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A definitive version was subsequently published:
http://aut.sagepub.com/content/early/2015/04/23/1362361315577517.full

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Word Count: 2853

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Acknowledgements

Lisa Croen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Ousseny Zerbo and Yinge Qian from the Division of Research, Kaiser Permanente Northern California, conducted and are responsible for the data analyses. All authors have no conflicts of interest. We thank the members of the KPNC ASD in Adults Workgroup for their valuable insights and generous input regarding study design, data analysis, and interpretation of study results. No compensation was received for these contributions. The members include Stephen Rich, MD, Scott Rich, MA, Opal Thornton, MD, Clarissa Kripke, MD, Agnes Amistoso, MA, Elizabeth Dixon, LCSW, Chuck Trumble, MFT, Stephen Sidney, MD, Ousseny Zerbo, PhD, Maria Massolo, PhD, Carmen Ancinas-Gee, MFT and Neeraja Maramreddy, MD. Preliminary findings were presented at the International Meeting for Autism Research in Atlanta, Georgia in May, 2014.

Funder

This study was funded by a grant from the Special Hope Foundation, who had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript.

Abstract

Compared to the general pediatric population, children with autism have higher rates of co-occurring medical and psychiatric illnesses, yet very little is known about the general health status of adults with autism. The objective of this study was to describe the frequency of psychiatric and medical conditions among a large, diverse, insured population of adults with autism in the US. Participants were adult members of Kaiser Permanente Northern California enrolled from 2008-2012. ASD cases (N=1,507) were adults with ASD diagnoses (ICD-9-CM 299.0, 299.8, 299.9) recorded in medical records on at least 2 separate occasions. Controls (N=15,070) were adults without any ASD diagnoses sampled at a 10:1 ratio and frequency matched to cases on sex and age. Adults with autism had significantly increased rates of all major psychiatric disorders including depression, anxiety, bipolar disorder, obsessive compulsive disorder, schizophrenia, and suicide attempts. Nearly all medical conditions were significantly more common in adults with autism, including immune conditions, GI and sleep disorders, seizure, obesity, dyslipidemia, hypertension, and diabetes. Rarer conditions, such as stroke and Parkinson's disease, were also significantly more common among adults with autism. Future research is needed to understand the social, health care access and biological factors underlying these observations.

Introduction

Autism spectrum disorders (ASDs) are a heterogeneous group of complex neurodevelopmental conditions apparent in early childhood, characterized by persistent deficits in social communication and social interaction and restricted, repetitive patterns of behavior, interests or activities (APA 2013). While a small minority of individuals develops sufficient adaptive skills that they no longer meet criteria for an ASD diagnosis, ASD's are generally considered lifelong developmental disabilities (Fein, Barton et al. 2013; Anderson, Liang et al. 2014). The prevalence of ASD has been rising since the 1980s as the definition has evolved and awareness has increased. The most recent estimate suggests that 1 in 68 children in the USA are on the autism spectrum (CDC 2014). As the number of children diagnosed with ASD increases, the number of autistic children entering adulthood will continue to rise. To date, however, very little is known about ASD in adults, including their health status and healthcare needs (Mandell 2013).

Children and adolescents with ASD have been reported to have many medical and psychiatric conditions, including seizure, sleep disorders, gastrointestinal disorders, metabolic disorders, hormone dysfunction, obesity, nutritional deficits, anxiety, depression, attention deficit hyperactivity disorder (ADHD), and oppositional defiant disorder (Ghaziuddin, Weidmer-Mikhail et al. 1998; Bradley and Bolton 2006; Leyfer, Folstein et al. 2006; de Bruin, Ferdinand et al. 2007; Simonoff, Pickles et al. 2008; Bauman 2010; Joshi, Petty et al. 2010; Levy, Giarelli et al. 2010; Schieve, Gonzalez et al. 2012). Robust estimates of the rate of medical and psychiatric conditions among adults with ASD are largely lacking from the scientific literature. In the only study to

examine the prevalence of co-occurring conditions across multiple organ systems among a large sample of adults with ASD, Kohane et al reported a higher prevalence of epilepsy, schizophrenia, inflammatory bowel disease, CNS/cranial anomalies, diabetes mellitus type I, muscular dystrophy, and sleep disorders among autism cases compared to controls (Kohane, McMurry et al. 2012). Only major conditions shown to be associated with ASD in previous studies were included in the Kohane study, and the study population was restricted to young adults < 35 years of age.

The objective of the current study was to determine the prevalence of psychiatric and medical conditions, including those not previously associated with ASD, among a large population of adults with ASD of all ages. A better understanding of health status may identify specific targets for intervention and lead to improvements in the delivery of appropriate and effective health care and quality of life for this growing population of adults.

Methods

Setting

This study was set within Kaiser Permanente in Northern California (KPNC), the largest and oldest group model pre-paid, integrated health care delivery organization in the United States providing health care to over 3 million residents (approximately 25%-30%) of the San Francisco and Sacramento metropolitan areas and surrounding counties. KPNC members are broadly representative of the local and statewide population in terms of sociodemographic characteristics, except for the extremes of the income distribution (Krieger 1992). KPNC membership provides health insurance

coverage for inpatient and outpatient medical and mental health services delivered at KPNC clinics and hospitals and approved outside facilities. All patient interactions with the health care system are recorded in a comprehensive electronic medical record (EMR) system and summarized in several clinical databases.

Study population

All adults ≥ 18 years of age as of January 2008 who were members of KPNC for at least 9 months in each calendar year from January 2008 to December 2012 were eligible for inclusion (N=1,578,657). Cases (N=1,507) were defined as adults with ASD diagnoses (Autism: International Classification of Diseases-9-Clinical Modification (ICD-9-CM) 299.0; Asperger's Disorder (ICD-9-CM 299.8), Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS) (ICD-9-CM 299.9)) recorded in KPNC electronic medical records on at least two separate occasions anytime through December 2012.

A comparison population (N=15,070) was randomly sampled at a 10:1 ratio from among all adult members who did not have any ASD diagnoses recorded in KPNC medical records by December 2012. Controls were frequency matched to cases on sex and 5-year age group.

