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REGULAR ARTICLE

Association between the serum insulin-like growth factor-1 concentration in the first trimester of pregnancy and postpartum depression

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Aim: Patients with major depression present with an increased serum insulin-like growth factor-1 (IGF-1) concentration. However, the longitudinal relationship between serum IGF-1 levels and depression development remains unclear. This study aimed to investigate the longitudinal association between the serum IGF-1 concentration in the first trimester of pregnancy and postpartum depression development using data obtained from the Japan Environment and Children's Study (JECS).

Methods: The JECS included 97 415 pregnant women; among them, 8791 were enrolled in this study. Data regarding depression in the first trimester, postpartum depression development at 1 month after childbirth, and other covariates were collected using a self-administered questionnaire. Serum IGF-1 levels were measured in the first trimester of pregnancy. The participants were divided into four groups according to the serum IGF-1 level.

Results: In the first trimester, serum IGF-1 levels were not significantly associated with psychological distress in pregnant women. In the longitudinal analyses, however, postpartum depression development in mothers within the highest quartile for serum IGF-1 concentration in the first trimester was significantly less common than in those within the lowest quartile (odds ratio 0.48, 95% confidence interval 0.30–0.79).

Conclusion: Pregnant women with a high serum IGF-1 concentration in the first trimester were less likely to develop postpartum depression than those with a low concentration. A high serum IGF-1 concentration during pregnancy may help to protect against postpartum depression development.

Keywords: *birth cohort, insulin-like growth factor-1, Japan Environment and Children's Study, postpartum depression, pregnant women.*

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Postpartum depression is common with an approximate occurrence rate of 10% in new mothers.[1–3] Postpartum depression can become prolonged[4] and impair maternal functioning by interfering with breastfeeding, maternal–infant bonding, and care of the infant.[5, 6] Consequently, it can cause poor nutrition and poor health in the offspring.[1] Therefore, for mothers with postpartum depression, early detection, intervention, and treatment are crucial for the well-being of both mother and child. Although the mechanisms underlying depression, including postpartum depression, are complex and unclear, several reports have identified risk factors for postpartum depression, including young age,[7–9] multiparity,[10] depressed mood during pregnancy,[11] and low socioeconomic status.[12] Changes in the levels of certain hormones, including estrogen, have been reported in women with postpartum depression.[13]

Increased insulin-like growth factor-1 (IGF-1) levels have been reported in persons with severe depression[14–16]; however, its specific role in postpartum depression remains unclear. Together with growth hormone, IGF-1 constitutes the human somatotropic axis. IGF-1 is a peptide composed of 70 amino acids and is primarily synthesized in the liver and secreted into the blood under the control of growth hormone.[17, 18] Almost all IGF-1 present in the blood is bound to insulin-like growth factor binding proteins (IGFBP).[19] In addition to insulin-like effects, IGF-1 contributes to the growth, differentiation, and survival of neurons in the central nervous system.[20] Serum IGF-1 levels increase in childhood, peak during adolescence, and then decrease with age.[18] Moreover, IGF-1 is reported to decrease during the first trimester of pregnancy.[21]

The association between IGF-1 and depressive episodes is slowly being elucidated. Experimental studies in mice have demonstrated an antidepressant effect of IGF-1.[22–24] In humans, increased serum IGF-1 levels have been reported in patients with major depression.[14–16] However, longitudinal studies on the relationship between serum IGF-1 levels and depression development have yielded inconsistent results.[25–27] Furthermore, there have been very

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few relevant and limited cross-sectional and longitudinal studies on the association between serum IGF-1 levels and postpartum depression. We examined the associations between serum IGF-1 concentration and maternal depression before and after childbirth. Therefore, using data from a large-scale nationwide birth cohort study, we aimed to investigate the cross-sectional association between the serum IGF-1 concentration and the prevalence of psychological distress in the first trimester, as well as the longitudinal association of IGF-1 levels in the first trimester with postpartum depression development.

Methods

Study design and subjects

We analyzed data from the Japan Environment and Children's Study (JECS),[28] a large-scale prospective birth cohort study that recruited pregnant women between January 2011 and March 2014. Details regarding the JECS have been described elsewhere.[28, 29] The JECS protocol was approved by the Institutional Review Board on Epidemiological Studies of the Ministry of the Environment and all participating institutions. Further, it was conducted in accordance with the Declaration of Helsinki and other internationally recognized regulations and guidelines. Written informed consent was obtained from all study participants.

