Master's Thesis of Soo Jung Rim

The risk for comorbid psychiatric disorders in Autism Spectrum Disorder using a nationally representative cohort

국가 대표 코호트 자료를 이용한 자폐스펙트럼장애의 정신병리 공병 위험

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Abstract

Those with Autism Spectrum Disorder (ASD) have various adversities from childhood to adulthood. For instance, they are exposed to child abuse, bullying by peers, and have a lower quality of life (QoL) compared to the general population. Another major adversity related to ASD is the risk of psychiatric comorbidity. However, research on the psychiatric comorbidity of ASD is scarce and previous studies had various limitations (e.g., only included clinical samples without comparing with general population, studied a single type of psychiatric disorder, included limited age groups, etc.). Therefore, a more comprehensive understanding regarding the risk of psychiatric comorbidity in ASD is needed.

The current study conducted an explorative study to investigate the risk of psychiatric comorbidity in ASD using a nationally representative cohort. Also, the risk of psychiatric comorbidity was analyzed by intellectual functioning level and diagnosis timing.

Results indicate that those with ASD had significantly higher risk of having comorbid psychiatric disorder compared to the general public. Also, Late-Diagnosed ASD showed higher risk of having certain psychiatric disorders (i.e., depression, OCD, PTSD,

ADHD) compared to Early-Diagnosed ASD. Those with High-Functioning ASD had a lower odd of having schizophrenia spectrum and other psychotic disorders and Attention-deficit/hyperactivity disorder and had a higher odd of having depression compared to Low-Functioning ASD.

These results imply that those with ASD have a higher risk of psychiatric comorbidity compared to the general population and delayed diagnosis is associated with increased risk for psychiatric comorbidity. Moreover, the risk for psychiatric comorbidity by functioning level varied.

Based on the results of this study, screening for psychiatric comorbidity of ASD is needed. Especially, delayed diagnosis seems to be associated with higher risk of psychiatric comorbidity. Therefore, efforts to increase recognition of ASD are needed. Also, intellectual functioning needs to be considered when screening psychiatric comorbidity in ASD.

Keyword: Autism Spectrum Disorder (ASD), Psychiatric Comorbidity, National Health Insurance System-National Sample Cohort (NHIS-NSC), Functioning level, Diagnostic Timing, Korea

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Introduction

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder with communication problems and patients with ASD are dependent on routines and are highly sensitive to environmental changes (APA, 2013). From the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), disorders that were diagnosed separately in DSM-IV (e.g., Asperger's disorder, autistic disorder childhood disintegrative disorder, and pervasive developmental disorder not otherwise specified) are all diagnosed with ASD (APA, 2013).

The prevalence rate of ASD has been reported to be about 1% (Baird, Simonoff, Pickles, Chandler, Loucas, Meldrum, et al., 2006; CDC, 2014). Recent studies (Elsabbagh, Divan, Koh, Kim, Kauchiali, Marcin et al., 2012, Ouellette-Kuntz, Coo, Lam, Breitenbach, Hennessey, Jackman, et al., 2014) show that the prevalence rate of ASD is increasing. Moreover, a review study (Jensen, Steinhausen, & Lauritsen, 2014) also confirmed that the prevalence rate of ASD has been increasing in various countries. There are several reasons that are discussed for the increased prevalence of ASD, such as, due to the change of diagnostic criteria of ASD (Barbaresi, Colligan, Weaver, & Katusic, 2009, Keyes,

Susser, Cheslack-Postava, Fountain, Liu, & Bearman, 2012), more service available (Liu, King, & Bearman, 2010, Keyes et al., 2012), more people recognizing and have awareness of ASD (Idring, Lundberg, Sturm, Dalman, Gumpert, Rai, et al, 2014; Barbaresi et al., 2009; Liu et al., 2010), etc.

The prevalence rate of ASD in Korea shows a similar trend. Rah and colleagues (2020) estimated the incidence rate of ASD in Korea from 2003 to 2017. It was found that the incidence rate of ASD has increased 13.7% from 2003-2007 to 2013-2017. There could be various reasons for the increased incidence rates for ASD in Korea. One of the major reasons for the increased rate could be explained by the new system started by the government. The Korean government started to initiate developmental checkups for different stages of development since 2008 (Moon, Lee, Eun, Kim, Kim, Shin, et al., 2010). The checkup rate which was around 35% in 2008 and increased to around 70% in 2014 (Status of the Targets and the Examinees for the National Health Screening Program for Infant and Children by Gender, City, and Country, 2017). However, the rate in Korea is based on those who have been diagnosed (i.e., parents recognizing the child's condition and receiving treatment). Therefore, the rate could be underestimated. Especially, parents of developmental disorders tend to retain their child to be 'normal'

which hinders them from being diagnosed (Russell and Norwich, 2012). This tendency could be more pronounced in Korea since parents have a strong stigma towards autism. According to Kim and colleagues (2011), due to stigma parents had against autism about 70% of those with autism were not diagnosed.

ASD is associated with various adversities throughout different developmental stages. Berg, Shiu, Acharya Stolbach, & Msall (2016) conducted a population based survey of adverse events among ASD children and found that children child ASD have experienced more adverse events such as parental divorce, neighborhood violence, substance use compared to typically developed children. Moreover, a previous study (Bauminger & Kasari, 2000) found that those with ASD do have friends but the quality of their friendship is poorer compared to typically developing peers. Also, van Roekel and colleagues (2010) have studied victimization of ASD and found that victimization of ASD is prevalence. In one study (Little, 2001), victimization was found in 75% of children and adolescent with Asperger syndrome. Moreover, according to a previous literature (Berg, et al, 2016), those with ASD were more bullied than those with intellectual disability. These finding were also confirmed by an international review study (Due, Holstein, Lynch, Diderichsen, Nic Gabhein, Scheidt et al, 2005).

Specifically, the risk for being bullied was three times higher than that of the typically developing children. When they become adults, those with ASD show a higher unemployment rate compared to the general population (Fernell, Eriksson, & Gillberg, 2013).

ASD does not only affect the patient but also the family. Various previous studies (Estes, Munson, Dawson, Koehler, Zhou & Abbott, 2009; Eisenhower, Baker, & Blacher, 2005; Griffith, Hastings, Nash, & Hill, 2010; Hoffman, Sweeney, Hodge, Lopez-Wanger, & Looney, 2009; Wolf, Noh, Fisman, & Speechley, 1989) which studied parental stress found that parents' of ASD children experience greater stress than other families. According to a meta-analysis study (Hayes & Watson, 2013) parental stress was higher in families with child diagnosed with ASD compared to a family of typically developing child with large effect sizes. Previous studies (Davis & Carter 2008, Gabriels, Cuccaro, Hill, Ivers, & Goldson, 2005) which investigated parental stress found that the main reason for parental stress was due to ASD's core symptoms – social communication and restricted or repetitive behavior. Also, Totsika and colleagues (2011) have investigated the moderating role of functioning level of ASD and parental stress. According to their study, the high functioning level of the ASD child did not moderate parental stress. Therefore, the parents of the child with ASD have

increased parental stress regardless of the child's functioning level.

Moreover, the economic burden of ASD is high. Hong and colleagues (2020) has estimated the economic burden of ASD in South Korea. In 2008 the economic cost of ASD was around $2,700,000 in 2008 and increased to $9,645,503 in 2015. From the total economic cost from 2015, direct costs accounted for about 72% of the total cost and indirect costs accounted for about 28% and majority of the costs were associated with male ASD patients. This result implies that the economic burden of ASD is substantially increasing. In sum, those with ASD are confronted with various adversities and the burden of ASD is high and these burden lead to another great burden ASD patients have. The aforementioned adversities of ASD patients are linked with another great concern that ASD patients are faced with – psychiatric comorbidity.

Psychiatric Comorbidity of ASD

Psychiatric comorbidity is defined as one person having two or more psychopathology (Matson & Nebel-Schwalm, 2007). One study (DeFilippis, 2018) states that 70% of ASD patients have at least one comorbid psychiatric disorder and around 40% have two more comorbid psychiatric disorder. Lai, Kassee, Besney, Bonato,

Hull, Mandy et al (2019) conducted a review study to investigate psychiatric comorbidities in ASD. This study states that patients with ASD have psychiatric comorbidities such as ADHD, anxiety disorders, sleep–wake disorders, disruptive, impulse–control, and conduct disorders, depressive disorders, OCD (obsessive–compulsive disorder), bipolar disorder, and schizophrenia spectrum disorders.

One of the most prevalent comorbid psychiatric disorders among ASD is anxiety disorder. Hollocks and colleagues (2019) have estimated the pooled prevalence of anxiety disorder among ASD and found that the pooled prevalence of anxiety disorder was about 40%. According to a recent umbrella review study (Hossain, Khan, Sultana, Ma, McKyer, Ahmed, & Purohit, 2020), the prevalence rate of anxiety disorders of those with ASD varied greatly (1.47% to 54%) based on eight review studies.

Another common psychiatric comorbidity of ASD is depression (Hollocks et al., 2019; Hudson, Hall, Harkness, 2019; Wigham, Barton, Parr, & Rogers, 2017). According to a review study (Hudson et al., 2019), the lifetime prevalence of depression among ASD was 14.4% (95% CI = 10.3–19.8). Bipolar disorder is also evident in those with ASD. According to a previous review study (Vannucchi, Masi, Toni, Dell'Osso, Erfurth, & Perugi, 2014),

the prevalence rate of bipolar disorder varied from 6% to 21.4%. A more recent review study (Lai et al., 2019) analyzed the prevalence of bipolar disorders among ASD patients and the prevalence rate of bipolar disorder was 5% (95% CI = 3–6). Some studies have looked into the prevalence of mood disorders as a whole. The results varied from about 4% to almost 40% (Lugo–Marín, Magán–Maganto, Rivero–Santana, Cuellar–Pompa, Alviani, Jenaro–Rio, et al., 2019; Richa, Fahed, Khoury, & Mishara, 2014; Skokauskas and Gallagher, 2010; Stewart, Barnard, Pearson, Hasan, & O'Brien, 2006; Zahid & Upthegrove, 2017).