Medical and psychiatric conditions

Medical and psychiatric conditions documented in KPNC medical records between January 2008 and December 2012 were identified by electronically searching the KPNC outpatient and inpatient clinical databases. The definition of specific conditions was based on algorithms using ICD-9 diagnostic codes (International

Classification of Diseases, used in assigning diagnostic and procedure codes associated with inpatient, outpatient, and physician office utilization in the United States), laboratory results and medication reports previously validated for KPNC data, or groupings of ICD-9 codes used by phenotype-wide association studies (PheWAS)(Denny, Ritchie et al. 2010) (see Supplementary Table 1 for definitions of each condition). Diabetes and cancer diagnoses were considered present if the study participant was included in the KPNC diabetes or cancer registries, respectively, by December 31, 2012. The KPNC diabetes registry was established in 1993 and is updated annually by searching multiple clinical data sources including pharmacy, laboratory, hospitalization, and outpatient records to identify patients with diabetes (Karter, Ferrara et al. 2002). The KPNC cancer registry was established in 1994 and collects data on all cases of invasive and in-situ cancer, except non-melanoma skin cancer, diagnosed in KPNC members since 1947. Obesity (Body Mass Index (BMI) >=30) was defined by the average BMI recorded in medical records in the 5 year study period.

Statistical analysis

The prevalence of each specific medical and psychiatric condition was compared between ASD cases and controls using chi-square tests. Comparisons with p-values less than 0.01 were considered statistically significant. A separate multivariate logistic regression model was run for each condition to compare the odds of the condition between ASD cases and controls after controlling for sex, age, and race/ethnicity. Only conditions for which at least 14 cases were diagnosed are shown in Tables. All study procedures were approved by the KPNC Institutional Review Board.

Results

Among the 1,507 adult patients identified with ASD, 37.2% had a diagnosis of autistic disorder, 29.7% Asperger syndrome, 30.7% PDD-NOS, and for the remaining 2.3% the specific ASD diagnosis could not be determined. Approximately one fifth (19.2%) of adults with ASD also had a diagnosis of intellectual disability (12.8% mild, 3.1% moderate, 6.2% severe, 77.9% level not specified). Intellectual disability is a condition for which patients in our system are not routinely tested or receive treatment. Demographic characteristics of the study sample are shown in Table 1. The mean age of the study population was 29 years (standard deviation 12 years). Approximately half (52%) were between 18-24 years, and 9.5% were 50 years or older. The overall male/female ratio was 2.7. Adults with ASD were more likely to be White, non-Hispanic and less likely to be Asian than controls. The mean length of membership in KPNC since 1980 was 21.5 years for cases and 16.7 years for controls. Healthcare expenses were covered by Medicaid for 24.9% of the case group but only 1.3% of controls.

Psychiatric Conditions

More than half (54%) of adults with ASD were diagnosed with a psychiatric condition - 29% diagnosed with anxiety, 11% with bipolar disorder, 26% with depression, 8% with OCD, 8% with schizophrenia (Table 2). After adjusting for sex, age, and race/ethnicity, the risk of most psychiatric conditions was significantly elevated in adults with ASD - from 2.9-times higher for depression to 22-times higher for schizophrenia - compared to controls (Table 2). The risk of suicide attempts was 5-fold higher in adults with ASD compared to unaffected controls. While the rate of suicide

attempt was higher among adults with ASD with a diagnosis of depression (3.6%) compared to adults with ASD without a diagnosis of depression (1.2%), only 14/27 adults with ASD who attempted suicide had a diagnosis of depression. By contrast, adults with ASD were significantly less likely to be diagnosed with alcohol abuse/dependency (Table 2) and to self-report alcohol use (17.8% vs. 55.3%) and tobacco use (11.9% vs. 28.9%).

Women with ASD were diagnosed more often than men with anxiety (36.3% vs. 26.5%), bipolar disorder (13.8% vs. 9.3%), dementia (3.2% vs. 1.9%), depression (34.1% vs. 22.7%), schizophrenic disorders (10.4% vs. 6.9%), and suicide attempts (2.7% vs. 1.45%), but less often with OCD (6.2% vs. 8.2%), attention deficit disorder (8.6% vs. 12.0%), alcohol abuse (0.74% vs. 2.7%), drug abuse (1.74% vs. 2.9%), and drug dependence (1.0% vs. 2.1%). Both men and women had increased risks of most psychiatric conditions compared to sex-matched unaffected controls (Table 3). However, compared to sex-matched unaffected controls, risks were much higher among women than men with ASD for dementia, other psychoses, and schizophrenic disorders, and risk was much higher for men than women with ASD for OCD (Table 3).

Medical Conditions

Nearly all major chronic medical conditions were significantly more common in adults with ASD than controls (Table 4). These included conditions previously associated with ASD in children, such as autoimmune conditions (13.9% among ASD vs. 10.8% among controls), allergy (36.3% vs. 28.7%), GI disorders (34.7% vs. 27.5%), sleep disorders (17.6% vs. 9.6%), and seizure (11.9% vs. 0.73%). In addition, adults

with ASD had significantly higher prevalence of common chronic medical conditions, including dyslipidemia (22.8% vs. 15.1%), hypertension (25.6% vs. 15.6%), diabetes (7.6% vs. 4.3%), obesity (33.9% vs. 27.0%), and thyroid disease (7.0% vs. 3.1%). Rarer conditions, such as stroke, Parkinson's disease, vitamin deficiency, vision and hearing impairments, and genetic disorders were also significantly more common among adults with ASD than controls (Table 4). Interestingly, only a few conditions were diagnosed less often among adults with ASD; these included infections and genitourinary disorders (Table 4).

Most medical conditions were diagnosed more frequently among females with ASD compared to males with ASD (Table 5). However, both men and women had increased risks of most conditions compared to unaffected controls, except for autoimmune diseases and gastrointestinal disorders, which were significantly elevated only among men with ASD, and stroke which was significantly elevated only among women with ASD (Table 5).

Discussion

In a large and diverse population of adults insured within the same integrated health delivery system, the rates of most major psychiatric and chronic medical conditions were high among adults with ASD and significantly elevated compared to controls. These included conditions previously reported to be elevated in children and adolescents with ASD, and conditions which generally have onset in adulthood. The exceptions were alcohol abuse/dependency, infections, and genitourinary disorders, which were diagnosed less often among adults with ASD than controls. In general,

gender differences in the prevalence of psychiatric and medical disorders observed in the ASD group mirrored differences in the general population, resulting in similarly elevated risks for men and women with ASD compared to controls.

