THE DISSERTATION COMMITTEE FOR TIMOTHY MATTHEW HILL CERTIFIES THAT THIS IS THE APPROVED VERSION OF THE FOLLOWING DISSERTATION:

RETROSPECTIVE ANALYSIS OF TREATED PREVALENCE, PSYCHIATRIC CONDITION PREVALENCE, AND HEALTHCARE UTILIZATION AND EXPENDITURES IN COMMERCIALLY INSURED CHILDREN DIAGNOSED WITH AUTISM SPECTRUM DISORDER

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DEDICATION

To my son Anderson Clark Hill: may you change the world as much as you have changed my life.

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ABSTRACT

RETROSPECTIVE ANALYSIS OF TREATED PREVALENCE, PSYCHIATRIC COMORBIDITY PREVALENCE, AND HEALTHCARE UTILIZATION AND EXPENDITURES IN COMMERCIALLY INSURED CHILDREN DIAGNOSED WITH AUTISM SPECTRUM DISORDER

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Autism spectrum disorders (ASDs) are the leading cause of disability in children under five, and affect 1 in 59 children in the United States. The aims of this study were to explain geographic variation in the treated prevalence of ASD, compare the prevalence of selected psychiatric conditions between ASD and non-ASD patients, and to estimate incremental healthcare utilization and expenditures.

A commercial claims database was utilized to address all aims. Prevalence rates were generated for 819 ZIP3 regions, and a generalized linear model (GLM) was used to explain geographic variation in prevalence. Aims two and three were addressed in a separate cohort of ASD patients (n=17,787) matched to a non-ASD control group (n=35,574). Three sets of GLMs were fit to compare age-related prevalence rates of psychiatric conditions, utilization, and expenditures between ASD and non-ASD groups.

The overall prevalence of ASD was 6.84 per 1,000 children 3-18 years. Significant positive relationships with prevalence were identified for fully insured plan density

(p=0.018), median income (p<0.001), and private school enrollment density (p=0.015); and significant negative relationships were observed for percent white (p=0.012), and urbanicity (p=0.003). Stronger positive age-prevalence relationships were identified for anxiety (p<0.001), conduct and behavior (p<0.001), mood (p<0.001), and psychotic (p=0.003) disorders in ASD patients compared to non-ASD patients. Greater all-cause utilization was identified in the ASD group for office, occupational/physical therapy (OT/PT), speech therapy, emergency department (ED), and prescriptions; and greater mental health-related (MHR) utilization was identified for outpatient office visits, ED visits, and prescriptions (all p<0.001). Greater all-cause expenditures were identified for total, outpatient office, OT/PT, speech therapy, ED, prescriptions, and OOP; and greater MHR expenditures were identified for total, outpatient office, inpatient, ED, prescription, and OOP (all p<0.05).

In conclusion, geographic disparities in prevalence rates of ASD appear in commercially-enrolled children, and many psychiatric conditions manifest more strongly with respect to age in ASD patients when compared to rates in non-ASD patients. Healthcare utilization and expenditures are also greater for ASD patients. In summary, this study provides novel insight into at least three facets of the ASD patient journey, and implications for patients, providers, and health plans.

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List of abbreviations

AACAP	American Academy of Child and Adolescent Psychiatry
AAP	American Academy of Pediatrics
ABA	Applied Behavior Analysis
ACA	Affordable Care Act
ACS	American Community Survey
ADDM	Autism and Developmental Disabilities Monitoring
ADHD	Attention-Deficit/Hyperactivity Disorder
AHRQ	The Agency for Healthcare Research and Quality
ASD	Autism Spectrum Disorder
BM	Behavioral modification
CARS	Childhood Autism Rating Scale
CCC	Complex chronic conditions
COB	Coordination of benefits
CDC	Centers for Disease Control and Prevention
CPI	Consumer Price Index
CPT	Current Procedural Terminology
CRSE	Clustered Robust Standard Errors
DSM	Diagnostic and Statistical Manual of Mental Disorders
DTT	Discrete Trial Training
ED	Emergency Department

EIBI	Early Intensive Behavioral Intervention
ERISA	Employee Retirement Income Security Act
ESDM	Early Start Denver Model
FDA	Food and Drug Administration
GLM	Generalized Linear Model
GP	General Population
GPI_2	Generic Product Identifier
HCBS	Home and community-based service
HCUP	Healthcare Cost and Utilization Project
HMO	Health Maintenance Organization
IBI	Intensive Behavioral Therapy
ICD	International Classification of Disease
ID	Intellectual Disability
IRB	Institutional Review Board
KP	Kaiser Permanente
MEPS	Medical Expenditure Panel Survey
MHD	Mental Health Disorder
MHPAEA	Mental Health Parity and Addiction Equity Act
MMR	Measles, Mumps, and Rubella
NHIS	National Health Interview Survey
OLS	Ordinary Least Squares
OOC	Out-of-pocket cost

OOP	Out-of-pocket
OR	Odds Ratio
OT/PT	Occupational and Physical Therapy
P+	PharMetrics Plus
PEP-R	Psychoeducational Profile-Revised
PPO	Preferred Provider Organization
PUMS	Public Use Microdata Sample
RR	Rate ratio
SD	Standard deviation
SOFIA	Study of Fluoxetine in Autism
TEACCH	Treatment and Education of Autistic and Related Communication Handicapped Children
USPHS	United States Public Health Service
USPS	United States Postal Service
UT	University of Texas
WHO	World Health Organization
YOB	Year of birth
ZCTA	Zip Code Tabulation Area
ZIP3	3-digit zip codes
ZIP5	5-digit zip codes

CHAPTER 1: INTRODUCTION AND LITERATURE REVIEW

1.1 Significance of Autism Spectrum Disorders (ASDs) to health insurers and society

Autism spectrum disorders (ASDs) are the leading cause of disability in children younger than five years.[1] They are defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM) as a set of neurodevelopmental conditions characterized by severe impairment in reciprocal social interactions and communication skills, and the presence of restricted, stereotypical behaviors.[2] The Centers for Disease Control and Prevention (CDC) estimated the prevalence of ASDs at 16.9 per 1,000 (1 in 59) children aged eight years in 2014, an increase from 6.7 per 1,000 during 2000-2002 and 14.7 per 1,000 during 2010-2012.[3] The total costs per year for children with ASD were estimated to be between $11.5 billion and $60.9 billion per year.[4] At the patient level, lifetime costs of ASD are estimated to be between $2.4 and $3.1 million. Although medical expenses represent only 12 percent of lifetime costs, they account for almost half of costs in children from 3-7 years.[4,5] Given the resource-intensive nature and increasing prevalence, understanding the economic burden of ASDs is essential to both health insurers and society.

1.2 History of Autism Spectrum Disorders

The concept of autism was first described by German psychiatrist Eugen Bleuler in 1911 and was then viewed as a severe manifestation of another psychiatric illness called schizophrenia.[6] According to Bleuler, the autistic mindset was illustrated by infantile wishes to avoid the patient's unsatisfying realities and replacing them with fantasies. The word 'autism' was used by Bleuler to define a subject's symbolic inner life that was not readily accessible to the observer.

By the 1940s, academic attention toward autism began to accelerate. In 1943, the psychiatrist Leo Kanner described a set of 10 patients exhibiting symptoms of autism.[7] Kanner's patients exhibited a behavior pattern laden with obsessiveness, stereotypy, and echolalia, and children also expressed a consistent desire for aloneness and sameness in their environments. In 1944, Austrian pediatrician Hans Asperger worked with a group of children with similar symptomology, except for the absence of echolalia as a linguistic problem. Unlike Kanner's patients, the children Asperger observed were articulate like adults, but exhibited awkward fine motor skills.[8] In his later years, Asperger drew a firm distinction between his 'autistic psychopathy of childhood' and Kanner's early infantile autism.[9] The first DSM was published in 1952, and despite increased attention and research on autism, it was not identified as a standalone psychiatric illness, but instead was described as part of a set of schizophrenic reactions occurring before puberty.[10] The DSM-II gave autism even less attention, with the word "autistic" being described as a symptom to partially describe childhood-onset schizophrenia.[11]

The early-nineteenth-century perception of autism continued for decades and was not successfully challenged until the late 1960s when child psychologists created new methods to validate child psychology itself as a science.[12] The shift to a new definition of autism was part of a more general alteration in psychiatric reasoning that set out to understand mental health as viewed through a group-level epidemiological lens over individual cases.

Since the mid-1960s, attention continued to accelerate, and child psychologists began describing autism in the way it is understood today. In 1980, "infantile autism" was added as a condition in the DSM-III, and was described separately from schizophrenia through a set of discrete symptoms: pervasive lack of responsiveness to others, gross deficits in language development, bizarre responses to various aspects of the environment,

and an absence of delusions and hallucinations. The final feature is what separated autism from schizophrenia, which was characterized as an excessive imagination triggering delusions and hallucinations.[13] In 1987, "infantile autism" was expanded into "autism disorder" in the revised DSM-III, which also alleviated the diagnostic process through a checklist of 16 specific items that gave explicit detail to the original DSM-III's broadly-defined domains.[14] The 1980s also brought forth treatments for autism with the introduction of behavioral therapies.[15] In 1987, the clinical psychologist Ivar Lovaas published the first study showing intensive behavior therapy as a method to improve autistic symptoms in affected children.[16]

With an official presence in the DSM and the emergence of treatments, public awareness toward autism began to grow as well in the 1980s. The movie *Rain Man* won four Academy Awards in 1989 and subsequently increased public awareness through its portrayal of an autistic savant with a photographic memory.[17] Attention in public education began to improve during this time with the addition of autism as a category of special education in 1991.[18] In 1994, the DSM-IV changed the diagnostic criteria to include a milder form of autism called Asperger's syndrome, which extended the autism diagnosis to higher functioning cases.[19]

Autism gained tremendous attention in 1998 when a study was published in a high-impact medical journal (*The Lancet*) linking the developmental disorder to childhood measles, mumps, and rubella (MMR) vaccination.[20] In response to the study and its resulting public outcry, the American Academy of Pediatrics issued a joint statement with the U.S. Public Health Service (USPHS) sharing concern with clinicians about a preservative in some vaccines called thimerosal, but only as a precautionary measure.[21] By 2001, U.S. manufacturers eliminated thimerosal from all multi-dose vaccines with the exception of influenza.[22] The MMR study was later found to contain critical flaws and the

journal later retracted it, but not without provoking profound public fright and apprehension toward childhood vaccinations.

As awareness of autism continued to accelerate in the 2000s, prevalence continued to increase as well. By 2009, the CDC estimated that about 9.1 per 1,000 children in the U.S. were diagnosed with autism.[3] During this period, the autism science and advocacy organization Autism Speaks was founded by the Wright family, inspired by their grandson who was diagnosed with autism. This organization has since won a place in the Time 100 "Heroes and Pioneers" category for its commitment to global autism advocacy.[23]

Society's understanding of ASDs has been evolving for over a century, and immense progress has been made since Bleuler's first observations in 1911. The challenging and pioneering work described above has paved the way for today's and tomorrow's vital treatments. In 2013, after almost 20 years, the DSM was updated to its 5th version, in which all forms of autism, including less severe forms such as Asperger's, were grouped into one umbrella diagnosis called autism spectrum disorder (ASD).[2] The term ASD will be used hereafter to refer to all conditions on the autism spectrum.

1.3 Epidemiology of ASD

1.3.1 Pathophysiology, etiology, and risk factors of ASD

The pathophysiology and etiology of ASD are currently thought to be multifactorial and heterogeneous across patients. Although the pathophysiology of ASD is not entirely understood, it is believed to be driven by a combination of genetic and environmental risk factors that alter brain development and subsequent neural connectivity.[24,25] Atypical neural connectivity is thought to play an essential role in the development of ASD, and children with ASD experience higher than average head growth during infancy and overall higher brain volume compared to children without ASD.[26–28] Patients with ASD also

exhibit different gray and white matter volumes, neurotransmitter concentrations, cortical structures, and brain lateralization compared to those without ASD.[29–35]

The genetic etiology of ASD is supported by a greater prevalence in males vs. females, and a higher prevalence among both twins and non-twin siblings.[25,36] There is also a positive association between ASD and any form of genetic relatedness. A population-based cohort study showed that, by age 20, the cumulative risk of ASD was approximately 10 percent for maternal half-siblings, 13 percent for full siblings and dizygotic twins, and 59 percent for monozygotic twins.[37] Given that ASD is diagnosed primarily in males, an X-linked form of inheritance has been suggested. However, male-to-male transmission has been documented in many families, eliminating X-linkage as a single genetic source of inheritance.[38] Family history of autoimmune disorders has also been suggested as an inherited risk factor for ASD.[39]

Many genetic syndromes have been linked to ASD, and there is variability in ASD penetrance across syndromes. Specific genetic syndromes associated with ASD include tuberous sclerosis complex, fragile X syndrome, chromosome 15q11-q13 duplication syndrome, Angelman syndrome, Rett syndrome, CHARGE syndrome, Joubert syndrome, Smith-Lemli-Opitz syndrome, PTEN-associated macrocephaly syndromes, and Timothy syndrome.[40–45] Penetrance of ASD-related symptoms is variable across syndromes, but the incidence of ASD is still profoundly higher than baseline rates in these populations. Fewer than half of patients with Tuberous sclerosis complex and fragile X syndrome meet diagnostic criteria for ASD, while virtually all patients diagnosed with Smith-Lemli-Opitz syndrome meet criteria. [43–45]

Environmental factors are also thought to play a role in ASD risk and are believed to do so not alone, but through interaction with other environmental factors as well as known and unknown genetic and predispositions. The extent to which environmental

exposures elevate risk has been difficult to quantify, as vulnerabilities appear to be time-dependent and highly variant in terms of a threshold of exposure and time required for the onset of disease.[46,47] Examples of associated environmental risk factors include toxic perinatal exposures, teratogens, and prenatal infections.[46]

Much progress has been made in the understanding of the neurobiology and etiology of ASD. The scientific community has developed a thorough understanding of ASD in terms of brain chemistry and neural connectivity. Many inherited and acquired genetic links have been established, and numerous environmental risk factors have been identified from the perinatal period through infancy. Despite an expanded biological understanding, and numerous genetic and environmental associations, complete elucidation of the cause of ASD remains to be accomplished.

1.3.2 Prevalence of ASD in children

Many studies have estimated the frequency of ASD, and agreement exists that the prevalence of ASD is overall increasing worldwide. Although incidence rates are widely considered the gold-standard measure of disease frequency, its application in ASD is difficult and often impractical, as ASD is uncommon and often a lifelong condition diagnosed in early childhood.[48] Point prevalence, period prevalence, and cumulative incidence are more common in ASD epidemiology, as disease initiation can begin long before diagnosis, and the time between initiation and diagnosis is influenced by many factors unrelated to disease risk. However, prevalence estimates can vary greatly depending on study methodologies, sampling methods, and contemporary diagnostic criteria.[49] There is also debate on whether increasing prevalence has been due to a true increase in cases, or instead explained better through increased attention to the disease.

Overall prevalence estimates in the U.S. are close to 7.5 per 1,000 children according to a 2010 systematic review of epidemiologic studies.[1] In the U.S., two national databases are used to estimate ASD prevalence. The first is called The Autism and Developmental Disabilities Monitoring Network (ADDM), which is a program funded by the Centers for Disease Control and Prevention (CDC), and identifies ASD through screening and abstraction of the health and education records of eight-year-old children, the age at which evidence suggests prevalence peaks.[3] Data are collected from selected study sites across 11 demographically diverse states: Arizona, Arkansas, Colorado, Georgia, Maryland, Minnesota, Missouri, New Jersey, North Carolina, Tennessee, and Wisconsin. The latest prevalence estimates were from the year 2014, and were 16.9 per 1,000 children aged eight years, an increase from 6.7 per 1,000 during 2000-2002 and 14.7 per 1,000 during 2010-2012.[3] U.S. prevalence is also estimated through The National Health Interview Survey (NHIS), which is a parent-reported nationally representative survey that collects data through the U.S. Census Bureau, and estimates the prevalence of ASD in children three through seventeen years of age.[50] The 2014 to 2016 NHIS survey, which is household-reported, estimated the prevalence of ASD at 24.7 per 1,000 (95% CI 22.0 to 27.3 per 1,000) in children aged 3 and 17, which is almost 50 percent higher than ADDM estimates.[50]

1.3.2.1 Geographic variation in prevalence

Studies evaluating state-level variation in ASD prevalence have been published. A 2014 analysis of the most recent CDC ADDM report showed significant variation in ASD prevalence by state, with prevalence estimates being lowest in Arizona (14.0 per 1,000, 95% CI=12.6-15.5/1,000) and highest in New Jersey (29.3 per 1,000, 95% CI=27.5-31.2/1,000).[3,51]

An analysis of Medicaid claims from 2004 evaluated county-level variation in the treated prevalence of ASD in Medicaid-enrolled children.[52] The overall treated prevalence was 7.01 per 1,000 children. This analysis found significant variation in the county-level treated prevalence, and the adjusted analysis showed that variation in prevalence was a function of per-student education expenditures, overall number of students, number of students in special education, and number of pediatricians.

1.3.2.2 Treated prevalence

Treated prevalence is defined as the proportion of patients in a population who are receiving treatment at a given time, and is often much lower than overall prevalence estimates. Prevalence estimates that are generated from healthcare claims data are usually more indicative of treated prevalence than overall prevalence given that data are obtained through claims from treatment providers. Treated ASD prevalence estimates in Medicaid and commercially insured populations are consistently lower than overall prevalence rates estimated by the CDC (**Table 1.1**). This discrepancy in overall prevalence and treated prevalence may exist for a number of reasons. Higher-functioning children may not seek treatment from healthcare providers, and instead rely exclusively on resources available in local community and education systems. Also, state-level mandates requiring ASD-related healthcare services do not cover self-insured commercial health plans. Providers are thus unable to bill for ASD-related health services through many self-insured plans, creating an environment where ASD patients must instead pay out-of-pocket or not receive services at all.[53]

Variance in treated prevalence also exists between different insured populations. During the 2000s, prevalence estimates were on average lower in commercially insured children compared to those enrolled in Medicaid-sponsored health plans. An analysis of

children enrolled in Medicaid from 1994 to 1996 reported population values that allowed estimation of treated prevalence, which varied slightly around 1.1 per 1,000 children.[54] However, this analysis was conducted in a single Pennsylvania county and may not be representative of populations in other states in the 1990s. Later studies conducted in broader Medicaid populations report higher treated prevalence estimates, with some rates being as high as 7.4 per 1,000 children.[55,56] Treated prevalence estimates in commercially insured children are historically lower compared to estimates from Medicaid populations. One analysis reported prevalence estimations in adults, but the population was limited to patients enrolled in the Kaiser Permanente Northern California health plan.[57]

A difference-in-difference analysis estimated the impact of state insurance ASD mandates on the treated prevalence in commercially insured patients, and compared the impact between those enrolled in fully insured and self-insured plans.[53] Self-insured plans served as a control group as they were not within the scope of state-level legislation. The adjusted differences in treated prevalence at one, two, and three or more years after mandate initiation were 0.17 (95% CI=0.09-0.24; $p<0.001$), 0.27 (95% CI=0.13-0.42; $p<0.001$), and 0.29 (95% CI=0.15-0.42; $p<0.001$) per 1,000, respectively. Unadjusted prevalence rates varied between 1.4 and 2.0 per 1,000 across groups and time, which are similar to other analyses that estimated treated prevalence in commercially insured ASD patients (**Table 1.1**).

Table 1.1: Treated prevalence in Medicaid and commercially insured ASD populations

Reference*	Year of observation	Treated Prevalence
Analyses in Medicaid Health Plans		
Mandell et al., 2006[58]	1994	1.18 per 1,000†
	1995	1.10 per 1,000†
	1996	1.13 per 1,000†
Wang et al., 2010[55]	2000	5.75 per 1,000†
	2001	6.09 per 1,000†
	2002	6.72 per 1,000†
	2003	7.4 per 1,000†
Wang et al., 2013[59]	2003	6.23 per 1,000
Analyses in Commercial Health Plans		
Leslie et al., 2007[60]	2000	0.95 per 1,000†
	2001	1.30 per 1,000†
	2002	1.78 per 1,000†
	2003	2.11 per 1,000†
	2004	1.92 per 1,000†
Shimabukuro et al., 2008[61]	2003	1.9 per 1,000
	1993-2003	2.9 per 1,000
Wang et al., 2013[59]	2003	1.11 per 1,000
Croen et al., 2015[62]‡	2008-2012	0.95 per 1,000†
Stuart et al., 2017[63]	2007-2009	3.0 per 1,000†
	2010-2012	4.0 per 1,000†

* Shea et al., 2018[64] and Mandell et al., 2016[53] are not listed because not enough information was reported to calculate overall treated prevalence in a given year

† Prevalence is calculated from summary statistics presented by authors

‡ Study sample was adult patients ≥ 18 years

1.3.2.3 Prevalence: Conclusion

The prevalence of ASD is consistently increasing in the U.S. population, but treated prevalence is increasing at different rates, sometimes at insignificant rates in some commercially insured populations. Also, no studies quantitatively compared treated prevalence rates across geographic regions. It is important to update treated prevalence estimates in commercially insured populations given a contemporary regulatory environment. This study aims to fill this gap in the literature by providing updated treated prevalence estimates in commercially insured children and explain variation as a function of state-level characteristics.

1.3.3 Psychiatric and neurologic conditions

Approximately 70% of individuals with ASD have at least one comorbid medical condition.[65–67] Approximately 45 percent of patients are intellectually disabled, and as many as 50 percent have attention deficit hyperactivity disorder (ADHD). Up to 24 percent of those diagnosed with ASD have comorbid epilepsy, which is particularly prevalent in ASD patients who are intellectually disabled or have associated genetic conditions.[68,69] A greater prevalence of anxiety, mood, and conduct disorders has also been shown in children with ASD compared to those without ASD.[65,67] An elevated prevalence of psychiatric comorbidities has been seen in adults as well.[66,70–72]

Healthcare claims analyses covered in sections 1.3.2.2 and 1.7.2 reported psychiatric comorbidity prevalence in ASD patients.[54,73–77] One study extended analyses to assess age-related variation in psychiatric comorbidity prevalence in Medicaid patients, but did not include a control group.[78] No studies were found that assessed age-related variation in psychiatric comorbidity prevalence in commercially insured children.

1.4 Diagnosis of ASD

Diagnosis of ASD usually occurs by four years of age. Diagnostic criteria for ASD are evolving, and recommendations for diagnosis and screening have been introduced through various clinical organizations.[2,41,79] Initial identification of ASD and related neurodevelopmental conditions is accomplished through many dimensions, including screening tools, structured interviews, assessment of behavior in multiple settings, assessment of language and cognitive function, and assessment of family history.[80,81] Confirmatory diagnosis of ASD is based on a comprehensive review of the patient and includes structured interviews, evaluation of behavior and language under multiple conditions, medical examination of both the patient and family, and assessment of the child's gestational history.[2,79]

1.4.1 DSM-V diagnostic criteria

The fifth edition of the DSM was published in 2013 and is widely accepted by guidelines and practice parameters as the gold standard for the diagnosis of ASD.[2] ASD is now an umbrella diagnosis newly-included in the DSM-V that includes diagnoses previously considered independent in the DSM-IV.[19] ASD-related diagnoses from the DSM-IV that are included in the DSM-V are autistic disorder, Asperger's syndrome, and pervasive developmental disorder not otherwise specified. For a confirmatory diagnosis of an ASD in the DSM-V, patients must meet specific criteria in 2 primary domains:[2]

A. social communication and social interaction; and
B. restricted, repetitive patterns of behavior, interests, or activities.

To meet diagnostic criteria in the social communication and social interaction domain (A), patients must show deficits in all of 3 subdomains:

a) social-emotional reciprocity;

b) nonverbal communicative behaviors used for social interaction; and

c) developing, maintaining, and understanding relationships.

To meet diagnostic criteria in the restricted, repetitive patterns of behavior, interests, or activities domain (B), patients must demonstrate 2 or more additional criteria:

a) stereotyped or repetitive movements, use of objects, or speech;

b) insistence on sameness, unwavering adherence to routines, or ritualized patterns of verbal or nonverbal behavior;

c) highly restricted, fixated interests that are abnormal in strength or focus; and

d) increased or decreased response to sensory input or unusual interest in sensory aspects of the environment."

Symptoms in both primary domains must be severe enough to impair function, and must not be better-explained by intellectual disability or a global developmental delay. The DSM specifies that symptoms must present during the early development period, but can become more apparent later in less severe cases when social demand exceeds the limited capacity of the patient. ASD may be diagnosed with or without comorbid genetic, neurodevelopmental, mental, or behavioral disorders, all of which must be specified alongside the ASD diagnosis. For example, if a patient is diagnosed with ASD and is also intellectually impaired, the final determination would be considered ASD with intellectual impairment.[2]

The DSM-V also introduced a set of severity levels to allow providers to distinguish severe cases of ASD from mild cases of ASD such as Asperger's. Determination of severity considers only two domains of symptoms: communication and socialization diagnostic domains are collapsed into a single "social communication" domain, and the restricted/repetitive behaviors diagnostic domain is second.

Level 1 autism is the least severe, and is characterized by noticeable issues with communication and socialization skills, and inflexibility of behavior that causes significant interference with functioning. Patients at level 1 can usually maintain conversations despite difficulty, but require at least some support. Patients with level 2 autism require "substantial support" with communication and socialization, and may exhibit difficulty coping with change. Restrictive and repetitive behaviors must appear frequently enough to be obvious to a casual observer at level 2. Patients may also have an unusual or reduced response to social cues and communicate through overtly simple sentences.

Level 3 is the most extreme level of severity, and patients at this level require "very substantial support" according to the DSM-V. Patients at level 3 exhibit a highly visible lack of communication skills, and have a drastically limited desire to socialize at all. Restrictive and repetitive behaviors must markedly interfere with functioning at level 3, with behavior that creates a significant distance between the patient and the outside world.

1.4.2 ICD diagnostic criteria

The International Statistical Classification of Diseases and Related Health Problems (ICD) is a medical classification list maintained by the World Health Organization (WHO).[82] The ICD system is used by healthcare providers to classify, code, and bill for diagnoses and procedures in the United States. The 10th revision of the ICD replaced ICD-9 in the U.S. healthcare system on October 1, 2015, and is currently the primary method that medical providers and payers utilize for medical billing.

Compared to the criteria defined in the DSM-V, ICD-10 diagnostic criteria are defined in less detail, and group all conditions along the autism spectrum under a broader category called "pervasive developmental disorders." The ICD-10 describes symptoms as belonging to 3 primary domains similar to the two domains presented in the DSM-V, with

the exception of the communication domain of the DSM-V being split into general communication and reciprocal social interaction. The ICD-10 is more restrictive than the DSM-V in terms of age at onset, and specifies that abnormal development must be present before the age of three years, a deadline the DSM-V defines less strictly as "the early development period."[2,82] Unlike the DSM-V, the ICD-10 does not require thresholds to meet criteria in symptom domains.

ICD-11 was released in June[1–6] 2018, and compared to ICD-10, aligns more closely to the DSM-V.[2,83] The ICD-11 collapses the two communication-related criteria in the ICD-10 into one domain, aligning criteria with the two domains listed in the DSM-V. ICD-11 provides a detailed guideline for discriminating the ASD diagnosis with and without intellectual disability, while DSM-V simply states that autism and intellectual disability may coincide. Despite the new alignment between ICD and the DSM, differences remain between the latest versions, and adoption of ICD-11 by WHO member states will not be possible until January 2022, and likely even more delayed in the U.S. system given the U.S. experience with ICD-10 adoption.

1.4.3 Practice parameters and recommendations for ASD diagnosis

The American Academy of Pediatrics (AAP) and the American Academy of Child and Adolescent Psychiatry (AACAP) have developed guidelines and practice parameters to guide primary care practitioners and specialists in the diagnosis of ASD. The most recent AACAP practice parameters were published in 2014, one year after the release of the DSM-V.[84] The latest AAP recommendations for management and screening were published in 2007.[81,85] AAP recommendations for early screening and intervention in children younger than three years were published in 2015.[86–88]

In addition to U.S. guidelines, others have been published in many locations around the world, including countries in Europe and Asia, and in Australia.[189–93] These are not be covered in this section given that the scope of this study is limited to the U.S.

1.4.3.1 AAP recommendations

The AAP recommends that all children be screened for ASD, and screening is recommended sequentially in primary and specialty care, respectfully. Level 1 screening is recommended for all children during 18- and 24-month primary care well visits and is intended to compliment overall developmental surveillance.[94] The AAP does not recommend one specific instrument at level 1 but does encourage immediate diagnostic evaluation and appropriate intervention for those children who screen positive. Positive screens at level 1 are not confirmatory, but are meant to identify children at higher risk for ASD who need confirmatory diagnostic testing by specialists at level 2. Level 2 instruments are used primarily to distinguish between children at risk of ASD from those at risk of other developmental disorders. Level 2 screening tools generally require more training to administer, score, and interpret than level 1 instruments. The AAP specifies that level 2 screening tools should not be used alone for diagnosis, but as a complement to a full medical and psychological evaluation. Screening and diagnostic instruments recognized by the AAP are presented in **Table 1.2**.

Table 1.2: Instruments recognized by the AAP[81,94]

Level 1 Screening Instruments
Baby Infant Screen for Children with aUtIsm Traits (BISCUIT)
Early Screening for Autistic Traits (ESAT)
First-Year Inventory (FYI)
Modified Checklist for Autism in Toddlers (M-CHAT)
PDDST- II, Primary Care Screener (PDDST-II PCS)
Pervasive Developmental Disorders Rating Scale (PDDRS)
Quantitative Checklist for Autism in Toddlers (Q-CHAT)
Screening Tool for Autism in Toddlers & Young Children (STAT)
Systematic Observation of Red Flags (SORF)
Level 2 Diagnostic Instruments
Asperger Syndrome Diagnostic Scale (ASDS)†
Autism Behavior Checklist (ABC)
Autism Quotient (AQ)–Adolescent Version
Autism Spectrum Screening Questionnaire (ASSQ)
Childhood Autism Rating Scale (CARS)
Gilliam Asperger's Disorder Scale (GADS)
Gilliam Autism Rating Scale– 2nd Edition (GARS-2)
Krug Asperger's Disorder Index (KADI)
PDDST-II, Autism Clinic Severity Screener (PDDST-II, ACSC)
Screening Tool for Autism in Two-Year-Olds (STAT)
Social Communication Questionnaire (SCQ) *

AAP=American Academy of Pediatrics; PDDST-II= Pervasive Developmental Disorders Screening Test

* SCQ was formerly called the Autism Screening Questionnaire

† "Asperger" used synonymously with the possessive "Asperger's"

The AAP recommends level 1 screening of all children at 18- and 24-month well visits and recognizes the instruments listed in **Table 1.2**. It is recommended that clinicians provide peer-reviewed information on ASD to parents of children who test negative and schedule an additional primary care visit if residual parental concerns are present. If children screen positive for possible ASD at level 1, referrals are recommended to early childhood education or intervention services (if older than 18 months) for comprehensive ASD evaluation, and for an audiological evaluation to rule out auditory causes of developmental delay.

For a comprehensive diagnostic evaluation, the AAP recommends referral to a pediatric subspecialist such as a child neurologist, developmental pediatrician, or psychiatrist with at least some experience diagnosing ASD. The AAP recognizes both child psychologists and speech-language pathologists with appropriate training and experience as final diagnosticians of ASD, especially when other resources are unavailable. Three components are specified for comprehensive diagnostic evaluation: determining the child's overall level of function, making a categorical diagnosis of an ASD, and determining the extent of a search for an etiology. Evaluation using multiple sources is recommended, as children may present or perform differently in different settings.

1.4.3.2 AACAP recommendations

Practice parameters for the assessment of ASD in children were recently updated by the AACAP in 2014.[84] Screening tools recognized by the AACAP are listed in **Table 1.3**. AACAP recommendations are broadly defined with closer reference to the DSM compared to AAP recommendations. The AACAP recommends that the developmental assessment of young children and the psychiatric evaluation of all children should include ASD-related questions but does not specify a specific process by which to do so like the

AAP. Another important distinction is temporal: the AACAP guidelines leave discretion of when to screen children to clinicians, although suggested age ranges are provided in specific screening tools recognized by the AACAP. Similar to AAP level 2 screening, a comprehensive ASD diagnostic evaluation is recommended by the AACAP for those children who screen positive. The DSM-V criteria are recommended for final diagnosis after ruling out conditions similar to ASD.

There are also differences between AAP and AACAP recommendations in terms of genetic testing. AACAP guidelines recommend a form of genetic testing called chromosomal microarray as "typically included" as the genetic component of the medical evaluation. AAP recommendations present genetic testing as an option and clinicians are cautioned with evidence of disagreement on thresholds for positive yields and sensitivity issues with some tests.[81] These differences may be explained as a function of when each set of recommendations were published. AAP and AACAP recommendations were published in 2007 and 2014, respectively. During the seven-year period between AAP and AACAP publications, much progress was made in the genetic analysis of children diagnosed with developmental disorders. For example, AACAP's more supportive stance towards genetic testing could be explained by a 2010 consensus statement published by medical geneticists that strongly supported a validated form of genetic testing called chromosomal microarray for all patients with unexplained developmental delay, intellectual disability, ASD, or multiple congenital anomalies.[95]

Table 1.3: ASD assessment instruments recommended by the AACAP[84]

Autism Behavior Checklist (ABC)*
Autism Diagnostic Interview Revised (ADI)
Autism Diagnostic Observation Schedule (ADOS)
Autism Quotient (AQ)*
Autism Screening Questionnaire (ASQ)*
Asperger Syndrome Diagnostic Interview (ASDI)†
Asperger Syndrome Diagnostic Scale (ASDS)*
Childhood Autism Rating Scale (CARS)*
Childhood Autism Screening Test (CAST)
CSBS Developmental Profile Infant-Toddler Checklist (CSBS-DP-IT-Checklist)
Diagnostic Interview for Social and Communication Disorders (DISCO)
Gilliam Asperger's Disorder Scale (GADS)*
Modified Checklist for Autism in Toddlers (M-CHAT)*
Social Responsiveness Scales (SRS)

CSBS=Communication and Symbolic Behavior Scales;

* Recognized by both the American Academy of Pediatrics and the American Academy of Child and Adolescent Psychiatry[81,84,87]

† "Asperger" used synonymously with the possessive "Asperger's"

1.4.4 Diagnosis of ASD: Conclusion

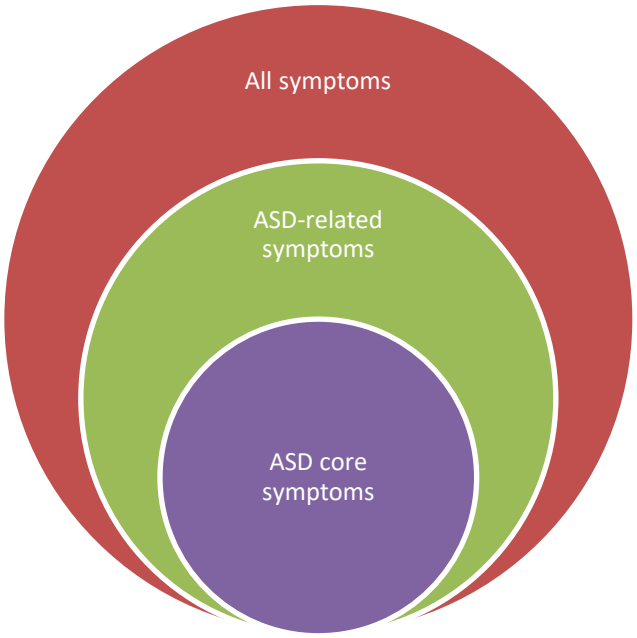
Many recommendations are available for the screening and diagnosis of ASD in children. Recommendations consistently give specific suggestions regarding the diagnostic process, but are relatively impartial when recommending tools for screening children. Despite some disagreement among guidelines and manuals on diagnostic criteria, agreement is increasing and alignment is occurring as guidelines are updated.

1.5 Treatment of ASD-related symptoms

Treatment of ASD varies and is highly-individualized, as ASD is characterized by various degrees of severity in the core social, communication, and behavioral symptoms.[96] Children with ASD are often diagnosed with neurological and physical comorbidities that require medical intervention targeting non-ASD symptoms (**Section 1.4**). Even though this analysis incorporates costs from these other domains of care, there is no substantive interest in the clinical aspect of medical interventions targeting non-ASD-related symptoms. Therefore, the focus of this section will be only in those treatments that target ASD-related symptoms.

Before covering treatment options for ASD, it is important to distinguish among the types of ASD symptoms. ASD-related symptoms are any symptoms that are related to ASD, while core ASD symptoms are only those ASD-related symptoms that belong to the 3 domains included in the DSM-V diagnostic criteria: social interaction, verbal and non-verbal communication, and restrictive and repetitive behaviors (**Figure 1.1**). For example, communication deficits would be considered a core symptom and agitation would not.

Figure 1.1 Hierarchy of ASD symptoms



Available treatments that target core symptoms include behavioral, developmental, and educational interventions.[85] Currently no pharmacologic therapy is available for the treatment of core ASD symptoms. Treatment is recommended in a variety of settings, including one-on-one interventions with a therapist, and family-based interventions that are parent-driven. Telehealth options are also becoming available for patients with healthcare access issues.[97] Once children reach five to six years of age, school-based services become available as well.

Goals of treatment include improving social functioning and play, communication, and adaptive skills, decreasing nonfunctional or negative behaviors, and promoting academic functioning and cognition.[80,85,96] There is variation in the strength of evidence supporting behavioral and educational interventions for ASD, but agreement exists on the importance of intervening early.[85,98,99] Most research evaluating available treatments is in populations of pre-school and elementary-aged children, and some research is developing

that supports interventions in children younger than two years.[100] Practice parameters caution that only a small number of adolescents with ASD make marked developmental gains, and some subgroups can even deteriorate behaviorally, so it is vital that treatments targeting core symptoms of ASD begin early in life.[84] Based on current evidence, the National Research Council recommends that educational services begin as soon as a child is suspected of having ASD, and take place for at least 25 hours a week and 12 months duration.[101]

1.5.1 Behavioral and educational interventions

1.5.1.1 Intensive behavioral interventions

Intensive behavioral interventions (IBIs) seek to target all defining symptoms of ASD and are based upon modifying behavior. Interventions include Applied Behavior Analysis (ABA), Discrete Trial Training (DTT), and Early Intensive Behavioral Intervention (EIBI).[85] IBIs have an overall larger body of supportive evidence than other classes of interventions.[102] Within the IBIs, ABA is the most widely studied, and is intended to generate gains in IQ, language, academic performance, and adaptive behavior, as well as some measures of social behavior efficacy. The specific goals of ABA are to increase desirable behaviors and decrease undesirable behaviors, then generalize learned behaviors to new environments and situations. ABA is recommended to take place across a variety of settings, including home, self-contained and inclusive classrooms, and community-oriented settings.[103]

Published systematic reviews and meta-analyses consistently show IBIs as efficacious, although there is disagreement on how much therapy is necessary and at what ages efficacy becomes exhausted.[104–111] The National Autism Center's National Standards Report also considers intensive behavioral intervention to be an "established" treatment for

ASD. Research comparing specific IBIs to each other is ongoing, and there is little clarity on what interventions are most effective across different ASD subpopulations. There is also little evidence evaluating the efficacy of IBIs in older children and adolescents, and the existing studies are characterized by relatively short study durations and small sample sizes.[112]

1.5.1.2 TEACCH/Structured teaching method

Another treatment method is called the Treatment and Education of Autistic and Related Communication Handicapped Children, or "TEACCH" method. This method applies structured teaching to address areas of weakness in communication and behavioral domains.[85] Important features of the TEACCH method include organizing the physical environment, developing predictable sequences of activities, visual schedules, flexible routines, structured activity systems, and visually structured activities.[113] The TEACCH method is advantageous by approaching the patient through two facets: one being skill development like other methods, but also involves the establishment of an accommodating patient environment that helps guide development.