The present study is based on the jecs-an-20180131 dataset, which was released in March 2018. The JECS study enrolled 97 415 pregnant women; among them, we enrolled 8791 pregnant women with available Kessler Psychological Distress Scale (K6) scores[30, 31] and serum IGF-1 concentration measurements recorded in the first trimester (Fig. 1).

Variables

After enrollment in the JECS, information on the pregnant women, including the K6 score,[30, 31] was collected using a self-administered questionnaire during the first trimester. The K6 performs well in detecting mood and anxiety disorders.[31] We dichotomized the pregnant women into groups with (K6 ≥ 13)[32–34] and without (K6 ≤ 12) severe psychological distress. The following factors possibly associated with serum IGF-1 levels[35] or depression[7–10, 12] were selected as covariates: maternal age (<25 years/25–34 years/≥35 years); body mass index (BMI; <18.5/18.5–24.9/≥25); smoking status (non-smoker/ex-smoker [quit before pregnancy]/ex-smoker [quit during early pregnancy]/current smoker); alcohol consumption (non-drinker/ex-drinker/current drinker); educational status (≤12 years/13–16 years/≥17 years); and parity. Data on household income (<4 million JPY/≥4 million JPY) were collected in a similar manner during the second/third trimester. During the interview in the first trimester, information regarding the use of selective serotonin reuptake inhibitors (SSRI) and other antidepressant drugs from the time of pregnancy confirmation to gestational week 12 was collected. Additionally, the total serum IGF-1 concentration, including free and IGFBP-bound IGF-1, was measured through specific radioimmunoassay in the first trimester of pregnancy from maternal blood samples collected between January and July 2011. The participants were divided into four groups depending on the serum IGF-1 concentration, with each group consisting of approximately one-quarter of all participants. At delivery, the medical records at parturition, including birth outcome, multiple versus singleton birth, sex of the child, birthweight, and gestational age, were recorded. At 1 month after childbirth, the maternal Edinburgh Postnatal Depression Scale (EPDS)[36] score was collected using a questionnaire. Subsequently, the mothers were classified into the postpartum depression group (EPDS ≥ 13)[36–38] and the normal group (EPDS ≤ 12). Moreover, an additional analysis was performed by changing the cut-off value for postpartum depression to an EPDS score ≥9.[39]

Statistical analysis

In the cross-sectional analyses performed in the first trimester, serum IGF-1 levels were compared between pregnant women with and without severe psychological distress. A multiple logistic regression model was used to estimate the association of quartiles of serum IGF-1 level with severe psychological distress during the first trimester after adjusting for maternal age, BMI, socioeconomic status, smoking status, alcohol consumption, education, parity, multiple versus singleton birth, SSRI usage, and use of other antidepressant medication.