Our findings of high prevalence of psychiatric disorders, including depression, anxiety, psychoses, obsessive compulsive disorder, bipolar disorder, and attention deficit disorder, are consistent with previous studies which typically included fewer than 200 cases and focused on young adults (Morgan, Roy et al. 2002; Russell, Mataix-Cols et al. 2005; Gillott and Standen 2007; Eaves and Ho 2008; Sterling, Dawson et al. 2008; Hofvander, Delorme et al. 2009; Kanne, Christ et al. 2009; Lugnegard, Hallerback et al. 2011; Joshi, Wozniak et al. 2013; Buck, Viskochil et al. 2014; Vannucchi, Masi et al. 2014). As in the study by Kohane et al (Kohane, McMurry et al. 2012) schizophrenia was diagnosed significantly more often in adults with ASD in our study population, especially among women. An association between autism and schizophrenia has been suggested in a few other studies in adult populations (Stahlberg, Soderstrom et al. 2004; Daniels, Forssen et al. 2008; Mouridsen, Rich et al. 2008; Sprong, Becker et al. 2008).

Of particular concern is the 5-fold higher rate of diagnosed suicide attempts we observed among adults with ASD compared to controls. Nearly half of the adults with ASD with a diagnosis of attempted suicide did not also have a diagnosis of depression, suggesting that depression may be underdiagnosed in the autistic population, resulting in lack of needed treatment. Our findings are consistent with the few previously published studies of suicidal ideation and attempt among small clinical samples of individuals with ASD (Raja, Azzoni et al. 2011; Mayes, Gorman et al. 2013; Storch,

Sulkowski et al. 2013; Cassidy, Bradley et al. 2014; Paquette-Smith, Weiss et al. 2014), which reported rates in the range of 11%-40%. The rate in our study (1.8%) was substantially lower, likely because it reflected suicide attempts only (not ideation) in a 5-year period, and not lifetime experiences.

In terms of medical conditions, two prior studies compared rates of several conditions between adults with and without ASD using data stored in electronic medical records. Similar to our findings, Tyler et al reported significantly elevated rates of hyperlipidemia, epilepsy and constipation among 108 autistic adults (average age 29 years) receiving primary care through the Cleveland Clinic in 2005-2008 compared to age, sex, race, and insurance status matched controls (Tyler, Schramm et al. 2011). Kohane et al studied adults aged 18-34 years receiving care in 3 general hospitals and reported higher rates of epilepsy, bowel disorders, diabetes, and sleep disorders in adults with ASD compared to unaffected controls (Kohane, McMurry et al. 2012).

Children and adolescents with autism have also been found to have higher rates of overweight and obesity than population controls (Curtin, Anderson et al. 2010; Broder-Fingert, Brazauskas et al. 2014). Obesity increases the risk for many chronic diseases including diabetes, cardiovascular disease, and cancer (Guh, Zhang et al. 2009), and in our study population, adults with ASD did have elevated rates of diabetes, hypertension, and dyslipidemia, but marginally lower rates of cancer. A recent review of the genetic and developmental bases of autism in relation to genes and pathways associated with cancer risk concluded that cancer risk may be altered in autism (Crespi 2011). Further epidemiologic research in large populations is needed to elucidate the association

between autism and chronic conditions including cancer and identify explanatory factors for our observed associations.

There are several possible explanations for our observations of increased rates of psychiatric and medical conditions among adults with ASD. First, the communication and social impairments and deficits in sensory processing that define core features of ASD may prevent individuals from accessing preventive healthcare, or accurately reporting pain or localizing discomfort, leading to missed or delayed diagnoses and opportunities for prevention or early treatment. Tactile sensitivities may interfere with routine medical exams, further leading to delayed diagnosis and treatment of medical conditions (Bauman 2010). Social isolation, discrimination, and difficulties with communication may lead to psychiatric disorders such as anxiety and depression. In an internet survey of 209 autistic adults and 228 adults with other disabilities, adults with ASD reported poorer doctor-patient communication, lower scores on general healthcare and chronic condition self-efficacy, and significantly higher levels of unmet healthcare needs related to physical and mental health and prescription medications, and were less likely to have received preventive healthcare (Nicolaidis, Raymaker et al. 2013).

Second, the core impairments in autism and lack of health education, supports and accommodations may result in lifestyle factors that are known risk factors for many psychiatric and medical conditions. For example, sensory sensitivities could lead to a limited diet with poor nutritional value (Kral, Eriksen et al. 2013). Lack of accommodation for social and language impairments can create barriers to participating in organized sports and physical activity (Pan and Frey 2006). Poor, restricted diets and lack of exercise are risk factors for obesity, which in turn is associated with

increased risk of many major chronic conditions (Guh, Zhang et al. 2009). Interestingly, smoking and alcohol use, social behaviors known to increase risk for chronic medical conditions (Ezzati and Riboli 2013), were significantly less often reported by adults with ASD than controls.

Third, ASD and other psychiatric and medical conditions may share similar genetic factors. For example, a recent study of genome-wide single-nucleotide polymorphism (SNP) data in over 60,000 individuals in the Psychiatric Genomics Consortium identified specific variants in calcium-channel activity genes which were shared between autism spectrum disorder, attention deficit-hyperactivity disorder, bipolar disorder, major depressive disorder, and schizophrenia (Consortium 2013).

Fourth, medications used to treat psychiatric and neurologic comorbidities may raise the risk for other conditions. For example, obesity and hyperlipidemia may be a consequence of the cardiometabolic risks associated with psychoactive medications (Correll 2009) which are commonly used in adults with autism (Buck, Viskochil et al. 2014). Antipsychotics use in autistic children has been associated with significantly increased weight gain compared to placebo controls (McCracken, McGough et al. 2002; Shea, Turgay et al. 2004). Antiepileptics have been associated with osteoporosis (Srikanth, Cassidy et al. 2011) and sleep problems (van de Wouw, Evenhuis et al. 2012) both of which were observed to be elevated in the autistic population.

Several study limitations deserve mention. ASD status and presence of psychiatric and medical conditions was determined by diagnoses recorded in electronic medical records and were not validated by standardized clinical exam. While the validity of

electronic health record data in primary care has been found to be good overall (Thiru, Hassey et al. 2003), diagnoses of some chronic conditions are less reliable when not linked to medications or procedures (Tyler, Schramm et al. 2011). Grouping of ICD9 codes into phenotypic categories may have resulted in misclassification. Only 21% of our study population had a recorded diagnosis of intellectual disability. Given that intellectual disability is a condition for which patients in our system are not routinely tested or receive treatment, it is likely that the diagnosis is under-reported in our medical records.

