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Maternal prenatal psychological distress and motor/cognitive development in two-year-old offspring: The Japan Environment and Children's Study

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Abstract

Maternal prenatal psychological distress, including depression and anxiety, may affect offspring's motor/cognitive development. However, research findings have been inconsistent. We used a dataset from the Japan Environment and Children's Study to evaluate associations between maternal six-item Kessler Psychological Distress Scale (K6) scores and motor/cognitive development among offspring at two years of age. Their offspring's motor/cognitive development was assessed using the Kyoto Scale of Psychological Development 2001. Records for 1859 male and 1817 female offspring were analyzed. The maternal K6 was administered twice during pregnancy: at a median of 14.6 weeks (M-T1) and 27.3 weeks (M-T2) of gestation. Multiple regression analysis was performed with the group with K6 scores ≤4 at both M-T1 and M-T2 as a reference. In the group with K6 scores ≥5 at both M-T1 and M-T2, male offspring had significantly lower developmental quotients (DQ) in the posture-motor area (partial regression coefficient [B]: −3.68, 95% confidence interval [CI]: −5.92 to −1.44) and language-social area (B: −1.93; 95%CI: −3.73 to −0.12), while female offspring had a lower DQ for the language-social area (B: −1.95; 95%CI: −3.73 to −0.17). In those with K6 scores ≥5 only at M-T1 or M-T2, male and female offspring did not differ significantly in DQ for any area. Continuous maternal psychological distress from the first to the second half of pregnancy was associated with lower motor and verbal cognitive development in male offspring and lower verbal cognitive development in female offspring at 2 years compared with the group without persistent maternal prenatal psychological distress.

Introduction

Maternal prenatal psychological distress, which includes depression symptoms and anxiety, has been found to affect the offspring's neurodevelopment, including motor and cognitive development, temperament, and mental health through effects on the developing fetus; a process commonly known as the Developmental Origins of Health and Disease hypothesis.[1–12]

The impact of maternal psychological distress during pregnancy on offspring development can depend on the offspring's developmental age and sex; however, research results in this regard remain inconsistent. There are also inconsistent findings regarding the periods of pregnancy during which maternal psychological distress has the greatest impact on the offspring.[2,3] Furthermore, it has been reported that genetic variations related to race and ethnicity can influence this impact.[13] In other words, there may be racial or ethnic differences regarding sensitivity

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to exposure to maternal psychological distress during gestation. Despite these issues, however, there has been no independent research on this topic in Japan.

In 2011, Japan commenced the Japan Environment and Children's Study (JECS) – a nationwide birth cohort study of 100,000 pairs of parents and offspring – to investigate this population's development and environments.[14,15] The JECS is currently ongoing, and is planned to continue until the participating offspring turn 18 years old. As a sub-cohort study of the JECS, trained testers have conducted evaluations of the motor and cognitive development of 5000 offspring randomly selected from the sample. In the present study, we used this dataset to examine the association between maternal prenatal psychological distress and the motor/cognitive development of two-year-old offspring.

Materials and methods

Design and participants

The JECS protocol was reviewed and approved by the Ministry of the Environment's Institutional Review Board on Epidemiological Studies (no. 100910001) and the ethics committees of all participating institutions. It was also conducted in accordance with the latest version of the Declaration of Helsinki. Participants for the JECS were recruited between January 2011 and March 2014, and all pregnant women nationwide were eligible for participation. Participants were recruited from 15 regional centers located in Hokkaido, Miyagi, Fukushima, Chiba, Kanagawa, Yamanashi, Toyama, Aichi, Kyoto, Osaka, Hyogo, Tottori, Kochi, Fukuoka, and South Kyushu / Okinawa, respectively. Written informed consent was obtained from all participants. From the JECS cohort, a sub-cohort comprising 5% of the participating offspring, who were randomly selected and met specific eligibility criteria, was extracted.[16] This sub-cohort subsequently underwent extended outcome measurements, including face-to-face interviews with the offspring when they reached two and four years of age, respectively (conducted by specialized staff); the aim of these interviews was to evaluate the offspring's neurological development using the Kyoto Scale of Psychological Development (KSPD).[14]

The present study used the jecs-ta-20190930 dataset, which was revised in April 2020. It contains the results of neurological development assessments (based on the KSPD) of the two-year-old offspring. As the present study investigated effects on unborn offspring, records for offspring born during multiple births (e.g., twins) were excluded from the analysis. Offspring with any congenital anomalies were excluded from the analysis.[17]

Maternal psychological distress

The JECS examiners administered the six-item version of the Kessler Psychological Distress Scale (K6) to the mothers on two occasions: during the first (M-T1) and second (M-T2) half of pregnancy, respectively.[16] The K6 is widely used to assess psychological distress.[18,19] It is a self-administered questionnaire comprising six items (scored using a scale of 0 to 4) that evaluates depressive mood and anxiety over the preceding four weeks, and is based on the Diagnostic and Statistical Manual of Mental Disorders, fourth edition. Total K6 score is determined by summing the scores for each of the six items, with total scores ranging from 0 to 24. The Japanese version of the K6 was used in the JECS. We considered K6 scores ≥5 to indicate psychological distress; this accords with the approach used in previous studies of populations in Japan.[20,21,22] We analyzed the data to determine associations between maternal K6 scores ≥5 and the psychological development of their two-year-old offspring.

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

Motor and cognitive development in two-year-old offspring

The KSPD is a standardized developmental assessment tool for Japanese offspring that has been widely used in clinical settings in Japan.[23–25] The KSPD covers the posture-motor (P-M), cognitive-adaptive (C-A), and language-social (L-S) areas of development.[23–25] The P-M area consists of gross motor skills, such as take a few steps forward, climb stairs using a handrail, and jump. The C-A area consists of nonverbal cognitive skills, such as pile up blocks, identify shapes, draw lines and shapes following a model, fold origami paper following a model, and stack cups of different sizes in sequence. The L-S area consists of verbal cognitive skills, such as point to a picture of the object being communicated, state the name of the object, recite numbers, select the indicated facial expression, and state the name of a color. A developmental quotient (DQ) was calculated by dividing the developmental age in days by the chronological age in days and multiplying the quotient by 100.

