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Association between maternal prenatal psychological distress and autism spectrum disorder among 3-year-old children: The Japan Environment and Children's Study

Toshie Nishigori[1,2], Koichi Hashimoto[1,2], Miyuki Mori[2,3,4], Taeko Suzuki[2,3,5], Madoka Watanabe[2,4], Karin Imaizumi[2,6], Tsuyoshi Murata[2,6], Hyo Kyozuka[2,6], Yuka Ogata[2], Akiko Sato[2], Kosei Shinoki[2], Seiji Yasumura[2,7], Keiya Fujimori[2,6], Hidekazu Nishigori[2,3], Mitsuaki Hosoya[1,2] and The Japan Environment and Children's Study Group

[1]Department of Pediatrics, Fukushima Medical University School of Medicine, Fukushima, Japan; [2]Fukushima Regional Center for the Japan Environmental and Children's Study, Fukushima, Japan; [3]Department of Development and Environmental Medicine, Fukushima Medical Center for Children and Women, Fukushima Medical University Graduate School of Medicine, Fukushima, Japan; [4]Department of Midwifery and Maternal Nursing, Fukushima Medical University School of Nursing, Fukushima, Japan; [5]Preparing Section for School of Midwifery, Fukushima Medical University, Fukushima, Japan; [6]Department of Obstetrics and Gynecology, Fukushima Medical University School of Medicine, Fukushima, Japan and [7]Department of Public Health, Fukushima Medical University School of Medicine, Fukushima, Japan

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Address for correspondence:
Hidekazu Nishigori MD, PhD, Department of Development and Environmental Medicine, Fukushima Medical Center for Children and Women, Fukushima Medical University Graduate School of Medicine, 1 Hikarigaoka, Fukushima-City, Fukushima 960-1295, Japan.
Email: nishigo@fmu.ac.jp

Abstract

Maternal prenatal psychological distress, which includes depression and anxiety, affects the onset of autism spectrum disorder (ASD). However, there is no consistent knowledge regarding at which term during pregnancy psychological distress affects the risk of ASD among children. We used a dataset obtained from the Japan Environment and Children's Study, which is a nationwide prospective birth cohort study, to evaluate the association between the six-item Kessler Psychological Distress Scale (K6) and ASD among 3-year-old children. A total of 78,745 children were analyzed, and 355 of them were diagnosed with ASD (0.45%). The maternal K6 was administered twice during pregnancy: at a median of 15.1 weeks (M-T1) and at that of 27.4 weeks (M-T2) of gestation. Multivariate logistic regression analyses demonstrated that the group with a maternal K6 score of ≥5 at both M-T1 and M-T2 was significantly associated with ASD among the children (adjusted odds ratio, 1.440; 95% confidence interval, 1.104–1.877) compared to the group with a score of ≤4 at both M-T1 and M-T2. There was no significant difference between the group with a score of ≥5 only at M-T1 or M-T2 and that with a score of ≤4 at both M-T1 and M-T2. In conclusion, from the first to the second half of pregnancy, continuous maternal psychological distress was associated with ASD among 3-year-old children. Contrarily, in the group without persistent maternal psychological distress during pregnancy, there was no significant association.

Introduction

Maternal prenatal psychological distress, which includes depression and anxiety, is known to be a risk factor for autism spectrum disorder (ASD) among children through fetal programing.[1,2,3,4] However, there is no consistent knowledge regarding at which term during pregnancy psychological distress affects the risk of ASD among children.[5] Despite these issues, no independent studies on this topic have been conducted in Japan.

Over the recent years, Japan has been conducting the Japan Environment and Children's Study (JECS), which is a nationwide birth cohort study involving 100,000 pairs of parents and their children, to investigate children's development and environment.[6,7] In this study, we used this dataset to examine the association between maternal prenatal psychological distress and ASD among 3-year-old children.

Materials and methods

Design and participants

The JECS protocol has been described previously.[6,7] Recruitment to the JECS occurred between January 2011 and March 2014, and it included pregnant women nationwide. The JECS is

currently underway and plans to continue until the children are 13 years of age. A dataset containing the results of this test for all 3-year-old children was provided in 2021. In this study, we used the jecs-ta-20190930 dataset, which was revised in June 2021. Among the 104,062 records in this dataset, the records of 78,745 women were analyzed. Because this study investigated single pregnancies, records of twin or triplet pregnancies were excluded from the analysis.