ASD patients also show comorbid schizophrenia spectrum and other psychotic disorders. According to Lugo–Marín and colleagues (Lugo–Marín et al., 2019), 11.8% of those with ASD had comorbid schizophrenia spectrum disorders. The prevalence rate of schizophrenia spectrum disorders among ASD patients varies greatly among review studies (ranging from 4% to 67%) (Hossain et al., 2020).

Another psychiatric disorder that ASD patients have is attention–deficit/ hyperactivity disorder (ADHD). According to Hedley and Uljarević, (2018), about 65% of those with ASD have comorbid ADHD. Along with other mental disorders, the prevalence rate of ADHD in ASD varied among studies ranging from 25.7% to

65%. Post-traumatic stress disorder (PTDS) is also a mental disorder that those with ASD may have. According to Hollocks and colleagues (2019), the lifetime prevalence of PTSD of those with ASD was 5% (95% CI = 1-10).

Compared to other disorders, there are fewer studies which investigated comorbid Obsessive-Compulsive disorder in ASD. A previous study states that about 20% of those with ASD are comorbid with OCD (Hollocks et al., 2019). Another study states that the lifetime prevalence rate of OCD among those with ASD was about 17% (van Steensel Bögels, & Perrin, 2011). An umbrella review found that the prevalence of OCD among those with ASD ranged from 9% to 22% (Hossain et al., 2020).

Based on the results from these studies it could be concluded that psychiatric comorbidity is evident with great variance. For instance, the prevalence for depressive disorder ranged from 1-70% (Lai et al., 2019). There are several reasons for the wide range of prevalence rates. First, prevalence rates varied depending on the characteristic of the data source (registry based data vs. clinical sample data), age group, geographical location, etc. (Hossain et al., 2020). Therefore, a more comprehensive research needs to be done by various researchers with validated measures.

As mentioned, the burden of ASD is tremendous. However, when a patient is comorbid with other psychiatric disorder the burden becomes even greater. First of all, having another psychiatric disorder is associated with worsened core ASD symptoms (e.g., social impairment, repetitive behavior) (Bellini, 2004; Wood, Drahota, Sze, Har, Chiu, Langer, 2009; Sukhodolsky, Scahill, Gadow, Arnold, Aman, McDougle, McCracken et al, 2008). Also, Schendel and colleagues (2016) found that neurologic comorbidity increases mortality risk of ASD patients. Another study found that psychiatric comorbidity is related to lower quality of life among ASD patients (Sikora, Vora, Coury, Rosenberg, 2012). Moreover, Hedley and Uljarevic (2019) investigated the risk factors for suicide in ASD and found that psychiatric comorbidity was a risk factor for suicide.

Despite these burdens of ASD patients, research on mental health of ASD is greatly understudied (Cassidy & Rodgers, 2017). This could be due to the shortage of experts who understand both autism and its comorbidity (Raja, 2014) and the lack of appropriate assessment tools (Cassidy, Bradley, Bowen, et al, 2018b, 2018c) to make diagnosis of psychiatric disorders among ASD.

Since there are limited studies which investigated psychiatric comorbidity of ASD, there is much room for further

understanding. Previous studies on psychiatric comorbidity of ASD have several limitations or issues that need to be addressed. For instance, according to Matson and Goldin (2014), about 80% (199 out of 261 studies) of the studies which investigated the psychiatric comorbidity of ASD dealt with only one psychiatric disorder. Also, to estimate the risk of psychiatric comorbidity, a reference group (e.g., general population) is needed. However, majority of the studies have simply studied the prevalence rate of comorbid psychiatric disorders and most of them utilized clinical samples without comparing with the general population. Another factor that needs to be considered is functioning level of ASD patients. A review study (Hollocks et al., 2019) has stated that functioning level (i.e., intellectual functioning) of ADS needs to be considered when investigating psychiatric comorbidity of ASD. However, scarcity of studies considered functioning level of ASD when studying comorbid psychiatric disorders. Moreover, diagnosis timing (i.e., when the patient receives diagnosis for ASD) which is key in treatment outcomes of ASD was not considered when investigating psychiatric comorbidity. Also, there is scarcity of study which studied psychiatric comorbidity in eastern countries; most studies were conducted in western countries. Lastly, majority of studies did not include a wide range of age groups when

investigating comorbid psychiatric disorders. For instance, some have included only children or adolescents (Díaz-Román, Zhang, Delorme, Beggiato, & Cortese, 2018; Elrod & Hood, 2015; Menezes Robinson, Sanchez et al., 2018) and some only included adults (Hollocks et al., 2019; Morgan et al., 2020). However, considering the fact that mental disorders are common in every developmental stage, it is important to include wide range of age groups in the study (Hossain et al., 2020). Therefore, a more comprehensive overview of the risk of psychiatric comorbidity of ASD patients using a nationally representative longitudinal data is needed. Among various factors that needs to be considered when studying psychiatric comorbidity of ASD, this study focused on functioning level and diagnosis timing of ASD. These two factors were selected since it was possible to analyze through the data which this study has utilized.

Psychiatric Comorbidity of ASD and Functioning Level

Previous studies (Hollocks et al., 2019; Storch, Larson, Merlo, Keeley, Jacob, Geffken, & Goodman, 2008) have suggested that intellectual functioning should be considered when investigating psychiatric comorbidity in ASD. When studying intellectual functioning of ASD patients, those with Intellectual Disability (ID)

are considered to be Low-Functioning ASD and those without ID are considered to be High-Functioning ASD.

High-Functioning ASD patients may be more vulnerable to mental disorders compared to Low-Functioning ASD patients since higher cognitive ability may lead to higher capacity to realize the failures in their daily social life (De-LaLglesia et al., 2015). This ability may lead to decreased self-esteem which in turn increases risk of having a comorbid psychiatric disorder in High-Functioning ASD (Barnhill & Myles, 2001). Moreover, researchers found that High-Functioning ASD patients 'camouflage' in social situations by hiding or suppressing autistic tendencies to fit in (Hull, Mandy, Lai, Baron-Cohen, Allison, Smith et al., 2019). However, their autistic symptoms are not disappeared by camouflaging. Therefore, those who camouflage show lower level of self-esteem, and higher stress (Cage & Troxell-Whitman, 2019; Milner, McIntosh, Colvert, Happé, 2019).

Despite these adversities, High-Functioning ASD patients have a hard time being treated. For instance, Camm-Crosbie, Bradley, Shaw, Baron-Cohen, and Cassidy (2018) conducted an online survey to explore the difficulties of treatment and support for mental health problems. One major problem was the lack of appropriate intervention programs for high-functioning ASD. One of

the participants stated that “I feel ‘lost’….I am too high functioning for most ASD programming in my area, but not neurotypical enough to function well in conventional work and social situations and environments.” (pg. 5, Camm-Crosbie et al, 2018). Another critical problem was the negative experiences they had because the professionals they met lack understanding of High-Functioning ASD. Another participant stated “The biggest difficulty in getting support I need is the lack of understanding autism. Even after decades of research, many institutions still don’t have the first clue in dealing with such a condition.” (pg. 5 in Camm-Crosbie et al., 2018).

Furthermore, a recent cohort study (Rai, Heuvelman, Dalman, Culpin, Lundberg, Carpenter, Magnusson, 2018) has investigated the risk of being diagnosed with depression among High-Functioning ASD and Low-Functioning ASD compared to the general population. According to the results, High-Functioning ASD showed higher risk of being diagnosed with depression than Low-Functioning ASD when compared with the general population. Other studies also states (Brereton, Tonge, & Einfeld, 2006; Vickerstaff, Heriot, Wong, Lopes, Dossetor, 2007; Mayes, Calhoun, Murray, Ahuja, & Smith, 2011a) that among those with ASD, higher intelligence quotient (IQ) was associated with depression and

anxiety. Moreover, Hirvikoski and colleagues (2016) investigated the mortality risk of ASD, High-Functioning ASD and Low-Functioning ASD. This study found that High-Functioning ASD showed higher suicidal death compared to Low-Functioning ASD.

On the other hand, some study (Gjevik, Eldevik, Fjaeran-Granum, & Sphonheim, 2011) found no association between functioning level and psychiatric comorbidity. Therefore, a longitudinal study to compare the risk of having a psychiatric comorbidity between High-Functioning ASD and Low-Functioning ASD is needed.

However, there is limited study which compared the psychiatric risk of ASD by intellectual functioning level. Also, as of my knowledge there is no study which investigated the risk of multiple psychiatric comorbidity based on intellectual functioning level of ASD using a nationally representative longitudinal data. Therefore, this study will explore the risk of psychiatric comorbidity by functioning level in ASD.

Psychiatric Comorbidity of ASD and Diagnosis Timing

Another factor that may influence psychiatric comorbidity of ASD is diagnosis timing. ASD could be recognized and diagnosed around 2years old (Chawarska & Volkmar, 2005). However,

children usually get diagnosed 4 years old (Zuckerman, Lindly, Chavez, 2017) and those with Asperger syndrome get diagnosed around 7 (Mandell, Novak, Zubritsky, 2005).

