

A Study on the Incidence and Comorbidities of Autism Spectrum Disorders Accompanied by Intellectual Disabilities in Yonago City, Japan

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ABSTRACT

Background Autism spectrum disorders (ASD) with intellectual disabilities may be associated with many factors. This study focused on patients with ASD with intellectual disabilities, defined by a threshold intelligence quotient (IQ) or development quotient (DQ) of 70. We also discuss comorbidities and other factors related to ASD.

Method We extracted case records of patients born between April 1995 and March 2001 who lived in Yonago City, as of January 2011, and had visited the two specialist institutions for consultation regarding developmental issues. The list was further narrowed down to patients identified, as having ASD by pediatric neurologists based on Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition) (DSM-5). We selected patients with < IQ/DQ 70 using the most recent intelligence/development test to determine comorbidities and other factors related to ASD.

Results The data of 81 patients (59 males and 22 females) were extracted, corresponding to an incidence of 76.2 patients out of every 10,000 births. The male-to-female ratio was 2.7:1. Comorbidities and related factors of ASD were observed in 25 cases (30.9%). Eleven cases had perinatal abnormalities. Other abnormalities were observed in 17 cases, including epilepsies in 7, chromosomal abnormalities in 4, familial mental retardation in 1, and acquired brain injury in 1.

Conclusion It is important to treat and support individuals with ASD and intellectual disabilities taking

into account the characteristics and prognosis of the comorbidities and related factors.

Key words autism spectrum disorder; intellectual disabilities; incidence; related factors

Since the report by Lotter¹, several studies have reported on the increasing prevalence of autism spectrum disorders (ASD) (Table 1). However, some researchers believe that this rise is only superficial and that it is attributable to the differences in research methods, regions, and diagnostic criteria.^{2,3} Diagnostic criteria refers to expansion of the definition of ASD, changes in diagnostic standards, improvements in diagnostic technology, age at diagnosis, and the ability to distinguish between mild and severe symptoms.^{1,4,5}

In Japan, many studies utilize the infant health checkup system. However, the findings of past reports were affected by subjects' low age and frequent relocation, given that many study populations resided in metropolitan areas. Individuals living in Yonago City, in the Tottori Prefecture, have lower rates of relocation, compared to people residing in metropolitan areas. Yonago City has several medical facilities and features close coordination among medical, educational, and social welfare institutions. Thus, children with intellectual disabilities receive good support from an early stage in Yonago city.

Children with ASD without intellectual disabilities exhibit symptoms caused by functional abnormalities in the brain before birth and, in recent years, several reports have identified specific genes that are responsible for this condition.⁶ On the other hand, symptom of ASD with intellectual disorders is believed to be associated with genetic factors, perinatal brain injuries, and postnatal brain injuries. In this study, we investigated ASD with intellectual disabilities with a focus on its incidence, comorbidities, and related factors.

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Abbreviations: ADI-R, autism diagnostic interview-revised; ADOS, autism diagnostic observation schedule; ASD, autism spectrum disorders; ASSQ, autism spectrum screening questionnaire; DSM, diagnostic and statistical manual of mental disorders; IQ, intelligence quotient; DQ, development quotient; PDD, pervasive developmental disorders; PDD-NOS, pervasive developmental disorder not otherwise specified; ICD, international classification of diseases; WISC-III, Wechsler Intelligence Scale for Children III