Compared to IBI methods, efficacy data is not as comprehensive in TEACCH methods given their more recent development. A systematic review by the Agency for Healthcare Research and Quality (AHRQ) found some evidence of benefit in cognitive and motor function, but concluded the body of evidence was still insufficient to estimate a magnitude of an effect.[110]

There is also evidence that TEACCH methods can serve as an after-school compliment to other methods. One study evaluated 4-month changes in Psychoeduc1ational Profile-Revised (PEP-R) scores in children who enrolled in a TEACCH-based home program in addition to daytime treatment programs. The PEP-R is

an instrument designed to measure development specifically in ASD patients.[114] The investigators compared this augmented group to a control group of children enrolled in daytime treatment programs only, and demonstrated a significantly better posttest PEP-R scores in the treatment group vs. the control group ($p<0.05$).[115]

1.5.1.3 Developmental and relationship models

Developmental models utilize developmental theory to organize hypotheses regarding the fundamental nature of ASD, and approaches are designed by the therapist to address specific deficits. Developmental and relationship-based models are intended to teach skills that are essential to development that are not adequately absorbed at a given age. Examples of skills addressed include social communication, emotional relationships, and cognitive abilities. The Early Start Denver Model (ESDM) is a model intended to integrate the science of child development and the science of applied behavior analysis.[97] One study showed that children who received 15 hours a week of ESDM in their homes and ongoing parent coaching for 2 years showed large, and statistically significant improvements in IQ, language, and adaptive behavior.[116] Other developmental models include the Developmental Individual Difference Relationship-based approach, Milieu therapy, More Than Words, Relationship-development intervention, and responsive teaching. A 2008 systemic review found evidence of benefit for some developmental approaches, but overall evidence across all types of developmental approaches is still inconclusive.[106,117]

1.5.2 Medical and psychopharmacologic management

No pharmacological treatment for the core symptoms of ASD is approved by the FDA. Given the limited understanding of pathophysiology, high heterogeneity, and

inadequate development of valid outcome measures for treated patients, pharmaceutical and biotechnology companies have been hesitant to develop innovative drug therapies to treat the core symptoms of ASD.[118] However, treatments are available for target symptoms, which include inattention, hyperactivity, maladaptive behaviors, repetitive behaviors, rigidity, anxiety, and depression.

Pharmacologic therapy is available to treat associated symptoms and comorbidities. Approximately 70% of individuals with ASD have at least one comorbid medical condition.[65–67] Approximately 45 percent of patients are intellectually disabled, and as many as 50 percent have attention deficit hyperactivity disorder (ADHD). Up to 24 percent of those diagnosed with ASD have comorbid epilepsy, which is particularly prevalent in ASD patients who are intellectually disabled or have associated genetic conditions.[68,69]

Two medications are currently approved by the Food and Drug Administration (FDA) for use in ASD patient populations: risperidone and aripiprazole.[119] Both are indicated specifically for irritability and aggression. After approval in adults and other pediatric populations, risperidone's FDA approval was extended to ASD patients in 2006 and aripiprazole's approval was extended in 2009. There is also positive evidence supporting the use of clozapine and haloperidol in ASD patients with agitation and disruptive behavior.[120–122] There is some evidence that risperidone and haloperidol are effective for the treatment of aberrant social behavior in ASD patients, with risperidone being superior to haloperidol at 8 and 12 weeks after treatment initiation.[123,124]

Up to half of patients with ASD are diagnosed with comorbid ADHD. Methylphenidate and venlafaxine have been evaluated for inattention and hyperactivity in ASD populations. One double-blind, placebo-controlled, crossover study of methylphenidate in 13 children demonstrated improvements in hyperactivity and impulsivity, as measured by the Conners Hyperactivity Index.[125] However, no changes in

core ASD symptoms were observed in the Childhood Autism Rating Scale (CARS). There is some anecdotal evidence supporting venlafaxine for hyperactivity in ASD, but no empirical evidence was found.[126]

There is also evidence evaluating some medications in the repetitive behaviors domain of ASD. The most widely studied are fluoxetine and citalopram, which are both traditionally utilized in mood disorders. These medications are also guideline-recommended for obsessive-compulsive disorder, which like ASD, is also characterized by anxiety, repetitive behaviors, and social problems.[127] Evidence evaluating fluoxetine is conflicting. A 12-week double-blind placebo-controlled trial of fluoxetine in adult patients showed a 50 percent improvement in Clinical Global Impression scores, compared to an eight percent improvement in the placebo group.[128] However, in the Study of Fluoxetine in Autism (SOFIA) trial in children and adolescents, fluoxetine was found to be no more effective than placebo in treating repetitive behaviors.[129]

Results for citalopram are less favorable. To date only one randomized, placebo-controlled trial has been published, which found that citalopram was ineffective in treating children with ASD, including those with Asperger's disorder and unspecified developmental disorders.[130]

Despite no FDA-approved medications for core symptoms of ASD, attention to this condition is growing. One area where the scientific community has recently increased its attention is towards the oxytocin system. Oxytocin is an endogenous hormone best known for its role in lactation and parturition in women. There is also evidence that it plays a major role in relationship formation and social functioning in both humans and animals.[131] A systematic review of seven studies showed promising results in the effects of oxytocin on repetitive emotion recognition and eye gaze, which are impaired early in the course of ASD and may inhibit the development of social skills learning in children.[132] Roche, a

pharmaceutical manufacturer, is currently investigating a new medication called balovaptan, which targets the oxytocin system and is currently undergoing Phase-III clinical trials in adult and pediatric populations.[133] Other medications that have been evaluated for effects on social deficits include D-cycloserine and tetrahydrobiopterin.[134,135]

1.6 ASD legislation

With the influx of biological and clinical research in recent decades through increased societal attention, ASD has gained significant consideration from a health policy perspective. Healthcare coverage for ASD patients enrolled in public and private health plans has increased considerably in the past two decades. However, despite increased attention and coverage, ASD prevalence estimates remain considerably lower in health plans compared to CDC estimates.[3,56,136]

1.6.1 Medicaid: Home and community-based service (HCBS) waivers and state-level Medicaid legislation

HCBS waivers are community-based service waivers that allow states to provide medical and non-medical services to patients who may otherwise receive those services in an institutional setting.[137] Nearly all states and the District of Columbia offer services through HSBC waivers, and waivers are regulated at the federal level through Section 1915 of The Social Security Act. For states to receive waivers, several programmatic criteria must be met, primarily that states must demonstrate that providing waiver services will not cost more than providing those services in an institutional setting.

State-level legislation requiring coverage for ASD-related diagnosis and treatment has been enacted targeting both public and private health plans. HCBS 1915(c) waivers targeting patients with ASD began to appear in 2001, and 29 states had enacted ASD waivers as of January 2015. Many waivers extend Medicaid coverage to children with ASD independent of family income level.[138] Some HCBS waivers go as far as extending coverage to those who are simultaneously enrolled in commercial plans that do not cover ASD-related services, which serves as an important safety net for commercially insured patients who do not have access to ASD-related services.

1.6.2. State-level commercial health plan legislation

Legislation has also been passed at the state level targeting commercial health plans, particularly fully insured plans. State-level commercial legislation began to appear around 2010, before which only 15 states had enacted legislation targeting commercial plans. By April 2018, 48 states and the District of Columbia had established policies mandating private insurance plans to cover services for both diagnosis and treatment of ASD. Only one state, Tennessee, has not passed commercial health plan ASD legislation as of the time of this writing.[139] The state-level interventions are important because approximately half of commercially insured patients are enrolled in health plans that are regulated by these policies.[140] Self-insured health plans sponsored by large employers, however, are not subject to state-level requirements, but are instead regulated at the federal level by the Federal Employee Retirement Income Security Act (ERISA) (**Table 1.4**). Despite being exempt from state-mandated coverage requirements, many self-insured health plans have been proactive with covering ASD-related services. The Mercer National Survey of Employer-Sponsored Health Plans showed that 36% of large employers covered intensive behavioral therapies for ASD patients in 2013, and approximately 45% provided coverage in 2017.[141–143]

Table 1.4: Fully insured vs self-insured commercial health plans

Attribute	Fully insured	Self-insured
Level of regulation	State	Federal (ERISA)
% of health plan-covered workers[140]	40%	60%
Risk location	Insurance carrier	Employer
Number of employees[140]	Typically <500	Typically ≥ 500

* ERISA –Employee Retirement Income Security Act

Understanding the timing and reach of ASD-related health policy is important. Not only has legislative intervention shifted responsibility from public to private health payers, but it has transferred a significant economic burden as well. With commercial health plan legislation in place, commercially insured patients who would have previously received ASD-related services through Medicaid 1915(c) waivers become qualified to receive ASD services through their respective commercial plans. This legislation is important not only in terms of preventing the fragmentation of care across two payers, but it also shifts the economic burden of ASD-related services from the public sector back into the private market.

Since the enactment of these state-level policies, research evaluating the economic impact of mandates on public and commercial health plans has begun to appear in the literature. A study in the Pennsylvania Medicaid population evaluated the impact of commercial health plan legislation on Medicaid utilization through HCBS waivers. The analysis showed that Medicaid enrollment of ASD patients through HCBS waivers declined by 50% during the 2-year period following legislation.[144] However, some research suggests that state mandates do not significantly impact patient out-of-pocket costs. One analysis measured the impact of state mandates on out-of-pocket costs through a difference-in-difference analysis, and found that mandates were not associated with a significant reduction in out-of-pocket costs or access to care.[145] An analysis comparing mandate-eligible children in fully insured plans to ineligible children in self-insured plans showed a positive association between patient-reported ASD service use and enrollment in fully insured plans, with a stronger association in younger children.[146]

1.6.3 Federal legislation

ASD-related legislation has also been passed at the federal level. Both the Mental Health Parity and Addiction Equity Act (MHPAEA) and the Affordable Care Act (ACA) addressed many access issues impacting patients with ASD.

The MHPAEA was passed by the federal government in 2008, and was designed to prevent group health plans that provide mental health or substance use disorders benefits from imposing less favorable benefit limitations on those benefits than on comparable medical and surgical benefits. Unlike the state-level mandates, the MHPAEA regulations are extended to self-insured plans as well.

The ACA expanded care to patients with ASD on many levels.[147] Private health plans were required to cover preventive services, including screening for ASD at 18- and 24-month well-check visits for children without charging a copayment or coinsurance. Prior to the ACA, many plans established annual and lifetime dollar limits on plan spending for covered benefits during the time individuals were enrolled, deferring responsibility to ASD patients for costs exceeding those limits. The ACA began eliminating these dollar limits in 2011.

1.6.4 ASD legislation: Conclusion

Several pieces of ASD-related legislation have been enacted at both state and federal levels, and policy researchers are beginning to evaluate their impact on coverage and utilization of healthcare resources from multiple perspectives. One aim of this analysis is to update treated prevalence, healthcare utilization, and expenditure estimates from the commercial payer perspective in light of a contemporary regulatory environment.

1.7 Economic burden

This section describes the economic burden of ASD. Even though the focus of this analysis is in pediatric populations from the commercial health plan perspective, it is important to gather insight from multiple perspectives. The intent of this section is to complement the health policy perspective presented in **Section 1.6** in providing insight into why a pediatric commercially insured population was chosen for this analysis.

Evidence of ASD-related economic burden is presented from the perspectives of the family, payor, and society. The societal perspective is given first to provide evidence of where different costs occur with respect to both age and cost type (direct medical, direct nonmedical, and indirect).

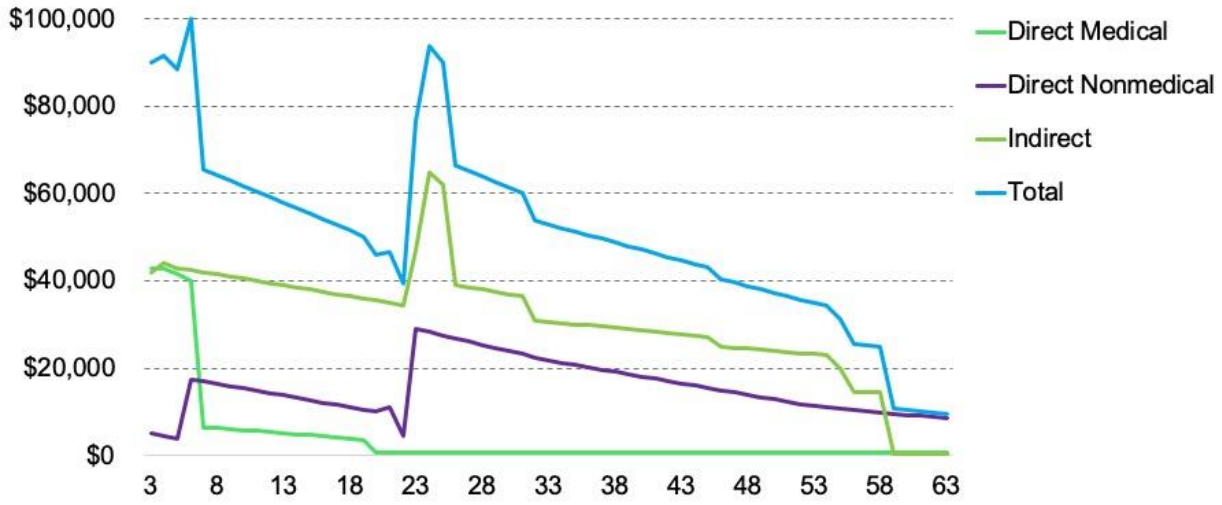
1.7.1 Societal perspective and age-specific estimates of economic burden

Due to the early onset, lifelong disease course, and disabling nature of ASD, the humanistic and economic costs are high. Lifetime costs with respect to age and type are shown in **Figure 1.2**. The lifetime incremental costs of ASD have been estimated to be $3.1 million per patient, with direct medical costs making up almost 10 percent of total discounted lifetime costs. A majority of direct medical costs occur during childhood, and behavioral therapies account for roughly two-thirds of direct medical costs (2003 dollars).[148] The substantial direct medical costs early in life are driven primarily by behavioral therapies that cost around $32,000 from diagnosis until age 8. After age 8, behavioral therapy utilization declines, and cost estimates subsequently decrease to $4,000 between ages 8 and 12 years, then decline again to approximately $1,250 between ages 18 and 22. Estimates for direct medical costs are variable in insured populations. Disparities have also been documented between public and private health plans, and are at least partially explained by reduced coverage of ASD-related services.[59]

Lifetime direct nonmedical costs are also unbalanced with respect to age. The age distribution of direct nonmedical costs is different from direct medical costs. Nonmedical costs begin to outweigh medical costs at age 8, then peak between the ages 23 and 27. Direct nonmedical costs are driven primarily by adult care for those patients who are considered disabled.[148] Evidence suggests that childhood direct nonmedical costs are driven by childcare, special education, and respite care.

Indirect costs drive the majority of lifetime costs and evidence shows they are the most dynamic, with a distribution that first peaks in early childhood and again in early adulthood.

Figure 1.2 Incremental cost of ASD by age and cost type. Adapted from Ganz, 2007[148]



1.7.2 Public and commercial payer perspectives

Many studies have evaluated healthcare utilization and expenditures in ASD patients from both the public and commercial perspective (**Table 1.5)**. One analysis of Medicaid-insured Pennsylvania children estimated an average annual medical cost per patient at $9,080 (range $8,214-$12,135), with 67% of costs driven by psychiatric inpatient

visits.[58] An analysis comparing Medicaid-insured to commercially insured children in 2003 estimated annual costs at $22,653 in a Medicaid-insured population, and $5,254 in a self-insured commercial population.[59] Data from this study showed a positive association between total healthcare expenditures and age in both Medicaid and commercial groups.[78,149]

A 2005 Medicaid analysis with data from 50 U.S. states estimated a mean annual cost of $14,034, with older children utilizing more healthcare resources across multiple domains of care.[78] The study also showed a shift in utilization and services as children entered the education system. Utilization of long-term care, psychiatric medications, medication management, day treatment and partial hospitalization, and respite care services increased substantially, while utilization of speech therapy, occupational and physical therapy, and diagnostic services declined.

Age-related changes in healthcare utilization and costs have also been evaluated in commercially insured populations. A study of children enrolled in the Kaiser Permanente (KP) Medical Care Program in northern California between 2008 and 2012 also showed a positive association between age and healthcare costs.[149] The investigators compared healthcare service utilization and costs to two control groups of children without an ASD diagnosis: one being a general population and the other a population with ADHD. Median overall costs were three times higher in ASD patients compared to the general population ($2,520 vs. $806), and increasing disparity in expenditures was demonstrated as children approached adulthood. Median overall costs of ASD patients were greater than those patients with ADHD ($2,520 vs. $1,984), but the difference was not as great as compared to the general population.

Another analysis followed healthcare utilization and expenditures in a cohort of Medicaid-insured children with ASD who were transitioning to adulthood.[64] The analysis

demonstrated that mean expenditures increased between 2001 and 2005 in all categories, which included outpatient, inpatient, long-term care, and medication-related expenditures.

An analysis in a population of commercially insured children demonstrated that mean expenditures ranged from $4,965 to $6,073 per patient with an ASD diagnosis between 2000 and 2004.[60] Median expenditures were more stable and grew slightly from $2,881 to $3,368 during the same period. Virtually all patients in this analysis were enrolled in self-insured commercial health plans.

Table 1.5: Healthcare expenditures in Medicaid and commercially insured ASD populations

Reference*	Population (*N*, age, observation period)	Comparison group	Mean annual cost†
Analyses in Medicaid Health Plans			
Mandell et al., 2006[58]	*N*=334, <21 years, 1994-1999	ID	$17,226
Wang et al., 2010[75]	*N*=69,542, <17 years, 2000-2003	None	$36,438
Cidav et al., 2013[78]	*N*=94,201, 3-20 years, 2005	None	$20,637‡
Wang et al., 2013[59]	*N*=2,906,819, <17 years, 2003	Commercially insured	$36,248
Vohra et al., 2017[150]	*N*=1,772, 22-40 years, 2000-2008	GP	$17,887
Analyses in Commercial Health Plans			
Croen et al., 2006[149]	*N*=3,053, 2-18 years, 2003-2004	GP	$4,160
Leslie et al., 2007[60]	*N*=9,506, <17 years, 2000-2004	MHD	$8,889‡
Shimabukuro et al., 2008[151]	*N*=1,202,861, 1-21 years, 2003	GP	$10,929
Wang et al., 2013[59]	*N*=2,906,819, <17 years, 2003	Medicaid-insured	$8,407
Zerbo et al., 2018[57]	*N*=1,507, ≥ 18 years, 2012	GP & ADHD	$8,155

ADHD=Attention-deficit/hyperactivity disorder; ASD=Autism Spectrum Disorder; GP=General Population; ID=Intellectual disability; MHD=Mental Health Disorder;

* Costs reported by Barry et al., 2017[152] and Shea et al., 2018[64] are not presented in the table because data could not be aggregated with reported information

† Costs are adjusted to 2017 dollars using the medical component of the Consumer Price Index published by the Bureau of Labor and Statistics

‡ Value is calculated weighted by sample size from each subgroup of analysis

1.7.2.1 Health policy analyses

There is some research evaluating the impact of state and federal legislation on ASD-related healthcare utilization and costs. A 2008-2012 study evaluated the impact of state insurance mandates on healthcare utilization and costs in ASD patients.[152] The analysis showed that mandates raised spending on ASD-specific services by an estimated

annual average of $77 per month ($924 per year), with a 3.4% increase in monthly ASD-related service use.

Another analysis evaluated the impact of the MHPAEA (**Section 1.6.3**) on mental health service use in ASD patients.[63] The analysis showed a slight increase in treated prevalence (3 per 1,000 - 4 per 1,000). A time series analysis showed no significant increase in the probability of per-month m service use at the time of MHPAEA (-0.0011, $p > 0.1$), but did show an increase in the time by parity interaction (0.0014, $p<0.001$), which represented the change in trend associated with MHPAEA. This analysis was limited by the absence of a control group.

1.7.2.2 Public and commercial payer perspectives: Conclusion

It is important to highlight that most studies summarized above evaluating ASD-related healthcare expenditures from the commercial health plan perspective took place before most state-level ASD mandates were passed, and a majority of studies included only patients enrolled in self-insured health plans. Although one recent study was found evaluating expenditures in adult patients, the most recent observation period found in pediatric populations was 2008 in Medicaid studies and 2012 in commercial claims studies. In 2004, only one state (Indiana) had required coverage for ASD treatment in commercial plans, and by the end of 2008, only eight states had mandated coverage. This timing discrepancy underscores the importance of updating healthcare resource utilization and cost estimates with more recent observation periods aligned with the new coverage landscape.

Only one study evaluating commercial utilization and expenditures included ASD patients from both fully- and self-insured health plans, but only followed patients to the end of 2012.[152] It is important to update ASD-related utilization and expenditure data in a

new coverage landscape, and to do so from a population more generalizable to today's commercial insurance market where one in two patients are enrolled in fully insured plans. Another aim of this study is to address this literature gap with more recent expenditure data in a broader population of commercially insured children.

1.7.3 Patient and family perspectives

Patient and family perspectives are other key considerations when estimating the economic burden of disease. This is particularly true in neurodevelopmental conditions where coverage disparities can be prevalent (**See section 1.6**). Many studies have been conducted that estimate out-of-pocket costs in patients and families affected by ASD. Studies evaluating out-of-pocket costs are presented in **Table 1.6**.

An analysis conducted from 1997-2000 using Medical Expenditure Panel Survey (MEPS) data showed mean annual out-of-pocket costs of $613, which was significantly greater than a group of patients with intellectual disability ($161), but not significantly different than a group of patients with depression ($687) ($F=4.51$; $p=0.004$).[153]

Another analysis measured an association between per-capita state Medicaid spending and patient-reported out-of-pockets costs reported by the National Survey of Children with Special Health Care Needs.[154] The analysis showed that a $100 increase in annual per capita Medicaid spending was associated with a 43% lower odds of having any out-of-pocket costs ($p<0.01$). A similar analysis with the same data measured the association of out-of-pocket costs with state insurance parity legislation, which showed that parity legislation was associated with a 28% lower likelihood of having out-of-pocket costs among families of children with autism ($OR=0.72$; $p<0.05$).[155]

Another study using MEPS data showed an additional $154 (95% CI=$3-$344) in out-of-pocket costs for a group of ASD patients compared to a control group of children

without an ASD diagnosis, but the difference lost statistical significance after controlling for epilepsy and intellectual disability.[156]

ASD-specific out-of-pocket costs have been evaluated as well. One 2008-2012 study showed an association of state-level ASD insurance mandates with ASD-specific out-of-pocket costs and found a modest decline in the share of spending paid out-of-pocket, particularly among those patients with higher utilization.[157]

Table 1.6: Out-of-pocket expenditures in ASD populations

Reference*	Population (*N*, age, observation period)	Data source	Mean annual OOC*
Liptak et al., 2006[153]	*N*=14,489, <19 years, 1997-2000	MEPS, NAMCS, & NHAMCS	$1,117†
Shimabukuro et al., 2008[151]	*N*=1,202,861, 1-21 years, 2003	Commercial claims	$801-$960
Parish et al., 2015[155]	*N*=316, <18 years 2000-2009	NSCSHCN	$924
Candon et al., 2019[157]	*N*=106,977, <21 years, 2008-2012	Commercial claims	$1,471‡

OOC=out-of-pocket cost; MEPS= Medical Expenditure Panel Survey; NAMCS=National Ambulatory Medical Care Survey; NHAMCS=National Hospital Ambulatory Care Survey; NSCSHCN=National Survey of Children with Special Health Care Needs

* Costs are adjusted to 2017 dollars using the medical component of the Consumer Price Index published by the Bureau of Labor and Statistics

† Discounting of costs was not mentioned by authors

‡ Out-of-pocket estimates considers only patients who received ASD-related treatments

§ Parish et al., 2012[154,158]; Lavelle et al., 2014[156]; and Chatterji et al., 2015[145] are not listed because not enough information was reported to calculate overall out-of-pocket costs

1.7.4 Economic burden: Conclusion

Gathering a complete picture of the patient experience is not possible without first developing an understanding of the economic burden of illness from multiple perspectives. This section presented evidence describing the dynamics of economic burden from the

societal, payer, and patient perspectives. Many studies extended analyses into measuring associations between healthcare costs and the implementation of state-level policies.

1.8 Study rationale, purpose, and objectives

1.8.1 Study rationale

ASD is a set of profoundly disabling conditions that are often lifelong, particularly when diagnosis and treatment are delayed. Treatments for ASD have been shown to generate gains in IQ, language, academic performance, adaptive behavior, and some measures of social behavior efficacy. Treatment is most effective at early ages and ideally includes the alignment of community, educational, and healthcare resources. Although there is currently no pharmacological treatment for the core symptoms of ASD, pharmacologic therapy is available to treat associated symptoms and comorbidities.

Despite the presence of literature on treated prevalence and its geographic variation in children diagnosed with ASD, the literature review revealed no studies that estimated geographic variation in treated prevalence rates of commercially insured patients. This study addresses this gap in the literature by estimating geographic variation in prevalence as well as incorporating U.S. Census data to investigate factors that may explain this variation. Literature measuring age-specific differences in psychiatric comorbidity prevalence in commercially insured ASD patients is also limited. Studies report age-related variation in overall psychiatric comorbidity prevalence (**Section 1.3.3**), but no studies were found that compare age-related comorbidity prevalence to a control group of children without ASD.

Additionally, most studies of ASD-related healthcare expenditures from the commercial health plan perspective took place before most state-mandates were passed. This timing discrepancy underscores the value of updating treated prevalence, and

healthcare resource utilization and cost estimates with more recent observation periods aligned with a contemporary healthcare coverage landscape. Many studies incorporated control groups to compare utilization and expenditures to non-ASD populations, but few studies in commercially enrolled populations included those enrolled in fully insured health plans. This study aims to fill this gap in the literature by providing annual medical, prescription, and total utilization and cost estimates in a more generalizable sample of commercial patients. Utilization and expenditures were also compared between ASD and non-ASD patients.

1.8.2 Study purpose

The primary purpose of this study is to contribute to the growing body of evidence in commercially insured children diagnosed with ASD. The first component of this study estimates and explains geographic variation in the treated prevalence of ASD. The second component compares the prevalence of psychiatric conditions between ASD and non-ASD groups. The third component of this study estimates the difference in healthcare utilization and expenditures between ASD and non-ASD groups.

1.8.3 Study objectives and hypotheses

Objective 1: To quantify and explain geographic variation in treated prevalence of ASD in commercially insured children

1a: To determine the overall treated prevalence of ASD in children 18 or younger enrolled in commercial healthcare plans

No hypothesis-overall prevalence was calculated to serve as a central value to compare ZIP3-level prevalence

1b: To quantify treated prevalence of ASD in children 18 or younger enrolled in commercial healthcare plans within each ZIP3 region

No hypothesis – values were used to generate a heatmap to visualize variance in treated prevalence across ZIP3 regions

1c: To explain variation in the treated prevalence of ASD as a function of geographic, health-system, and socioeconomic characteristics.

$H_0(1c)_1$: There is no significant difference in the treated prevalence of ASD with respect to **geographic region**, after controlling for covariates.

$H_0(1c)_2$: There is no significant difference in the treated prevalence of ASD with respect to **fully insured plan density**, after controlling for covariates.

$H_0(1c)_3$: There is no significant difference in the treated prevalence of ASD with respect to **pediatrician density**, after controlling for covariates.

$H_0(1c)_4$: There is no significant difference in the treated prevalence of ASD with respect to **psychologist density**, after controlling for covariates.

$H_0(1c)_5$: There is no significant difference in the treated prevalence of ASD with respect to **median family income**, after controlling for covariates.

$H_0(1c)_6$: There is no significant difference in the treated prevalence of ASD with respect to **single-parent family density**, after controlling for covariates.

$H_0(1c)_7$: There is no significant difference in the treated prevalence of ASD with respect to **private school enrollment density**, after controlling for covariates.

$H_0(1c)_8$: There is no significant difference in the treated prevalence of ASD with respect to **poverty status density**, after controlling for covariates.

$H_0(1c)_9$: There is no significant difference in the treated prevalence of ASD with respect to **percent white**, after controlling for covariates.

$H_0(1c)_{10}$: There is no significant difference in the treated prevalence of ASD with respect to **ZIP3 region urbanicity**, after controlling for covariates.

Objective 2: To describe and compare demographic, health system, and clinical characteristics of patients diagnosed with ASD to those without ASD.

No hypothesis- descriptive statistics were used to draw comparisons

Objective 3: To quantify and compare the age-related likelihood of psychiatric conditions between ASD and non-ASD groups (i.e., interaction between age and ASD diagnosis).

$H_0(3)_1$: There is no significant difference in the age-related likelihood of **adjustment disorder** between ASD and non-ASD groups, after controlling for covariates.

$H_0(3)_2$: There is no significant difference in the age-related likelihood of **anxiety disorder** between ASD and non-ASD groups, after controlling for covariates.

$H_0(3)_3$: There is no significant difference in the age-related likelihood of **attention-deficit conduct or disruptive behavior** between ASD and non-ASD groups, after controlling for covariates.

$H_0(3)_4$: There is no significant difference in the age-related likelihood of **mood disorder** between ASD and non-ASD groups, after controlling for covariates.

$H_0(3)_5$: There is no significant difference in the age-related likelihood of **personality disorder** between ASD and non-ASD groups, after controlling for covariates.

$H_0(3)_6$: There is no significant difference in the age-related likelihood of **schizophrenia or other psychotic disorder** between ASD and non-ASD groups, after controlling for covariates.

$H_0(3)_7$: There is no significant difference in the age-related likelihood of **alcohol or substance-related disorder** between ASD and non-ASD groups, after controlling for covariates.

Objective 4: To quantify and compare healthcare utilization between children diagnosed with ASD and those without ASD.

4a: To quantify and compare healthcare utilization for **all-cause** outpatient office, inpatient, and emergency department (ED) visits, and outpatient prescriptions between ASD and non-ASD groups. Within outpatient office visits, this objective also quantifies and compares occupational and physical therapy (OT/PT), and speech therapy visits between ASD and non-ASD groups.

$H_0(4a)_1$: There is no significant difference in the number of **all-cause outpatient office visits** between ASD and non-ASD groups, after controlling for covariates.

$H_0(4a)_2$: There is no significant difference in the number of **all-cause OT/PT visits** between ASD and non-ASD groups, after controlling for covariates.

$H_0(4a)_3$: There is no significant difference in the number of **all-cause speech therapy visits** between ASD and non-ASD groups, after controlling for covariates.

$H_0(4a)_4$: There is no significant difference in the number of **all-cause inpatient visits** between ASD and non-ASD groups, after controlling for covariates.

$H_0(4a)_5$: There is no significant difference in the number of **all-cause ED visits** between ASD and non-ASD groups, after controlling for covariates.

H_0(4a)$_6$: There is no significant difference in the number of **all-cause prescriptions** between ASD and non-ASD groups, after controlling for covariates.

4b: To quantify and compare healthcare utilization for **mental health-related (MHR)** outpatient office, inpatient, and ED visits, and outpatient prescriptions between ASD and non-ASD groups. Within mental health-related office visits, this objective also quantifies and compares behavioral modification visits between ASD and non-ASD groups.

H_0(4b)$_1$: There is no significant difference in the number of **MHR outpatient office visits** between ASD and non-ASD groups, after controlling for covariates.

H_0(4b)$_2$: There is no significant difference in the number of **behavioral modification visits** between ASD and non-ASD groups, after controlling for covariates.

H_0(4b)$_3$: There is no significant difference in the number of **MHR inpatient visits** between ASD and non-ASD groups, after controlling for covariates.

H_0(4b)$_4$: There is no significant difference in the number of **MHR ED visits** between ASD and non-ASD groups, after controlling for covariates.

H_0(4b)$_5$: There is no significant difference in the number of **MHR prescriptions** between ASD and non-ASD groups, after controlling for covariates.

Objective 5: To quantify and compare healthcare expenditures between children diagnosed with ASD and those without ASD.

5a: To quantify and compare **all-cause** expenditures both overall, and for outpatient office visits, inpatient visits, ED visits, outpatient prescriptions, and out-of-pocket (OOP) between ASD and non-ASD groups. Within outpatient office expenditures, this objective also quantifies and compares OT/PT and speech therapy expenditures between ASD and non-ASD groups.

$H_0(5a)_1$: There is no significant difference in **all-cause total expenditures** between ASD and non-ASD groups, after controlling for covariates.

$H_0(5a)_2$: There is no significant difference in **all-cause outpatient office expenditures** between ASD and non-ASD groups, after controlling for covariates.

$H_0(5a)_3$: There is no significant difference in **all-cause OT/PT expenditures** between ASD and non-ASD groups, after controlling for covariates.

$H_0(5a)_4$: There is no significant difference in **all-cause speech therapy expenditures** between ASD and non-ASD groups, after controlling for covariates.

$H_0(5a)_5$: There is no significant difference in **all-cause inpatient expenditures** between ASD and non-ASD groups, after controlling for covariates.

$H_0(5a)_6$: There is no significant difference in **all-cause ED expenditures** between ASD and non-ASD groups, after controlling for covariates.

$H_0(5a)_7$: There is no significant difference in **all-cause prescription** expenditures between ASD and non-ASD groups, after controlling for covariates.

$H_0(5a)_8$: There is no significant difference in **all-cause OOP** expenditures between ASD and non-ASD groups, after controlling for covariates.

5b: To quantify and compare **mental health-related (MHR)** expenditures both overall, and for outpatient, inpatient, ED visits, outpatient prescriptions, and OOP between ASD and non-ASD groups. Within MHR office expenditures, this objective also quantifies and compares OT/PT and speech therapy expenditures between ASD and non-ASD groups.

$H_0(5b)_1$: There is no significant difference in **total MHR expenditures** between ASD and non-ASD groups, after controlling for covariates.

$H_0(5b)_2$: There is no significant difference in **MHR outpatient office expenditures** between ASD and non-ASD groups, after controlling for covariates.

$H_0(5b)_3$: There is no significant difference in **behavioral modification expenditures** between ASD and non-ASD groups, after controlling for covariates.

$H_0(5b)_4$: There is no significant difference in **MHR inpatient expenditures** between ASD and non-ASD groups, after controlling for covariates.

$H_0(5b)_5$: There is no significant difference in **MHR ED expenditures** between ASD and non-ASD groups, after controlling for covariates.

$H_0(5b)_6$: There is no significant difference in **MHR prescription expenditures** between ASD and non-ASD groups, after controlling for covariates.

$H_0(5b)_7$: There is no significant difference in **MHR OOP expenditures** between ASD and non-ASD groups, after controlling for covariates.

CHAPTER 2: METHODOLOGY

2.1 Chapter overview

This chapter describes the methodology utilized to meet the study objectives. Separate details are provided for institutional review board (IRB) approval, data sources, study design, patient selection, study timeframe, data elements, statistical analyses, and power analyses. The statistical methodologies including model assumptions and limitations are also presented in detail.

Although the same primary data source was used for the entire study, the level of analysis in objective 1 was higher than the level of analysis in objectives 2-5. Therefore, study design and data elements sections are outlined separately for objective 1 and objectives 2-5.

2.2. Institutional review board (IRB) review

Before commencement of the study, approval was sought from the Institutional Review Board of The University of Texas at Austin (UT). Approval with a waiver of informed consent was granted (UT protocol number 2019-01-0135) because this was a retrospective database study containing de-identified data, which presents no more than a minimal risk to the welfare and privacy of subjects.

2.3 Data sources

This study utilized completely adjudicated medical and pharmacy claims data from IQVIA's PharMetrics Plus (P+) Database. The P+ database represents over 140 million enrollees, and the patient mix represented is a majority commercial, with a small subset of commercial Medicare and commercial Medicaid patients. P+ is also considered nationally-representative for both age and geography. Seventy-eight percent of patients represented

in P+ are enrolled in commercial health plans, with one-third of those enrolled in self-insured plans, and the remainder enrolled in fully insured plans. The P+ database contains demographic, and health system-level data elements and geographically identifies patients at the level of 3-digit zip codes (ZIP3).

In addition to P+ data, objective 1 also incorporates data from The American Community Survey (ACS) published by the United States Census Bureau. The ACS is a supplement to the decennial census that provides annual updates to housing and demographic statistics representing the United States.[159] Data are available as 1-, 3-, and 5-year summary files, and as a Public Use Microdata Sample (PUMS), which contain de-identified and unaggregated samples of ACS data. The 1- and 3-year summary files are limited to areas with populations of 65,000, and 20,000 or more, respectively. The 5-year summary files contain data at all geographic levels and provide more stable and precise estimates than the 1- and 3-year summary files. The 5-year summary files from 2013 to 2017 were used in objective 1 of this analysis in addition to the P+ database described above.

2.4 Study design

This section presents the study design for objective 1 (manuscript 1) first, followed by the study design for objectives 2 through 5 (manuscripts 2 and 3).

2.4.1 Objective 1 study design (Manuscript 1)

2.4.1.1 Study design and timeframe

This study was a retrospective cross-sectional claims database analysis using data from January 1, 2017 through December 31, 2017. Inpatient, outpatient, and enrollment data were extracted from the P+ database; pharmacy claims were not utilized for this

objective as it assumes no substantive interest in pharmacy-related data elements. Socioeconomic characteristics were integrated from the ACS database. The level of observation is ZIP3, and the unit of analysis is the ASD patient count.

2.4.1.2 Patient selection

The initial selection consisted of patients enrolled in the P+ database for at least nine months of the year 2017 **(Figure 2.1)**. To maximize comparability to studies evaluating the treated prevalence of ASD in healthcare claims data, a previously published algorithm using inpatient, outpatient, and enrollment data was followed to identify patients.[160]

Enrollees who met the following eligibility criteria were included in the study cohort:

A. were enrolled in a commercial health plan for at least nine months during the year 2017;
B. had years of birth between 1999 and 2014 (approximately 3 through 18 years of age during the year 2017);
C. had at least two claims (at least 30 days apart) with a diagnosis of ASD (**Table 2.1**)

Figure 2.1 Study timeline for objective 1

Table 2.1: ICD diagnosis codes classified as ASD

Diagnosis	ICD-9-CM	ICD-10-CM
Autistic disorder	299.0x	F84.0
Other specified PDD*	299.8x	F84.5
PDD, NOS	299.9x	F84.9

CM=Clinical modification; ICD=International Classification of Diseases; NOS=Not otherwise specified; PDD=Pervasive developmental disorder

* Asperger's syndrome is grouped into the diagnostic code "Other specified PDD"

2.4.2 Objectives 2-5 study design (Manuscripts 2 and 3)

2.4.2.1 Study design and timeframe

This component of the study is a retrospective cohort claims database analysis using data from January 1, 2015 through December 31, 2017. Inpatient, outpatient, pharmacy, and enrollment data were used for this analysis. This analysis was conducted at the patient level.

2.4.2.2 Patient selection

The initial selection consisted of patients enrolled in the P+ database between January 1, 2015 and December 31, 2017. To maximize comparability to studies of ASD populations using administrative healthcare claims, a previously published algorithm using

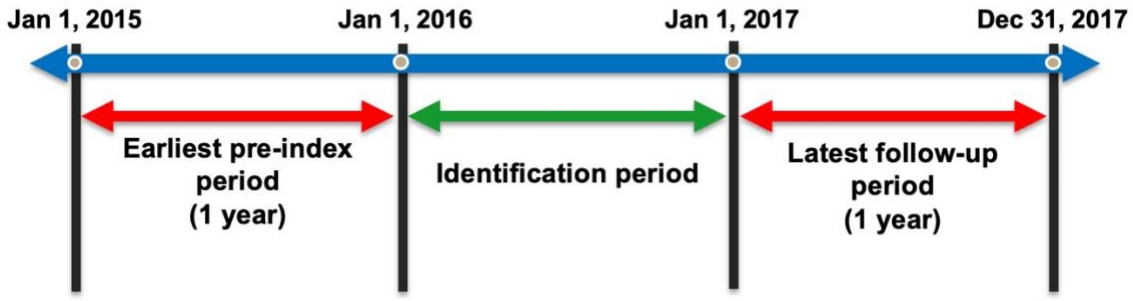
inpatient, outpatient, and enrollment data was followed to identify patients.[160] Enrollees who meet the following eligibility criteria were included in the study cohort:

A. had at least two claims (at least 30 days apart) with a diagnosis of ASD (**Table 2.5.1**);
B. were approximately 3 through 18 years of age at the index date (the date of the first claim with an ASD diagnosis), as defined in **Section 2.4.2.2.1**;
C. had continuous medical and pharmacy enrollment, and mental health coverage 12 months before and after the index date.

2.4.2.2.1 Index date

The study timeline for objectives 2-5 is presented in **Figure 2.2**. The index date was considered the date of the first ASD diagnosis. The pre-index period was defined as the 1-year period before the first ASD diagnosis (index date). The post-index period was defined as the 12-month period after the first ASD diagnosis including the index date.

Figure 2.2 Study timeline for objectives 2-5



2.4.2.2.2 Control group selection

In objectives 2-5, the study hypotheses are concerned with comparing baseline characteristics (Objective 2), age-related prevalence of psychiatric conditions (Objective 3), incremental utilization (Objective 4), and incremental expenditures (Objective 5) for children with ASD to a group of children without an ASD diagnosis. Therefore, patients without an ASD diagnosis (the control group) were matched to the group of ASD patients based on year of birth, gender, and enrollment data. Enrollment data were used to isolate control patients enrolled throughout the entire 3-year observation period. The control group was selected at a 2-to-1 ratio without replacement. In instances where more than two controls are matched, two were chosen at random. After matching, the index date for each ASD patient was carried over to the respective control group patients.

2.5 Data elements

This section describes the data elements related to the five objectives. The first objective of this study was to estimate and explain geographic variation in the treated prevalence of ASD. The second objective was to compare baseline characteristics between ASD and non-ASD groups. The third objective was to compare age-related prevalence of psychiatric conditions between ASD and non-ASD groups. The fourth and fifth objectives were to compare healthcare utilization and expenditures between ASD and non-ASD groups, respectively.