Administrative procedures and evaluations were strictly standardized to ensure testers' reliability in this survey. For the reliability of administration, the testers received rigorous training before they were certified to conduct testing. The testers were certified by the JECS and the Kyoto International Social Welfare Exchange Centre, Kyoto, Japan.

Statistical analysis and covariables

We compared each group in terms of the characteristics of the mothers and their offspring by applying analysis of variance (ANOVA). Bivariate and multiple regression analyses were then performed to assess the association between maternal prenatal psychological distress and offspring's psychological development.

The multiple regression analyses were adjusted for maternal age at delivery; whether the pregnancy was unplanned, use of infertility treatment, marital status, highest level of education (maternal and paternal), smoking during pregnancy (maternal and paternal), alcohol consumption during pregnancy, annual household income, whether the mother had any neuropsychiatric disorders, psychoactive drug use during pregnancy, whether pregnancy complications occurred, whether obstetric labor complications occurred, mode of delivery, offspring's birth weight, gestational week of delivery, feeding method at six months postpartum, family structure, number of offspring (including the subject), offspring's age at beginning attendance at a daycare center, location of regional center, and offspring's sex for overall. Information regarding maternal neuropsychiatric disorders, pregnancy complications, obstetric labor complications, mode of delivery, offspring's birth weight, and gestational week of delivery was obtained from physician's records. All other information was obtained from the participants' responses to the questionnaire, which was not verified.

These confounding factors were mostly chosen with reference to previous relevant studies.[1–3] None of the confounding factors in this analysis were found to have multicollinearity. Multicollinearity was considered to be present should the following conditions arise: an association with the independent variables that featured a correlation coefficient of $r \approx 1$, and/or a variance inflation factor of 10 or

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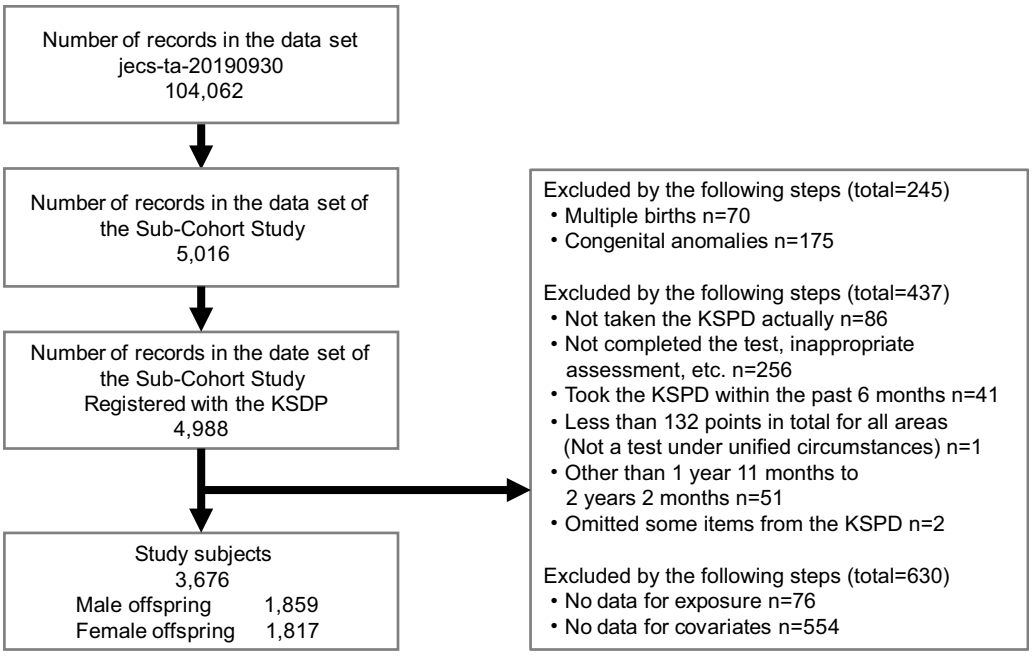

Fig. 1. Flow chart depicting research participants' selection.

higher. For reference, parity and number of offspring (including the subject) were found to be multicollinear.

All analyses were performed using SAS statistical software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Overview

Of the 104,062 records in this dataset, records for 3676 offspring were analyzed (Fig. 1). Table 1 shows the characteristics of the participant sample, which comprised 3676 two-year-old offspring from single pregnancies without congenital anomalies who had undergone evaluation using the KSPD. This sample comprised 1859 male and 1817 female offspring.

For male offspring, the maternal K6 score at M-T1 was collected at median 14.7 weeks of gestation (interquartile range; IQR: 12.0–18.1), and that for M-T2 was collected at median 27.4 weeks of gestation (IQR: 25.3–30.1). For female offspring, the maternal K6 score at M-T1 was collected at median 14.4 weeks of gestation (IQR: 11.7–17.7), and that for M-T2 was collected at median 27.1 weeks of gestation (IQR: 25.1–30.0). Overall, for M-T1 the maternal K6 score was collected at median 14.6 weeks of gestation (IQR: 12.0–18.0), and for M-T2 it was collected at median 27.3 weeks of gestation (IQR: 25.3–30.0).

Male offspring

Mothers of male offspring were divided into four groups: (1) 358 mothers (19.3%) had K6 scores ≥5 at both M-T1 and M-T2, (2) 248 mothers (13.3%) had a K6 score ≥5 at M-T1 and a score ≤4 at M-T2, (3) 167 mothers (9.0%) had a K6 score ≤4 at M-T1 and a score ≥5 at M-T2, and (4) 1086 mothers (58.4%) had K6 scores ≤4 at both M-T1 and M-T2. Table 2 shows the results of the one-way ANOVA for maternal K6 scores and offspring's KSPD scores; Table 3 shows the results of the bivariate analysis for maternal K6 scores and offspring's KSPD scores.