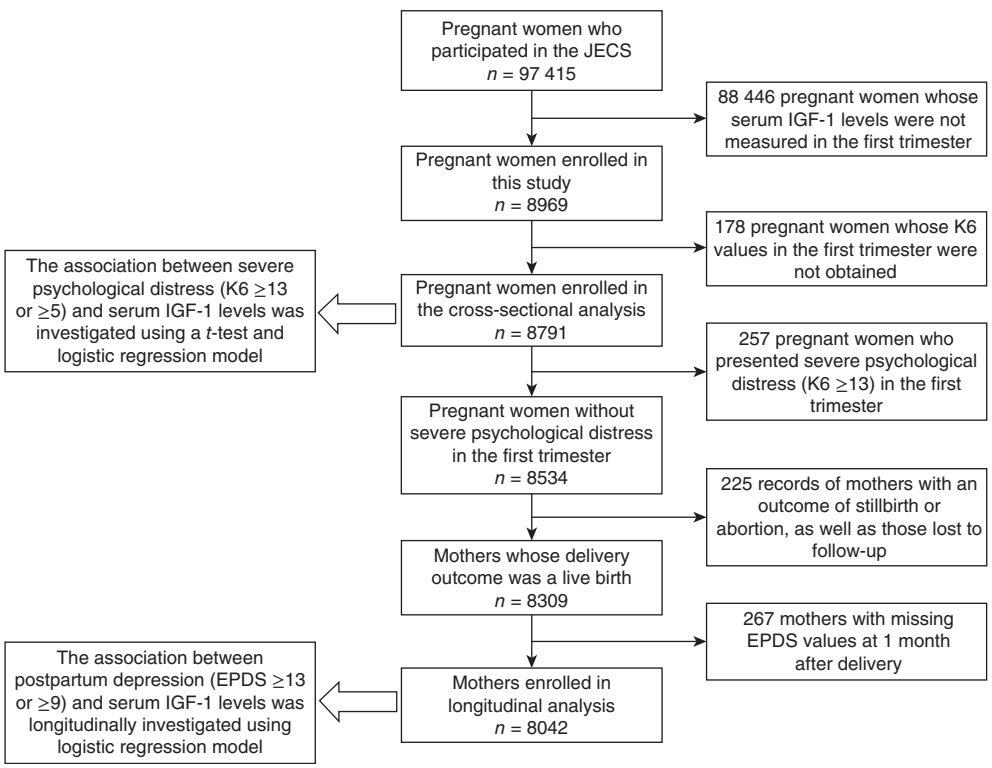

Fig.1 Flow chart showing the process used to select the study participants. EPDS, Edinburgh Postnatal Depression Scale; IGF-1, insulin-like growth factor-1; JECS, Japan Environment and Children's Study; K6, Kessler Psychological Distress Scale.

Table 1. Characteristics of pregnant women in the first trimester of pregnancy

	Pregnant women (n = 8791)		
	K6 ≥ 13	K6 ≤ 12	
	n = 257	n = 8534	
	n (%)	n (%)	P-value
Serum IGF-1 (mean ± SD)	124.8 ± 36.7	119.6 ± 32.5	0.012
Quartile of serum IGF-1 (range)			0.587
Q1 (17–97 ng/mL)	59 (23.0)	2130 (25.0)	
Q2 (98–116 ng/mL)	63 (24.5)	2117 (24.8)	
Q3 (117–138 ng/mL)	61 (23.7)	2143 (25.1)	
Q4 (139–299 ng/mL)	74 (28.8)	2144 (25.1)	
Age, years			<0.001
≤24	49 (19.2)	891 (10.5)	
25–34	171 (67.1)	5612 (66.0)	
≥35	35 (13.7)	1995 (23.5)	
BMI			0.268
≤18.4 kg/m^2	49 (19.6)	1355 (16.2)	
18.5–24.9	173 (69.2)	6158 (73.7)	
≥25.0	28 (11.2)	848 (10.1)	
Smoking status			<0.001
Non-smoker	112 (44.3)	4918 (58.0)	
Ex-smoker (quit before pregnancy)	58 (22.9)	2075 (24.5)	
Ex-smoker (quit during early pregnancy)	59 (23.3)	1077 (12.7)	
Current smoker	24 (9.5)	414 (4.9)	
Alcohol consumption			0.969
Non-drinker	91 (35.5)	2964 (34.8)	
Ex-drinker	140 (54.7)	4720 (55.4)	
Current drinker	25 (9.8)	830 (9.7)	
Education, years			0.029†
≤12	109 (44.0)	2967 (35.7)	
13–16	137 (55.2)	5215 (62.8)	
≥17	2 (0.8)	120 (1.4)	
Parity			0.401
Primiparous	103 (41.2)	3148 (38.4)	
Multiparous	147 (58.8)	5056 (61.6)	
Use of an SSRI	3 (1.2)	12 (0.1)	0.009†
Use of antidepressant medication	2 (0.8)	10 (0.1)	0.046†
Annual household income			0.005
<4 000 000 JPY	115 (49.6)	3148 (40.1)	
≥4 000 000 JPY	117 (50.4)	4702 (59.9)	

†Comparison using Fisher's exact test.
Groups were compared using the t-test and Pearson's χ^2-test for continuous and categorical variables, respectively.
BMI, body mass index; IGF-1, insulin-like growth factor-1; JPY, Japanese yen; K6, Kessler Psychological Distress Scale; Q1, first quartile; Q2, second quartile; Q3, third quartile; Q4, fourth quartile; SSRI, selective serotonin reuptake inhibitor.

Additionally, a sensitivity analysis was performed by changing the cut-off value for psychological distress to K6 score ≥5.[40]

In the longitudinal analyses, participants with severe psychological distress in the first trimester were excluded. Only participants whose delivery outcome was live birth and who had completed the EPDS at 1 month after childbirth were analyzed. Characteristics, including serum IGF-1 levels in the first trimester, were compared among three groups classified according to the EPDS score (≥13/9–12/≤8). The proportions of mothers with postpartum depression were compared among the quartiles of serum IGF-1 levels in the first trimester of pregnancy. Multiple logistic regression models were used to estimate the association of quartiles of serum IGF-1 levels in the first trimester of pregnancy with postpartum depression development at 1 month after childbirth. Here, we adjusted for maternal age, BMI, socioeconomic status, smoking status, alcohol consumption, education, parity, multiple versus singleton birth, sex of the child, gestational age (<37 weeks/37–41 weeks/≥42 weeks), small for gestational age (birth weight below the 10th percentile for babies of the same gestational age), use of SSRI, use of other antidepressant drugs, and K6 score ≥5 in the first trimester. Sensitivity analyses were performed by including mothers with severe psychological distress during pregnancy. Furthermore, all multivariable analyses were performed using serum IGF-1 levels as continuous values. Cases