Along with other neurodevelopmental disorders, ASD is considered to be incurable. However, through early intensive care, the outcome could vary, with higher quality of life, alleviating family distress, increased independence in daily functioning, etc. (Myers, 2009; Vismara & Rogers, 2010; Eldevik, Hastings, Hughes et al., 2009).

Specifically, being diagnosed with ASD during early childhood is important in cognitive and language development (Mazurek, Handen, Wodka, Mowinski, Butter, Engelhardt, 2014). Early intervention is associated with improvement in autism symptoms and communication skills (Aldred, Green, & Adams, 2004). Therefore, delayed diagnosis of ASD may contribute to lower functioning in various aspects and ASD symptoms of those with ASD which in turn could be associated with psychiatric comorbidity.

Moreover, there is less attention for intervention programs that are focuses in ASD patients in late childhood or adolescence. There are some programs like Applied Behavior Analysis (ABA) – the process of applying evidence-based research into interventions

to improve and maintain adaptive behavior of those with ASD, which increases functioning level, language skills, academic outcomes, and social behaviors which could be utilized to all ages (Matson, Benavidez, Compton, Paclawskyj, Baglio, 1996b). However, majority of programs specialized in ASD are targeted for those in their early childhood and scarcity of research focuses on interventions programs for adolescents (Myers, 2009). Therefore, those who are diagnosed with ASD in late childhood or adolescence may lack resource that could help them.

Cultural factors need to be considered when studying the association between comorbid psychiatric disorders and diagnosis timing. In Korea, there is high stigma associated with ASD. Especially, there is a misconception that ASD is a disorder that is hereditary which leads parents to avoid their children to be diagnosed or evaluated for ASD (Kim et al., 2011). In fact, Kim and colleagues (2011), around 70% of the main stream school population was undiagnosed and untreated with ASD. Moreover, the general public's awareness or recognition of ASD may be associated with diagnosis timing of ASD in Korea. Rim and colleagues (2019) have conducted an online survey to measure the mental health literacy (MHL) (Jorm, Korten, Jacomb, Christensen, Rodgers, & Pollitt, 1997) of ASD in Korea. The authors showed a

vignette which explained the symptoms of a child with ASD and only about 25% of the participants have correctly recognized that the child had ASD. This rate is much lower than that of other countries such as China (57.8%) or Japan (45.8%) (Wang, Zhou, Xia, Sun, Wu, Wang, 2012, Koyama, Tachimori, Sawamura, Koyama, Naganuma, Makino, 2009).

As of my knowledge there is no study which studied the psychiatric comorbidity risk of early diagnosed and late diagnosed ASD. Therefore, this study will explore the risk of having a comorbid psychiatric based on the diagnosis timing using a nationally representative longitudinal data.

Current Study

This current study is an explorative study which investigated the risk of having seven different psychiatric disorders of ASD compared to the general population. Also, it analyzed the risk of having a comorbid psychiatric disorder based on intellectual functioning level and diagnosis timing, using a nationally representative cohort data.

Methods

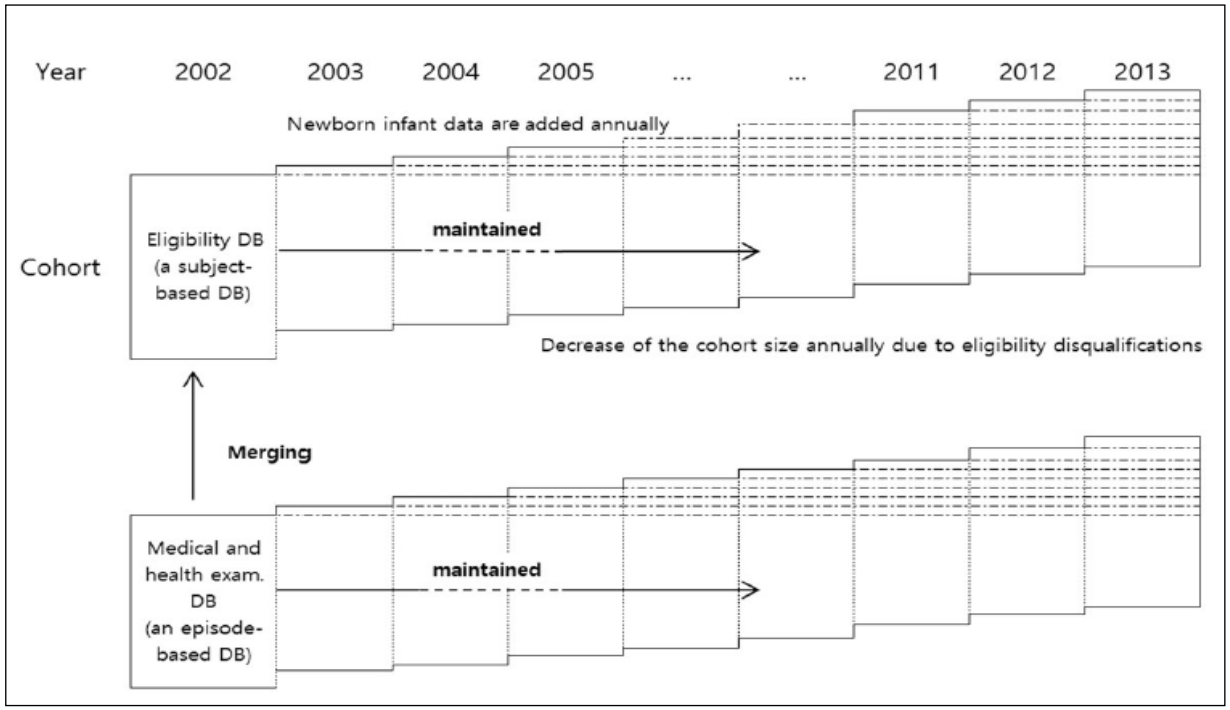
Information regarding the data utilized in this study, participant selection process, measures and statistical analysis are as follows.

Data

South Korea has reached universal health insurance (around 99% of the population) coverage in 1989. The healthcare system in Korea has started to concentrate on disease prevention and constructed the National Health Insurance Database. Along with this plan, the NHIS has built NHIS-NSC for research purposes. NHIS-NSC contains about a million participants which is 2% of Korea's population. A systematic sampling was done for 18 strata based on sex, age group, insurance type and income level.

In 2002, 1,025,340 individuals were initially included in the cohort. Due to death or emigration, there were dropouts each year. To fill this gap, around 9,000 infants aged 0 were newly included in the cohort each year. During 2003-2013, a total of 76,354 infants were newly added. A detailed representation of the data construction is figure 1.

Figure 1. Data construction of NHIS-NSC



Lee et al (2016)

The NHIS-NSC is comprised of three databases: insured database, medical treatment database, and health checkups database. The insured database has are information regarding sex, age, region, eligibility status, etc. The medical treatment database is comprised of information such as treatment, medication, hospital information, etc. The health checkup database includes individual's medical checkup data and information of their health behaviors. More information regarding NHIS-NSC could be found elsewhere (Lee, Lee, Park, Shin, & Kim, 2016).

Participant Selection

Participants were classified as having ASD if an individual received a diagnosis code for autism (F84.0), Asperger syndrome (F84.5), atypical autism (F84.1), pervasive developmental disorder – not otherwise specified (F84.9), other childhood disintegrative disorder (F84.3) or other pervasive developmental disorders (F84.8) which is considered as ASD in DSM-5. These codes have been utilized in previous study (Hirvikoski et al., 2016). Non-ASD (i.e., general population) was classified as those who did not receive an F code for autism, Asperger syndrome, atypical autism, and pervasive developmental disorder – not otherwise specified, other childhood disintegrative disorder and other pervasive

developmental disorders. All diagnostic codes were based on ICD-10.

This study focused on intellectual functioning of ASD when classifying functioning level. Therefore, those with intellectual disorder (ID, F70-79) were classified as Low-Functioning ASD and those without ID were classified as High-Functioning ASD. Based on the ICD-10 code, diagnosis of mild (F70), moderate (F71), severe (F72), profound (F73), other (F78) and unspecified (F79) intellectual disability could be differentiated. However, since our analysis is on intellectual functioning, regardless of its severity, those diagnosed with F70-79 were classified as low-functioning ASD. This method has been utilized in classifying functioning level with registry data elsewhere (Hirvikoski et al., 2016).

Diagnosis timing was determined based on the first record of ASD during the follow-up period. We have considered those who have received diagnosis before 10 as early-diagnosis ASD and those who have received ASD diagnosis between 10 and 19 were considered as late-diagnosis ASD. This was based on previous study (Kim et al., 2011) which showed that 70% of school aged children not being diagnosed. Those with first record of ASD over 20 were excluded from the analysis. These excluded individuals were considered as those who were 20 or above from the baseline

(i.e., 2002). Therefore, it is impossible to track their first diagnosis age from the record.

Measures

Sociodemographic variables that were included in the analysis were those available from the NHIS-NSC insured database, which are sex, age, medical insurance type, income level, and region.

Psychiatric comorbidity was based on the diagnosis code for each different disorder. The F-code for each disorder is shown in table 1. Each participant was considered to have a schizophrenia spectrum and other psychotic disorders (F20-F29), bipolar disorder (F31), depression (F32, F33), anxiety disorder (F40, F41), Obsessive Compulsive Disorder (F42), Post-traumatic Stress Disorder (F43), and Attention-Deficit/Hyperactivity Disorder (F90) by receiving at least one outpatient or inpatient record for the certain disorder.