Table 1. Prevalence of autism spectrum disorders

Author	Investigation area	Age of subjects	Prevalence (/10,000)			Criteria
			Total	Intelligent level*		
				LFA	HFA	
Lotter V (1966) ¹	UK	8–10	4.5	3.8	0.6	Infantile autism (Kanner)
Wing & Gould (1979) ⁷	UK	0–14	26.1	–	–	Traiad
Ishi & Takahashi (1983) ⁸	Japan	6–12	16.0	13.4	2.6	DSM-III
Sugiyama & Abe (1989) ⁹	Japan	3	13.0	–	–	DSM-III
Honda et al. (1996) ¹⁰	Japan	5	21.1	10.6	10.6	DSM-III
Chakrabarti&Fombonne (2001) ¹¹	UK	2.5–6.5	62.6	16.3	46.3	DSM-IIIR,DSM-IV
Sumi et al. (2004) ¹²	Japan	6-8	212.4	65.6	146.8	DSM-IV
Honda et al. (2005) ¹³	Japan	5	27.2	22.6	7.6	ICD-10
Baird et al. (2006) ¹⁴	UK	9–10	116.1	65.0	51.1	ICD-10, ADI-R, ADOS
Kawamura et al. (2008) ¹⁵	Japan	1–7	181.1	59.6	117.6	DSM-IV
Baron-Cohen et al. (2009) ¹⁶	UK	5–9	157.0	–	–	ICD-10, ADI-R, ADOS
Kim et al. (2011) ¹⁷	Korea	7–12	264.0	–	–	ASSQ, ADI-R, ADOS
Imai & Ito (2014) ¹⁸	Japan	5	374.4	118.4	232.4	DSM-5

*Intelligence level was classified as follows except for the study of Lotter V: high function autism (HFA) was \geq IQ/DQ70 and low function autisms (LFA) was $<$ IQ/DQ70. Lotter (1966) classified HFA if the IQ/DQ was \geq 85 and LFA if the IQ was $<$ IQ85.

ADI-R, autism diagnostic interview-revised; ADOS, autism diagnostic observation schedule; ASSQ, autism spectrum screening questionnaire; DSM, diagnostic and statistical manual of mental disorders; DQ, developmental quotient; ICD, international classification of diseases; IQ, intelligent quotient.

SUBJECTS AND METHODS

Tested area

The population of Yonago City, Tottori Prefecture was 148,090 people in December 2010. The total area is 132.2 km², with limited migration to and from the city, unlike metropolitan areas. Individuals suspected of exhibiting language or developmental problems are typically referred to the Division of Child Neurology at Tottori University Hospital or Tottori Prefecture Rehabilitation Center for Children with Disabilities.

Screening system in Yonago City

In Yonago city, there are 5 timepoints at which a child's developmental status is checked; 6-month checkup; 18-month- checkup; 3-year- checkup: developmental consultation at 5-years-old; and when meeting with the School Guidance Committee.

At the 6-month-, 18-month-, and 3-year- health checkups, public health nurses check each child's sociability and cognitive development. Cases with suspected language or developmental problems are referred to Tottori University Hospital or Tottori Prefecture Rehabilitation Center for Children with Disabilities for diagnosis. Thereafter, parents of children with developmental disorders often seek support from child-care facilities in the city or seek occupational therapy, physical therapy, or social skill training.

The 5-year developmental consultation can be

conducted at the parent's request. Information about group and interpersonal behaviors is provided by multiple sources, from nursery schools to doctors. Children suspected of exhibiting intellectual disabilities or developmental disorders are referred to the above-mentioned medical facilities.

The School Guidance Committee consists of child psychologists, child neurologists, clinical psychologists, and school teachers. Children facing challenges or with behavioral issues may be referred to these specialized institutions, with input from the School Guidance Committee to assist parents with determining the most suitable school for their children. Teachers who specialize in developmental disorders perform rounds at elementary and junior high schools to advise the schools on issues related to children with suspected intellectual disabilities or developmental disorders, and coordinate hospital visits. In Yonago City, this process is used to identify children with developmental disorders and intellectual disabilities at an early stage.

Subjects

Case records were extracted for patients who visited the Division of Child Neurology at Tottori University Hospital or the Tottori Prefecture Rehabilitation Center for Children with Disabilities for consultation on developmental issues. Patients born between April 1995 and March 2001 residing in Yonago City at the end January

Table 2. Annual incidence of ASD with intellectual disabilities and sex ratio

Birth year	The number of patients with ASD			Birth cohort	Incidence/10,000 birth	Sex ratio (Male : Female)
	Male	Female	Total			
1995	8	4	12	1,409	85.2	2 : 1
1996	7	3	10	1,446	69.2	2.3 : 1
1997	10	2	12	1,472	81.5	5 : 1
1998	9	3	12	1,624	73.9	3 : 1
1999	9	5	14	1,547	90.5	2 : 1
2000	7	2	9	1,581	56.9	3.5 : 1
2001	9	3	12	1,551	77.4	3 : 1
Total	59	22	81	10,630	76.2	2.7 : 1

ASD, autism spectrum disorders.