Table 2. Odds ratios for having severe psychological distress (K6 ≥ 13) during the first trimester of pregnancy (n = 7545)

	Crude OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
Quartile of serum IGF-1 (range)				
Q1 (17–97 ng/mL)	Reference		Reference	
Q2 (98–116 ng/mL)	1.03 (0.69–1.53)	0.902	0.96 (0.64–1.44)	0.846
Q3 (117–138 ng/mL)	1.07 (0.72–1.59)	0.726	1.04 (0.70–1.54)	0.856
Q4 (139–299 ng/mL)	1.27 (0.87–1.86)	0.214	1.19 (0.81–1.75)	0.370
Serum IGF-1 concentration (per 10 ng/mL increase)	1.05 (1.00–1.09)	0.028	1.04 (1.00–1.09)	0.054

Adjusted for maternal age, body mass index, socioeconomic status, smoking status, alcohol consumption, education, parity, multiple versus singleton birth, use of a selective serotonin reuptake inhibitor, and the use of other anti-depressant medication.
CI, confidence interval; IGF-1, insulin-like growth factor-1; K6, Kessler Psychological Distress Scale; OR, odds ratio; Q1, first quartile; Q2, second quartile; Q3, third quartile; Q4, fourth quartile.

Table 3. Proportions of mothers with postpartum depression (EPDS ≥13 or ≥9) according to the quartile of serum IGF-1 in longitudinal analyses (n = 8042)

	EPDS ≥13/≤12			EPDS ≥9/≤8		
	EPDS ≥13, n = 199	EPDS ≤12, n = 7843		EPDS ≥9, n = 917	EPDS ≤8, n = 7125	
Quartile of serum IGF-1 (range)	n (%)	n (%)	*P*-value†	n (%)	n (%)	*P*-value†
Q1 (17–97 ng/mL)	56 (2.8)	1957 (97.2)	0.023	237 (11.8)	1776 (88.2)	0.062
Q2 (98–116 ng/mL)	55 (2.8)	1926 (97.2)		243 (12.3)	1738 (87.7)	
Q3 (117–138 ng/mL)	55 (2.7)	1963 (97.3)		233 (11.5)	1785 (88.5)	
Q4 (139–299 ng/mL)	33 (1.6)	1997 (98.4)		204 (10.0)	1826 (90.0)	

†Cochran–Armitage test for the trend among the quartiles.
EPDS, Edinburgh Postnatal Depression Scale; IGF-1, insulin-like growth factor-1; Q1, first quartile; Q2, second quartile; Q3, third quartile; Q4, fourth quartile.

with missing values were excluded from all analyses. The significance level of all statistical analyses was set at $P < 0.05$. All statistical analyses were performed using R software (Ver. 3.5.0; R Foundation for Statistical Computing, Vienna, Austria).

Results

In this study, serum IGF-1 levels and K6 scores were obtained in the first trimester in 8791 pregnant women (Table 1); among them, 257 (2.9%) women had severe psychological distress in the first trimester. The 25–34-year age group had the highest proportion of pregnant women with severe psychological distress, which accounted for 66.5% and 65.8% of individuals with a K6 score of ≥13 and ≤12, respectively. There was almost no difference in age, BMI, smoking status, or household income between the enrolled and excluded pregnant women (Table S1).

In the first trimester, serum IGF-1 levels were significantly higher in pregnant women with severe psychological distress than in those without (Table 1). After adjusting for covariates, there was no significant association between quartiles of serum IGF-1 concentration and severe psychological distress in pregnant women (Table 2). Additionally, for analysis using serum IGF-1 levels as continuous values, the odds ratio (OR) for having severe psychological distress was 1.04 (95% confidence interval [CI] 1.00–1.09) per 10 ng/mL increase, which was not significant. Sensitivity analyses using a K6 score ≥5 for ≥13 as the cut-off value of psychological distress also revealed no association between serum IGF-1 concentration and psychological distress (Table S2). There were similar serum IGF-1 levels and K6 scores between the pregnant women included and excluded (for missing values) in these analyses; however, there were differences in age and BMI (Table S3).