Table 1. ICD-10 Code for each psychiatric disorder

No.	Disorder Name	F-Code
1	Schizophrenia spectrum and other psychotic disorders	F20-F29
2	Bipolar Disorder	F31

3	Depression	F32, F33
4	Anxiety Disorder	F40, F41
5	Obsessive Compulsive Disorder (OCD)	F42
6	Post-traumatic Stress Disorder (PTSD)	F43
7	Attention-Deficit / Hyperactivity Disorder (ADHD)	F90

Sex was determined by registered information in the insurance system and was categorized into male and female. Age was categorized in to nine groups which were 0 years old, 1-9 years old, 10-19 years old, 20-29 years old, 30-39years old, 40-49years old, 50-59years old, 60 years old and over based on each participants' age at entry to the cohort. Insurance type was based on how each participant was registered by the NHIS (i.e., medical aid and national health insurance). Region was categorized into metropolitan ('si') and others ('do'). Seoul, Busan, Daegu, Incheon, Gwangju, Deajeon, Ulsan, and Sejong were included in metropolitan areas. Others included Gyeonggido, Gangwondo, Chungcheongbuk-do, Chungcheongnam-do, Jeollabuk-do, Jeollanam-do, Gyeongsangbuk-do, Gyeongsangnam-do, and Jeju Island. Income level was categorized into 10 levels with higher levels meaning higher income. Charlson Comorbidity Index (CCI) (Charlson, Pompei, Ales, & MacKenzie, 1987) was also calculated for each participant. CCI is an index to know the comorbid physical disease of an individual. Certain physical disease (e.g., diabetes, tumor,

etc.) have its own weight based on the severity. A score of 0 indicates that an individual do not have having comorbid disease. Higher CCI scores mean that he or she has multiple comorbid diseases or a severe disease.

Statistical Analysis

The characteristic of 1) ASD and non-ASD 2) High-Functioning ASD and Low-Functioning ASD 3) Late-Diagnosed ASD and Early-Diagnosed ASD were compared through chi-square test.

Logistic regression was done to estimate the crude odd ratio for each comorbid psychiatric disorder. Then, multiple logistic regression was done while controlling for associated variables which showed difference in chi-square test.

A p-value of < 0.05 was considered statistically significant. Also, for Odd Ratios, 95% Confidence Interval (CI) not including 1.0 was considered to be significant. All statistical analysis was performed with SAS software version 9.4 (SAS Institute Inc., Cary, NC).

In Korea to prescribe a certain medication a diagnostic code for an appropriate disorder or disease is required. Therefore, it is possible to make a diagnosis for a psychiatric disorder for other

disease or purposes (e.g., weight loss for antidepressants). To reduce this bias, additional analysis was done with a more strict diagnostic qualification – two or more outpatient or one inpatient record for a specific psychiatric disorder. The results are presented in the Appendix.

Moreover, Early-Diagnosed ASD was classified as those who were diagnosed between 0 ~ 9 and Late-Diagnosed ASD were those who have been diagnosed between 10 ~ 19. However, since early diagnosis is usually considered as those who were diagnosed before 5 (Zuckerman, Lindly, Chavez, 2017), additional analysis was done with this standard; those who were diagnosed between 0~4 were considered as Early-Diagnosed ASD and those who were diagnosed between 5~9 were considered as Late-Diagnosed ASD. The results of the additional analyses are provided in the Appendix.

Results

The risk for psychiatric comorbidity was compared between ASD vs. Non-ASD, High vs. Low functioning ASD, and Early vs. Late diagnosed ASD.

ASD vs. Non-ASD (General Population)

As shown in table 2, there were total of 1,259 individuals diagnosed with ASD during the follow-up period. There was a significant difference in sex χ^2 (1, N =1,115,850) = 401.62, p < 0.01, between ASD and non-ASD. There was a statistical difference of age between ASD and non-ASD, $\chi 2$ (7, N = 1,115,850) = 2774.20, p < 0.01. Also, there was a statistically significant difference in income level between ASD and non-ASD χ^2 (1, N = 1,115,850) = 86.62, p < 0.01. Moreover, there was a significant difference of CCI between ASD and non-ASD, χ^2 (4, N = 1,115,850) = 350.38, p < 0.01. Lastly, there was a significant difference of region between ASD and non-ASD, χ^2 (1, N = 1,115,850) = 8.92, p < 0.01.

Table 2. Participants' baseline characteristics: ASD and non-ASD

	ASD (N = 1,259)	Non-ASD (N = 1,114,591)

	N	%	N	%	χ^2
Sex					401.62**
Male	987	78.40	558,854	50.14	
Female	272	21.60	555,737	49.86	
Age (years old)					2774.20**
0	484	38.44	108,141	9.70	
1-9	521	41.38	126,229	11.33	
10-19	184	14.61	141,109	12.66	
20-29	33	2.62	169,905	15.24	
30-39	20	1.59	186,255	16.71	
40-49	7	0.56	167,090	14.99	
50-59	6	0.48	96,522	8.66	
60+	4	0.32	119,340	10.71	
Medical Insurance					0.48
Medical Aid	36	2.86	28,445	2.55	
NHIS	1,223	97.14	1,086,146	97.45	
Income					86.62**
0	36	2.86	28,445	2.55	
1	29	2.30	63,736	5.72	
2	35	2.78	65,755	5.90	
3	72	5.72	77,842	6.98	
4	74	5.88	91,543	8.21	
5	128	10.17	105,455	9.46	
6	143	11.36	119,448	10.72	
7	185	14.69	131,496	11.80	
8	212	16.84	142,508	12.79	
9	184	14.61	145,797	13.08	
10	161	12.79	142,566	12.79	

Region					8.92**
Metropolitan cities	650	51.63	528,559	47.42	
Others	609	48.37	586,032	52.58	
CCI					350.38**
0	275	21.84	243,212	21.82	
1	666	52.90	346,537	31.09	
2	153	12.15	177,587	15.93	
3	92	7.31	116,680	10.47	
4+	73	5.80	230,575	20.69	

*p <0.05, ** p <0.01

As shown in table 3, those with ASD showed higher risk for schizophrenia spectrum and other psychotic disorders (*OR* = 32.66, 95%CI = 27.20, 39.21), bipolar disorder (*OR* = 106.67, 95% CI = 83.18, 136.80), depression (*OR* = 10.71, 95% CI = 9.04, 12.69), anxiety disorder (*OR* = 2.06, 95% CI = 1.74, 2.44), OCD (*OR* = 43.30, 95% CI = 30.14, 62.21), PTSD (*OR* = 6.14, 95% CI = 4.84, 7.80), and ADHD (*OR* = 110.49, 95% CI = 97.17, 125.63) compared to non-ASD.

Multiple logistic regression was done by adjusting sex, age, income and CCI which showed difference in the chi-square test and results are shown in table 4. After controlling for these associated variables, ASD still showed higher risk for schizophrenia spectrum

and other psychotic disorders (*AOR* = 232.90, 95% CI = 183.07, 296.30), bipolar disorder (*AOR* = 314.00, 95% CI = 229.81, 429.02), depression (*AOR* = 43.95, 95% CI = 36.31, 53.19), anxiety disorder (*AOR* = 9.04, 95% CI = 7.53, 10.84), OCD (*AOR* = 53.62, 95% CI = 36.33, 79.12), PTSD (*AOR* = 9.72, 95% CI = 7.61, 12.42), and ADHD (*AOR* = 34.62, 95% CI = 30.12, 39.80) compared to non-ASD (also see figure 2).

An additional analysis was done while applying a stricter standard for classification for diagnosis of psychiatric disorder (at least two inpatient or one inpatient record) and results are presented in the Appendix (Tables11, 12).

Table 3. Psychiatric comorbidity risk of ASD compared to Non-ASD

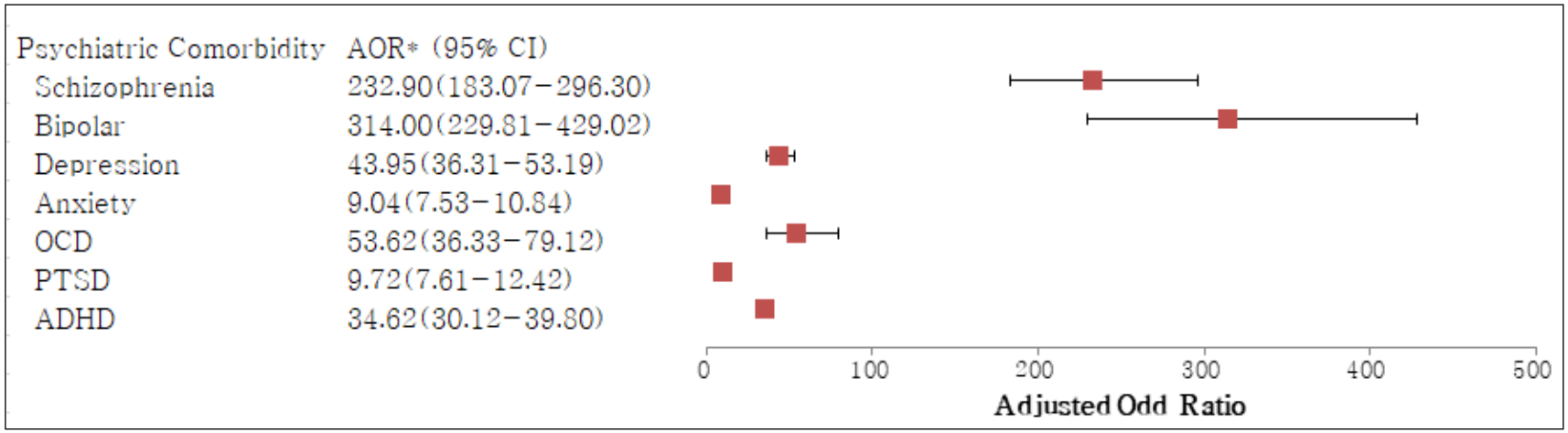
Psychiatric Disorder	ASD (*N*=1,259)		Non-ASD (Ref) (*N*=1,114,591)		ß	SE	*p*	OR	95% CI	
	N	%	*N*	%						
Schizophrenia	134	10.64	2,876	0.36	1.74	0.05	<.01	32.66	27.20	39.21
Bipolar	76	6.04	475	0.06	2.33	0.06	<.01	106.67	83.18	136.80
Depression	154	12.23	10,421	1.29	1.19	0.04	<.01	10.71	9.04	12.69
Anxiety	153	12.15	52,991	6.30	0.36	0.04	<.01	2.06	1.74	2.44
OCD	32	2.54	475	0.06	1.88	0.09	<.01	43.30	30.14	62.21
PTSD	72	5.72	7,791	0.98	0.91	0.06	<.01	6.14	4.84	7.80
ADHD	353	28.04	2,781	0.35	2.35	0.03	<.01	110.49	97.17	125.63