Table 3. Distribution of IQ/DQ in patients of Autism Spectrum Disorders with intellectual disabilities

IQ/DQ		≤ 34	35–49	50–69
IQ	Male	6	8	27
	Female	1	5	9
	Total	7	13	36
DQ	Male	8	0	1
	Female	1	0	3
	Total	9	0	4
Test name undescribed	Male	1	2	0
	Female	1	0	0
	Total	2	2	0
Test not obtained	Male	6	0	0
	Female	2	0	0
	Total	8	0	0
Total	Male	21	10	28
	Female	5	5	12
	Total	26	15	40
		32.1%	18.5%	49.4%

DQ, development quotient; IQ, intelligence quotient.

2011 were included. The study group was further limited to children diagnosed with autistic disorder or pervasive developmental disorder (PDD) by child neurologists, based on DSM-IV criteria. After the introduction of DSM-5 in 2014, PDD and autistic disorder were integrated to form ASD. Therefore, the term of “ASD” was used in this study.

Of the patients identified by the above criteria, those with an IQ/DQ score of < 70 on the most recent intelligence/development test were enrolled as study subjects. The present research was approved by the Institutional Review Board of Tottori University (No. 1215).

RESULTS

Incidence of ASD and male/female ratio

Eighty-one children (59 males, 22 females) were diagnosed ASD with intellectual disabilities and the mean

annual incidence was 76.2 of 10,000 births. Table 2 shows the annual incidence rates of ASD with intellectual disabilities. Patients' ages at the time of the evaluation ranged from 8 years 11 months to 14 years 10 months. The male: female ratio was 2.7:1.

Intellectual development

IQ or DQ were obtained for 73 cases. IQ and DQ were not obtained for eight cases because of severe mental retardation. Alternatively, these children were graded as demonstrating a severe disability (IQ/DQ ≤ 34). Other tests administered to the children included the Wechsler Intelligence Scale for Children III (WISC-III) (41.4%), Tanaka-Binet Intelligence Scale V (38.6%), Kyoto Scale of Psychological Development Test (11/4%), and the Enjoji Infantile Development Test (7.1%). Three boys had IQ/DQ scores, but the test name was not specified. There were 71 cases where the test date was stated in the patient record. The mean patient age at testing was 106 months (8 years and 10 months) (SD = 38.3).

All included cases were divided into three categories IQ/DQ scores of ≤ 34 (severe disability), 35–49 (moderate disability), and 50–69 (mild disability), accounting for 32.1%, 18.5%, and 49.4% of all subjects, respectively (Table 3)

Type of school attended

Forty-three patients (30 males, 13 females) were attending a special support education school at the time of testing, and 38 were attending normal classes or special needs classes at local schools.

Information in perinatal period

Gestational ages of 47 patients were obtained from the medical records, and the average gestational age was 38 weeks 5 days (SD = 19.7 days). Records related to body weight at time of birth were obtained from 53 patients, and the average weight was 2995.4 g (SD = 549.9). Records related to height at time of birth were

Table 4. Comorbidities and related factors of ASD with intellectual disabilities

Comorbidities and related factors	Number of patients	Diagnosis (number of patients)
Perinatal abnormality	11	
Low birth weight	5	Ultra-low-birth-weight infants (1), Low-birth-weight infants (4, cerebral palsy and epilepsy in 1)
Neonatal asphyxia	3	
Meconium aspiration syndrome	3	
Chromosomal abnormality/Congenital disorder	4	13q monosomy (2, epilepsy in 1), 46XXadd (1) (q42.1) (1), Angelman syndrome (1, epilepsy)
Epilepsy	7	Severe myoclonic epilepsy in infancy (1), Infantile seizure (1), Secondary epilepsy (3)
Congenital anomaly of the brain	4	Macrocephaly (2), Callosal agenesis (1), Intracranial cyst (1)
Familial developmental disorder	1	
Postnatal disorder	1	Sequela after acute encephalopathy
Total number	28 (real number 25)	