We excluded pregnant women with severe psychological distress in the first trimester and those whose pregnancy outcome was stillbirth or abortion from the longitudinal analysis. Moreover, we analyzed 8042 pregnant women and observed that the mean serum IGF-1 levels non-significantly decreased with the severity of postpartum depression based on the EPDS score at 1 month after childbirth (Table S4). The proportion of women with an EPDS score ≥13 was significantly lower within higher quartiles of serum IGF-1 levels (Table 3). Additionally, the proportion of women with an EPDS score ≥9 was lower within higher quartiles of serum IGF-1 levels; however, this trend was not significant. In multivariable analysis, mothers in the fourth quartile of serum IGF-1 levels were significantly less likely to develop postpartum depression (EPDS score ≥13 and ≥9) compared with those in the first quartile (OR 0.48, 95% CI 0.30–0.79 and OR 0.76, 95% CI 0.61–0.95, respectively). However, there was a considerably high risk among mothers with a K6 score ≥5 in the first trimester (Table 4). Analysis performed using serum IGF-1 levels as continuous values revealed a significant decrease in the risks for developing postpartum depression with EPDS score ≥13 and ≥9 (OR 0.94, 95% CI 0.89–0.98 and OR 0.97, 95% CI 0.95–0.99 per 10 ng/mL increase, respectively). There was no significant difference in serum IGF-1 levels and EPDS scores between the postpartum women included and excluded (for missing values) in these analyses (Table S5).

Sensitivity analysis of mothers with severe psychological distress during pregnancy revealed that the OR of developing postpartum

Table 4. Odds ratios for postpartum depression (EPDS ≥13 or ≥9) at 1 month after childbirth in 7061 mothers

	EPDS ≥13				EPDS ≥9			
	Crude OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value	Crude OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
Quartile of serum IGF-1 (range)								
Q1 (17–97 ng/mL)	Reference		Reference		Reference		Reference	
Q2 (98–116 ng/mL)	1.02 (0.68–1.53)	0.932	0.93 (0.61–1.41)	0.739	1.10 (0.90–1.35)	0.358	1.03 (0.83–1.28)	0.770
Q3 (117–138 ng/mL)	0.87 (0.58–1.33)	0.524	0.82 (0.54–1.26)	0.372	0.95 (0.77–1.17)	0.656	0.91 (0.73–1.13)	0.381
Q4 (139–299 ng/mL)	0.55 (0.34–0.88)	0.013	0.48 (0.30–0.79)	0.004	0.84 (0.68–1.04)	0.107	0.76 (0.61–0.95)	0.017
K6 score at first-trimester (≥5/≤ 4)	5.84 (4.17–8.17)	<0.001	5.50 (3.91–7.73)	<0.001	4.36 (3.74–5.08)	<0.001	4.17 (3.57–4.87)	<0.001
Serum IGF-1 concentration (per 10 ng/mL increase)	0.95 (0.90–1.00)	0.045	0.94 (0.89–0.98)	0.011	0.98 (0.96–1.00)	0.106	0.97 (0.95–0.99)	0.010
K6 score at first-trimester (≥5/≤4)	5.84 (4.17–8.17)	<0.001	5.55 (3.95–7.79)	<0.001	4.36 (3.74–5.08)	<0.001	4.19 (3.59–4.90)	<0.001

Adjusted for maternal age, body mass index, socioeconomic status, smoking status, alcohol consumption, education, parity, multiple versus singleton birth, sex of the child, gestational age, small for gestational age, use of a selective serotonin reuptake inhibitor, use of other antidepressant medication, and K6 score at first-trimester.

CI, confidence interval; EPDS, Edinburgh Postnatal Depression Scale; K6, Kessler Psychological Distress Scale; IGF-1, insulin-like growth factor-1; OR, odds ratio; Q1, first quartile; Q2, second quartile; Q3, third quartile; Q4, fourth quartile.

depression (EPDS ≥ 13) was 0.56 (95% CI 0.37–0.86) within the fourth quartile of serum IGF-1 levels in the first trimester compared with the first quartile. Additionally, the association remained significant (Table S6).

Discussion

The main findings of this study were that there was no association between serum IGF-1 levels and prenatal psychological distress in the first trimester, but that pregnant women with high serum IGF-1 levels in the first trimester were less likely to develop postpartum depression at 1 month after childbirth. This is indicative of a relationship between elevated serum IGF-1 concentration and depression that changes over time.

Several studies have reported increased serum IGF-1 levels in patients with major depression.[14–16] Levada and Troyan reviewed 23 articles on the association between serum IGF-1 levels and major depression.[41] They observed across-study discrepancies in serum IGF-1 levels in patients with major depression; however, most studies reported higher levels in patients with major depression than those in healthy participants. These discrepancies could be attributed to various factors, including age at onset, disease course, therapy, and general health status.[41, 42] In the present study, univariable analysis showed that the mean serum IGF-1 concentration was higher in pregnant women with severe psychological distress during the first trimester than in those without, which is consistent with previous findings on the association between serum IGF-1 concentration and depression.[14–16] However, there was no significant association between the quartiles of serum IGF-1 concentration and severe psychological distress after adjusting for covariates.

