiles. The adjusted proportion of each sample with a fill for the

^{xvi} US 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. Washington, DC: U.S. Dept. of Labor, Bureau of Labor Statistics, 2008. <http://data.bls.gov/cgi-bin/surveymost?su>

medication type 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.

All results are stratified by case sample (children with ASD, parents of children with ASD, and siblings of children with ASD) and the respective comparison group. Further, select results were produced for each sample by gender and age groups at index date (See Appendix C).

It is important to note that many, but not all, of these variables were also analyzed under Task A: Baseline Claims Analysis. Across all these variables, the results for the sample of children with ASD (and their associated parents and siblings) differ from those presented in the Task A: Baseline Claims Analysis final report because of the changes in these samples described earlier, namely our decision to limit the sample for Task C to the children with ASD (and family members) who met the revised criteria for “Likely ASD”. In many instances, the results presented in this Task C report for the comparison group-related samples are the same as those reported under Task A but for a few of the variables, the results differ due to changes in variable definition and methods.

Note that with large sample sizes (such as those of our study samples), tests of association tend to be statistically significant.

C. Results

Table 6 presents data on all-cause and other health care utilization (annualized) for children with ASD and our comparison group of children without ASD. **Table 7** provides the same information for the parent and sibling samples.

Overall, children with ASD had higher utilization and costs than children without ASD (Table 6). For example, children with ASD had a median of 9.6 total office visits and 1.5 total outpatient facility visits per year, whereas for the comparison group the medians were 2.9 and 0.0, respectively. A similar pattern was observed for behavioral health visits. While preventive care and ancillary therapy visits (physical, occupational, speech, etc.) were modest in both groups, the annualized count of visits was still higher for children with ASD (median of 1.0 and 0.2 visits per year, compared to 0.7 and 0.0 for the comparison group). Children with ASD also had a median of 8.0 medication dispensings per year, compared to 1.6 for children without ASD. Note that zero median values for emergency department and inpatient utilization reflect that at least half of children, including children with ASD, did not have an emergency department visit or inpatient stay in a year’s time.

We also examined health care utilization by select gender/age group categories (see Appendix C). Among children with ASD, total and behavioral health ambulatory care visits, preventive care visits, and ancillary therapy visits were highest among the youngest age group, and this was true for both girls and boys. In contrast, not surprisingly, medication dispensings increased with age for both girls and boys.

Table 6. Annualized All-Cause Health Care Utilization among ASD and Comparison Groups

Utilization	ASD (N=33,565)			Comparison (N=138,876)			p-value
	mean	SD	median	mean	SD	median	
Total Health Care Visits							
Office Visits	16.90	24.31	9.61	4.36	5.50	2.87	<0.001
Outpatient Visits	3.73	7.75	1.48	0.92	2.33	0.00	<0.001
Ambulatory (Office + Outpatient) Visits	20.51	26.52	12.49	5.27	6.68	3.40	<0.001
Emergency Department Visits	0.94	3.65	0.13	0.28	1.09	0.00	<0.001
Inpatient Stays	0.10	0.37	0.00	0.07	0.29	0.00	<0.001
Behavioral Health Visits*							
Office Visits	9.32	19.21	3.66	0.37	2.15	0.00	<0.001
Outpatient Visits	1.76	5.93	0.22	0.04	0.76	0.00	<0.001
Ambulatory (Office + Outpatient) Visits	10.98	20.61	4.80	0.42	2.38	0.00	<0.001
Emergency Department Visits	0.55	3.31	0.00	0.03	0.67	0.00	<0.001
Inpatient Stays	0.05	0.25	0.00	0.00	0.07	0.00	<0.001
Preventive Care Visits*	1.45	1.73	1.04	1.26	2.08	0.71	<0.001
Ancillary Therapy Visits*	7.96	20.33	0.17	0.29	2.65	0.00	<0.001
Unique Medications	2.90	2.56	2.28	1.77	2.13	1.16	<0.001
Medication Dispensings	12.97	14.93	7.98	3.45	5.45	1.60	<0.001

*Behavioral health visits, preventive care visits, and ancillary care visits were identified based on select diagnosis and/or procedure codes. These are a subset of total health care visits and overlap with one or all of the total health care visits components listed. Please refer to Section V.B of this report for more information about these types of health care utilization.

Table 7 reports the utilization experience of parents and siblings of children with ASD, with the relevant comparison groups of parents and siblings of children without ASD in the final two table columns. For every service category examined in the table, with the exception of parent use of inpatient services, family members of children with ASD had higher health care utilization than their comparison groups. For example, parents of children with ASD had a median of 6.2 ambulatory visits per year, compared to 4.5 for comparison parents. Siblings of children with ASD had a median of 4.6 total ambulatory visits per year, compared to 3.0 for comparison siblings. The median number of medication dispensings was 6.3 and 4.0 for ASD and comparison parents respectively, and 2.2 and 1.4 for and ASD and comparison siblings, respectively.

Appendix C provides parent and sibling health care utilization for select gender/age groups.

Table 7. Annualized All-Cause Health Care Utilization of ASD and Comparison Group Family Members

Utilization		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)		
Total Health Care Visits							
Office Visits	mean	7.40	5.34	5.72	3.79	<0.001	<0.001
	SD	8.84	6.81	6.93	5.17		
	median	4.74	3.39	3.90	2.40		
Outpatient Visits	mean	1.98	1.69	1.17	0.85	<0.001	<0.001
	SD	3.42	3.32	2.97	2.41		
	median	0.93	0.60	0.31	0.00		
Ambulatory (Office + Outpatient) Visits	mean	9.35	7.01	6.87	4.63	<0.001	<0.001
	SD	10.64	8.68	8.41	6.41		
	median	6.15	4.50	4.60	2.99		
Emergency Department Visits	mean	0.64	0.46	0.34	0.26	<0.001	<0.001
	SD	2.36	1.79	1.22	1.00		
	median	0.00	0.00	0.00	0.00		
Inpatient Stays	mean	0.08	0.08	0.07	0.05	<0.001	<0.001
	SD	0.25	0.28	0.26	0.25		
	median	0.00	0.00	0.00	0.00		
Behavioral Health Visits*							
Office Visits	mean	1.39	0.58	0.98	0.36	<0.001	<0.001
	SD	4.20	2.40	3.65	2.28		
	median	0.00	0.00	0.00	0.00		
Outpatient Visits	mean	0.08	0.05	0.11	0.04	<0.001	<0.001
	SD	0.55	0.47	1.18	1.18		
	median	0.00	0.00	0.00	0.00		
Ambulatory (Office + Outpatient) Visits	mean	1.48	0.64	1.09	0.39	<0.001	<0.001
	SD	4.33	2.52	4.04	2.83		
	median	0.00	0.00	0.00	0.00		
Emergency Department Visits	mean	0.10	0.04	0.06	0.02	<0.001	<0.001
	SD	1.10	0.58	0.70	0.44		
	median	0.00	0.00	0.00	0.00		
Inpatient Stays	mean	0.01	0.01	0.01	0.00	<0.001	<0.001
	SD	0.09	0.09	0.08	0.06		
	median	0.00	0.00	0.00	0.00		

Utilization		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)		
Preventive Care Visits*	mean	1.94	1.73	1.32	1.04	<0.001	<0.001
	SD	1.99	2.03	1.71	1.62		
	median	1.50	1.20	0.92	0.60		
Ancillary Therapy Visits*	mean	0.70	0.45	0.69	0.28	<0.001	<0.001
	SD	2.74	2.20	4.53	2.62		
	median	0.00	0.00	0.00	0.00		
Unique Medications	mean	3.24	2.83	1.88	1.59	<0.001	<0.001
	SD	3.24	3.11	2.01	1.99		
	median	2.40	2.00	1.34	1.00		
Medication Dispensings	mean	11.80	8.69	4.61	3.15	<0.001	<0.001
	SD	15.67	12.81	7.11	5.36		
	median	6.29	4.00	2.21	1.35		

*Behavioral health visits, preventive care visits, and ancillary care visits were identified based on select diagnosis and/or procedure codes. These are a subset of total health care visits and overlap with one or all of the total health care visits components listed. Please refer to Section V.B of this report for more information about these types of health care utilization.

Tables 8 and 9 focus on psychotropic medication prescription fills for children with and without ASD and their siblings. The enrollment -adjusted proportions shown in these tables indicate that children with ASD were more likely to have a psychotropic medication fill compared to children without ASD (59.2% vs. 10.5% overall), and this was true across all classes of psychotropic medications examined. About 40% of children with ASD had at least one fill for an ADD medication, and over a quarter had at least one fill for an antidepressant or antipsychotic medication. **Appendix C** provides these results for select gender/age groups.

**Table 8. Psychotropic Use 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
	%	%				
Anticonvulsants/Antiepileptics	15.50	1.30	14.43	13.64	15.26	<0.001
Antidepressants	29.80	4.10	9.97	9.62	10.33	<0.001
Antipsychotics	26.70	0.80	43.93	41.26	46.77	<0.001
Anxiolytics	11.30	3.30	3.70	3.55	3.86	<0.001
Attention Deficit Medications	40.40	4.90	13.27	12.84	13.71	<0.001
Lithium Medications	2.00	0.10	19.45	16.29	23.24	<0.001
Anticholinergic/Antiparkinsonian Medications	1.80	0.10	22.52	18.40	27.55	<0.001
Any Psychotropic Medication	59.20	10.50	12.33	11.98	12.68	<0.001

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

Siblings of children with ASD were also more likely than siblings of children without ASD to have a claim for a psychotropic medication (Table 9). Overall, however, the adjusted proportions for both sibling groups were significantly lower than those observed for the sample of children with ASD.

Appendix C provides these sibling results for select gender/age groups.

**Table 9. Psychotropic Use 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
	%	%				
Anticonvulsants/Antiepileptics	2.30	1.30	1.75	1.63	1.87	<0.001
Antidepressants	7.20	4.00	1.86	1.79	1.94	<0.001
Antipsychotics	2.30	0.80	2.85	2.64	3.08	<0.001
Anxiolytics	3.60	3.00	1.21	1.15	1.27	<0.001
Attention Deficit Medications	9.70	4.80	2.14	2.06	2.22	<0.001
Lithium Medications	0.20	0.10	2.46	2.00	3.03	<0.001
Anticholinergic/Antiparkinsonian Medications	0.10	0.10	1.78	1.34	2.36	<0.001
Any Psychotropic Medication	16.70	10.40	1.73	1.68	1.78	<0.001

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

Greater utilization of health care services translated into higher health care costs for children with ASD (**Table 10**) as well as for their family members (**Table 11**). As described above, these are total allowed costs, which is the combination of health plan costs as well as patient out of pocket costs (deductibles, copays, etc.) Median monthly costs for children with ASD exceeded those for children without ASD for total medical care (\$202.28 vs. \$39.53), behavioral health care (\$72.26 vs. \$0.00), and medications (\$46.22 vs. \$3.86).

Table 10. Per Member Per Month All-Cause Health Care Costs of ASD and Comparison Groups

Costs		ASD (N=33,565)	Comparison (N=138,876)	p-value
Medical Costs	mean	479.91	155.89	<0.001
	SD	1,328.26	1,234.11	
	median	202.28	39.53	
Office	mean	163.30	43.86	<0.001
	SD	444.82	123.45	
	median	84.08	24.38	
Outpatient	mean	135.99	37.49	<0.001
	SD	310.62	149.10	
	median	40.66	0.00	
Ambulatory (office + outpatient)	mean	299.29	81.35	<0.001
	SD	563.16	211.44	
	median	157.07	33.97	
Emergency	mean	11.80	5.52	<0.001
	SD	40.74	21.37	
	median	0.00	0.00	
Inpatient	mean	119.37	60.83	<0.001
	SD	925.87	1,094.62	
	median	0.00	0.00	
Other	mean	49.46	8.20	<0.001
	SD	436.63	272.36	
	median	2.50	0.00	
Behavioral Health Care Costs*	mean	218.59	8.72	<0.001
	SD	772.11	167.76	
	median	72.26	0.00	
Costs for Ambulatory-Sensitive Conditions (inpatient and ED costs only)*	mean	38.99	11.23	<0.001
	SD	651.91	581.36	
	median	0.00	0.00	
Pharmacy Costs	mean	138.73	19.42	<0.001
	SD	311.41	81.43	
	median	46.22	3.86	
Total Costs (Medical + Pharmacy)	mean	618.64	175.31	<0.001
	SD	1,407.74	1,246.05	
	median	317.48	51.85	

*Behavioral health care costs and costs for ambulatory-sensitive conditions were identified and calculated based on select diagnoses and provider types. These are a subset of medical care costs and overlap with one or more of the medical care cost components listed. Please refer to Section V.B of this report for more information about these types of health care costs.

Median medical, behavioral, and medication costs were also higher for parents and siblings of children with ASD compared to the family members of children without ASD (**Table 11**). Total

monthly costs were \$176.51 and \$115.12 for ASD and comparison parents, respectively, and \$78.05 and \$43.57 for ASD and comparison siblings, respectively.

We also sought to measure whether there were differences in inpatient costs between the groups for ambulatory-sensitive conditions (ASCs). Although precise definitions of ASCs vary, in general, ASC are those conditions for which emergency care or hospital admission is thought to be preventable by the use of appropriate and high quality interventions in primary care. Examples of ASC include gastroenteritis, asthma and pneumonia. Inpatient or emergency visits for ACSs may be an indicator of insufficient primary care that is a more nuanced indicator than simply counting the number of primary care visits. In our results, the median monthly costs for ASCs were \$0.00 for both children with ASD and comparison children (**Table 10**), but the mean PMPM costs did exhibit a difference: nearly \$40 per member per month for children with ASD versus about \$11 for children without ASD. In contrast, however, there were no differences in inpatient and emergency department costs of ACSs between parents and siblings of children with and without ASD.

Table 11. Per Member Per Month All-Cause Health Care Costs of ASD and Comparison Group Family Members

Costs		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)		
Medical Costs	mean	298.16	251.39	184.97	131.10	<0.001	<0.001
	SD	840.99	845.10	1,172.74	994.04		
	median	119.40	77.61	58.21	33.48		
Office	mean	86.79	62.74	55.78	37.81	<0.001	<0.001
	SD	233.39	175.05	89.18	397.20		
	median	47.16	31.61	34.74	20.78		
Outpatient	mean	102.74	88.21	47.97	35.48	<0.001	<0.001
	SD	359.69	389.99	283.09	172.80		
	median	22.03	8.61	2.58	0.00		
Ambulatory (office + outpatient)	mean	189.54	150.95	103.75	73.29	<0.001	<0.001
	SD	463.43	461.74	311.34	447.91		
	median	87.97	57.19	49.66	28.76		
Emergency	mean	8.88	7.50	6.04	4.99	<0.001	<0.001
	SD	33.25	30.95	21.24	19.11		
	median	0.00	0.00	0.00	0.00		
Inpatient	mean	80.84	78.04	63.00	45.90	0.221	<0.001
	SD	483.73	535.67	989.21	769.43		
	median	0.00	0.00	0.00	0.00		
Other	mean	18.90	14.91	12.18	6.92	<0.001	<0.001
	SD	180.04	169.30	251.43	171.37		
	median	3.80	2.10	0.00	0.00		

Costs		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)		
Behavioral Health Care Costs*	mean	26.44	15.89	19.44	7.79	<0.001	<0.001
	SD	174.99	231.46	230.01	188.83		
	median	0.00	0.00	0.00	0.00		
Costs for Ambulatory- Sensitive Conditions (inpatient and ED costs only)*	mean	9.88	8.34	11.48	7.64	0.177	0.173
	SD	237.46	282.45	543.87	390.50		
	median	0.00	0.00	0.00	0.00		
Pharmacy Costs	mean	79.05	51.41	32.24	18.16	<0.001	<0.001
	SD	170.57	132.69	126.85	78.35		
	median	24.36	12.72	6.59	3.21		
Total Costs (Medical + Pharmacy)	mean	377.21	302.80	217.21	149.26	<0.001	<0.001
	SD	906.33	886.40	1,197.17	1,005.02		
	median	176.51	115.12	78.05	43.57		

*Behavioral health care costs and costs for ambulatory-sensitive conditions were identified and calculated based on select diagnoses and provider types. These are a subset of medical care costs and overlap with one or more of the medical care cost components listed. Please refer to the Methodology section of this report for more information about these types of health care costs.