Multiple regression analysis showed that the group with maternal K6 scores ≥5 at both M-T1 and M-T2 had significantly lower scores for the P-M DQ (partial regression coefficient [B]: −3.68, 95% confidence interval [CI]: −5.92 to −1.44, β: −0.080, $p = 0.001$) and L-S DQ (B: −1.93; 95% CI: −3.73 to −0.12, β: −0.052, $p = 0.04$) compared with the group with maternal K6 scores ≤4 at both M-T1 and at M-T2 (Table 4).

Female offspring

Mothers of female offspring were divided into four groups: (1) 351 mothers (19.3%) had K6 scores ≥5 at both M-T1 and M-T2, (2) 242 mothers (13.3%) had a K6 score ≥5 at M-T1 and a score ≤4 at M-T2, (3) 163 mothers (9.0%) had a K6 score ≤4 at M-T1 and a score ≥5 at M-T2, and (4) 1,061 mothers (58.4%) had K6 scores ≤4 at both M-T1 and M-T2. Table 2 shows the results of the one-way ANOVA for maternal K6 scores and offspring's KSPD scores (Table 2).

Multiple regression analysis showed that the group with maternal K6 scores ≥5 at both M-T1 and M-T2 had significantly lower scores for the L-S DQ (B: −1.95; 95% CI: −3.73 to −0.17, β: −0.053, $p = 0.03$) compared to the group with maternal K6 scores ≤4 at both M-T1 and M-T2 (Table 4). Otherwise, the group with maternal K6 scores ≥5 at both M-T1 and M-T2, did not have significantly lower scores for the P-M DQ compared to the group with maternal K6 scores ≤4 at both M-T1 and M-T2 (Table 4).

Overall

Multiple regression analysis showed that the group with maternal K6 scores ≥ 5 at both M-T1 and M-T2 had significantly lower scores for P-M DQ (B: −2.54; 95% CI: −4.11 to −0.97, β: −0.056, $p = 0.002$), and L-S DQ (B: −2.06; 95% CI: −3.32 to −0.80, β: −0.055, $p = 0.001$) compared to the group with maternal K6 scores ≤4 at both M-T1 and M-T2 (Table 4).

Discussion

Overall findings

In our analysis, among the group of mothers who showed continuous psychological distress during pregnancy (evidenced

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Table 1. Characteristics of participants (total = 3676)

		Analysis set							Excluded		
		Overall (*n* = 3676)		Male offspring (*n* = 1859)		Female offspring (*n* = 1817)		Reference for multipleregression analysis	Overall (*n* = 1067)		p-Value (Chi-Square)
Variables	Category	*n*	%	*n*	%	*n*	%		*n*	%	
Age of mother at the delivery (years)	Means ± SD	32.0 ± 4.8		32.0 ± 4.8		32.1 ± 4.9		Continuous variable	31.6 ± 5.2		0.01 *
	<20	8	0.2	5	0.3	3	0.2		9	0.8	<0.0001
	20–24	220	6.0	108	5.8	112	6.2		97	9.1	
	25–34	2262	61.5	1158	62.3	1104	60.8		632	59.2	
	≥35	1186	32.3	588	31.6	598	32.9		328	30.7	
	No answer								1	0.1	
Unplanned pregnancy	No	3411	92.8	1722	92.6	1689	93.0	ref	959	89.9	<0.0001
	Yes	265	7.2	137	7.4	128	7.0		92	8.6	
	No answer								16	1.5	
Parity	Primipara	1471	40.0	748	40.2	723	39.8		429	40.2	0.98
	Multipara	2149	58.5	1082	58.2	1067	58.7		621	58.2	
	No answer	56	1.5	29	1.6	27	1.5		17	1.6	
Infertility treatment	No	3424	93.1	1730	93.1	1694	93.2	ref	966	90.5	<0.0001
	Yes	252	6.9	129	6.9	123	6.8		89	8.3	
	No answer								12	1.1	
Marital status	Married, Common-law marriage	3636	98.9	1840	99.0	1796	98.8	ref	1012	94.9	<0.0001
	Divorced	16	0.4	6	0.3	10	0.6		8	0.8	
	Widowed	1	0.0	1	0.1	0	0.0		0	0.0	
	Other	23	0.6	12	0.7	11	0.6		17	1.6	
	No answer								30	2.8	
Maternal highest level of education	College/University	1660	45.2	848	45.6	812	44.7		396	37.1	<0.0001
	Senior high school	1902	51.7	962	51.8	940	51.7	ref	584	54.7	
	Junior high school	114	3.1	49	2.6	65	3.6		65	6.1	
	No answer								22	2.1	
Paternal highest level of education	College/University	1565	42.6	812	43.7	753	41.4		383	35.9	<0.0001
	Senior high school	1923	52.3	955	51.4	968	53.3	ref	577	54.1	
	Junior high school	188	5.1	92	5.0	96	5.3		69	6.5	
	No answer								38	3.6	
Maternal smoking during pregnancy	No	3569	97.1	1805	97.1	1764	97.1	ref	996	93.4	<0.0001
	Yes	107	2.9	54	2.9	53	2.9		52	4.9	
	No answer								19	1.8	

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Table 1. (*Continued*)