This study had several strengths. The large, ethnically diverse study population was representative of an insured population, and also included a significant % of patients who received healthcare through government health insurance (Medicaid). This is the first study to include adults of all ages across the full range of intellectual functioning. Information on psychiatric and medical conditions were derived from comprehensive data collected prospectively and recorded by health care providers in electronic medical records, which avoided biases due to self- or care-giver report. Cases and controls were matched on length of enrollment in the same health plan during the most recent 5 year period, and all had at least 9 months of membership in each study year. Thus, our data captured the vast majority of healthcare encounters occurring for this population. Finally, the large size of the study enabled us to address low-prevalence conditions.

Conclusions

In this large, insured population, we see significantly increased rates of medical and psychiatric conditions among adults with ASD. These findings indicate an urgent need

for the development of improved strategies for delivering effective health education and health care to this growing population (Nicolaidis, Kripke et al. 2014). A better understanding of the possible mechanisms leading to poorer health status will enable improved patient care and ultimately enhance the quality of life for adults on the autism spectrum.

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Table 1: Characteristic of Study Population: Adults 18 Years and Older From the Kaiser Permanente Medical Care Program in Northern California

Characteristics	ASD (N =1,507)	Controls (N=15,070)	Chi-square P value
	Mean (SD)	**Mean (SD)**	
Age, mean (SD), y	29.0 (12.2)	29.4 (12.1)	0.26
	N (%)	**N (%)**	
Age categories			1.00
18 -24	790 (52.4)	7900 (52.4)	
25 -29	193 (12.8)	1930 (12.8)	
30 - 34	123 (8.2)	1230 (8.2)	
35 - 39	89 (5.9)	890 (5.9)	
40 - 44	87 (5.8)	870 (5.8)	
45 - 49	82 (5.4)	820 (5.4)	
50 - 54	62 (4.1)	620 (4.1)	
55 – 59	47 (3.1)	470 (3.1)	
60 - 64	28 (1.9)	280 (1.9)	
65+	6 (0.40)	60 (0.4)	
Race/ethnicity			<0.001
White, non-Hispanic	988 (65.6)	6628 (44.0)	
White, Hispanic	59 (3.9)	631 (4.2)	
Black	115 (7.6)	1107 (7.3)	
Asian	168 (11.1)	2525 (16.8)	
Other	177 (11.7)	4179 (27.7)	
Sex			1.00
Male	1102 (73.1)	11020 (73.1)	
Female	405 (26.9)	4050 (26.9)	
Total KP membership, mean (SD), years	21.5 (7.66)	16.7 (8.29)	<0.001
Type of Insurance			<0.001
KP	1107 (73.5)	14421 (95.7)	
Medicaid	375 (24.9)	204 (1.3)	
Self-Pay	25 (1.7)	445 (2.9)	

Table 2. Prevalence of psychiatric conditions in adults with ASD and controls

Psychiatric Conditions	Adults with ASD (N=1,507) n (%)	Controls (N=15,070) n (%)	Chi-square P-value	OR_a (99% CI)*
Alcohol Abuse	33 (2.19)	591 (3.92)	0.0008	0.49 (0.31-0.78)
Alcohol Dependence	16 (1.06)	296 (1.96)	0.014	0.44 (0.23-0.86)
Anxiety Disorder	439 (29.13)	1371 (9.10)	<.0001	3.69 (3.11-4.36)
Attention Deficit Disorders	167 (11.08)	294 (1.95)	<.0001	5.33 (4.08-6.97)
Bipolar Disorder	159 (10.55)	251 (1.67)	<.0001	5.82 (4.41-7.68)
Dementia	34 (2.26)	75 (0.50)	<.0001	4.40 (2.50-7.71)
Depression	388 (25.75)	1490 (9.89)	<.0001	2.86 (2.40-3.40)
Drug Abuse	39 (2.59)	418 (2.77)	0.67	0.75 (0.48-1.17)
Drug Dependence	27 (1.79)	325 (2.16)	0.35	0.66 (0.39-1.12)
Obsessive Compulsive Disorder	115 (7.63)	74 (0.49)	<.0001	14.63 (9.81-21.82)
Other psychoses	95 (6.30)	83 (0.55)	<.0001	11.81 (7.87-17.73)
Schizophrenic disorders	118 (7.83)	56 (0.37)	<.0001	22.24 (14.34-34.48)
Suicide attempts	27 (1.79)	48 (0.32)	<.0001	5.05 (2.67-9.54)

* OR=Odds Ratio; CI=Confidence Interval; adjusted for sex, age, and race/ethnicity.

Table 3. Variation in prevalence of psychiatric conditions among adults with ASD by gender.

Psychiatric Conditions	ASD Male (N=1,102) %	ASD Female (N=405) %	ASD vs Control Male OR_a (99% CI)	ASD vs Control Female OR_a (99% CI)
Alcohol Abuse	30 (2.72)	3 (0.74)	0.53 (0.33-0.88)	0.26 (0.06-1.21)
Alcohol Dependence	12 (1.09)	4 (0.99)	0.40 (0.19-0.87)	0.61 (0.16-2.35)
Anxiety Disorder	292 (26.50)	147 (36.30)	4.00 (3.27-4.91)	3.11 (2.31-4.18)
Attention Deficit Disorders	132 (11.98)	35 (8.64)	5.29 (3.91-7.16)	5.52 (3.07-9.93)
Bipolar Disorder	103 (9.35)	56 (13.83)	5.81 (4.12-8.20)	5.83 (3.65-9.31)
Dementia	21 (1.91)	13 (3.21)	3.39 (1.70-6.76)	8.12 (2.96-22.28)
Depression	250 (22.69)	138 (34.07)	3.14 (2.54-3.88)	2.36 (1.76-3.18)
Drug Abuse	32 (2.90)	7 (1.73)	0.71 (0.44-1.16)	1.02 (0.36-2.90)
Drug Dependence	23 (2.09)	4 (0.99)	0.69 (0.39-1.22)	0.54 (0.14-2.06)
Obsessive Compulsive Disorder	90 (8.17)	25 (6.17)	19.52 (11.93-31.96)	7.60 (3.67-15.73)
Other psychoses	66 (5.99)	29 (7.16)	9.37 (5.88-14.94)	24.62 (10.48-57.83)
Schizophrenic disorders	76 (6.90)	42 (10.37)	16.91 (10.20-28.04)	46.38 (18.07-118.99)
Suicide attempts	16 (1.45)	11 (2.72)	4.32 (1.93-9.68)	6.68 (2.35-19.02)