While these data are adjusted for varying observation time, it is important to emphasize that they have not been adjusted to account for other differences (e.g., demographic characteristics such as race/ethnicity) between children with and without ASD and their family members.

Appendix C provides summary health care costs broken down for select gender/age groups for all of our study samples. Among children with ASD, total medical costs were highest for the oldest age group and lowest for the middle age group, and this was true for both boys and girls. Behavioral health care costs were lower among the older age groups, whereas medication costs were higher among the older age groups.

D. Discussion

Combined with our diverse set of health care utilization and cost variables, which includes many different types of medical visits, drug use, and cost measures, our study gives a description of the patterns of medical use and expenditure for our large and heterogeneous study population. Furthermore, these estimates are made more useful by the ability to compare them to a large control group, and our use of documented, adjudicated claims data (as opposed to some previous studies' use of survey data) improves upon the reliability and objectivity of our estimates.²¹ Our findings confirm what has been reported in the literature to date: children with ASD utilize more health care services and incur more health care costs compared to children without ASD.^{16, 17, 18, 19, 20, 22, 25} Our results indicate that children with ASD have more inpatient and emergency department visits, total office visits, total outpatient facility visits, behavioral health care visits, preventive care visits, ancillary therapy visits, and medication dispensings than do children without ASD. In addition, children with ASD were more likely to have psychotropic medication fills, a finding which holds true across all classes of psychotropic medications examined. The high

rate of use of any psychotropic medication we reported for children with ASD (59.2%) is consistent with findings in the literature.^{22,23} Correlated with these results are the findings on health care costs: children with ASD incurred greater health care costs, as measured by total medical care, behavioral health care, and pharmaceutical total costs. However, the analysis in this section was meant to provide a crude estimate of utilization and cost measures for our samples. Therefore caution needs to be taken in interpreting these results as they were calculated without adjusting for other potential confounders in these comparisons (e.g., demographic and clinical differences or surveillance bias) beyond the enrollment time which was a significant confounder even in calculating crude utilization and cost measures.

While our results are comparable to other studies measuring utilization and costs in private insurance, our results show lower overall costs and a smaller difference in costs between children with and without ASD than seen among patients covered by Medicaid.^{24,25} Mandell and colleagues found that among children with ASD covered by Medicaid in one large county in Pennsylvania, costs were nine times greater than those of other Medicaid eligible children without ASD and amounted to about \$10,000 annually (in 1999 dollars).²⁵ The comparable ratio from our data, when comparing medians, was 6. Furthermore, a more recent study that assessed health care expenditures using Medicaid data from 42 states from 2000 to 2003 based on almost 70,000 children with ASD estimated that mean total health expenditures was \$22,772 (in 2003 dollars). Although the results are not completely comparable to our study, the costs are greater than our reported costs by a factor of more than 3.²⁴ Similar types of costs were included in this study and ours, including prescription medications and ancillary therapies such as speech and occupational therapies. However, within our utilization results, minimal use of ancillary therapies was found, which may be related to the lack of coverage for these therapies by commercial insurance. If parental reports from a national survey are correct²⁶ suggesting that over 70% of children with ASD are receiving such therapies, our results suggest that families are incurring these costs themselves or services are being funded by alternative means such as by school systems or supplementary insurance plans that were not reported within our data. In either scenario, our results support findings that children with ASD covered by public insurance have higher costs on average than children with ASD in our sample. Further detailed analyses are needed to determine the factors driving those differences as well as to ascertain whether there are additional costs incurred by our sample of children with commercial insurance that are unaccounted for within our claims data.

Considering the morbidity of ASD itself and the high rates of co-occurring conditions, it is somewhat reassuring to see that these children are making use of health care services substantially more than comparison children without ASD. Still unanswered, however, are questions regarding whether they are receiving appropriate or enough care for ASD and co-occurring conditions as well as if they are receiving the well child care that all children should receive. While we found that children with ASD have more preventive visits than children without ASD, our finding regarding increased inpatient care and emergency department costs related to ambulatory sensitive conditions such as asthma and gastroenteritis could indicate that children with ASD are still not receiving high quality comprehensive preventive care routinely, at least as measured by mean cost (the median of 0 indicating this is a skewed distribution of cost across the individuals). In other words, children with ASD are indeed participating in preventive care visits more often than children without ASD yet those visits may not be adequate to “cover” everything in those visits, especially if much of the visit is taken up with symptoms related to

ASD and co-occurring conditions. Furthermore, communication difficulties in the child with ASD may be limiting their ability to articulate early signs of illness to their caregivers, clinicians, or both, such that they appear for care relatively late in their illness with symptoms that are of higher acuity or severity compared to children without communication problems.

It is also unknown whether the care received by children with ASD is of high quality and effective for their conditions and symptoms and whether children with ASD are *not* receiving ineffective or harmful care (such as overuse of particular medications). As ASD is so heterogeneous in terms of what is optimal care for a given individual, appropriateness or quality can be difficult to assess. And there are not yet universally agreed-upon standards for the components of high quality care for children with ASD. Still, the AAP and other national bodies have issued some preliminary evidence-based guidance for the identification and management of children with ASD^{27,28} that includes early screening for ASD and common co-occurring conditions, a basic workup and referral to a developmental pediatrician or other specialist skilled in ASD, and referral to early intervention services that typically include developmental therapy and speech and occupational therapy evaluation and services. Ongoing management usually includes periodic visits with the ASD specialist, counseling and psychopharmacologic treatments, if needed, regular speech and OT services to be integrated into educational settings if possible, and a treatment approach based on Applied Behavioral Analysis whenever accessible. Social skills training and family support interventions are also recommended as is general well child care by a primary care provider as would be expected for all children, with and without ASD. Future research is needed to determine whether the services children with ASD are receiving align with care that is of the highest quality and evidence-based.

Based on our review of the literature, little research exists on health care utilization and costs of family members of children with ASD. To our knowledge, ours is the first study to investigate this topic. Our study found that parents and siblings of children with ASD had higher rates of health care utilization and costs relative to family members of children without ASD. This finding held true for the overwhelming majority of categories, including total health care visits, behavioral health care visits, ancillary therapy visits, and medications. However, as mentioned above, caution is warranted in interpreting these results as they were not calculated adjusting for other important potential confounders other than enrollment time. A thorough examination and multivariate analysis of all of the outcomes examined here was beyond the scope of this study. Instead, we focused our in-depth analysis on two specific outcomes of interest - psychotropic polypharmacy use and MMR vaccinations - presented in the next two sections.

There are several potential explanations for our findings. Without knowledge about a clear etiologic pattern for ASD, and the high rates of associated conditions among children who have ASD, it is likely that the causes of ASD and perhaps many of the common co-occurring conditions are multifactorial and include both genetic/biological and environmental factors. Family members in most cases share both biological and environmental risk factors, thus these same factors contributing to poorer health among children with ASD may be increasing the risk of poor health in family members whether or not ASD itself is present. Poorer health and resulting increased use of health care services among parents and siblings might also be partly explained by the increased levels of anxiety and behavioral difficulties associated with having a family member with a chronic illness or disability, which has been reported in the literature.²⁹ Yet it might also be a result of increased exposure to the health care system in general (often termed

“surveillance bias”), which can make accessing care more convenient or more automatic in situations where a less frequent health care user might delay or avoid seeing a provider altogether. More immediately, however, our findings demonstrate that the medical use and cost patterns of the entire family may be influenced by having a child with ASD. Supportive interventions for the family as a whole rather than each individual separately are therefore necessary in order to improve the health care experience and quality of life of children with ASD and their families.

VI. Psychotropic Polypharmacy

A. Background

Psychotropic medication use and particularly concomitant use of psychotropic medications (psychotropic polypharmacy) among children is a growing concern. Recent sources have reported a high use of psychotropic medication and psychotropic polypharmacy among children with ASD or mental disorders and it is on the rise^{30,23,31}. Recent information from the U.S. Department of Health and Human Services indicated that over half of children with ASD use one or more psychotropic medications.³⁰ Our final report for Task A: Baseline Claims Analysis highlighted that a similarly high percentage (59%) of children with ASD had at least one psychotropic medication fill compared with 11% of children without ASD. A study by Mandell and colleagues reported that 56% of Medicaid-enrolled children with ASD used at least one psychotropic medication, while 11% use three or more concurrent medications.²³ In addition, the clinical practice of polypharmacy treatment is on the rise. A recent study found that among physician visits of children with a mental disorder diagnosis, the percentage involving prescriptions of two or more classes of psychotropic medication rose from 22% during 1990-1999 to 32% during 2004-2007.³¹

The high use of psychotropic medications among children generally and children with ASD, and particularly psychotropic polypharmacy, is of growing concern for multiple reasons. Of greatest concern is the lack of sufficient clinical research of these powerful medications in the face of few controlled trials for psychotropic medications singly or in combination. Without sufficient clinical research, safety and effectiveness of many of these medications has not been established for children, especially when used in combination with other psychotropic medications. Therefore, many of these medications do not have Federal Drug Administration (FDA) Indications of Use Statements resulting in off-label use being a common practice when prescribing psychotropic medications to children.³² For ASD specifically, the only FDA-approved medications are risperidone and aripiprazole (indicated specifically for the treatment of irritability including symptoms of aggression). However, physicians often prescribe multiple medications to individuals with ASD in a trial-and-error fashion to help manage the troublesome symptoms of these clinically complex patients.³³ The small body of literature on psychotropic polypharmacy use among children with ASD supports the lack of empirical evidence to inform psychotropic medication prescribing. According to one study examining patterns of psychotropic use among children with ASD and/or ADHD, the research justifying psychotropic polypharmacy treatment lags behind its clinical use.³⁴ Other experts have commented that the evidence base to inform multi-drug treatment decisions is “woefully inadequate.”³⁵ The second concern is one of rising expense, especially in the absence of effectiveness. As children with ASD use more medications, the prescription costs of a polypharmacy regimen also increase, and even more so since ASD prevalence is increasing. Researchers recently found that among children with ASD who have prescriptions, the mean/median annual prescription cost was \$1670/\$550 in 2007, a number which rises to \$6480/\$1880 if isolated to an older age group.³⁶ These numbers are part of the national trend of increasing costs associated with psychotropic medication.

These findings, along with the limited knowledge in the literature about the use of psychotropic medications among commercially-insured children with ASD, motivated our focus on psychotropic polypharmacy. The objective of our psychotropic polypharmacy analysis was to

examine the extent and nature of psychotropic polypharmacy among children with ASD in the commercially-insured population. Our analysis does not attempt to address the appropriateness of psychotropic polypharmacy nor do we analyze the cost associated with these medications. Our specific research questions were the following:

1. Among children with ASD, how common is psychotropic polypharmacy (within and across medication classes)?
 - How many unique overlapping psychotropic medications are observed for children with ASD?
 - What types of health care providers have children with psychotropic polypharmacy seen?
 - Among children with ASD with evidence of multi-class psychotropic polypharmacy, what are the most common combinations of medication classes used?
2. What individual and provider characteristics are related to psychotropic medication use, including psychotropic polypharmacy, among children with ASD?

B. Methods

1. Polypharmacy Definition

Measures of psychotropic polypharmacy variables were determined for children with ASD based on pharmacy claims for prescriptions filled during the child's total enrollment time during the study. We examined seven classes of psychotropic medications: 1) anticonvulsants/antiepileptics, 2) antidepressants, 3) antipsychotics, 4) anxiolytics, 5) attention deficit disorder (ADD) medications, 6) lithium, and 7) anticholinergic/antiparkinson's medications (see Appendix A Table A-4). Polypharmacy was assessed within a psychotropic class (single-class) and across classes (multi-class). To examine polypharmacy within the claims data, we identified episodes of polypharmacy or overlapping fills of more than one psychotropic medication.

a. Episode of single-class psychotropic polypharmacy

An episode of single-class psychotropic polypharmacy was defined as overlapping fills of two or more psychotropic medications within the same class for at least 30 days. Two definitions were created – one that captured episodes of *specific* within-class medication combinations lasting 30 days or more (“combination-specific” polypharmacy episodes) and a broader definition that captured episodes of *any* within-class combination(s) lasting 30 days or more (“overall” polypharmacy episodes). For the combination-specific measure, any specific combination was counted as long as it lasted at least 30 days. Any change in the combination of medications indicated the end of the episode and possibly the start of a new episode (that is, if there was a new combination of medications and it lasted at least 30 days). An overall polypharmacy episode could include changes in medication combinations but ended as soon as no overlapping combination of medications within the class was in effect. It is important to note that all combination-specific episodes also contributed to an overall episode. However, an overall episode may or may not involve a combination-specific episode (as the multiple specific combinations comprising the overall episode may have lasted less than 30 days and therefore did not meet the requirements of a combination-specific episode).

Episodes were identified using the prescription fill date and days' supply information available on pharmacy claims. Before identifying specific polypharmacy episodes, overlapping fills of the same medication were pushed out (i.e., extended) to the sum of both fills. If multiple fills for the same medication occurred on the same day, the claim for the longest day supply was used. Inpatient stays occurring during a fill were added to the overall length of the fill (with the assumption that the medication was being administered by the hospital and the child continued use of their outpatient fill following hospitalization). Gaps in fills of the same medication that were seven days or fewer were permitted and included in the calculation of the length of that fill (i.e., two fills for the same medication for 15 days each, separated by 6 days totaled 36 days in length).

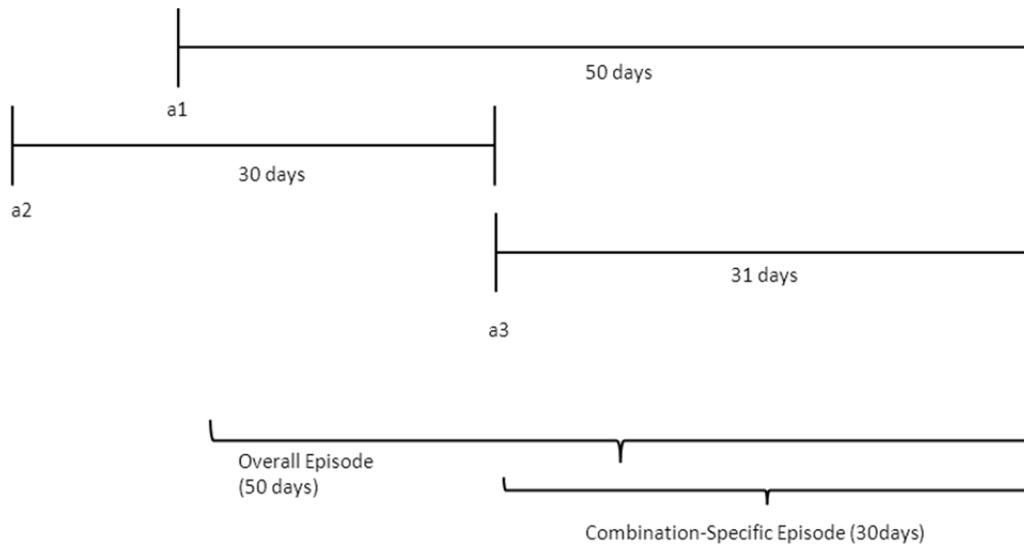
Figure 4 provides examples of how we defined single-class psychotropic polypharmacy within the claims data. Each row in the figure (denoted by a letter and number) represents a unique medication. The letter refers to a class of medication and the number refers to a specific medication. In the first example in Figure 4, the two fills for different medications in the same class do not overlap for the minimum of 30 days and therefore would not be flagged as an episode of single-class polypharmacy based on either the combination-specific or the overall definition. In Example 2, a specific combination of medications (a1 and a3) meets the combination-specific definition of polypharmacy because it lasts 30 days or longer but an overall episode of polypharmacy is also observed involving a1, a2 and a3. In Example 3, none of the unique combinations meet the requirements of a combination-specific episode because they do not last at least 30 days. However, because the multiple combinations are adjacent, they form an overall episode of single-class polypharmacy.