Paternal smoking during pregnancy	No	2193	59.7	1123	60.4	1070	58.9	ref	552	51.7	<0.0001
	Yes	1483	40.3	736	39.6	747	41.1		452	42.4	
	No answer								63	5.9	
Maternal alcohol consumption during pregnancy	No	3594	97.8	1813	97.5	1781	98.0	ref	992	93.0	<0.0001
	Yes	82	2.2	46	2.5	36	2.0		36	3.4	
	No answer								39	3.7	
Annual household income (×1000 yen/year) during pregnancy	< 4,000	1342	36.5	663	35.7	679	37.4	ref	338	31.7	<0.0001
	4,000 ≤ - <6,000	1260	34.3	649	34.9	611	33.6		303	28.4	
	≥6,000	1074	29.2	547	29.4	527	29.0		218	20.4	
	No answer								208	19.5	
Maternal neuropsychiatric disorders	No	3311	90.1	1678	90.3	1633	89.9	ref	944	88.5	0.13
	Yes	365	9.9	181	9.7	184	10.1		123	11.5	
Psychoactive drugs use during pregnancy	no	3559	96.8	1805	97.1	1754	96.5	ref	1003	94.0	<0.0001
	Yes	117	3.2	54	2.9	63	3.5		39	3.7	
	No answer								25	2.3	
Pregnancy complications	No	3069	83.5	1546	83.2	1523	83.8	ref	875	82.0	<0.0001
	Yes	607	16.5	313	16.8	294	16.2		169	15.8	
	No answer								23	2.2	
Obstetric labor complications	No	1935	52.6	981	52.8	954	52.5	ref	581	54.5	<0.0001
	Yes	1741	47.4	878	47.2	863	47.5		476	44.6	
	No answer								10	0.9	
Mode of delivery	Vaginal	3048	82.9	1555	83.7	1493	82.2	ref	851	79.8	<0.0001
	Cesarean	628	17.1	304	16.4	324	17.8		209	19.6	
	No answer								7	0.7	
Sex of offspring	Male	1859	50.6	1859	100.0	0	0.0		554	51.9	0.44
	Female	1817	49.4	0	0.0	1817	100.0		513	48.1	
Birth weight of offspring (grams)	Means ± SD	3059.0 ± 392.2		3109.2 ± 400.5		3008.2 ± 376.9		Continuous variable			
	0 < - < 1500	2	0.1	1	0.1	1	0.1				
	1500 ≤ - < 2500	242	6.6	97	5.2	145	8.0				
	2500 ≤ - < 4000	3395	92.4	1733	93.2	1662	91.5				
	≥4000	37	1.0	28	1.5	9	0.5				
Gestation week of delivery	22 ≤-< 28	0	0.0	0	0.0	0	0.0				
	28 ≤-< 34	14	0.4	4	0.2	10	0.6				

(*Continued*)

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Table 1. (*Continued*)

Variables	Category	Analysis set						Reference for multipleregression analysis	Excluded		p-Value (Chi-Square)
		Overall ($n = 3676$)		Male offspring ($n = 1859$)		Female offspring ($n = 1817$)			Overall ($n = 1067$)		
		n	%	*n*	%	*n*	%		*n*	%	
	34 ≤-< 37	115	3.1	72	3.9	43	2.4				
	37 ≤-< 42	3541	96.3	1781	95.8	1760	96.9	ref			
	≥ 42	6	0.2	2	0.1	4	0.2				
Feeding method at postpartum 6 months	Breastfeeding	2346	63.8	1173	63.1	1173	64.6	ref			
	Breastfeeding and infant formula	815	22.2	430	23.1	385	21.2				
	Infant formula	515	14.0	256	13.8	259	14.3				
Family structure	Extended family	682	18.6	359	19.3	323	17.8				
	Nuclear family	2994	81.5	1500	80.7	1494	82.2	ref			
Number of offspring included subject	1	1497	40.7	770	41.4	727	40.0	ref			
	2	1460	39.7	738	39.7	722	39.7				
	≥ 3	719	19.6	351	18.9	368	20.3				
Attendance at daycare center (attendance age)	No	1872	50.9	935	50.3	937	51.6	ref			
	Yes; 0 ≤ - <1	845	23.0	432	23.2	413	22.7				
	Yes; => 1	959	26.1	492	26.5	467	25.7				
Regional Center	Hokkaido	302	8.2	151	8.1	151	8.3		93	8.7	<0.0001
	Miyagi	326	8.9	169	9.1	157	8.6		99	9.3	
	Fukushima	466	12.7	250	13.5	216	11.9	ref	137	12.8	
	Chiba	199	5.4	93	5.0	106	5.8		87	8.2	
	Kanagawa	230	6.3	114	6.1	116	6.4		79	7.4	
	Koshin	257	7.0	130	7.0	127	7.0		77	7.2	
	Toyama	207	5.6	110	5.9	97	5.3		48	4.5	
	Aichi	204	5.6	94	5.1	110	6.1		68	6.4	
	Kyoto	119	3.2	66	3.6	53	2.9		59	5.5	
	Osaka	275	7.5	128	6.9	147	8.1		84	7.9	
	Hyogo	200	5.4	118	6.4	82	4.5		33	3.1	
	Tottori	109	3.0	49	2.6	60	3.3		23	2.2	
	Kochi	263	7.2	129	6.9	134	7.4		66	6.2	
	Fukuoka	297	8.1	149	8.0	148	8.2		67	6.3	
	South Kyusyu and Okinawa	222	6.0	109	5.9	113	6.2		47	4.4	
M-T1; pregnant week	Median (IQR)	14.6 (12.0–18.0)		14.7 (12.0–18.1)		14.4 (11.7–17.7)			14.9 (12.0–18.7)		0.09 **

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Table 1. (*Continued*)