Three longitudinal cohort studies have assessed the association between serum IGF-1 concentration and major depression; however, they were not limited to postpartum depression.[25–27] The English Longitudinal Study of Aging reported by Chigogora *et al*., which enrolled participants aged ≥50 years, reported a U-shaped association of both lower and higher serum IGF-1 levels with an increased risk of subsequent depression.[27] In the Study of Health in Pomerania, which has a mean participant age of 50 years, Sievers *et al*. found that women and men with a serum IGF-1 level below the 10th percentile and above the 90th percentile, respectively, had a higher risk of subsequent depressive disorder compared with those within the 10th to 90th percentile.[25] In the Longitudinal Aging Study Amsterdam, which enrolled patients aged ≥65 years, van Varsseveld *et al*. reported that women with middle-range serum IGF-1 levels had a decreased risk of subsequent minor depression compared with those with high-range levels.[26] Participants in these studies were relatively elderly and had differences compared with those included in our study, which focused on women of reproductive age and postpartum depression. Furthermore, in contrast with our present study, depression onset and initial IGF-1 evaluation in the previous studies often had a considerable time difference. Contrastingly, our results showed that women with high serum IGF-1 levels were less likely to develop postpartum depression after adjusting for covariates including psychological distress in the first trimester. This is consistent with the results of the Study of Health in Pomerania.[25] Additionally, the mean serum IGF-1 levels in the first trimester numerically, but not significantly, decreased with depression severity based on the EPDS score at 1 month after childbirth. This study demonstrated the longitudinal association between serum IGF-1 levels during pregnancy and postpartum depression development.

Almost all the IGF-1 in circulation is bound to IGFBP, which regulate IGF-1 binding to the IGF-1 receptor.[19] Although serum IGFBP-1 levels are known to increase during pregnancy,[21] we did not measure them. In an experimental study using mice, Kondo *et al*. reported that a serotonin type 3 receptor (5HT3R) regulates hippocampal extracellular IGF-1 levels and that 5HT3R-dependent hippocampal neurogenesis is mediated by increased IGF-1 levels.[43] Moreover, there have been several reports indicating the antidepressant-like effects of subcutaneous or

intracerebroventricular administration of IGF-1 in mice.[22–24] However, IGF-1 can cross the blood–brain barrier[44] and is rapidly cleared from cerebrospinal fluid.[45] Therefore, the association between serum and intracerebral IGF-1 levels remains unclear.

Maternal plasma levels of estradiol are known to increase by 100-fold during pregnancy and then rapidly decrease within a few days after childbirth.[46] The neurobiological effect of such steroid withdrawal could predispose one to postpartum depression development.[2] Treatment with estradiol has been found to have a biphasic effect on IGF-I levels in females.[35] In the central nervous system, interactions between estradiol and IGF-1 signaling have been observed in various neural functions.[47] Numerous neurons and glial cells co-express estrogen and IGF-1 receptors; further, IGF-1 receptor activity regulates estrogen receptor expressions in the rat brain.[45] Munive *et al*. recently reported that mood regulation through exercise is involved in the interaction between estradiol and IGF-1 in mice.[48] In this study, the association between serum IGF-1 concentration and depression status changed over time. The interaction between IGF-1 and estrogen may change before and after childbirth due to decreases in estrogen levels. Our findings may be derived from the estrogen-mediated effects of IGF-1. However, we did not measure estrogen levels. The role of estrogen during pregnancy and postpartum should be further evaluated.

This is the first study to investigate the longitudinal association of serum IGF-1 levels with postpartum depression using data from a large-scale nationwide birth cohort study. However, despite including a relatively uniform population of pregnant women, this study has several limitations. First, among the 97 415 pregnant women enrolled in the JECS, this was study was limited to include 8791 pregnant women with measured serum IGF-1 levels and available K6 scores. However, there was almost no difference in age, BMI, smoking status, alcohol consumption, education, parity, or household income between the enrolled and excluded pregnant women (Table S1). Second, data regarding severe psychological distress during pregnancy and postpartum depression after childbirth were obtained from responses to self-administered questionnaires (the K6 and EPDS). Therefore, these states may not have been objectively evaluated and did not amount to a clinical diagnosis of depression. However, the K6 and EPDS are commonly used and widely accepted tools with numerous reports on their validity and cut-off points.[30, 32–34, 36–39, 49] Finally, our study design precluded the clarification of the relationship between serum IGF-1 concentration and several other hormones associated with postpartum depression or serum IGF-1 levels, including estrogen,[13, 50] cortisol,[51] melatonin,[52] thyroid hormone,[53, 54] and growth hormone.[17] There is a need for further studies to confirm these associations.