Figure 4. Identifying Single-Class Polypharmacy within the Claims Data

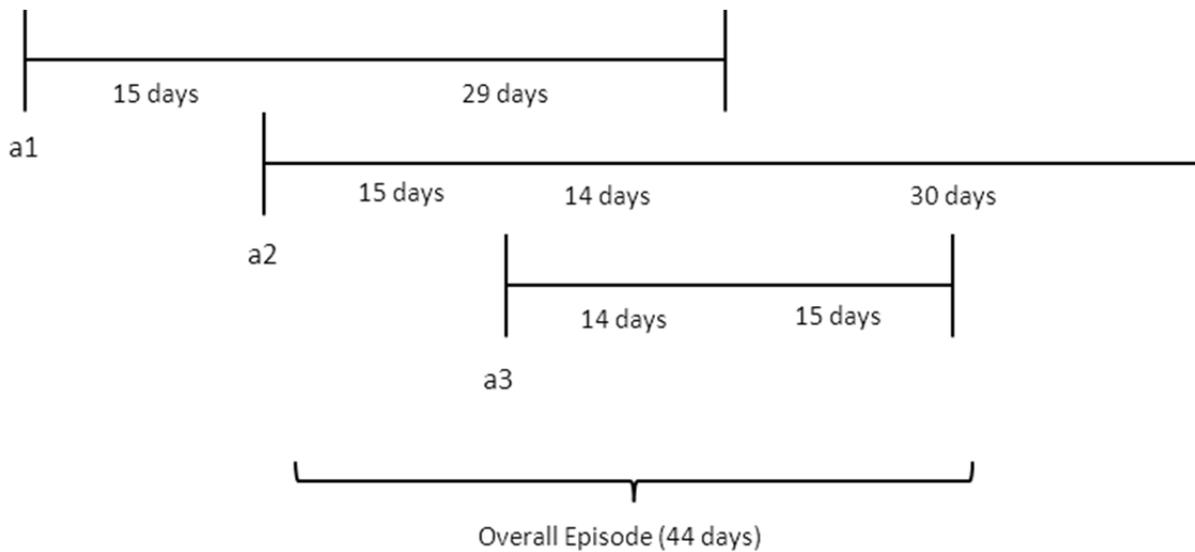
Example 1



Example 2



Example 3



b. Episode of multi-class psychotropic polypharmacy

An episode of multi-class psychotropic polypharmacy was defined as overlapping fills of medications across two or more classes for at least 30 days.^{xvii} As with single-class polypharmacy, two definitions were created – one that captured episodes of *specific* class combinations lasting 30 days or more and an overall definition that captured episodes of *any* multi-class combination(s) lasting 30 days or more. In measuring multi-class polypharmacy, no single medication within a class needed to overlap by 30 days with a particular medication in another class. We were only interested in unique combinations of *classes* of at least 30 days. For the combination-specific measure, any specific combination of classes was counted as long as it lasted at least 30 days. Any change in the combination of classes indicated the end of the combination-specific episode and possibly the start of a new episode (that is, if there was a new combination of classes and it lasted at least 30 days). As with single-class polypharmacy, an overall multi-class polypharmacy episode could include changes in class combinations but ended as soon as no combinations of classes were in effect. It is important to note that all combination-specific multi-class episodes also contributed to an overall multi-class episode. However, an overall episode may or may not have involved any combination-specific episodes (as the multiple specific class combinations comprising the overall episode may have lasted less than 30 days and therefore did not meet the requirements of a combination-specific episode).

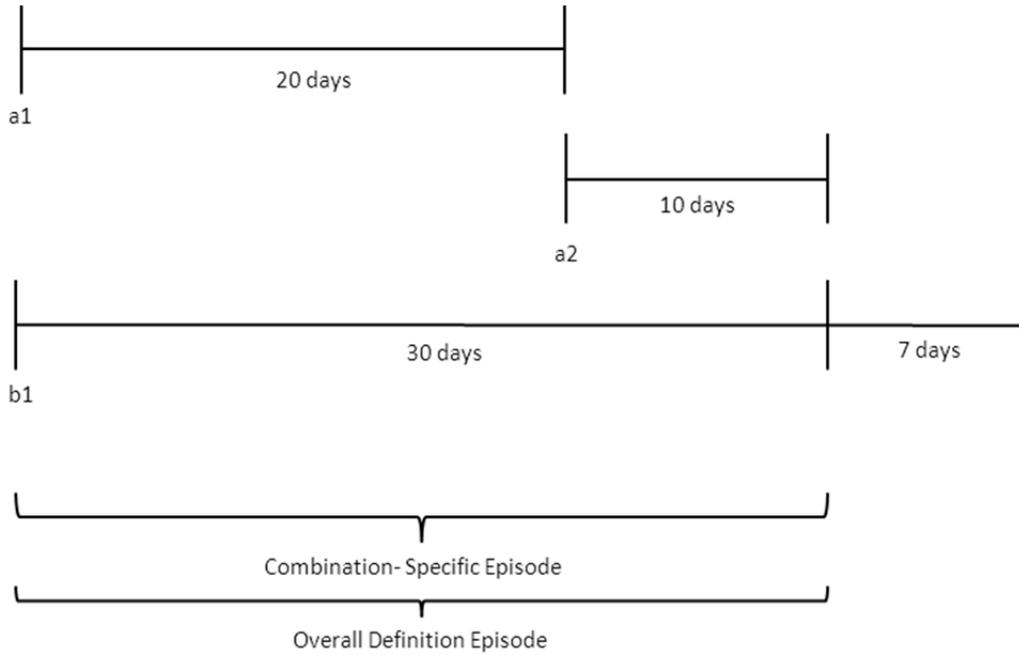
Episodes were identified using the prescription fill date and days' supply information available on pharmacy claims. Before identifying specific polypharmacy episodes, overlapping fills of the same medication were pushed out (i.e., extended) to the sum of both fills. If multiple fills for the same medication occurred on the same day, the claim for the longest day supply was used. Inpatient stays occurring during a fill were added to the overall length of the fill (with the assumption that the medication was being administered by the hospital and the child continued use of their outpatient fill following hospitalization). Gaps in fills of the same medication seven days or fewer were permitted and included in the calculation of days of overlapping fills (i.e., two fills for the same medication for 15 days each, separated by 6 days totaled 36 days in length).

Figure 5 provides examples of how we defined multi-class psychotropic polypharmacy in the claims data. Similar to Figure 4, each row in the figure (denoted by a letter and number) represents a unique medication. The letter refers to a class of medication and the number refers to a specific medication. The first example in Figure 5 demonstrates that no single medication within a class needed to overlap by 30 days with a medication in another class. Instead, the definition of multi-class polypharmacy was met as long as a medication or more than one medication within a class overlaps with medication(s) in another class for at least 30 days – i.e., that a unique combination of classes lasts at least 30 days. Example 2 shows that none of the unique class combinations meet the definition of a combination-specific episode (while b1 and c1 overlap for 31 days, a medication from another class, a1, is also in play for some of that time) but together, the multiple class combinations meet the overall definition of multi-class polypharmacy. In Example 3, two unique combinations of classes meet the definition of a combination-specific episode, and together, they amount to a longer overall definition of multi-polypharmacy.

^{xvii} One exception pertained to select combination medications: a claim for some combination medications were counted as polypharmacy because they included two or more medications even if there was not a fill for another medication in another class. See medications listed in Appendix A. Combination medications that were treated as polypharmacy in and of themselves are noted in this Appendix.

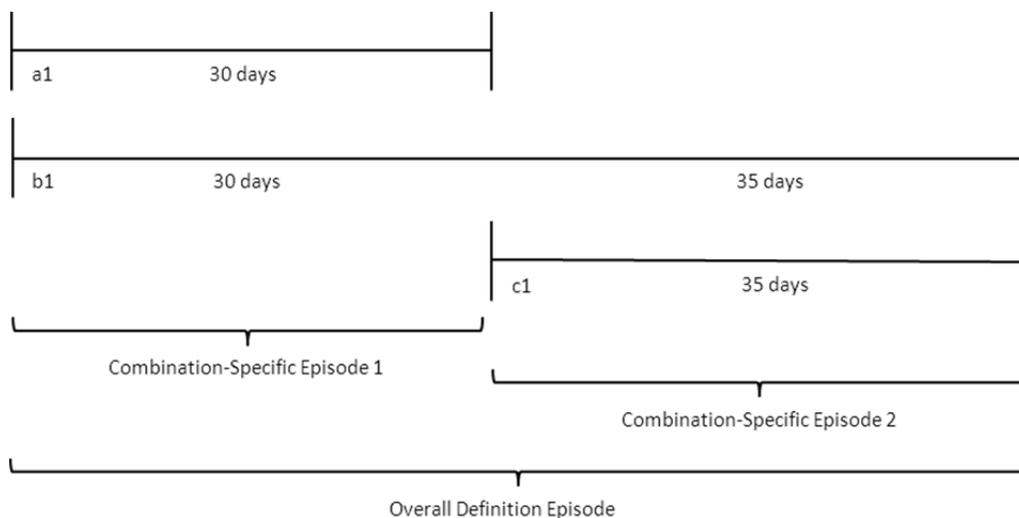
Figure 5. Identifying Multi-Class Polypharmacy within the Claims Data

Example 1



Example 2



Example 3

The preceding examples of single and multi-class polypharmacy are not intended to be exhaustive.

It is important to keep in mind that our analyses are based on medication prescriptions filled that overlapped for 30 days or more. We do not have data on actual use (consumption) of medications, and we recognize that overlapping fills may signal treatment patterns other than polypharmacy, such as a dose adjustment (titrating) or a switch in medications. To minimize mischaracterization, we applied the 30-day requirement in our measurement of polypharmacy. Nevertheless, the potential for misclassification is a limitation of our analyses.

2. Variable Definitions

a. Polypharmacy

- **Single-class psychotropic polypharmacy.** Whether or not a child with ASD had at least one episode of single-class psychotropic polypharmacy. A binary variable (yes/no) was created for each of the seven classes, and an overall binary variable (yes/no) was created for children with evidence of single-class polypharmacy for at least one class of psychotropic medications. These variables were created based on both overall and combination-specific definitions of polypharmacy.
- **Count of single-class psychotropic polypharmacy episodes.** The sum of unique single-class polypharmacy episodes for each child by class and overall. These variables were calculated for both overall and combination-specific episodes of polypharmacy.
- **Length of single-class psychotropic polypharmacy.** The duration (in days) of each single-class episode. The total number of days of single-class psychotropic polypharmacy by class and overall was calculated for each child by summing the duration of episodes observed for a child. These variables were calculated for both overall and combination-specific episodes of polypharmacy.
- **Single-class psychotropic polypharmacy count of medications.** For each episode of single-class polypharmacy, a count of unique medications comprising the episode of

polypharmacy. For each child, the largest number of medications observed across single-class psychotropic polypharmacy episodes was determined by class and overall. These variables were calculated based on combination-specific episodes of polypharmacy only.

- **Single-class polypharmacy medications.** For each episode of single-class polypharmacy, the most common medications involved. The medications were determined for combination-specific episodes of polypharmacy only.
- **Types of providers for children with single-class polypharmacy.** For each child with ASD with evidence of single-class polypharmacy, the types of providers seen. Specifically, whether a child had a medical claim from a primary care physician, developmental pediatrician, psychiatrist, or other type of provider were flagged. These variables were determined for children with at least one episode of combination-specific single-class polypharmacy. Medical claims between 30 days before the first fill and the last fill of the psychotropic class involved were used.^{xviii} Primary care providers included family, general practice, and internal medicine providers as well as pediatricians. Developmental pediatricians were included in this category as well as examined as a unique and separate category. “Other” providers included all providers other than primary care physicians and psychiatrists.
- **Multi-class psychotropic polypharmacy.** Whether or not a child with ASD had at least one episode of multi-class psychotropic polypharmacy. An overall binary variable (yes/no) was created. This variable was created for overall and combination-specific definitions of multi-class polypharmacy.
- **Count of multi-class psychotropic polypharmacy episodes.** The sum of unique multi-class polypharmacy episodes for each child. This variable was calculated for both overall and combination-specific episodes of polypharmacy.
- **Length of multi-class psychotropic polypharmacy.** The duration (in days) of each multi-class episode. The total number of days of multi-class psychotropic polypharmacy was calculated by summing the duration of multi-class episodes for a child. This was calculated for both overall and combination-specific episodes of polypharmacy.
- **Multi-class psychotropic polypharmacy count of classes and medications.** For each episode of multi-class polypharmacy, a count of unique medications and a count of the classes of medications comprising the episode of polypharmacy were determined. These variables were determined for both overall and combination-specific episodes.
- **Select multi-class psychotropic polypharmacy combinations.** For each episode of multi-class polypharmacy, selected combinations of classes of psychotropic medications were flagged. These combinations were examined for combination-specific episodes only.
- **Types of providers for children with multi-class polypharmacy.** For each child with ASD with evidence of multi-class polypharmacy, the types of providers seen. Specifically, whether a child had a medical claim from a primary care physician, developmental pediatrician, psychiatrist, or other type of provider was flagged. These

^{xviii} Medical claims were used to identify providers due to limitations with the provider information available on pharmacy claims. For this reason, we measure the types of providers involved in the care of the subject during his/her psychotropic use but were not able to directly capture the types of providers who prescribed the psychotropic medications.

variables were determined for children with at least one episode of combination-specific multi-class polypharmacy. Medical claims between 30 days before the first fill and the last fill of the psychotropic classes involved in any of the multi-class episodes were used. Primary care providers included family, general practice, and internal medicine providers as well as pediatricians. Developmental pediatricians were included in this category as well as examined as a unique and separate category. “Other” providers included all providers other than primary care physicians and psychiatrists.

b. Co-occurring Conditions

Our multivariate analyses of psychotropic polypharmacy included several covariates in addition to the demographic, enrollment, and socio-economic variables described earlier in the report (Section III.D: Variable Definitions). We also created additional variables for five distinct behavioral health conditions that often co-occur with ASD and may be related to psychotropic use. These variables are:

- **Attention deficit disorders (ADD).** Whether or not a child had evidence of an attention deficit disorder during their total enrollment during the study. To qualify, a child had at least two medical claims with a relevant diagnosis code in any position at least 30 days apart OR a child had one claim with a diagnosis code in any position and one claim for an ADD medication. One binary variable (yes/no) was created. 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 child had evidence of anxiety during their total enrollment during the study. To qualify, a child had at least two medical claims with a relevant diagnosis code in any position at least 30 days apart. One binary variable (yes/no) was created. 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.
- **Bipolar.** Whether or not a child had evidence of bipolar disorder during their total enrollment during the study. To qualify, a child had at least two medical claims with a relevant diagnosis code in any position at least 30 days apart. One binary variable (yes/no) was created. 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 child had evidence of depression during their total enrollment during the study. To qualify, a child had at least two medical claims with a relevant diagnosis code in any position at least 30 days apart. One binary variable (yes/no) was created. 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.

- **Seizure disorder/epilepsy (Seizures).** Whether a child had evidence of seizures during their total enrollment during the study. To qualify, a child had at least two medical claims with a relevant diagnosis code in any position at least 30 days apart OR a child had one medical claim with a diagnosis code in any position and one claim for a medication for seizures. One binary variable (yes/no) was created. 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 indicators are not comprehensively coded in claims and may not be correlated with a clinical diagnosis or use of health care services. ASD severity may be related, however, to certain diagnoses or co-occurring conditions that are associated with ASD. For example, the presence of seizures is correlated with ASD severity and level of functioning³⁷ and is also a condition commonly treated by psychotropic medication. Thus, we included seizures as an important covariate in our multivariate models. Following this same general rationale we also adjusted for other co-occurring conditions that are known to be treated with psychotropic drugs (i.e., ADD, anxiety, depression, bipolar) as additional control for possible case complexity and use indications.²³

3. Analytic Approach

Descriptive and multivariate analyses were conducted to examine psychotropic polypharmacy among children with ASD. To address our first research question about the prevalence and extent of polypharmacy, the number and percentage of children with ASD who had evidence (i.e., at least one episode) of polypharmacy-- single-class polypharmacy and/or multi-class polypharmacy – were determined. Means, medians, and standard deviations were generated to summarize children’s count of episodes, duration on polypharmacy, and the maximum number of medications or classes involved. The number and percentage of children with ASD with the most common medications within single-class polypharmacy and classes within multi-class polypharmacy are shown. Finally, the types of providers seen by children with single-class and multi-class polypharmacy are summarized. All single-class polypharmacy descriptive analyses were generated by class type. Results are presented for both combination-specific and overall definitions of psychotropic polypharmacy as appropriate.