M-T2; pregnant week	Median (IQR)	27.3 (25.3–30.0)		27.4 (25.3–30.1)		27.1 (25.1–30.0)		27.3 (25.3–30.0)	0.86 **
Maternal K6 ; M-T1	<5	2477	67.4	1253	67.4	1224	67.4		
	5 ≤ - <13	1053	28.7	526	28.3	527	29.0		
	≥ 13	146	4.0	80	4.3	66	3.6		
Maternal K6 ; M-T2	<5	2637	71.7	1334	71.8	1303	71.7		
	5 ≤ - <13	940	25.6	472	25.4	468	25.8		
	≥ 13	99	2.7	53	2.9	46	2.5		
Maternal K6 ; four groups	M-T1; K6 ≤ 4 and M-T2; K6 ≤ 4	2147	58.4	1086	58.4	1061	58.4	ref	
	M-T1; K6 ≤ 4 and M-T2; K6 ≥ 5	330	9.0	167	9.0	163	9.0		
	M-T1: K6 ≥ 5 and M-T2; K6 ≤ 4	490	13.3	248	13.3	242	13.3		
	M-T1: K6 ≥ 5 and M-T2; K6 ≥ 5	709	19.3	358	19.3	351	19.3		
KSPD									
Total DQ	Means ± SD	94.4 ± 10.5		92.4 ± 10.0		96.4 ± 10.5			
P-M DQ	Means ± SD	93.6 ± 17.9		93.1 ± 18.2		94.1 ± 17.7			
C-A DQ	Means ± SD	95.9 ± 12.6		93.8 ± 12.1		98.0 ± 12.8			
L-S DQ	Means ± SD	92.7 ± 14.9		89.8 ± 14.7		95.7 ± 14.5			

Abbreviations: Kyoto Scale of Psychological Development 2001(KSPD), developmental quotient (DQ), posture-motor (P-M), cognitive-adaptive (C-A), language-social (L-S), standard deviation (SD), interquartile range (IQR), the 6-item Kessler Psychological Distress Scale (K6; total point scores ranged from 0 to 24).
*t-test and ** Mann–Whitney U test were applied.

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Table 2. ANOVA of maternal K6 and KSPD in four groups

		Overall ($n = 3676$)				Male offspring ($n = 1859$)				Female offspring ($n = 1817$)			
	Maternal K6	*n*	%	Means ± SD	*p*	*n*	%	Means ± SD	*p*	*n*	%	Means ± SD	*p*
Total DQ	M-T1; K6 ≤ 4 and M-T2; K6 ≤ 4	2147	58.4	94.8 ± 10.5	0.003	1086	58.4	92.7 ± 10.0	0.02	1061	58.4	96.9 ± 10.6	0.10
	M-T1; K6 ≤ 4 and M-T2; K6 ≥ 5	330	9.0	95.0 ± 10.5		167	9.0	93.5 ± 9.9		163	9.0	96.6 ± 10.9	
	M-T1: K6 ≥ 5 and M-T2; K6 ≤ 4	490	13.3	94.1 ± 9.9		248	13.3	92.3 ± 9.2		242	13.3	96.0 ± 10.1	
	M-T1: K6 ≥ 5 and M-T2; K6 ≥ 5	709	19.3	93.2 ± 10.5		358	19.3	91.1 ± 10.4		351	19.3	95.3 ± 10.1	
P-M DQ	M-T1; K6 ≤ 4 and M-T2; K6 ≤ 4	2147	58.4	94.1 ± 18.2	0.01	1086	58.4	93.8 ± 18.7	0.001	1061	58.4	94.4 ± 17.7	0.43
	M-T1; K6 ≤ 4 and M-T2; K6 ≥ 5	330	9.0	95.2 ± 18.6		167	9.0	96.9 ± 18.9		163	9.0	93.6 ± 18.2	
	M-T1: K6 ≥ 5 and M-T2; K6 ≤ 4	490	13.3	93.2 ± 16.5		248	13.3	91.4 ± 16.0		242	13.3	95.1 ± 16.8	
	M-T1: K6 ≥ 5 and M-T2; K6 ≥ 5	709	19.3	91.7 ± 17.7		358	19.3	90.5 ± 17.2		351	19.3	92.9 ± 18.0	
C-A DQ	M-T1; K6 ≤ 4 and M-T2; K6 ≤ 4	2147	58.4	96.1 ± 12.7	0.11	1086	58.4	94.0 ± 12.1	0.23	1061	58.4	98.3 ± 13.0	0.46
	M-T1; K6 ≤ 4 and M-T2; K6 ≥ 5	330	9.0	96.6 ± 13.1		167	9.0	94.8 ± 12.6		163	9.0	98.4 ± 13.4	
	M-T1: K6 ≥ 5 and M-T2; K6 ≤ 4	490	13.3	95.6 ± 12.1		248	13.3	93.8 ± 11.6		242	13.3	97.5 ± 12.3	
	M-T1: K6 ≥ 5 and M-T2; K6 ≥ 5	709	19.3	94.9 ± 12.5		358	19.3	92.8 ± 12.4		351	19.3	97.2 ± 12.2	
L-S DQ	M-T1; K6 ≤ 4 and M-T2; K6 ≤ 4	2147	58.4	93.3 ± 14.9	0.001	1086	58.4	90.3 ± 14.7	0.04	1061	58.4	96.4 ± 14.5	0.02
	M-T1; K6 ≤ 4 and M-T2; K6 ≥ 5	330	9.0	93.5 ± 14.4		167	9.0	90.8 ± 14.0		163	9.0	96.2 ± 14.4	
	M-T1: K6 ≥ 5 and M-T2; K6 ≤ 4	490	13.3	92.2 ± 14.5		248	13.3	89.9 ± 14.7		242	13.3	94.5 ± 14.0	
	M-T1: K6 ≥ 5 and M-T2; K6 ≥ 5	709	19.3	90.8 ± 15.0		358	19.3	87.8 ± 15.1		351	19.3	93.9 ± 14.4	

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Table 3. Bivariate analysis of maternal K6 and KSPD in four groups