Table 4. Prevalence of medical conditions among adults with ASD and controls

Medical Conditions	Adults with ASD (N=1,507) N (%)	Controls (N=15,070) N (%)	Chi-square P-value	OR_a (99% CI)*
Immune Conditions				
Autoimmune Disease	209 (13.87)	1625 (10.78)	<.001	1.24 (1.01-1.52)
Allergy	547 (36.30)	4326 (28.71)	<.001	1.38 (1.19-1.60)
Asthma	189 (12.54)	1547 (10.27)	0.006	1.18 (0.95-1.46)
Infection	1065 (70.67)	10919 (72.46)	0.14	0.82 (0.70-0.96)
Cancer	26 (1.73)	333 (2.21)	0.22	0.66 (0.39-1.14)
Cardiovascular Diseases	557 (36.96)	3470 (23.03)	<.001	2.54 (2.13-3.02)
Dyslipidemia	344 (22.83)	2282 (15.14)	<.001	2.12 (1.74-2.60)
Hypertension	386 (25.61)	2356 (15.63)	<.001	2.19 (1.81-2.64)
Any Hospitalized CVD	26 (1.73)	150 (1.00)	0.008	1.68 (0.94-2.97)
Metabolic Disorders				
Gout	15 (1.00)	209 (1.39)	0.21	0.89 (0.44-1.82)
Diabetes	114 (7.56)	653 (4.33)	<.001	2.18 (1.62-2.93)
Obesity	511 (33.91)	4070 (27.01)	<.001	1.41 (1.21-1.64)
Endocrine Disorders				
Pituitary gland and hypothalamic control	20 (1.33)	32 (0.21)	<.001	5.50 (2.59-10.69)
Pubertal and Gonadal Disorders	19 (1.26)	119 (0.79)	0.05	1.50 (0.78-2.88)
Thyroid Disease	106 (7.03)	467 (3.10)	<.001	2.46 (1.81-3.33)
Neurologic Diseases	592 (39.28)	3323 (22.05)	<.001	2.21 (1.90-2.57)
Cerebral palsy	54 (3.58)	31 (0.21)	<.001	16.56 (9.09-30.14)
Disorders of Peripheral Nervous System	76 (5.04)	843 (5.59)	0.37	0.85 (0.61-1.18)
Epilepsy and recurrent seizures	180 (11.94)	110 (0.73)	<.001	16.34 (11.77-22.68)
Headache	84 (5.57)	805 (5.34)	0.70	1.06 (0.78-1.44)
Migraines	75 (4.98)	878 (5.83)	0.18	0.75 (0.54-1.04)
Other Disorders of CNS	279 (18.51)	629 (4.17)	<.001	4.97 (4.04-6.12)
Stroke	17 (1.13)	86 (0.57)	0.009	2.12 (1.03-4.37)
Hereditary and Degenerative Diseases of CNS	159 (10.55)	1123 (7.45)	<.001	1.34 (1.06-1.70)
Parkinson Disease & Spectrum	14 (0.93)	5 (0.03)	<.001	32.73 (7.76-137.96)

Medical Conditions	Adults with ASD (N=1,507) n (%)	Controls (N=15,070) n (%)	Chi-square P-value	OR_a (99% CL)*
Gastrointestinal Disorders	523 (34.70)	4139 (27.47)	<.001	1.35 (1.16-1.57)
Constipation	67 (4.45)	210 (1.39)	<.001	3.11 (2.13-4.54)
Diarrhea	79 (5.24)	510 (3.38)	0.002	1.41 (1.02-1.95)
Disorders of stomach or duodenum	20 (1.33)	220 (1.46)	0.68	1.00 (0.54-1.85)
Functional disorders	208 (13.80)	2075 (13.77)	0.97	0.96 (0.78-1.17)
GERD	193 (12.81)	1161 (7.70)	<.001	1.77 (1.42-2.21)
Gallbladder disorders	28 (1.86)	213 (1.41)	0.17	1.34 (0.79-2.28)
Lower GI	50 (3.32)	242 (1.61)	<.001	1.92 (1.27-2.91)
Other Disease of esophagus	69 (4.58)	421 (2.79)	<.001	1.66 (1.17-2.35)
Diseases of rectum and anus	39 (2.59)	295 (1.96)	0.09	1.26 (0.80-1.97)
Hepatic disease	33 (2.19)	228 (1.51)	0.04	1.58 (0.96-2.60)
Upper GI motility	114 (7.56)	593 (3.93)	<.001	1.85 (1.40-2.45)
Sleep Disorders	265 (17.58)	1446 (9.60)	<.001	1.92 (1.58-2.33)
Organic sleep apnea	64 (4.25)	404 (2.68)	0.005	1.54 (1.07-2.21)
Dyssomnia	236 (15.66)	1183 (7.85)	<.001	2.05 (1.67-2.52)
Nutrition Conditions	561 (37.23)	2821 (18.72)	<.001	2.68 (2.29-3.12)
Symptom concerning nutrition metabolism and development	524 (34.77)	2609 (17.31)	<.001	2.62 (2.24-3.06)
Vitamin Deficiency	75 (4.98)	344 (2.28)	<.001	2.35 (1.65-3.33)
Other Conditions				
Osteoarthritis	45 (2.99)	397 (2.63)	0.42	1.06 (0.68-1.65)
Hearing impairment	71 (4.71)	305 (2.02)	<.001	2.35 (1.63-3.38)
Low vision and blindness	16 (1.06)	20 (0.13)	<.001	7.85 (3.21-19.20)
Genitourinary disorders	83 (5.51)	1173 (7.78)	0.001	0.65 (0.48-0.89)
Renal disorders	172 (11.41)	1396 (9.26)	0.006	1.26 (1.00-1.59)
Musculoskeletal	94 (6.24)	295 (1.96)	<.001	2.89 (2.11-3.98)
Hematology Anemia	120 (7.96)	760 (5.04)	<.001	1.72 (1.30-2.27)
Pulmonary Other	80 (5.31)	574 (3.81)	0.004	1.33 (0.96-1.83)
Genetic Disorders	52 (3.45)	32 (0.21)	<.001	14.67 (8.09-26.59)
Downs Syndrome	21 (1.39)	15 (0.10)	<.001	11.89 (4.89-28.93)

* OR=Odds Ratio; CI=Confidence Interval; Adjusted for sex, age, and race/ethnicity

Table 5. Variation in prevalence of medical conditions among adults with ASD by gender.