For each objective, dependent variables are described separately. For independent variables, those for objective 1 (manuscript 1) will be presented first, followed by independent variables for objectives 2-5 (manuscripts 2 and 3).

2.5.1 Dependent variables

2.5.1.1 Objective 1 dependent variables

2.5.1.1.1 ZIP3 prevalence

Operational definitions of dependent variables in objective 1 are presented in **Table 2.2**. The dependent variables in objective 1 were the treated prevalence rates of ASD, both overall and within each ZIP3 region. The overall prevalence rate (**Objective 1a**) was determined by dividing the number of ASD-diagnosed children by the number of all children enrolled for at least 9 months during 2017. The term "children" is used to refer to P+ patients aged 3 to ≤18 years. Unadjusted prevalence rates in each ZIP3 region (**Objective 1b**) are represented by dividing the number of ASD-diagnosed children (**Section 2.4.1.2)** by the number of all children enrolled for at least 9 months during 2017 in each ZIP3 region. To minimize zero-inflation of prevalence rates, at least 200 patients were required for each ZIP3 region to be included in the final analysis. Attrition will be

discussed in the Results section (3.1.1.1). State-level prevalence rates were also generated for descriptive purposes in objective **1b**. Adjusted prevalence rates (**Objective 1c**) were generated through regression techniques, which are explained in **Section 2.6** (Statistical analysis).

Table 2.2: Summary of operational definitions for dependent variables for objective 1 (Prevalence)

Variable (Objective)	Variable type Operational definition
Overall prevalence (1a)	Proportion Proportion of commercially insured patients 3 to ≤18 years who are diagnosed with ASD (cases/1,000)
Unadjusted ZIP3 prevalence (1b)	Proportion Proportion of commercially insured patients 3 to ≤18 years who are diagnosed with ASD in each ZIP3 region (cases/1,000)
Adjusted ZIP3 prevalence (1c)	Count Number of commercially insured patients 3 to ≤18 years who are diagnosed with ASD in each ZIP3 region adjusted for covariates (See Section 2.6)

ASD=Autism spectrum disorder; ZIP3=3-digit zip codes

2.5.1.2 Objectives 2-5 dependent variables

2.5.1.2.1 Study characteristics

The purpose of objective 2 is to describe and compare the demographic, geographic, health system, and clinical characteristics of patients diagnosed with ASD to those without ASD. Therefore, the dependent variables for objective 2 become the independent variables (covariates) for objectives 3-5, which are defined in **Section 2.5.2.2** (Independent variables).

2.5.1.2.2 Psychiatric conditions

The dependent variables in objective 3 are psychiatric conditions shown to be more common in children with ASD compared to those without ASD. Operational definitions of objective 3 dependent variables are presented in **Table 2.3**. Selection of psychiatric conditions for this analysis was based on previous research in ASD.[75,78,150] Psychiatric diagnoses were bundled into categories using the Agency for Healthcare Research and Quality (AHRQ) Clinical Classifications Software (CCS) published by the Healthcare Cost and Utilization Project (HCUP). Categories include adjustment disorders, anxiety disorders, attention-deficit conduct or disruptive behavior disorders, mood disorders, personality disorders, schizophrenia or other psychotic disorders, and alcohol- or substance-related disorders.[161,162] ICD-9-CM and ICD-10-CM codes were used to identify psychiatric conditions and are listed in **Appendix A**. Criteria for condition presence was either one inpatient or two outpatient diagnoses in any position in post-index claims.[150]

Table 2.3: Categories of psychiatric conditions[63,152,163]

CCS description	CCS code	Variable type Operational definition
Adjustment disorders	650	Binary 0=Absent 1=Present
Anxiety disorders	651	Binary 0=Absent 1=Present
Attention-deficit, conduct, and disruptive behavior disorders	652	Binary 0=Absent 1=Present
Mood disorders	657	Binary 0=Absent 1=Present
Personality disorders	658	Binary 0=Absent 1=Present
Schizophrenia and other psychotic disorders	659	Binary 0=Absent 1=Present
Alcohol and substance-related disorders	660 & 661	Binary 0=Absent 1=Present

CCS=Clinical classification software

* International classification of disease codes for each category are presented in **Appendix A**

2.5.1.2.3 Healthcare utilization

Operational definitions of dependent variables addressed in objective 4 are listed in **Table 2.4**. Healthcare utilization was measured in the follow-up period. Primary outcomes in objective 4 include healthcare resource utilization variables associated with office-based, inpatient, and emergency department (ED) visits, and outpatient prescriptions in the follow-up period. Physical and occupational therapy (OT/PT), and speech therapy were measured separately within outpatient utilization.

All outpatient claims not associated with an ED visit or an inpatient visit which were populated with a place of service code of 11 were included in the outpatient office

visit category. Within outpatient office visits, OT/PT and speech therapy were measured separately using Current Procedural Terminology (CPT®) codes. Outpatient OT/PT and speech and language services were identified based on previous literature and the University of Pennsylvania Center for Mental Health Policy and Services Research.[63,164] Specific CPT codes are listed in **Appendix B**.

In addition to overall utilization, mental health-related (MHR) utilization was measured as well. Established algorithms were utilized to identify MHR claims (**Appendix C**) and corresponding ICD-10 codes were used for service dates after October 1, 2015.[63,152,163] Estimates for outpatient BM visits were generated in addition to total MHR outpatient visits and were identified by CPT codes published by the Behavior Analyst Certification Board (**Appendix B**).[165]

ED-specific visits were measured both overall and for MHR visits, and must be associated with an ED place of service and not occur on the same day as an inpatient admission. A place of service of inpatient hospital or inpatient psychiatric hospital were necessary for visits to be considered inpatient. Partial inpatient care such as day programs were considered outpatient in this analysis.[166,167]

All claims for outpatient prescription medications in the follow-up period were analyzed. For psychotropic medications, Medi-Span Generic Product Identifier codes (GPI-2) were used to identify at the class level. Outpatient prescriptions for antidepressants (GPI_2=58), stimulants (GPI_2=61), anticonvulsants (GPI_2=72), antipsychotics/antimanics (GPI_2=59), and anxiolytics/sedative/hypnotics (GPI_2=57 & 60) were considered psychotropic.[168,169]

Table 2.4: Operational definitions of dependent variables for objective 4 (Utilization)

Variable	Operational definition
All-cause	
Outpatient	Number of outpatient office visits
OT/PT	Number of OT/PT visits
Speech	Number of speech therapy visits
Inpatient	Number of inpatient visits
ED visits	Number of ED visits
Outpatient Rx	Number of outpatient prescriptions
MHR	
Outpatient	Number of mental health-related outpatient office visits
BM	Number of behavioral modification visits
Inpatient	Number of mental health inpatient hospital visits
ED	Number of mental health ED visits
Outpatient Rx	Number of psychotropic prescriptions

BM=Behavioral modification; ED=Emergency department; MHR=Mental health-related; OT/PT=Occupational or physical therapy; Rx=Prescription

2.5.1.2.4 Healthcare expenditures

Operational definitions of dependent variables addressed in objective 5 are listed in **Table 2.5**. All-cause and MHR healthcare expenditures are both assessed in objective 5. All expenditures were generated from claims occurring during the follow-up period. Categories within all-cause expenditures included outpatient, inpatient, ED, prescription, and OOP. Outpatient expenditures not associated with an ED visit or inpatient visit were included in the outpatient category. Outpatient OT/PT and speech therapy expenditures were generated separately in addition to overall outpatient expenditures. Behavioral modification expenditures, which includes autism-related IBIs (**Section 1.8.1.1**), were generated in addition to MHR outpatient expenditures. OOP and total expenditures were generated for all-cause and MHR categories. Expenditures occurring in 2016 were adjusted to 2017 dollars using the medical care services component of the annual consumer price index (CPI).[170]

Table 2.5: Operational definitions of dependent variables for objective 5 (Expenditures)

Variable	Operational definition
All-cause	
Total	Sum of all expenditures
Outpatient	Sum of outpatient office expenditures
OT/PT	Sum of OT/PT expenditures
Speech	Sum of speech therapy expenditures
Inpatient	Sum of inpatient expenditures
ED	Sum of ED expenditures
Prescriptions	Sum of outpatient prescription expenditures
OOP	Sum of OOP expenditures
MHR	
Total	Sum of all MHR expenditures
Outpatient	Sum of MHR outpatient office expenditures
BM	Sum of behavioral modification expenditures
Inpatient	Sum of MHR inpatient expenditures
ED	Sum of MHR ED expenditures
Prescriptions	Sum of psychotropic prescription expenditures
OOP	Sum of MHR OOP expenditures

BM=Behavioral modification; ED=Emergency department; MHR=Mental health-related; OOP=Out-of-pocket; OT/PT=Occupational or physical therapy

2.5.2 Independent variables

Independent variables are outlined separately for objective 1 (manuscript 1) and objectives 2-5 (manuscripts 2 and 3). The independent variables were grouped into five domains: demographic characteristics, economic characteristics, geographic characteristics, health system-related characteristics, and socioeconomic characteristics. All independent variables extracted from the P+ database were considered baseline

measures generated from claims and enrollment data from the pre-index period. Socioeconomic characteristics used in objective 1 were obtained from the ACS 5-year summary file from 2013 to 2017.

2.5.2.1 Objective 1 independent variables

Operational definitions of all independent variables used in objective 1 are included in **Table 2.6**. Geographic, socioeconomic, and health system characteristics were incorporated into this analysis to explain variation in treated prevalence rates across ZIP3 regions. Fully insured plan density was obtained from P+ enrollment tables, and pediatrician and psychologist densities were selected from P+ claims tables. With the exception of urbanicity, all socioeconomic characteristics were extracted from the U.S. Census Bureau's 2003-2017 American Community Survey 5-Year Estimates published through American FactFinder.[159] Metro status is published with data from the decennial census, so 2010 data were used to define urbanicity.

Table 2.6: Operational definitions of independent variables for objective 1

Variable	Variable type Operational definition
Geographic characteristics	
U.S. Census Region	Categorical E=Northeast (ref) S=South MW=Midwest W=West O=Unknown
State	Categorical State of origin for each ZIP3 region
ZIP3 region	Categorical First 3 digits of enrollee's zip code
Health system characteristics	
Fully insured plan density	Continuous Proportion of commercially insured patients 3 to ≤18 years who are enrolled in a fully insured health plan
Pediatrician density	Continuous Number of pediatricians per 1,000 patients 3 to ≤18 years
Psychologist density	Continuous Number of clinical psychologists per 1,000 patients 3 to ≤18 years

ACS=American Community Survey; ZIP3=3-digit zip code

* Socioeconomic characteristics derived from American Community Survey estimates published by the U.S. Census Bureau; all other variables were generated using the P+ database. ACS source table numbers are provided for each characteristic.

Table 2.6: Operational definitions of independent variables for objective 1 (continued)

Variable	Variable type Operational definition
Socioeconomic characteristics (ACS table number)*	
Median family income level (DP03)	Continuous Median family income in 2017 dollars
Single-parent family density (DP02)	Proportion Number of single-parent families/total number of families
Private school enrollment density (S1401)	Proportion Number of children 3 years and older enrolled in private school/number of children 3 years and older enrolled in public or private school
Poverty status density (DP03)	Proportion Proportion of households with income below the 2017 federal poverty line
Percent white (DP02)	Proportion Proportion of residents who are white
Urbanicity (HCT1 [2010])[171]	Proportion Proportion of total population that belongs to an urban area or urban cluster, as defined by the 2010 U.S. Census[172]

ACS=American Community Survey; ZIP3=3-digit zip code

* Socioeconomic characteristics derived from American Community Survey estimates published by the U.S. Census Bureau; all other variables were generated using the P+ database. ACS source table numbers are provided for each characteristic.

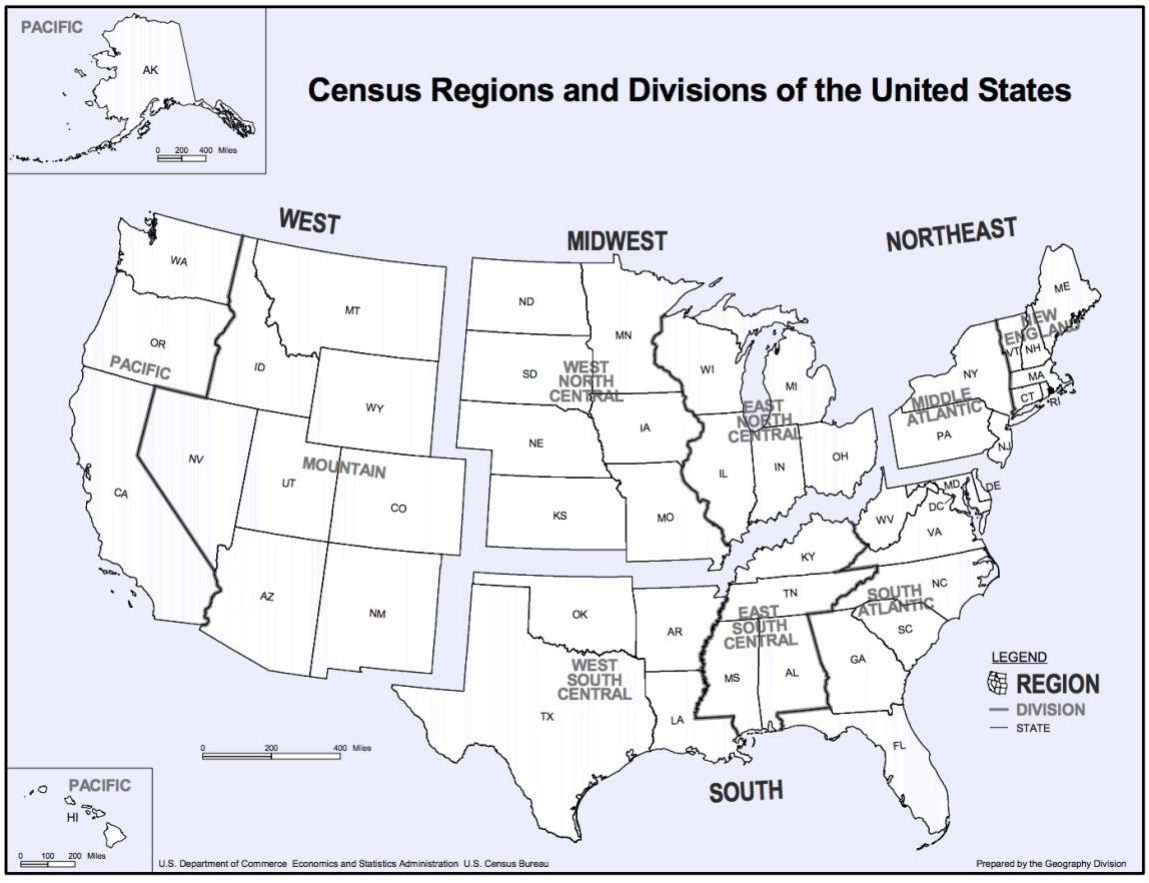
2.5.2.1.1 Geographic characteristics

Geographic characteristics include ZIP3 region, state, and U.S. census region, and were obtained from enrollment tables in the P+ database. Geographic region was defined consistently with the 2010 U.S. Census Bureau, and states were included in one of 5 regions: Northeast, South, Midwest, West, and other (**Figure 2.3**). All 50 states (including Alaska and Hawaii) were included in the analysis, as well as the District of Columbia.

ZIP3 region information were defined using 2010 definitions for Zip Code Tabulation Areas (ZCTAs).[173] The U.S. Census Bureau considers ZCTAs as generalized

areal representations of United States Postal Service (USPS) zip codes. Although zip code level data was published at the ZIP3 and ZIP5 levels before 2010, data are now published only at the more-granular 5-digit level (ZIP5). This analysis was conducted at the ZIP3 level because the ZIP3 region is the lowest geo-granular level available in the P+ database, and therefore, the lowest geographic level possible for analyses. Therefore, ACS estimates for socioeconomic characteristics were aggregated from ZIP5 to ZIP3 level using guidelines for derived estimates published by the U.S. Census Bureau. ZCTAs from all 50 states were incorporated into the analysis.[174]

Figure 2.3 U.S. census regions. Adapted from *census.gov*[175]



2.5.2.1.2 Health system characteristics

Health system characteristics included fully insured plan density, pediatrician density, and psychologist density, and were obtained from the P+ database. All health system characteristics were expressed as proportions.

2.5.2.1.3 Socioeconomic characteristics

Socioeconomic characteristics, chosen based on previous literature in Medicaid populations, included median family income, single-parent family density, private school enrollment density, poverty status density, percent white, and urbanicity.[52] Median income was considered an integer, and all other socioeconomic characteristics are derived as proportions (**Table 2.6**).

2.5.2.2 Objectives 2-5 independent variables

Operational definitions of all independent variables used in objectives 2-5 are shown in **Table 2.7.**

2.5.2.2.1 Group membership

In objectives 2-5, groups were stratified based on ASD diagnosis (present or absent), as these objectives are primarily concerned with estimating differences between ASD and non-ASD groups in patient characteristics (Objective 2), psychiatric comorbidity prevalence (Objective 3), utilization (Objective 4), and expenditures (Objective 5).

2.5.2.2.2 Demographic characteristics

Demographic characteristics included age-at-index, gender, state, and U.S. Census Region. The P+ database does not include date-of-birth granularity deeper than the year, so this analysis assumed that all children are born on the 183rd day (midpoint) of each

patient's birth year. This date was subtracted from the index date to determine age-at-index. Gender was obtained from enrollment data in the P+ database.

2.5.2.2.3 Geographic characteristics

Geographic information was obtained from enrollment data in the P+ database. U.S. Census regions are consistent with 2010 U.S. Census Bureau definitions (**Figure 2.3**).

2.5.2.2.4 Clinical characteristics

To address potential group imbalances driven by comorbid medical conditions, the second version of the pediatric complex chronic conditions (CCC) classification system was used to identify chronic medical conditions for each patient.[176] CCC v2 is an algorithm developed by the University of Pennsylvania and The Children's Hospital of Philadelphia. Its purpose is to identify children with any of 12 chronic conditions associated with increased specialty pediatric care utilization and hospitalizations. Three approaches to covariate definition were considered: dummy coding each condition and introducing each as a fixed effect, dichotomizing all conditions to single flag (presence or absence of any condition), and collapsing the patient-level sum of all conditions to a three-level ordinal score (0, 1, and 2 or greater). A three-level ordinal score was chosen based on previous literature,[177,178] as well as empirically comparing model fit statistics from each of the three approaches.

2.5.2.2.5 Health system characteristics

Health system characteristics included health plan type, health product type, pediatrician density, and psychologist density. Health plan type was categorized as self- or fully insured. Definitions of plan type are listed in **Section 1.4.2**. Health product type was categorized as a health maintenance organization (HMO), preferred provider organization

(PPO), or other. Pediatrician density is represented by a count of the number of pediatricians per 1,000 children in each ZIP3 region. Psychologist density is represented by a count of the number of clinical psychologists per 1,000 children in the ZIP3 region.

Table 2.7: Operational definitions of independent variables for objectives 3-5

Variable	Variable type Operational definition
Group membership	
Group membership	Categorical 0=non-ASD (ref) 1=ASD
Demographic characteristics	
Age-at-index	Continuous Calculated by subtracting the 183rd day (mid-point) of each patient's birth-year from the index date (rounded to the nearest year)
Gender	Categorical 0=Male (ref) 1=Female
Geographic characteristics	
State	Categorical Each of the 50 U.S. states were included as a fixed effect in the analyses.
U.S. Census Region	Categorical E=Northeast (ref) S=South MW=Midwest W=West O=Unknown

ASD=Autism spectrum disorder

Table 2.7: Operational definitions of independent variables for objectives 3-5 (continued)

Variable	Variable type Operational definition
Clinical characteristics	
CCC count	Count 0, 1, and ≥ 2
Health system characteristics	
Health payer type	Categorical C=Fully insured (ref) S=Self-insured
Health plan product type	Categorical H=HMO (ref) P=PPO O=Other
Pediatrician density	Continuous Number of pediatricians per 1,000 patients 3 to ≤18 years in patient's ZIP3 region
Psychologist density	Continuous Number of clinical psychologists per 1,000 patients 3 to ≤18 years in patient's ZIP3 region

ASD=Autism spectrum disorder; HMO=Health maintenance organization; PPO=Preferred provider organization; ZIP3=3-digit zip codes

2.6 Statistical analyses

A series of preliminary analyses were conducted to confirm and gain insight into the underlying distributions of the dependent and independent variables. Distributions of all variables were inspected visually and numerically. For continuous variables, any values greater than 3 standard deviations from the mean were flagged as outliers. Sensitivity analyses were conducted to evaluate the impact of outlier values on tested hypotheses.

All variables were inspected for missingness after sample selection. Missingness of identified variables were correlated with all other analysis variables to determine the presence of a missingness mechanism. If missingness is at least moderately correlated with any other analysis variables (Pearson's $\rho > \pm 0.5$)[179], missing data techniques (e.g., maximum likelihood estimation, multiple imputation) were considered along with variable exclusion.[180,181]

All independent variables were evaluated through descriptive statistics. Categorical variables were summarized with frequencies and percentages, and continuous variables were summarized with means, standard deviations, medians, and interquartile ranges. All statistical analyses were conducted using R (Version 3.5.1) and the R Studio environment (Version 1.1.463).[182] Patient characteristics were compared across ASD and non-ASD groups in objective 2.

Dependent variables in objectives 1, 3, 4, and 5 have unique properties that violate assumptions in traditional statistical analysis approaches for continuous and categorical data such as ordinary least squares (OLS) regression and Chi-square techniques. Dependent variables in objectives 1 and 4 are count data represented by non-negative integers. Dependent variables in objective 3 are binary, and dependent variables in objective 5 are continuous and right-skewed.

Generalized linear models (GLMs) are extensions of standard ordinary least square (OLS) models that can accommodate a variety of distributions. Three components are incorporated into GLMs: a random component, a linear predictor, and a linearizing link function.[183] The random component of GLMs specifies a conditional distribution which the dependent variable (Y_i) is assumed to follow. Distributions considered for this analysis are listed in **Table 2.8**. The assumptions of GLMs are as follows[184,185]:

1. the observations are independent;
2. the dependent variable Y_i follows a distribution from the natural exponential family; and
3. the specified link function has a linear relationship with the specified set of covariates.

A summary of study objectives, hypotheses, variables, measures, and statistical analyses is presented in **Table 2.9**.

2.6.1 Covariate selection

Due to the observational nature of this study, covariates were included in regression models to adjust for potential imbalances on observed variables. The ultimate exclusion of poverty status, and pediatrician and psychologist densities as covariates is discussed in the results section (**Section 3.1.2.1**).

For each hypothesis addressed in objective 1, the remaining independent variables were included as covariates for adjusted parameter estimates. Covariates included are geographic region, fully insured plan density, median family income, poverty status density, single-parent family density, private school enrollment density, percent white, and urbanicity.

Objective 2 includes only unadjusted univariate and bivariate statistics; therefore, covariates were not included.

Covariates included in objective 3 are age-at-index, U.S. state, health payer type, and health plan product type.

Covariates included in objectives 4 and 5 are age-at-index, health payer type, and health plan product type. U.S. state was used to generate cluster-robust standard errors (CRSEs) in place of being included as a fixed effect.

2.6.2 Objectives 1 and 4: Treated prevalence rates and healthcare utilization

Dependent variables in objectives 1 and 4 were obtained through count data represented by non-negative integers, and models were fit using GLMs based on distributions in the exponential family. The Poisson distribution can accommodate count data, but necessitates a relatively strong assumption that the distribution's variance is equal to its mean. A negative binomial model extension of the Poisson model was used because it relaxes the Poisson distribution's variance assumption and yields better coverage probabilities for confidence intervals.[183,184] All dependent variables in objectives 1 and 4 were assessed for Poisson appropriateness, and all models were fit by a negative binomial instead of a Poisson GLM procedure.

Many dependent variables in this analysis are expected to have particularly low counts based on previous literature (e.g., inpatient and ED visits).[59,149] Vuong tests were conducted to assess the appropriateness of hurdle models.[186,187] Dichotomized utilization variables were analyzed using binomial (logistic) regression models to report relative likelihoods across covariates.[188] GLM assumptions were assessed prior to final analysis implementation.

Table 2.8: Exponential families considered for model specification

Family	Canonical link	Range of Y_i	$V(Y_i\|\eta_i)$
Objectives 1 and 4			
Poisson	$\log \mu$	0, 1, 2, …	μ_i
Negative binomial	$\text{Log}[\mu/k(1+\frac{\mu}{k})]$	0, 1, 2, …	$\mu r/(1-\mu)^2$
Objective 3			
Binomial	$\log \frac{\mu}{1-\mu}$	$(0,1,\ldots n)/(n)$	$n\mu(1-\mu)$
Objective 5			
Gaussian	μ_i	(-∞ ,+∞)	ϕ
Gamma	$-1/\mu$	(0,∞)	$\phi\mu_i^2$
Inverse-Gaussian	$-1/\mu^2$	(0,∞)	$\phi\mu_i^3$

Adapted from: Generalized Linear Models. In Fox J., Applied Regression Analysis and Generalized Linear Models. 2nd ed. Chapter 15. Thousand Oaks, CA: Sage Publications, 2008[183]

2.6.2.1 Special considerations for objective 1

Given objective 1's ZIP3 level of analysis, the statistical model needs to address variable population sizes in ZIP3 regions, and potential clustering of effects at the state level. The model includes an offset term of the total number of children at or below 18 years of age in each ZIP3 region, which functions as a denominator for the prevalence calculation.[52] To generate confidence intervals robust to potential violations of independence associated with state-level clustering of observations, cluster-robust standard errors (CRSE) were incorporated into the model.[189] There are many techniques to control for state-level clustering, which include incorporating state-level fixed effects or fitting multilevel/mixed models. CRSEs were utilized over multilevel and mixed modeling due to a lack of substantive interest in explaining variation in prevalence at the state level.[190] States were not included as fixed effects in objective 1 to preserve power.[189]

2.6.3 Objective 2 Comparing patient characteristics between groups

Baseline demographic, economic, and health system characteristics were compared between treatment and control groups in objective 2. Psychiatric conditions in objective 3 were also descriptively compared between groups. Independent samples t-tests were used to analyze continuous variables following a normal distribution. Wilcoxon 2-sample rank-sum tests were used for continuous variables violating normality. Categorical variables were analyzed using Pearson's Chi-square tests when expected frequency assumptions were met; Fisher's exact tests were used in cases where more than 20% of cells have expected frequencies <5 or any single cell has an expected frequency <1.[184]

2.6.4 Objective 3: Psychiatric condition prevalence

All dependent variables in objective 3 are binary. Therefore, logistic regressions were used to test all hypotheses in objective 3. In addition to the inclusion of the main effects of group membership and age, a quadratic term for age was included to control for non-linear relationships. An age-by-group membership interaction term was introduced to test for non-additive effects of age and ASD diagnosis, which served as the term of interest for objective 3 hypotheses.

2.6.5 Objective 5: Healthcare expenditures

All dependent variables addressed in objective 5 are healthcare expenditures. Like healthcare utilization data, expenditure data are typically right skewed and represented by non-negative values. However, expenditure data differ from utilization data in that they are continuous and allow non-integers (dollars and cents). The continuous nature of expenditure data may suggest the use of OLS regression with a log-transformed dependent variable. However, OLS techniques assume that the variance of the dependent variable is homogenous across all covariates, which can lead to falsely-narrow confidence intervals

and inflated type one error rates when this assumption is not met.[191] Literature suggests that appropriately specified GLMs may model the error structure of expenditure data more precisely compared to log-transformed OLS models, as GLMs allow specification of model error structure, which is not feasible in OLS.[192,193] The selection of a link function for expenditure variables was guided by comparing model fit statistics (e.g., Pregibon Link Test, Hosmer-Lemeshow Test, and Pearson's correlation) and visual inspection of variance and mean expenditure scatterplots.[194,195]

A summary of study objectives, hypotheses, variables, measures, and statistical analyses is presented in **Table 2.9**.

Table 2.9: Summary of study objectives, hypotheses, variables, measures, and statistical analyses

Objectives/Hypotheses	Dependent variable	Measurement level	Independent variable	Measurement level	Statistical analysis
Objective 1: *To quantify and explain geographic variation in treated prevalence of ASD in commercially-enrolled children*					
1a: To determine the overall treated prevalence of ASD in children 18 or less enrolled in commercial healthcare plans.	Proportion of commercially insured patients 3 to ≤18 years who are diagnosed with ASD	Proportion	N/A	N/A	Descriptive
1b: To quantify treated prevalence of ASD in children 18 or less enrolled in commercial healthcare plans within each ZIP3 region.	Proportion of commercially insured patients 3 to ≤18 years who are diagnosed with ASD in each ZIP3 region	Proportion	N/A	N/A	Descriptive
1c: To explain geographic variation in the treated prevalence in ASD as a function of geographic, health system, and socioeconomic characteristics.					
$H_0(1c)_1$: There is no significant difference in the treated prevalence of ASD with respect to **geographic region**, after controlling for covariates*.	Treated prevalence (number of children diagnosed with ASD)	Count	**U.S. Census Region** (E, S, MW, W, O)	Categorical	Poisson or negative binomial GLM
$H_0(1c)_2$: There is no significant difference in the treated prevalence of ASD with respect to **fully insured plan density**, after controlling for covariates*.	Treated prevalence (number of children diagnosed with ASD)	Count	**Fully insured plan density** Proportion of children in a FI health plan	Continuous	

Table 2.9: Summary of study objectives, hypotheses, variables, measures, and statistical analyses (continued)

H_0(1c)$_3$: There is no significant difference in the treated prevalence of ASD with respect to **pediatrician density**, after controlling for covariates*.	Treated prevalence (number of children diagnosed with ASD)	Count	**Pediatrician density** Number of pediatricians per 1,000 children	Continuous	Poisson or negative binomial GLM (continued)
H_0(1c)$_4$: There is no significant difference in the treated prevalence of ASD with respect to **psychologist density**, after controlling for covariates*.	Treated prevalence (number of children diagnosed with ASD)	Count	**Psychologist density** Number of clinical psychologists per 1,000 children	Continuous	
H_0(1c)$_5$: There is no significant difference in the treated prevalence of ASD with respect to **median family income**, after controlling for covariates*.	Treated prevalence (number of children diagnosed with ASD)	Count	**Median family income** in 2017 dollars	Continuous	
H_0(1c)$_6$: There is no significant difference in the treated prevalence of ASD with respect to **single-parent family density**, after controlling for covariates*.	Treated prevalence (number of children diagnosed with ASD)	Count	**Single-parent family density** Number of single-parent families/number of families	Continuous	

Table 2.9: Summary of study objectives, hypotheses, variables, measures, and statistical analyses (continued)

$H_0(1c)_7$: There is no significant difference in the treated prevalence of ASD with respect to **private school enrollment density**, after controlling for covariates*.	Treated prevalence (number of children diagnosed with ASD)	Count	**Private school enrollment density** Number of children > 3 years enrolled in private school/number of children > 3 years enrolled in public or private school	Continuous	
$H_0(1c)_8$: There is no significant difference in the treated prevalence of ASD with respect to **poverty status density**, after controlling for covariates*.	Treated prevalence (number of children diagnosed with ASD)	Count	**Poverty status density** Proportion of households with income below the 2017 federal poverty line	Continuous	Poisson or negative binomial GLM (continued)
$H_0(1c)_9$: There is no significant difference in the treated prevalence of ASD with respect to **percent white**, after controlling for covariates*.	Treated prevalence (number of children diagnosed with ASD)	Count	**Percent white** Proportion of residents who are white	Continuous	
$H_0(1c)_{10}$: There is no significant difference in the treated prevalence of ASD with respect to **urbanicity**, after controlling for covariates*.	Treated prevalence (number of children diagnosed with ASD)	Count	**Urbanicity** Proportion of households belonging to an urban area or cluster	Continuous	

Table 2.9: Summary of study objectives, hypotheses, variables, measures, and statistical analyses (continued)

Objective 2: *To describe and compare study characteristics of patients diagnosed with ASD to those without ASD*					
To describe and compare baseline socio-demographic and health system characteristics, and baseline expenditures of patients diagnosed with ASD to those without ASD.	Psychiatric conditions, age-at-index, gender, state, U.S. Census Region, health payer type, health plan product type, pediatrician density, psychologist density, and a numeric measure of pre-index complex chronic conditions	Continuous and categorical	**Treatment groups** (ASD vs. Non-ASD)	Categorical	Chi-square or Fisher's Exact for categorical variables, and t-tests or Mann-Whitney U tests for continuous variables
Objective 3: *To quantify and compare age-specific treated prevalence of psychiatric conditions between ASD and non-ASD groups.*					
$H_0(3)_1$: There is no significant difference in the age-related **likelihood of adjustment disorder** between ASD and non-ASD groups, after controlling for covariates†.	Presence or absence of **adjustment disorder**	Categorical	**Treatment groups** (ASD vs. Non-ASD)	Categorical	Binomial GLM (logistic regression)
$H_0(3)_2$: There is no significant difference in the age-related **likelihood of anxiety disorder** between ASD and non-ASD groups, after controlling for covariates†.	Presence or absence of **anxiety disorder**	Categorical	**Treatment groups** (ASD vs. Non-ASD)	Categorical	Binomial GLM (logistic regression)
$H_0(3)_3$: There is no significant difference in the in the age-related **likelihood attention-deficit conduct or disruptive behavior disorder** between ASD and non-ASD groups, after controlling for covariates†.	Presence or absence of **attention-deficit conduct or disruptive behavior disorder**	Categorical	**Treatment groups** (ASD vs. Non-ASD)	Categorical	Binomial GLM (logistic regression)

Table 2.9: Summary of study objectives, hypotheses, variables, measures, and statistical analyses (continued)

$H_0(3)_4$: There is no significant difference in the in the age-related **likelihood of mood disorder** between ASD and non-ASD groups, after controlling for covariates†.	Presence or absence of **mood disorder**	Categorical	**Treatment groups** (ASD vs. Non-ASD)	Categorical	Binomial GLM (logistic regression)
$H_0(3)_5$: There is no significant difference in the in the age-related **likelihood of personality disorder** between ASD and non-ASD groups, after controlling for covariates†.	Presence or absence of **personality disorder**	Categorical	**Treatment groups** (ASD vs. Non-ASD)	Categorical	Binomial GLM (logistic regression)
$H_0(3)_6$: There is no significant difference in the in the age-related **likelihood of schizophrenia or other psychotic disorder** between ASD and non-ASD groups, after controlling for covariates†.	Presence or absence of **schizophrenia or other psychotic disorder**	Categorical	**Treatment groups** (ASD vs. Non-ASD)	Categorical	Binomial GLM (logistic regression)
$H_0(3)_7$: There is no significant difference in the in the age-related **likelihood of alcohol or substance-related disorder** between ASD and non-ASD groups, after controlling for covariates†.	Presence or absence of **alcohol or substance-related disorder**	Categorical	**Treatment groups** (ASD vs. Non-ASD)	Categorical	Binomial GLM (logistic regression)

Table 2.9: Summary of study objectives, hypotheses, variables, measures, and statistical analyses (continued)

Objective 4: *To quantify and compare healthcare utilization between children diagnosed with ASD to those without ASD*					
4a: To quantify and compare healthcare utilization for all-cause outpatient office, inpatient, and ED visits, and psychotropic medications between ASD and non-ASD groups. Within outpatient office visits, this objective also quantifies and compares OT/PT and speech therapy visits.					
H_0(4a)$_1$: There is no significant difference in number of **all-cause outpatient office visits** between ASD and non-ASD groups, after controlling for covariates†.	**All-cause number of outpatient office visits**	Count	**Treatment groups** (ASD vs. Non-ASD)	Categorical	Poisson or negative binomial GLM
H_0(4a)$_2$: There is no significant difference in number of **all-cause OT/PT visits** between ASD and non-ASD groups, after controlling for covariates†.	**All-cause number of OT/PT visits**	Count	**Treatment groups** (ASD vs. Non-ASD)	Categorical	Poisson or negative binomial GLM
H_0(4a)$_3$: There is no significant difference in number of **all-cause speech therapy visits** between ASD and non-ASD groups, after controlling for covariates†.	**All-cause number of speech therapy visits**	Count	**Treatment groups** (ASD vs. Non-ASD)	Categorical	Poisson or negative binomial GLM

Table 2.9: Summary of study objectives, hypotheses, variables, measures, and statistical analyses (continued)

H_0(4a)$_4$: There is no significant difference in number of **all-cause inpatient visits** between ASD and non-ASD groups, after controlling for covariates†.	**All-cause number of inpatient visits**	Count	**Treatment groups** (ASD vs. Non-ASD)	Categorical	Poisson or negative binomial GLM
H_0(4a)$_5$: There is no significant difference in number of **all-cause ED visits** between ASD and non-ASD groups, after controlling for covariates†.	**All-cause number of ED visits**	Count	**Treatment groups** (ASD vs. Non-ASD)	Categorical	Poisson or negative binomial GLM
H_0(4a)$_6$: There is no significant difference in number of **all-cause outpatient prescriptions** between ASD and non-ASD groups†.	**All-cause number of outpatient prescriptions**	Count	**Treatment groups** (ASD vs. Non-ASD)	Categorical	Poisson or negative binomial GLM
4b: To quantify and compare healthcare utilization for MHR outpatient office, inpatient, and ED visits, and psychotropic prescriptions between ASD and non-ASD groups. Within MHR office visits, this objective also quantifies and compares Behavioral modification visits between ASD and non-ASD groups.					
H_0(4b)$_1$: There is no significant difference in the number of **MHR outpatient office visits** between ASD and non-ASD groups, after controlling for covariates†.	**Number of MHR outpatient visits**	Count	**Treatment groups** (ASD vs. Non-ASD)	Categorical	Poisson or negative binomial GLM

Table 2.9: Summary of study objectives, hypotheses, variables, measures, and statistical analyses (continued)

H_0(4b)$_2$: There is no significant difference in the number of **behavioral modification visits** between ASD and non-ASD groups, after controlling for covariates†.	**Number of behavioral modification visits**	Count	**Treatment groups** (ASD vs. Non-ASD)	Categorical	Poisson or negative binomial GLM
H_0(4b)$_3$: There is no significant difference in the **MHR inpatient visits** between ASD and non-ASD groups, after controlling for covariates†.	**Number of MHR inpatient visits**	Count	**Treatment groups** (ASD vs. Non-ASD)	Categorical	Poisson or negative binomial GLM
H_0(4b)$_4$: There is no significant difference in the number of **MHR ED visits** between ASD and non-ASD groups, after controlling for covariates†.	**Number of MHR ED visits**	Count	**Treatment groups** (ASD vs. Non-ASD)	Categorical	Poisson or negative binomial GLM
H_0(4b)$_5$: There is no significant difference in the number of **outpatient psychotropic prescriptions** between ASD and non-ASD groups†.	**Number of outpatient psychotropic prescriptions**	Count	**Treatment groups** (ASD vs. Non-ASD)	Categorical	Poisson or negative binomial GLM

Table 2.9: Summary of study objectives, hypotheses, variables, measures, and statistical analyses (continued)

Objective 5: *To quantify and compare healthcare expenditures between children diagnosed with ASD to those without ASD*					
5a: To quantify and compare all-cause expenditures both overall, and for outpatient visits, inpatient visits, ED visits, outpatient prescriptions, and OOP between ASD and non-ASD groups. Within outpatient office expenditures, this objective also quantifies and compares OT/PT and speech therapy expenditures between ASD and non-ASD groups.					
$H_0(5a)_1$: There is no significant difference in **all-cause expenditures** between ASD and non-ASD groups, after controlling for covariates†.	**All-cause expenditures**	Continuous	**Treatment groups** (ASD vs. Non-ASD)	Categorical	Gaussian, Gamma, or Inverse-Gaussian GLM
$H_0(5a)_2$: There is no significant difference in **all-cause outpatient office expenditures** between ASD and non-ASD groups, after controlling for covariates†.	**All-cause outpatient office expenditures**	Continuous	**Treatment groups** (ASD vs. Non-ASD)	Categorical	Gaussian, Gamma, or Inverse-Gaussian GLM
$H_0(5a)_3$: There is no significant difference in **all-cause OT/PT expenditures** between ASD and non-ASD groups, after controlling for covariates†.	**All-cause OT/PT expenditures**	Continuous	**Treatment groups** (ASD vs. Non-ASD)	Categorical	Gaussian, Gamma, or Inverse-Gaussian GLM

Table 2.9: Summary of study objectives, hypotheses, variables, measures, and statistical analyses (continued)

H_0(5a)$_4$: There is no significant difference in **all-cause speech therapy expenditures** between ASD and non-ASD groups, after controlling for covariates†.	**All-cause speech therapy expenditures**	Continuous	**Treatment groups** (ASD vs. Non-ASD)	Categorical	Gaussian, Gamma, or Inverse-Gaussian GLM
H_0(5a)$_5$: There is no significant difference in **all-cause inpatient expenditures** between ASD and non-ASD groups, after controlling for covariates.†.	**All-cause inpatient expenditures**	Continuous	**Treatment groups** (ASD vs. Non-ASD)	Categorical	Gaussian, Gamma, or Inverse-Gaussian GLM
H_0(5a)$_6$: There is no significant difference in **all-cause ED expenditures** between ASD and non-ASD groups, after controlling for covariates†.	**All-cause ED expenditures**	Continuous	**Treatment groups** (ASD vs. Non-ASD)	Categorical	Gaussian, Gamma, or Inverse-Gaussian GLM
H_0(5a)$_7$: There is no significant difference in **all-cause prescription expenditures** between ASD and non-ASD groups†.	**All-cause prescription expenditures**	Continuous	**Treatment groups** (ASD vs. Non-ASD)	Categorical	Gaussian, Gamma, or Inverse-Gaussian GLM
H_0(5a)$_8$: There is no significant difference in all-cause **OOP expenditures** between ASD and non-ASD groups†.	**All-cause OOP expenditures**	Continuous	**Treatment groups** (ASD vs Non-ASD)	Categorical	Gaussian, Gamma, or Inverse-Gaussian GLM

Table 2.9: Summary of study objectives, hypotheses, variables, measures, and statistical analyses (continued)

5b: To quantify and compare MHR expenditures both overall, and for outpatient, inpatient, ED visits, outpatient prescription, and OOP between ASD and non-ASD groups. Within MHR office expenditures, this objective also quantifies and compares OT/PT and speech therapy expenditures between ASD and non-ASD groups.					
H_0(5b)$_1$: There is no significant difference in **MHR expenditures** between ASD and non-ASD groups, after controlling for covariates†.	**MHR expenditures**	Continuous	**Treatment groups** (ASD vs. Non-ASD)	Categorical	Gaussian, Gamma, or Inverse-Gaussian GLM
H_0(5b)$_2$: There is no significant difference in **MHR outpatient office expenditures** between ASD and non-ASD groups, after controlling for covariates†.	**MHR outpatient office expenditures**	Continuous	**Treatment groups** (ASD vs. Non-ASD)	Categorical	Gaussian, Gamma, or Inverse-Gaussian GLM
H_0(5b)$_3$: There is no significant difference in **behavioral modification expenditures** between ASD and non-ASD groups, after controlling for covariates†.	**Behavioral modification expenditures**	Continuous	**Treatment groups** (ASD vs. Non-ASD)	Categorical	Gaussian, Gamma, or Inverse-Gaussian GLM
H_0(5b)$_4$: There is no significant difference in **MHR inpatient expenditures** between ASD and non-ASD groups, after controlling for covariates†.	**MHR inpatient expenditures**	Continuous	**Treatment groups** (ASD vs. Non-ASD)	Categorical	Gaussian, Gamma, or Inverse-Gaussian GLM

Table 2.9: Summary of study objectives, hypotheses, variables, measures, and statistical analyses (continued)

H_0(5b)$_5$: There is no significant difference in **MHR ED expenditures** between ASD and non-ASD groups, after controlling for covariates†.	**MHR ED expenditures**	Continuous	**Treatment groups** (ASD vs. Non-ASD)	Categorical	Gaussian, Gamma, or Inverse-Gaussian GLM
H_0(5b)$_6$: There is no significant difference in **MHR prescription expenditures** between ASD and non-ASD groups†.	**MHR prescription expenditures**	Continuous	**Treatment groups** (ASD vs. Non-ASD)	Categorical	Gaussian, Gamma, or Inverse-Gaussian GLM
H_0(5b)$_7$: There is no significant difference in **MHR OOP expenditures** between ASD and non-ASD groups†.	**MHR OOP expenditures**	Continuous	**Treatment groups** (ASD vs. Non-ASD)	Categorical	Gaussian, Gamma, or Inverse-Gaussian GLM

ASD=Autism Spectrum Disorder; BM=Behavioral modification; E=East; ED=Emergency department; FI=Fully insured; MHR=Mental health-related; MW=Midwest; O=Other; OOP=Out-of-pocket; OT/PT=Occupational or physical therapy; S=South; W=West

* Covariates for objective 1 include geographic region, fully insured plan density, median family income, single-parent family density, private school enrollment density, pediatrician density, psychologist density, poverty status density, percent white, urbanicity

† Covariates for objectives 3-5 include age-at-index, gender, U.S. Census Region, health payer type, health plan product type, and a numeric measure of pre-index complex chronic conditions

2.7 Power analyses

GLMs were utilized to address objectives 1, 3, 4, and 5. Power analyses were conducted to inform sample sizes necessary to achieve adequate power given effect sizes identified from the literature or considered reasonable. All power analyses were conducted using G*Power (Version 3.1.9.3) software.[196]

2.7.1 Power analysis: Objective 1

Given that 894 ZIP3 regions were defined in the 2010 U.S. Census, the power analysis to address objective 1 was conducted assuming a maximum of 894 observations. A conservative base prevalence rate of 1 percent was obtained from the literature (**Table 1.4)** and a two-tailed alpha was specified. A sample size of 732 was calculated based on the following parameters: base rate=0.01, two-tailed α=0.05, binomial-distributed X_1 with 50:50 balance, e^{β_1}=1.125, and R-squared=0.2. Based on this power analysis, the expected sample size (894 ZIP3 regions) is more than adequate to achieve 80% power given the input parameters (**Table 2.10**).