Table 4. Psychiatric comorbidity risk of ASD compared to Non-ASD controlling for associated variables

Psychiatric Disorder	ASD (*N*=1,259)		Non-ASD (Ref) (*N*=1,114,591)		ß	SE	*p*	AOR*	95% CI	
	N	%	*N*	%						
Schizophrenia	134	10.64	2,876	0.36	2.73	0.06	<.01	232.90	183.07	296.30
Bipolar	76	6.04	475	0.06	2.87	0.08	<.01	314.00	229.81	429.02
Depression	154	12.23	10,421	1.29	1.89	0.05	<.01	43.95	36.31	53.19
Anxiety	153	12.15	52,991	6.30	1.10	0.05	<.01	9.04	7.53	10.84
OCD	32	2.54	475	0.06	1.99	0.10	<.01	53.62	36.33	79.12
PTSD	72	5.72	7,791	0.98	1.14	0.06	<.01	9.72	7.61	12.42
ADHD	353	28.04	2,781	0.35	1.77	0.04	<.01	34.62	30.12	39.80

* Adjusted for sex, age, income, and CCI

Figure 2. Psychiatric comorbidity risk of ASD compared to Non-ASD controlling for associated variables



*Adjusted for sex, age, income and CCI

High-Functioning vs. Low-Functioning ASD

Next, the baseline characteristics of High-Functioning and Low-Functioning ASD were compared and the results are in table 5. According the results, only age was statistically different between high-functioning and low-functioning ASD χ^2 (7, N =1,259) = 31.33, $p < 0.01$.

Table 5. Baseline Characteristics of High and Low-functioning ASD

	High-Functioning N = 827		Low-Functioning (Ref) N = 432		
	N	%	N	%	χ^2
Sex					0.11
Male	646	78.11	341	78.94	
Female	181	21.89	91	21.06	
Age (years old)					31.33**
0	357	43.17	127	29.40	
1-9	323	39.06	198	45.83	
10-19	100	12.09	84	19.44	
20-29	20	2.42	13	3.01	
30-39	14	1.69	6	1.39	
40-49	4	0.48	3	0.69	
50-59	5	0.60	1	0.23	
60+	4	0.48	0	0.00	
Medical Insurance					2.74

Medical Aid	19	2.30	17	3.94	
NHIS	808	97.70	415	96.06	
Income					5.63
0	19	2.30	17	3.94	
1	19	2.30	10	2.31	
2	24	2.90	11	2.55	
3	46	5.56	26	6.02	
4	49	5.93	25	5.79	
5	79	9.55	49	11.34	
6	98	11.85	45	10.42	
7	126	15.24	59	13.66	
8	135	16.32	77	17.82	
9	125	15.11	59	13.66	
10	107	12.94	54	12.50	
Region					0.91
Metropolitan cities	435	52.60	215	49.77	
Others	392	47.40	217	50.23	
CCI					3.90
0	174	21.04	101	23.38	
1	452	54.66	214	49.54	
2	100	12.09	53	12.27	
3	58	7.01	34	7.87	
4+	43	5.20	30	6.94	

*p <0.05, ** p <0.01

As shown in table 6, High-Functioning ASD showed a lower risk of having schizophrenia spectrum and other psychotic disorders (*OR* = 0.42, 95% CI = 0.29, 0.60), bipolar disorder (*OR* = 0.56,

95% CI = 0.35, 0.89), and ADHD (*OR* = 0.65, 95% CI = 0.51, 0.84) compared to Low-Functioning ASD.

The risk of comorbid psychiatric disorders while controlling for associated variables by functioning level is shown in table 7. When age was adjusted, High-Functioning ASD had lower odd of having comorbid schizophrenia spectrum and other psychotic disorders (*AOR* = 0.50, 95% 0.34, 0.73) and ADHD (*AOR* = 0.68, 95% CI = 0.52, 0.88) compared to Low-Functioning ASD. Moreover, High-Functioning ASD had higher risk of being diagnosed with comorbid depression (*AOR* = 1.69, 95% CI = 1.15, 2.49) compared to Low-Functioning ASD (also see figure 3).

Table 6. Psychiatric comorbidity risk of High-Functioning ASD compared to Low-Functioning ASD

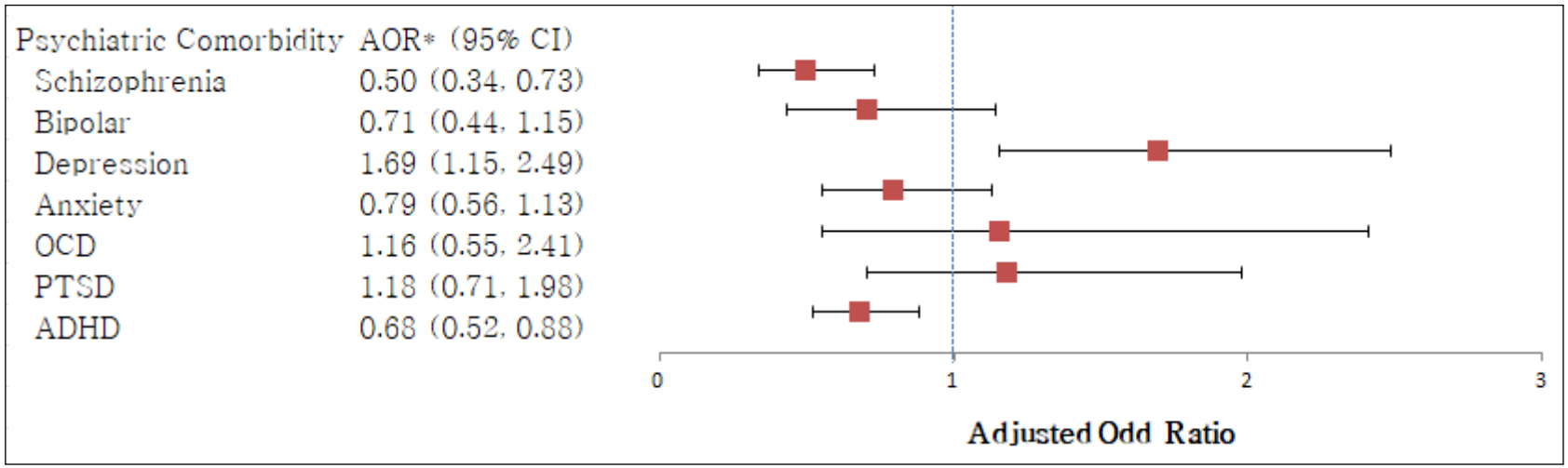
Psychiatric Disorder	High-functioning N=827		Low-functioning (Ref) N=432		ß	SE	*p*	OR	95% CI	
	N	%	N	%						
Schizophrenia	63	7.62	71	16.44	**-0.43**	**0.09**	**<.01**	**0.42**	**0.29**	**0.60**
Bipolar	40	4.84	36	8.33	**-0.29**	**0.12**	**0.01**	**0.56**	**0.35**	**0.89**
Depression	108	13.06	46	10.65	0.12	0.09	0.22	1.26	0.87	1.82
Anxiety	90	10.88	63	14.58	-0.17	0.09	0.06	0.72	0.51	1.01
OCD	20	2.42	12	2.78	-0.07	0.19	0.70	0.87	0.42	1.79
PTSD	47	5.68	25	5.79	-0.01	0.13	0.94	0.98	0.60	1.62
ADHD	207	25.03	146	33.80	**-0.21**	**0.06**	**<.01**	**0.65**	**0.51**	**0.84**

Table 7. Psychiatric comorbidity risk of High-Functioning ASD compared to Low-Functioning ASD controlling associated variables

Psychiatric Disorder	High-Functioning *N*=827		Low-Functioning (Ref) *N*=432		ß	SE	*p*	AOR*	95% CI	
	N	%	N	%						
Schizophrenia	63	7.62	71	16.44	**−0.35**	**0.10**	**<.01**	**0.50**	**0.34**	**0.73**
Bipolar	40	4.84	36	8.33	−0.17	0.12	0.16	0.71	0.44	1.15
Depression	108	13.06	46	10.65	**0.26**	**0.10**	**<.01**	**1.69**	**1.15**	**2.49**
Anxiety	90	10.88	63	14.58	−0.12	0.09	0.20	0.79	0.56	1.13
OCD	20	2.42	12	2.78	0.07	0.19	0.70	1.16	0.55	2.41
PTSD	47	5.68	25	5.79	0.08	0.13	0.52	1.18	0.71	1.98
ADHD	207	25.03	146	33.80	**−0.19**	**0.07**	**<.01**	**0.68**	**0.52**	**0.88**

*Adjusted for age

Figure 3. Psychiatric comorbidity risk of High-Functioning ASD compared to Low-Functioning ASD controlling for associated variable



*Adjusted for age

Late Diagnosed vs. Early Diagnosed ASD

The baseline characteristics of Late-Diagnosed ASD and Early-Diagnosed ASD were compared using chi-square test and the results are shown in table 8. There was a statistically significant difference of sex, χ^2 (1, N =1,120) = 4.60, p < 0.03, age, χ^2 (4, N = 1,120) = 635.44, p < 0.01 medical insurance type, χ^2 (1, N =1,120) = 6.24, p = 0.01, income χ^2 (10, N =1,120) = 48.00, p < 0.01, and CCI χ^2 (4, N =1,120) = 37.56, p < 0.01 between Late-Diagnosed and Early-Diagnosed ASD.