To address research question # 2 regarding the individual and provider characteristics related to psychotropic use and psychotropic polypharmacy, four multivariate models were run based on the sample of children with ASD. In the first two analyses, binary measures of any psychotropic use and any combination-specific multi-class polypharmacy, respectively, were modeled using a logistic regression model. The third model, a multinomial logistic regression, modeled psychotropic use and combination-specific multi-class polypharmacy. The dependent variable for this model categorized children with ASD into five mutually-exclusive groups: 0) no psychotropic use, 1) at least one psychotropic medication without multi-class polypharmacy, 2) multi-class polypharmacy with a maximum of 2 classes, 3) multi-class polypharmacy with a maximum of 3 classes, and 4) multi-class polypharmacy with a maximum of 4 or more classes.

The second group (psychotropic use without multi-class polypharmacy) included children with evidence of one type of psychotropic medication and children with evidence of multiple psychotropic medications but who did not meet the definition of polypharmacy. All children with evidence of psychotropic use were compared to children without a fill for a psychotropic medication. Finally, a generalized linear model with gamma distribution and log link was used to model length of polypharmacy among the subset of children with ASD with evidence of combination-specific multi-class polypharmacy.

The covariates included in all models were: gender, income, race, region, age, whether the child had at least one medical claim for a psychiatrist visit and binary indicators for the following co-occurring conditions: seizures, ADD, anxiety, depression, and bipolar disorder. Each model also controlled for children's total duration of health plan enrollment during the study, with enrollment time included as one of five categorical variables representing the distribution of enrollment time divided into quintiles. The variables "psychiatrist visit" and "co-occurring conditions" were based on the child's total enrollment time as were the model psychotropic outcome variables. Age was measured as age at index date (first day of enrollment during study). On average, children with ASD had approximately three and half years of enrollment during the study. Therefore, subjects may have been using a psychotropic medication at their index age and/or at older ages. For each model, regression diagnostics (e.g., Likelihood ratio) were examined to assess goodness-of-fit. The results of these diagnostics are provided with the model results.

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.^{38, 39} While there is no one agreed-upon criterion for what level of VIF indicates multicollinearity, some believe VIF values exceeding 10 should warrant concern.⁴⁰ 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

1. Prevalence and characteristics of polypharmacy

Table 18 presents the number and percentage of children with ASD with evidence of single-class and multi-class psychotropic polypharmacy. Results based on both the combination-specific and overall definitions of polypharmacy are provided. As is shown, 20.3% of the 33,565 children with ASD had evidence of combination-specific single-class polypharmacy, and 34.6% of the sample had evidence of combination-specific multi-class polypharmacy. The most common type of single-class polypharmacy was among ADD medications (11.6% of our sample of children with ASD had evidence of this type of single-class polypharmacy, and the least common was among anxiolytics (<1.0%). (Note: Lithium was dropped from our analysis of single-class polypharmacy because so few children with ASD had evidence of this type of polypharmacy; however, lithium, as a class of medications, was retained in our multiclass polypharmacy analysis.) Just under 40% of all children with ASD had either single-class or multi-class polypharmacy. Although we expected these results to be higher for the broader definition of overall polypharmacy, the two definitions (combination-specific and overall polypharmacy) yielded very similar results.

Table 18. Psychotropic Polypharmacy among ASD Group

Polypharmacy	ASD (N=33,565)			
	Combination-Specific		Overall	
	n	%	n	%
Single-Class Polypharmacy	6,805	20.27	6,895	20.54
Anticonvulsants/Antiepileptics	1,245	3.71	1,259	3.75
Antidepressants	1,740	5.18	1,765	5.26
Antipsychotics	1,560	4.65	1,591	4.74
Anxiolytics	162	0.48	167	0.50
Attention Deficit Medications	3,905	11.63	3,973	11.84
Multiple-class Polypharmacy	11,598	34.55	11,675	34.78
Either Single-Class or Multi-Class Polypharmacy	12,777	38.07	12,877	38.36

Note: This table presents the number and percent of children with at least one episode of polypharmacy by type.

Tables 19 and 20 provide additional results pertaining to the characteristics of single-class polypharmacy observed during children's observation time during the study. For children with evidence of combination-specific single-class polypharmacy, the average count of episodes ranged from 2.2 (anxiolytics) to 3.5 (anticonvulsants/antiepileptics and ADD medications). Likewise, the mean number of days of single-class polypharmacy ranged from 144 days (anxiolytics) to over 400 days (anticonvulsants/antiepileptics). The average maximum number of medications involved in an episode of combination-specific single-class polypharmacy hovered around 2 for all classes.

Table 19. Characteristics of Polypharmacy among Children with ASD with Single-Class Psychotropic Polypharmacy

Characteristic	Children with ASD with Single-Class Psychotropic Polypharmacy (N=6,895)					
	Combination-Specific			Overall		
	mean	SD	median	mean	SD	median
Anticonvulsants/Antiepileptics	(n=1,245)			(n=1,259)		
Count of Episodes per Child	3.46	3.74	2.00	2.72	2.61	2.00
Total Length of Polypharmacy (days) per Child	427.71	509.74	226.00	440.80	527.87	233.00
Maximum Number of Medications Involved per Child	2.27	0.55	2.00			
Antidepressants	(n=1,740)			(n=1,765)		
Count of Episodes per Child	2.76	3.03	2.00	2.63	2.82	2.00
Total Length of Polypharmacy (days) per Child	248.73	343.07	112.50	252.58	349.99	113.00
Maximum Number of Medications Involved per Child	2.07	0.27	2.00			

Characteristic	Children with ASD with Single-Class Psychotropic Polypharmacy (N=6,895)					
	Combination-Specific			Overall		
	mean	SD	median	mean	SD	median
Antipsychotics	(N=1,560)			(N=1,591)		
Count of Episodes per Child	2.34	2.33	1.00	2.20	2.20	1.00
Total Length of Polypharmacy (days) per Child	218.75	296.60	96.00	221.68	298.97	98.00
Maximum Number of Medications Involved per Child	2.08	0.30	2.00			
Anxiolytics	(N=162)			(N=167)		
Count of Episodes per Child	2.17	2.43	1.00	2.12	2.42	1.00
Total Length of Polypharmacy (days) per Child	143.79	247.53	61.00	144.13	247.37	60.00
Maximum Number of Medications Involved per Child	2.02	0.14	2.00			
Attention Deficit Medications	(N=3,905)			(N=3,973)		
Count of Episodes per Child	3.55	3.83	2.00	3.26	3.46	2.00
Total Length of Polypharmacy (days) per Child	320.75	404.66	159.00	326.03	412.44	161.00
Maximum Number of Medications Involved per Child	2.12	0.35	2.00			

The most common medications comprising single-class polypharmacy episodes are listed in **Table 20**. The top medication within each class were divalproex (anticonvulsants/antiepileptic), trazodone (antidepressant), risperidone (antipsychotic), clonazepam (anxiolytic), and methylphenidate (ADD medication).

Table 20. Most Common Medications within Single-Class Polypharmacy among Children with ASD by Class (Combination-Specific Only)

Medication	Children with ASD with Single-Class Psychotropic Polypharmacy (N=6,805)	
	n	%
Anticonvulsants/ Antiepileptics	1,245	18.30
Divalproex	639	51.33
Lamotrigine	496	39.84
Topiramate	461	37.03
Oxcarbazepine	428	34.38
Levetiracetam	366	29.40
Antidepressants	1,740	25.57
Trazodone	638	36.67
Sertraline	606	34.83
Fluoxetine	509	29.25
Bupropion	461	26.49
Escitalopram	333	19.14
Antipsychotics	1,560	22.92
Risperidone	965	61.86
Aripiprazole	920	58.97
Quetiapine	780	50.00
Ziprasidone	331	21.22
Olanzapine	319	20.45
Anxiolytics	162	2.38
Clonazepam	99	61.11
Lorazepam	76	46.91
Buspirone	58	35.80
Alprazolam	38	23.46
Diazepam	34	20.99
Attention Deficit Medications	3,905	57.38
Methylphenidate	2,213	56.67
Clonidine	1,982	50.76
Dextroamphetamine	1,660	42.51
Atomoxetine	1,271	32.55
Guanfacine	1,049	26.86

Tables 21 and 22 provide similar information for children with evidence of multi-class psychotropic polypharmacy. Using the combination-specific measure of polypharmacy, the mean number of multi-class episodes per child was 5.6, totaling a median of approximately 346 days of polypharmacy. The average maximum number of classes and medications involved in a multi-class episode were 2.6 and 3.3, respectively.

Table 21. Characteristics of Polypharmacy among Children with ASD with Multi-Class Psychotropic Polypharmacy

Characteristic	Combination-Specific (N=11,598)			Overall (N=11,675)		
	mean	SD	median	mean	SD	median
Count of Episodes per Child	5.63	5.23	4.00	4.11	3.86	3.00
Total Length of Polypharmacy (days) per Child	524.91	523.27	346.00	570.26	565.87	375.00
Maximum Number of Classes Involved per Child	2.59	0.79	2.00	2.82	0.99	3.00
Maximum Number of Medications Involved per Child	3.32	1.42	3.00	3.88	2.28	3.00

Table 22 identifies the most common class combinations involved in multi-class polypharmacy among children with ASD. Approximately 38% of the children with multiclass polypharmacy had at least one episode involving an antidepressant and ADD medication, and just over a quarter had at least one episode with an antipsychotic and ADD medication. About 20% of the children with multi-class polypharmacy had at least one episode with an antipsychotic and antidepressant or an antipsychotic, antidepressant and ADD medication.

Table 22. Select Class Combinations among Children with ASD with Multi-Class Polypharmacy (Combination-Specific Only)

Class Combination within an Episode	Children with ASD with Multi-Class Psychotropic Polypharmacy (N=11,598)	
	n	%
Antipsychotic and Attention Deficit Medication	3,238	27.92
Antidepressant and Attention Deficit Medication	4,362	37.61
Antipsychotic and Antidepressant	2,330	20.09
Antipsychotic, Antidepressant, and Attention Deficit Medication	2,100	18.11
Antipsychotic, Attention Deficit Medication, and Anticonvulsant/Antiepileptic	1,096	9.45
Antipsychotic, Antidepressant, Attention Deficit Medication, and Anticonvulsant/Antiepileptic	742	6.40

Finally, **Tables 23 and 24** provide descriptive information about the types of providers seen among children with ASD with single-class and multi-class polypharmacy. As is shown in Table 23, the overwhelming majority (over 90%) of children with single-class polypharmacy had a primary care provider visit during the time they had medications filled for the relevant type of psychotropic medication, and this did not vary by medication class. In contrast, very few had a visit with a development pediatrician (<5.0%). Whether or not a child had at least one visit with a psychiatrist varied by class of polypharmacy, with only 55.8% of children with anticonvulsant/antiepileptic single-class polypharmacy and as many as 86.3% of children with antipsychotic single-class polypharmacy having seen a psychiatrist. Not surprisingly, a large majority of our children had seen other types of providers (including providers practicing other

medical specialties and other types of health service providers.) Similar results were observed for children with evidence of multi-class polypharmacy (Table 24).

Table 23. Providers among Children with ASD with Single-Class Polypharmacy (Combination-Specific Only)

Provider Type	Children with ASD with Single-Class Psychotropic Polypharmacy (N=6,805)	
	n	%
Anticonvulsants/Antiepileptics	1,245	18.30
Primary Care	1,185	95.18
Developmental Pediatrician	40	3.21
Psychiatrist	695	55.82
Other ¹	1,235	99.20
Antidepressants	1,740	25.57
Primary Care	1,669	95.92
Developmental Pediatrician	69	3.97
Psychiatrist	1,425	81.90
Other	1,706	98.05
Antipsychotics	1,560	22.92
Primary Care	1,497	95.96
Developmental Pediatrician	54	3.46
Psychiatrist	1,346	86.28
Other	1,527	97.88
Anxiolytics		2.38
Primary Care	152	93.83
Developmental Pediatrician	6	3.70
Psychiatrist	125	77.16
Other	160	98.77
Attention Deficit Medications	3,905	57.38
Primary Care	3,778	96.75
Developmental Pediatrician	189	4.84
Psychiatrist	2,765	70.81
Other	3,780	96.80

¹ Other providers included all providers other than primary care physicians, development pediatricians, and psychiatrists.

Table 24. Providers among Children with ASD with Multi-Class Polypharmacy (Combination-Specific)

Provider Type	Children with ASD with Multi-Class Psychotropic Polypharmacy (N=11,598)	
	n	%
Primary Care	11,011	94.94
Developmental Pediatrician	478	4.12
Psychiatrist	8,296	71.53
Other	11,214	96.69

2. Individual and Provider Characteristics related to Psychotropic Use and Polypharmacy

In this section, we present the results of our multivariate analyses conducted to address our second research question about the individual and provider characteristics related to psychotropic use and multi-class polypharmacy among children with ASD. **Table 25** below displays the descriptive results for the demographic and clinical variables included in our models for our sample. Children with ASD were divided into three categories of psychotropic drug use (none, psychotropic drug use but no multi-class polypharmacy, and multi-class polypharmacy). Noteworthy patterns are observed across these groups in terms of race/ethnicity, age at index, evidence of co-occurring conditions, and whether or not a child had seen a psychiatrist. Specifically, children with evidence of psychotropic use were more likely to be white than nonusers, and children who use psychotropic medication (especially those with multi-class polypharmacy) were older than children without a fill for a psychotropic medication. All co-occurring conditions examined (epilepsy, attention deficit disorder, anxiety, depression, and bipolar disorder) were more common among psychotropic users, with higher percentages of each of these conditions seen for the polypharmacy group. Psychotropic users, and especially those with evidence of polypharmacy, were (not surprisingly) much more likely to have seen a psychiatrist during the study observation time.

Table 25. Demographic and Other Characteristics among Children with ASD by Psychotropic Drug Use

	Children with ASD without Evidence of Psychotropic Use (N=12,231)		ASD Psychotropic Users without Evidence of Multi-Class Polypharmacy (Combination-Specific) (N=9,736)		ASD Psychotropic Users with Evidence of Multi-Class Polypharmacy (Combination-Specific) (N=11,598)	
	n	%	n	%	n	%
Gender						
Male	10,016	81.89	8,020	82.37	9,443	81.42
Female	2,215	18.11	1,716	17.63	2,155	18.58
Household Income*						
<\$50,000	1,035	8.46	943	9.69	1,112	9.59
\$50,000 - \$74,999	1,680	13.74	1,579	16.22	1,890	16.30
\$75,000 - \$99,999	1,697	13.87	1,416	14.54	1,725	14.87
\$100,000 - \$124,999	1,330	10.87	1,028	10.56	1,238	10.67
\$125,000 +	1,059	8.66	774	7.95	1,082	9.33
Unknown	5,430	44.40	3,996	41.04	4,551	39.24
Race/Ethnicity*						
White	5,814	47.53	5,214	53.55	6,768	58.35
African American/Black	277	2.26	214	2.20	200	1.72
Asian	253	2.07	142	1.46	71	0.61
Hispanic	602	4.92	409	4.20	355	3.06
Other	178	1.46	100	1.03	61	0.53
Unknown	5,107	41.75	3,657	37.56	4,143	35.72
Geographic Region						
Northeast	2,317	18.94	1,455	14.94	1,499	12.92
Midwest	3,724	30.45	3,288	33.77	4,549	39.22
South	4,116	33.65	3,744	38.46	4,230	36.47
West	2,074	16.96	1,249	12.83	1,320	11.38
	mean	SD	mean	SD	mean	SD
Age at Index Date (continuous)	4.29	4.21	6.81	4.69	9.23	4.57
Co-occurring Conditions	n	%	n	%	n	%
Seizures	111	0.91	803	8.25	1,640	14.14
ADD	856	7.00	4,671	47.98	7,491	64.59
Anxiety	731	5.98	1,509	15.50	3,267	28.17
Depression	408	3.34	892	9.16	2,765	23.84
Bipolar	111	0.91	301	3.09	2,677	23.08
Psychiatrist Visit	2,322	18.98	4,133	42.45	8,752	75.46

*From merged socioeconomic data.