		Overall ($n = 3676$)				Male offspring ($n = 1859$)				Female offspring ($n = 1817$)			
	Maternal K6	*B*	95% CI	*β*	*p*	*B*	95% CI	*β*	*p*	*B*	95% CI	*β*	*p*
Total DQ	M-T1; K6 ≤ 4 and M-T2; K6 ≤ 4	ref				ref				ref			
	M-T1; K6 ≤ 4 and M-T2; K6 ≥ 5	0.24	−0.97 to −1.45	0.007	0.70	0.73	−0.90 to −2.36	0.021	0.38	−0.26	−1.99 to −1.47	−0.007	0.77
	M-T1: K6 ≥ 5 and M-T2; K6 ≤ 4	−0.69	−1.72 to −0.33	−0.023	0.19	−0.48	−1.86 to −0.90	−0.016	0.50	−0.91	−2.38 to −0.56	−0.030	0.22
	M-T1: K6 ≥ 5 and M-T2; K6 ≥ 5	−1.60	−2.48 to −0.71	−0.060	0.0004	−1.67	−2.87 to −0.48	−0.066	0.01	−1.53	−2.80 to −0.26	−0.058	0.02
P-M DQ	M-T1; K6 ≤ 4 and M-T2; K6 ≤ 4	ref				ref				ref			
	M-T1; K6 ≤ 4 and M-T2; K6 ≥ 5	1.14	−0.94 to −3.22	0.018	0.28	3.09	0.14 to −6.04	0.049	0.04	−0.86	−3.78 to −2.06	−0.014	0.56
	M-T1: K6 ≥ 5 and M-T2; K6 ≤ 4	−0.86	−2.62 to −0.90	−0.016	0.34	−2.35	−4.85 to −0.15	−0.044	0.07	0.67	−1.80 to −3.14	0.013	0.59
	M-T1: K6 ≥ 5 and M-T2; K6 ≥ 5	−2.35	−3.88 to −0.83	−0.052	0.002	−3.22	−5.38 to −1.05	−0.070	0.004	−1.47	−3.61 to −0.66	−0.033	0.18
C-A DQ	M-T1; K6 ≤ 4 and M-T2; K6 ≤ 4	ref				ref				ref			
	M-T1; K6 ≤ 4 and M-T2; K6 ≥ 5	0.47	−1.00 to −1.93	0.011	0.53	0.78	−1.20 to −2.76	0.018	0.44	0.14	−1.97 to −2.26	0.003	0.89
	M-T1: K6 ≥ 5 and M-T2; K6 ≤ 4	−0.49	−1.74 to −0.75	−0.013	0.43	−0.21	−1.88 to −1.47	−0.006	0.81	−0.79	−2.58 to −1.00	−0.021	0.39
	M-T1: K6 ≥ 5 and M-T2; K6 ≥ 5	−1.20	−2.28 to −0.13	−0.038	0.03	−1.29	−2.74 to −0.16	−0.042	0.08	−1.12	−2.67 to −0.42	−0.035	0.15
L-S DQ	M-T1; K6 ≤ 4 and M-T2; K6 ≤ 4	ref				ref				ref			
	M-T1; K6 ≤ 4 and M-T2; K6 ≥ 5	0.19	−1.53 to −1.91	0.004	0.83	0.55	−1.85 to −2.95	0.011	0.65	−0.18	−2.56 to −2.20	−0.004	0.88
	M-T1: K6 ≥ 5 and M-T2; K6 ≤ 4	−1.12	−2.57 to −0.34	−0.026	0.13	−0.34	−2.37 to −1.69	−0.008	0.74	−1.91	−3.92 to −0.11	−0.045	0.06
	M-T1: K6 ≥ 5 and M-T2; K6 ≥ 5	−2.49	−3.75 to −1.23	−0.066	0.0001	−2.44	−4.20 to −0.68	−0.065	0.01	−2.54	−4.29 to −0.80	−0.070	0.004

Abbreviations: Kyoto Scale of Psychological Development 2001(KSPD), developmental quotient (DQ), posture-motor (P-M), cognitive-adaptive (C-A), language-social (L-S), partial regression coefficient (B), confidence interval (CI), standardized partial regression coefficients (β), Interquartile range (IQR).
M-T1; Overall median 14.6 (IQR 12.0–18.0), Male median 14.7 (IQR 12.0–18.1), Female median 14.4 (IQR 11.7–17.7) pregnant weeks.
M-T2; Overall median 27.3 (IQR 25.3–30.0), Male median 27.4 (IQR 25.3–30.1), Female median 27.1 (IQR 25.1–30.0) pregnant weeks.

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Table 4. Multiple regression analysis of maternal K6 and KSPD in four groups