Table 8. Baseline characteristic of Late Diagnosed ASD and Early Diagnosed ASD

	Late Diagnosis N = 320		Early Diagnosis N = 800		
	N	%	N	%	χ^2
Sex					4.60*
Male	265	82.81	616	77.00	
Female	55	17.19	184	23.00	
Age					635.44**
0 years old	5	1.56	479	59.88	
1-4 years old	52	16.25	242	30.25	
5-9 years old	145	45.31	79	9.88	
10-14 years old	104	32.50	0	0.00	
15-19 years old	14	4.38	0	0.00	

Medical Insurance					6.24*
Medical Aid	21	6.56	26	3.25	
NHIS	299	93.44	774	96.75	
Income					48.00**
0	21	6.56	26	3.25	
1	19	5.94	38	4.75	
2	13	4.06	30	3.75	
3	19	5.94	29	3.63	
4	22	6.88	39	4.88	
5	19	5.94	70	8.75	
6	23	7.19	72	9.00	
7	21	6.56	110	13.75	
8	31	9.69	143	17.88	
9	59	18.44	138	17.25	
10	73	22.81	105	13.13	
Region					1.75
Metropolitan cities	164	51.25	375	46.88	
Others	156	48.75	425	53.13	
CCI					37.56**
0	89	27.81	134	16.75	
1	135	42.19	488	61.00	
2	55	17.19	84	10.50	
3	24	7.50	61	7.63	
4+	17	5.31	33	4.13	

*p <0.05, ** p <0.01

The risk of having comorbid psychiatric disorder based on diagnosis timing is shown in table 9. Late-Diagnosed ASD had a higher risk of being diagnosed with schizophrenia spectrum and

other psychotic disorders (*OR* = 3.79, 95% CI = 2.44, 5.87), bipolar (*OR* = 4.70, 95% CI = 2.70, 8.19), depression (*OR* = 5.05, 95% CI = 3.39, 7.51), anxiety disorder (*OR* = 1.80, 95% CI = 1.22, 2.65), OCD (*OR* = 8.82, 95% CI = 3.51, 22.18), PTSD (*OR* = 4.94, 95% CI = 2.82, 8.68), and ADHD (*OR* = 1.70, 95% CI = 1.29, 2.24) compared to Early-Diagnosed ASD.

When associated variables (i.e., sex, medical insurance, income and CCI) were adjusted, Late-Diagnosed ASD had higher risk of being diagnosed with depression (*AOR* = 2.21 95% CI = 1.35, 3.64), OCD (*AOR* = 3.66, 95% CI = 1.30, 10.31), PTSD (*AOR* = 3.48, 95% CI = 1.57, 7.70), and ADHD (*AOR* = 1.62, 95% CI = 1.12, 2.34) compared to Early-Diagnosed ASD (see table 10 and figure 4).

Additional analysis was done by setting early diagnosis as those who were diagnosed before 5 years old and late diagnosis as those who were diagnosed between 5 and 9 years old. The results are shown in the appendix.

Table 9. Psychiatric comorbidity risk of Late−Diagnosed ASD compared to Early−Diagnosed ASD

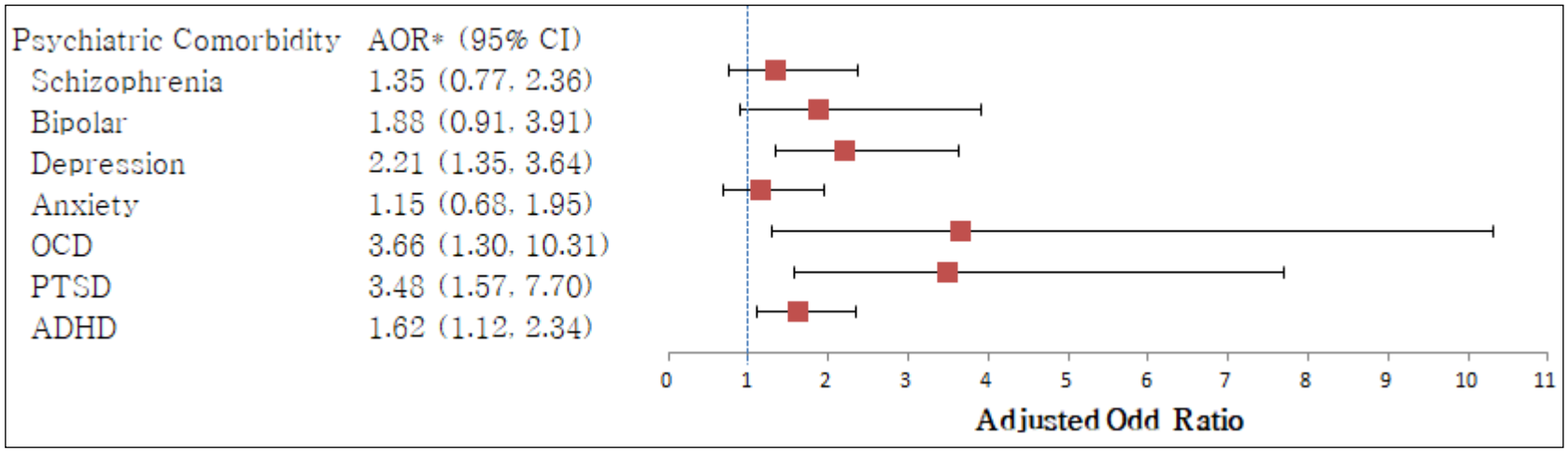
Psychiatric Disorder	Late−Diagnosed ASD (*N* = 320)		Early−Diagnosed ASD (ref) (*N* = 800)		ß	SE	*p*	OR	95% CI	
	N	%	*N*	%						
Schizophrenia	52	16.25	39	4.88	0.67	0.11	<.01	3.79	2.44	5.87
Bipolar	36	11.25	21	2.63	0.77	0.14	<.01	4.70	2.70	8.19
Depression	74	23.13	45	5.63	0.81	0.10	<.01	5.05	3.39	7.51
Anxiety	49	15.31	73	9.13	0.29	0.10	<.01	1.80	1.22	2.65
OCD	20	6.25	6	0.75	1.09	0.24	<.01	8.82	3.51	22.18
PTSD	36	11.25	20	2.50	0.80	0.14	<.01	4.94	2.82	8.68
ADHD	125	39.06	219	27.38	0.27	0.07	<.01	1.70	1.29	2.24

Table 10. Psychiatric comorbidity risk of Late Diagnosed ASD compared to Early Diagnosed ASD controlling for associated variable

Psychiatric Disorder	Late Diagnosis (*N* = 320)		Early Diagnosis (ref) (*N* = 800)		ß	SE	*p*	AOR*	95% CI	
	N	%	*N*	%						
Schizophrenia	52	16.25	39	4.88	0.15	0.14	0.30	1.35	0.77	2.36
Bipolar	36	11.25	21	2.63	0.32	0.19	0.10	1.88	0.91	3.91
Depression	74	23.13	45	5.63	**0.40**	**0.13**	**<.01**	**2.21**	**1.35**	**3.64**
Anxiety	49	15.31	73	9.13	0.07	0.13	0.60	1.15	0.68	1.95
OCD	20	6.25	6	0.75	**0.65**	**0.26**	**0.01**	**3.66**	**1.30**	**10.31**
PTSD	36	11.25	20	2.50	**0.62**	**0.20**	**<.01**	**3.48**	**1.57**	**7.70**
ADHD	125	39.06	219	27.38	**0.24**	**0.09**	**0.01**	**1.62**	**1.12**	**2.34**

*Adjusted for sex, age, medical insurance, income and CCI

Figure 4. Psychiatric comorbidity risk of Late Diagnosed ASD compared to Early Diagnosed ASD controlling for associated variables



*Adjusted for sex, age, medical insurance, income and CCI

Discussion

This study conducted an explorative study to investigate the risk of comorbid psychiatric disorders in ASD using a nationally representative cohort. The results are discussed in three different sections: 1) ASD and psychiatric comorbidity, 2) Psychiatric comorbidity of ASD and functioning level, and 3) Psychiatric comorbidity of ASD and diagnosis timing.

ASD and Psychiatric Comorbidity

According to the results of this study, ASD showed significantly higher risk of having all seven different psychiatric disorders compared to the general population. The risk ranged from 9 folds to 314 folds depending on the disorder. This result is in line with previous studies (DeFilippis, 2018; Hedley et al., 2018; Hossain, 2020; Lai et al., 2019; Matson et al., 2007; Vannucchi et al., 2014) showing high prevalence rate of comorbid psychiatric disorders in ASD. Majority of previous literatures have simply estimated the prevalence of psychiatric comorbidity among clinical samples. This study adds value to previous literature by comparing the risk with the general population. Those with ASD may be more vulnerable to psychiatric disorders compared to the general public

due to clinical, genetic and environmental factors.