Tables 26 and 27 present the logistic regression results for any psychotropic use and combination-specific multi-class polypharmacy among children with ASD. In both models, race/ethnicity, region, age at index date, evidence of the co-occurring conditions, and having a psychiatrist visit were statistically significant covariates. Specifically, Asian and Hispanic children with ASD had lower odds of any psychotropic use and multi-class polypharmacy compared to white children,

and the odds of psychotropic use and polypharmacy increased for each year of age at index. Compared to children living in the south, children living in the northeast, midwestern, and western regions had lower odds of psychotropic use, and children living in the northeast and western regions also had lower odds of multi-class polypharmacy. In both models, the odds ratio associated with children who had a psychiatrist visit was greater than 3; that is, children who had seen a psychiatrist were three times more likely to have evidence of psychotropic polypharmacy. Finally, children with evidence of seizures, ADD, anxiety, and bipolar disorder were all more likely to use psychotropic medication and, along with children with depression, to have evidence of polypharmacy compared to children without these conditions.

Table 26. Logistic Regression for Any Psychotropic Use among ASD Group

Independent Variables	Psychotropic Use			
	odds ratio	lower 95% CI	upper 95% CI	p-value
Gender				
Female	ref.	–	–	–
Male	1.033	0.955	1.117	0.418
Household Income*				
<\$50,000	ref.	–	–	–
\$50,000 - \$74,999	1.021	0.897	1.162	0.752
\$75,000 - \$99,999	0.982	0.861	1.119	0.782
\$100,000 - \$124,999	0.888	0.773	1.021	0.094
\$125,000 +	0.877	0.756	1.017	0.082
Unknown	0.974	0.852	1.113	0.696
Race/Ethnicity*				
White	ref.	–	–	–
African American/Black	0.838	0.679	1.034	0.099
Asian	0.733	0.575	0.936	0.013
Hispanic	0.808	0.694	0.940	0.006
Other	0.769	0.576	1.026	0.074
Unknown	0.921	0.836	1.014	0.095
Geographic Region				
South	ref.	–	–	–
Northeast	0.642	0.586	0.702	<0.001
Midwest	0.894	0.831	0.963	0.003
West	0.695	0.632	0.764	<0.001
Age at Index Date (continuous)	1.165	1.157	1.173	<0.001

Independent Variables	Psychotropic Use			
	odds ratio	lower 95% CI	upper 95% CI	p-value
Comorbid Conditions				
Seizures	23.837	19.486	29.160	<0.001
ADD	12.881	11.888	13.957	<0.001
Anxiety	1.824	1.640	2.027	<0.001
Depression	1.119	0.978	1.280	0.103
Bipolar	3.237	2.622	3.995	<0.001
Psychiatrist Visit	3.219	3.013	3.439	<0.001
Total Enrollment during Study (quintiles)**				
1st quintile	ref.	–	–	–
2nd quintile	1.124	1.025	1.232	0.013
3rd quintile	1.226	1.116	1.348	<0.001
4th quintile	1.388	1.260	1.529	<0.001
5th quintile	1.869	1.690	2.068	<0.001

Observations read = 33,565, Observations used= 33,565
 Likelihood ratio: chi-square=17602.803, DF=25, p-value=<0.001
 Hosmer and Lemeshow: chi-square=161.646, DF=8, p-value=<0.001
 c statistic = 0.893
 *From merged socioeconomic data.
 **Subjects may have had gap(s) in enrollment during this time. Quintiles calculated among combined ASD group.

Table 27. Logistic Regression for Combination-Specific Multi-Class Polypharmacy among ASD Group

Independent Variables	Combination-Specific Multi-Class Polypharmacy***			
	odds ratio	lower 95% CI	upper 95% CI	p-value
Gender				
Female	ref.	–	–	–
Male	1.043	0.967	1.125	0.277
Household Income*				
<\$50,000	ref.	–	–	–
\$50,000 - \$74,999	1.000	0.887	1.128	0.997
\$75,000 - \$99,999	1.016	0.899	1.148	0.801
\$100,000 - \$124,999	0.995	0.873	1.134	0.943
\$125,000 +	1.143	0.995	1.312	0.058
Unknown	0.998	0.882	1.131	0.979

Independent Variables	Combination-Specific Multi-Class Polypharmacy***			
	odds ratio	lower 95% CI	upper 95% CI	p-value
Race/Ethnicity*				
White	ref.	–	–	–
African American/Black	0.860	0.696	1.063	0.163
Asian	0.504	0.374	0.681	<0.001
Hispanic	0.799	0.682	0.937	0.006
Other	0.600	0.424	0.848	0.004
Unknown	0.963	0.880	1.054	0.409
Geographic Region				
South	ref.	–	–	–
Northeast	0.755	0.690	0.826	<0.001
Midwest	1.021	0.954	1.094	0.544
West	0.806	0.732	0.886	<0.001
Age at Index Date (continuous)	1.148	1.140	1.155	<0.001
Comorbid Conditions				
Seizures	6.192	5.574	6.879	<0.001
ADD	3.666	3.453	3.891	<0.001
Anxiety	1.519	1.405	1.642	<0.001
Depression	1.282	1.170	1.406	<0.001
Bipolar	5.065	4.500	5.700	<0.001
Psychiatrist Visit	3.682	3.463	3.914	<0.001
Total Enrollment during Study (quintiles)**				
1st quintile	ref.	–	–	–
2nd quintile	1.002	0.913	1.099	0.969
3rd quintile	1.022	0.931	1.123	0.645
4th quintile	1.189	1.082	1.307	<0.001
5th quintile	1.449	1.317	1.595	<0.001

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

Likelihood ratio: chi-square=14527.337, DF=25, p-value=<0.001

Hosmer and Lemeshow: chi-square=132.887, DF=8, p-value=<0.001

c statistic = 0.868

*From merged socioeconomic data.

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

***0 = Without polypharmacy (Observations = 21,967); 1 = With polypharmacy (minimum length of polypharmacy = 30 days, Observations = 11,598).

Table 28 presents the results of the multinomial logistic regression modeling psychotropic use and multi-class polypharmacy using a dependent variable categorizing children with ASD into five groups based on their psychotropic drug use. The five groups were: 0) no psychotropic use (representing 36.4% of our ASD sample), 1) at least one psychotropic medication without multi-class polypharmacy (29.0%), 2) multi-class polypharmacy with a maximum of 2 classes (19.7%), 3) multi-class polypharmacy with a maximum of 3 classes (10.4%), and 4) multi-class polypharmacy with 4 or more classes (4.5%). The second group (at least one psychotropic fill) included both children with evidence of only one psychotropic medication and children with multiple psychotropic medications but who did not meet the definition of polypharmacy. All groups of children with psychotropic use were compared to children without psychotropic use. The columns in the table present the results for each of the comparisons examined.

Table 28. Multinomial Logistic Regression for Psychotropic Use and Combination-Specific Multi-Class Polypharmacy among ASD Group***

Independent Variables	1 vs 0		2 vs 0		3 vs 0		4 vs 0		Overall p-value
	odds ratio	p-value							
Gender									
Female	ref.	-	ref.	-	ref.	-	ref.	-	-
Male	1.022	0.601	1.038	0.469	1.155	0.025	0.996	0.960	0.157
Household Income*									
<\$50,000	ref.	-	ref.	-	ref.	-	ref.	-	-
\$50,000 - \$74,999	1.020	0.769	1.063	0.463	0.907	0.332	0.962	0.777	0.481
\$75,000 - \$99,999	0.970	0.665	1.062	0.478	0.884	0.229	0.839	0.216	0.205
\$100,000 - \$124,999	0.878	0.080	0.981	0.829	0.762	0.014	0.815	0.177	0.042
\$125,000 +	0.825	0.016	1.006	0.949	0.990	0.932	0.948	0.736	0.048
Unknown	0.970	0.673	1.018	0.833	0.890	0.264	0.916	0.534	0.647
Race/Ethnicity*									
White	ref.	-	ref.	-	ref.	-	ref.	-	-
African American/Black	0.868	0.206	0.783	0.085	0.767	0.141	0.714	0.204	0.432
Asian	0.864	0.249	0.453	<0.001	0.455	0.003	0.492	0.102	<0.001
Hispanic	0.846	0.038	0.760	0.008	0.571	<0.001	0.753	0.140	0.002
Other	0.860	0.316	0.617	0.024	0.413	0.006	0.258	0.016	0.015
Unknown	0.922	0.116	0.915	0.153	0.883	0.103	1.024	0.813	0.252
Geographic Region									
Northeast	0.675	<0.001	0.597	<0.001	0.532	<0.001	0.516	<0.001	<0.001
Midwest	0.876	<0.001	0.945	0.228	0.924	0.169	0.852	0.041	0.008
South	ref.	-	ref.	-	ref.	-	ref.	-	-
West	0.719	<0.001	0.673	<0.001	0.593	<0.001	0.566	<0.001	<0.001

Independent Variables	1 vs 0		2 vs 0		3 vs 0		4 vs 0		Overall p-value
	odds ratio	p-value							
Age at Index Date (continuous)	1.130	<0.001	1.218	<0.001	1.283	<0.001	1.346	<0.001	<0.001
Comorbid Conditions									
Seizures	16.781	<0.001	37.371	<0.001	79.542	<0.001	153.572	<0.001	<0.001
ADD	10.683	<0.001	17.788	<0.001	21.612	<0.001	25.049	<0.001	<0.001
Anxiety	1.643	<0.001	2.260	<0.001	2.090	<0.001	1.874	<0.001	<0.001
Depression	0.949	0.484	1.235	0.006	1.226	0.015	1.407	<0.001	<0.001
Bipolar	1.236	0.083	3.223	<0.001	8.475	<0.001	24.254	<0.001	<0.001
Psychiatrist Visit	2.261	<0.001	5.240	<0.001	9.276	<0.001	14.153	<0.001	<0.001
Total Enrollment during Study (quintiles)**									
1st quintile	ref.	-	ref.	-	ref.	-	ref.	-	-
2nd quintile	1.141	0.008	1.030	0.626	1.206	0.018	1.409	0.005	0.003
3rd quintile	1.243	<0.001	1.107	0.104	1.287	0.002	1.882	<0.001	<0.001
4th quintile	1.362	<0.001	1.303	<0.001	1.699	<0.001	2.705	<0.001	<0.001
5th quintile	1.784	<0.001	1.871	<0.001	2.545	<0.001	4.139	<0.001	<0.001

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

Likelihood ratio: chi-square=25123.624, DF=100, p-value=<0.001

AIC-intercept: 95388.094, AIC-intercept and covariates: 70464.470

Pseudo R-Square = 0.263

*From merged socioeconomic data.

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

***() no psychotropic use 1) at least one psychotropic medication without multi-class polypharmacy, 2) multi-class polypharmacy with a maximum of 2 classes, 3) multi-class polypharmacy with a maximum of 3 classes, and 4) multi-class polypharmacy with 4 or more classes

Overall, household income, race/ethnicity, geographic region, age at index date, all the co-occurring conditions included, and having had a psychiatrist visit were found to be significantly related to the outcomes of interest but some of the results varied across comparisons of interest. For example, children with household incomes between \$100,000 and \$124,999 were less likely than children with household incomes less than \$50,000 to have polypharmacy involving three classes rather than no psychotropic use at all. Compared to white children, Asian and Hispanic children and children who fell into the “other” race/ethnicity category had lower odds of polypharmacy involving two or three classes vs. no psychotropic use. Children living in the northeast and western regions had lower odds of all outcomes versus no psychotropic use compared to those living in the southern region.

Older age at index, having had a psychiatrist visit, and evidence of the co-occurring conditions were consistently related to higher odds across all outcomes (psychotropic use no multi-class polypharmacy, polypharmacy use involving many classes of medications) relative to no psychotropic use. In fact, in many cases, the odds ratios for these covariates were larger in the far right columns of the tables, for the comparisons between the more complicated polypharmacy users (with three or more classes involved) and children without psychotropic use, meaning that these covariates were especially predictive of more complicated psychotropic polypharmacy.

Finally, **Table 29** presents the model of the total number of days of polypharmacy among children with ASD and evidence of combination-specific multi-class polypharmacy. As presented above, the average length of days on combination-specific polypharmacy was 5245 days with a median of 346 days. Compared to children with household incomes of less than \$50,000, children with household incomes of \$75,000 or higher had 7-11% longer duration on polypharmacy. African American children and Hispanic children had fewer days of polypharmacy compared to white children, and children living in the midwestern region had longer time on polypharmacy compared to children living in the southern region. Not surprisingly, older children had more days of polypharmacy on average: Each year of age at index was associated with 4.4% longer duration on polypharmacy. With the exception of anxiety and depression, for which no significant relationship and a negative relationship were observed, respectively, all the other co-occurring conditions were significantly associated with more days of polypharmacy. Specifically, having seizures, ADD, or bipolar disorder was associated with a 27.7%, 15.4%, and 29.8% increase in polypharmacy duration, respectively. Children who had visited a psychiatrist also had more days on polypharmacy than those who had not.

Table 29. Generalized Linear Model of Total Length (Days) of Combination-Specific Multi-Class Polypharmacy among ASD Group***

Independent Variables	Total Length of Polypharmacy (Days)			
	Days Ratio	lower 95% CI	upper 95% CI	p-value
Gender				
Female	ref.	–	–	–
Male	1.024	0.983	1.066	0.256
Household Income*				
<\$50,000	ref.	–	–	–
\$50,000 - \$74,999	1.048	0.984	1.117	0.147
\$75,000 - \$99,999	1.072	1.004	1.144	0.036
\$100,000 - \$124,999	1.086	1.013	1.165	0.021
\$125,000 +	1.114	1.035	1.198	0.004
Unknown	1.013	0.949	1.082	0.693
Race/Ethnicity*				
White	ref.	–	–	–
African American/Black	0.870	0.771	0.983	0.025
Asian	0.974	0.797	1.189	0.793
Hispanic	0.850	0.776	0.932	0.001
Other	0.998	0.805	1.238	0.987
Unknown	1.014	0.968	1.063	0.554
Geographic Region				
Northeast	1.025	0.974	1.078	0.343
Midwest	1.085	1.046	1.125	<0.001
South	ref.	–	–	–
West	0.994	0.942	1.048	0.816
Age at Index Date (continuous)	1.044	1.040	1.048	<0.001
Comorbid Conditions				
Seizure	1.277	1.220	1.337	<0.001
ADD	1.155	1.115	1.196	<0.001
Anxiety	0.982	0.946	1.019	0.323
Depression	0.937	0.900	0.976	0.002
Bipolar	1.299	1.250	1.351	<0.001
Psychiatrist Visit	1.065	1.025	1.107	0.002
Total Enrollment during Study (quintiles)**				
1st quintile	ref.	–	–	–
2nd quintile	1.689	1.603	1.780	<0.001
3rd quintile	2.323	2.205	2.448	<0.001
4th quintile	3.245	3.080	3.418	<0.001
5th quintile	4.451	4.224	4.690	<0.001

Observations read = 11,598, Observations used = 11,598

*From merged socioeconomic data.

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

***Generalized linear model with gamma distribution and log link.

D. Discussion

1. Prevalence and Characteristics of Polypharmacy among Children with ASD

Psychotropic polypharmacy, or the concomitant use of multiple psychotropic medications, was prevalent in our sample of children with ASD. Nearly 40% had evidence of either single or multi-class polypharmacy. This is, however, not altogether dissimilar to previous estimates, and is consistent with nationwide trends toward increased medication use.^{23, 31, 33} In our study, the most commonly prescribed drugs in single-class polypharmacy were ADD medications – an expected finding, as over half of children with ASD in our sample also had ADD diagnoses. We also found anti-depressants and ADD medication to be the most common multi-class combination, which is similar to the literature.^{31, 35, 41} Additionally, we found that although the proportion of children with psychotropic polypharmacy who visited a psychiatrist varied somewhat by medication class, the overwhelming majority of children with psychotropic polypharmacy had a primary care visit within the time period surrounding receiving medication fills, which would be expected among children in general, especially those who receive medications. It remains unclear, however, if the primary care provider was the prescriber, or was refilling a medication initiated by another provider such as a specialist, or if the primary care visit was part of routine care and un-related to the psychotropic medication use.