Table 2.10: Sample size estimates for Poisson regression (Objective 1)

Parameters				
Effect size	1.050	1.100	1.125	1.150
R-squared*	0.1	0.1	0.1	0.1
Required ASD patients	**3,919**	**1,004**	**650**	**457**
Effect size	1.050	1.100	1.125	1.150
R-squared*	0.2	0.2	0.2	0.2
Required ASD patients	**4,409**	**1,130**	**732**	**514**
Effect size	1.050	1.100	1.125	1.150
R-squared*	0.3	0.3	0.3	0.3
Required ASD patients	**5,039**	**1,291**	**836**	**588**

Base rate=0.01; two-tailed α=0.05; binomial-distributed X_1; e^{β_1}=0.01; power=0.80; mean exposure 365 days

* Represents the value obtained when X_1 is regressed over all other covariates in the Poisson model

2.7.2 Power analysis: Objective 3

A power analysis was conducted for objective 3 assuming a binomial-distributed outcome. A minimum total sample size of 6,381 ASD patients was calculated based on the following: power=0.80, two-tailed α=0.05, odds ratio=1.25, R-square=0.3, probability $(Y=1|X=1)H_0$=0.05, and a binomial independent variable distribution with 33% of patients diagnosed with ASD.[59,149] **Table 2.11** provides the range of estimated sample sizes needed to achieve 80% power based on a binomial-distributed GLM.

Table 2.11: Sample size estimates for logistic regression (Objective 3)

Objective 3: ASD vs. non-ASD (1:2 patient to control ratio)				
Parameters				
Odds Ratio	1.25	1.50	2.00	4.00
R-squared	0.10	0.10	0.10	0.10
Total sample (ASD pts)	**14,889 (4,963)**	**4,133 (1,378)**	**1,245 (415)**	**241 (81)**
Odds Ratio	1.25	1.50	2.00	4.00
R-squared	0.20	0.20	0.20	0.20
Total sample (ASD pts)	**16,750 (5,584)**	**4,650 (1,550)**	**1,401 (467)**	**271 (91)**
Odds Ratio	1.25	1.50	2.00	4.00
R-squared	0.30	0.30	0.30	0.30
Total sample (ASD pts)	**19,143 (6,381)**	**5,314 (1,772)**	**1,601 (534)**	**310 (104)**

* Probability (Y=1|X=1) H_0=0.05; two-tailed α=0.05; power=0.80; binomial-distributed X_1

2.7.3 Power analysis: Objective 4

A power analysis was conducted for objective 4 assuming a Poisson-distributed outcome. For objective 4, a minimum total sample size of 190 ASD patients was calculated based on the following: power=0.80, two-tailed α=0.05, R-squared=0.3, e^{β_1}=1.05 based on the literature[149,151], a mean exposure of 365 days, a binomial independent variable distribution with 33 percent of patients diagnosed with ASD, and a baseline health care utilization rate (e.g., hospitalizations) range of 10% to 25% based on the literature.[59,149] **Table 2.12** provides the range of estimated sample sizes needed to achieve 80% power based on a Poisson-distributed GLM.

Due to the potential for zero-inflation in some categories of healthcare utilization (e.g., inpatient visits), a power analysis was also conducted for a possible logistic regression model in case hurdle models are employed. For objective 4 (as with objective 3), a minimum total sample size of 6,381 ASD patients was calculated based on the following: power=0.80, two-tailed α=0.05, odds ratio=1.25, R-square=0.3, probability

(Y=1|X=1)H_0=0.05, and a binomial independent variable distribution with 33% of patients diagnosed with ASD.[59,149] **Table 2.13** provides the range of estimated sample sizes needed to achieve 80% power based on a binomial-distributed GLM.

Table 2.12: Sample size estimates for Poisson regression (Objective 4)

Objective 4: ASD vs. non-ASD (1:2 patient to control ratio)				
Parameters				
Base Rate	0.10	0.15	0.20	0.25
R-squared*	0.1	0.1	0.1	0.1
Total sample (ASD pts)	**442 (148)**	**295 (132)**	**221 (74)**	**177 (59)**
Base Rate	0.10	0.15	0.20	0.25
R-squared*	0.2	0.2	0.2	0.2
Total sample (ASD pts)	**497 (166)**	**332 (111)**	**249 (83)**	**199 (67)**
Base Rate	0.10	0.15	0.20	0.25
R-squared*	0.3	0.3	0.3	0.3
Total sample (ASD pts)	**568 (190)**	**379 (127)**	**284 (95)**	**228 (76)**

pts=patients;
e^{β_1}=1.05; two-tailed α=0.05; power-0.80; binomial-distributed X_1
* Represents the value obtained when X_1 is regressed over all other covariates in the Poisson model

Table 2.13: Sample size estimates for logistic regression (Objective 4)

Objective 4: ASD vs. non-ASD (1:2 patient to control ratio)				
Parameters				
Odds Ratio	1.25	1.50	2.00	2.50
R-squared	0.10	0.10	0.10	0.10
Total sample (ASD pts)	**14,889 (4,963)**	**4,133 (1,378)**	**1,245 (415)**	**651 (217)**
Odds Ratio	1.25	1.50	2.00	2.50
R-squared	0.20	0.20	0.20	0.20
Total sample (ASD pts)	**16,750 (5,884)**	**4,650 (1,550)**	**1,401 (467)**	**733 (244)**
Odds Ratio	1.25	1.50	2.00	2.50
R-squared	0.30	0.30	0.30	0.30
Total sample (ASD pts)	**19,143 (6,381)**	**5,314 (1,771)**	**1,601 (534)**	**837 (279)**

* Probability (Y=1|X=1) H_0=0.05; two-tailed α=0.05; power=0.80; binomial-distributed X_1

2.7.4 Power analysis: Objective 5

Gamma distributions were considered to address objective 5. Research shows that the sample size necessary for a Gamma distribution are not greater than the sample size required for a normal distribution at the same power level.[197] Therefore, a sample size based on multiple linear regression was calculated, and an estimated sample size of 395 patients was necessary based on the following parameters: power=0.80; two-tailed α=0.05; Cohen's small effect size, f_2=0.02; and the total number of predictors=65 (after dummy-coding categorical variables with more than 2 groups).[196,198]

CHAPTER 3: RESULTS

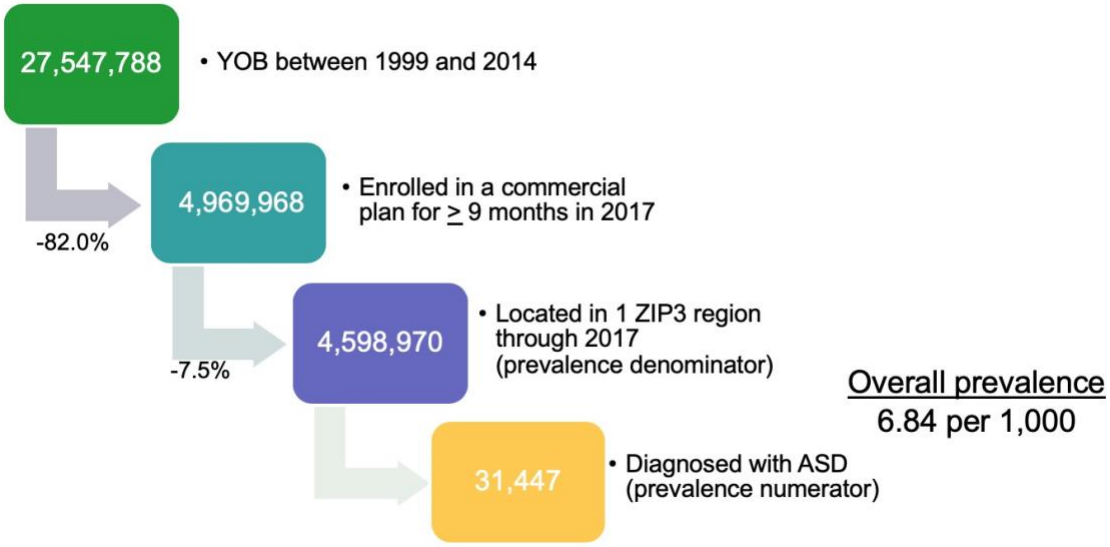
This chapter presents the study results generated to address the five study objectives and 40 hypotheses. Cohort sampling, attrition, and descriptive statistics of study characteristics are discussed separately for objective 1 and objectives 2-5, which also includes group comparisons of study characteristics between the ASD and non-ASD groups (Objectives 2-5 only). Next, model selection processes and parameter estimates are presented with interpretations. The chapter ends with a tabular summary of all hypothesis tests (**Table 3.14**).

3.1 Objective 1: To quantify and explain geographic variation in treated prevalence of ASD in commercially insured children

3.1.1 Sample selection

The initial selection contained 27,547,788 P+ enrollees with a year of birth between 1999 and 2014. Of the initial selection, 4,969,968 were enrolled in a commercial health plan for at least nine months during the year 2017. Of the enrollees, 4,598,970 enrollees were located in a single U.S. state and ZIP3 region during the year 2017 (**Figure 3.1**). A total of 861 ZIP3 regions were represented after the sampling process.

Figure 3.1 Objective 1 patient selection

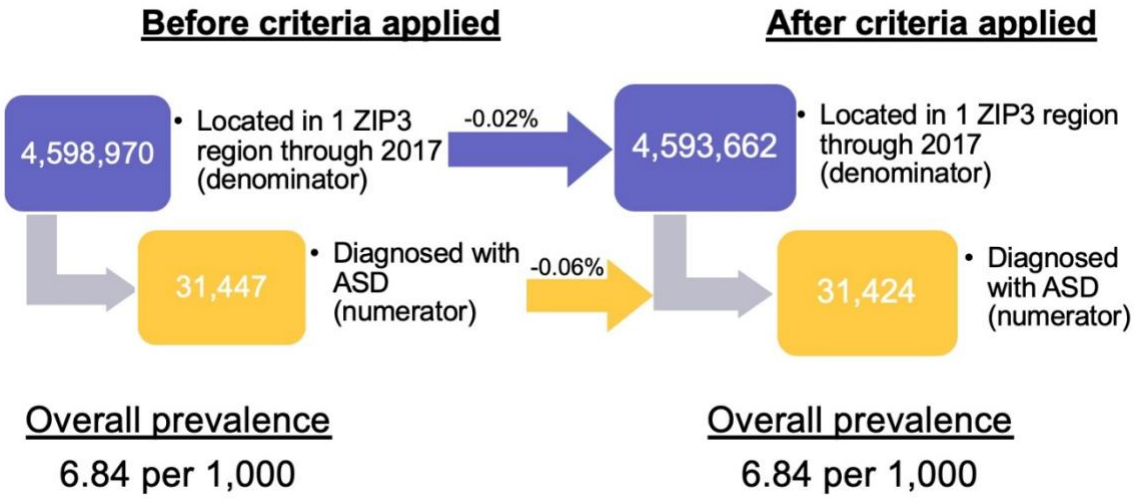


ASD=Autism spectrum disorder; YOB=Year of birth

3.1.1.1 Threshold for minimum ZIP3 sample size

After applying selection criteria, it was discovered that some ZIP3 regions reflected small population sizes, resulting in 51 regions (5.9%) with zero ASD counts. In order to minimize zero inflation while maintaining adequate power, a 200-enrollee threshold was set for inclusion of ZIP3 regions in the final analysis. As a result of the threshold, 5,308 enrollees across 43 ZIP3 regions (5.0% of all enrollees) were excluded (**Figure 3.2**). The final selection was 818 ZIP3 regions with 4,593,662 enrollees, which was above the minimum sample size of 738 ZIP3 regions determined by power analyses (**Figure 3.2**).

Figure 3.2: ZIP3 sample population criteria (≥ 200 enrollees)



ASD=Autism spectrum disorder

3.1.2 Enrollee and ZIP3 characteristics and descriptive statistics

This section presents the demographic, geographic, health-system, and socioeconomic characteristics included in this study. Demographic, geographic, and health-system summaries will first be presented at the enrollee level, then, with the addition of socioeconomic characteristics, will be presented at the ZIP3 level as well.

3.1.2.1 Excluded covariates

Two of the planned health-system covariates were pediatrician density and psychologist density, which were intended to be used as proxies for health provider access. It was discovered during the sampling process that the P+ data source no longer contained the provider ID variable, which is necessary to count unique providers in each ZIP3 region. Therefore, the two provider variables were no longer definable with available information and hypotheses testing was not possible for $\mathbf{H_0(1c)_3}$ and $\mathbf{H_0(1c)_4}$.

A high correlation existed between poverty status density and median family income (Pearson's ρ=-0.74), and the variance inflation factor of poverty status density was

9.05. Variance inflation factors of all other covariates ranged from 1.32 to 5.80. Because the variance inflation factor for poverty status density was relatively high, poverty status density was excluded from the final adjusted model.

3.1.2.2 Enrollee-level descriptive statistics and bivariate tests

The final cohort consisted of 4,593,662 enrollees. Overall, the mean age was 11.0 (SD=4.6) years, 51.1 percent of enrollees were male, and 52.9 percent were enrolled in a fully insured health plan. The southern region was represented by the most enrollees at 41.5 percent, while the west region was least represented with 12.7 percent.

Bivariate analyses showed significant differences between the ASD and Non-ASD groups. ASD patients were slightly younger (10.9 (SD=4.3) vs. 11.1 (SD=4.6) years, $p<0.001$) more likely to be male (80.1% vs. 50.9%, $p<0.001$), and non-ASD patients were slightly more likely to be enrolled in fully insured plans (48.8% vs. 52.9%, $p<0.001$). There was also evidence that geographic imbalances existed between ASD and non-ASD patients (**Table 3.1**).

Table 3.1: Patient-level descriptive statistics

Parameters	Overall	ASD	Non-ASD	p*
n	4,593,662	31,424	4,562,238	
Age (Mean(SD))	11.04 (4.55)	10.85 (4.33)	11.05 (4.55)	< 0.001
Age group, n (%)				< 0.001
3-7	1,217,465 (26.5)	8,343 (26.5)	1,209,122 (26.5)	
8-11	1,140,028 (24.8)	8,473 (27.0)	1,131,555 (24.8)	
12-15	1,243,865 (27.1)	8,990 (28.6)	1,234,875 (27.1)	
16-18†	992,304 (21.6)	5,618 (17.9)	986,686 (21.6)	
Gender, n (%)				< 0.001
Male	2,346,566 (51.1)	25,181 (80.1)	2,321,385 (50.9)	
Female	2,247,096 (48.9)	6,243 (19.9)	2,240,853 (49.1)	
Commercial mix, n (%)				<0.001
Self-insured	2,165,880 (47.1)	16,093 (51.2)	2,149,787 (47.1)	
Fully insured	2,427,782 (52.9)	15,331 (48.8)	2,412,451 (52.9)	
Region, n (%)				< 0.001
Northeast	836,967 (18.2)	8,361 (26.6)	828,606 (18.2)	
Midwest	1,266,315 (27.6)	8,904 (28.3)	1,257,411 (27.6)	
South	1,905,166 (41.5)	10,235 (32.6)	1,894,931 (41.5)	
West	585,214 (12.7)	3,924 (12.5)	581,290 (12.7)	

ASD=Autism spectrum disorder; SD=Standard deviation

* An independent groups t-test was used for age and chi-square tests were used for other variables

† Age 18 is possible in patients with 1999 as their year of birth

3.1.2.3 ZIP3-level descriptive statistics and quartile conversion

In addition to being assessed at the patient-level, all variables were descriptively assessed at the ZIP3 level as well (**Table 3.2**). The mean sample size across ZIP3 regions was 5,616 patients (SD=8,316), and the mean fully insured plan density was 47.2 % fully insured (SD=18.8%) percent. ZIP3 regions were geographically distributed similarly to the patient level, with 36.1% of ZIP3 regions located in the south and only 17.5% located in the west. The mean of the median family incomes across regions was $56,570 (SD=$15,607), and the mean poverty status density was 10.8% (SD=4.5%). Mean single-parent family density

was 13.7% (SD=3.6) and mean private school enrollment density was 15.2% (SD=6.7). The mean percent white was 78.9% white (SD=15.9), and the mean urbanicity was 60.2% urban (SD=12.2).

Table 3.2: ZIP3-level descriptive statistics ($n_{ZIP3\ regions}$=803)

Source	Variable	Overall
P+	Enrollees (Mean (SD))	5,616 (8,316)
	Region, n (%)	
	Northeast	160 (19.6%)
	Midwest	220 (26.9%)
	South	295 (36.1%)
	West	143 (17.5%)
	Fully insured plan density, (Mean (SD))	47.2 (18.8)
ACS	Median family income (1,000s), Mean (SD)	$69.9 ($18.8)
	Single-parent family density, Mean (SD)	13.7 (3.6)
	Private school enrollment density, Mean (SD)	15.2 (6.7)
	Poverty status density, Mean (SD)	10.8 (4.5)
	Percent white, Mean (SD)	78.9 (15.9)
	Urbanicity, Mean (SD)	60.2 (12.2)

ACS=American Community Survey; SD=Standard deviation; P+=PharMetrics Plus

Distributions of all covariates were assessed numerically and visually. Kolmogorov-Smirnov tests for normality were conducted but not used for normality assessment due to the large sample size (n=803). Skewness was observed in five of the eight covariates. Twenty three ZIP3 regions were considered 100% urban, and right skewness was observed in median income, private school enrollment density, poverty status density, and left skewness was observed in percent white. After assessing distributions of covariates, all continuous covariates were incorporated in the statistical model as quartiles (**Table 3.3**).

Table 3.3: Quartile definitions for continuous objective 1 covariates

Variable	Quartile 1*	Quartile 2*	Quartile 3*	Quartile 4*
Fully insured plan density (%)	[6.7 - 33.1]	(33.1 - 46.6]	(46.6 - 61.2]	(61.2 - 97.5]
Median family income (1,000s)	[35.7 - 58.0]	(58.0 - 65.8]	(65.8 - 76.0]	(76.0 - 191.0]
Single-parent family density (%)	[4.6 - 11.4]	(11.4 - 13.0]	(13.0 - 15.5]	(15.5 - 29.9]
Private school enrollment density (%)	[3.4 - 10.6]	(10.6 - 14.2]	(14.2 - 18.2]	(18.2 - 61.1]
Poverty status density (%)	[2.7 - 7.6]	(7.6 - 10.1]	(10.1 - 13.2]	(13.2 - 32.0]
Percent white (%)	[16.6 - 69.0]	(69.0 - 83.3]	(83.3 - 91.8]	(91.8 - 98.1]
Urbanicity (%)	[33.8 - 52.4]	(52.4 - 57.1]	(57.1 - 64.3]	(64.3 - 100.0]

* Brackets include associated numeric boundary and parentheses do not

3.1.3 Objective 1: Overall prevalence of ASD

3.1.3.1 Overall prevalence of ASD

Objective 1a: *To determine the overall treated prevalence of ASD in children 18 or less enrolled in commercial healthcare plans*

The final cohort consisted of 4,593,662 patients, 31,424 of whom met the criteria for ASD. The overall prevalence of ASD in the sample selected was 6.84 per 1,000 children.

3.1.3.2 State-level prevalence of ASD

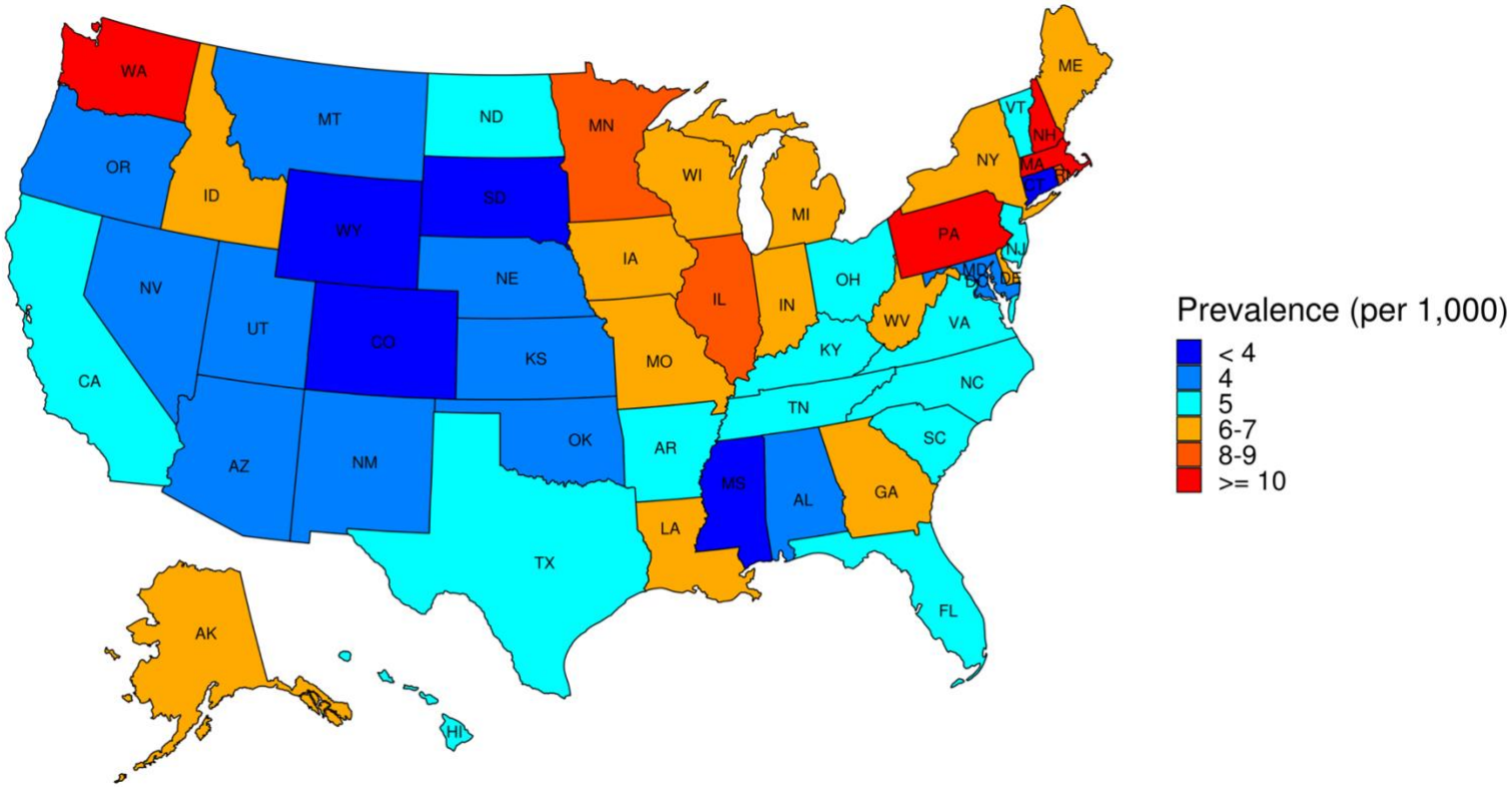
Prevalence was also assessed at the state level (**Table 3.4**). The lowest prevalence rate was observed in Mississippi at 2.65 per 1,000, and the highest prevalence rate was observed in Massachusetts 14.08 per 1,000. A heatmap was also generated to provide a visual representation of state-level prevalence (**Figure 3.3**).

Table 3.4: State-level prevalence of ASD per 1,000 enrollees 18 and younger (including the District of Columbia)

State	Prevalence	State	Prevalence
Alabama	4.91	Montana	4.89
Alaska	7.65	Nebraska	4.57
Arizona	4.85	Nevada	4.71
Arkansas	5.29	New Hampshire	12.36
California	5.38	New Jersey	5.39
Colorado	3.19	New Mexico	4.43
Connecticut	3.91	New York	6.84
Delaware	7.39	North Carolina	5.52
District of Columbia	2.76	North Dakota	5.77
Florida	5.45	Ohio	5.67
Georgia	6.67	Oklahoma	4.56
Hawaii	5.58	Oregon	4.77
Idaho	7.12	Pennsylvania	10.16
Illinois	9.08	Rhode Island	9.55
Indiana	7.46	South Carolina	5.92
Iowa	6.26	South Dakota	2.91
Kansas	4.45	Tennessee	5.25
Kentucky	5.79	Texas	5.35
Louisiana	6.32	Utah	4.30
Maine	6.00	Vermont	5.37
Maryland	4.91	Virginia	5.07
Massachusetts	14.08	Washington	10.79
Michigan	6.58	West Virginia	7.05
Minnesota	8.26	Wisconsin	6.87
Mississippi	2.65	Wyoming	3.79
Missouri	6.04		

ASD=Autism spectrum disorder

Figure 3.3 State-level prevalence of autism spectrum disorder



3.1.3.3 ZIP3 prevalence of ASD

Objective 1b: *To quantify treated prevalence of ASD in children 18 or less enrolled in commercial healthcare plans within each ZIP3 region*

Unadjusted prevalence rates were calculated for each ZIP3 region. After applying the 200 patient threshold for ZIP3 inclusion, there were 25 ZIP3 regions (of the new 818 total) with zero patients who met criteria for ASD, and 34 ZIP3 regions with one patient who met ASD criteria, which suggests zero inflation was minimal.

The ASD patient counts were inspected visually and numerically to decide between Poisson and negative binomial GLMs. The mean ASD count was 38.42 and the distribution was right-skewed, with a variance of 5,585.42 (variance > mean).

3.1.3.4 Explaining prevalence variation at the ZIP3 level

Objective 1c: *To explain variation in the treated prevalence in ASD as a function of geographic, health-system, and socioeconomic characteristics*

The purpose of the third component of objective 1 was to evaluate geographic, health-system, and socioeconomic characteristics as predictors of ZIP3-level prevalence of ASD. The dependent variable was the ASD patient count in each ZIP3 region, and covariates included were geographic region, fully insured plan density, median family income, single-parent family density, private school enrollment density, percent white, and urbanicity. Poverty status density was not included in the final analysis due to collinearity issues and interactions with other covariates (**Section 3.1.2.1**). Two GLMs (Poisson and negative binomial) were fit to generate adjusted relationships between each covariate and ZIP3 prevalence. A significant likelihood ratio suggested the negative binomial model provided a better fit than the Poisson model (χ_2=324,367, p<0.001), so the negative

binomial model was used for interpretation of relationships between covariates and ASD patient count.

A likelihood ratio test comparing the full negative binomial model to a constant-model indicated that at least one covariate was related to ZIP3 prevalence (χ^2=2,510.579; df=21; p <0.001). **Figure 3.4** displays the results of the negative binomial regression analysis; forest plots were generated to facilitate interpretation of the multiple quartiles represented within each covariate. Numeric results are presented in tabular format as well (**Table 3.5**).

Neither of the P+ covariates (geographic region and fully insured plan density) was significantly related to prevalence rates after controlling for other covariates. After controlling for other covariates and clustering at the state level, no geographic region was related to prevalence rate (**Figure 3.4**). A significant relationship was observed in fully insured plan density in the third quartile vs. the first quartile (IRR_{Q3}=2.007; 95% CI=1.129-3.568; p=0.018), but not in the second or fourth quartiles (**Figure 3.4**).

Some socioeconomic characteristics were significantly related to prevalence rates. After adjusting for other covariates, regions with median family incomes over $63,000 exhibited 2.6 times the prevalence rate of regions with median incomes below $46,400 ($IRR_{Q4}$=2.552; 95% CI=1.562-4.170; p<0.001). Significant relationships between median income and ASD prevalence also existed for ZIP3 regions when 2nd and 3rd quartiles were compared to the 1st quartile (**Figure 3.4**).

A univariate test demonstrated a relationship between single-parent family density and prevalence rates (IRR_{Q4}=0.499; 95% CI=0.338-0.735; p<0.001), but the relationship was lost after other covariates were introduced in the model. After adjusting for other covariates, no relationship was found between single-parent family density and ASD prevalence rates (IRR_{Q4}=0.709; 95% CI=0.409-1.230; p=0.221).

Regions with a higher percentage of children enrolled in private schools were associated with higher prevalence rates. After controlling for other covariates, regions with over 18.1 percent of children enrolled in private schools demonstrated a prevalence rate 1.58 times greater than that for regions with 10.6 percent or fewer children enrolled in private schools (IRR=1.581; 95% CI=1.093-2.287; p=0.015). Significant positive relationships between private school enrollment density and ASD prevalence also existed for ZIP3 regions when 2nd and 3rd quartiles were compared to the 1st quartile, after controlling for other covariates (**Figure 3.4**).

There was a significant relationship between the proportion of white residents of each region and prevalence. Regions with over 91.9 percent white residents showed a prevalence rate 0.462 times that for regions below 69.4 percent white (IRR_{Q4}=0.462; 95% CI=0.253-0.843; p=0.012). However, regions in the second and third quartile failed to show significant relationships (**Figure 3.4**), and no significant relationships were observed in univariate analyses. The variance inflation factor of percent white was 2.669.

One significant relationship was found between the percentage of urban residents in ZIP3 regions and prevalence. After controlling for other covariates, regions with percentages of urban residents over 57.1 percent and below 64.1 percent showed a prevalence rate 0.635 times the prevalence of regions with 52.4 percent urban residents and below (IRR_{Q3}=0.635; 95% CI=0.471-0.856; p=0.003). However, no significant relationships were observed in the second and fourth quartiles, and the trend in parameter estimates was not consistent between quartile 2 and quartile 3 (IRR_{Q2}=0.868; IRR_{Q4}=0.947).

$H_0(1c)_1$: There is no significant difference in the treated prevalence of ASD with respect to **geographic region**, after controlling for covariates.

[Failed to reject]

$H_0(1c)_2$: There is no significant difference in the treated prevalence of ASD with respect to **fully insured plan density**, after controlling for covariates.

[Rejected]

$H_0(1c)_3$: There is no significant difference in the treated prevalence of ASD with respect to **pediatrician density**, after controlling for covariates.

[Unable to test]

$H_0(1c)_4$: There is no significant difference in the treated prevalence of ASD with respect to **psychologist density**, after controlling for covariates.

[Unable to test]

$H_0(1c)_5$: There is no significant difference in the treated prevalence of ASD with respect to **median family income**, after controlling for covariates.

[Rejected]

$H_0(1c)_6$: There is no significant difference in the treated prevalence of ASD with respect to **single-parent family density**, after controlling for covariates.

[Failed to reject]

$H_0(1c)_7$: There is no significant difference in the treated prevalence of ASD with respect to **private school enrollment density**, after controlling for covariates.

[Rejected]

$H_0(1c)_8$: There is no significant difference in the treated prevalence of ASD with respect to **poverty status density**, after controlling for covariates.

[Unable to test]

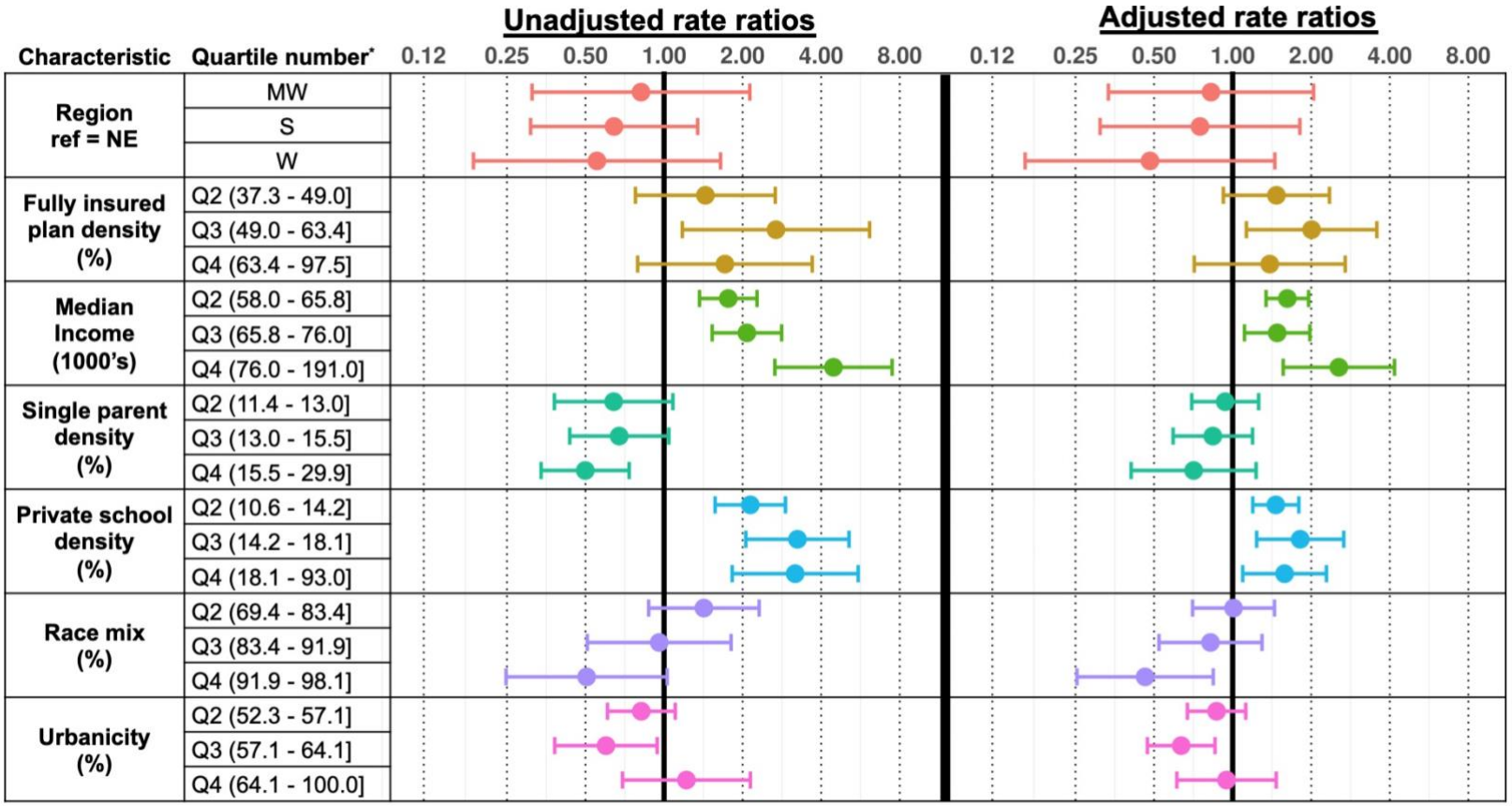
$H_0(1c)_9$: There is no significant difference in the treated prevalence of ASD with respect to **percent white**, after controlling for covariates.

[Rejected]

$H_0(1c)_{10}$: There is no significant difference in the treated prevalence of ASD with respect to **ZIP3 region urbanicity**, after controlling for covariates.