ASD and psychiatric disorders compared in this study share clinical risk factors. For instance, the core symptom of ASD (i.e., restricted interest and sensitive to environmental changes) is also found in those with schizophrenia (Esterberg, Trotman, Brasfield, Compton, and Walker, 2008). In fact, ASD and schizophrenia were interchangeably used in the past (Bleuler, 1950) believing autistic behaviors being the core symptom of schizophrenia. Two disorders were separated in 1970 by researchers (Rutter, 1972; Kolvin, 1971) who stated that two disorders are distinct from each other. These overlapping symptoms could be explained by the impairment in theory of mind (ToM) of both conditions (Baron-Cohen, 2000; Solomon, Olsen, Niedam, Ragland, Yoon, Minzenberg et al., 2011). Moreover, there is an overlap between the symptom of OCD and ASD which is repetitive behavior. Based on the overlap in clinical factors, common etiology of comorbid psychiatric disorders and ASD is suggested.

Recently, researchers are putting effort in figuring out genetic links between ASD and other psychiatric disorders. Several studies (Baumeister, Lightman, & Pariante, 2014; Daniels, Forssen, Hultman et al., 2008; Larsson, Eaton, Madsen et al., 2005; Mazefskky, Herrington, Siegel, Scarpa, Maddox, Scahill et al., 2013;

O’ Connell, McGregor, Lochner, Emsley, Warnich, 2018 ; Reiersen, Constantino, Grimmer, Martin, & Todd, 2008; Rommelse, Granke, Geurts, Hartman, & Buitelaar, 2010; Sullivan, Magnusson, Reichenberg et al., 2012) found that shared genetic factors are associated with psychiatric disorders (e.g., schizophrenia, bipolar disorder, PTSD, OCD, and ADHD) and ASD.

Moreover, those with ASD are confronted with environmental risk factors that could increase the risk of comorbid psychiatric disorders compared to the general public. As previously mentioned, those with ASD experience childhood trauma more than typically developing children (Bauminger et al., 2000; Berg et al., 2016; Little, 2001; Roekel et al., 2010). In addition, those with ASD suffer from adversities such as unemployment and relationship problems in adulthood (Fernall et al., 2013). Moreover, impairment and deficits shown in ASD such as impairment in ToM (Baron-Cohen, 2000), weak capacity in integrating information (Happe, 1994), repetitive experience of being bullied (Berg et al., 2016), impairment in recognizing social cues (Lugnegard, Hallerback, & Gillberg, 2011), hardness in emotion regulation and poor ability to cope with stress (Mazefsky et al., 2013) may have integrating affects in increasing the risk for psychiatric disorders.

Previous literature emphasizes that psychiatric comorbidity

in ASD is associated with severe ASD symptoms (Bellini, 2004; Wood et al., 2009; Sukhodolsky et al., 2008), impaired functioning at home, school, and social interaction (Griffiths, Farrell, Waters, White, 2017) and suicidal behaviors (Hedley & Uljarevic, 2019; Richa et al., 2014). Therefore, researchers, clinicians, and other related experts need to play close attention to the psychiatric comorbidity of those with ASD.

Psychiatric Comorbidity of ASD and Functioning Level

Some previous studies suggested that the risk for psychiatric comorbidity may be associated with functioning level (Hollocks et al., 2019; Storch, et al., 2008). Therefore, this study explored whether the risk of having comorbid psychiatric disorder differs by intellectual functional level. According to the results of this study, High-Functioning ASD had lower odds of having comorbid schizophrenia spectrum and other psychotic disorders and ADHD and higher odds of having comorbid depression compared to Low-Functioning ASD.

This result is consistent with the previous studies (Rai, et al, 2018; Brereton et al., 2006; Vickerstaff, et al., 2007; Mayes et al., 2011a) which found that High-Functioning ASD had a higher risk of having comorbid depression than Low-Functioning ASD.

For typically developing children, low functioning is associated with depression (Koenen, Moffitt, Roberts, Martin, Kubzansky, Harrington, et al, 2009). However, the direction of the relationship between functioning level and depression in ASD are found to be opposite from typically developing children. Some previous studies (Hodgins, Kelley, Kloosterman et al., 2018; van Roekel et al, 2010) have stated that ASD patients have lower ability in recognizing bullying compared to non-ASD. However, others suggest that ASD patients have the ability to report their experiences for being bullied quite accurately (Adams, Fredstrom, Duncan, Holleb, &Bishop, 2014; DeNigris et al., 2018). High-Functioning ASD may have more understanding of the problems they encounter and therefore are more vulnerable to depression (Chandrasekhar & Sikich, 2015). In contrast, low-functioning ASD may have hardness in processing their difficulties and have deficit in expressing their feelings (Hudson et al., 2019). Therefore, High-Functioning ASD may have been more diagnosed with depression. High-Functioning ASD do not only have higher risk for depression but also have trouble accessing treatment and limited professional who understand them (Camm-Crosbie, et al, 2018). Therefore, interventions targeted for comorbid depression in High-Functioning ASD seems important.

High-Functioning ASD had lower risk of being diagnosed with ADHD compared to Low-Functioning ASD. This could be due to how symptoms are expressed in Low-Functioning ASD. Previous studies (Sinzig, Walter, & Doepfner, 2009; Lee & Ousley, 2006) indicate that Low-Functioning ASD patients show more problems with hyperactivity. Therefore, ADHD symptoms of Low-Functioning ASD may be more recognizable for parents or teachers and this may lead to a more diagnosis of ADHD in Low-Functioning ASD.

Along with ADHD, High-Functioning ASD had a lower risk of having comorbid schizophrenia compared to Low-Functioning ASD. There are limited studies which compared the risk of comorbid schizophrenia between High-Functioning and Low-Functioning ASD. Selten and colleagues (2015) found that the risk for having nonaffective psychotic disorder for High-Functioning ASD was higher than that of Low-Functioning ASD when compared to the general population. This is inconsistent with the results from this current study. However, according to a meta-analysis (Lai et al., 2019) which analyzed psychiatric comorbidity of ASD (prevalence), comorbid schizophrenia was more prevalent in samples with ID. Also, previous studies indicate weak but evident correlation between low IQ and schizophrenia (Selten, et al., 2015).

Future studies need to figure out the underlying mechanism between intellectual functioning of ASD and schizophrenia.

In sum, it could be concluded that psychiatric disorders related to internalizing problems are associated with High-Functioning ASD and disorders related to externalizing problems (i.e., ADHD & schizophrenia) are associated with Low-Functioning ASD. This could be associated with the limited ability to express their feelings or struggles in Low-Functioning ASD (Hudson et al., 2019). Moreover, it could be due to the fact that those with High-Functioning ASD may not seek help compared to Low-Functioning ASD or are less recognized by parents to get diagnosed or get diagnosed late (Mazurek et al., 2014). More research on the association between comorbid psychiatric disorders and functioning level in ASD needs to be conducted.

Psychiatric Comorbidity of ASD and Diagnosis Timing

Diagnosis timing showed association with psychiatric comorbidity of ASD. Specifically, Late-Diagnosed ASD showed higher risk for depression, OCD, PTSD, and ADHD compared to Early-Diagnosed ASD while controlling for associated variables (i.e., sex, age, medical insurance, income, and CCI).

There are limited studies which investigated the risk of

having a specific psychiatric comorbidity based on diagnosis timing. However, it is clear that early intervention is associated with better outcomes of ASD in various aspects (Vismara et al., 2010). The fact that ASD is a lifelong neurodevelopmental disorder remains, however, studies show that there could be plasticity in symptom severity through appropriate intervention or therapy (Mazurek et al., 2014; Vismara et al., 2010; Eldevik et al., 2009). Therefore, those who are diagnosed late may have a worse outcome including psychiatric comorbidity.

This could be related to the association between diagnosis timing and what type of treatment or services patients seek or receive. Zuckerman and colleagues (2017) conducted a research to investigate the association between diagnosis timing and the use of health services of children with ASD. The authors found that late diagnosed ASD patients had a lower likelihood to use behavioral intervention therapy or school-based therapy. Moreover, delayed diagnosis of two or more years (the time duration of initial recognition of the symptom and actually being diagnosed) was associated with higher risk of using complementary and alternative medicine (CAM) and psychotropic medication such as stimulants, antidepressants, anxiolytics, mood stabilizers, antipsychotics, etc. This result indicates that diagnosis timing and the delay of diagnosis

is associated with the type of service the patients use. Not receiving an evidence-based therapy may worsen their symptoms, which in turn increase the likely hood of having a comorbid psychiatric disorder.

However, not all comorbid psychiatric disorders were associated with diagnosis timing of ASD. Late-Diagnosed ASD had a higher risk of having comorbid depression, OCD, PTSD, and ADHD compared to Early-Diagnosed ASD. Future studies need to investigate the factors associated with these psychiatric disorders and diagnosis timing of ASD. Moreover, the psychiatric comorbidity risk by using a longer period which is sufficient to include psychiatric disorders which usually show onset during adulthood, for instance, schizophrenia.

Implications and Limitation

The current study has explored the risk of having a comorbid psychiatric disorder of ASD using a nationally representative cohort in Korea. Moreover the risk of psychiatric comorbidity of ASD was further analyzed by intellectual functioning level and diagnosis timing. It added meaningful values to previous studies which have studied the psychiatric comorbidity of those with ASD.