Maternal psychological distress

The JECS protocol was designed to administer the six-item Kessler Psychological Distress Scale (K6) twice during the pregnancy: the first (M-T1) and the second (M-T2) half of pregnancy.[7] The K6 has been used widely to assess psychological distress during the perinatal and postnatal periods.[8,9] It is a self-administered questionnaire comprising six questions that evaluate depressive moods and anxiety according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV), over the preceding four weeks on a scale of 0 to 4. The total score was the sum of the six items, and it ranged from 0 to 24. We used the Japanese version of the K6 with a cutoff of ≥5 to identify cases of psychological distress, as used in previous studies involving populations and affected communities in Japan.[10,11,12]

We classified the participants into four groups based on their K6 scores of ≥5 at M-T1 and M-T2: (1) K6 scores of ≤4 at M-T1 and M-T2, (2) K6 scores of ≤4 at M-T1 and ≥5 at M-T2, (3) K6 scores of ≥5 at M-T1 and ≤4 at M-T2, and (4) K6 scores of ≥5 at M-T1 and M-T2.

Outcome: ASD among 3-year-old children

Based on data obtained from the C-3y questionnaire (when the child was three years of age), which was self-reported by the participants, we estimated the incidence of ASD among 3-year-old children. In the questionnaire, caregivers were asked, "Has your child been diagnosed with ASD by physicians?", and children whose parents answered "Yes" were defined as diagnosed with ASD. ASD was diagnosed among children aged between 2 and 3 years. The diagnostic categories for neurodevelopmental disorders, which caregivers were asked, were based on the International Statistical Classification of Diseases and Related Health Problems Tenth Revision (ICD-10) (codes: F84.0, childhood autism; F84.1, atypical autism; F84.5, Asperger's syndrome; F84.8, other pervasive developmental disorders; F84.9, pervasive developmental disorder unspecified; F84.2, Rett syndrome; and F84.3, childhood disintegrative disorder).

Statistical analysis and covariables

We analyzed the data to determine the association between K6 scores of ≥5 and ASD among 3-year-old children. Crude and multivariate logistic regression analyses were used to obtain odds ratios (ORs) and 95% confidence intervals (CI). The multivariate logistic regression analyses were adjusted for maternal age at delivery, paternal age at conception, maternal body mass index (kg/m^2) before pregnancy, parity, marital status, treatment for infertility, unexpected pregnancies, maternal and paternal academic history, maternal job during pregnancy, maternal and paternal smoking during pregnancy, maternal alcohol consumption during pregnancy, household income (×10^3 yen/year) during pregnancy, maternal neuropsychiatric disorders, maternal autism spectrum quotient Japanese version (AQ-J) 10 ≥7,[13] psychoactive drug use, folic supplement use, multivitamin supplement use, pregnancy complications, obstetric labor complications, intrauterine infections, gender of the child, birth weight of the child, chromosome abnormalities of the child, gestational week, and breastfeeding. These covariates were also analyzed in previous studies.[14,15,16,17] For each confounder, "no answer" was analyzed as a single item. The AQ-J10, which is a self-reported questionnaire, was designed to measure autistic traits distributed among the general population, and 9 of the 10 items referred to social communication difficulties. The cutoff of the AQ-J10 score was ≥7,[13] which we defined as higher autistic traits among mothers in this study.[18] We conducted maternal AQ-J10 during the second or third trimester. Maternal neuropsychiatric disorders included depression, anxiety disorders, obsessive-compulsive disorder, panic disorder, schizophrenia, epilepsy, migraines, autonomic dysreflexia, attention deficit hyperactivity disorder, learning disabilities, pervasive developmental disorders, Asperger's syndrome, and ASD.

All statistical analyses were performed using SPSS version 27 (IBM Corp., Armonk, NY, USA).

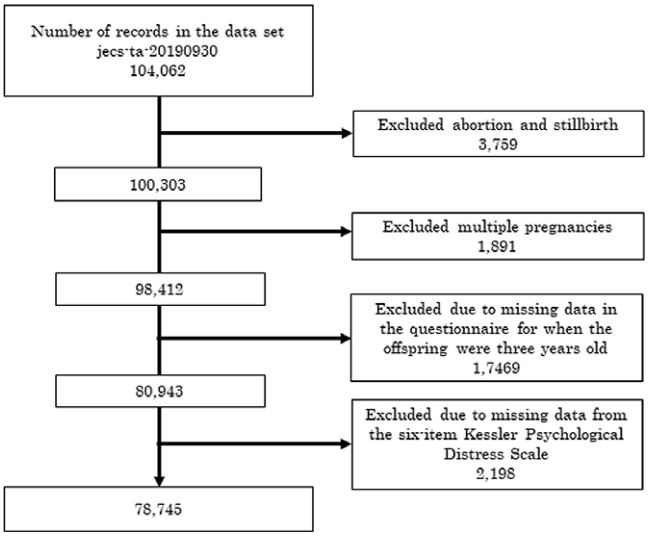

Fig. 1. The flow chart for selected research participants.