[Rejected]

Figure 3.4: Objective 1 forest plots of negative binomial regression incident rate ratios and confidence intervals describing the relationships between study characteristics and ZIP3 prevalence of ASD (n=803)



MW=Midwest; NE=Northeast; S=South; W=West

* Brackets include associated numeric boundary and parentheses do not, and reference category is Q1

Table 3.5: Objective 1 negative binomial regression results describing the relationships between study characteristics and ZIP3 prevalence of ASD (n=803)

Covariate	Level/Quartile*	Unadjusted model results					Adjusted model results					
		IRR	95% CI		Z-score	p	IRR	95% CI		Z-score	p	
Region ref=NE	MW	0.816	0.312	2.131	-0.416	0.678	0.826	0.334	2.042	-0.414	0.679	
	S	0.643	0.308	1.345	-1.172	0.241	0.750	0.311	1.809	-0.641	0.521	$H_0(1c)_1$
	W	0.553	0.186	1.646	-1.065	0.287	0.482	0.160	1.451	-1.298	0.194	
Fully insured plan density (%)	Q2 (37.3 - 49.0]	1.440	0.777	2.668	1.159	0.246	1.471	0.921	2.349	1.616	0.106	
	Q3 (49.0 - 63.4]	2.684	1.175	6.131	2.342	0.019	2.007	1.129	3.568	2.373	**0.018**	$H_0(1c)_2$
	Q4 (63.4 - 97.5]	1.711	0.792	3.697	1.366	0.172	1.387	0.713	2.700	0.963	0.336	
Median Income (1000's)	Q2 (46.4 - 53.2]	1.762	1.367	2.271	4.369	<0.001	1.620	1.343	1.954	5.039	**< 0.001**	
	Q3 (53.2 - 63.0]	2.077	1.529	2.822	4.677	<0.001	1.481	1.110	1.977	2.668	**0.008**	$H_0(1c)_5$
	Q4 (63.0 - 131.0]	4.458	2.658	7.480	5.662	<0.001	2.552	1.562	4.170	3.740	**< 0.001**	
Single-parent density (%)	Q2 (11.4 - 13.0]	0.641	0.380	1.081	-1.667	0.096	0.936	0.697	1.258	-0.436	0.663	
	Q3 (13.0 - 15.5]	0.673	0.435	1.043	-1.770	0.077	0.840	0.591	1.192	-0.978	0.328	$H_0(1c)_6$
	Q4 (15.5 - 29.9]	0.499	0.338	0.735	-3.514	<0.001	0.709	0.409	1.230	-1.223	0.221	
Private school enrollment density (%)	Q2 (10.6 - 14.2]	2.140	1.569	2.919	4.802	<0.001	1.463	1.194	1.793	3.671	**< 0.001**	
	Q3 (14.2 - 18.1]	3.244	2.058	5.113	5.069	<0.001	1.815	1.236	2.664	3.040	**0.002**	$H_0(1c)_7$
	Q4 (18.1 - 93.0]	3.180	1.824	5.544	4.080	<0.001	1.581	1.093	2.287	2.431	**0.015**	
Percent white (%)	Q2 (69.4 - 83.4]	1.421	0.873	2.314	1.414	0.157	1.008	0.702	1.446	0.042	0.967	
	Q3 (83.4 - 91.9]	0.958	0.508	1.807	-0.131	0.896	0.822	0.522	1.296	-0.843	0.399	$H_0(1c)_9$
	Q4 (91.9 - 98.1]	0.505	0.248	1.028	-1.884	0.060	0.462	0.253	0.843	-2.517	**0.012**	
Urbanicity (%)	Q2 (52.3 - 57.1]	0.818	0.607	1.104	-1.313	0.189	0.868	0.671	1.122	-1.081	0.280	
	Q3 (57.1 - 64.1]	0.599	0.381	0.941	-2.222	0.026	0.635	0.471	0.856	-2.982	**0.003**	$H_0(1c)_{10}$
	Q4 (64.1 - 100.0]	1.218	0.693	2.141	0.684	0.494	0.947	0.611	1.469	-0.242	0.809	

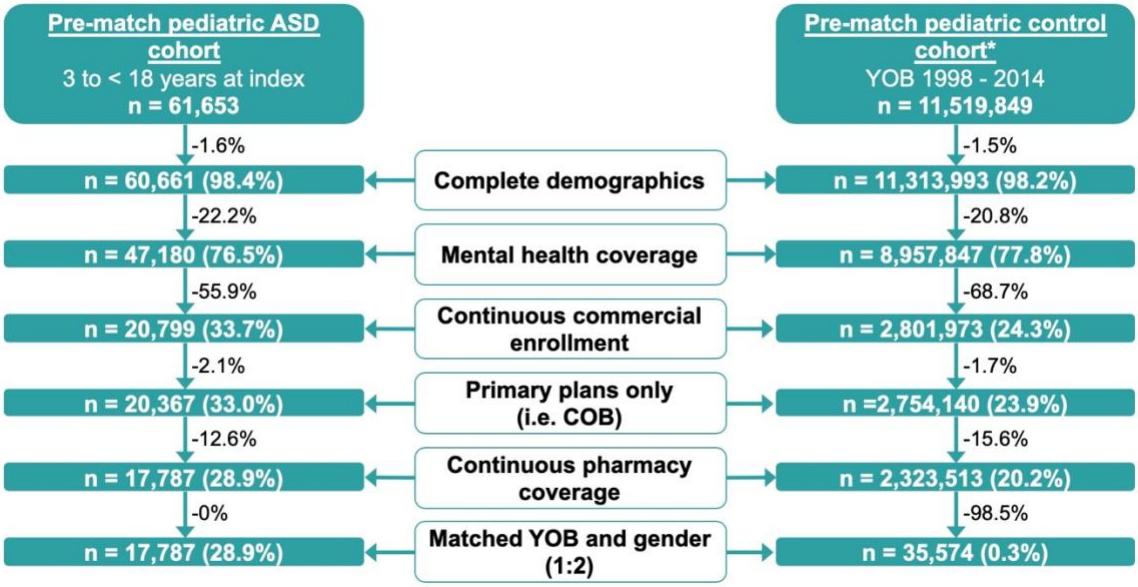
CI=Confidence interval; IRR=Incident rate ratio; MW=Midwest; NE=Northeast; S=South; W=West

3.2 Objectives 2-5

3.2.1 ASD sample selection and matching process

Using medical claims from 2016, 61,653 patients had at least two diagnoses of ASD separated by at least 30 days. Of those patients, 17,787 (28.9%) met all criteria for inclusion in the study. The initial pool of potential controls contained 11,519,849 patients with years of birth between 1998 and 2013. Of those patients, 2,323,513 met all criteria for inclusion in the pool of potential controls. A 100% 2:1 match was achieved based on year of birth and gender. Index dates were then carried over from the ASD group to the non-ASD group. The patient selection process and attrition statistics of the ASD and non-ASD groups are presented in **Figure 3.5**.

Figure 3.5 Patient selection and attrition



ASD=Autism spectrum disorder; COB=Coordination of benefits; YOB=Year of birth
* The initial selection of control patients also required a minimum total of 36 months of enrollment

3.2.2 Baseline characteristics of final sample

The final cohort consisted of 53,361 patients (**Table 3.6**). Overall, the mean age was 11.05 years, 80.4 percent of the patients were male, and 52.5 percent were enrolled in a fully insured health plan. The most prevalent health plan product type was PPO at 87.4 percent. The southern region was represented by the most patients at 35.0 percent, while the west region was least represented with 11.4 percent. The most prevalent CCCs overall were congenital or genetic disorders (2.5%), metabolic disorders (2.5%), neurologic or neuromuscular disorders (2.4%), and malignancy (1.1%).

Table 3.6: Baseline summary statistics of overall sample (N=53,361)

Variable	N	%
Demographics		
Gender		
Male	42,876	80.4
Female	10,485	19.6
Age group		
3-7	14,433	27.0
8-11	15,708	29.4
12-14	12,510	23.4
15-17	10,710	20.1
Region		
East	12,036	22.6
Midwest	16,552	31.0
South	18,684	35.0
West	6,089	11.4
Health System		
Plan type		
Self-insured	25,350	47.5
Fully insured	28,011	52.5
Product type		
HMO	3,620	6.8
PPO	46,204	86.6
Other	3,537	6.6
Clinical		
CCCs		
Congenital or genetic	1,351	2.5
Metabolic	1,334	2.5
Neurologic or neuromuscular	1,265	2.4
Malignancy	561	1.1
Cardiovascular	557	1.0
Respiratory	536	1.0
Hematologic or immunologic	299	0.6

Table 3.6: Baseline summary statistics of overall sample (N=53,361) (continued)

Gastrointestinal	287	0.5
Technology dependence	259	0.5
Renal	160	0.3
Premature or neonatal	46	0.1
Transplantation	45	0.1
CCC count		
0	48,250	90.4
1	4,002	7.5
2+	1,109	2.1

CCC=Complex chronic conditions; HMO=Health maintenance organization; PPO=Preferred provider organization

3.2.3 Objective 2: Comparison of baseline characteristics

The purpose of objective 2 was to describe and compare baseline demographic, health-system, and clinical characteristics of the ASD and non-ASD cohorts. **Table 3.7** provides descriptions and comparisons of baseline characteristics between cohorts.

The non-ASD control group was matched with the ASD group on age and gender, so groups were identical with respect to both age and gender. Geographically, regional imbalances were observed across cohorts ($p<0.001$). Post-hoc chi-square tests with Bonferroni corrections (significant $p=0.05/4=0.0125$) were conducted for geographic region, which showed significantly greater proportions of patients with ASD in the East region (29.2% vs. 19.3%; $p<0.001$) and West region (11.9% vs. 11.2%; $p=0.009$), lower proportions of ASD in the South region (28.0% vs. 38.5%; $p<0.001$), and no significant difference in the Midwest region ($p=0.650$).

There was no significant difference between the two cohorts regarding enrollment in fully insured health plans ($p=0.905$). However, significant differences in health plan product type (e.g., HMO, PPO) were observed across cohorts ($p<0.001$). Post-hoc chi-square tests with Bonferroni corrections (significant $p=0.05/3=0.0167$) were conducted for

health plan product type, which showed a significantly greater proportion of patients with ASD in the HMO plans (8.7% vs. 5.8%; p<0.001), and a lower proportion of patients with ASD the PPO plans (85.0% vs. 87.4%;p<0.001), but no significant difference in ASD proportions in other plans (6.3% vs. 6.8%; p=0.062).

The 11 CCCs and technology dependence characteristics were assessed individually and as an ordinal summary of all 12 variables. Overall, the most common CCCs observed during the pre-index period were congenital or genetic defects (2.5%), metabolic conditions (2.5%), and neurologic or neuromuscular conditions (2.4%). Across all CCCs, the largest difference observed was in neurologic or neuromuscular conditions, which includes epilepsy, where 5.9% of the ASD group received diagnoses versus 0.6% of the control group. Significant differences in pre-index CCCs were observed for congenital or genetic, metabolic, neurologic or neuromuscular, cardiovascular, hematologic or immunologic, gastrointestinal, renal, technology dependence, and premature or neonatal conditions, all of which were more prevalent in the ASD cohort (all p-values<0.001) (**Table 3.7**). No significant differences were observed between cohorts on malignancy and respiratory conditions (p=0.822 and p=0.591, respectively). Despite demonstrating a p-value of 0.040, the prevalence of transplantation was not considered significantly different between the two groups as p-values were interpreted with Bonferroni corrections.

Some CCCs were particularly infrequent in the study population. Six CCCs were present in under one percent of the overall cohort, which caused cell size and convergence issues in the statistical models for objectives 3-5. Therefore, the CCCs were collapsed into one ordinal variable (CCC count) to be used in all statistical models in objectives 3-5. For the ordinal CCC covariate, an omnibus chi-square test detected a significant difference in cell frequencies between the ASD and non-ASD groups (p<0.001). Post-hoc chi-square tests with Bonferroni corrections (significant p=0.05/3=0.0167) were conducted for each

of the CCC levels (e.g., 0, 1, or ≥2), which showed significantly more zero values in the non-ASD group (93.8% vs. 83.7%; $p<0.001$), and greater proportions of one (12.2% vs. 5.2%; $p<0.001$) and ≥ two (4.1% vs. 1.1%; $p<0.001$) values in the ASD group.

Table 3.7: Baseline summary statistics by group

Variable	Non-ASD (N=35,574)	ASD (N=17,787)	p*
Demographics			
Gender=M (%)†	80.4	80.4	1.000
Age (quartiles) (%)†			1.000
3-7	27.0	27.0	
8-11	29.4	29.4	
12-14	23.4	23.4	
15-17	20.1	20.1	
Region (%)			< 0.001
East	19.3	29.2	
Midwest	31.1	30.9	
South	38.5	28.0	
West	11.2	11.9	
Health System			
Fully insured (%)	47.5	47.5	0.905
Product type (%)			< 0.001
HMO	5.8	8.7	
Other	6.8	6.3	
PPO	87.4	85.0	
Clinical			
CCCs (%)			
Congenital or genetic	1.3	5.1	< 0.001
Metabolic	1.9	3.7	< 0.001
Neurologic or neuromuscular	0.6	5.9	< 0.001
Malignancy	1.0	1.1	0.822
Cardiovascular	0.7	1.6	< 0.001
Respiratory	1.0	1.0	0.591
Hematologic or immunologic	0.3	1.0	< 0.001
Gastrointestinal	0.3	1.1	< 0.001
Technology dependence	0.2	1.0	< 0.001
Renal	0.2	0.5	< 0.001
Premature or neonatal‡	0.0	0.2	< 0.001

Table 3.7: Baseline summary statistics by group (continued)

Transplantation	0.1	0.1	0.040
At least one CCC	6.2	9.6	< 0.001
CCC count			< 0.001
0	93.8	83.7	
1	5.2	12.2	
2+	1.1	4.1	

CCC=Complex chronic conditions; HMO=Health maintenance organization; PPO=Preferred provider organization

⁎ An independent groups t-test was used for age and chi-square tests were used for other variables.

† Cohorts were matched on age and gender

‡ Fisher's exact test was conducted to test group differences in proportions

3.2.4 Objective 3: Comparing age-related prevalence in psychiatric conditions between groups

The purpose of objective 3 was to compare the age-related prevalence of seven psychiatric conditions between ASD and non-ASD groups, while controlling for other covariates. A total of seven logit models were fit to test the seven hypotheses. The primary independent variable was the interaction between age and group membership (group*age), which represents the dependence of age-related likelihood of each psychiatric condition on group membership. The study covariates utilized in all seven models included: age, group, state of residence, health plan type, health plan product type, and ordinal CCC count. Collinearity statistics showed that variance inflation factors ranged from 1.02 to 4.51, which indicated multicollinearity was not a statistical issue of concern. **Table 3.8** provides overall descriptions of the study population with psychiatric disorders, as well as comparisons between ASD and non-ASD groups.

The most prevalent psychiatric conditions overall were in the category of attention-deficit, conduct, and disruptive behavior disorders, of which 18.5% of the study population received at least two diagnoses in separate visits during the post-index period. The least

prevalent psychiatric conditions were in the category of alcohol and substance-related disorders, of which 0.4 percent of the population received diagnoses. Bivariate tests showed significantly greater proportions of all psychiatric conditions in the ASD group versus the non-ASD group (all p-values<0.001), with the largest group differences seen in attention-deficit, conduct, and disruptive behavior disorders (43.3% vs. 6.1%; p<0.001) and anxiety disorders (30.0% vs. 3.4%; p<0.001).

Table 3.8: Overall prevalence of psychiatric disorders by group

Variable	Overall (N=53,361)	Non-ASD (n=35,574)	ASD (n=17,787)	p
Psychiatric condition prevalence				
Adjustment disorders (%)	3.2	2.3	5.0	<0.001
Anxiety disorders (%)	12.3	3.4	30.0	<0.001
Attention-deficit, conduct, and disruptive behavior disorders (%)	18.5	6.1	43.3	<0.001
Mood disorders (%)	6.1	1.8	14.6	<0.001
Personality disorders (%)	0.3	0.0*	0.8	<0.001
Schizophrenia and other psychotic disorders (%)	0.3	0.0*	0.8	<0.001
Alcohol and substance-related disorders (%)	0.4	0.4	0.6	<0.001

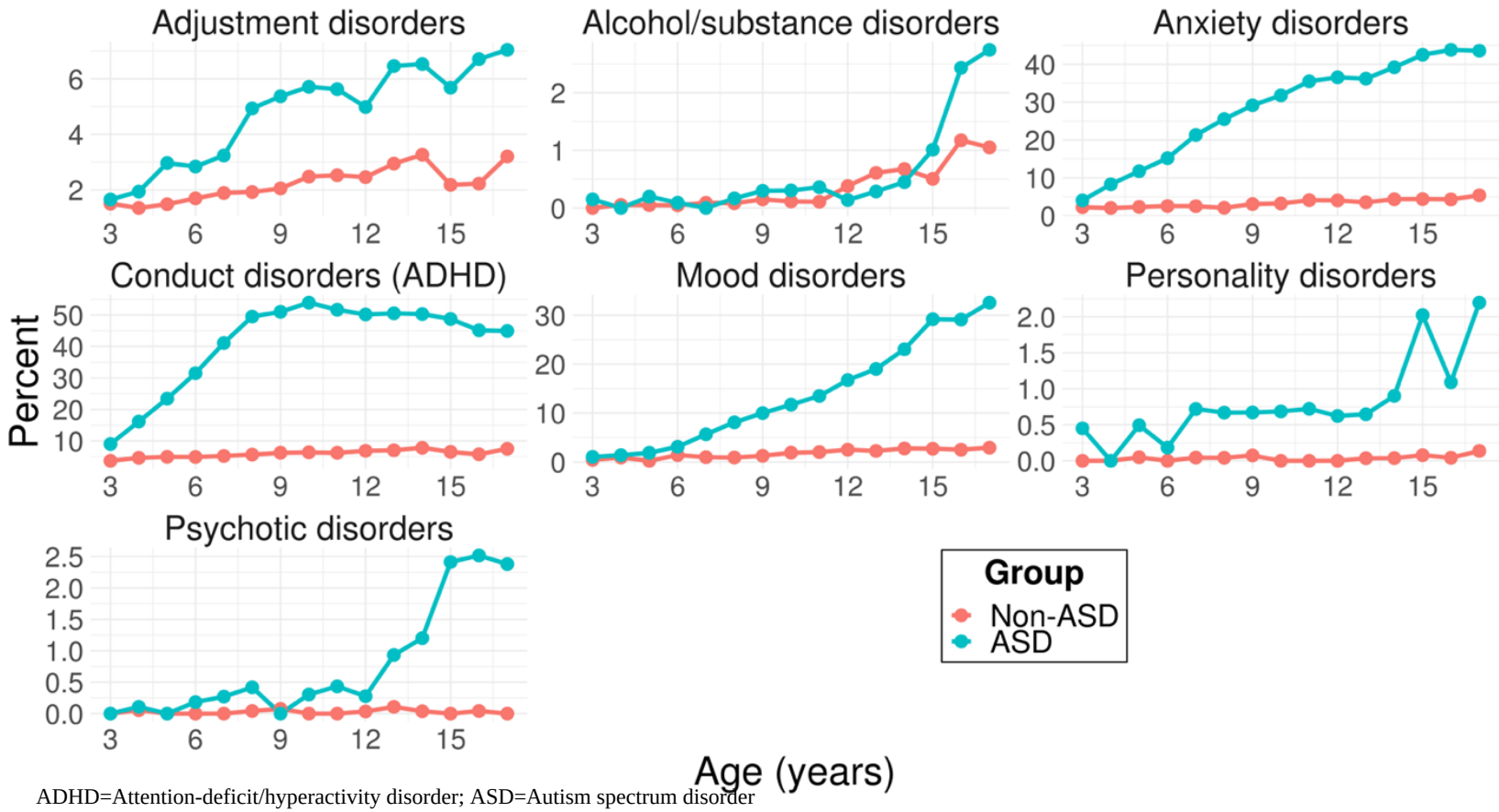
ASD=Autism spectrum disorder

* All expected cell frequencies of personality disorders and schizophrenia and other psychotic disorders remained above 5, so Chi square tests were used

3.2.4.1 Visualizing the relationship between age and psychiatric conditions by group

The proportion of patients represented for each psychiatric condition were visually assessed across both age and group membership for model diagnostic purposes (**Figure 3.6**). During visual inspection of the prevalence of psychiatric conditions with respect to age, non-linear relationships were identified between age and the proportion of patients with each psychiatric condition, so a quadratic term for the main effect of age was included in each of the seven logistic regression models.

Figure 3.6 Proportions of psychiatric conditions across age by group membership



ADHD=Attention-deficit/hyperactivity disorder; ASD=Autism spectrum disorder

3.2.4.2 Regression results and hypothesis tests

After bivariate tests were conducted, logistic regression models were fit for each of the seven outcomes. Age was centered at 11 years for all models (mean age=11.05 years) so the group membership parameter could be interpreted at the approximate mean age of the cohort. Hosmer-Lemeshow Goodness of Fit tests yielded non-significant p-values for six of the seven models, which suggested low evidence of poor model fits. The model for attention-deficit, conduct, and disruptive behavior disorders yielded a Hosmer-Lemeshow p-value of 0.005, so a likelihood ratio test was conducted. The likelihood ratio test comparing a constant-only logit model to the full model indicated at least one covariate was related to the likelihood of the outcome (χ_2=11,182, p<0.001).

Logistic regression results testing objective 3 hypotheses are presented in **Table 3.9**. After controlling for other covariates, significant positive relationships were observed between age and the likelihood of psychiatric disorders for five of the seven outcomes: adjustment disorders (OR=1.056; 95% CI=1.037-1.076; p<0.001), anxiety disorders (OR=1.080; 95% CI=1.063-1.097; p<0.001), conduct and behavior disorders (OR=1.042; 95% CI=1.029-1.055; p<0.001), mood disorders (OR=1.138; 95% CI=1.112-1.165; p<0.001), and alcohol and substance-related disorders (OR=1.284; 95% CI=1.201-1.374; p<0.001). Significant relationships between age and psychiatric disorder diagnosis were not found in personality disorders (p=0.099) or in schizophrenia and psychotic disorders (p=0.569), after controlling for other covariates. Where significant relationships were found between linear age and psychiatric disorder diagnosis, relationships were also observed in the quadratic term for age (all p-values<0.001).

For the relationship between group membership and likelihood of psychiatric disorders ("Group: ASD" term), after controlling for other covariates, significant positive

relationships were found in six of the seven outcomes: adjustment disorders (OR=2.121; 95% CI =1.910-2.356 ; p<0.001), anxiety disorders (OR=10.863; 95% CI=10.121-11.660; p<0.001), conduct and behavior disorders (OR=12.260; 95% CI=11.594-12.965; p<0.001), mood disorders (OR=7.416; 95% CI=6.672-8.242; p<0.001), personality disorders (OR=20.215; 95% CI=10.585-38.606; p<0.001), and schizophrenia and psychotic disorders (OR=15.736; 95% CI=7.694-32.186; p<0.001). A significant relationship between group membership and diagnosis was not found in alcohol and substance-related disorders (p=0.440), after controlling for other covariates.

The parameters of primary interest in each model were the interactions between age and group membership, which represent the dependency of age-related prevalence rates on ASD diagnosis. After controlling for other covariates, ASD diagnosis was not significantly related to the age-related likelihood of three of the seven psychiatric disorders: adjustment disorders (p=0.071), personality disorders (p=0.905), and alcohol and substance-related disorders (0.254).

Significant relationships were identified in four of the groups of psychiatric disorders: anxiety disorders, conduct and behavior disorders, mood disorders, and schizophrenia and psychotic disorders. ASD diagnosis strengthened the odds ratio of the age-related likelihood of anxiety disorders by a factor of 1.076, after controlling for other covariates (OR=1.076; 95% CI=1.057-1.096; p<0.001). In other words, for patients in the ASD group, every year increase in age was associated with a marginal increase in the likelihood of anxiety disorder diagnosis by 16% ($e^{0.077+0.073}=1.162$), while a marginal increase of 8.0% was observed in the group of non-ASD patients ($e^{0.077}=1.080$).

ASD diagnosis increased the odds ratio of the age-related likelihood of conduct and behavior disorders by a factor of 1.046, after controlling for other covariates (OR=1.046; 95% CI=1.031-1.062; p<0.001). For mood disorders, ASD diagnosis increased the age-

related odds ratio by a factor of 1.133, after controlling for other covariates (OR=1.133; 95% CI=1.103-1.164; p<0.001).

A significant relationship was also observed in schizophrenia and psychotic disorders. ASD diagnosis increased the age-related odds ratio by a factor of 1.322, after controlling for other covariates (OR=1.322; 95% CI=1.101-1.588; p=0.003). However, the main effect of age was not significantly related to the likelihood of schizophrenia and psychotic disorder diagnoses (p=0.569).

$H_0(3)_1$: There is no significant difference in the age-related **likelihood of adjustment disorder** between ASD and non-ASD groups, after controlling for covariates.

[Failed to reject]

$H_0(3)_2$: There is no significant difference in the age-related **likelihood of anxiety disorder** between ASD and non-ASD groups, after controlling for covariates.

[Rejected]

$H_0(3)_3$: There is no significant difference in the age-related **likelihood attention-deficit conduct or disruptive behavior** between ASD and non-ASD groups, after controlling for covariates.

[Rejected]

$H_0(3)_4$: There is no significant difference in the age-related **likelihood of mood disorder** between ASD and non-ASD groups, after controlling for covariates.

[Rejected]

$H_0(3)_5$: There is no significant difference in the age-related **likelihood of personality disorder** between ASD and non-ASD groups, after controlling for covariates.

[Failed to reject]

$H_0(3)_6$: There is no significant difference in the age-related **likelihood of schizophrenia or other psychotic disorder** between ASD and non-ASD groups, after controlling for covariates.

[Rejected]

$H_0(3)_7$: There is no significant difference in the age-related **likelihood of alcohol or substance-related disorder** between ASD and non-ASD groups, after controlling for covariates.

[Failed to reject]

Table 3.9: Logistic regression analysis comparing likelihood of psychiatric conditions between ASD and non-ASD groups (N=53,361)

Outcome	Parameter*	Est	OR	95% CI		Z statistic	p	
Adjustment disorders	AGE_{11}	0.055	1.056	1.037	1.076	5.778	< 0.001	
	Group: ASD	0.752	2.121	1.910	2.356	14.047	< 0.001	
	AGE_{112}	-0.007	0.993	0.990	0.997	-3.960	< 0.001	
	AGE_{11}*GRP: ASD	0.024	1.024	0.998	1.052	1.808	0.071	$H_0 3_1$
Anxiety disorders	AGE_{11}	0.077	1.080	1.063	1.097	9.509	< 0.001	
	Group: ASD	2.385	10.863	10.121	11.660	66.076	< 0.001	
	AGE_{112}	-0.011	0.989	0.987	0.991	-10.307	< 0.001	
	AGE_{11}*GRP: ASD	0.073	1.076	1.057	1.096	7.861	< 0.001	$H_0 3_2$
Conduct and behavior disorders	AGE_{11}	0.041	1.042	1.029	1.055	6.506	< 0.001	
	Group: ASD	2.506	12.260	11.594	12.965	87.900	< 0.001	
	AGE_{112}	-0.019	0.981	0.980	0.983	-21.188	< 0.001	
	AGE_{11}*GRP: ASD	0.045	1.046	1.031	1.062	6.033	< 0.001	$H_0 3_3$
Mood disorders	AGE_{11}	0.129	1.138	1.112	1.165	11.004	< 0.001	
	Group: ASD	2.004	7.416	6.672	8.242	37.151	< 0.001	
	AGE_{112}	-0.011	0.989	0.986	0.992	-6.782	< 0.001	
	AGE_{11}*GRP: ASD	0.125	1.133	1.103	1.164	9.198	< 0.001	$H_0 3_4$
Personality disorders	AGE_{11}	0.120	1.127	0.978	1.300	1.651	0.099	
	Group: ASD	3.006	20.215	10.585	38.606	9.107	< 0.001	
	AGE_{112}	0.006	1.006	0.996	1.017	1.170	0.242	
	AGE_{11}*GRP: ASD	0.009	1.009	0.870	1.170	0.120	0.905	$H_0 3_5$
Schizophrenia & psychotic disorders	AGE_{11}	0.047	1.048	0.892	1.231	0.569	0.569	
	Group: ASD	2.756	15.736	7.694	32.186	7.549	< 0.001	
	AGE_{112}	-0.004	0.996	0.981	1.012	-0.513	0.608	
	AGE_{11}*GRP: ASD	0.279	1.322	1.101	1.588	2.989	0.003	$H_0 3_6$
Alcohol & substance-related disorders	AGE_{11}	0.250	1.284	1.201	1.374	7.275	< 0.001	
	Group: ASD	0.175	1.192	0.763	1.861	0.772	0.440	
	AGE_{112}	0.007	1.007	0.996	1.019	1.225	0.221	
	AGE_{11}*GRP: ASD	0.053	1.054	0.963	1.155	1.140	0.254	$H_0 3_7$

ASD=Autism spectrum disorder; CI=Confidence interval; GRP=Group; OR=Odds ratio

* All parameters generated after adjusting for plan type, product type, complex chronic conditions, and U.S. state. Group-related parameter estimates should be interpreted as ASD vs. non-ASD

3.2.5 Objective 4: Comparing healthcare utilization between groups

The purpose of objective 4 was to determine if all-cause and MHR healthcare utilization rates differ between ASD and non-ASD patients. The six all-cause outcomes included outpatient office visits, OT/PT visits, speech therapy visits, inpatient visits, ED visits, and outpatient prescriptions. The five MHR outcomes included outpatient office visits, BM visits, inpatient visits, ED visits, and psychotropic prescriptions. Utilization and zero inflation statistics are presented in **Table 3.10**. Overall mean (±SD) all-cause outpatient office visits, OT/PT visits, speech therapy visits, inpatient visits, ED visits, and outpatient prescriptions were 12.7 (+25.7) visits, 2.4 (±10.9) visits, 2.2 (±11.6) visits, 0.0 (±0.4), 0.2 (±0.6) visits, and 8.0 (±14.0) prescriptions, respectively. Mean (±SD) MHR outpatient office visits, BM visits, inpatient visits, ED visits, and psychotropic prescriptions were 7.0 (±22.1) visits, 0.8 visits (±9.6), 0.0 (±0.3) visits, 0.0 (±0.2) visits, and 4.2 (±9.9) prescriptions, respectively. Bivariate Mann-Whitney U tests indicated significantly greater utilization in the ASD group compared to the non-ASD group (all p-values<0.001) across all 11 utilization outcomes.

Table 3.10: Descriptive statistics for post-index healthcare utilization overall and by group

	Overall (N=53,361)	ASD (n=17,787)	Non-ASD (n=35,574)	p*
All-cause utilization				
Outpatient office visits				
Mean (SD)	12.72 (25.69)	28.23 (38.61)	4.96 (8.01)	
Median	4	14	3	< 0.001
% 0	9.1	1.2	13.0	
OT/PT visits				
Mean (SD)	2.42 (10.86)	6.03 (17.46)	0.62 (3.84)	
Median	0	0	0	< 0.001
% 0	88.2	78.4	93.1	
Speech therapy visits				
Mean (SD)	2.19 (11.60)	6.26 (19.12)	0.15 (2.57)	
Median	0	0	0	< 0.001
% 0	93.5	82.0	99.2	
Inpatient visits				
Mean (SD)	0.04 (0.41)	0.09 (0.60)	0.02 (0.25)	
Median	0	0	0	< 0.001
% 0	97.5	94.6	99.0	
ED visits				
Mean (SD)	0.20 (0.62)	0.29 (0.82)	0.16 (0.49)	
Median	0	0	0	< 0.001
% 0	85.5	81.2	87.6	
Outpatient Rx count				
Mean (SD)	8.00 (14.01)	16.56 (19.52)	3.71 (6.98)	
Median	2	10	1	< 0.001
% 0	30.8	15.8	38.2	
Mental health-related utilization				
Outpatient office visits				
Mean (SD)	6.96 (22.05)	19.18 (34.51)	0.85 (4.64)	
Median	0	6	0	< 0.001
% 0	63.9	15.1	88.3	
BM visits				
Mean (SD)	0.82 (9.61)	2.41 (16.34)	0.02 (1.74)	
Median	0	0	0	< 0.001
% 0	97.7	93.4	99.9	
Inpatient visits				
Mean (SD)	0.02 (0.33)	0.06 (0.48)	0.01 (0.21)	
Median	0	0	0	< 0.001
% 0	98.7	96.7	99.7	

Table 3.10: Descriptive statistics for post-index healthcare utilization overall and by group (continued)

ED visits				
Mean (SD)	0.02 (0.21)	0.05 (0.34)	0.00† (0.07)	
Median	0	0	0	< 0.001
% 0	98.8	96.9	99.7	
Outpatient Rx count				
Mean (SD)	4.19 (9.88)	10.58 (14.05)	1.00 (4.13)	
Median	0	5	0	< 0.001
% 0	72.6	39.6	89.1	

ASD=Autism spectrum disorder; BM=Behavioral modification; ED=Emergency department; OT=Occupational therapy; Rx=Prescription; PT=Physical therapy; SD=Standard deviation

* All bivariate tests were conducted using Mann-Whitney U

† Means rounded down to 0.0

Prior to fitting statistical models, normality was checked numerically and visually. Kolmogorov-Smirnov tests for normality were conducted but not used for normality assessment due to the large sample size (n=53,361). Visual inspection of all 11 utilization variables suggested right-skewness. Significant likelihood ratio tests suggested that the negative binomial model provided a better fit than the Poisson model for all 11 outcomes (all p-values<0.001); therefore, negative binomial distributions were assumed in hurdle model evaluations.

Vuong tests were conducted to compare two-part logit-negative binomial hurdle models to one-part negative binomial models. Vuong tests suggested that hurdle models provided better fit for 10 of the 11 healthcare utilization outcomes (all p-values<0.001). The Vuong test for BM utilization did not converge due to extremely low utilization (< 0.1 %) in the non-ASD group, which itself supports the hurdle model process over a one-part negative binomial model.

The final dependent variables were outpatient office visits, OT/PT visits, speech therapy visits, inpatient visits, ED visits, and outpatient prescriptions, MHR outpatient office visits, BM visits, MHR inpatient visits, MHR ED visits, and MHR psychotropic prescriptions. The primary independent variable was ASD group membership (ASD vs. non-ASD), and covariates included health plan type (fully- vs. self-insured) and health plan product type (e.g., HMO, PPO, or other). Gender and age were not included in the statistical models because ASD and non-ASD were matched and balanced on both covariates. Cell size and convergence issues were encountered when U.S. state was included as a fixed effect; therefore, state-level clustering was addressed through cluster-robust standard errors in all objective 4 hypothesis tests.

Table 3.11 displays the parameter estimates generated by the logistic and zero-truncated negative binomial regression models. Likelihood ratio chi-square tests were

significant for all hurdle models, indicating that at least one coefficient was significantly different from zero in each model.

Part one of the two-part models was a logistic regression model predicting the presence or absence of any utilization during the one-year follow-up period. After controlling for other covariates, the ASD group was significantly more likely to have utilization across all outcomes (all p-values<0.001). For all-cause utilization, ASD patients were 11.6 times more likely to have at least one outpatient office visit versus the non-ASD group (OR=11.646; 95% CI=8.196-16.548; p<0.001), 3.6 times more likely to have at least one OT/PT visit (OR=3.583; 95% CI=2.933-4.378; p<0.001), 27.6 times more likely to have at least one speech therapy visit (OR =27.575; 95% CI=23.263-32.685; p<0.001), 4.5 times more likely to have at least one inpatient visit (OR=4.546; 95% CI=3.919-5.273; p<0.001), 1.5 times more likely to have at least one ED visit (OR=1.534; 95% CI=1.440-1.633; p<0.001), and 3.1 times more likely to have at least one outpatient prescription (OR =3.122; 95% CI =2.832-3.443; p<0.001), after controlling for other covariates. For MHR utilization, after controlling for other covariates, ASD patients were 42.3 times more likely to have at least one MHR outpatient office visit versus the non-ASD group (OR=42.262; 95% CI =37.068-48.185; p<0.001), 73.3 times more likely to have at least one BM visit (OR=73.286; 95% CI=45.145-118.971; p<0.001), 9.6 times more likely to have at least one MHR inpatient visit (OR=9.648; 95% CI=7.777-11.968; p<0.001), 9.8 times more likely to have at least one MHR ED visit (OR=9.785; 95% CI=8.080-11.850; p<0.001), and 12.0 times more likely to have at least one psychotropic outpatient prescription (OR=11.999; 95% CI=10.927-13.176; p<0.001).

Part two of the two-part models was a zero-truncated negative binomial regression model that, among those patients with at least one visit or prescription during the one-year follow-up period, compared the rates of utilization between ASD and non-ASD groups

while adjusting for other covariates. After controlling for other covariates and state-level clustering, the ASD group had higher rates of utilization across five of the six all-cause outcomes: outpatient office visits ($p<0.001$), OT/PT visits ($p<0.001$), speech therapy visits ($p<0.001$), outpatient ED visits ($p<0.001$), and outpatient prescription count ($p<0.001$), but not all-cause inpatient visits ($p=0.053$). After controlling for other covariates and state-level clustering, the ASD group had greater rates of utilization across three of the five MHR outcomes: outpatient office visits ($p<0.001$), outpatient ED visits ($p<0.001$), and outpatient psychotropic prescription count ($p<0.001$), but not BM visits ($p=0.749$) nor MHR inpatient visits ($p=0.671$).

Among those patients with at least one visit or prescription in each respective all-cause outcome, after controlling for other covariates, ASD patients were expected to have a rate of outpatient office visits 6.203 greater than non-ASD patients (IRR =6.203; 95% CI=5.350-7.193; $p<0.001$), a rate of OT/PT visits 3.5 times greater than non-ASD patients (IRR=3.464; 95% CI =3.051-3.932; $p<0.001$), a rate of speech therapy visits 1.8 times greater than non-ASD patients (IRR=1.775; 95% CI=1.581-1.992; $p<0.001$), a rate of outpatient ED visits 2.0 times greater than non-ASD patients (IRR=2.045; 95% CI =1.791-2.336; $p<0.001$), a rate of outpatient prescription count 3.8 times greater than non-ASD patients (IRR=3.759; 95% CI =3.590-3.935; $p<0.001$).

Among those patients with at least one visit or prescription in each respective MHR outcome, after controlling for other covariates, ASD patients were expected to have a rate of MHR outpatient office visits 3.9 times greater than non-ASD patients (IRR=3.896; 95% CI=3.237-4.688; $p<0.001$), a rate of MHR ED visits 2.6 times greater than non-ASD patients (IRR=2.571; 95% CI =1.555-4.252; $p<0.001$), and a rate of psychotropic outpatient prescriptions 2.0 times greater than non-ASD patients (IRR=1.955; 95% CI =1.840-2.078; $p<0.001$).

$H_0(4a)_1$: There is no significant difference in the number of **all-cause outpatient office visits** between ASD and non-ASD groups, after controlling for covariates.

[Rejected]

$H_0(4a)_2$: There is no significant difference in the number of **all-cause OT/PT visits** between ASD and non-ASD groups, after controlling for covariates.

[Rejected]

$H_0(4a)_3$: There is no significant difference in the number of **all-cause speech therapy visits** between ASD and non-ASD groups, after controlling for covariates.

[Rejected]

$H_0(4a)_4$: There is no significant difference in the number of **all-cause inpatient visits** between ASD and non-ASD groups, after controlling for covariates.

[Failed to reject]

$H_0(4a)_5$: There is no significant difference in the number of **all-cause ED visits** between ASD and non-ASD groups, after controlling for covariates.

[Rejected]

$H_0(4a)_6$: There is no significant difference in the number of **all-cause prescriptions** between ASD and non-ASD groups, after controlling for covariates.

[Rejected]

$H_0(4b)_1$: There is no significant difference in the number of **MHR outpatient office visits** between ASD and non-ASD groups, after controlling for covariates.

[Rejected]

$H_0(4b)_2$: There is no significant difference in the number of **behavioral modification visits** between ASD and non-ASD groups, after controlling for covariates.

[Failed to reject]

$H_0(4b)_3$: There is no significant difference in the number of **MHR inpatient visits** between ASD and non-ASD groups, after controlling for covariates.

[Failed to reject]

$H_0(4b)_4$: There is no significant difference in the number of **MHR ED visits** between ASD and non-ASD groups, after controlling for covariates.

[Rejected]

$H_0(4b)_5$: There is no significant difference in the number of **MHR prescriptions** between ASD and non-ASD groups, after controlling for covariates.