		Overall ($n = 3676$)				Male offspring ($n = 1859$)				Female offspring ($n = 1817$)			
	Maternal K6	*B*	95% CI	*β*	*p*	*B*	95% CI	*β*	*p*	*B*	95% CI	*β*	*p*
Total DQ	M-T1; K6 ≤ 4 and M-T2; K6 ≤ 4	ref				ref				ref			
	M-T1; K6 ≤ 4 and M-T2; K6 ≥ 5	0.28	−0.89 to 1.45	0.008	0.64	0.73	−0.87 to 2.33	0.021	0.37	−0.12	−1.85 to 1.60	−0.003	0.89
	M-T1: K6 ≥ 5 and M-T2; K6 ≤ 4	−0.63	−1.63 to 0.36	−0.021	0.21	−0.38	−1.74 to 0.98	−0.013	0.58	−0.88	−2.34 to 0.58	−0.028	0.24
	M-T1: K6 ≥ 5 and M-T2; K6 ≥ 5	−1.24	−2.13 to −0.35	−0.047	0.01	−1.14	−2.37 to 0.08	−0.045	0.07	−1.20	−2.51 to 0.10	−0.045	0.07
P-M DQ	M-T1; K6 ≤ 4 and M-T2; K6 ≤ 4	ref				ref				ref			
	M-T1; K6 ≤ 4 and M-T2; K6 ≥ 5	0.87	−1.19 to 2.94	0.014	0.41	2.45	−0.46 to 5.37	0.039	0.10	−0.49	−3.43 to 2.44	−0.008	0.74
	M-T1: K6 ≥ 5 and M-T2; K6 ≤ 4	−0.85	−2.60 to 0.91	−0.016	0.35	−2.43	−4.91 to 0.06	−0.045	0.06	0.57	−1.92 to 3.06	0.011	0.66
	M-T1: K6 ≥ 5 and M-T2; K6 ≥ 5	−2.54	−4.11 to −0.97	−0.056	0.002	−3.68	−5.92 to −1.44	−0.080	0.001	−1.34	−3.57 to 0.88	−0.030	0.24
C-A DQ	M-T1; K6 ≤ 4 and M-T2; K6 ≤ 4	ref				ref				ref			
	M-T1; K6 ≤ 4 and M-T2; K6 ≥ 5	0.51	−0.92 to 1.93	0.011	0.49	0.83	−1.12 to 2.77	0.019	0.40	0.24	−1.86 to 2.35	0.005	0.82
	M-T1: K6 ≥ 5 and M-T2; K6 ≤ 4	−0.36	−1.57 to 0.84	−0.010	0.55	0.10	−1.56 to 1.75	0.003	0.91	−0.73	−2.52 to 1.06	−0.019	0.42
	M-T1: K6 ≥ 5 and M-T2; K6 ≥ 5	−0.72	−1.80 to 0.37	−0.022	0.19	−0.42	−1.91 to 1.07	−0.014	0.58	−0.85	−2.44 to 0.75	−0.026	0.30
L-S DQ	M-T1; K6 ≤ 4 and M-T2; K6 ≤ 4	ref				ref				ref			
	M-T1; K6 ≤ 4 and M-T2; K6 ≥ 5	0.34	−1.32 to 2.00	0.007	0.69	0.77	−1.59 to 3.12	0.015	0.52	−0.08	−2.43 to 2.28	−0.002	0.95
	M-T1: K6 ≥ 5 and M-T2; K6 ≤ 4	−1.09	−2.50 to 0.32	−0.025	0.13	−0.43	−2.43 to 1.58	−0.010	0.68	−1.81	−3.81 to 0.18	−0.043	0.08
	M-T1: K6 ≥ 5 and M-T2; K6 ≥ 5	−2.06	−3.32 to −0.80	−0.055	0.001	−1.93	−3.73 to −0.12	−0.052	0.04	−1.95	−3.73 to −0.17	−0.053	0.03

Abbreviations: Kyoto Scale of Psychological Development 2001(KSPD), developmental quotient (DQ), posture-motor (P-M), cognitive-adaptive (C-A), language-social (L-S), partial regression coefficient (B), confidence interval (CI), standardized partial regression coefficients (β), Interquartile range (IQR).

M-T1; Overall median 14.6 (IQR 12.0–18.0), Male median 14.7 (IQR 12.0–18.1), Female median 14.4 (IQR 11.7–17.7) pregnant weeks.

M-T2; Overall median 27.3 (IQR 25.3–30.0), Male median 27.4 (IQR 25.3–30.1), Female median 27.1 (IQR 25.1–30.0) pregnant weeks.

Adjusted for age of mother at the delivery, unplanned pregnancy, infertility treatment, marital status, maternal highest level of education, paternal highest level of education, maternal smoking during pregnancy, paternal smoking during pregnancy, maternal alcohol consumption during pregnancy, annual household income, maternal neuropsychiatric disorders, psychoactive drug use during pregnancy, pregnancy complications, obstetric labor complications, mode of delivery, birth weight of offspring, gestational week of delivery, feeding method at 6 months postpartum, family structure, number of offspring included subject, attendance age of daycare center, location of regional center, and sex of offspring for overall.

by K6 scores ≥5 at approximately 14 and 27 weeks of gestation), male two-year-old offspring tended to have a lower DQ for the P-M and L-S development areas, while female two-year-old offspring tended to have a lower DQ for the L-S development area.

In contrast, in the group for which maternal psychological distress was present at approximately 14 weeks of gestation but absent at approximately 27 weeks of gestation, and the group for which maternal psychological distress was absent at approximately 14 weeks of gestation but present at approximately 27 weeks of gestation, there was no significant impact on the DQ of any development area, regardless of the offspring's sex.

This indicates that continuous maternal psychological distress from the first to the second half of pregnancy may impair the motor development and verbal cognitive development of male offspring at two years of age, and the verbal cognitive development of female offspring at two years of age. In other words, if maternal psychological distress is detected in the early stages of pregnancy, it may be possible to prevent negative effects on the offspring by immediately implementing appropriate interventions. However, this study did not examine the mother's postpartum psychological distress. Since maternal postnatal psychological distress also affects the offspring's motor and cognitive development, further study is needed.[2,26,27] However, our finding and suggestions were also fully consistent with our previous study examining the association between maternal prenatal psychological distress and autism spectrum disorder (ASD) among offspring.[28] That study showed that from the first to the second half of pregnancy, continuous maternal psychological distress was associated with ASD among offspring.[28]

Our study focused on two-year-old offspring. In many related studies, the age of the offspring examined varied greatly. Previous studies have reported that the effects of maternal prenatal psychological distress on offspring vary as they age.[1,2,29] Therefore, in this discussion section, in which we contrast our findings with those of existing studies, we limit our focus to studies concerning offspring of approximately two years of age (from 12 months to three years).

Motor development

Koutra et al. reported that motor development at 18 months of age is not significantly affected by maternal prenatal depression symptoms.[30] However, Lin et al. found maternal prenatal psychological distress to have a negative effect on gross motor skills at 24–36 months of age.[31] Notably, these two studies assessed maternal mental health only once, at 28–32 weeks, and at 28–36 weeks of gestation, respectively.[30,31]

Additionally, stress in the form of exposure to disasters during pregnancy may affect offspring's motor development. An examination conducted during the 2010 Queensland Floods in Australia found that maternal prenatal subjective stress, especially post-traumatic stress, has a negative effect on the offspring's fine motor skills at 16 months of age, particularly when the stress exposure occurs later than 26 weeks of gestation.[32]