Results

Of the 104,062 records in the provided dataset, records from 78,745 children were analyzed (Fig. 1). The characteristics of the participants are listed in Table 1. At M-T1, the maternal prenatal K6 was estimated at a median of 15.1 (interquartile range 12.3–18.9) weeks of gestation. At M-T2, it was estimated at a median of 27.4 (interquartile range 25.3–30.1) weeks of gestation.[19]

Participants were divided into four groups: (1) 46,463 mothers (59.0%) had K6 scores of ≤4 at M-T1 and M-T2, (2) 7697 mothers (9.8%) had K6 scores of ≤4 at M-T1 and ≥5 at M-T2, (3) 10,629 mothers (13.5%) had K6 scores of ≥5 at M-T1 and ≤4 at M-T2, and (4) 13,956 mothers (17.7%) had K6 scores of ≥5 at both M-T1 and M-T2. A total of 355 children (0.45%) were diagnosed with ASD, which was based on the survey questions presented to the participants.

Multivariate logistic regression analyses demonstrated that a maternal K6 score of ≥5 at both M-T1 and M-T2 was significantly associated with ASD among 3-year-old children (adjusted odds

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Table 1. The characteristics of participants

		Total		ASD	
		n = 78,745		n = 355	
		n	%	n	%
Maternal age at delivery	<20	442	0.6	2	0.6
	20 ≤–< 25	6046	7.7	10	2.8
	25 ≤–< 35	50,044	63.6	217	61.1
	≥ 35	22,212	28.2	126	35.5
	No answer	1	0.001	0	0.00
Paternal age at conception	<20	128	0.2	0	0.00
	20 ≤–< 25	2326	3.0	4	1.1
	25 ≤–< 35	23,486	29.8	83	23.4
	≥ 35	15,620	19.8	88	24.8
	No answer	37,185	47.2	180	50.7
Maternal BMI (kg/m^2) before pregnancy	<18.5	12,723	16.2	40	11.3
	18.5 ≤–< 25.0	58,131	73.8	262	73.8
	≥ 25.0	7863	10.0	53	14.9
	No answer	28	0.04	0	0.00
Parity	Primipara	31,981	40.6	183	51.5
	Multipara	44,853	57.0	160	45.1
	No answer	1911	2.4	12	3.4
Marital status	Married, Common-law marriage	75,926	96.4	338	95.2
	Divorce, Lost, Other	1218	1.5	6	1.7
	No answer	1601	2.0	11	3.1
Infertility treatment	No	72,957	92.6	321	90.4
	Yes	5456	6.9	32	9.0
	No answer	332	0.4	2	0.6
Unexpected pregnancy	No	73,001	92.7	325	91.5
	Yes	5524	7.0	29	8.2
	No answer	220	0.3	1	0.3
Maternal academic history	College, University	32,551	41.3	162	45.6
	Senior high school	42,970	54.6	176	49.6
	Junior high school	2950	3.7	14	3.9
	No answer	274	0.3	3	0.8
Paternal academic history	College, University	29,060	36.9	146	41.1
	Senior high school	44,067	56.0	185	52.1
	Junior high school	4958	6.3	21	5.9
	No answer	660	0.8	3	0.8
Maternal job during pregnancy	No	30,386	38.6	187	52.7
	Yes	45,868	58.2	153	43.1
	No answer	2491	3.2	15	4.2
Maternal smoking during pregnancy	No	75,323	95.7	332	93.5
	Yes	2942	3.7	19	5.4
	No answer	480	0.6	4	1.1

(*Continued*)

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Table 1. (*Continued*)