ASD, autism spectrum disorders.

obtained from 34 patients, and average height was 47.6 cm (SD = 3.4). Records related to head circumference were obtained for 29 patients, and the average was 32.4 cm (SD = 6.8). Father's age was obtained for 49 patients, and the average was 34.1 years (SD = 14.2). Regarding father's age at time of birth, 5 (9.8%) were 20–24-years old, 14 (28.6%) were 25–29-years old, 18 (38.3%) were 30–34-years old, 11 (23.4%) were 35–39-years old, 2 (3.8%) were 40–44-years old and 1 (1.9%) was 45–50-years old. Mother's age was obtained for 53 patients, and the average was 30.7 years (SD = 9.9). Regarding mother's age at time of birth, 6 (11.3%) were 20–24-years old, 18 (34.0%) were 25–29-years old, 26 (49.1%) were 30–34-years old, 2 (3.8%) were 35–39-years old and 1 (1.9%) was 42-years old. Data on birth order was obtained for 50 patients. We found that 29 children were firstborn, 20 were second born, and 1 was fourth born. The average age of the mother at time of birth was 29.1 years (SD = 4.8) for the first-born child and 33.5 years for the second-born child (SD = 14.9).

Comorbidities

In 25 cases (30.9%), comorbidities, perinatal problems, and other factors related to ASD were identified. There were 53 cases where data were obtained for the perinatal period. Of these, 11 showed perinatal abnormalities (11/53 cases, 20.8%). There was one case of very low birth weight (< 1,000 g) at 686 g, 4 cases of low birth weight (2500 g or less), 3 cases of neonatal asphyxia, and 3 cases of meconium aspiration syndrome.

For other comorbidities and related factors, there were 4 cases of chromosomal or congenital abnormalities, 7 cases of epilepsy, 4 cases of congenital brain anomalies, 1 case of familial developmental disorder, and 1 case of acquired brain injury (Table 4).

DISCUSSION

The annual incidence of ASD plus intellectual disabilities in children was 76.2 out of every 10,000 births. This is lower than the rate reported by Imai and Ito¹⁸ but higher than that reported in other studies (Table 1). Fombonne et al¹⁹ reported that 8–12 years is ideal for diagnosis of developmental disorders, since that is when concrete intellectual symptoms appear that can be recognized by other people and, in many children, ASD symptoms become apparent at that age. In some children with ASD, intellectual disabilities that could not be discerned during childhood gradually emerge alongside intellectual development. The patients in the present study ranged in age from 8 years 11 months to 14 years 10 months and all were suitable for formal evaluation of ASD symptoms. Generally, study populations for this condition include more males than females, with a male-to-female ratio of 2.7:1 reported by Honda et al.,¹⁴ 3.2:1 by Kawamura et al.,¹⁶ and 2.7:1 in the present study.

Many recent studies have reported other factors related to ASD occurring in the perinatal and neonatal periods. These factors included low birth weight,^{20–24} meconium aspiration syndrome,^{20, 24} older father,^{22, 25} older mother,^{26, 27} and both parents of advanced age.^{26, 27, 28} In addition, reproductive medicine²⁹ and umbilical cord coiling²⁰ have appear to be related factors. However, these factors have mainly been studied in children with ASD without intellectual disabilities, and caution must be taken when applying these findings to children with ASD who demonstrate concomitant intellectual disabilities.

In this study, 5 patients had a low birth weight of ≤ 2500 g. Although it has been reported that ASD is more frequent in children with a birth weight of ≤ 2000 g,³⁰ there were only 2 such cases in this study. Lampi

et al.³¹ reported that low birth weight was a factor related to ASD, even controlling for birth order and gestational age. They did not bundle symptoms together and analyzed childhood autism (ASD with intellectual disabilities), Asperger's syndrome (ASD without intellectual disabilities), and PDD not otherwise specified (PDD-NOS) separately; the authors found that low birth weight was linked to childhood autism and PDD-NOS. Matsumoto³² hypothesized that genetic factors help determine the onset of autistic disorders in children with ASDs, whereas other conditions such as PDD-NOS are determined by genetic factors, coupled with external factors such as low birth weight. There were 3 cases of neonatal asphyxia and 3 cases of meconium aspiration syndrome in our study, implying that low oxygen during the neonatal period may correlate with ASD with intellectual disabilities.