2. Individual and Provider Characteristics Related to Polypharmacy

The co-occurring conditions (possible indications for the psychotropic medications included) we selected for inclusion as covariates were, reassuringly, among the strongest and most consistent predictors of psychotropic use, multi-class polypharmacy, and length of polypharmacy. Our results suggest that seizures, ADD, bipolar disorder, and anxiety are all significant predictors of psychotropic use and, along with depression, of multi-class polypharmacy among children with ASD. Furthermore, children with ASD who also have seizures, ADD, or bipolar disorder had the highest odds of more complicated multi-class polypharmacy (as measured by a higher number of medication classes involved). Additionally, among children with multi-class polypharmacy, these three conditions were associated with a 15%-30% longer duration in polypharmacy. Previous studies on psychotropic medication use have shown similar results. Mandell reported that in the Medicaid-enrolled youth population with ASD, co-occurring conditions such as bipolar disorder, ADD, anxiety, and schizophrenia were all associated with higher odds of psychotropic medication use.²³ The presence of a co-occurring condition suggests greater clinical and/or symptomatic complexity; this complexity likely accounts for the higher rate of medication use among this population, but appropriateness was not assessed in our study. Similarly, children who have received care from a psychiatrist may have greater complexity which likely accounts for the higher odds of psychotropic use and psychotropic polypharmacy we observed for these children, a finding compatible with Olfson's results on the prescription of anti-psychotics.⁴²

Demographic characteristics were also significant for psychotropic use and psychotropic polypharmacy. Our study found older age (at index) to be significantly associated with psychotropic use, multi-class polypharmacy, and length of polypharmacy, which is congruent with Comer's findings on multi-class psychotropic use.³¹ This was an expected finding as medication use itself and parental and provider perception of safety and, thus, acceptance of psychotropic use, likely increases as a child's age increases.⁴³ Across all models, gender was not significantly related to psychotropic use, including multi-class polypharmacy, after controlling for the other covariates in the analyses. Boys and girls with ASD were just as likely to have evidence of psychotropic

medication use during the study. Additionally, children from the southern region were significantly more likely than any other region to use psychotropic medications. This pattern, also true for the odds of multi-class polypharmacy, has not been widely reported in the literature and may be related to health care practices, access, and utilization which are known to vary by geography.^{44,45} Finally, while race/ethnicity was not always significant in our models and the results were somewhat inconsistent, we found some support for whites having greater odds of psychotropic medication use and psychotropic polypharmacy. This result is similar to the literature, which has reported that white children tend to have more psychotropic drug use than other races.^{23,33} Differences seen between white and minority children could be attributable to disparities in access to health care, beliefs about the benefits and harms of medications, and lack of a sense of trust in the health care system.²³ However, our race-related results should be interpreted with caution in view of the large proportion of children (38%) in our sample without race data.

3. Study Implications and Contributions

This study contributes to the existing literature on psychotropic medication use among children with ASD. First, to our knowledge, this is the first claims-based study to examine psychotropic polypharmacy among commercially-insured children with ASD. We have been able to corroborate some of Mandell's findings in the Medicaid population. Our results suggest more unity than discord on the use of psychotropic medications between children with ASD with private insurance and Medicaid: the prevalent use of psychotropic medications, the high rate of polypharmacy, and the significance of age, race, and co-occurring conditions in psychotropic use. Our results suggest that patterns of psychotropic medication use and psychotropic polypharmacy from one population may be more generalizable to the broader ASD population than previously thought.

Second, we developed outcomes beyond the common metrics in this research area. Previous studies have tended to focus on identifying predictors of the use of psychotropic medication and/or polypharmacy. Our multinomial logistic model expands on the methods heretofore used by presenting the effects of many independent variables on four different definitions of psychotropic use and multi-class polypharmacy (psychotropic use with no polypharmacy, polypharmacy with 2 classes, 3 classes, and 4 or more classes). In addition, our sample of children with ASD and evidence of psychotropic polypharmacy allowed us to model total length of time or the extent of polypharmacy in addition to documenting its occurrence in a binary fashion.

Finally, the high use of concomitant pharmacotherapy with powerful psychotropic medications merits concern and further investigation about the safety and effectiveness of such practices on developing children. Our estimates of the prevalence of polypharmacy among children with ASD emphasize the need for additional evidence on the appropriateness, effectiveness and safety of psychotropic medications in this population. Moreover, further research into the sociodemographic and geographic variation in the practice of polypharmacy and whether the variation is driven by clinical need or other factors may provide a better understanding of differences in treatment patterns across the country.

VII. Adherence to MMR Vaccination

A. Background

In the past several decades, parental perceptions about the safety of routinely administered vaccines have varied and have been a source of continuing controversy and concern about public health.⁴⁶ In the late 1990s, a study (later shown to be invalid) prompted substantial concern about an alleged causal connection between the measles-mumps-rubella (MMR) vaccine and autism.⁴⁷ Although this study has since been discredited and refuted by the scientific community,^{48, 49, 50, 51, 52} both the medical literature and lay press confirm that parental concerns about the safety of vaccines have continued, or even increased.^{52,53} Some of these concerns are directly tied to fears about etiologic factors relating to autism, which itself seems to be increasing without an understanding of why.^{52, 53, 54, 55} If concerns about vaccine safety result in decreased immunization rates, both individual and herd immunity may be threatened, resulting in outbreaks of vaccine-preventable conditions. Herd immunity is the phenomenon whereby the inoculation of a critical percentage of the population (usually 85% or more) provides indirect protection for members of society who cannot receive the vaccination themselves due to immunodeficiency or other contraindications.⁵⁶ Should herd immunity be lessened, the reemergence of vaccine-preventable diseases could reduce some of the public health gains provided by vaccines and result in increased morbidity and mortality that are preventable.

Current rates of vaccination vary by data source; for example, some researchers have found that states' MMR vaccination rates range from 64% to 84%, while others have found coverage rates of 80% for all recommended vaccines.^{57,58} Nevertheless, encouraging data show that the U.S. vaccination rate remains quite high. The National Committee for Quality Assurance (NCQA) indicates that MMR rates among commercially- insured toddlers rose steadily from 1999 (87.0%) through 2008 (93.5%) before dropping to 90.6% in 2009.⁵⁶ The Medicaid-insured population, starting at 83.7% in 2001, exhibited a similar trend through 2006 (91.1%).⁵⁶ Although a slight dip to 90.4% was observed in 2007, rates rose back to 91.2% by 2009.⁵⁶ Using the National Immunization Survey, the CDC estimates that the rate of immunization for MMR before 24 months of age was 89.7% in 2010.⁵⁹

Despite these improvements, current vaccination rates do not meet national or international goals. A 2009 study revealed that approximately 12% of parents had refused a vaccine for a child that his/her doctor had recommended; 18% of these cases were refusals for the MMR vaccine.⁵³ Moreover, the World Health Organization's MMR coverage target of 95% is neither met by the United States (with coverage estimated near 90%) nor, as noted in a 2012 study, the United Kingdom, with an estimated rate of 84.8%.^{52, 60} Furthermore, parental concern and refusal related to the MMR vaccine precipitated a measles outbreak in the United Kingdom, when England and Wales saw 1,000 measles cases in 2006.⁶¹ On a smaller scale, a community in the state of Indiana with low vaccination rates saw a measles outbreak affecting 35 individuals, 32 of whom were unvaccinated.⁵¹ Concern over a particular vaccine can have a spillover effect on less "controversial" vaccines; researchers have observed this type of reduction in uptake of vaccines that extended beyond MMR to other less controversial and established immunizations.⁴⁹

Less is known about vaccine concerns and practices among families in which a child has ASD; in particular, we have found no studies to date that examine vaccine adherence in siblings of children with ASD. Thus, we sought to determine whether parents of children with ASD

vaccinate their children, both children with ASD and those without. We focused specifically on the MMR vaccination due to the controversy and subsequent misunderstanding about the safety of this vaccine that persists in the general population.

Our research questions were the following:

1. Overall, how do children with ASD and their siblings compare to children without ASD and their siblings in terms of adherence to recommended MMR vaccinations?
2. Is having a child with ASD related to adherence to recommended MMR vaccinations in younger siblings?

B. Sampling

To address the research questions above, we focused on children with observation time during two specific age periods (between the ages of 12 and 24 months and between the ages of 4 and 6 years) when one dose of MMR vaccination is recommended based on standard vaccination schedules.⁶² We included in the analysis our samples of children with and without ASD as well as their respective siblings. To be included in the analysis for an age period, the sample members had to have continuous health plan enrollment for the entire period; some had continuous enrollment during both age periods.

In some analyses, a subset of siblings (specifically, younger siblings) of children with and without ASD was examined. To identify younger siblings within the sibling samples, we used date of birth to determine siblings born later than their respective subject child with ASD or subject child without ASD. Siblings born on the same day as a child with ASD or child without ASD were excluded from the subgroup of younger siblings. Siblings associated with more than one child with ASD or more than one child without ASD were included as long as they were younger than at least one of the children.

C. Methods

1. Variable Definitions

a. Vaccination Adherence

Adherence to recommended MMR vaccinations was determined for children with and without ASD and their siblings. Specifically, whether or not a subject had a claim for an MMR vaccination between the ages of 12 and 24 months and between the ages of 4 to 6 years was determined.

- **MMR vaccine between the ages of 12 to 24 months.** Whether or not a subject had evidence of an MMR vaccination or vaccinations during this age period. MMR vaccination was measured by five combinations of CPT codes for MMR vaccination: 1) separate claims for measles, mumps, and rubella vaccinations; 2) a claim for measles and rubella combination vaccination and a separate claim for mumps vaccination; 3) a claim for mumps and rubella combination vaccination and a separate claim for measles vaccination; 4) a claim for an MMR combination vaccination; and 5) a claim for an MMR plus varicella combination vaccination. A flag (yes/no) was set for each of the five scenarios indicating an MMR vaccination so that the manner in which a subject was vaccinated could also be determined. See Appendix A for the list of CPT codes used.

- **MMR vaccine between the ages of 4 to 6 years.** Whether or not a subject had evidence of an MMR vaccination or vaccinations during this age period. As for the 12 to 24 month age period, a flag was set for each of the five scenarios indicating an MMR vaccination so that the manner in which a subject was vaccinated could be determined. See Appendix A for the list of CPT codes used.

b. Co-occurring Conditions

- **Seizure disorder/epilepsy (Seizures).** Whether or not children with and without ASD and their siblings had evidence of seizures. One binary variable (yes/no) was created based on total study enrollment time. To qualify, a subject had at least two medical claims with a relevant diagnosis code in any position at least 30 days apart OR a subject had one medical claim with a diagnosis code in any position and one claim for a medication for seizures. 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.
- **Allergies.** Whether or not children with or without ASD and their siblings had evidence of an allergy. One binary variable (yes/no) was created based on subjects' total study enrollment time. To qualify, a subject had at least two medical claims with a relevant diagnosis code in any position at least 30 days apart. See Appendix A for conditions included and corresponding ICD-9-CM diagnosis codes.

2. Analytic Approach

a. Descriptive Analysis

To address our first research question - how children with ASD and their siblings compare to children without ASD and their siblings in terms of recommended MMR vaccination - the proportion of children with evidence of MMR vaccination between the age periods of 12 to 24 months and 4 to 6 years was calculated. These analyses were conducted to compare 1) children with ASD and their siblings to children without ASD and their siblings, 2) children with and without ASD to their respective siblings, and 3) siblings of children with ASD to siblings of children without ASD. All analyses were based on the entire study time frame (2001-2009) but some analyses were conducted separately for 2001-2004 and 2005-2009 to examine secular changes. Descriptive analyses were also conducted to examine the types of MMR vaccinations received among the children samples.

b. Multivariate Analysis

To address the second research question - whether having a child with ASD is related to adherence to recommended MMR vaccinations among younger siblings - logistic regression analyses modeling vaccination were conducted, one model for the age period of 12 to 24 months and another for the age period of 4 to 6 years. The analyses were based on a sample of matched pairs, including children with and without ASD with enrollment during the entire age period who also had a *younger* sibling with enrollment during the entire same age period. Therefore, the models were based on a subset of children with and without ASD and a subset of siblings based on these requirements. These samples were included as four point categorical variable (1=children with ASD, 2=ASD younger siblings, 3=comparison group children, 4=comparison

younger siblings) with the 4th category set as the reference group. Comparisons examined within the models included children with ASD vs. children without ASD, and ASD younger siblings vs. comparison younger siblings. We also tested whether there was a difference between children with ASD and their younger siblings and between children without ASD and their younger siblings. Analyses were conducted using the GENMOD procedure in SAS. Each subject and younger sibling included in the model was assigned a pair identification number (representing a subject/sibling pair), and a repeated measure step was used to acknowledge the covariance structure of these pairs. An individual could belong to more than one pair; if so, they were included in the model more than once. Our model did not adjust for this clustering. It should also be reiterated that siblings could exist within the ASD sample and within the comparison sample. Our analyses did not adjust for this clustering as well, and these siblings were not included with other siblings in the comparisons examined.

For each model, specific covariates for inclusion were finalized based upon clinical rationale, descriptive analyses, and/or statistical significance. Specifically, gender, household income, race, region, seizures, and allergies were included in the models.

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.^{63, 64} While there is no one agreed-upon criterion for what level of VIF indicates multicollinearity, some believe VIF values exceeding 10 should warrant concern.⁶⁵ All of the correlations and VIF values observed fell below these thresholds, indicating little need to be concerned about multicollinearity among our model variables.

D. Results

1. MMR Vaccination among Children with and without ASD and their Siblings

Table 30 presents the proportion of children with ASD and all of their siblings (not just younger) with evidence of MMR vaccination compared to children without ASD and their siblings. Vaccinations received between the ages of 12 to 24 months and between the ages of 4 to 6 years are shown. A total of 6,914 and 4,897 subjects out of a combined total of 74,778 children with ASD and their siblings, and 18,630 and 8,209 of children without ASD and their siblings (out of a combined total of 334,744) had continuous enrollment during the entire 12 to 24 months and the entire 4 to 6 years age period, respectively. Of the subjects with enrollment during these periods, slightly more children without ASD and their siblings had evidence of MMR vaccination during both age periods: Specifically, 79.3% of comparison group children and siblings had a vaccination for MMR between the ages of 12 and 24 months and 77.3% had an MMR vaccination between the ages of 4 and 6 years. In contrast, 75.2% and 74.2% of children with ASD and their siblings had MMR vaccination during these same age periods. **Table 31** presents the data with separate proportions for ASD and comparison subjects and their siblings. Siblings of both groups were less likely to have a vaccination for MMR between 12 to 24 months compared to children with ASD and the comparison group, particularly siblings of children with ASD. The reverse was true, however, for ASD subjects and siblings during the 4 to 6 year period: during this older age period, siblings of children with ASD had higher vaccination rates than the children with ASD. Comparison subjects and their siblings did not differ in vaccination rate during the 4 to 6 years age period.