Despite the meaningful findings of this study, there are several limitations. First of all, the follow up time was a bit short compared to previous studies. Previous studies which utilized longitudinal data for finding comorbid psychiatric disorders had much longer follow-up period. For instance, a study by Mouridsen and colleagues (2008) had a mean observation time of around 40 years and another study had a mean of 32.5 years of follow-up (Selten et al., 2015) The relatively short follow-up period may have shown less comorbidity. Therefore, a future study with longer follow-up time is needed to investigate the psychiatric comorbidity of ASD in Korea.

Another limitation is that the exact age of first diagnosis was not available. For instance, those who were classified as being diagnosed at 10 in the data may have actually been diagnosed at 10 or may have entered the cohort in 2002 at 10 years old. Therefore, this individual may have been diagnosed earlier. Moreover, this study relied on the diagnostic data by physicians so related psychological factors were not included.

Also, the age that was used in this study was the age each individual were included or newly added to the cohort. Therefore, the age of those who were included in the cohort in 2002 is his or her age in 2002. However, for those who were newly added to the

cohort, their age were all 0 since newly born infants were included to the cohort every year.

Moreover, the NHIS-NSC does not include psychological measures. Therefore, the functioning level of ASD patients was solely dependent on participant's intellectual functioning (i.e., presence of ID). Therefore, future study needs to investigate functioning level of ASD in various domains.

Regardless of these limitations, the current study added valuable results to the field of ASD and psychiatric comorbidity. Physicians, psychologist, and other experts need to imply the results of this current study in research, practice, and policy. Future studies need to use longer follow-up data to confirm the results of this study.

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국문초록

자폐스펙트럼장애를 가진 환자들은 아동기부터 성인기까지 다양한 어려움을 겪는다. 예컨대, 아동 폭력, 또래 괴롭힘, 낮은 삶의 질, 등의 어려움을 겪는다. 더불어, 자폐스펙트럼장애를 가진 자녀의 부모 또한 극심한 스트레스를 호소한다. 이러한 자폐스펙트럼장애 환자들이 직면해야 하는 다른 문제는 정신질환 공병(psychiatric comorbidity) 위험이다. 이미 자폐스펙트럼장애만으로도 어려움을 겪지만, 다른 정신질환(예컨대, 우울장애, ADHD, 등)을 동반하게 되면, 삶의 질은 더 낮아지며 자살 위험 또한 높아지게 되는 것으로 보고되고 있다. 그러나 이런 연구결과들에도 불구하고, 자폐스펙트럼장애와 정신질환 공병에 대한 연구는 드물며 국가단위의 데이터를 사용한 연구는 극히 드물다. 더불어, 대부분의 연구들은 한 연구에서 한 가지 정신질환을 살펴보았으며, 다양한 연령대가 포함된 데이터를 사용하지 않았다는 제한점이 있다.

본 연구는 국가를 대표할 수 있는 자료를 사용하여, 자폐스펙트럼장애의 정신질환 공병 위험을 살펴보는 탐색적인 연구를 진행하였으며, 관련 요인 (지적 수준 및 진단 시기)에 따라 그 위험에 차이가 있는지를 추가적으로 살펴보았다.

연구 결과, 자폐스펙트럼장애를 가진 환자들은 일반인에 비해 조현병, 양극성장애, 우울장애, 불안장애, 강박장애, 외상후스트레스장애, 주의력결핍 과잉행동장애를 동반할 위험이 일반인에 비해 높은 것으로 나타났다. 고기능 (high-functioning) 자폐스펙트럼장애 환자들은 저기

능 (low-functioning) 자폐스펙트럼 환자들에 비해 조현병 및 주의력결핍 과잉행동장애를 가질 위험이 낮았으며, 우울장애를 가질 위험은 더 높았다. 더불어, 진단시기에 따른 정신동반 위험을 살펴보았을 때, 늦은 진단을 받은 자폐스펙트럼장애 환자들이 이른 진단을 받은 자폐스펙트럼장애 환자들에 비해 우울장애, 강박장애, 외상후스트레스장애, 주의력결핍 과잉행동장애를 동반할 위험이 높은 것으로 나타났다.

이러한 결과는 자폐스펙트럼장애 환자들이 일반인에 비해 다른 정신질환을 동반할 위험이 높다는 것을 보여주며, 특히 진단을 늦게 받는 것은 다른 정신질환 동반을 높이는 것으로 보여진다. 또한, 기능 수준(지적 수준)에 따른 정신질환 동반 위험은 질환에 따라 상이한 결과가 나타난 것으로 보아, 지적 수준에 따라 동반할 위험이 높은 정신질환이 다르다는 것을 시사한다. 그러나, 기능 수준에 따른 정신질환 동반 위험은 보다 많은 연구가 필요할 것으로 보인다.

본 연구 결과를 토대로, 자폐스펙트럼장애 환자들을 대상으로 정신질환 공병에 대한 평가가 필요하다는 것을 알 수 있다. 특히, 진단 시기가 늦을 경우, 정신질환 동반 위험이 높아지는 것으로 나타났으므로 이른 진단을 받을 수 있도록 자폐스펙트럼장애에 대한 인식이 높아질 수 있도록 노력해야 하며, 지적 수준에 따른 개입이 다르게 진행되어야 할 것으로 보인다.

Appendix

Table 11. Risk of having a comorbid psychiatric disorder of ASD vs. Non-ASD (at least two outpatient or one inpatient record)

Psychiatric Disorder	ASD (*N*=1,259)		Non-ASD (Ref) (*N*=1,114,591)		ß	SE	*p*	OR	95% CI	
	N	%	*N*	%						
Schizophrenia	114	9.05	2,055	0.26	1.82	0.05	<.01	38.27	31.42	46.62
Bipolar	59	4.69	261	0.03	2.50	0.07	<.01	148.60	111.39	198.22
Depression	154	12.23	10,421	1.29	1.19	0.04	<.01	10.71	9.04	12.69
Anxiety	97	7.70	21,480	2.55	0.58	0.05	<.01	3.19	2.59	3.92
OCD	19	1.51	220	0.03	2.00	0.12	<.01	54.95	34.28	88.09
PTSD	39	3.10	2,642	0.33	1.13	0.08	<.01	9.60	6.97	13.24
ADHD	302	23.99	1,963	0.25	2.42	0.03	<.01	126.91	110.69	145.50

Table 12. Risk of having a comorbid psychiatric disorder of ASD vs. Non-ASD controlling for associated variables (at least two outpatient or one inpatient record)

Psychiatric Disorder	ASD (*N*=1,259)		Non-ASD (Ref) (*N*=1,114,591)		ß	SE	*p*	AOR**	95% CI	
	N	%	*N*	%						
Schizophrenia	114	9.05	2,055	0.26	2.93	0.07	<.01	348.86	264.87	459.49
Bipolar	59	4.69	261	0.03	3.02	0.10	<.01	421.72	290.18	612.89
Depression	154	12.23	10,421	1.29	1.89	0.05	<.01	43.95	36.31	53.19
Anxiety	97	7.70	21,480	2.55	1.47	0.06	<.01	19.05	15.19	23.90
OCD	19	1.51	220	0.03	2.04	0.13	<.01	59.61	35.79	99.28
PTSD	39	3.10	2,642	0.33	1.34	0.08	<.01	14.48	10.41	20.15
ADHD	302	23.99	1,963	0.25	1.82	0.04	<.01	38.27	33.02	44.36

*Adjusted for sex, age, income and CCI

Table 13. Risk of having a comorbid psychiatric disorder by diagnosis timing (0~4 vs. 5~9)

Psychiatric Disorder	Late−Diagnosis (N = 361)		Early−Diagnosis (ref) (N = 439)		ß	SE	p	OR	95% CI	
	N	%	N	%						
Schizophrenia	28	7.76	11	2.51	0.59	0.18	<.01	3.27	1.61	6.67
Bipolar	13	3.60	8	1.82	0.35	0.23	0.12	2.01	0.83	4.91
Depression	31	8.59	14	3.19	0.52	0.17	<.01	2.85	1.49	5.45
Anxiety	45	12.47	28	6.38	0.37	0.13	<.01	2.09	1.28	3.43
OCD	4	1.11	2	0.46	0.45	0.43	0.30	2.45	0.45	13.44
PTSD	11	3.05	9	2.05	0.20	0.23	0.37	1.50	0.62	3.66
ADHD	143	39.61	76	17.31	0.57	0.08	<.01	3.13	2.26	4.34

Table 14. Risk of having a comorbid psychiatric disorder by diagnosis timing controlling for associated variables (0~4 vs. 5~9)

Psychiatric Disorder	Late−Diagnosis (*N* = 361)		Early−Diagnosis (ref) (*N* = 439)		ß	SE	*p*	AOR**	95% CI	
	N	%	*N*	%						
Schizophrenia	28	7.76	11	2.51	0.10	0.19	0.60	1.22	0.57	2.61
Bipolar	13	3.60	8	1.82	0.02	0.25	0.93	1.04	0.39	2.76
Depression	31	8.59	14	3.19	0.06	0.18	0.73	1.13	0.56	2.27
Anxiety	45	12.47	28	6.38	**0.30**	**0.14**	**0.03**	**1.81**	**1.05**	**3.12**
OCD	4	1.11	2	0.46	−0.12	0.44	0.79	0.79	0.14	4.38
PTSD	11	3.05	9	2.05	0.20	0.25	0.44	1.48	0.55	3.98
ADHD	143	39.61	76	17.31	**0.47**	**0.09**	**<.01**	**2.55**	**1.79**	**3.65**

*Adjusted for sex