In conclusion, compared with pregnant women with low serum IGF-1 levels in the first trimester, those with high levels are less likely to develop postpartum depression. Our findings suggest that a high serum IGF-1 concentration in the first trimester helps to protect against postpartum depression development. Serum IGF-1 levels in the first trimester may serve as a predictor of the risk of developing postpartum depression.

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Disclosure statement

All authors declare that they have no conflicts of interest.

Author contributions

S.A. conceptualized the study. H.T., H.Sa., H.Sh., and M.S. contributed to collect the data. S.A. analyzed the data and drafted the initial manuscript. M.S. assisted in the data analyses and critically revised the manuscript. All authors participated in result interpretation; moreover, they reviewed and approved the final version of the manuscript.

References

1. Vesga-López O, Blanco C, Keyes K, Olfson M, Grant BF, Hasin DS. Psychiatric disorders in pregnant and postpartum women in the United States. *Arch. Gen. Psychiatry* 2008; **65**: 805–815.
2. O'Hara MW, Wisner KL. Perinatal mental illness: Definition, description and aetiology. *Best Pract. Res. Clin. Obstet. Gynaecol.* 2014; **28**: 3–12.
3. Baker R, Orton E, Kendrick D, Tata LJ. Maternal depression in the 5 years after childbirth among women with and without perinatal depression: A population-based cohort study. *Lancet* 2015; **386**: S22.
4. Howard LM, Molyneaux E, Dennis C-L, Rochat T, Stein A, Milgrom J. Non-psychotic mental disorders in the perinatal period. *Lancet* 2014; **384**: 1775–1788.
5. Stein A, Pearson RM, Goodman SH *et al*. Effects of perinatal mental disorders on the fetus and child. *Lancet* 2014; **384**: 1800–1819.
6. Tikotzky L. Postpartum maternal sleep, maternal depressive symptoms and self-perceived mother-infant emotional relationship. *Behav. Sleep Med.* 2016; **14**: 5–22.
7. Sword W, Landy CK, Thabane L *et al*. Is mode of delivery associated with postpartum depression at 6 weeks: A prospective cohort study. *BJOG* 2011; **118**: 966–977.
8. Dennis C-L, Dowswell T. Psychosocial and psychological interventions for preventing postpartum depression. *Cochrane Database Syst. Rev.* 2013; **28**: CD001134.
9. Katon W, Russo J, Gavin A. Predictors of postpartum depression. *J. Womens Health* 2014; **23**: 753–759.
10. Paschetta E, Berrisford G, Coccia F *et al*. Perinatal psychiatric disorders: An overview. *Am. J. Obstet. Gynecol.* 2014; **210**: 501–509.
11. Gaillard A, Le Strat Y, Mandelbrot L, Keïta H, Dubertret C. Predictors of postpartum depression: Prospective study of 264 women followed during pregnancy and postpartum. *Psychiatry Res.* 2014; **215**: 341–346.
12. O'hara MW, Mccabe JE. Postpartum depression: Current status and future directions. *Annu. Rev. Clin. Psychol.* 2013; **9**: 379–407.
13. Ahokas A, Kaukoranta J, Wahlbeck K, Aito M. Estrogen deficiency in severe postpartum depression: Successful treatment with sublingual physiologic 17beta-estradiol: A preliminary study. *J. Clin. Psychiatry* 2001; **62**: 332–336.
14. Deuschle M, Blum WF, Strasburger CJ *et al*. Insulin-like growth factor-I (IGF-I) plasma concentrations are increased in depressed patients. *Psychoneuroendocrinology* 1997; **22**: 493–503.
15. Lesch KP, Rupprecht R, Müller U, Pfüller H, Beckmann H. Insulin-like growth factor I in depressed patients and controls. *Acta Psychiatr. Scand.* 1988; **78**: 684–688.
16. Franz B, Buysse DJ, Cherry CR *et al*. Insulin-like growth factor 1 and growth hormone binding protein in depression: A preliminary communication. *J. Psychiatr. Res.* 1999; **33**: 121–127.
17. Denley A, Cosgrove LJ, Booker GW, Wallace JC, Forbes BE. Molecular interactions of the IGF system. *Cytokine Growth Factor Rev.* 2005; **16**: 421–439.
18. Juul A. Serum levels of insulin-like growth factor I and its binding proteins in health and disease. *Growth Horm. IGF Res.* 2003; **13**: 113–170.
19. Allard JB, Duan C. IGF-binding proteins: Why do they exist and why are there so many? *Front. Endocrinol.* 2018; **9**: 117.
20. Szczęsny E, ⊠lusarczyk J, Głombik K *et al*. Possible contribution of IGF-1 to depressive disorder. *Pharmacol. Rep.* 2013; **65**: 1622–1631.
21. Åsvold BO, Eskild A, Jenum PA, Vatten LJ. Maternal concentrations of insulin-like growth factor I and insulin-like growth factor binding protein