According to a summary published by the Ministry of Health, Labour and Welfare of Japan,³³ the average age of mothers giving birth in 1995 was 27.5 years for their first child and 29.3 years for their second child. In the present study, the average maternal age at birth was higher than previously-reported values. Regarding the father's age at the time of birth, Tsuchiya et al.³⁴ reported that fathers of children with ASD without intellectual disabilities were older than fathers of neurotypical children. They found that when the father was aged ≥ 33 years at the time of birth, the ASD risk was approximately three-fold greater than that when the father was aged ≤ 29 years. Although the present study focused on children with ASD and IQ scores < 70 , the average age of the fathers was comparable at 34.1 years.

In general, severe intellectual disabilities are rarer than mild or moderate intellectual disabilities. According to epidemiological research conducted by Bourke et al.³⁵ in western Australia, 15.0 out of 1000 births demonstrated mild to moderate intellectual disabilities, whereas severe intellectual disabilities were manifest in 1.2 out of every 1000 births. In addition, ASD occurred at a rate of 4.1, whereas ASD with intellectual disabilities occurred at a rate of 2.6, more than twice the rate of ASD without intellectual disabilities (1.2). In this study, cases of children with ASD and severe intellectual disabilities comprised 32.1% of the total cases, implying that severe forms of intellectual disabilities were closely correlated to ASD.

Epilepsy is a common comorbidity in children with ASD, especially those with lower IQ scores.³⁶ According to a review by Woolfenden et al.³⁷ 1.8% of children aged < 12 years with ASD have epileptic seizures, whereas 23.7% of children aged ≥ 12 years with ASD and intellectual disabilities have epileptic seizures. There were

7 cases with epilepsy in this study. Although ASD was previously not thought to occur with cerebral palsy, studies are gradually reporting patients with ASD and cerebral palsy, such as Kilincaslan et al.³⁸ These authors reported that 15% of 126 children with cerebral palsy also exhibited ASD symptoms and 31.7% of those with IQ scores of 70 or less had ASD. Our results include one case of cerebral palsy. There are many cases of ASD symptoms in children with chromosomal and congenital anomalies, with Down's syndrome being the best known.³⁹ We had 4 cases with chromosomal and congenital anomalies.

One limitation of this study was that the intelligence and developmental tests used to determine intellectual disabilities were not consistently matched to age.

Although the concept of ASD had expanded due to the introduction of the DSM-5, it is important to provide treatment and support for children with ASD, with and without intellectual disabilities. Children with ASD and intellectual disabilities, and other forms of ASD, must be distinguished to allow more thorough consideration going forward.

The authors declare no conflicts of interest.

REFERENCES

- 1 Lotter V. Epidemiology of autistic conditions in young children: 1. Prevalence. *Soc Psychiatry*. 1966;1:124-37.
- 2 Rutter M. Aetiology of autism: findings and questions. *J Intellect Disabil Res*. 2005;49:231-8. PMID: 15816809.
- 3 Parner ET, Schendel DE, Thorsen P. Autism prevalence trends over time in Denmark: changes in prevalence and age at diagnosis. *Arch Pediatr Adolesc Med*. 2008;162:1150-6. PMID:19047542.
- 4 Wing L. The definition and prevalence of autism: a review. *Eur Child Adolesc Psychiatry*. 1993;2:61-74. PMID: 21590530.
- 5 Schechter R, Grether JK. Continuing increases in autism reported to California's developmental services system: mercury in retrograde. *Arch Gen Psychiatry*. 2008;65:19-24. PMID: 18180424.
- 6 Yoo H. Genetics of Autism spectrum disorder: current status and possible clinical applications. *Exp Neurobiol*. 2015;24:257-72. PMID: 26713075.
- 7 Wing L, Gould J. Severe impairments of social interaction and associated abnormalities in children: epidemiology and classification. *J Autism Dev Disord*. 1979;9:11-29. PMID: 155684.
- 8 Ishii T, Takahashi O. The epidemiology of autistic children in Toyota, Japan: Prevalence. *Children Adolesc Psychiatry*. 1982;368:179-81. Japanese.
- 9 Sugiyama T, Abe T. The prevalence of autism in Nagoya, Japan: a total population study. *J Autism Dev Disord*. 1989;19:87-96. PMID: 2708306.
- 10 Honda H, Shimizu Y, Misumi K, Niimi M, Ohashi Y. Cumulative incidence and prevalence of childhood autism in children in Japan. *British Journal of Psychiatry*. 1996;169:228-35. PMID: 8871801.