Table 30. MMR Vaccination Adherence Among ASD and Comparison Groups and their Siblings

Vaccination	ASD & Siblings (N=74,778)		Comparison & Siblings (N=334,744)		p-value
	n	%	n	%	
12-24 Months					
Enrolled during entire 12-24 months	6,914	9.25	18,360	5.48	
MMR Vaccination	5,201	75.22	14,559	79.30	<0.001
4-6 Years					
Enrolled during entire 4-6 years	4,897	6.55	8,209	2.45	
MMR Vaccination	3,631	74.15	6,348	77.33	<0.001

Table 31. MMR Vaccination Adherence Among ASD and Comparison Groups and their Siblings

Vaccination	ASD (N=33,565)		Siblings of ASD Group (N=41,213)		Comparison (N=138,876)		Siblings of Comparison Group (N=195,868)		ASD vs. Siblings p-value	Comparison vs. Siblings p-value
	n	%	n	%	n	%	n	%		
12-24 Months										
Enrolled during entire 12-24 months	2,967	8.84	3,947	9.58	8,253	5.94	10,107	5.16		
MMR Vaccination	2,407	81.13	2,794	70.79	6,653	80.61	7,906	78.22	<0.001	<0.001
4-6 Years										
Enrolled during entire 4-6 years	2,539	7.56	2,358	5.72	3,215	2.32	4,994	2.55		
MMR Vaccination	1,800	70.89	1,831	77.65	2,504	77.88	3,844	76.97	<0.001	0.335

To examine secular trends in vaccination, **Table 32** below presents the proportion of children with evidence of MMR vaccination between 2001-2004 and 2005-2009. Only children with complete enrollment during the ages of 12 to 24 months and 4 to 6 years during these years were included. Subjects whose enrollment during these age periods spanned the two time frames (e.g., turned 24 months in the beginning of 2005) were excluded from the analysis. As is shown, the proportion of children overall with an MMR vaccination was lower during the early time period (2001-2004) compared to the latter, and this was true at both 12 to 24 months and 4 to 6 years of age. No statistically significant difference was observed between the ASD subjects and their siblings and between comparison subjects and their siblings during 2001-2004. Between 2005-2009, however, more children in the comparison sample had a vaccination during the two age periods than children in the ASD sample, with up to 83.0% of children without ASD and their siblings having evidence of an MMR vaccination during both age periods of 12 to 24 months and 4 to 6 years. Therefore, the higher MMR vaccination rates among the comparison children and their siblings relative to the ASD children and their siblings seen above in Table 30 were only evident in the later years (2005-2009).

Table 32. MMR Vaccination Adherence among ASD and Comparison Groups and their Siblings, 2001-2004 vs. 2005-2009

Vaccination	2001-2004					2005-2009				
	ASD & Siblings (N=74,778)		Comparison & Siblings (N=334,744)		p-value	ASD & Siblings (N=74,778)		Comparison & Siblings (N=334,744)		p-value
	n	%	n	%		n	%	n	%	
12-24 Months										
Enrolled during entire 12-24 months	2,443	3.27	6,646	1.99		3,369	4.51	9,228	2.76	
MMR Vaccination	1,799	73.64	4,922	74.06	0.685	2,536	75.27	7,631	82.69	<0.001
4-6 Years										
Enrolled during entire 4-6 years	553	0.74	1,065	0.32		1,940	2.59	2,970	0.89	
MMR Vaccination	394	71.25	758	71.17	0.975	1,509	77.78	2,451	82.53	<0.001

Table 33 presents the type of MMR vaccination children received. Among those who were enrolled during the two age periods (12 to 24 months and 4 to 6 years) and who had evidence of vaccination during these age periods, the overwhelming majority (99.0%) were vaccinated through a single combination vaccination/injection, and this was true for both the ASD and comparison samples. Very few children had separate injections of vaccinations for measles, mumps or rubella during either age period.

Table 33. Composition of MMR Vaccination Adherence Among Vaccinated ASD and Comparison Group Members and Their Siblings

Vaccination	ASD & Siblings (N=74,778)		Comparison & Siblings (N=334,744)		p-value
	n	%	n	%	
MMR Vaccinated at 12-24 Months	5,201	75.22	14,559	79.30	
Single combination vaccination	5,167	99.35	14,541	99.88	<0.001
Multiple vaccinations	35	0.67	18	0.12	<0.001
MMR Vaccinated at 4-6 Years	3,631	74.15	6,348	77.33	
Single combination vaccination	3,622	99.75	6,347	99.98	<0.001
Multiple vaccinations	11	0.30	1	0.02	<0.001

2. Adherence to MMR Vaccination among Younger Siblings

Our second and final research question related to MMR vaccination was: Is having a child with ASD related to adherence to recommended MMR vaccinations among younger siblings?

To address this question, we conducted analyses focusing on children with and without ASD with enrollment during either the entire age period of 12 to 24 months or 4 to 6 years and who also had a *younger* sibling with enrollment during the entire same age period. Therefore, the models were based on a subset of children with and without ASD and a subset of siblings.

A total of 609 ASD and 1,002 comparison subject/sibling pairs were identified for the 12 to 24 month period, and 310 ASD and 378 comparison pairs were identified for the 4 to 6 year period. Because an individual could contribute to more than one pair (for example, a child with ASD had more than one younger sibling with the necessary enrollment or a sibling was younger than more than one child with ASD), the number of ASD, comparison, and sibling subjects included in the model could be less than the number of pairs. The number of ASD subjects contributing to the 12 to 24 month and 4 to 6 year models was 551 and 286, respectively, and the number of ASD siblings contributing to the models was 607 and 307, respectively. The number of comparison subjects contributing to the 12 to 24 month and 4 to 6 year models were 925 and 359, respectively, and the number of comparison siblings contributing to the models was 1,000 and 378, respectively.

Table 34 presents the descriptive results for the demographic and clinical variables included in our models for the subjects included in the pairs used in the analysis. Data are shown for the 12 to 24 months and 4 to 6 years samples, respectively. Compared to the demographic make-up of our entire samples of children with and without ASD (Table 4) and their siblings (Table 5), a few differences are observed for the subjects included in the paired samples. For example, a higher proportion of boys with ASD are included and fewer white children with ASD (and younger siblings of children with ASD) but more white children without ASD were included in the 12 to 24 month analysis, compared to the entire samples of children. Also, fewer children in the lower income categories and more in the higher income categories were included in the analysis for this younger age period. For the analysis during the 4 to 6 years age period, we observe a higher percentage of male siblings of comparison children and more white children with ASD, comparison group members, and comparison siblings included in the vaccination model. As with the 12 to 24 month sample, more children in the higher income categories are included in the paired samples.

Table 34. Select Demographic and Clinical Characteristics of Paired ASD/Comparison Subjects and Younger Siblings Fully Enrolled between 12-24 Months and 4-6 Years

Characteristic	ASD		Younger Siblings of ASD Group		Comparison		Younger Siblings of Comparison Group	
	n	%	n	%	n	%	n	%
12-24 Months Paired Sample	551		607		925		1,000	
Gender								
Male	476	86.39	301	49.59	464	50.16	499	49.90
Female	75	13.61	306	50.41	461	49.84	501	50.10
Geographic Region								
Northeast	79	14.34	82	13.51	86	9.30	94	9.40
Midwest	185	33.58	213	35.09	346	37.41	382	38.20
South	206	37.39	220	36.24	368	39.78	395	39.50
West	81	14.70	92	15.16	125	13.51	129	12.90
Race/Ethnicity*								
White	265	48.09	252	41.52	445	48.11	422	42.20
African American/Black	5	0.91	8	1.32	17	1.84	22	2.20
Asian	11	2.00	8	1.32	15	1.62	16	1.60
Hispanic	25	4.54	18	2.97	39	4.22	39	3.90
Other	6	1.09	8	1.32	8	0.86	8	0.80
Unknown	239	43.38	313	51.57	401	43.35	493	49.30

Characteristic	ASD		Younger Siblings of ASD Group		Comparison		Younger Siblings of Comparison Group	
	n	%	n	%	n	%	n	%
Household Income*								
<\$50,000	32	5.81	31	5.11	82	8.86	74	7.40
\$50,000 - \$74,999	73	13.25	72	11.86	136	14.70	128	12.80
\$75,000 - \$99,999	90	16.33	82	13.51	136	14.70	134	13.40
\$100,000 - \$124,999	66	11.98	69	11.37	91	9.84	90	9.00
\$125,000 +	43	7.80	44	7.25	74	8.00	70	7.00
Unknown	247	44.83	309	50.91	406	43.89	504	50.40
Seizures	6	1.09	3	0.49	2	0.22	4	0.40
Allergies	11	2.00	12	1.98	7	0.76	10	1.00
4-6 Years Paired Sample	286		307		359		378	
Gender								
Male	226	79.02	149	48.53	198	55.15	205	54.23
Female	60	20.98	158	51.47	161	44.85	173	45.77
Geographic Region								
Northeast	31	10.84	33	10.75	46	12.81	50	13.23
Midwest	118	41.26	124	40.39	118	32.87	121	32.01
South	100	34.97	106	34.53	158	44.01	170	44.97
West	37	12.94	44	14.33	37	10.31	37	9.79
Race/Ethnicity*								
White	172	60.14	159	51.79	198	55.15	187	49.47
African American/Black	4	1.40	6	1.95	8	2.23	7	1.85
Asian	5	1.75	6	1.95	10	2.79	9	2.38
Hispanic	12	4.20	9	2.93	23	6.41	24	6.35
Other	2	0.70	3	0.98	5	1.39	4	1.06
Unknown	91	31.82	124	40.39	115	32.03	147	38.89
Household Income*								
<\$50,000	18	6.29	19	6.19	33	9.19	26	6.88
\$50,000 - \$74,999	35	12.24	33	10.75	51	14.21	51	13.49
\$75,000 - \$99,999	48	16.78	47	15.31	53	14.76	46	12.17
\$100,000 - \$124,999	56	19.58	51	16.61	63	17.55	60	15.87
\$125,000 +	34	11.89	33	10.75	49	13.65	52	13.76
Unknown	95	33.22	124	40.39	110	30.64	143	37.83
Seizures	13	4.55	1	0.33	2	0.56	0	0.00
Allergies	12	4.20	7	2.28	7	1.95	6	1.59

Table 35 presents the unadjusted proportion of children included in the paired samples who had evidence of MMR vaccination during the 12 to 24 months and 4 to 6 years age periods. During the younger age period, the results were similar across all groups (just over 80% vaccinated) except younger siblings of children with ASD, who were less likely to be vaccinated between the

ages of 12 and 24 months compared to their older sibling (69.2% vs. 82.2%). During the older age period (4 to 6 years), there was no statistically significant difference observed between children with ASD and their younger siblings, however, children without ASD were less likely to be vaccinated than their younger siblings.

Table 35. MMR Vaccination Adherence Among Paired ASD/Comparison Subjects and Younger Siblings Fully Enrolled between 12-24 Months and 4-6 Years

Vaccination	ASD		Younger Siblings of ASD Group		Comparison		Younger Siblings of Comparison Group		ASD vs. Younger Siblings p-value	Comparison vs. Younger Siblings p-value
	n	%	n	%	n	%	n	%		
12-24 Months Paired Sample	551		607		925		1,000			
MMR Vaccination	453	82.21	420	69.19	771	83.35	849	84.90	<0.001	0.353
4-6 Years Paired Sample	286		307		359		378			
MMR Vaccination	214	74.83	240	78.18	275	76.60	314	83.07	0.336	0.028

Tables 36 and 37 below present the results of logistic regression models of MMR vaccination based on pairs of children with ASD and their younger siblings and pairs of comparison children without ASD and their younger siblings. Table 36 contains the model results for the age period of 12 to 24 months, and Table 37 contains the model results for the age period of 4 to 6 years. Both models controlled for the same demographic and enrollment variables as well as two co-occurring conditions that may be contraindications to receiving vaccines, seizures and allergies.

As mentioned above, several comparisons were of interest: 1) children with ASD compared to children without ASD, 2) ASD siblings compared to comparison siblings, and 3) comparisons between subject (both ASD and comparison) and their younger siblings. Table 36 shows that after controlling for the other variables in the model, there was no significant difference between children with and without ASD between the ages of 12 to 24 months: both groups were equally likely to be MMR vaccinated during this age. However, the younger siblings between the two samples did differ, with younger siblings of children with ASD less likely to be vaccinated during this age period than younger siblings of children without ASD (OR=0.387, $p<0.001$). Looking within pairs, while younger siblings of the comparison sample did not differ from their sibling without ASD ($p=0.1983$), children with ASD were more likely than their younger siblings to be vaccinated during the ages of 12 to 24 months (OR=2.066, $p<0.001$). Put in opposite terms, younger siblings of children with ASD were approximately half as likely to be vaccinated as their older sibling with ASD after adjusting for covariates. Given these results, it was not surprising to find that the difference in vaccination rates between children with ASD and their younger siblings was larger than the difference between children without ASD and their younger siblings (OR=2.348, $p<0.001$).

Table 36. Logistic Model for MMR Vaccination among Paired ASD/Comparison Subjects and Younger Siblings Fully Enrolled between 12 and 24 Months

Independent Variables	MMR Vaccination			
	odds ratio	lower 95% CI	upper 95% CI	p-value
Sample				
Comparison Younger Siblings	ref.	–	–	–
ASD	0.799	0.605	1.054	0.112
ASD Younger Siblings	0.387	0.302	0.495	<.001
Comparison	0.880	0.724	1.069	0.198
Gender				
Female	ref.	–	–	–
Male	0.895	0.743	1.078	0.241
Household Income*				
<\$50,000	ref.	–	–	–
\$50,000 - \$74,999	1.229	0.790	1.911	0.360
\$75,000 - \$99,999	1.548	0.998	2.400	0.051
\$100,000 - \$124,999	2.000	1.247	3.209	0.004
\$125,000 +	2.583	1.496	4.459	0.001
Unknown	0.999	0.622	1.603	0.996
Race/Ethnicity*				
White	ref.	–	–	–
African American/Black	0.666	0.349	1.273	0.219
Asian	1.174	0.506	2.722	0.709
Hispanic	1.045	0.641	1.704	0.859
Other	0.964	0.411	2.259	0.932
Unknown	1.300	0.902	1.872	0.159
Geographic Region				
South	ref.	–	–	–
Northeast	1.236	0.876	1.743	0.228
Midwest	1.415	1.112	1.801	0.005
West	0.905	0.669	1.224	0.516
Seizure	1.688	0.366	7.800	0.502
Allergies	0.843	0.419	1.694	0.631
Contrasts**				
ASD vs. ASD Younger Siblings	2.066	1.614	2.645	<.001
Comparison vs. Comparison Younger Siblings	0.880	0.724	1.069	0.198
ASD vs. Comparison	0.908	0.692	1.190	0.483
ASD Younger Siblings vs. Comparison Younger Siblings	0.387	0.302	0.495	<.001
(ASD- ASD Younger Siblings)- (Comparison-Comparison Younger Siblings) #	2.348	1.717	3.210	<.001

Observations read = 3,222; Observations used = 3,222; Number of pairs = 1,611

*From merged socioeconomic data.

**This output was obtained using ESTIMATE statement in PROC GENMOD in SAS.

#Hypothesis testing using Score statistic yielded similar results.

Looking at **Table 37**, which shows the model results for the age period of 4 to 6 years, we find both similar and different results. As observed above for the 12 to 24 month period, there was no significant difference in MMR vaccination status between children with and without ASD during the ages of 4 to 6 years: again, they were equally likely to be vaccinated during these ages ($p=0.611$). Also as above, younger siblings of children with ASD were less likely than younger siblings of children without ASD to be vaccinated with MMR during this age period ($OR=0.653$, $p=0.033$). Within pairs, however, the results are opposite of what we observed above for the 12 to 24 month age period. Here, while children with ASD did not differ significantly from their younger siblings ($p=0.597$), children without ASD were less likely to be vaccinated than their younger siblings ($OR=0.661$, $p=0.007$), or expressed in reversed terms, younger siblings of children without ASD were more likely to be vaccinated. Nonetheless, the difference between children with ASD and their younger siblings was *not* statistically different from the difference between children without ASD and their younger siblings during the ages of 4 and 6 years ($p=0.128$).