Medical Conditions	ASD Male (N=1,102) %	ASD Female (N=405) %	ASD vs Control Male OR_a (99% CI)	ASD vs Control Female OR_a (99% CI)
Immune Conditions				
Autoimmune Disease	12.3	18.0	1.30 (1.01-1.68)	1.12 (0.78-1.60)
Allergy	31.7	48.9	1.27 (1.06-1.52)	1.66 (1.27-2.19)
Asthma	10.3	18.5	1.09 (0.83-1.43)	1.35 (0.94-1.92)
Infection	67.6	79.0	0.82 (0.69-0.98)	0.79 (0.56-1.11)
Cancer	1.5	2.2	0.72 (0.36-1.40)	0.58 (0.23-1.46)
Cardiovascular Diseases				
Dyslipidemia	22.1	24.9	1.89 (1.49-2.40)	2.87 (1.97-4.19)
Hypertension	24.6	28.4	2.19 (1.75-2.76)	2.19 (1.56-3.08)
Metabolic Disorders				
Diabetes	6.6	10.1	1.74 (1.21-2.50)	3.74 (2.23-6.27)
Obesity	32.2	38.5	1.35 (1.13-1.61)	1.59 (1.19-2.13)
Endocrine Disorders				
Thyroid Disease	5.0	12.6	3.34 (2.18-5.11)	1.85 (1.20-2.85)
Neurologic Diseases				
Cerebral palsy	3.3	4.4	11.98 (6.13-23.41)	56.69 (10.98-292.69)
Disorders of Peripheral Nervous System	3.5	9.4	0.70 (0.45-1.11)	1.08 (0.67-1.73)
Epilepsy and recurrent seizures	9.4	19.0	11.53 (7.74-17.17)	34.09 (18.51-62.79)
Headache	4.5	8.4	1.13 (0.76-1.68)	0.97 (0.60-1.58)
Migraines	3.4	9.4	0.87 (0.55-1.38)	0.66 (0.42-1.05)
Other Disorders of CNS	16.0	25.0	4.85 (3.74-6.29)	5.29 (3.72-7.51)
Stroke	0.9	1.7	1.48 (0.59-3.70)	4.97 (1.46-16.86)

Table 5 (continued). Variation in prevalence of medical conditions among adults with ASD by gender.

Medical Conditions	ASD Male (N=1,102) %	ASD Female (N=405) %	ASD vs Control Male OR_a (99% CI)	ASD vs Control Female OR_a (99% CI)
Gastrointestinal Disorders	32.8	40.0	1.50 (1.25-1.79)	1.05 (0.80-1.39)
Constipation	3.5	6.9	3.57 (2.15-5.91)	2.63 (1.48-4.68)
Diarrhea	5.1	5.7	1.62 (1.10-2.38)	1.06 (0.59-1.91)
Disorders of stomach or duodenum	1.1	2.0	1.08 (0.49-2.40)	0.89 (0.34-2.35)
Functional disorders	11.6	19.8	1.02 (0.79-1.32)	0.86 (0.61-1.21)
GERD	12.6	13.3	1.97 (1.51-2.57)	1.37 (0.91-2.07)
Gallbladder disorders	1.4	3.2	1.49 (0.72-3.09)	1.20 (0.55-2.62)
Lower GI	3.4	3.2	2.04 (1.26-3.31)	1.65 (0.74-3.68)
Other Disease of esophagus	4.4	5.2	1.77 (1.16-2.69)	1.44 (0.77-2.69)
Diseases of rectum and anus	2.2	3.7	1.18 (0.67-2.09)	1.40 (0.67-2.91)
Hepatic disease	2.3	2.0	1.57 (0.89-2.78)	1.66 (0.60-4.53)
Upper GI motility	5.9	12.1	1.88 (1.31-2.71)	1.81 (1.17-2.78)
Sleep	16.7	20.0	1.90 (1.50-2.39)	1.98 (1.38-2.83)
Nutrition Conditions	32.5	50.1	2.67 (2.22-3.21)	2.70 (2.04-3.58)
Symptom concerning nutrition metabolism and development	30.4	46.7	2.61 (2.16-3.15)	2.65 (2.00-3.52)
Vitamin Deficiency	3.3	9.6	2.24 (1.36-3.68)	2.46 (1.50-4.04)
Other Conditions				
Osteoarthritis	2.1	5.4	0.80 (0.44-1.45)	1.62 (0.83-3.18)
Hearing impairment	4.1	6.4	2.06 (1.31-3.23)	3.10 (1.67-5.75)
Low vision and blindeness	0.7	2.0	5.80 (1.78-18.90)	12.58 (2.98-53.03)
Genitourinary disorders	6.9	1.7	0.63 (0.45-0.87)	1.03 (0.36-2.94)
Renal disorders	8.3	20.0	1.20 (0.88-1.64)	1.35 (0.96-1.90)
Genetic Disorders	2.8	5.2	10.96 (5.38-22.32)	29.34 (9.17-93.86)
Downs Syndrome	1.2	2.0	9.19 (3.21-26.27)	22.20 (3.72-132.55)

Supplemental Table 1: ICD 9 codes for each medical and psychiatric condition.