[Rejected]

Table 3.11: Negative binomial-logit hurdle model regression analysis comparing healthcare utilization between ASD and non-ASD groups (N=53,361)

Logistic regression*							
Outcome	**Est**	**OR**	**95% CI**		**Z statistic**	**p**	
All-cause utilization							
Outpatient office visits	2.455	11.646	8.196	16.548	13.696	< 0.001	
OT/PT visits	1.276	3.583	2.933	4.378	12.489	< 0.001	
Speech therapy visits	3.317	27.575	23.263	32.685	38.236	< 0.001	
Inpatient visits	1.514	4.546	3.919	5.273	19.991	< 0.001	
ED visits	0.428	1.534	1.440	1.633	13.337	< 0.001	
Outpatient Rx count	1.139	3.122	2.832	3.443	22.841	< 0.001	
Mental health-related utilization							
Outpatient office visits	3.744	42.262	37.068	48.185	55.953	< 0.001	
BM visits	4.294	73.286	45.145	118.971	17.372	< 0.001	
Inpatient visits	2.267	9.648	7.777	11.968	20.613	< 0.001	
ED visits	2.281	9.785	8.080	11.850	23.352	< 0.001	
Outpatient Rx count	2.485	11.999	10.927	13.176	52.062	< 0.001	
Zero-truncated negative binomial regression*							
Outcome	**Est**	**IRR**	**95% CI**		**Z statistic**	**p**	
All-cause utilization							
Outpatient office visits	1.825	6.203	5.350	7.193	24.165	< 0.001	**$H_0(4a)_1$**
OT/PT visits	1.242	3.464	3.051	3.932	19.184	< 0.001	**$H_0(4a)_2$**
Speech therapy visits	0.574	1.775	1.581	1.992	9.748	< 0.001	**$H_0(4a)_3$**
Inpatient visits	0.379	1.461	0.995	2.146	1.933	0.053	**$H_0(4a)_4$**
ED visits	0.716	2.045	1.791	2.336	10.558	< 0.001	**$H_0(4a)_5$**
Outpatient Rx count	1.324	3.759	3.590	3.935	56.618	< 0.001	**$H_0(4a)_6$**
Mental health-related utilization							
Outpatient office visits	1.360	3.896	3.237	4.688	14.398	< 0.001	**$H_0(4b)_1$**
BM visits	0.187	1.205	0.384	3.781	0.320	0.749	**$H_0(4b)_2$**
Inpatient visits	-0.093	0.911	0.593	1.401	-0.425	0.671	**$H_0(4b)_3$**
ED visits	0.944	2.571	1.555	4.252	3.680	< 0.001	**$H_0(4b)_4$**
Outpatient Rx count	0.670	1.955	1.840	2.078	21.629	< 0.001	**$H_0(4b)_5$**

BM=Behavioral modification; CI=Confidence interval; ED=emergency department; Est=Estimate; OR=Odds ratio; IRR; incidence rate ratio; OT=Occupational therapy; PT=Physical therapy; Rx=Prescription

* All parameters represent the relationship of ASD vs. non-ASD groups, and were generated while adjusting for plan type, product type, and complex chronic conditions. All confidence intervals were generated with cluster-robust standard errors for U.S. state-level clustering

3.2.6 Objective 5: Comparing healthcare expenditures between groups

The purpose of objective 5 was to determine if all-cause and MHR healthcare expenditures differ between ASD and non-ASD patients. The eight all-cause outcomes included total expenditures, outpatient office expenditures, OT/PT expenditures, speech therapy expenditures, inpatient expenditures, outpatient ED expenditures, prescription expenditures, and out-of-pocket expenditures. The seven MHR outcomes were total MHR expenditures, MHR outpatient office expenditures, BM expenditures, MHR inpatient expenditures, MHR ED expenditures, MHR prescription expenditures, and MHR OOP expenditures. Expenditure and zero inflation statistics are presented in **Table 3.12**. Overall mean (±SD) all-cause total expenditures, outpatient expenditures, OT/PT expenditures, speech therapy expenditures, inpatient expenditures, outpatient ED expenditures, prescription expenditures, and out-of-pocket expenditures were $6,861.79 (±$25,242.83), $2,181.37 (±$8,196.71), $252.17 (±$1,507.39), $199.85 (±$1,242.63), $881.43 (±$12,867.95), $150.19 (±$590.00), $1,186.27 (±$7,474.93), and $1,275.45 (±$4,560.48), respectively. Mean (±SD) MHR total expenditures, MHR outpatient expenditures, BM expenditures, MHR inpatient expenditures, MHR ED expenditures, MHR prescription expenditures, and MHR OOP expenditures were $3,398.15 (±$13,342.20), $1,286.48 (±$7,614.34), $163.51 (±$2,593.01), $283.73 (±$5,620.59), $13.58 (±$176.26), $613.33 (±$2,661.54), $417.44 (±$1,522.81), respectively. Bivariate Mann-Whitney U tests indicated significantly greater expenditures in the ASD group compared to the non-ASD group (all p-values<0.001) across all 15 expenditure-related outcomes.

Table 3.12 Descriptive statistics for post-index healthcare utilization overall and by group

	Overall (N=53,361)	ASD (n=17,787)	Non-ASD (n=35,574)	p*
All-cause expenditures				
Total				
Mean (SD)	$6,861.79 ($25,242.83)	$15,521.05 ($36,136.84)	$2,532.16 ($15,705.20)	
Median	$1,348.83	$5,954.85	$664.52	< 0.001
% 0	6.23	0.17	9.25	
Outpatient office				
Mean (SD)	$2,181.37 ($8,196.71)	$5,118.57 ($13,578.88)	$712.77 ($1,455.68)	
Median	$633.75	$1,894.72	$406.72	< 0.001
% 0	9.34	1.46	13.28	
OT/PT				
Mean (SD)	$252.17 ($1,507.39)	$648.03 ($2,485.24)	$54.24 ($450.22)	
Median	$0	$0	$0	< 0.001
% 0	88.34	78.62	93.20	
Speech therapy				
Mean (SD)	$199.85 ($1,242.63)	$570.37 ($2,070.63)	$14.60 ($263.75)	
Median	$0	$0	$0	< 0.001
% 0	93.68	82.50	99.26	
Inpatient				
Mean (SD)	$881.43 ($12,867.95)	$1,966.25 ($19,495.02)	$339.02 ($7,581.11)	
Median	$0	$0	$0	< 0.001
% 0	97.52	94.63	98.96	
Outpatient ED				
Mean (SD)	$150.19 ($590.00)	$226.80 ($755.01)	$111.89 ($482.43)	
Median	$0	$0	$0	< 0.001
% 0	85.60	81.33	87.73	
Outpatient Rx				
Mean (SD)	$1,186.27 ($7,474.93)	$2,521.06 ($10,921.88)	$518.87 ($4,778.53)	
Median	$47.97	$555.70	$14.88	< 0.001
% 0	30.84	15.83	38.34	
OOP				
Mean (SD)	$1,275.45 ($4,560.48)	$2,243.17 ($5,623.14)	$791.59 ($3,832.17)	
Median	$244.48	$1,007.67	$115.18	< 0.001
% 0	20.47	11.27	25.06	

Table 3.12 Descriptive statistics for post-index healthcare utilization overall and by group (continued)

Mental health-related expenditures				
Total				
Mean (SD)	$3,398.15 ($13,342.20)	$9,488.88 ($21,512.27)	$352.78 ($2,796.06)	
Median	$0	$3,077.99	$0	< 0.001
% 0	58.11	5.85	84.24	
Outpatient office				
Mean (SD)	$1,286.48 ($7,614.34)	$3,641.25 ($12,806.63)	$109.10 ($898.20)	
Median	$0	$827.68	$0	< 0.001
% 0	64.21	15.78	88.42	
BM				
Mean (SD)	$163.51 ($2,593.01)	$480.85 ($4,427.91)	$4.84 ($455.20)	
Median	$0	$0	$0	< 0.001
% 0	98.06	94.33	99.93	
Inpatient				
Mean (SD)	$283.73 ($5,620.59)	$749.51 ($9,426.67)	$50.84 ($1,671.70)	
Median	$0	$0	$0	< 0.001
% 0	98.70	96.74	99.68	
Outpatient ED				
Mean (SD)	$13.58 ($176.26)	$36.05 ($292.50)	$2.34 ($58.70)	
Median	$0	$0	$0	< 0.001
% 0	98.79	96.96	99.70	
Outpatient Rx				
Mean (SD)	$613.33 ($2,661.54)	$1,555.17 ($4,303.96)	$142.40 ($835.89)	
Median	$0	$129.90	$0	< 0.001
% 0	72.60	39.60	89.10	
OOP				
Mean (SD)	$417.44 ($1,522.81)	$1,111.93 ($2,429.96)	$70.20 ($405.50)	
Median	$0	$465.76	$0	< 0.001
% 0	63.12	17.88	85.74	

BM=Behavioral modification; CI=Confidence interval; ED=emergency department; Est=Estimate; OOP=Out-of-pocket; OT=Occupational therapy; PT=Physical therapy; Rx=Prescription; SD=Standard deviation

⁎ All bivariate tests were conducted using Mann-Whitney U

† Mean rounded down to 0.0

Prior to fitting statistical models, normality was checked numerically and visually. Kolmogorov-Smirnov tests for normality were conducted but not used for normality assessment due to the large sample size (n=53,361). Visual inspection of all 15 expenditure variables suggested right-skewness. Vuong tests were conducted and Akaike information criterion (AIC) values were generated to compare GLM fits between Gamma and Gaussian

(i.e., normal) models. Vuong tests were all significant (all p-values < 0.001) and AIC values were all higher in the Gaussian models when compared to the Gamma models, suggesting Gamma distributions provided better fit for all 15 expenditure models (all p-values < 0.001). Inverse Gaussian-distributed (i.e., Wald) GLMs were attempted to compare with Gamma-distributed models, but convergence issues were encountered. Therefore, a Gamma-distributed GLM was assumed for all dependent variables in objective 5.

The final dependent variables were total expenditures, outpatient office expenditures, OT/PT expenditures, speech therapy expenditures, inpatient expenditures, outpatient ED expenditures, prescription expenditures, out-of-pocket expenditures, total MHR expenditures, MHR outpatient office expenditures, BM expenditures, MHR inpatient expenditures, MHR ED expenditures, MHR prescription expenditures, and MHR OOP expenditures. The primary independent variable was ASD group membership (ASD vs. non-ASD), and covariates included health plan type (fully- vs. self-insured) and health plan product type (e.g., HMO, PPO, or other). Gender and age were not included in the statistical models because ASD and non-ASD were matched and balanced on both covariates. Cell size and convergence issues were encountered when U.S. state was included as a fixed effect, so state-level clustering was addressed through cluster-robust standard errors in all objective 5 hypothesis tests. **Table 3.13** displays the parameter estimates generated by the logistic and Gamma regression models addressing objective 5 hypotheses. Likelihood ratio chi-square tests were significant for all hurdle models, indicating that at least one coefficient was significantly different from zero in each model.

Part one of the two-part models was a logistic regression model predicting the presence or absence of any expenditures during the one-year follow-up period. After controlling for other covariates, the ASD group was significantly more likely to have expenditures for all outcomes (all p-values<0.001). For all-cause expenditures, ASD

patients were 55.3 times more likely to incur any expenditures versus the non-ASD group (OR=55.253; 95% CI=31.866-95.805; p<0.001), 9.7 times more likely to incur outpatient office expenditures (OR=9.668; 95% CI=6.927-13.494; p<0.001), 3.6 times more likely to incur OT/PT expenditures (OR=3.564; 95% CI=2.916-4.357; p<0.001), 27.8 times more likely to incur speech therapy expenditures (OR=27.840; 95% CI=23.444-33.060; p<0.001), 4.6 times more likely to incur inpatient expenditures (OR=4.566; 95% CI=3.933-5.302; p<0.001), 1.5 times more likely to incur outpatient ED expenditures (OR=1.535; 95% CI=1.442-1.633; p<0.001), 3.1 times more likely to incur outpatient prescription expenditures (OR=3.133; 95% CI=2.838-3.459; p<0.001), and 2.6 times more likely to incur OOP expenditures (OR=2.565; 95% CI=1.784-3.687; p<0.001). For MHR expenditures, after controlling for other covariates, ASD patients were 82.9 times more likely to incur any MHR expenditures versus the non-ASD group (OR=82.917; 95% CI=69.490-98.938; p<0.001), 40.7 times more likely to incur MHR outpatient office expenditures (OR=40.694; 95% CI=35.686-46.405; p<0.001), 82.2 times more likely to incur any behavioral modification expenditures (OR=82.168; 95% CI=49.240-137.114; p<0.001), 9.8 times more likely to incur any MHR inpatient expenditures (OR=9.817; 95% CI=7.879-12.231; p<0.001), 10.0 times more likely to incur any outpatient ED expenditures (OR=10.004; 95% CI=8.150-12.279; p<0.001), 12.0 times more likely to incur any psychotropic prescription expenditures (OR=11.997; 95% CI=10.932-13.166; p<0.001), and 27.9 times more likely to incur any MHR OOP expenditures (OR=27.898; 95% CI=20.761-37.491; p<0.001).

Part two of the two-part models was a Gamma regression model that, among those who incurred any expenditures in each respective outcome, compared rates of expenditures between ASD and non-ASD patients while controlling for other covariates.

Significant differences in mean expenditures between ASD and non-ASD groups were observed in seven of the eight all-cause outcomes, with the exception of inpatient expenditures (p=0.951). Among those patients who incurred any expenditures in each respective all-cause outcome, after controlling for other covariates, the expected mean total expenditures for ASD patients were 5.3 times the expected mean total expenditures of non-ASD patients (e^{β} =5.278; 95% CI=4.454-6.254; p<0.001), 6.0 times greater for mean outpatient office expenditures (e^{β}=6.033; 95% CI=4.507-8.077; p<0.001), 3.8 times for mean OT/PT expenditures (e^{β}=3.766; 95% CI=3.204-4.426; p<0.001), 1.7 times for mean speech therapy expenditures (e^{β}=1.651; 95% CI=1.429-1.906; p<0.001), 1.3 times for mean outpatient ED expenditures (e^{β}=1.289; 95% CI=1.181-1.407; p<0.001), 3.3 times for mean outpatient prescription expenditures (e^{β}=3.263; 95% CI=2.886-3.688; p<0.001), and 2.3 times for mean OOP expenditures (e^{β}=2.333; 95% CI=2.164-2.515; p<0.001).

Significant differences in mean expenditures between ASD and non-ASD groups were observed in six of the seven MHR outcomes, with the exception of behavioral modification (p=0.953). Among those patients who incurred any expenditures in each respective MHR outcome, after controlling for other covariates, the expected mean total MHR expenditures for ASD patients were 4.3 times the expected mean total expenditures of non-ASD patients (e^{β}=4.294; 95% CI=3.499-5.269; p<0.001), 4.4 times for mean MHR outpatient office expenditures (e^{β}=4.394; 95% CI=3.069-6.289; p<0.001), 1.3 times for mean MHR inpatient expenditures (e^{β}=1.338; 95% CI=1.051-1.702; p=0.018), 1.5 times for mean MHR ED expenditures (e^{β}=1.490; 95% CI=1.192-1.862; p<0.001), 1.8 times for mean psychotropic prescription expenditures (e^{β}=1.841; 95% CI=1.700-1.995; p<0.001), and 2.7 times for mean MHR OOP expenditures (e^{β}=2.737; 95% CI=2.446-3.061; p<0.001).

$H_0(5a)_1$: There is no significant difference in **all-cause total expenditures** between ASD and non-ASD groups, after controlling for covariates.

[Rejected]

$H_0(5a)_2$: There is no significant difference in **all-cause outpatient office expenditures** between ASD and non-ASD groups, after controlling for covariates.

[Rejected]

$H_0(5a)_3$: There is no significant difference in **all-cause OT/PT expenditures** between ASD and non-ASD groups, after controlling for covariates.

[Rejected]

$H_0(5a)_4$: There is no significant difference in **all-cause speech therapy expenditures** between ASD and non-ASD groups, after controlling for covariates.

[Rejected]

$H_0(5a)_5$: There is no significant difference in **all-cause inpatient expenditures** between ASD and non-ASD groups, after controlling for covariates.

[Failed to reject]

$H_0(5a)_6$: There is no significant difference in **all-cause ED expenditures** between ASD and non-ASD groups, after controlling for covariates.

[Rejected]

H_0(5a)$_7$: There is no significant difference in **all-cause prescription** expenditures between ASD and non-ASD groups, after controlling for covariates.

[Rejected]

H_0(5a)$_8$: There is no significant difference in **all-cause OOP** expenditures between ASD and non-ASD groups, after controlling for covariates.

[Rejected]

H_0(5b)$_1$: There is no significant difference in **total MHR expenditures** between ASD and non-ASD groups, after controlling for covariates.

[Rejected]

H_0(5b)$_2$: There is no significant difference in **MHR outpatient office expenditures** between ASD and non-ASD groups, after controlling for covariates.

[Rejected]

H_0(5b)$_3$: There is no significant difference in **behavioral modification expenditures** between ASD and non-ASD groups, after controlling for covariates.

[Failed to reject]

H_0(5b)$_4$: There is no significant difference in **MHR inpatient expenditures** between ASD and non-ASD groups, after controlling for covariates.

[Rejected]

H_0(5b)$_5$: There is no significant difference in **MHR ED expenditures** between ASD and non-ASD groups, after controlling for covariates.

[Rejected]

H_0(5b)$_6$: There is no significant difference in **MHR prescription expenditures** between ASD and non-ASD groups, after controlling for covariates.

[Rejected]

H_0(5b)$_7$: There is no significant difference in **MHR OOP expenditures** between ASD and non-ASD groups, after controlling for covariates.

[Rejected]

Table 3.13: Gamma-logit hurdle model regression analysis comparing healthcare expenditures between ASD and non-ASD groups, while controlling for other covariates (N=53,361)

Logistic regression*								
Outcome	**n**	**Est**	**OR**	**95% CI**		**Z statistic**	**p**	
All-cause expenditures								
Total	53,361	4.012	55.253	31.866	95.805	14.287	< 0.001	
Outpatient office	53,361	2.269	9.668	6.927	13.494	13.336	< 0.001	
OT/PT	53,361	1.271	3.564	2.916	4.357	12.410	< 0.001	
Speech therapy	53,361	3.326	27.840	23.444	33.060	37.938	< 0.001	
Inpatient	53,361	1.519	4.566	3.933	5.302	19.942	< 0.001	
ED	53,361	0.428	1.535	1.442	1.633	13.448	< 0.001	
Outpatient Rx	53,361	1.142	3.133	2.838	3.459	22.600	< 0.001	
OOP	53,361	0.942	2.565	1.784	3.687	5.086	< 0.001	
Mental health-related expenditures								
Total	53,361	4.418	82.917	69.490	98.938	49.014	< 0.001	
Outpatient office	53,361	3.706	40.694	35.686	46.405	55.312	< 0.001	
BM	53,361	4.409	82.168	49.240	137.114	16.875	< 0.001	
Inpatient	53,361	2.284	9.817	7.879	12.231	20.362	< 0.001	
ED	53,361	2.303	10.004	8.150	12.279	22.024	< 0.001	
Outpatient Rx	53,361	2.485	11.997	10.932	13.166	52.371	< 0.001	
OOP	53,361	3.329	27.898	20.761	37.491	22.076	< 0.001	
Gamma regression*								
Outcome	**n**	**Est**	**e^{Est}**	**95% CI**		**Z statistic**	**p**	
All-cause expenditures								
Total	50,039	1.664	5.278	4.454	6.254	19.205	< 0.001	**$H_0(5a)_1$**
Outpatient office	48,377	1.797	6.033	4.507	8.077	12.075	< 0.001	**$H_0(5a)_2$**
OT/PT	6,221	1.326	3.766	3.204	4.426	16.091	< 0.001	**$H_0(5a)_3$**
Speech therapy	3,374	0.501	1.651	1.429	1.906	6.817	< 0.001	**$H_0(5a)_4$**
Inpatient	1,326	0.007	1.007	0.807	1.257	0.062	0.951	**$H_0(5a)_5$**
ED	7,686	0.254	1.289	1.181	1.407	5.707	< 0.001	**$H_0(5a)_6$**
Outpatient Rx	36,905	1.182	3.263	2.886	3.688	18.918	< 0.001	**$H_0(5a)_7$**
OOP	42,440	0.847	2.333	2.164	2.515	22.107	< 0.001	**$H_0(5a)_8$**
Mental health-related expenditures								
Total	22,354	1.457	4.294	3.499	5.269	13.957	< 0.001	**$H_0(5b)_1$**
Outpatient office	19,100	1.480	4.394	3.069	6.289	8.088	< 0.001	**$H_0(5b)_2$**
BM	1,034	-0.038	0.963	0.269	3.442	-0.058	0.953	**$H_0(5b)_3$**
Inpatient	693	0.291	1.338	1.051	1.702	2.368	0.018	**$H_0(5b)_4$**

Table 3.13: Gamma-logit hurdle model regression analysis comparing healthcare expenditures between ASD and non-ASD groups, while controlling for other covariates (N=53,361)

ED	647	0.399	1.490	1.192	1.862	3.498	< 0.001	**H_0(5b)$_5$**
Outpatient Rx	14,622	0.611	1.841	1.700	1.995	14.946	< 0.001	**H_0(5b)$_6$**
OOP	19,680	1.007	2.737	2.446	3.061	17.595	< 0.001	**H_0(5b)$_7$**

BM=Behavioral modification; CI=Confidence interval; ED=emergency department; Est=Estimate; IRR; incidence rate ratio; OOP=Out-of-pocket; OR=Odds ratio; OT=Occupational therapy; PT=Physical therapy; Rx=Prescription

* All parameters represent the relationship of ASD vs. non-ASD groups, and were generated while adjusting for plan type, product type, and complex chronic conditions. All confidence intervals were generated with cluster-robust standard errors for U.S. state-level clustering

Table 3.14: Results of hypothesis tests

Objectives/hypotheses	Statistical analysis	Result
Objective 1: *To quantify and explain geographic variation in treated prevalence of ASD in commercially-enrolled children*		
1a: To determine the overall treated prevalence of ASD in children 18 or less enrolled in commercial healthcare plans.	Calculation	**No hypothesis**
1b: To quantify treated prevalence of ASD in children 18 or less enrolled in commercial healthcare plans within each ZIP3 region.	Descriptive statistics	**No hypothesis**
1c: To explain geographic variation in the treated prevalence of ASD as a function of geographic, health system, and socioeconomic characteristics.		
$H_0(1c)_1$: There is no significant difference in the treated prevalence of ASD with respect to **geographic region**, after controlling for covariates*.	Negative binomial regression	**Failed to reject**
$H_0(1c)_2$: There is no significant difference in the treated prevalence of ASD with respect to **fully insured plan density**, after controlling for covariates*.		**Rejected**
$H_0(1c)_3$: There is no significant difference in the treated prevalence of ASD with respect to **pediatrician density**, after controlling for covariates*.		**Unable to test**
$H_0(1c)_4$: There is no significant difference in the treated prevalence of ASD with respect to **psychologist density**, after controlling for covariates*.		**Unable to test**
$H_0(1c)_5$: There is no significant difference in the treated prevalence of ASD with respect to **median family income**, after controlling for covariates*.		**Rejected**
$H_0(1c)_6$: There is no significant difference in the treated prevalence of ASD with respect to **single-parent family density**, after controlling for covariates*.		**Failed to reject**
$H_0(1c)_7$: There is no significant difference in the treated prevalence of ASD with respect to **private school enrollment density**, after controlling for covariates*.		**Rejected**
$H_0(1c)_8$: There is no significant difference in the treated prevalence of ASD with respect to **poverty status density**, after controlling for covariates*.		**Unable to test**
$H_0(1c)_9$: There is no significant difference in the treated prevalence of ASD with respect to **percent white**, after controlling for covariates*.		**Rejected**
$H_0(1c)_{10}$: There is no significant difference in the treated prevalence of ASD with respect to **urbanicity**, after controlling for covariates*.		**Rejected**
Objective 2: *To describe and compare study characteristics of patients diagnosed with ASD to those without ASD*	Bivariate analyses	**No hypotheses**
Objective 3: *To quantify and compare age-specific treated prevalence of psychiatric conditions between ASD and non-ASD groups*		
$H_0(3)_1$: There is no significant difference in the age-related **likelihood of adjustment disorder** between ASD and non-ASD groups, after controlling for covariates†.	Logistic regression	**Failed to reject**
$H_0(3)_2$: There is no significant difference in the age-related **likelihood of anxiety disorder** between ASD and non-ASD groups, after controlling for covariates†.	Logistic regression	**Rejected**

Table 3.14: Results of hypothesis tests (continued)

$H_0(3)_3$: There is no significant difference in the in the age-related **likelihood attention-deficit conduct or disruptive behavior disorder** between ASD and non-ASD groups, after controlling for covariates†.	Logistic regression	**Rejected**
$H_0(3)_4$: There is no significant difference in the in the age-related **likelihood of mood disorder** between ASD and non-ASD groups, after controlling for covariates†.	Logistic regression	**Rejected**
$H_0(3)_5$: There is no significant difference in the in the age-related **likelihood of personality disorder** between ASD and non-ASD groups, after controlling for covariates†.	Logistic regression	**Failed to reject**
$H_0(3)_6$: There is no significant difference in the in the age-related **likelihood of schizophrenia or other psychotic disorder** between ASD and non-ASD groups, after controlling for covariates†.	Logistic regression	**Rejected**
$H_0(3)_7$: There is no significant difference in the in the age-related **likelihood of alcohol or substance-related disorder** between ASD and non-ASD groups, after controlling for covariates†.	Logistic regression	**Failed to reject**
Objective 4: *To quantify and compare healthcare utilization between children diagnosed with ASD to those without ASD*		
4a: To quantify and compare healthcare utilization for all-cause outpatient office, inpatient, and ED visits, and psychotropic medications between ASD and non-ASD groups. Within outpatient office visits, this objective also quantifies and compares OT/PT and speech therapy visits.		
$H_0(4a)_1$: There is no significant difference in number of **all-cause outpatient office visits** between ASD and non-ASD groups, after controlling for covariates†.	Negative binomial GLM	**Rejected**
$H_0(4a)_2$: There is no significant difference in number of **all-cause OT/PT visits** between ASD and non-ASD groups, after controlling for covariates†.	Negative binomial GLM	**Rejected**
$H_0(4a)_3$: There is no significant difference in number of **all-cause speech therapy visits** between ASD and non-ASD groups, after controlling for covariates†.	Negative binomial GLM	**Rejected**
$H_0(4a)_4$: There is no significant difference in number of **all-cause inpatient visits** between ASD and non-ASD groups, after controlling for covariates†.	Negative binomial GLM	**Failed to reject**
$H_0(4a)_5$: There is no significant difference in number of **all-cause ED visits** between ASD and non-ASD groups, after controlling for covariates†.	Negative binomial GLM	**Rejected**
$H_0(4a)_6$: There is no significant difference in number of **all-cause outpatient prescriptions** between ASD and non-ASD groups†.	Negative binomial GLM	**Rejected**

Table 3.14: Results of hypothesis tests (continued)

4b: To quantify and compare healthcare utilization for MHR outpatient office, inpatient, and ED visits, and psychotropic prescriptions between ASD and non-ASD groups. Within MHR office visits, this objective also quantifies and compares Behavioral modification visits between ASD and non-ASD groups.		
H_0(4b)$_1$: There is no significant difference in the number of **MHR outpatient office visits** between ASD and non-ASD groups, after controlling for covariates†.	Negative binomial GLM	**Rejected**
H_0(4b)$_2$: There is no significant difference in the number of **behavioral modification visits** between ASD and non-ASD groups, after controlling for covariates†.	Negative binomial GLM	**Failed to reject**
H_0(4b)$_3$: There is no significant difference in the number of **MHR inpatient visits** between ASD and non-ASD groups, after controlling for covariates†.	Negative binomial GLM	**Failed to reject**
H_0(4b)$_4$: There is no significant difference in the number of **MHR ED visits** between ASD and non-ASD groups, after controlling for covariates†.	Negative binomial GLM	**Rejected**
H_0(4b)$_5$: There is no significant difference in the number of **outpatient psychotropic prescriptions** between ASD and non-ASD groups†.	Negative binomial GLM	**Rejected**
Objective 5: *To quantify and compare healthcare expenditures between children diagnosed with ASD to those without ASD*		
5a: To quantify and compare all-cause expenditures both overall, and for outpatient visits, inpatient visits, ED visits, outpatient prescriptions, and OOP between ASD and non-ASD groups. Within outpatient office expenditures, this objective also quantifies and compares OT/PT and speech therapy expenditures between ASD and non-ASD groups.		
H_0(5a)$_1$: There is no significant difference in **all-cause expenditures** between ASD and non-ASD groups, after controlling for covariates†.	Gamma GLM	**Rejected**
H_0(5a)$_2$: There is no significant difference in **all-cause outpatient office expenditures** between ASD and non-ASD groups, after controlling for covariates†.	Gamma GLM	**Rejected**
H_0(5a)$_3$: There is no significant difference in **all-cause OT/PT expenditures** between ASD and non-ASD groups, after controlling for covariates†.	Gamma GLM	**Rejected**
H_0(5a)$_4$: There is no significant difference in **all-cause speech therapy expenditures** between ASD and non-ASD groups, after controlling for covariates†.	Gamma GLM	**Rejected**
H_0(5a)$_5$: There is no significant difference in **all-cause inpatient expenditures** between ASD and non-ASD groups, after controlling for covariates.†.	Gamma GLM	**Failed to reject**
H_0(5a)$_6$: There is no significant difference in **all-cause ED expenditures** between ASD and non-ASD groups, after controlling for covariates†.	Gamma GLM	**Rejected**
H_0(5a)$_7$: There is no significant difference in **all-cause prescription expenditures** between ASD and non-ASD groups†.	Gamma GLM	**Rejected**

Table 3.14: Results of hypothesis tests (continued)

H_0(5a)$_8$: There is no significant difference in all-cause **OOP expenditures** between ASD and non-ASD groups†.	Gamma GLM	**Rejected**
5b: To quantify and compare MHR expenditures both overall, and for outpatient, inpatient, ED visits, outpatient prescription, and OOP between ASD and non-ASD groups. Within MHR office expenditures, this objective also quantifies and compares OT/PT and speech therapy expenditures between ASD and non-ASD groups.		
H_0(5b)$_1$: There is no significant difference in **MHR expenditures** between ASD and non-ASD groups, after controlling for covariates†.	Gamma GLM	**Rejected**
H_0(5b)$_2$: There is no significant difference in **MHR outpatient office expenditures** between ASD and non-ASD groups, after controlling for covariates†.	Gamma GLM	**Rejected**
H_0(5b)$_3$: There is no significant difference in **behavioral modification expenditures** between ASD and non-ASD groups, after controlling for covariates†.	Gamma GLM	**Failed to reject**
H_0(5b)$_4$: There is no significant difference in **MHR inpatient expenditures** between ASD and non-ASD groups, after controlling for covariates†.	Gamma GLM	**Rejected**
H_0(5b)$_5$: There is no significant difference in **MHR ED expenditures** between ASD and non-ASD groups, after controlling for covariates†.	Gamma GLM	**Rejected**
H_0(5b)$_6$: There is no significant difference in **MHR prescription expenditures** between ASD and non-ASD groups†.	Gamma GLM	**Rejected**
H_0(5b)$_7$: There is no significant difference in **MHR OOP expenditures** between ASD and non-ASD groups†.	Gamma GLM	**Rejected**

ASD=Autism Spectrum Disorder; BM=Behavioral modification; E=East; ED=Emergency department; FI=Fully insured; MHR=Mental health-related; MW=Midwest; O=Other; OOP=Out-of-pocket; OT/PT=Occupational or physical therapy; S=South; W=West

* Covariates for objective 1 include geographic region, fully insured plan density, median family income, single-parent family density, private school enrollment density, percent white, and urbanicity

† Covariates for objectives 3-5 include age-at-index, gender, U.S. State, health payer type, health plan product type, and a numeric measure of pre-index complex chronic conditions

CHAPTER 4: DISCUSSION AND CONCLUSION

4.1 Chapter overview

This chapter provides a comprehensive discussion of the study results. The chapter begins by reintroducing the study purpose and objectives. It then provides comparisons of the study findings with those of related studies found in the literature, and offers possible explanations of study findings. The chapter ends with a description of study limitations, implications, and suggestions for future research.

4.2 Review of purpose, study objectives, and comparisons with previous literature

This section will restate the purpose of the current study, both overall and for each of the three components (i.e., manuscripts). Objective-level conclusions will then be drawn, and findings will be compared with those found in previous literature.

4.2.1: Study purpose

The primary purpose of this study is to contribute to the growing body of evidence regarding the prevalence of ASD, and utilization of and expenditures for healthcare services used in treating commercially insured children diagnosed with ASD. The first component of this study estimates and explains geographic variation in the treated prevalence of ASD. The second component describes and compares prevalence rates of psychiatric conditions between ASD and non-ASD groups. The third component of this study estimates the difference in healthcare utilization and expenditures between ASD and non-ASD groups.

4.2.2 Objective 1: ASD prevalence

The aims of objective 1 were to: (1) determine the overall treated prevalence of ASD in children 18 or less enrolled in commercial healthcare plans; (2) to quantify treated

prevalence of ASD within each ZIP3 region; and (3) to explain geographic variation in the treated prevalence in ASD as a function of geographic, health system, and socioeconomic characteristics.

Previous publications have measured state-level ASD prevalence rates from various perspectives, including provider,[3,51] parent,[50] commercial payers,[56,61,63,74] and public payers[54,55,59]. From the commercial payer perspective, the overall one-year prevalence of 6.84 per 1,000 children observed in the current study exceeds the most-recent three-year period prevalence rate in commercially insured children by over 50 percent (4.0 per 1,000).[199] The overall ASD prevalence observed in this study also exceeds some prevalence rates such as those in the Pennsylvania Medicaid population reported by Mandell, 2006 (1.10-1.13 per 1,000) and a nationally-representative Medicaid sample reported by Wang, 2013 (6.23 per 1,000 children).[54,55,59] The present findings are consistent with previous literature suggesting that ASD prevalence rates are increasing over time, and provides support for the notion that treated prevalence rates sampled from health plan populations are increasing as well.

The most recent provider-reported prevalence rate obtained through the CDC's ADDM Network (described in **Section 1.3.2**) is 16.9 per 1,000 8-year-olds, and the latest parent-reported rate is 24.7 per 1,000 children aged 3-17 years.[3,50] The 2017 prevalence observed in this study was 6.84 per 1,000 children; although the rate is consistent with previous payer-sampled estimates, it is below both clinic and parent-reported estimates. This finding supports the notion that prevalence estimates using claims data may better-represent treated prevalence than true prevalence estimates, as ASD diagnoses identified in claims data are driven by healthcare service use.

Of the 11 state-level ADDM sites, the state of New Jersey exhibited the highest prevalence rate at 29.3 per 1,000 8-year-olds, while our state-level estimates in a sample

of commercially-enrolled 3-17 year-olds ranked New Jersey as sixth among the 11 states represented by ADDM data. The highest prevalence rate we observed from the ADDM states was for Wisconsin at 6.87 per 1,000. One possible explanation for these inconsistent findings is that site-level estimates may not be generalizable to entire states in which they belong. The results of this study were also obtained through a broader sample in terms of age when compared to the ADDM analysis (3-17 vs. 8 years of age).

The second and third components of objective 1 were to measure prevalence rates at the ZIP3 level, then explain variation in prevalence using demographic, health-system, and socioeconomic characteristics. This study reflects a novel approach of measuring ASD prevalence at the ZIP3 level. To date, only one other study (Mandell, et al., 2010) has evaluated geographic variation in ASD prevalence. That 2004 study evaluated ASD prevalence rates of Medicaid enrollees at the county level.[52] Mandell and colleagues evaluated education, healthcare resource, and demographic characteristics, and converted all continuous covariates into quartiles, consistent with the approach taken in the present study.

Some explanatory variables included by Mandell and associates were not accessible at the ZIP3 level for the current study including education, healthcare resource, and provider (e.g., pediatrician density and psychologist density) characteristics. Characteristics evaluated in both the present and the Mandell, 2010 analyses included median income and percent white.

This analysis found a significant relationship between median income and prevalence in both unadjusted and adjusted analyses, which contrasted with results reported in the Medicaid population by Mandell and colleagues, where no relationship was observed between median income and prevalence rates in adjusted analyses. One possible explanation is that poverty status density and median income were both included in

Mandell and colleagues' adjusted model; however, inclusion of both variables created collinearity issues in our analysis and poverty status density was ultimately excluded. The present study's findings are also consistent with those from analyses outside the health plan perspective that found direct relationships between income and ASD prevalence.[200–202]

A contrast between the current study and Mandell, 2010 was also observed in the relationship between percent white and prevalence. The present study showed an inverse relationship between percent white and prevalence after adjusting for other covariates with significance in quartile 4 (RR_{Q4}=0.462; p=0.012), while Mandell and colleagues observed a direct relationship in the adjusted analysis (RR_{Q4}=1.271; p<0.001). However, the relationship was not significant in the present study's unadjusted analysis, which may suggest type I error in the adjusted model.

According to analyses of patients sampled outside health plan populations, a relationship between race and ASD prevalence does not exist after controlling for income.[201] Therefore, an absence of a significant race-prevalence relationship in the adjusted model is consistent with previous studies outside health plan populations. For example, an analysis of CDC ADDM Network data by Durkin and colleagues observed lower prevalence rates among ethnic minorities only in the low socioeconomic status (SES) category, but found no significant disparity in medium and high SES categories, suggesting a race-prevalence relationship may be driven by greater proportions of ethnic minorities in lower income categories.[201] In other words, race may be related to ASD prevalence, but only through its relationship with income.

The present analysis is the first to evaluate geographic region, fully insured plan density, single-parent family density, private school enrollment density, and urbanicity as predictors of ASD prevalence in a population of health plan enrollees. No relationship was observed between ZIP3 prevalence and geographic region in both unadjusted and adjusted

analyses after standard errors were adjusted for state-level clustering, which suggests that state-level factors may be driving regional differences in prevalence rates.

Fully insured plan density, a variable unique to commercial health plans, was significantly related to ASD prevalence, which became significant when comparing the third quartile to the first (RR_{Q3} =2.007; p=0.018). However, the parameter's loss of significance in the fourth quartile may suggest the absence of a true relationship. This finding contrasts with a previous analysis by Mandell and colleagues indicating that treated prevalence is directly related to enrollment in fully insured versus self-insured commercial health plans.[53]

A significant relationship was not observed between single-parent family density and ASD prevalence in the adjusted model. This finding could be explained by the limited range reflected in the single parent family density covariate (11.4%-29.9%).

A significant relationship was observed between private school enrollment density and prevalence but did not strengthen from quartile two to quartiles three and four (all vs. quartile 1), which suggests the relationship may be asymptotic. In other words, there may not be a marginal increase in ASD prevalence once a region's private school enrollment density exceeds the range reflected in quartile two (18.1%).

One significant relationship was observed between urbanicity and ASD prevalence (RR_{Q3} =0.635; p=0.003); however, similar to fully insured plan density, it may not represent a true relationship in light of the trend's reversal towards the null in the fourth quartile.

In summary, the present analysis sheds light on the current ASD coverage landscape represented by commercial health plans. The present findings suggest that overall prevalence rates in health plans are increasing concurrently with prevalence rates observed from outside the health plan perspective. The results also suggest that, despite

increases in overall prevalence, significant geographic variation remains at both the state and ZIP3 levels. Relationships between prevalence rates and geographic, health system, and socioeconomic characteristics were also assessed, and differences were compared with a previous analysis of Medicaid enrollees. The current findings and comparisons suggest that relationships between median income and percent white may differ in commercial and Medicaid populations.

4.2.3 Objective 2: Comparison of baseline characteristics

The purpose of objective 2 was to describe and compare demographic, health-system, and clinical characteristics of patients diagnosed with ASD to an age- and gender-matched control group of patients without an ASD diagnosis. Based on the literature review, this is the first study that compares commercially insured ASD and non-ASD patients with respect to geographic region, health plan type, health product type, and a set of medical comorbidities.

The ASD and non-ASD groups were matched, and thus perfectly balanced, on age and gender. Despite being identically distributed across groups, overall age and gender distributions were assessed and compared with those observed in previous literature. The ratio of male-to-female patients in the current analysis was 4:1, which is consistent with ratios observed in previous literature.[38,60] The mean age overall was 11.05 years, which is higher than mean ages published in other studies in commercially insured pediatric cohorts.[59,60,149,151] One likely explanation is the current analysis excluded patients younger than three years for reliability concerns, a threshold not required in previous analyses. One previous analysis required the same age threshold for inclusion, but was conducted in a publicly insured population and did not report an overall mean age.[76]

Group differences were also observed with respect to geographic region. A greater proportion of patients were observed in the eastern and western regions of the United States. No previous studies were found that presented prevalence rates at the level of Census Region. However, CDC data suggest that prevalence rates are higher in the eastern United States, with the New Jersey ADDM site reporting the highest ASD prevalence of the 11 sites.[51] However, ADDM states in the Midwest also reported high prevalence rates. This finding suggests that ADDM estimates may not be representative of entire states in which they belong. The findings of this study were also obtained through a broader sample of patients with respect to age (3-18 vs. 8 years).

In contrast with previous analyses in commercial populations, no significant group difference in proportions of patients with ASD was observed with respect to health plan type in the current study.[53] This finding supports data by Autism Speaks and groups of large employers, both of which suggest that self-insured health plans have increased coverage of ASD-related services, and may suggest that parity in ASD coverage exists between fully- and self-insured health plans.[141–143] This contrast in findings between the current study and previous literature highlights the need to update ASD prevalence rates in current commercial populations, and supports the notion that current ASD commercial populations may be different with respect to ASD-related coverage than samples observed in previous studies.

Group differences in ASD frequency were also observed with respect to health plan product type. The present study found a 2.9 percent greater proportion of ASD patients in HMO plans, and a 0.5 percent lower rate in PPO plans when compared to the non-ASD group. A previous analysis of a commercial pediatric population by Barry and colleagues observed a slightly lower proportion of ASD patients in HMO plans (13.5% vs. 14.1%).[146] This finding suggests that ASD patients may be more likely to be diagnosed in managed

care settings, although the 2.9 and 0.5 percent differences observed in the current analysis may not be considered meaningful.