		Total		ASD	
		n = 78,745		n = 355	
		n	%	n	%
Paternal smoking during pregnancy	No	42,764	54.3	209	58.9
	Yes	34,633	44.0	142	40.0
	No answer	1348	1.7	4	1.1
Maternal alcohol consumption during pregnancy	No	70,467	89.5	326	91.8
	Yes	7990	10.1	27	7.6
	No answer	288	0.4	2	0.6
Household income ($\times 10^3$ yen/year) during pregnancy	<4000	28,692	36.4	128	36.1
	4000 ≤–< 6000	24,798	31.5	114	32.1
	≥ 6000	20,370	25.9	93	26.2
	No answer	4885	6.2	20	5.6
Maternal neuropsychiatric disorders	No	68,048	86.4	277	78.0
	Yes	10,697	13.6	78	22.0
Maternal Autism Spectrum Quotient Japanese version (AQ-J)10 ≥ 7	No	75,112	95.4	324	91.3
	Yes	2028	2.6	21	5.9
	No answer	1605	2.0	10	2.8
Psychoactive drugs use during pregnancy	No	76,601	97.3	339	95.5
	Yes	2144	2.7	16	4.5
Folic acid supplements	started using before pregnancy	6104	7.8	36	10.1
	started between pregnancy recognition and 12 pregnant weeks	19,351	24.6	104	29.3
	started after 12 pregnant weeks	5788	7.4	23	6.5
	No use	47,172	59.9	188	53.0
	No answer	330	0.4	4	1.1
Multivitamin supplements	started using before pregnancy	3280	4.2	21	5.9
	started between pregnancy recognition and 12 pregnant weeks	1531	1.9	5	1.4
	started after 12 pregnant weeks	1069	1.4	11	3.1
	No use	72,535	92.1	314	88.5
	No answer	330	0.4	4	1.1
Diabetes or gestational diabetes	No	76,297	96.9	338	95.2
	Yes	2448	3.1	17	4.8
Pregnancy complication	No	65,536	83.2	275	77.5
	Yes	11,647	14.8	73	20.6
	No answer	1562	2.0	7	2.0
Obstetric labor complication	No	41,614	52.8	159	44.8
	Yes	35,644	45.3	188	53.0
	No answer	1487	1.9	8	2.3
Intrauterine infection	No	78,297	99.4	349	98.3
	Yes	448	0.6	6	1.7
Gender of children	Boy	40,313	51.2	277	78.0
	Girl	38,432	48.8	78	22.0
Birth weight of children	0 ≤–< 1500	345	0.4	5	1.4
	1500 ≤–< 2500	5795	7.4	29	8.2

(*Continued*)

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Table 1. (*Continued*)

		Total		ASD	
		n = 78,745		n = 355	
		n	%	n	%
	2500 ≤–< 4000	71,738	91.1	313	88.2
	≥ 4000	685	0.9	6	1.7
	No answer	182	0.2	2	0.6
Chromosome abnormalities of children	No	78,570	99.8	354	99.7
	Yes	175	0.2	1	0.3
Gestation week	22 ≤–< 28	90	0.1	1	0.3
	28 ≤–< 34	570	0.7	4	1.1
	34 ≤–< 37	2817	3.6	11	3.1
	37 ≤–< 42	74,945	95.2	337	94.9
	≥ 42	183	0.2	1	0.3
	No answer	140	0.2	1	0.3
Breast feeding	Breast milk	33,616	42.7	116	32.7
	Breast milk or milk	43,611	55.4	226	63.7
	Milk	964	1.2	10	2.8
	No answer	554	0.7	3	0.8
Maternal K6	M-T1; K6 ≤ 4 and M-T2; K6 ≤ 4	46,463	59.0	182	51.3
	M-T1; K6 ≤ 4 and M-T2; K6 ≥ 5	7697	9.8	27	7.6
	M-T1: K6 ≥ 5 and M-T2; K6 ≤ 4	10,629	13.5	55	15.5
	M-T1: K6 ≥ 5 and M-T2; K6 ≥ 5	13,956	17.7	91	25.6

Abbreviations: Autism spectrum disorder (ASD); body mass index (BMI; kg/m^2); the Kessler 6-item psychological distress scale (K6).
M-T1: median 15.1 (interquartile range 12.3–18.9) pregnant weeks; M-T2: median 27.4 (interquartile range 25.3–30.1) pregnant weeks.

Table 2. Maternal K6 and ASD among 3-year-old children (n = 78,745)

Maternal K6			ASD among 3-year-old children (n = 355)							
	n	%	n	%	COR	95%CI	P-value	AOR	95%CI	P-value
M-T1; K6 ≤ 4 and M-T2; K6 ≤ 4	46,463	59.0	182	0.39	ref			ref		
M-T1; K6 ≤ 4 and M-T2; K6 ≥ 5	7697	9.8	27	0.35	0.895	0.597–1.342	0.59	0.863	0.574–1.298	0.48
M-T1: K6 ≥ 5 and M-T2; K6 ≤ 4	10,629	13.5	55	0.52	1.323	0.978–1.790	0.07	1.236	0.911–1.678	0.17
M-T1: K6 ≥ 5 and M-T2; K6 ≥ 5	13,956	17.7	91	0.65	1.669	1.297–2.148	<0.001	1.440	1.104–1.877	0.01