	ICD 9 codes
Immune Conditions	
Autoimmune Disease	099.3x; 135.xx; 136.1x; 242.0x; 242.2x; 242.4x; 242.8x; 242.9x; 245.2x; 250.01x; 2 250.11; 250.13; 250.21; 250.23; 250.31; 250.33; 250.41; 250.43; 250.51; 250.53; 25 250.63; 250.71; 250.73; 250.81; 250.83; 250.91; 250.93; 255.4x; 258.1x; 273.2x; 27 279.1x; 279.2x; 279.3x; 279.4x; 279.5x; 279.8x; 279.9x; 283.0x; 286.52; 287.31; 28 287.4x; 287.5x; 321.4x; 323.51; 323.52; 337.1x; 337.2x; 340.xx; 355.9x; 357.0x; 35 357.81; 358.0x; 358.1x; 359.71; 360.11; 360.12; 362.18; 363.2x; 364.3x; 373.34; 37 377.30; 377.31; 377.39; 386.0x; 390.xx; 391.xx; 392.xx; 393.xx; 394.xx; 395.xx; 39 397.xx; 398.xx; 443.0x; 446.0x; 446.1x; 446.20; 446.21; 446.29; 446.4x; 446.5x; 44 446.7x; 447.6x; 447.8x; 516.31; 517.2x; 517.8x; 536.3x; 555.xx; 556.xx; 558.xx; 57 571.49; 571.6x; 573.3x; 576.1x; 579.0x; 579.1x; 579.2x; 579.3x; 579.4x; 579.8x; 57 581.81; 583.81; 583.89; 583.9x; 585.xx; 694.4x; 694.5x; 694.9x; 695.13; 695.14; 69 696.0x; 696.1x; 697.xx; 701.0x; 704.0x; 707.1x; 709.00; 709.01; 709.09; 709.1x; 70 709.3x; 709.4x; 709.8x; 709.9x; 710.0x; 710.1x; 710.2x; 710.3x; 710.4x; 710.8x; 71 711.1x; 711.2x; 711.9x; 713.5x; 714.0x; 714.1x; 714.2x; 714.3x; 714.9x; 719.5x; 72 720.9x; 725.xx; 728.11; 728.81; 733.99; 775.2x; 791.0x; V12.3; V65.3
Allergy	287.0x; 372.0x; 372.10; 372.11; 372.12; 372.13; 372.14; 372.2x; 372.3x; 373.32; 38 381.05; 381.06; 477.xx; 495.0x; 495.1x; 495.2x; 495.3x; 495.4x; 495.5x; 495.6x; 49 495.9x; 518.3x; 518.6x; 530.19; 558.3x; 691.xx; 692.0x; 692.1x; 692.3x; 692.4x; 69 692.6x; 692.70; 692.71; 692.72; 692.76; 692.79; 692.81; 692.83; 692.89; 692.9x; 69 708.0x; 708.1x; 708.9x; 716.2x; 989.82; 995.0x; 995.0x; 995.1x; 995.2x; 995.3x; 99 995.4x; 995.6x; 995.6x; 999.4x; V14.xx; V15.01x; V15.02x; V15.03x; V15.04x; V15 V15.07; V15.0x; V64.04x
Asthma	493.xx; 495.8x; 518.3x; 518.6x; 518.81x; 518.82x; 518.83x; 518.84x; 519.11x; 786 V06.6; v117.5
Immune Conditions	**ICD 9 codes**
Infection	001.xx - 018.xx; 020.xx - 027.xx; 030.xx - 042.xx; 045.xx - 066.xx; 070.xx - 078.81; 0 078.89; 079.0x - 079.6x; 079.81; 079.82; 079.83; 079.89; 079.99; 080.xx - 104.xx; 1 118.xx; 289.1x; 289.2x; 289.3x; 320.xx - 326.xx; 357.0x; 360.0x; 360.1x; 363.0x; 363 364.0x; 364.1x; 364.2x; 364.3x; 372.xx; 373.0x; 373.1x; 373.4x; 373.5x; 37 373.8x; 373.9x; 380.0x; 380.14; 380.15; 380.16; 380.21; 380.23; 381.0x; 381.1x; 38 381.3x; 381.4x; 381.5x; 382.xx; 383.0x; 383.1x; 383.2x; 383.3x; 383.8x; 383.9x; 38 384.1x; 385.xx; 386.0x; 386.1x; 386.2x; 386.3x; 387.xx; 388.0x; 388.1x; 388.2x; 38 388.4x; 388.5x; 388.8x; 388.9x; 389.xx; 390.xx; 391.xx; 392.xx; 420.xx; 421.xx; 42 424.9x; 460.xx; 461.xx; 462.xx; 463.xx; 464.xx; 465.xx; 466.xx; 472.xx; 473.xx; 47 480.xx; 481.xx; 482.xx; 483.xx; 484.xx; 485.xx; 486.xx; 487.xx; 488.01; 488.02; 48 488.11; 88.12; 488.19; 488.81; 488.82; 488.89; 488.xx; 490.xx; 491.xx; 522.5x; 52 522.7x; 527.2x; 527.3x; 535.xx; 540.xx; 567.xx; 590.xx; 595.xx; 597.xx; 599.0x; 60 604.xx; 614.xx; 615.xx; 616.xx; 680.xx; 681.xx; 682.xx; 683.xx; 684.xx; 685.xx; 68

	711.6x; 770.0x; 771.xx; 785.6x; 795.71; V04.82; V08; V65.44
Cancer	Retrieved information from cancer registry at KPNC
Cardiovascular Disease	272.xx; 390.xx – 459.xx;
Dyslipidemia	Based on outpatient pharmacy information and/or outpatient diagnosis ICD-9 codes Pharmacy: >=1 prescription for lipid-lowering drug or AHFS Therapeutic Class: 240 240605, 240606, 240608, 240692, 562400, 800000, 880800 Outpatient diagnosis: >=1 outpatient diagnosis of dyslipidemia (ICD-9 code 272.xx)
Hypertension	>2 outpatient diagnoses of hypertension (ICD-9 codes: 401.xx, 402.xx, 403.xx, 404 or >1 outpatient diagnosis of hypertension plus >1 anti-hypertensive drug prescription one year of outpatient diagnosis.
Any Hospitalized CVD	≥ 1 inpatient primary diagnosis of ICD-9 codes 390.xx – 459.xx
Metabolic Disorders	
Gout	274.xx
Diabetes	Retrieved information from diabetes registry at KPNC
Obesity	Based on 5 years average BMI>30
Endocrine Disorders	
Pituitary gland and hypothalamic control	253.xx
Pubertal and Gonadal Disorders	256.xx; 257.xx; 259.xx
Endocrine Disorders	**ICD 9 codes**
Thyroid Disease	240.xx; 241.xx; 242.xx; 243.xx; 244.xx; 246.xx
Neurologic Diseases	249.3x; 250.3x; 251. 0x; 307.81x; 325.xx; 330.xx; 331.xx; 333.xx - 339.xx;341.xx;34 346.xx; 348.xx; 349.xx - 359.xx; 430.xx; 432.9x; 433.xx; 434.xx; 435.xx; 741.xx; 74 742.xx; 754.00x; 756.0X; 767.0x; 767.6x; 772.2x; 779.0x; 780.01x; 780.31x; 780.32 780.39x; 781.xx; 783.xx; 784.0X; 786.90x; 852.xx; V48.x
Cerebral palsy	343.xx
Disorders of Peripheral Nervous System	350.xx - 358.xx; 767.6x
Epilepsy and recurrent seizures	345.xx
Headache	307.81X; 784.0X
Migraines	346.X
Other Disorders of CNS	325.X; 341.xx; 342.xx; 344.xx; 348.xx; 349.xx; 741.xx; 781.xx; 783.xx; 786.90x; V4
Stroke	433.xx; 434.xx; 435.xx
Hereditary and Degenerative Diseases of CNS	330.xx; 331.xx; 333.xx; 334.xx; 335.xx; 336.xx; 337.xx; 338.xx; 339.xx
Parkinson Disease & Spectrum	Retrieved information from Parkinson registry at KPNC
Gastrointestinal Disorders	070.4x; 306.4x; 307.53x; 307.7x; 530.xx - 538.xx; 555.xx - 558.xx; 560.xx; 564.0x; 564.2x; 564.3x; 564.4x; 564.5x; 564.6x; 564.7x; 564.9x; 569.0x; 569.1x; 569.2x; 56 569.4x; 570.xx -; 571.xx; 572.2x; 572.3x; 572.4x; 572.8x;573.0x; 573.3x; 573.4x; 57 573.9x; 574.xx; 575.xx; 576.xx; 577.xx; 578.xx; 579.xx; 750.xx; 751.xx; 756.6x; 75 787.0x; 787.1x; 787.2x; 787.3x; 787.6x; 787.7x; 787.91x; 789.0x; 789.1x; 789.2x; 7 789.4x; 789.5x; 789.6x; 789.7x; 789.9x; 793.6x
Constipation	307.7x ; 564.0x