The present study is also innovative in its approach to measuring and comparing the rates of baseline medical conditions between ASD and non-ASD populations. Previous literature suggests higher rates of genetic conditions and epilepsy in ASD populations when compared to rates in the general population.[68,69,79,80,203] The current study found that 5.1 percent of ASD patients were diagnosed with a congenital or genetic condition, which is much lower than the 25% estimated by the American Academy of Pediatrics .[79] The current analysis also found that almost six percent of patients with ASD were diagnosed with comorbid neurologic or neuromuscular conditions, including epilepsy. This estimate is lower than the previous prevalence estimates of epilepsy in ASD populations, which are as high as 30%. The lower rates of genetic conditions and neurologic or neuromuscular conditions observed in this commercial population could be explained by previous observations that these conditions are more prevalent in intellectually disabled ASD patients, which qualifies for Medicaid enrollment in a majority of U.S. states.[204–206] This finding underscores the importance of measuring rates of medical comorbidities in ASD populations, and highlights the need of doing so in Medicaid populations as well, where rates of medical comorbidities are likely more magnified.

4.2.4 Objective 3: Comparing age-related prevalence in psychiatric conditions between groups

Although the primary purpose of objective 3 was to compare the age-related prevalence of the seven categories of psychiatric conditions between ASD and non-ASD groups, prevalence rates were also compared at an overall level to contribute to a growing body of evidence comparing overall prevalence rates of psychiatric conditions between

ASD and non-ASD populations.[73,149] The most recently-published analysis measuring rates of psychiatric comorbidities in ASD populations was an analysis of 2000-2004 data by Leslie and colleagues, which measured rates of adjustment disorders, anxiety disorders, bipolar disorder, depression, hyperactivity disorders, intellectual disability, psychosis, and substance abuse in commercially insured children 18 years and younger.[60] Leslie and colleagues observed that hyperactivity disorders were the most-prevalent of all psychiatric conditions at 18.3%. The current study estimated 43% of ASD patients were diagnosed with attention-deficit, conduct, and disruptive behavior disorders, a broader category that also includes conduct and emotional disorders in addition to the hyperactivity disorders included by Leslie and colleagues. Leslie and colleagues observed prevalence rates of 3.9% for adjustment disorders, 7.6% for anxiety disorders, 1.0% for psychosis, and 0.01% for substance abuse (not including alcohol). The current analysis observed a 5.0% rate of adjustment disorders, 30% rate for anxiety disorders, a 0.8% rate of schizophrenia and other psychotic disorders, and a 0.6% rate of alcohol and substance-related disorders. Leslie and colleagues observed prevalence rates of 14.0% for depression and 3.1% for bipolar disorder, while a prevalence rate of 14.6% for mood disorders, which included depression and bipolar, was observed in the current study.

There are a few possible explanations for the observed differences between the current observations and those made by Leslie and colleagues. Due to the nature of CCS definitions, all types of psychiatric disorders in the current analysis were more-broadly defined compared to the approach taken by Leslie and colleagues.

The primary and novel purpose of objective 3 was to compare the age-related prevalence of the seven groups of psychiatric conditions between ASD and non-ASD groups. In the current study, adjusted analyses suggest that age-related trends in prevalence rates of anxiety disorders, conduct and behavior disorders, mood disorders, and

schizophrenic and psychotic disorders are higher for commercially insured ASD patients when compared to an age and gender-matched non-ASD group.

Although group differences were observed in the overall prevalence of adjustment disorders, personality disorders, and alcohol and substance-related disorders, no group differences were observed in the age-related prevalence trends. Visual inspection suggested that prevalence rates were not as stable across age for adjustment and personality disorders when compared to those psychiatric conditions on which significant group differences were observed. Visual inspection of age-related trends of alcohol and substance-related disorders show a separation beginning around 16 years of age, which may suggest significant trend differences in older, young adult population

4.2.5 Objectives 4 and 5: Comparing healthcare utilization and expenditures between ASD and non-ASD groups

4.2.5.1 Objective 4: Healthcare utilization

The primary purpose of objective 4 was to determine if six all-cause and five MHR healthcare utilization rates differ between groups of ASD and non-ASD patients, after controlling for covariates. At least three previous analyses have evaluated healthcare utilization in commercially insured children with ASD.[59,149]

Findings from the current analysis suggest that, when compared to patients without ASD, commercially insured pediatric patients with ASD are significantly more likely to engage in all types of all-cause utilization measured, including outpatient office, OT/PT, speech therapy, inpatient, ED visits, and outpatient prescriptions. ASD patients were also more likely to utilize MHR healthcare resources, which suggests that MHR utilization is partly driving all-cause utilization. Among those patients in ASD and non-ASD groups with any healthcare utilization in each category, ASD patients experienced higher rates of

utilization than non-ASD patients across all categories except all-cause and MHR inpatient visits, and MHR BM visits. The lack of significant relationships between groups in inpatient and BM visits could be due to high zero-inflation, which is supported by the significance of adjusted part one models (i.e., logit models).

4.2.5.1.1 Comparison of utilization findings with previous analyses of commercial populations

Two previous studies have estimated healthcare utilization in commercially insured ASD populations. The first analysis, published by Croen and colleagues, was conducted in a sample of California patients enrolled in the Kaiser Permanente Medical Care program between July 2003 and June 2004.[149] The analysis captured mean annual rates of outpatient visits, ED visits, and overall and psychotropic prescriptions. Compared to Croen, 2006, the current analysis found higher mean rates of outpatient visits (28.2 vs. 5.6 visits per year), ED visits (0.3 vs. 0.2 visits per year), and prescriptions (16.6 vs. 6.1 prescriptions per year). Mean psychotropic prescription utilization was also higher in the current analysis (10.6 vs. 3.4 prescriptions per year). MHR visits were assessed by Croen and colleagues as well, but only visits with psychiatric providers were considered MHR utilization, in contrast to our approach of capturing MHR visits through MHR diagnosis codes, which included MHR visits to any providers. Therefore, MHR utilization comparisons between the current study and Croen and colleagues were not considered meaningful.

4.2.5.1.2 Comparison of utilization findings with previous analyses of Medicaid populations

Of the previous utilization and expenditure analyses in health plan populations, Wang, 2013 most-closely resembles the current analysis, and presented mean utilization rates from OT/PT visits, speech therapy visits, and BM visits in both a Medicaid and

commercial population of ASD patients. Findings from the current analysis suggest higher mean rates of OT/PT visits (6.0 vs. 0.9 visits per year), speech therapy visits (6.3 vs. 3.6 visits per year), and BM visits (2.4 vs. 1.1 visits per year) when compared to the commercially insured cohort in Wang, 2013. When compared to the Medicaid cohort presented in Wang and colleagues, the current analysis observed slightly lower rates of OT/PT visits (6.0 vs. 6.4 visits per year) and BM visits (2.4 vs. 3.8 visits per year), and less than half the rate of speech therapy visits (6.3 vs. 13.0 visits per year).

The findings from Wang, 2013 provide a unique opportunity to compare results from the current study to previous commercial ASD populations as well as previous Medicaid ASD populations. The current study suggests that healthcare utilization is now greater than those seen in previous commercial populations and closer to that seen in previous Medicaid populations.

4.2.5.1.1 Summary of utilization findings

The present findings suggest that healthcare utilization by commercially insured ASD populations have increased significantly since 2003, but may still fall short of healthcare utilization represented by ASD populations in Medicaid health plans. These 2016-2017 data also support literature suggesting coverage of ASD-related services has increased overall utilization over time in light of state-level ASD coverage mandates.[146]

4.2.5.2 Objective 5: Healthcare expenditures

The primary purpose of objective 5 was to determine if eight all-cause and seven MHR healthcare expenditure rates differ between ASD and non-ASD patients, after controlling for covariates. Findings from the current analysis suggest that, when compared to patients without ASD, commercially insured pediatric patients with ASD are

significantly more likely incur all types of all-cause expenditures measured, including total, outpatient office, OT/PT, speech therapy, inpatient, ED visits, outpatient prescription, and OOP expenditures. ASD patients were also more likely to incur all types of MHR healthcare expenditures, which suggests that MHR visits are partly driving all-cause expenditures. Among those patients with any healthcare expenditures in each category, ASD patients experienced greater rates of expenditures than non-ASD patients across all categories except all-cause inpatient visits and BM visits, which could be explained by the high zero-inflation observed for both variables. Outpatient expenditures measured in previously-published analyses included all outpatient expenditures and not just those from outpatient office visits (our approach); therefore, outpatient expenditures will not be compared between the current study and previous commercial and Medicaid populations.

4.2.5.2.1 Comparison of expenditure findings with previous analyses of commercial populations

Four previous analyses have evaluated total healthcare expenditures in commercially insured children with ASD and were all conducted in 2003 or 2004.[56,60,149,151] The total mean expenditures of $15,521 found in this analysis were greater than all four previously published total mean expenditures, which ranged from $4,160 to $10,929 per year after adjusting to 2017 dollars.

Two of the four ASD expenditure studies also evaluated specific expenditures (e.g., outpatient office) in addition to total expenditures.[56,149] Croen and colleagues estimated mean annual expenditures for inpatient ($630) and ED ($103) visits, as well as expenditures for all-cause and psychotropic prescriptions ($1,110 and $921, respectively).[149] The mean inpatient ($1,966) and ED ($227) expenditures in the current study were all higher than those observed in Croen, 2006. All-cause outpatient prescription

and psychotropic prescription expenditures were also greater in the current study ($2,521 and $1,555, respectively).

Wang, 2013 is the only previous study found in the literature review that provided mean expenditure estimates for MHR services in addition to all-cause estimates.[56] Wang and colleagues calculated mean annual expenditures overall ($8,407), as well as for OT/PT ($72), speech therapy ($363), inpatient ($1,727), and outpatient prescription ($1,807) categories. Total MHR expenditures were calculated ($3,669) in addition to MHR BM ($107), inpatient ($546), and psychotropic prescription ($1,400) expenditures. In the current study, mean OT/PT ($648), speech therapy ($570), and inpatient ($1,966) expenditures were all greater than those observed by Wang and colleagues. For MHR expenditure categories, total ($9,489), BM ($481), inpatient ($750), and psychotropic prescription ($1,555) expenditures were all greater than those expenditures observed by Wang and colleagues.

4.2.5.2.2 Comparison of expenditure findings with previous analyses of commercial populations

Three previous analyses evaluated total healthcare expenditures in commercial-insured children with ASD, and were all conducted between 1994 and 2005.[54,56,76] Expenditures generated by Cidav and colleagues were generated from only those utilizers of each respective service type and will not be compared to expenditures in the current analysis using a larger denominator of all ASD patients. The total mean expenditures observed in the current study of $15,521 were less than 2017-adjusted expenditures reported by Wang and colleagues ($36,248) and Mandell and colleagues ($17,226).

In addition to total expenditures, Mandell, 2006 also provided mean estimates for inpatient ($376) and outpatient ED ($34) expenditures, as well as for MHR inpatient

($12,737) expenditures. In the current study, mean inpatient ($1,150), ED ($227), and MHR inpatient ($1,966), expenditures were greater than those estimated by Mandell and colleagues. MHR comparisons between our study and Mandell, 2006 may also be limited by the fact that Mandell and colleagues required claims to have a psychiatrist provider type, while visits from any clinician could have been considered MHR in the current analysis since diagnosis codes were used to determine MHR visits.

Wang, 2013 calculated mean annual expenditures overall ($36,248), as well as for OT/PT ($433), speech therapy ($910), inpatient ($1,150), and outpatient prescription ($3,176) categories. Total MHR expenditures were calculated ($29,563) in addition to BM ($704), inpatient ($558), and psychotropic prescription ($2,359) expenditures. In the current study, mean speech therapy ($570) expenditures were less than those estimated by Wang and colleagues, while OT/PT ($648) and inpatient ($1,966) were greater. For MHR expenditure categories, total ($9,489), BM ($481), and psychotropic prescription ($1,555) expenditures were all less than those estimated by Wang and colleagues, while inpatient ($750) was greater.

Consideration of utilization comparisons in addition to expenditure comparisons provides more insight into resource consumption by ASD patients. Compared to the Medicaid cohort observed by Wang, 2013, the commercial ASD group in our study incurred greater OT/PT expenditures ($648 vs. $433) but slightly lower utilization rates (6.0 vs. 6.4 visits per year, respectively). This suggests that health plans included in our study could be providing greater reimbursement per visit for OT/PT services, or that ASD patients in our study participated in more cost-intensive types of OT/PT interventions than the Medicaid ASD group observed by Wang and colleagues. For inpatient expenditures, comparisons cannot be made regarding utilization as no inpatient utilization summaries were reported by Wang, 2013.

In summary, with the exception of OT/PT and inpatient expenditures, all mean annual expenditures incurred by this study's ASD patients were less than similar measures in previous Medicaid-enrolled ASD populations. These findings suggest that although expenditures may have increased when compared to previously-observed commercial ASD populations, they may still fall short of those incurred by previously-observed Medicaid populations.

4.2.5.2.3 Out-of-pocket expenditures

The current study also estimated annual mean all-cause OOP expenditures ($2,243 (±$5,623)) and mean MHR OOP ($1,193 (±$2,430)) expenditures for ASD patients, which were both shown to be greater than all-cause OOP expenditures ($792 (±$3,832)) and MHR OOP expenditures ($70 ($±406)) generated by non-ASD patients, after controlling for covariates. Median estimates of all-cause and MHR OOP expenditures were $1,008 and $466, respectively.

Four previous analyses were found that reported OOP expenditures in ASD populations, both from healthcare claims and nationally-representative surveys.[151,153,157,207] Liptak and colleagues combined caregiver-reported survey results from the Medical Expenditure Panel Survey, the National Ambulatory Medical Care Survey, and the National Hospital Ambulatory Care Survey, and reported an estimated annual OOP cost of $1,117.[153] A later OOP estimate was published by Parish and colleagues, who estimated mean annual OOP expenditures at $924.[154] Even after adjusting for inflation, our all-cause OOP estimate of $2,243 is over twice that of survey-reported estimates.

Two previous analyses estimated OOP expenditures using commercial healthcare claims. Shimabukuro and colleagues observed mean annual OOP expenditures between $801 and $960 across four pediatric age groups (overall estimate not reported).[61] Candon

and colleagues estimated OOP expenditures at $1,471, but only measured expenditures of those ASD patients who utilized any ASD-related service instead of all patients with an ASD diagnosis.[157]

Results from the present analysis suggest that healthcare cost sharing is much higher for children with ASD compared to children of similar age and gender without ASD. When compared to previous studies conducted between 2003 and 2012, results suggest that OOP expenditures of children with ASD have increased over time, even after adjusting previous estimates for inflation. One alternative explanation for the greater OOP expenditures observed in our study when compared to those obtained through surveys could be that the we sampled expenditure estimates from commercially insured patients, while survey estimates are sampled from all caregivers, including those with children enrolled in Medicaid plans with low or zero patient cost sharing. However, OOP expenditure estimates generated by Shimabukuro, 2008 and Candon, 2019 were both sampled from commercial populations, and were also both lower than those observed in the present analysis.

There are a few possible reasons why our OOP expenditures are higher than those estimated from previous commercial populations. One possible explanation is the increased enrollment of young working adults in health savings accounts and consumer-directed health plans, which was much lower during observation periods used in previous analyses. [208] For example, over 21 million people in the U.S. were enrolled in consumer-directed health plans in 2017, compared to only 8 million in 2009 when the study by Candon and colleagues was conducted. However, the current findings could suggest that increased coverage of ASD-related services occurred at the expense of high cost-sharing.

4.2.5.3 Objectives 4 and 5: Summary and shared methodological distinctions from previous literature

In summary, ASD patients observed in the present study incurred significantly greater rates of all-cause healthcare utilization and incurred more expenditures when compared to an age- and gender-matched control group of patients without an ASD diagnosis, with the exception of inpatient utilization and expenditures, where significant differences were not observed among those children with any utilization. Many categories of MHR utilization and expenditures were also greater in the ASD group, with the exception of inpatient utilization and BM utilization and expenditures, where significant differences were not observed among those children with any utilization. These results also suggest that utilization and expenditures are greater than those estimated in previous samples of ASD populations.

A possible explanation for greater utilization and expenditures in the current study is the 13-year separation between study observation periods (2016-2017 vs. 2003-2004). By 2016, at least 43 of the 50 U.S. states had enacted legislation requiring coverage of ASD-related services, compared to one state when the next most recent analysis was conducted (2004).[141] Although all expenditures from all previous studies were adjusted to 2017 dollars using the medical component of the CPI for comparison with the current study, specific expenditures such as those incurred from inpatient and ED visits may not adjust as precisely as more general expenditures (e.g., total expenditures).

The current findings may also differ from previous analyses due to differences in patient distribution with respect to plan type. About half of the sample of patients in the present analysis was fully insured and about half was self-insured, while the cohorts defined in Leslie, 2007, Shimabukuro, 2008, and Wang, 2013 were sampled from the MarketScan database, where most patients are enrolled through self-insured employers.

One opposing argument could be that the cohort defined by Croen and colleagues was sampled from the Kaiser Permanente Medical Care Program, which covered ASD-related services at the time of the study. However, the inclusion criteria required only one diagnosis to be included in the ASD group, which, according to ASD methodologic literature, likely increased the risk of misidentified ASD patients and skewing expenditures of the ASD group toward lower control group estimates.[160] Another possible explanation for the greater observed expenditures is the extreme right skewness of the observed data; therefore, median expenditures may provide a more appropriate comparison with previous literature.

4.3 Study limitations

The results of this study should be interpreted in light of some limitations. The first limitation consistent across all five objectives is the use of healthcare claims data to identify children with ASD. Although methodological literature suggests high sensitivity and specificity in identifying ASD patients with a two-visit threshold, it is still possible some patients were either misidentified or not captured. This limitation is particularly magnified in younger patients who may have been in the diagnostic process during our observation period. It is also possible that children with related neurodevelopmental disorders could be misclassified as having ASD considering the recent increase in attention by society.

The second limitation is due to the level of analysis in objective 1. Even though an a priori power analysis suggested objective 1 was adequately powered, analyzing similar data at a deeper level of geo-granularity (e.g., county or census tract) can provide more power and more precise parameter estimates through possible decreases in within-group variation. Another limitation unique to objective 1 is that 5-year household-reported ACS estimates were used to represent the sociodemographic characteristics evaluated. Although five-year estimates are more stable than one- and three-year ACS estimates, they may not be as generalizable to ZIP3 regions undergoing changes in economic development in 2017. Sociodemographic characteristics obtained through surveys can also be susceptible to underreported estimates from households represented by lower incomes or ethnic minority populations.

A fourth limitation is that the control group used in objectives 2-5 was required to be enrolled for the entire three-year observation period, versus the two years required for the ASD group. This criterion was set to guarantee each matched control patient was enrolled during the two-year observation period of each respective ASD patient, and

produced a 12.8% difference in attrition between the ASD group and potential controls. We considered this difference to be a minimal threat of selection bias.

A fifth limitation is that age-related prevalence rates of psychiatric comorbidities were measured through a cross-sectional approach. Although relationships were discovered between ASD diagnosis and the age-related prevalence rates of psychiatric conditions, the study design limits any longitudinal extrapolations, particularly incidence rates and within-patient associations over time. Sixth, psychiatric comorbidities included in this analysis (e.g., psychotic disorders) may have been underestimated due to social stigma and subsequent label avoidance by patients and providers.

Seventh, objectives 2-5 were addressed through regression approaches that controlled for group imbalances on baseline demographic, geographic, health-system, and clinical characteristics. However, due to the nature of healthcare claims data, not all potential confounders can be captured, and group imbalances on unobservable confounders could influence parameter estimates and subsequent hypothesis tests. Healthcare claims are unable to capture direct nonmedical and indirect costs, which have been shown to be greater than direct medical costs in older children and adolescents (> 8 years).[148]

Eighth, the CPT codes representing OT/PT, speech therapy, and BM have undergone changes in the time between previous and current analyses, which may limit the comparison of utilization and expenditure estimates from the current study to previous analyses.[164,165,199] David Mandell and colleagues from the Penn Center of Mental Health, who published a majority of previous research in ASD-related utilization and expenditures, kindly collaborated with us to uncover and partially address CPT code inconsistencies. Another potential limitation is that some clinics may not submit healthcare claims when patients pay completely OOP, especially in cases where self-insured health plans provide

no coverage of ASD-related services. Therefore, the current analysis could have underestimated true OOP expenditures, and BM utilization and expenditures.

Ninth, this analysis was conducted in a sample of patients enrolled in commercial health plans, which may limit extrapolating results to patients enrolled in public plans such as Medicaid. Generalization to the 30% of ASD patients with intellectual disability may be limited as well, as this qualifies patients to enroll in Medicaid health plans in a majority of states.

4.4 Conclusions, implications, and future directions

The overall purpose of this study was to evaluate and explain geographic variation in ASD prevalence, compare the age-related prevalence of psychiatric conditions between ASD and non-ASD patients, and compare healthcare utilization and expenditures between ASD and non-ASD patients. The current analysis observed many consistencies and contrasts with previous literature, as well as novel findings not previously reported.

Findings from the current study imply that, despite an increase in ASD healthcare coverage, geographic disparities in prevalence rates still exist among commercially insured children. Although some relationships were discovered between study characteristics and ASD prevalence rates, some trends did not achieve statistical significance. Future work at a deeper level of geo-granularity such as the county level would provide more power to detect relationships. A county-level analysis would also allow the incorporation of additional health system characteristics not included in the current study (e.g., pediatricians per 1,000 population). Future research could explore geographic variation in prevalence rates in adult populations as well.

This study was novel in its approach to measuring and comparing baseline medical conditions between ASD and non-ASD patients. Based on our literature review, previous analyses in commercial and Medicaid populations have compared rates of psychiatric conditions between ASD and non-ASD patients, but not rates of medical conditions such as epilepsy. Our analysis suggests that baseline rates of ASD-related medical conditions such as epilepsy and genetic disorders were more prevalent in the ASD group, but rates were not as high as those reported in studies using data outside administrative claims. These results highlight the need to control for group imbalances on medical comorbidities in future ASD research using healthcare claims, especially in situations where ASD-related associations are to be considered independent of other medical conditions. Future research

measuring rates of medical conditions could be conducted in Medicaid ASD populations, where a greater proportion of patients are intellectually disabled, and medical comorbidities are likely magnified. Rates of medical comorbidities could also be explored in adult ASD health plan populations as well.

Other novel findings from the present study were the age-related trends in psychiatric conditions, many of which were shown to be stronger in ASD populations when compared to those without ASD. This analysis also suggests the possibility that some psychiatric conditions may manifest at earlier ages in ASD populations when compared to children without ASD. These estimates may provide a starting point for future analyses to address age-related trends of psychiatric conditions. Longitudinal and incidence-based approaches would offer more depth into trend differences as well. Regression discontinuity analyses could provide more insight into ages at which the separation of psychiatric comorbidity prevalence begins.

This analysis provides confirmatory evidence that healthcare utilization and expenditures are significantly greater in commercially insured children with ASD when compared to those children without ASD. The current data suggest that this disparity may be growing as a result of increased coverage of ASD-related services by commercial health plans, which has obvious budgetary implications for commercial payers. This wide disparity in MHR utilization and expenditures implies that MHR conditions may be partially driving the differences seen at the all-cause level.

Another notable finding was the group balance observed with respect to health plan type. In other words, the proportions of patients enrolled in fully- and self-insured health plans were similar in ASD and non-ASD groups. This is important because previous studies demonstrate trends towards parity in coverage between fully- and self-insured health plans,[53,152,199] and the group balance on plan type observed in the current analysis

supports the notion that parity in ASD coverage may exist in the current landscape. However, future research should look deeper into payer types to evaluate whether parity of prevalence translates into parity in ASD-related utilization and expenditures.

In summary, this study provides insight into at least three facets of the ASD patient journey: some novel and others previously explored. The analysis also identifies opportunities for future research in ASD populations. The authors hope these study findings provide a step forward in society's understanding of this burdensome condition.

APPENDICES

Appendix A: Diagnosis codes included in CCS mental health categories

Psychiatric comorbidity (CCS code)	ICD-9-CM	ICD-10-CM
Adjustment disorder (650)	3090, 3091, 30922, 30923, 30924, 30928, 30929, 3093, 3094, 30982, 30983, 30989, 3099	F4320, F4321, F4322, F4323, F4324, F4325, F4329, F438, F439
Anxiety disorders (651)	29384, 30000, 30001, 30002, 30009, 30010, 30020, 30021, 30022, 30023, 30029, 3003, 3005, 30089, 3009, 3080, 3081, 3082, 3083, 3084, 3089, 30981, 3130, 3131, 31321, 31322, 3133, 31382, 31383	F064, F4000, F4001, F4002, F4010, F4011, F40210, F40218, F40220, F40228, F40230, F40231, F40232, F40233, F40240, F40241, F40242, F40243, F40248, F40290, F40291, F40298, F408, F409, F410, F411, F413, F418, F419, F42, F422, F423, F424, F428, F429, F430, F4310, F4311, F4312, F488, F489, R452, R453, R454, R455, R456, R457, R4581, R4582, R4583, R4584
Attention-deficit conduct or disruptive behavior disorders (652)	31200, 31201, 31202, 31203, 31210, 31211, 31212, 31213, 31220, 31221, 31222, 31223, 3124, 3128, 31281, 31282, 31289, 3129, 31381, 31400, 31401, 3141, 3142, 3148, 3149	F900, F901, F902, F908, F909, F910, F911, F912, F913, F918, F919, R460, R461, R462, R463, R464, R465, R466, R467, R4681, R4689
Developmental disorders (654)	3070, 3079, 31500, 31501, 31502, 31509, 3151, 3152, 31531, 31532, 31534, 31535, 31539, 3154, 3155, 3158, 3159, 317, 3180, 3181, 3182, 319, V400, V401	F70, F71, F72, F73, F78, F79, F800, F801, F802, F804, F8081, F8082, F8089, F809, F810, F812, F8181, F8189, F819, F82, F88, F89, F985, R4183, R480

Appendix A: Diagnosis codes included in CCS mental health categories (continued)

Mood disorders (657)	29383, 29600, 29601, 29602, 29603, 29604, 29605, 29606, 29610, 29611, 29612, 29613, 29614, 29615, 29616, 29620, 29621, 29622, 29623, 29624, 29625, 29626, 29630, 29631, 29632, 29633, 29634, 29635, 29636, 29640, 29641, 29642, 29643, 29644, 29645, 29646, 29650, 29651, 29652, 29653, 29654, 29655, 29656, 29660, 29661, 29662, 29663, 29664, 29665, 29666, 2967, 29680, 29681, 29682, 29689, 29690, 29699, 3004, 311	F0630, F0631, F0632, F0633, F0634, F3010, F3011, F3012, F3013, F302, F303, F304, F308, F309, F310, F3110, F3111, F3112, F3113, F312, F3130, F3131, F3132, F314, F315, F3160, F3161, F3162, F3163, F3164, F3170, F3171, F3172, F3173, F3174, F3175, F3176, F3177, F3178, F3181, F3189, F319, F320, F321, F322, F323, F324, F325, F328, F3281, F3289, F329, F330, F331, F332, F333, F3340, F3341, F3342, F338, F339, F340, F341, F348, F3481, F3489, F349, F39, R4586
Personality disorders (658)	3010, 30110, 30111, 30112, 30113, 30120, 30121, 30122, 3013, 3014, 30150, 30151, 30159, 3016, 3017, 30181, 30182, 30183, 30184, 30189, 3019	F600, F601, F602, F603, F604, F605, F606, F607, F6081, F6089, F609, F69
Schizophrenia and other psychotic disorders (659)	29381, 29382, 29500, 29501, 29502, 29503, 29504, 29505, 29510, 29511, 29512, 29513, 29514, 29515, 29520, 29521, 29522, 29523, 29524, 29525, 29530, 29531, 29532, 29533, 29534, 29535, 29540, 29541, 29542, 29543, 29544, 29545, 29550, 29551, 29552, 29553, 29554, 29555, 29560, 29561, 29562, 29563, 29564, 29565, 29570, 29571, 29572, 29573, 29574, 29575, 29580, 29581, 29582, 29583, 29584, 29585, 29590, 29591, 29592, 29593, 29594, 29595, 2970, 2971, 2972, 2973, 2978, 2979, 2980, 2981, 2982, 2983, 2984, 2988, 2989	F060, F062, F200, F201, F202, F203, F205, F2081, F2089, F209, F21, F22, F23, F24, F250, F251, F258, F259, F28, F29
Alcohol-related disorders (660)	2910, 2911, 2912, 2913, 2914, 2915, 2918, 29181, 29182, 29189, 2919, 30300, 30301, 30302, 30303, 30390, 30391, 30392, 30393, 30500, 30501, 30502, 30503, 3575, 4255, 5353, 53530, 53531, 5710, 5711, 5712, 5713, 76071, 9800	F1010, F1011, F10120, F10121, F10129, F1014, F10150, F10151, F10159, F10180, F10181, F10182, F10188, F1019, F1020, F1021, F10220, F10221, F10229, F10230, F10231, F10232, F10239, F1024, F10250, F10251, F10259, F1026, F1027, F10280, F10281, F10282, F10288, F1029, F10920, F10921, F10929, F1094, F10950, F10951, F10959, F1096, F1097, F10980, F10981, F10982, F10988, F1099, G621, I426, K2920, K2921, K700, K7010, K7011, K702, K7030, K7031, K7040, K709, O99310,

Appendix A: Diagnosis codes included in CCS mental health categories (continued)

Substance-related disorders (661)	2920, 29211, 29212, 2922, 29281, 29282, 29283, 29284, 29285, 29289, 2929, 30400, 30401, 30402, 30403, 30410, 30411, 30412, 30413, 30420, 30421, 30422, 30423, 30430, 30431, 30432, 30433, 30440, 30441, 30442, 30443, 30450, 30451, 30452, 30453, 30460, 30461, 30462, 30463, 30470, 30471, 30472, 30473, 30480, 30481, 30482, 30483, 30490, 30491, 30492, 30493, 30520, 30521, 30522, 30523, 30530, 30531, 30532, 30533, 30540, 30541, 30542, 30543, 30550, 30551, 30552, 30553, 30560, 30561, 30562, 30563, 30570, 30571, 30572, 30573, 30580, 30581, 30582, 30583, 30590, 30591, 30592, 30593, 64830, 64831, 64832, 64833, 64834, 65550, 65551, 65553, 76072, 76073, 76075, 7795, 96500, 96501, 96502, 96509, V6542	F1110, F1111, F11120, F11121, F11122, F11129, F1114, F11150, F11151, F11159, F11181, F11182, F11188, F1119, F1120, F1121, F11220, F11221, F11222, F11229, F1123, F1124, F11250, F11251, F11259, F11281, F11282, F11288, F1129, F1190, F11920, F11921, F11922, F11929, F1193, F1194, F11950, F11951, F11959, F11981, F11982, F11988, F1199, F1210, F1211, F12120, F12121, F12122, F12129, F12150, F12151, F12159, F12180, F12188, F1219, F1220, F1221, F12220, F12221, F12222, F12229, F1223, F12250, F12251, F12259, F12280, F12288, F1229, F1290, F12920, F12921, F12922, F12929, F1293, F12950, F12951, F12959, F12980, F12988, F1299, F1310, F1311, F13120, F13121, F13129, F1314, F13150, F13151, F13159, F13180, F13181, F13182, F13188, F1319, F1320, F1321, F13220, F13221, F13229, F13230, F13231, F13232, F13239, F1324, F13250, F13251, F13259, F1326, F1327, F13280, F13281, F13282, F13288, F1329, F1390, F13920, F13921, F13929, F13930, F13931, F13932, F13939, F1394, F13950, F13951, F13959, F1396, F1397, F13980, F13981, F13982, F13988, F1399, F1410, F1411, F14120, F14121, F14122, F14129, F1414, F14150, F14151, F14159, F14180, F14181, F14182, F14188, F1419, F1420, F1421, F14220, F14221, F14222, F14229, F1423, F1424, F14250, F14251, F14259, F14280, F14281, F14282, F14288, F1429, F1490, F14920, F14921, F14922, F14929, F1494, F14950, F14951, F14959, F14980, F14981, F14982, F14988, F1499, F1510, F1511, F15120, F15121, F15122, F15129, F1514, F15150, F15151, F15159, F15180, F15181, F15182, F15188, F1519, F1520, F1521, F15220, F15221, F15222, F15229, F1523, F1524, F15250, F15251, F15259, F15280, F15281, F15282, F15288, F1529, F1590, F15920, F15921, F15922, F15929, F1593, F1594, F15950, F15951, F15959, F15980, F15981, F15982, F15988, F1599, F1610, F1611, F16120, F16121, F16122, F16129, F1614, F16150, F16151, F16159, F16180, F16183, F16188, F1619, F1620, F1621, F16220, F16221, F16229, F1624, F16250, F16251, F16259, F16280, F16283, F16288, F1629, F1690, F16920, F16921, F16929, F1694, F16950, F16951, F16959, F16980, F16983, F16988, F1699, F17200, F17201, F17203, F17208, F17209, F17210, F17211, F17213, F17218, F17219, F17220, F17221, F17223, F17228, F17229, F17290, F17291, F17293, F17298, F17299, F1810, F1811, F18120, F18121, F18129, F1814, F18150, F18151, F18159, F1817, F18180, F18188, F1819, F1820, F1821, F18220, F18221, F18229, F1824, F18250, F18251, F18259, F1827, F18280, F18288, F1829, F1890, F18920, F18921, F18929, F1894, F18950, F18951, F18959, F1897, F18980, F18988, F1899, F1910, F1911, F19120, F19121, F19122, F19129, F1914, F19150, F19151, F19159, F1916, F1917, F19180, F19181, F19182, F19188, F1919, F1920, F1921, F19220, F19221, F19222, F19229, F19230, F19231, F19232, F19239, F1924, F19250, F19251, F19259, F1926, F1927, F19280, F19281, F19282, F19288, F1929, F1990, F19920, F19921, F19922, F19929, F19930, F19931, F19932, F19939, F1994, F19950, F19951, F19959, F1996, F1997, F19980, F19981, F19982, F19988, F1999, F550, F551, F552, F553, F554, F558, O355XX0, O355XX1, O355XX2, O355XX3, O355XX4, O355XX5, O355XX9, O99320, O99321, O99322, O99323, O99324, O99325, P0441, P0449, P961, P962, T400X1A, T400X1D, T400X1S, T400X3A, T400X3D, T400X3S, T400X4A, T400X4D, T400X4S, T400X5A, T400X5D, T400X5S, T400X6A, T400X6D, T400X6S, T401X1A, T401X1D, T401X1S, T401X3A, T401X3D, T401X3S, T401X4A, T401X4D, T401X4S, T401X5A, T401X5D, T401X5S, T405X1A, T405X1D, T405X1S, T405X3A, T405X3D, T405X3S, T405X4A, T405X4D, T405X4S, T405X5A, T405X5D, T405X5S, T405X6A, T405X6D, T405X6S, T407X1A, T407X1D, T407X1S, T407X3A, T407X3D, T407X3S, T407X4A, T407X4D, T407X4S, T407X5A, T407X5D, T407X5S, T407X6A, T407X6D, T407X6S, T408X1A, T408X1D, T408X1S, T408X3A, T408X3D, T408X3S, T408X4A, T408X4D, T408X4S, T408X5A, T408X5D, T408X5S, T40901A, T40901D, T40901S, T40903A, T40903D, T40903S, T40904A, T40904D, T40904S, T40905A, T40905D, T40905S, T40906A, T40906D, T40906S, T40991A, T40991D, T40991S, T40993A, T40993D, T40993S, T40994A, T40994D, T40994S, T40995A, T40995D, T40995S, T40996A, T40996D, T40996S

CM=Clinical modification; ICD=International Classification of Diseases

Appendix B: Summary of CPT codes used in objectives 4 & 5

Description	CPT codes
BM	97532, 97535, D9920, G0072, G0073, G0074, G0075, G0079, G0081, H2014, H2019, H2027, S9480, H2020, 90824, 90823, 90828, G0129, 90823, G0176
OT/PT	97001, 97002, 97003, 97004, 97039, 97100, 97110, 97112, 97113, 97116, 97140, 97533, 97760, 98960, 99091, G0151, G0152, G0283, H2033, S8990, S9129, S9131, G0176, G0176, G0129
Speech	92506, 92507, 92508, 92526, G0153, S9128, S9152, T1013, 92605

BM=Behavioral modification; CPT=Common procedural technology; OT=Occupational therapy; PT=Physical therapy

Appendix C: ICD diagnosis codes considered MHR

Diagnosis	ICD-9-CM	ICD-10-CM
Schizophrenic disorders	295.x	F20.89
Episodic mood disorders	296.x	F30.10
Delusional disorders	297.x	F22.x
Other nonorganic psychoses	298.x	F32.3x
Pervasive developmental disorders	299.x	F84.0x
Anxiety, dissociative and somatoform disorders	300.x	F41.9
Personality disorders	301.x	F21.x, F34.x, F60.x,
Sexual deviations and disorders	302.x	F64.x
Physiological malfunction arising from mental factors	306.x	F45.8
Special symptoms or syndromes not elsewhere classified	307.x	F98.x, F95.x, F91.x, F50.x, F51.x
Acute reaction to stress	308.x	F43.x
Adjustment reaction	309.x	F43.2, F43.22, F43.23, F43.24, F43.25, F43.8x, F43.29, F93, F94.8
Depressive disorder, not elsewhere classified	311.x	F32.9
Disturbance of conduct not elsewhere classified	312.x	F91.1, F91.8, F91.2, F63.9, F63.0, F63.2, F63.1, F63.81, F63.3,
Disturbance of emotions specific to childhood and adolescence	313.x	F93.8, F94.0, F94.1, F91.3, F98.8, F93.9, F94.8, F98.9
Hyperkinetic syndrome of childhood	314.x	F90.x

CM=Clinical modification; ICD=International Classification of Diseases; MHR=Mental health-related

BIBLIOGRAPHY

1. Baxter AJ, Brugha TS, Erskine HE, Scheurer RW, Vos T, Scott JG. The epidemiology and global burden of autism spectrum disorders. *Psychol Medicine*. 2015;45(03):601-613. doi:10.1017/S003329171400172X

2. American Psychiatric Association. *DSM-V: Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Washington, D.C: American Psychiatric Association; 2013.

3. Baio J. Prevalence of autism spectrum disorder among children aged 8 years — autism and developmental disabilities monitoring network, 11 sites, United States, 2014. *MMWR Surveill Summ*. 2018;67. doi:10.15585/mmwr.ss6706a1

4. Buescher AVS, Cidav Z, Knapp M, Mandell DS. Costs of autism spectrum disorders in the United Kingdom and the United States. *JAMA Pediatrics*. 2014;168(8):721. doi:10.1001/jamapediatrics.2014.210

5. Ganz ML. The lifetime distribution of the incremental societal costs of autism. *Arch Pediatr Adolesc Med*. 2007;161(4):343-349. doi:10.1001/archpedi.161.4.343

6. Bleuler E. *Dementia Praecox or the Group of Schizophrenias*. Oxford, England: International Universities Press; 1950.

7. Kanner L. Autistic disturbances of affective contact. *Nervous Child*. 1943;2:217-250.

8. Asperger H. Autistic psychopathy in childhood. In: Frith U, ed. *Autism and Asperger Syndrome*. Cambridge: Cambridge University Press; 1991:37-92. doi:10.1017/CBO9780511526770.002

9. Wolff S. Asperger's syndrome. *Arch Dis Child*. 1991;66(2):178-179. doi:10.1136/adc.66.2.178

10. American Psychiatric Association. *Mental Disorders; Diagnostic and Statistical Manual.* Washington: American Psychiatric Association; 1952.

11. American Psychiatric Association. *DSM-II: Diagnostic and Statistical Manual of Mental Disorders*. Washington, D.C.: American Psychiatric Association; 1968.

12. Evans B. How autism became autism. *Hist Human Sci*. 2013;26(3):3-31. doi:10.1177/0952695113484320

13. American Psychiatric Association. *DSM-III: Diagnostic and Statistical Manual of Mental Disorders*. Washington, D.C.: American Psychiatric Association; 1980.

14. American Psychiatric Association. *DSM-III-R: Diagnostic and Statistical Manual of Mental Disorders*. Washington, D.C.: American Psychiatric Association; 1987.

15. Eikeseth S. Outcome of comprehensive psycho-educational interventions for young children with autism. *Res Dev Disabil*. 2009;30(1):158-178. doi:10.1016/j.ridd.2008.02.003

16. Lovaas OI. Behavioral treatment and normal educational and intellectual functioning in autistic children. *J. Clin. Psychol*. 1987;55(1):19.

17. Academy of Motion Picture Arts and Sciences. The 61st academy awards | 1989. Oscars.org | Academy of Motion Picture Arts and Sciences. https://www.oscars.org/oscars/ceremonies/1989. Accessed November 16, 2018.

18. Brock SE. An examination of the changing rates of autism in special education. *The California School Psychologist*. 2006;11(1):31-40. doi:10.1007/BF03341113

19. American Psychiatric Association. *DSM-IV: Diagnostic and Statistical Manual of Mental Disorders*. 4. ed., 7. print. Washington, DC; 1998.