- 11 Chakrabarti S, Fombonne E. Pervasive developmental disorders in preschool children. *JAMA*. 2001;285:3093-9. PMID: 11427137.
- 12 Sumi S, Miyachi T, Taniai H, Ishikawa M. Prevalence of pervasive developmental disorder in the Western region of Nagoya City, Japan, *Psychiatria et Neurologia Paediatrica Japonica*. 2006;46:57-60. Japanese.
- 13 Honda H, Shimizu Y, Imai M, Nitto Y. Cumulative incidence of childhood autism: a total population study of better accuracy and precision. *Dev Med Child Neurol*. 2005;47:10-8. PMID: 15686284.
- 14 Baird G, Simonoff E, Pickles A, Chandler S, Loucas T, Meldrum D, et al. Prevalence of disorders of the autism spectrum in a population cohort of children in South Thames: the Special Needs and Autism Project (SNAP). *Lancet*. 2006;368:210-5. PMID: 16844490.
- 15 Kawamura Y, Takahashi O, Ishii T. Reevaluating the incidence of pervasive developmental disorders: impact of elevated rates of detection through implementation of an integrated system of screening in Toyota, Japan. *Psychiatry Clin Neurosci*. 2008;62:152-9. PMID: 18412836.
- 16 Baron-Cohen S, Scott FJ, Allison C, Williams J, Bolton P, Matthews FE, et al. Prevalence of autism-spectrum conditions: UK school-based population study. *Br J Psychiatry*. 2009;194:500-9. PMID: 19478287.
- 17 Kim YS, Leventhal BL, Koh YJ, Fombonne E, Laska E, Lim EC, et al. Prevalence of autism spectrum disorders in a total population sample. *Am J Psychiatry*. 2011;168:904-12. PMID: 21558103.
- 18 Imai M, Ito Y. Survey of autism disorder in Yokohama City Seibu Habilitation Center-(Part1): Cumulative incidence at preschool age. *Journal of Yokohama City Rehabilitation Corporation*. 2014;23: 41-6. Japanese.
- 19 Fombonne E, Tidmarsh L. Epidemiologic data on Asperger disorder. *Child Adolesc Psychiatr Clin N Am*. 2003;12:15-21. PMID: 16401144.
- 20 Gardener H, Spiegelman D, Buka SI. Perinatal and neonatal risk factors for autism: a comprehensive meta-analysis. *Pediatrics*. 2011;128:344-55. PMID: 21746727.
- 21 Mason-Brothers A, Ritvo ER, Pingree C, Petersen PB, Jenson WR, McMahon WM, et al. The UCLA-University of Utah epidemiologic survey of autism: prenatal, perinatal, and post-natal factors. *Pediatrics*. 1990;86:514-9. PMID: 2216614.
- 22 Burd L, Severud R, Kerbeshian J, Klug MG. Prenatal and perinatal risk factors for autism. *J Perinat Med*. 1999;27:441-50. PMID: 10732302.
- 23 Larsson HJ, Eaton WW, Madsen KM, Vestergaard M, Olesen AV, Agerbo E, et al. Risk factors for autism: perinatal factors, parental psychiatric history, and socioeconomic status *Am J Epidemiol*. 2005;161: 916-25; discussion 926-8. PMID: 15870155.
- 24 Finegan JA, Quarrington B. Pre-, peri-, and neonatal factors and infantile autism. *J Child Psychol Psychiatry*. 1979;20:119-28. PMID: 457822.
- 25 Reichenberg A, Gross R, Weiser M, Bresnahan M, Silverman J, Harlap S, et al. Advancing paternal age and autism. *Arch Gen Psychiatry*. 2006;63:1026-32. PMID: 16953005.