Diarrhea	787.6x; 787.7x; 787.91x
Disorders of stomach or duodenum	536.xx; 537.xx
Functional disorders	564.1x; 564.2x; 564.3x; 564.4x; 564.5x; 564.6x; 564.7x; 564.9x; 789.0x
GERD	530.81
Gallbladder disorders	574.xx; 575.xx; 576.xx
Lower GI	560.xx; 578.xx
Other Disease of esophagus	530.0x; 530.1x; 530.2x; 530.3x; 530.4x; 530.5x; 530.6x; 530.7x; 530.80; 530.82; 53 530.84; 530.85; 530.86; 530.87; 530.89; 530.9; 535.xx; 787.1x; 787.2x
Gastrointestinal Disorders	**ICD 9 codes**
Diseases of rectum and anus	569.0x ; 569.1x; 569.2x; 569.3x 569.4x
Hepatic disease	571.xx; 572.2x; 572.3x; 572.4x; 572.8x; 573.0x; 573.3x; 573.8x; 573.9x; 789.1x
Upper GI motility	307.53x; 787.0x; 787.3x
Sleep Disorders	307.40x; 307.42x; 307.44x; 307.46x; 307.47x; 307.49x; 327.0x; 327.1x; 327.2x; 327 327.40x; 327.41x; 327.42x; 327.43x; 327.44x; 327.49x; 327.5x; 327.8x; 347.xx; 780
Organic sleep apnea	327.0x
Dyssomnia	307.40x; 307.42x; 307.44x; 307.46x; 307.47x; 307.49x; 327.42x; 327.8x; 780.5x; V0
Nutrition Conditions	260.xx -269.xx; 275.0x; 278.xx; 280.xx; 783.0x; 783.1x; 783.2x; 783.3x; 783.4x; 78 783.6x; 783.9x; V78.0
Symptom concerning nutrition metabolism and development	275.0x; 278.xx; 280.xx; 783.1x; 783.2x; 783.3x; 783.4x; 783.5x; 783.6x; 783.9x; V7
Vitamin Deficiency	264.xx; 265.xx; 266.xx; 267.xx; 268.xx
Other Conditions	
Osteoarthritis	715.xx
Osteoporosis	733.0x
Hearing impairment	389.xx
Low vision and blindness	369.xx
Genitourinary disorders	600.x; 601.8x; 601.9x; 603.x; 605.x; 606.x ; 607.x; 608.x; 621.xx; 753.xx
Renal disorders	591.xx; 592.xx; 593.xx; 594.xx; 595.1X; 595.2X; 595.4x; 595.8x; 595.9x; 596.xx; 59 580.xx; 581.xx; 582.xx; 583.xx; 584.xx; 585.xx; 586.xx; 587.xx; 588.xx;589.xx; 7
Musculoskeletal	737.3x; 754.xx; 755.xx; 756.0x; 756.1x; 756.2x; 756.3x; 756.4x; 756.5x; 756.8x; 75
Hematology Anemia	280.xx; 281.xx; 282.xx; 283.xx; 284.xx; 285.xx
Pulmonary Other	511.xx; 512.xx; 514.xx; 516.xx; 518.xx; 519.xx
Genetic Disorders	237.7x; 270.xx - 279.xx; 330.8x; 758.xx; 759.5x; 759.6x; 759.81; 759.83; 759.89
Downs Syndrome	758.0x
Psychiatric Conditions	**ICD 9 codes**
Alcohol Abuse	305.00; 305.01; 305.02
Alcohol Dependence	303.xx
Anxiety Disorder	300.0x; 300.2x; 300.3x; 309.20; 309.21; 309.24; 309.81
Psychiatric Conditions	**ICD 9 codes**
Bipolar Disorder	296.0x; 296.1x; 296.4x; 296.5x; 296.6x; 296.7x; 296.80; 296.81; 296.89; 296.9x; 30
Attention Deficit Disorders	314.xx

Dementia	290.xx; 780.93x
Depression	296.2x; 296.3x; 296.82; 298.0x; 300.4x; 301.12; 309.0x; 309.1x; 309.28; 311.xx
Drug Abuse	305.20; 305.21; 305.22; 305.30; 305.31; 305.32; 305.40; 305.41 ; 305.42; 305.50; 3 305.52; 305.60; 305.61; 305.62; 305.70; 305.71; 305.72; 305.80; 305.81; 305.82; 3 305.91; 305.92
Drug Dependence	304.xx
OCD	300.3x
Other psychoses	297.1x; 297.3x; 298.8x; 298.9x; 301.22
Schizophrenic disorders	295.xx
Suicide attempts	E950 - E958