Table 37. Logistic Model for MMR Vaccination among Paired ASD/Comparison Subjects and Younger Siblings Fully Enrolled between 4 and 6 Years

Independent Variables	MMR Vaccination			
	odds ratio	lower 95% CI	upper 95% CI	p-value
Sample				
Comparison Younger Siblings	ref.	–	–	–
ASD	0.600	0.402	0.896	0.013
ASD Younger Siblings	0.653	0.442	0.966	0.033
Comparison	0.661	0.490	0.890	0.007
Gender				
Female	ref.	–	–	–
Male	0.662	0.499	0.878	0.004
Household Income*				
<\$50,000	ref.	–	–	–
\$50,000 - \$74,999	0.997	0.470	2.112	0.993
\$75,000 - \$99,999	1.083	0.513	2.284	0.834
\$100,000 - \$124,999	1.331	0.617	2.871	0.466
\$125,000 +	1.722	0.791	3.745	0.171
Unknown	1.212	0.501	2.927	0.670
Race/Ethnicity*				
White	ref.	–	–	–
African American/Black	0.821	0.247	2.735	0.748
Asian	3.698	0.489	27.953	0.205
Hispanic	0.850	0.428	1.686	0.641
Other	0.425	0.166	1.085	0.074
Unknown	0.694	0.377	1.278	0.241

Independent Variables	MMR Vaccination			
	odds ratio	lower 95% CI	upper 95% CI	p-value
Geographic Region				
South	ref.	–	–	–
Northeast	0.700	0.432	1.134	0.147
Midwest	1.529	1.059	2.208	0.023
West	0.865	0.525	1.426	0.570
Seizure	0.796	0.291	2.175	0.656
Allergies	2.519	0.798	7.956	0.115
Contrasts**				
ASD vs. ASD Younger Siblings	0.919	0.673	1.256	0.597
Comparison vs. Comparison Younger Siblings	0.661	0.490	0.890	0.007
ASD vs. Comparison	0.909	0.629	1.314	0.611
ASD Younger Siblings vs. Comparison Younger Siblings	0.653	0.442	0.966	0.033
(ASD- ASD Younger Siblings)- (Comparison-Comparison Younger Siblings)#	1.392	0.910	2.213	0.128

Observations read = 1,376; Observations used = 1,376; Number of pairs = 688

*From merged socioeconomic data.

**This output was obtained using ESTIMATE statement in PROC GENMOD in SAS.

#Hypothesis testing using Score statistic yielded similar results.

E. Discussion

To our knowledge, this is the first claims-based study to systematically address the topic of MMR vaccination patterns within families and across families of children with and without ASD. The purpose of our study was not to estimate rates of MMR vaccination per se but instead to examine if vaccination rates differed for the samples of interest. Nevertheless, even though some studies have found that claims data underestimate vaccination rates,⁶⁶ the rates of MMR vaccination we observed do not differ markedly from those found in other studies. We report that 75.2% of children with ASD and their siblings and 79.3% of comparison children and their siblings have evidence of an MMR vaccine during the second year of life. Other researchers using the National Immunization Survey from 2000 to 2002, found approximately 68% of children ages 19 to 24 months have received an MMR vaccination⁵⁸, while others report a national average of 74% of children from ages 24-35 months who have all recommended doses of MMR.⁵⁷ We also found that the rates of MMR adherence in 2005-2009 are higher than in 2001-2004, consistent with the general upward trend in vaccination coverage.⁵⁶

The vaccination literature emphasizes significant parental concerns over vaccines, some of which are directly tied to fears about autism.^{52, 53, 54, 55} The second component of our analysis was of particular interest to investigate if these concerns have translated into lower vaccination rates among younger siblings of children with ASD. Our study was interested in three comparisons in vaccination status: children with ASD vs. comparison children; younger siblings of children with ASD vs. younger siblings of children without ASD, and children with ASD vs. their younger siblings and children without ASD vs. their younger siblings. After controlling for demographic characteristics and the presence of allergies and seizures as vaccine contraindications, we found that children with ASD were just as likely as comparison children to be vaccinated with MMR

between the ages of 12 and 24 months and between the ages of 4 and 6 years. In contrast, younger siblings of children with ASD were less likely to have received the MMR vaccination than younger siblings of comparison children during both age periods. Most importantly, we found that between the ages of 12 and 24 months, while younger siblings of the comparison sample did not differ from their sibling without ASD, younger siblings of children with ASD were less likely to be vaccinated than the child with ASD. One interpretation of this finding is that in spite of an increase in the rate of vaccination over time, parents of children with ASD may continue to harbor some apprehension about a potential causal link between the MMR vaccine and ASD and, as a result, fewer younger siblings of children with ASD are vaccinated. The hesitation among parents to vaccinate may be particularly acute if the child with ASD had been vaccinated and seemed not to have developed behavioral symptoms suggestive of ASD until after vaccination. In addition, as research suggesting an autoimmune etiology for ASD builds, parents may worry about the function of their child's immune system and its ability to handle vaccinations without adverse effects. As a result, they may delay or forgo immunizations altogether, relying instead on herd immunity to prevent some of the potential infections.

Our modeling results for children between the ages of 4 and 6 years are perhaps harder to interpret. Unlike at the younger age groups, we found that between the ages of 4 and 6 years younger siblings of children with ASD were just as likely to have received an MMR vaccination as their older sibling with ASD. This could be related to a reduction in vaccination rates among children with ASD at this age (perhaps because of parents' safety concerns and not vaccinating a child with ASD after diagnosis fearing that a vaccine might have caused or worsened the problem). The result could also be a function of an increase in vaccination among siblings of children with ASD due to a belief that by the time a child is 4 years old or older, they are unlikely to develop ASD unless it is already present and thus the window of sensitivity to the vaccines effects has passed. In other words, parents may be foregoing the first MMR vaccination for the younger siblings but having them vaccinated after age four at which point the vaccines are needed for school entry and when parents' worries about the vaccine causing autism may be less. However, it should be noted that the pairs included for the age period of 4 to 6 years were not necessarily the same pairs included in the sample for the age period of 12 to 24 months so comparisons between the two age periods should be performed with caution. The younger siblings could also have been part of the overall secular trend of increasing vaccination rates in recent years compared to previous years.

It should be noted that we compared children with ASD to their younger siblings with an assumption that, in most cases, a child with ASD will have already received a diagnosis (or be suspected of having ASD) by the time their younger sibling had reached the 12 to 24 month age period. It is likely, however, that there are many instances when a sibling reaches the 12 to 24 month period before their older sibling was diagnosed with ASD. An ideal analysis would model vaccination patterns in families before and after an initial diagnosis of ASD, but as discussed in the Task B: Health Conditions Report, our sample size using such an approach in this study would have diminished markedly and would have been further limited to capture children with a younger sibling where both have continuous enrollment during the desired age groups.

It should be noted that all vaccination results are based on a subset of our larger Task A samples based on required enrollment during the age periods of interest. Our vaccination results are based on this smaller sample that appears to be somewhat different by demographic

characteristics and for this reason we are unable to speak to the vaccination experiences of the full Task A samples during these age periods.

Despite limitations, our study, using administrative claims data to objectively measure vaccination receipt is markedly different from other study designs found in the literature, such as those in which researchers rely on parental report from interviews and surveys. Our study does not directly assess, however, parental belief systems, personalities, or other factors that may affect a parent's decision about whether to vaccinate their child. On the other hand, our family-linked data, ample sample size, and longitudinal data, empirically captures important trends from one large commercially-insured population. Furthermore, our claims data was linked to socioeconomic data allowing us to use family income as a marker of socioeconomic status as well as control for and assess the relationship between race/ethnicity and income and MMR vaccination.

Current rates of MMR vaccination, as with the rates we observed in our study, emphasize that vaccination in children remains a pertinent public health discussion. Furthermore, our finding that younger siblings of children with ASD are less likely to be vaccinated between the ages of 12 and 24 months may underscore the need for continued public education on the topic of vaccination safety and importance, especially among families caring for children with ASD. In addition to further research and education on vaccination safety, the finding that younger siblings are less likely to get vaccinated also underscores the need to study and monitor the risks these children face by delaying or forgoing childhood vaccinations.

VIII. Conclusion

A. Summary of Results and Implications

1. General Health Care Utilization and Costs

Our results indicate that children with ASD have higher utilization of health care services compared to children without ASD and this corresponds to higher cost. Specifically, we found children with ASD had a median of 9.6 total office visits and 1.5 total outpatient facility visits per year, whereas for the comparison group the medians were 2.9 and 0.0, respectively. A similar pattern was observed for behavioral health visits. While preventive care and ancillary therapy visits (physical, occupational, speech, etc.) were modest in both groups, the annualized count of visits was still higher for children with ASD (median of 1.0 and 0.2 visits per year, compared to 0.7 and 0.0 for the comparison group). Children with ASD also had a median of 8.0 medication dispensings per year, compared to 1.6 for children without ASD. This higher utilization translated into higher costs. Median monthly costs for children with ASD exceeded those for children without ASD for total medical care (\$202.28 vs. \$39.53), behavioral health care (\$72.26 vs. \$0.00), and medications (\$46.22 vs. \$3.86).

Similarly, our study found that siblings and parents of children with ASD had higher utilization of health care services than siblings and parents of children without ASD. For example, parents of children with ASD had a median of 6.2 ambulatory visits per year, compared to 4.5 for comparison parents. Siblings of children with ASD had a median of 4.6 total ambulatory visits per year, compared to 3.0 for comparison siblings. The median number of medication dispensings was 6.3 and 4.0 for ASD and comparison parents respectively, and 2.2 and 1.4 for and ASD and comparison siblings, respectively. Similarly to children, this higher utilization translated into higher costs. Total monthly costs were \$176.51 and \$115.12 for ASD and comparison parents, respectively, and \$78.05 and \$43.57 for ASD and comparison siblings, respectively.

2. Psychotropic Polypharmacy

Psychotropic polypharmacy was prevalent in our sample of children with ASD. Nearly 40% had evidence of either single or multi-class polypharmacy. In our study, the most commonly prescribed drugs in single-class polypharmacy were ADD medications — an expected finding, as over half of children with ASD in our sample also had ADD diagnoses. We also found anti-depressants and ADD medication to be the most common multi-class combination.

Our results suggest that seizures, ADD, bipolar disorder, and anxiety are all significant predictors of psychotropic use and, along with depression, of multi-class polypharmacy among children with ASD. Furthermore, children with ASD who also have seizures, ADD, or bipolar disorder had the highest odds of more complicated multi-class polypharmacy (as measured by a higher number of medication classes involved). Additionally, among children with multi-class polypharmacy, these three conditions were associated with a 15%-30% longer duration in polypharmacy.

Demographic characteristics were also significant on psychotropic use and psychotropic polypharmacy. Our study found older age to be significantly associated with psychotropic use, multi-class polypharmacy, and length of polypharmacy. This was an expected finding as medication use and parental perception of safety likely increases as a child's age increases.⁴³

Across all models, gender was not significantly related to psychotropic use, including multi-class polypharmacy, after controlling for the other covariates in the analyses. Boys and girls with ASD were just as likely to have evidence of psychotropic medication use during the study. Additionally, children from the southern region were significantly more likely than any other region to use psychotropic medications. Finally, while race/ethnicity was not always significant in our models and the results were somewhat inconsistent, we found some support for whites having greater odds of psychotropic medication use and psychotropic polypharmacy. However, our race-related results should be interpreted with caution in view of the large proportion of subjects (38%) in our sample without race data.

3. Adherence to MMR Vaccination

Slightly more children without ASD and all of their siblings (not just younger) had evidence of MMR vaccination between the ages of 12 and 24 months and the ages of 4 and 6 years. Specifically, 79.3% of comparison group children and siblings had a vaccination for MMR during the ages of 12 to 24 months and 77.3% had a MMR vaccination during the ages of 4 to 6 years. In contrast, 75.2% and 74.2% of children with ASD and their siblings had MMR vaccination during these same age periods. The proportion of children overall with an MMR vaccination was lower during the early time period (2001-2004) compared to the latter (2005-2009), and this was true at both 12 to 24 months and 4 to 6 years age periods.

After controlling for demographic characteristics and the presence of allergies or seizures, we found that children with ASD were just as likely as comparison children to be vaccinated with MMR between the ages of 12 and 24 months and between the ages of 4 and 6 years. In contrast, younger siblings of children with ASD were less likely to have received the MMR vaccination than younger siblings of comparison children during both age periods. Most importantly, we found that between 12 and 24 months of age, while younger siblings of the comparison sample did not differ from their sibling without ASD, younger siblings of children with ASD were just as likely to be vaccinated as the child with ASD. Our interpretation of this finding is that in spite of an increase in the rate of vaccination over time, parents of children with ASD may continue to harbor some apprehension about a potential causal link between the MMR vaccine and ASD and, as a result, fewer younger siblings of children with ASD were vaccinated.

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. 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 Task A: 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. Other limitations include that we do not know if prescriptions filled were actually taken as prescribed by the child. 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 health outcomes in children with autism and their families, resulting in five reports summarizing our extensive analyses. Our Task B: Health Conditions report discussed in detail the value of claims data for research demonstrated by our work and the general further potential for future research using claims data.^{XIX} We believe there are significant further important research opportunities to be pursued related to understanding the health care needs of children of ASD and their families.

As reported above (Section V.E. Discussion) our study of health care utilization and costs showed that children with ASD and their families use more health care than children without ASD and their families. This finding is not surprising, as it is consistent with several other studies. However, the size of the study population we have been able to muster in claims data, the extended time period for which we were able to track subjects longitudinally, and the diversity of the samples signify that substantial further research can support a deeper understanding of the correlates of utilization, including the role of co-occurring conditions in utilization patterns, and the trajectories of utilization through time as children progress from early childhood to and through adolescence. Our finding in the Task B report regarding higher prevalence of co-occurring conditions in parents and siblings of children with ASD corresponds to this higher utilization of health care services. Such further analysis is likely to generate further findings with significant policy implications as well as spur new insights for interventions to improve health outcomes.

Still unanswered, however, are questions regarding whether children with ASD are receiving appropriate or enough care for ASD and co-occurring conditions as well as well child care that all children should receive. It is also unknown whether the care is of high quality and effective for their conditions and symptoms and whether children with ASD are *not* receiving ineffective or harmful care (such as overuse of particular medications). This is a critical area for future research using both claims data and other sources. Our rich data can be used to begin to link services and

^{XIX} Study of Health Outcomes in Children with Autism and their Families Task B: Health Conditions, pp. 79-81.

interventions with outcomes or to compare utilization patterns to treatment guidelines for specific diagnoses, when they exist.

We have merely touched the surface regarding family patterns of health care utilization. We believe it is important to conduct further research to assess the degree to which the observed higher family utilization is a population pattern or a family-specific pattern: that is, are the parents and siblings with high utilization the parents/siblings of higher utilizing children with ASD? Nor have we been able to delve into the correlation between parent, sibling, and the child with ASD utilization, or see if certain covariates are associated with the use of health care services by the parent, siblings, and child (such as a health event of the family child(ren) with ASD).

Our in-depth analysis of polypharmacy among children with ASD revealed a substantial amount of polypharmacy and the particular risk factors for polypharmacy. We have revealed some important covariates associated with this phenomena, but further research could reveal the factors that might be causally related. Further, our study was not designed to address the appropriateness of the polypharmacy observed. This is a critical area for further research. Our rich data can be used to compare utilization patterns to treatment guidelines for mental and behavioral health conditions where they exist and, in the absence of existence of guidelines, can be used as a foundation for assessing outcomes and subsequent guideline development. Moreover, further research into the sociodemographic and geographic variation in the practice of polypharmacy and whether the variation is driven by clinical need, access to care, access to behavioral health care, or other factors may provide a better understanding of differences in treatment patterns across the country. Our data can also be used to look at utilization patterns by geographic area controlling for health care market level variables and other characteristics that are known to influence differences in treatment patterns across the country. Moreover, the high use of pharmaceuticals among parents and siblings bears further analysis – again with the question, as raised above, regarding the degree to which these may be family patterns of health and health care use.

Perhaps implicit in the preceding discussion, we believe our analyses demonstrate the value of claims data for hypothesis generation. An important component of this project has been the collaboration (through the External Advisory Committee) with other researchers, health care providers, individuals with ASD and parents of children with ASD. The ability to quickly assess in the data the incidence, prevalence, sample sizes and other metrics for topics raised in these conversations has helped drive our research in fruitful directions and can contribute to future research agendas.

Finally, our research substantiates the value of claims data for addressing timely, crucial public policy issues, such as vaccination patterns in siblings of, as well as among, children with ASD. We believe that strategies for public health education and intervention related to vaccination need to be mindful of the entire family context.

In summary, our results confirm, indisputably, that the presence and consequences of ASDs have a family component that should be addressed in strategies for treatment interventions and for maximizing the potential that children with ASD and their siblings and parents can live happy and productive lives.

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