Cognitive development

Koutra et al. reported that cognitive development at 18 months of age is significantly negatively affected by maternal prenatal depression symptoms.[30] Meanwhile, Lin et al. reported that maternal prenatal psychological distress is marginally ($p = 0.060$) inversely associated with language development at 2–3 years of age.[31] Davis and Sandman reported that, among all measures of maternal distress (perceived stress, state anxiety, pregnancy-specific anxiety and depression), elevated levels of maternal pregnancy-specific anxiety early in pregnancy are independently associated with lower scores (among the offspring) on the Mental Developmental Index, but not the Psychomotor Development Index, at 12 months.[33] Henrichs et al. reported a negative correlation between prenatal stress at 20 weeks of pregnancy and the offspring's word comprehension at 18 months, but no such correlation with word production.[34] Henrichs et al. also found a negative correlation between prenatal stress at 20 weeks of pregnancy and nonverbal cognitive development at 24 months of age.[34] With regard to the effect of exposure to disasters during pregnancy, Moss et al. found the objective degree of exposure to the Queensland Floods in Australia to be associated with lower cognitive scores among the offspring at 16 months of age, especially if the flood occurred at 30 weeks of pregnancy or later.[32] King et al. and Laplante et al., in Canada-based studies, found high levels of objective stress during pregnancy as a result of exposure to ice storms to be negatively associated with offspring's intelligence quotient (IQ) scores at two years of age.[35,36] This effect of objective stress was more pronounced when mothers were exposed to ice storm disasters during the first or second trimester than during the third trimester.

Sex differences

Although we reviewed previous studies concerning the cognitive and motor development of offspring aged approximately two years, to the best of our knowledge no previous study has examined sex differences in terms of the development of these skills. In our study, maternal prenatal psychological distress was found to be associated with lower verbal cognitive and motor development among male offspring, and with lower verbal cognitive development among female offspring.

In a previous study of 11-year-olds, a linear decline in IQ with increasing maternal objective stress exposure was observed among male offspring; however, no such effect was observed among female offspring.[35,36]

Although not considering offspring's motor or cognitive development, there are some interesting previous studies on sex differences. Braithwaite et al. reported maternal prenatal stress predicted infant negative emotionality in a sex-dependent manner; female offspring exposed to high levels of maternal prenatal cortisol were more emotionally negative, whereas male offspring were less negative at 2 months of age.[37,38] Elevated maternal prenatal cortisol was also associated with lower child callous-unemotional traits in female offspring, but not in male offspring at 2.5–5.0 years of age.[39] Wei et al. reported that higher maternal prenatal depressive symptoms were associated with greater cortical surface area in male offspring and lower surface area in female offspring at 2 and 6 months of age, specifically in areas of the prefrontal cortex, superior temporal gyrus, and superior parietal lobule.[40]

For reference, sex differences have been observed among rodents. For instance, Weinstock found prenatally stressed male rats to show greater learning deficits and reductions in hippocampal long-term potentiation, hippocampal neurogenesis, and dendritic spine density in the prefrontal cortex when compared to female rats.[41] Furthermore, memory of novel objects and spatial locations and facilitated memory of novel object/context pairings have been found to be weaker in prenatally stressed male rats when compared to normally developing rats, but no such difference has been found among prenatally stressed female rats.[42,43] These gender differences may be due to the sensitivity of developing brain

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areas to stress hormones. A combination of reduced testosterone and aromatase activity, together with the action of other adrenal hormones, may foster learning deficits in male rats.[44] Meanwhile, estrogens have protective effects on brain regions associated with learning and memory in rats and mice.[45–47]

Period of exposure to psychological distress during pregnancy

Most related studies have only examined one period of maternal psychological distress during pregnancy. In our study, we examined whether, among our sample, mothers experienced continuous psychological distress during pregnancy (K6 scores of ≥5 over two periods) or only during one period. The group that experienced distress during both periods showed a negative correlation with their offspring's cognitive and motor development. In contrast, there was no such correlation for the groups that showed distress during only one period. This indicates that continuity of psychological distress during pregnancy affects the offspring's development, while temporary stress may not.[28]

Limitations

This study has several limitations. First, in the present study's data set, the K6 was used to assess psychological distress and the KSPD was used as a psychological developmental measure for the offspring; this combination has not been used in previous studies. Therefore, comparisons of the present findings with those of previous studies can only be for reference. Second, the K6 is a self-administered questionnaire; therefore, the mothers' psychological distress was not medically diagnosed. Third, many of the confounding factors in this study were based on the participants' responses to the questionnaire, and were not verified. Fourth, the sub-cohort study was based on 5% extraction of the 104,062 records/participants in the dataset. In reality, 3676 participants (3.5%) were analyzed in this study. There may be an intrinsic bias in the sub-sample used for the study. Fifth, the present study did not examine postpartum maternal mood. Sixth, differences in child-rearing practices for male and female offspring were not examined.

Strengths of the study

This was a prospective study of 3676 offspring aged around two years, making it the largest of its kind. Moreover, no previous studies have examined sex differences in the motor and cognitive development of two-year-old offspring whose mothers have experienced prenatal psychological distress. The confounding factors included a variety of maternal factors and child-rearing environment. To the best of our knowledge, the variables and number of confounding factors for statistical analyses were the largest compared to past studies.

Conclusion

Chronic maternal psychological distress from the first to the second half of pregnancy associated with lower motor and verbal cognitive development among male offspring and lower verbal cognitive development among female offspring at two years of age. This indicates that, if maternal psychological distress is detected in the early stages of pregnancy, it may be possible to prevent the negative effects on offspring through the administration of appropriate interventions.

The JECS is a prospective study that plans to follow and evaluate the development of the targeted offspring until they reach 18 years of age. The results of the current study are based on an interim report of the JECS, which featured data for that offspring at the age of two years. Further evaluations of the offspring's neurodevelopment are planned in the future, including how the effects of maternal distress during pregnancy change as the offspring develop.

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Conflict of interest. None.

Ethical standards. The JECS protocol has been reviewed and approved by the Ministry of the Environment's Institutional Review Board on Epidemiological Studies (no. 100910001) and the Ethics Committees of all the participating institutions. Written informed consent was obtained from all the participants.

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