- 26 Gillberg C, Gillberg IC. Infantile autism: a total population study of reduced optimality in the pre-, peri-, and neonatal period. Send to. *J Autism Dev Disord*. 1983;13:153-66. PMID: 6863210.
- 27 Hultman CM, Sparén P, Cnattingius S. Perinatal risk factors for infantile autism. *Epidemiology*. 2002;13:417-23. PMID: 12094096.
- 28 Croen LA, Najjar DV, Fireman B, Grether JK. Maternal and paternal age and risk of autism spectrum disorders. *Arch Pediatr Adolesc Med*. 2007;161:334-40. PMID: 17404129.
- 29 Hvidtjørn DI, Schieve L, Schendel D, Jacobsson B, Svaerke C, Thorsen P. Cerebral palsy, autism spectrum disorders, and developmental delay in children born after assisted conception: a systematic review and meta-analysis. *Arch Pediatr Adolesc Med*. 2009;163:72-83. PMID: 19124707.
- 30 Pinto-Martin JA, Levy SE, Feldman JF, Lorenz JM, Paneth N, Whitaker AH. Prevalence of Autism Spectrum Disorder in Adolescents Born Weighing <2000 Grams. *Pediatrics*. 2011;883-92. PMID: 22007018.
- 31 Lampi KM, Lehtonen L, Tran PL, Suominen A, Lehti V, Banerjee PN, et al. Risk of autism spectrum disorders in low birth weight and small for gestational age infants. *J Pediatr*. 2012;161:830-6. PMID: 22677565.
- 32 Matsumoto K, Tsuchiya KJ. 13. Mental Illness and DOHaD—Studies on Factor of ASD. *Obstetrics and Gynecology*. 802013; 633-7. Japanese.
- 33 Ministry of Health, Labor and Welfare of Japan. Statistics on birth [Internet]. Tokyo: Ministry of Health, Labor and Welfare of Japan; 2002 [cited 2018 November 21]. Available from: <http://www.mhlw.go.jp/toukei/saikin/hw/jinkou/tokusyusyussyo-4/syussyo2-1.html#1>. Japanese.
- 34 Tsuchiya KJ, Matsumoto K, Miyachi T, Tsujii M, Nakamura K, Takagai S, et al. Paternal age at birth and high-functioning autistic-spectrum disorder in offspring. *Br J Psychiatry*. 2008;193:316-21. PMID: 18827294.
- 35 Bourke J, de Klerk N, Smith T, Leonard H. Population-Based Prevalence of Intellectual Disability and Autism Spectrum Disorders in Western Australia: A Comparison With Previous Estimates. *Medicine (Baltimore)*. 2016;95:e3737. PMID: 27227936.
- 36 Kamio Y, Inada N, Koyama T. A nationwide survey on quality of life and associated factors of adults with high-functioning autism spectrum disorders. *Autism*. 2013;17:15-26. PMID: 22399449
- 37 Woolfenden S, Sarkozy V, Ridley G, Coory M, Williams K. A systematic review of two outcomes in autism spectrum disorder - epilepsy and mortality. *Dev Med Child Neurol*. 2012;54:306-12. PMID: 22348343.
- 38 Kilincaslan A, Mukaddes NM. Pervasive developmental disorders in individuals with cerebral palsy. *Dev Med Child Neurol*. 2009;51:289-94. PMID: 19335564.
- 39 Lowenthal R, Paula CS, Schwartzman JS, Brunoni D, Mercadante MT. Prevalence of pervasive developmental disorder in Down's syndrome. *J Autism Dev Disord*. 2007;37:1394-5. PMID: 17410415.