Abbreviations: The Kessler 6-item psychological distress scale (K6), autism spectrum disorder (ASD), crude odds ratio (COR), confidence interval (CI), adjusted odds ratio (AOR).
M-T1: median 15.1 (interquartile range 12.3–18.9) pregnant weeks; M-T2: median 27.4 (interquartile range 25.3–30.1) pregnant weeks.
Adjusted for maternal age at delivery, paternal age at conception, maternal body mass index (kg/m^2) before pregnancy, parity, marital status, treatment for infertility, unexpected pregnancies, maternal academic history, paternal academic history, maternal job during pregnancy, maternal smoking during pregnancy, paternal smoking during pregnancy, maternal alcohol consumption during pregnancy, household income during pregnancy, maternal neuropsychiatric disorders, maternal Autism Spectrum Quotient Japanese version 10 ≥7, psychoactive drugs use, folic supplements use, multivitamin supplements use, diabetes or gestational diabetes, pregnancy complications, obstetric labor complications, intrauterine infections, gender of children, birth weight of children, chromosome abnormalities of children, gestation week, and breast feeding.

ratio [AOR], 1.440; 95% CI, 1.104–1.877) compared to a maternal K6 score of ≤4 at both M-T1 and M-T2 (Table 2). There was no significant difference in the group with a maternal K6 score of ≥5 only at either M-T1 or M-T2 (Table 2).

Discussion

The group with continuous maternal psychological distress from the first to the second half of pregnancy showed a risk of ASD among 3-year-old children compared to other groups. Contrarily, in the group without persistent maternal psychological distress during pregnancy, there was no significant association with ASD among 3-year-old children.

Previous studies reported inconsistent findings on the impact of maternal stress during pregnancy on the risk of ASD among children.[1] A population-based cohort study, which followed prenatal exposure to ice storms in Quebec, Canada, suggested that first trimester prenatal objective stress increased the risk of ASD.[20] A population-based cohort study that followed prenatal exposure to hurricanes and tropical storms in Louisiana, United States

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suggested a significantly increased risk of ASD at a gestational age of 5–6 months during storm or hurricane exposure.[21] A retrospective survey in the United States suggested that a higher prevalence of prenatal stressors was found in ASD at 21–32 weeks of gestation, with a peak at 25–28 weeks.[22] A population-based cohort study in Sweden suggested that third-trimester prenatal stress increased the risk of ASD.[14] A cohort study in China suggested that the second-trimester might be the sensitive period for exposure to prenatal stress, thereby increasing the risk of autistic-like behaviors.[23]

In our nationwide birth cohort study, the risk of ASD was only observed in the group with maternal psychological distress at both approximately 15 and 27 weeks of pregnancy. This indicated that if psychological distress did not continue during pregnancy, the risk of the onset of ASD among the children could be reduced.

This study has certain limitations. First, the K6 was a self-administered questionnaire. Hence, it did not mean that the psychological distress was medically diagnosed. Second, gene polymorphisms were not studied. Third, in this study, the diagnosis of ASD by the physicians was based on participant self-reports. Diagnostic categories of the questionnaire were based on ICD-10. Therefore, misclassification may have occurred as the data were self-reported. However, our study targeted 3-year-old children in Japan, and the prevalence of ASD diagnosis was 0.45%. In a previous Japanese study that evaluated the cumulative incidence of ASD using the ICD-10 among 5-year-old children, the prevalence of ASD was 0.27%.[24] Previous population-based cohort studies conducted in Denmark,[16] Sweden,[15] and the United States[17] reported that the prevalence of ASD was approximately 0.16–0.83%. These prevalences were regarded as not significantly deviating from our results.

The strength of this study lies in the fact that it is the first to analyze the effect of maternal psychological distress on ASD among children in Japan using a large sample from a nationwide birth cohort study.

Conclusion

Continuous maternal psychological distress from the first to the second half of pregnancy was associated with ASD among 3-year-old children. Contrarily, in the group without persistent maternal psychological distress during pregnancy, there was no significant association. This indicates that if maternal mental health is assessed during the early stages of a pregnancy and psychological distress is detected, it may be possible to prevent negative effects on the children through appropriate interventions to improve the distressing situations experienced by mothers.

Supplementary materials. For supplementary material for this article, please visit https://doi.org/10.1017/S2040174422000411

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Conflict of interest. None.

Ethical standards. This study was conducted according to the guidelines laid down in the Declaration of Helsinki. It was reviewed and approved by the Ministry of the Environment's Institutional Review Board on Epidemiological Studies (no. 100910001) and by the ethics committees of all participating institutions. Written informed consent was obtained from all participants.

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