20. Wakefield A, Murch S, Anthony A, et al. RETRACTED: Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *The Lancet*. 1998;351(9103):637-641. doi:10.1016/S0140-6736(97)11096-0

21. Committee on Infectious Diseases and Committee on Environmental Health. Thimerosal in vaccines—an interim report to clinicians. *Pediatrics*. 1999;104(3):570-574. doi:10.1542/peds.104.3.570

22. Centers for Disease Control and Prevention. Thimerosal in vaccines thimerosal | concerns | vaccine safety. https://www.cdc.gov/vaccinesafety/concerns/thimerosal/index.html. Published March 21, 2017. Accessed November 16, 2018.

23. Our Founders. Autism Speaks. https://www.autismspeaks.org/our-founders. Accessed November 19, 2018.

24. Ecker C, Bookheimer SY, Murphy DGM. Neuroimaging in autism spectrum disorder: Brain structure and function across the lifespan. *Lancet Neurol*. 2015;14(11):1121-1134. doi:10.1016/S1474-4422(15)00050-2

25. Muhle RA, Reed HE, Stratigos KA, Veenstra-VanderWeele J. The Emerging clinical neuroscience of autism spectrum disorder: A review. *JAMA Psychiatry*. 2018;75(5):514-523. doi:10.1001/jamapsychiatry.2017.4685

26. Boddaert N, Zilbovicius M, Philipe A, et al. MRI findings in 77 children with non-syndromic autistic disorder. *PLoS ONE*. 2009;4(2):e4415. doi:10.1371/journal.pone.0004415

27. Courchesne E, Mouton PR, Calhoun ME, et al. Neuron number and size in prefrontal cortex of children with autism. *JAMA*. 2011;306(18):2001-2010. doi:10.1001/jama.2011.1638

28. Hazlett HC, Gu H, Munsell BC, et al. Early brain development in infants at high risk for autism spectrum disorder. *Nature*. 2017;542(7641):348-351. doi:10.1038/nature21369

29. Lainhart JE. Advances in autism neuroimaging research for the clinician and geneticist. *Am J Med Genet C Semin Med Genet*. 2006;142C(1):33-39. doi:10.1002/ajmg.c.30080

30. Pelphrey K, Adolphs R, Morris JP. Neuroanatomical substrates of social cognition dysfunction in autism. *Ment Retard Dev Disabil Res Rev*. 2004;10(4):259-271. doi:10.1002/mrdd.20040

31. Chen R, Jiao Y, Herskovits EH. Structural MRI in autism spectrum disorder. *Pediatr Res*. 2011;69(5 Pt 2):63R-8R. doi:10.1203/PDR.0b013e318212c2b3

32. Stoner R, Chow ML, Boyle MP, et al. Patches of disorganization in the neocortex of children with autism. *N Engl J Med*. 2014;370(13):1209-1219. doi:10.1056/NEJMoa1307491

33. Tang G, Gudsnuk K, Kuo S-H, et al. Loss of mTOR-dependent macroautophagy causes autistic-like synaptic pruning deficits. *Neuron*. 2014;83(5):1131-1143. doi:10.1016/j.neuron.2014.07.040

34. Foster NEV, Doyle-Thomas KAR, Tryfon A, et al. Structural gray matter differences during childhood development in autism spectrum disorder: a multimetric approach. *Pediatr Neurol*. 2015;53(4):350-359. doi:10.1016/j.pediatrneurol.2015.06.013

35. Supekar K, Kochalka J, Schaer M, et al. Deficits in mesolimbic reward pathway underlie social interaction impairments in children with autism. *Brain*. 2018;141(9):2795-2805. doi:10.1093/brain/awy191

36. Robinson EB, Neale BM, Hyman SE. Genetic research in autism spectrum disorders. *Curr Opin Pediatr*. 2015;27(6):685-691. doi:10.1097/MOP.0000000000000278

37. Sandin S, Lichtenstein P, Kuja-Halkola R, Larsson H, Hultman CM, Reichenberg A. The familial risk of autism. *JAMA*. 2014;311(17):1770-1777. doi:10.1001/jama.2014.4144

38. Muhle R, Trentacoste SV, Rapin I. The genetics of autism. *Pediatrics*. 2004;113(5):e472-486.

39. Atladóttir HO, Pedersen MG, Thorsen P, et al. Association of family history of autoimmune diseases and autism spectrum disorders. *Pediatrics*. 2009;124(2):687-694. doi:10.1542/peds.2008-2445

40. Cook EH, Lindgren V, Leventhal BL, et al. Autism or atypical autism in maternally but not paternally derived proximal 15q duplication. *Am J Hum Genet*. 1997;60(4):928-934.

41. Lai M-C, Lombardo MV, Baron-Cohen S. Autism. *Lancet*. 2014;383(9920):896-910. doi:10.1016/S0140-6736(13)61539-1

42. Numis AL, Major P, Montenegro MA, Muzykewicz DA, Pulsifer MB, Thiele EA. Identification of risk factors for autism spectrum disorders in tuberous sclerosis complex. *Neurology*. 2011;76(11):981-987. doi:10.1212/WNL.0b013e3182104347

43. Richards C, Jones C, Groves L, Moss J, Oliver C. Prevalence of autism spectrum disorder phenomenology in genetic disorders: a systematic review and meta-analysis. *Lancet Psychiat*. 2015;2(10):909-916. doi:10.1016/S2215-0366(15)00376-4

44. Sikora DM, Pettit-Kekel K, Penfield J, Merkens LS, Steiner RD. The near universal presence of autism spectrum disorders in children with Smith-Lemli-Opitz syndrome. *Am J Med Genet A*. 2006;140(14):1511-1518. doi:10.1002/ajmg.a.31294

45. Smalley SL. Autism and tuberous sclerosis. *J Autism Dev Disord*. 1998;28(5):407-414.

46. Gardener H, Spiegelman D, Buka SL. Perinatal and neonatal risk factors for autism: a comprehensive meta-analysis. *Pediatrics*. 2011;128(2):344-355. doi:10.1542/peds.2010-1036

47. Mazina V, Gerdts J, Trinh S, et al. Epigenetics of autism-related impairment: copy number variation and maternal infection. *J Dev Behav Pediatr*. 2015;36(2):61-67. doi:10.1097/DBP.0000000000000126

48. Coggon D, Rose GA, Barker DJP. *Epidemiology for the Uninitiated*. London: BMJ; 2002.

49. Williams JG. Systematic review of prevalence studies of autism spectrum disorders. *Archives of Disease in Childhood*. 2005;91(1):8-15. doi:10.1136/adc.2004.062083

50. Xu G, Strathearn L, Liu B, Bao W. Prevalence of autism spectrum disorder among U.S. children and adolescents, 2014-2016. *JAMA*. 2018;319(1):81-82. doi:10.1001/jama.2017.17812

51. Sheldrick RC, Carter AS. State-level trends in the prevalence of autism spectrum disorder (ASD) from 2000 to 2012: A reanalysis of findings from the autism and developmental disabilities network. *J Autism Dev Disord*. 2018;48(9):3086-3092. doi:10.1007/s10803-018-3568-z

52. Mandell DS, Morales KH, Xie M, Polsky D, Stahmer A, Marcus SC. County-level variation in the prevalence of Medicaid-enrolled children with autism spectrum disorders. *J Autism Dev Disord*. 2010;40(10):1241-1246. doi:10.1007/s10803-010-0982-2

53. Mandell DS, Barry CL, Marcus SC, et al. Effects of autism spectrum disorder insurance mandates on the treated prevalence of autism spectrum disorder. *JAMA Pediatrics*. 2016;170(9):887. doi:10.1001/jamapediatrics.2016.1049

54. Mandell DS, Cao J, Ittenbach R, Pinto-Martin J. Medicaid expenditures for children with autistic spectrum disorders: 1994 to 1999. *J Autism Dev Disord*. 2006;36(4):475-485. doi:10.1007/s10803-006-0088-z

55. Wang L, Leslie DL. Health care expenditures for children with autism spectrum disorders in Medicaid. *J Am Acad Child Adolesc Psychiatry*. 2010;49(11):1165-1171. doi:10.1016/j.jaac.2010.08.003

56. Wang L, Mandell DS, Lawer L, Cidav Z, Leslie DL. Healthcare service use and costs for autism spectrum disorder: A comparison between Medicaid and private insurance. *J Autism Dev Disord*. 2013;43(5):1057-1064. doi:10.1007/s10803-012-1649-y

57. Zerbo O, Qian Y, Ray T, et al. Healthcare service utilization and cost among adults with autism spectrum disorders in a U.S. integrated healthcare system. *Autism in Adulthood: Knowledge, Practice, and Policy*. April 2018:18-27. doi:10.1089/aut.2018.0004

58. Mandell DS, Cao J, Ittenbach R, Pinto-Martin J. Medicaid expenditures for children with autistic spectrum disorders: 1994 to 1999. *J Autism Dev Disord*. 2006;36(4):475-485. doi:10.1007/s10803-006-0088-z

59. Wang L, Mandell DS, Lawer L, Cidav Z, Leslie DL. Healthcare service use and costs for autism spectrum disorder: a comparison between Medicaid and private Insurance. *J Autism Dev Disord*. 2013;43(5):1057-1064. doi:10.1007/s10803-012-1649-y

60. Leslie DL, Martin A. Health care expenditures associated with autism spectrum disorders. *Arch Pediatr Adolesc Med*. 2007;161(4):350. doi:10.1001/archpedi.161.4.350

61. Shimabukuro TT, Grosse SD, Rice C. Medical expenditures for children with an autism spectrum disorder in a privately insured population. *J Autism Dev Disord*. 2008;38(3):546-552. doi:10.1007/s10803-007-0424-y

62. Croen LA, Zerbo O, Qian Y, et al. The health status of adults on the autism spectrum. *Autism*. 2015;19(7):814-823. doi:10.1177/1362361315577517

63. Stuart EA, McGinty EE, Kalb L, et al. Increased service use among children with autism spectrum disorder associated with mental health parity law. *Health Aff*. 2017;36(2):337-345. doi:10.1377/hlthaff.2016.0824

64. Shea LL, Xie M, Turcotte P, et al. Brief report: service use and associated expenditures among adolescents with autism spectrum disorder transitioning to adulthood. *J Autism Dev Disord*. 2018;48(9):3223-3227. doi:10.1007/s10803-018-3563-4

65. Simonoff E, Pickles A, Charman T, Chandler S, Loucas T, Baird G. Psychiatric disorders in children with autism spectrum disorders: prevalence, comorbidity, and associated factors in a population-derived sample. *J Am Acad Child Adolesc Psychiatry*. 2008;47(8):921-929. doi:10.1097/CHI.0b013e318179964f

66. Lugnegård T, Hallerbäck MU, Gillberg C. Psychiatric comorbidity in young adults with a clinical diagnosis of Asperger syndrome. *Res Dev Disabil*. 2011;32(5):1910-1917. doi:10.1016/j.ridd.2011.03.025

67. Mattila M-L, Kielinen M, Linna S-L, et al. Autism spectrum disorders according to DSM-IV-TR and comparison with DSM-5 draft criteria: an epidemiological study. *J Am Acad Child Adolesc Psychiatry*. 2011;50(6):583-592.e11. doi:10.1016/j.jaac.2011.04.001

68. Leitner Y. The co-occurrence of autism and attention deficit hyperactivity disorder in children - What do we know? *Front Hum Neurosci*. 2014;8:268. doi:10.3389/fnhum.2014.00268

69. Woolfenden S, Sarkozy V, Ridley G, Coory M, Williams K. A systematic review of two outcomes in autism spectrum disorder - Epilepsy and mortality. *Dev Med Child Neurol*. 2012;54(4):306-312. doi:10.1111/j.1469-8749.2012.04223.x

70. Hofvander B, Delorme R, Chaste P, et al. Psychiatric and psychosocial problems in adults with normal-intelligence autism spectrum disorders. *BMC Psychiatry*. 2009;9(1). doi:10.1186/1471-244X-9-35

71. Lunsky Y, Gracey C, Bradley E. Adults with Autism spectrum disorders using psychiatric hospitals in Ontario: Clinical profile and service needs. *Res Autism Spectr Disord*. 2009;3(4):1006-1013. doi:10.1016/j.rasd.2009.06.005

72. Buck TR, Viskochil J, Farley M, et al. Psychiatric comorbidity and medication use in adults with autism spectrum disorder. *J Autism Dev Disord*. 2014;44(12):3063-3071. doi:10.1007/s10803-014-2170-2

73. Leslie DL, Rosenheck RA, Horwitz SM. Patterns of mental health utilization and costs among children in a privately insured population. *Health Serv Res*. 2001;36(1 Pt 1):113-127.

74. Leslie DL, Martin A. Health care expenditures associated with autism spectrum disorders. *Arch Pediatr Adolesc Med*. 2007;161(4):350. doi:10.1001/archpedi.161.4.350

75. Wang L, Leslie DL. Health care expenditures for children with autism spectrum disorders in medicaid. *J Am Acad Child Adolesc Psychiatry*. 2010;49(11):1165-1171. doi:10.1016/j.jaac.2010.08.003

76. Cidav Z, Lawer L, Marcus SC, Mandell DS. Age-related variation in health service use and associated expenditures among children with autism. *J Autism Dev Disord*. 2013;43(4):924-931. doi:10.1007/s10803-012-1637-2

77. Vohra R, Madhavan S, Sambamoorthi U. Comorbidity prevalence, healthcare utilization, and expenditures of Medicaid enrolled adults with autism spectrum disorders. *Autism*. 2017;21(8):995-1009. doi:10.1177/1362361316665222

78. Cidav Z, Lawer L, Marcus SC, Mandell DS. Age-related variation in health service use and associated expenditures among children with autism. *J Autism Dev Disord*. 2013;43(4):924-931. doi:10.1007/s10803-012-1637-2

79. Johnson CP, Myers SM, and the Council on Children with Disabilities. Identification and evaluation of children with autism spectrum disorders. *Pediatrics*. 2007;120(5):1183-1215. doi:10.1542/peds.2007-2361

80. Lai M-C, Lombardo MV, Baron-Cohen S. Autism. *The Lancet*. 2014;383(9920):896-910. doi:10.1016/S0140-6736(13)61539-1

81. Johnson CP, Myers SM, and the Council on Children with Disabilities. Identification and evaluation of children with autism spectrum disorders. *Pediatrics*. 2007;120(5):1183-1215. doi:10.1542/peds.2007-2361

82. American Medical Association. *ICD-10-CM, 2018: The Complete Official Codebook*. Chicago: American Medical Association; 2017.

83. World Health Organization. ICD-11 - Mortality and morbidity statistics. https://icd.who.int/browse11/l-m/en. Published December 2018. Accessed January 27, 2019.

84. Volkmar F, Siegel M, Woodbury-Smith M, King B, McCracken J, State M. Practice parameter for the assessment and treatment of children and adolescents with autism spectrum disorder. *J Am Acad Child Adolesc Psychiatry*. 2014;53(2):237-257. doi:10.1016/j.jaac.2013.10.013

85. Myers SM, Johnson CP, the Council on Children with Disabilities. Management of children with autism spectrum disorders. *Pediatrics*. 2007;120(5):1162-1182. doi:10.1542/peds.2007-2362

86. Zwaigenbaum L, Bauman ML, Stone WL, et al. Early identification of autism spectrum disorder: recommendations for practice and research. *Pediatrics*. 2015;136(Supplement):S10-S40. doi:10.1542/peds.2014-3667C

87. Zwaigenbaum L, Bauman ML, Fein D, et al. Early screening of autism spectrum disorder: recommendations for practice and research. *Pediatrics*. 2015;136(Supplement):S41-S59. doi:10.1542/peds.2014-3667D

88. Zwaigenbaum L, Bauman ML, Choueiri R, et al. Early intervention for children with autism spectrum disorder under 3 years of age: recommendations for practice and research. *Pediatrics*. 2015;136(Supplement):S60-S81. doi:10.1542/peds.2014-3667E

89. Academy of Medicine Singapore-Ministry of Health Clinical Practice Guidelines Workgroup on Autism Spectrum Disorders. Academy of medicine Singapore-ministry of health clinical practice guidelines: autism spectrum disorders in pre-school children. *Singapore Med J*. 2010;51(3):255-263.

90. Whitehouse A, Evans K, Eapen V, Wray J. A national guideline for the assessment and diagnosis of autism spectrum disorders in Australia. July 2018.

91. Baird G, Douglas HR, Murphy S. Recognising and diagnosing autism in children and young people: Summary of nice guidance. *BMJ*. 2011;343:d6360-d6360. doi:10.1136/bmj.d6360

92. Hayes J, Ford T, Rafeeque H, Russell G. Clinical practice guidelines for diagnosis of autism spectrum disorder in adults and children in the UK: A narrative review. *BMC Psychiatry*. 2018;18(1):222. doi:10.1186/s12888-018-1800-1

93. New Zealand Ministries of Health and Education. *New Zealand Autism Spectrum Disorder: Guideline*. Wellington, New Zealand: Ministry of Health; 2016.

94. Zwaigenbaum L, Bauman ML, Fein D, et al. Early screening of autism spectrum disorder: recommendations for practice and research. *Pediatrics*. 2015;136(Supplement):S41-S59. doi:10.1542/peds.2014-3667D

95. Miller DT, Adam MP, Aradhya S, et al. Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. *Am J Hum Genet*. 2010;86(5):749-764. doi:10.1016/j.ajhg.2010.04.006

96. Maglione MA, Gans D, Das L, et al. Nonmedical interventions for children with ASD: recommended guidelines and further research needs. *Pediatrics*. 2012;130(Supplement 2):S169-S178. doi:10.1542/peds.2012-0900O

97. Rogers SJ, Vismara L. Interventions for infants and toddlers at risk for autism spectrum disorder. In: *Handbook of Autism and Pervasive Developmental Disorders, Fourth Edition*. Hoboken, NJ, USA: John Wiley & Sons, Inc.; 2014. doi:10.1002/9781118911389.hautc29

98. Rutter M. Autism: Its recognition, early diagnosis, and service implications. *J Dev Behav Pediatr*. 2006;27(2 Suppl):S54-58.

99. Orinstein AJ, Helt M, Troyb E, et al. Intervention for optimal outcome in children and adolescents with a history of autism. *J Dev Behav Pediatr*. 2014;35(4):247-256. doi:10.1097/DBP.0000000000000037

100. Zwaigenbaum L, Bryson S, Lord C, et al. Clinical assessment and management of toddlers with suspected autism spectrum disorder: insights from studies of high-risk infants. *Pediatrics*. 2009;123(5):1383-1391. doi:10.1542/peds.2008-1606

101. National Research Council (U.S.), ed. *Educating Children with Autism*. Washington, DC: National Academy Press; 2001.

102. Rogers SJ, Vismara LA. Evidence-based comprehensive treatments for early autism. *J Clin Child Adolesc Psychol*. 2008;37(1):8-38. doi:10.1080/15374410701817808

103. Levy SE, Mandell DS, Schultz RT. Autism. *Lancet*. 2009;374(9701):1627-1638. doi:10.1016/S0140-6736(09)61376-3

104. Bassett K, Green CJ, Kazanjian A, British Columbia Office of Health Technology Assessment. *Autism and Lovaas Treatment: A Systematic Review of Effectiveness Evidence*. Vancouver: BC Office of Health Technology Assessment, Centre for Health Services and Policy Research, University of British Columbia; 2000. http://catalog.hathitrust.org/api/volumes/oclc/47092620.html. Accessed December 12, 2018.

105. Howlin P, Magiati I, Charman T. Systematic review of early intensive behavioral interventions for children with autism. *Am J Intellect Dev Disabil*. 2009;114(1):23-41. doi:10.1352/2009.114:23;nd41

106. Ospina MB, Krebs Seida J, Clark B, et al. Behavioural and developmental interventions for autism spectrum disorder: A clinical systematic review. *PLoS ONE*. 2008;3(11):e3755. doi:10.1371/journal.pone.0003755

107. Reichow B, Wolery M. Comprehensive synthesis of early intensive behavioral interventions for young children with autism based on the UCLA young autism project model. *J Autism Dev Disord*. 2009;39(1):23-41. doi:10.1007/s10803-008-0596-0

108. Reichow B, Hume K, Barton EE, Boyd BA. Early intensive behavioral intervention (EIBI) for young children with autism spectrum disorders (ASD). *Cochrane Database Syst Rev*. 2018;5:CD009260. doi:10.1002/14651858.CD009260.pub3

109. Spreckley M, Boyd R. Efficacy of applied behavioral intervention in preschool children with autism for improving cognitive, language, and adaptive behavior: A systematic review and meta-analysis. *J Pediatr*. 2009;154(3):338-344. doi:10.1016/j.jpeds.2008.09.012

110. Warren Z, McPheeters ML, Sathe N, Foss-Feig JH, Glasser A, Veenstra-Vanderweele J. A systematic review of early intensive intervention for autism spectrum disorders. *Pediatrics*. 2011;127(5):e1303-1311. doi:10.1542/peds.2011-0426

111. Weitlauf AS, McPheeters ML, Peters B, et al. *Therapies for Children with Autism Spectrum Disorder: Behavioral Interventions Update*. Rockville (MD): Agency for Healthcare Research and Quality (US); 2014. http://www.ncbi.nlm.nih.gov/books/NBK241444/. Accessed December 12, 2018.

112. Granpeesheh D, Tarbox J, Dixon DR. Applied behavior analytic interventions for children with autism: A description and review of treatment research. *Ann Clin Psychiatry*. 2009;21(3):162-173.

113. Mesibov GB, Shea V, Schopler E. *The TEACCH Approach to Autism Spectrum Disorders*. New York: Kluwer Academic/Plenum Publishers; 2005.

114. Villa S, Micheli E, Villa L, Pastore V, Crippa A, Molteni M. Further empirical data on the psychoeducational profile-revised (PEP-R): Reliability and validation with the vineland adaptive behavior scales. *J Autism Dev Disord*. 2010;40(3):334-341. doi:10.1007/s10803-009-0877-2

115. Ozonoff S, Cathcart K. Effectiveness of a home program intervention for young children with autism. *J Autism Dev Disord*. 1998;28(1):25-32.

116. Dawson G, Rogers S, Munson J, et al. Randomized, controlled trial of an intervention for toddlers with autism: The early start Denver model. *Pediatrics*. 2010;125(1):e17-23. doi:10.1542/peds.2009-0958

117. National Autism Center. *Findings and Conclusions: National Standards Project, Phase 2*. National Autism Center; 2015:92.

118. Autism Speaks. Strategic plan for science 2013-2017. January 2013:74.

119. LeClerc S, Easley D. Pharmacological therapies for autism spectrum disorder: a review. *Pharm Ther*. 2015;40(6):389-397.

120. Beherec L, Lambrey S, Quilici G, Rosier A, Falissard B, Guillin O. Retrospective review of clozapine in the treatment of patients with autism spectrum disorder and severe disruptive behaviors. *J Clin Psychopharmacol*. 2011;31(3):341-344. doi:10.1097/JCP.0b013e318218f4a1

121. Perry R, Campbell M, Adams P, et al. Long-term efficacy of haloperidol in autistic children: Continuous versus discontinuous drug administration. *J Am Acad Child Adolesc Psychiatry*. 1989;28(1):87-92. doi:10.1097/00004583-198901000-00016

122. Remington G, Sloman L, Konstantareas M, Parker K, Gow R. Clomipramine versus haloperidol in the treatment of autistic disorder: A double-blind, placebo-controlled, crossover study. *J Clin Psychopharmacol*. 2001;21(4):440-444.

123. Miral S, Gencer O, Inal-Emiroglu FN, Baykara B, Baykara A, Dirik E. Risperidone versus haloperidol in children and adolescents with AD: a randomized, controlled, double-blind trial. *Eur Child Adolesc Psychiatry*. 2008;17(1):1-8. doi:10.1007/s00787-007-0620-5

124. Gencer O, Emiroglu FNI, Miral S, Baykara B, Baykara A, Dirik E. Comparison of long-term efficacy and safety of risperidone and haloperidol in children and adolescents with autistic disorder. An open label maintenance study. *Eur Child Adolesc Psychiatry*. 2008;17(4):217-225. doi:10.1007/s00787-007-0656-6

125. Handen BL, Johnson CR, Lubetsky M. Efficacy of methylphenidate among children with autism and symptoms of attention-deficit hyperactivity disorder. *J Autism Dev Disord*. 2000;30(3):245-255.

126. Carminati GG, Deriaz N, Bertschy G. Low-dose venlafaxine in three adolescents and young adults with autistic disorder improves self-injurious behavior and attention deficit/hyperactivity disorders (ADHD)-like symptoms. *Prog Neuropsychopharmacol Biol Psychiatry*. 2006;30(2):312-315. doi:10.1016/j.pnpbp.2005.10.002

127. Janardhan Reddy YC, Sundar AS, Narayanaswamy JC, Math SB. Clinical practice guidelines for obsessive-compulsive disorder. *Indian J Psychiatry*. 2017;59(Suppl 1):S74-S90. doi:10.4103/0019-5545.196976

128. Hollander E, Soorya L, Chaplin W, et al. A double-blind placebo-controlled trial of fluoxetine for repetitive behaviors and global severity in adult autism spectrum disorders. *Am J Psychiatry*. 2012;169(3):292-299. doi:10.1176/appi.ajp.2011.10050764

129. The National Institutes of Health. Study of fluoxetine in autism. Clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT00515320. Accessed December 14, 2018.

130. King BH, Hollander E, Sikich L, et al. Lack of efficacy of citalopram in children with autism spectrum disorders and high levels of repetitive behavior: Citalopram ineffective in children with autism. *Arch Gen Psychiatry*. 2009;66(6):583-590. doi:10.1001/archgenpsychiatry.2009.30

131. Yamasue H, Domes G. Oxytocin and autism spectrum disorders. In: Hurlemann R, Grinevich V, eds. *Behavioral Pharmacology of Neuropeptides: Oxytocin*. Current Topics in Behavioral Neurosciences. Cham: Springer International Publishing; 2018:449-465. doi:10.1007/7854_2017_24

132. Preti A, Melis M, Siddi S, Vellante M, Doneddu G, Fadda R. Oxytocin and autism: a systematic review of randomized controlled trials. *Journal of Child and Adolescent Psychopharmacology*. 2014;24(2):54-68. doi:10.1089/cap.2013.0040

133. The National Institutes of Health. Search of: Balovaptan or ro5285119 - list results - clinicaltrials.gov.

https://clinicaltrials.gov/ct2/results?cond=&term=balovaptan+OR+RO5285119&cntry=&state=&city=&dist=. Accessed December 20, 2018.

134. Danfors T, von Knorring A-L, Hartvig P, et al. Tetrahydrobiopterin in the treatment of children with autistic disorder: A double-blind placebo-controlled crossover study. *J Clin Psychopharmacol*. 2005;25(5):485-489.

135. Posey DJ, Kem DL, Swiezy NB, Sweeten TL, Wiegand RE, McDougle CJ. A pilot study of D-cycloserine in subjects with autistic disorder. *Am J Psychiatry*. 2004;161(11):2115-2117. doi:10.1176/appi.ajp.161.11.2115

136. Zerbo O, Qian Y, Ray T, et al. Healthcare service utilization and cost among adults with autism spectrum disorders in a U.S. integrated healthcare system. *Autism in Adulthood: Knowledge, Practice, and Policy*. April 2018:18-27. doi:10.1089/aut.2018.0004

137. Centers for Medicare & Medicaid Services. Home & community-based services 1915(c). https://www.medicaid.gov/medicaid/hcbs/authorities/1915-c/index.html. Accessed January 25, 2019.

138. Velott DL, Agbese E, Mandell D, et al. Medicaid 1915(c) home and community based services waivers for children with autism spectrum disorder. *Autism*. 2016;20(4):473-482. doi:10.1177/1362361315590806

139. Autism Speaks. Mental disorders; diagnostic and statistical manual. Autism Speaks. https://www.autismspeaks.org/state-regulated-health-benefit-plans. Accessed July 6, 2019.

140. Fronstin P. Self-Insured Health Plans: Recent trends by firm size. *Employee Benefit Research Institute*. 2016;37(7). doi:10.2139/ssrn.3160036

141. Autism Speaks. Self-funded health benefit plans. Autism Speaks. https://www.autismspeaks.org/self-funded-health-benefit-plans. Accessed December 19, 2018.

142. Mercer. National survey of employer-sponsored health plans (2017). 2018.

143. Mercer. National survey of employer-sponsored health plans (2013). 2014.

144. Stein BD, Sorbero MJ, Goswami U, Schuster J, Leslie DL. Impact of a private health insurance mandate on public sector autism service use in Pennsylvania. *J Am Acad Child Adolesc Psychiatry*. 2012;51(8):771-779. doi:10.1016/j.jaac.2012.06.006

145. Chatterji P, Decker SL, Markowitz S. The effects of mandated health insurance benefits for autism on out-of-pocket costs and access to treatment. *J Policy Anal Manage*. 2015;34(2):328-353. doi:10.1002/pam.21814

146. Barry CL, Epstein AJ, Marcus SC, et al. Effects of state insurance mandates on health care use and spending for autism spectrum disorder. *Health Aff*. 2017;36(10):1754-1761. doi:10.1377/hlthaff.2017.0515

147. U.S. Senate and House of Representatives assembled. *Patient Protection and Affordable Care Act*.; 2014:878.

148. Ganz ML. The lifetime distribution of the incremental societal costs of autism. *Arch Pediatr Adolesc Med*. 2007;161(4):343-349. doi:10.1001/archpedi.161.4.343

149. Croen LA, Najjar DV, Ray GT, Lotspeich L, Bernal P. A comparison of health care utilization and costs of children with and without autism spectrum disorders in a large group-model health plan. *Pediatrics*. 2006;118(4):e1203-e1211. doi:10.1542/peds.2006-0127

150. Vohra R, Madhavan S, Sambamoorthi U. Comorbidity prevalence, healthcare utilization, and expenditures of Medicaid enrolled adults with autism spectrum disorders. *Autism*. 2017;21(8):995-1009. doi:10.1177/1362361316665222

151. Shimabukuro TT, Grosse SD, Rice C. Medical expenditures for children with an autism spectrum disorder in a privately insured population. *J Autism Dev Disord*. 2008;38(3):546-552. doi:10.1007/s10803-007-0424-y

152. Barry CL, Epstein AJ, Marcus SC, et al. Effects of state insurance mandates on health care use and spending for autism spectrum disorder. *Health Aff*. 2017;36(10):1754-1761. doi:10.1377/hlthaff.2017.0515

153. Liptak GS, Stuart T, Auinger P. Health care utilization and expenditures for children with autism: data from U.S. national samples. *J Autism Dev Disord*. 2006;36(7):871-879. doi:10.1007/s10803-006-0119-9

154. Parish S, Thomas K, Rose R, Kilany M, McConville R. State insurance parity legislation for autism services and family financial burden. *Intellect Dev Disabil*. 2012;50(3):190-198. doi:10.1352/1934-9556-50.3.190

155. Parish SL, Thomas KC, Williams CS, Crossman MK. Autism and families' financial burden: the association with health insurance coverage. *Am J Intellect Dev Disabil*. 2015;120(2):166-175. doi:10.1352/1944-7558-120.2.166

156. Lavelle TA, Weinstein MC, Newhouse JP, Munir K, Kuhlthau KA, Prosser LA. Economic burden of childhood autism spectrum disorders. *Pediatrics*. 2014;133(3):E520-E529. doi:10.1542/peds.2013-0763

157. Candon MK, Barry CL, Marcus SC, et al. Insurance mandates and out-of-pocket spending for children with autism spectrum disorder. *Pediatrics*. 2019;143(1):e20180654. doi:10.1542/peds.2018-0654

158. Parish SL, Thomas KC, Rose R, Kilany M, Shattuck PT. State Medicaid spending and financial burden of families raising children with autism. *Am J Intellect Dev Disabil*. 2012;50(6):441-451. doi:10.1352/1934-9556-50.06.441

159. U.S. Census Bureau. American community survey information guide. https://www.census.gov/content/dam/Census/programs-surveys/acs/about/ACS_Information_Guide.pdf.

160. Burke JP, Jain A, Yang W, et al. Does a claims diagnosis of autism mean a true case? *Autism*. 2014;18(3):321-330. doi:10.1177/1362361312467709

161. Agency for Healthcare Research and Quality. HCUP-US Tools & Software Page. Healthcare Cost and Utilization Project. https://www.hcup-us.ahrq.gov/toolssoftware/ccs/ccs.jsp. Accessed February 16, 2019.

162. Agency for Healthcare Research and Quality. Beta clinical classifications software (ccs) for icd-10-cm/pcs. Healthcare Cost and Utilization Project. https://www.hcup-us.ahrq.gov/toolssoftware/ccs10/ccs10.jsp. Accessed February 16, 2019.

163. Busch AB, Yoon F, Barry CL, et al. The effects of mental health parity on spending and utilization for bipolar, major depression, and adjustment disorders. *Am J Psychiatry*. 2013;170(2):180-187. doi:10.1176/appi.ajp.2012.12030392

164. Center for Mental Health Policy and Services Research. Tools for researchers: procedure code categories. January 2018.

165. Behavior Analyst Certification Board. Adaptive behavior assessment and treatment code conversion table. October 2018. https://www.bacb.com/wp-content/uploads/CPT_Codes_Crosswalk_.pdf. Accessed June 4, 2019.

166. The National Association of Private Psychiatric Hospitals (NAPPH), American Association for Partial Hospitalization (AAPH). Definition of partial hospitalization. *Psychiatr Hosp*. 1990;21(2):89-90.

167. Centers for Medicare & Medicaid Services. Partial hospitalization coverage. https://www.medicare.gov/coverage/mental-health-care-partial-hospitalization. Accessed February 14, 2019.

168. Rubin DM, Feudtner C, Localio R, Mandell DS. State variation in psychotropic medication use by foster care children with autism spectrum disorder. *Pediatrics*. 2009;124(2):e305-e312. doi:10.1542/peds.2008-3713

169. Mandell DS, Morales KH, Marcus SC, Stahmer AC, Doshi J, Polsky DE. Psychotropic medication use among Medicaid-enrolled children with autism spectrum disorders. *Pediatrics*. 2008;121(3):e441-448. doi:10.1542/peds.2007-0984

170. Bureau of Labor Statistics. CPI Home: U.S. Bureau of Labor Statistics. https://www.bls.gov/cpi/. Published 2018. Accessed February 17, 2019.

171. Hall SA, Kaufman JS, Ricketts TC. Defining urban and rural areas in U.S. epidemiologic studies. *J Urban Health*. 2006;83(2):162-175. doi:10.1007/s11524-005-9016-3

172. U.S. Census Bureau. Urban area criteria for the 2010 census. August 2011. https://www2.census.gov/geo/pdfs/reference/fedreg/fedregv76n164.pdf.

173. US Census Bureau. 2010 geographic terms and concepts - zip code tabulation areas. https://www.census.gov/geo/reference/gtc/gtc_zcta.html. Accessed January 28, 2019.

174. U.S. Census Bureau. Calculating measures of error for derived estimates. In: *Understanding and Using American Community Survey Data: What All Data Users Need to Know*. ; 2018:51-59.

175. The United States Census Bureau. Census bureau regions and divisions with state FIPS codes. Census.gov. https://www2.census.gov/geo/docs/maps-data/maps/reg_div.txt. Accessed January 18, 2019.

176. Feudtner C, Feinstein JA, Zhong W, Hall M, Dai D. Pediatric complex chronic conditions classification system version 2: Updated for ICD-10 and complex medical technology dependence and transplantation. *BMC Pediatrics*. 2014;14(1):199. doi:10.1186/1471-2431-14-199

177. Simon TD, Berry J, Feudtner C, et al. Children with complex chronic conditions in inpatient hospital settings in the United States. *Pediatrics*. 2010;126(4):647-655. doi:10.1542/peds.2009-3266

178. Berry JG, Hall DE, Kuo DZ, et al. Hospital utilization and characteristics of patients experiencing recurrent readmissions within children's hospitals. *JAMA*. 2011;305(7):682-690. doi:10.1001/jama.2011.122

179. Mukaka M. A guide to appropriate use of Correlation coefficient in medical research. *Malawi Med J*. 2012;24(3):69-71.

180. Enders CK. *Applied Missing Data Analysis*. New York: Guilford Press; 2010.

181. Collins LM, Schafer JL, Kam CM. A comparison of inclusive and restrictive strategies in modern missing data procedures. *Psychol Methods*. 2001;6(4):330-351.

182. The R Foundation. R: what is R? https://www.r-project.org/about.html. Accessed February 4, 2019.

183. Fox J. *Applied Regression Analysis and Generalized Linear Models*. Third Edition. Los Angeles: SAGE; 2016.

184. Agresti A. *Categorical Data Analysis*. 3rd ed. Hoboken, NJ: Wiley; 2013.

185. Agresti A. Generalized linear models. In: *An Introduction to Categorical Data Analysis*. 2nd ed. Wiley series in probability and mathematical statistics. Hoboken, NJ: Wiley-Interscience; 2007:65-98.

186. Vuong QH. Likelihood ratio tests for model selection and non-nested hypotheses. *Econometrica*. 1989;57(2):307-333. doi:10.2307/1912557

187. Calvin J. Regression models for categorical and limited dependent variables. *Technometrics*. 1998;40(1):80-81. doi:10.1080/00401706.1998.10485496

188. Diehr P, Yanez D, Ash A, Hornbrook M, Lin DY. Methods for analyzing health care utilization and costs. *Annu Rev Public Health*. 1999;20:125-144. doi:10.1146/annurev.publhealth.20.1.125

189. Cameron AC, Miller DL. A practitioner's guide to cluster-robust inference. *J Hum Resour*. 2015;50(2):317-372. doi:10.3368/jhr.50.2.317

190. Raudenbush SW, Bryk AS. *Hierarchical Linear Models: Applications and Data Analysis Methods*. 2nd ed. Thousand Oaks: Sage Publications; 2002.

191. Hayes AF, Cai L. Using heteroskedasticity-consistent standard error estimators in OLS regression: An introduction and software implementation. *Behav Res Methods*. 2007;39(4):709-722. doi:10.3758/BF03192961

192. Moran JL, Solomon PJ, Peisach AR, Martin J. New models for old questions: Generalized linear models for cost prediction. *J Eval Clin Pract*. 2007;13(3):381-389. doi:10.1111/j.1365-2753.2006.00711.x

193. Barber J, Thompson S. Multiple regression of cost data: Use of generalised linear models. *J Health Serv Res Policy*. 2004;9(4):197-204. doi:10.1258/1355819042250249

194. Doshi J. Multivariable analysis of patient-level cost data. Presented at the: https://docplayer.net/38075919-Multivariable-analysis-of-patient-level-cost-data.html. Accessed February 4, 2019.

195. Jones A. Models for health care. January 2010. https://www.york.ac.uk/media/economics/documents/herc/wp/10_01.pdf. Accessed February 4, 2019.

196. Faul F, Erdfelder E, Lang A-G, Buchner A. G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods*. 2007;39(2):175-191. doi:10.3758/BF03193146

197. Jin H, Zhao X. Transformation and sample size. *Hogskolan Dalarna*. June 2009:20.

198. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. 2nd ed. Hillsdale, N.J: L. Erlbaum Associates; 1988.

199. Stuart EA, McGinty EE, Kalb L, et al. Increased service use among children with autism spectrum disorder associated with mental health parity law. *Health Aff*. 2017;36(2):337-345. doi:10.1377/hlthaff.2016.0824

200. Delobel-Ayoub M, Ehlinger V, Klapouszczak D, et al. Socioeconomic disparities and prevalence of autism spectrum disorders and intellectual disability. *PLoS One*. 2015;10(11):e0141964. doi:10.1371/journal.pone.0141964

201. Durkin MS, Maenner MJ, Meaney FJ, et al. Socioeconomic inequality in the prevalence of autism spectrum disorder: evidence from a U.S. cross-sectional study. *PLOS ONE*. 2010;5(7):e11551. doi:10.1371/journal.pone.0011551

202. King MD, Bearman PS. Socioeconomic status and the increased prevalence of autism in California. *Am Sociol Rev*. 2011;76(2):320-346. doi:10.1177/0003122411399389

203. Fernandez BA, Scherer SW. Syndromic autism spectrum disorders: moving from a clinically defined to a molecularly defined approach. *Dialogues Clin Neurosci*. 2017;19(4):353-371.

204. Fombonne E. Epidemiology of pervasive developmental disorders. *Pediatric Research*. 2009;65(6):591-598. doi:10.1203/PDR.0b013e31819e7203

205. L&M Policy Research, LLC. Autism spectrum disorders (ASD): state of the states of services and supports for people with ASD. January 2014.

206. Social Security Administration. Disability evaluation under social security. https://www.ssa.gov/disability/professionals/bluebook/112.00-MentalDisorders-Childhood.htm#112_05. Accessed January 30, 2019.

207. Parish SL, Thomas KC, Williams CS, Crossman MK. Autism and families' financial burden: the association with health insurance coverage. Am J Intellect Dev Disabil. 2015;120(2):166-175. doi:10.1352/1944-7558-120.2.166

208. America's Health Insurance Plans. Health savings accounts and consumer-directed health plans grow as valuable financial planning tools. *America's Health Insurance Plans*. April 2018.