1 during pregnancy and birth weight of offspring. *Am. J. Epidemiol.* 2011; **174**: 129–135.
22. Hoshaw BA, Malberg JE, Lucki I. Central administration of IGF-I and BDNF leads to long-lasting antidepressant-like effects. *Brain Res.* 2005; **1037**: 204–208.
23. Hoshaw BA, Hill TI, Crowley JJ *et al*. Antidepressant-like behavioral effects of IGF-I produced by enhanced serotonin transmission. *Eur. J. Pharmacol.* 2008; **594**: 109–116.
24. Park S-E, Dantzer R, Kelley KW, McCusker RH. Central administration of insulin-like growth factor-I decreases depressive-like behavior and brain cytokine expression in mice. *J. Neuroinflammation* 2011; **8**: 12.
25. Sievers C, Auer MK, Klotsche J *et al*. IGF-I levels and depressive disorders: Results from the Study of Health in Pomerania (SHIP). *Eur. Neuropsychopharmacol.* 2014; **24**: 890–896.
26. van Varsseveld NC, van Bunderen CC, Sohl E *et al*. Serum insulin-like growth factor 1 and late-life depression: A population-based study. *Psychoneuroendocrinology* 2015; **54**: 31–40.
27. Chigogora S, Zaninotto P, Kivimaki M, Steptoe A, Batty GD. Insulin-like growth factor 1 and risk of depression in older people: The English Longitudinal Study of Ageing. *Transl. Psychiatry* 2016; **6**: e898.
28. Kawamoto T, Nitta H, Murata K *et al*. Rationale and study design of the Japan Environment and Children's Study (JECS). *BMC Public Health* 2014; **14**: 25.
29. Michikawa T, Nitta H, Nakayama SF *et al*. Baseline profile of participants in the Japan Environment and Children's Study (JECS). *J. Epidemiol.* 2018; **28**: 99–104.
30. Kessler RC, Andrews G, Colpe LJ *et al*. Short screening scales to monitor population prevalences and trends in non-specific psychological distress. *Psychol. Med.* 2002; **32**: 959–976.
31. Furukawa TA, Kawakami N, Saitoh M *et al*. The performance of the Japanese version of the K6 and K10 in the World Mental Health Survey Japan. *Int. J. Methods Psychiatr. Res.* 2008; **17**: 152–158.
32. Mitchell CM, Beals J. The utility of the Kessler Screening Scale for Psychological Distress (K6) in two American Indian communities. *Psychol. Assess.* 2011; **23**: 752–761.
33. Kang Y, Guo W, Xu H *et al*. The 6-item Kessler Psychological Distress Scale to survey serious mental illness among Chinese undergraduates: Psychometric properties and prevalence estimate. *Compr. Psychiatry* 2015; **63**: 105–112.
34. Fushimi M, Saito S, Shimizu T, Kudo Y, Seki M, Murata K. Prevalence of psychological distress, as measured by the Kessler 6 (K6), and related factors in Japanese employees. *Community Ment. Health J.* 2012; **48**: 328–335.
35. Juul A. Serum levels of insulin-like growth factor I and its binding proteins in health and disease. *Growth Horm. IGF Res.* 2003; **13**: 113–170.
36. Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. *Br. J. Psychiatry* 1987; **150**: 782–786.
37. Nelson DB, Freeman MP, Johnson NL, McIntire DD, Leveno KJ. A prospective study of postpartum depression in 17 648 parturients. *J. Matern. Fetal Neonatal Med.* 2013; **26**: 1155–1161.
38. Banti S, Mauri M, Oppo A *et al*. From the third month of pregnancy to 1 year postpartum. Prevalence, incidence, recurrence, and new onset of depression. Results from the Perinatal Depression–Research & Screening Unit study. *Compr. Psychiatry* 2011; **52**: 343–351.
39. Okano T, Murata M, Masuji F. Validation and reliability of Japanese version of the EPDS. *Arch. Psychiatr. Diag. Clin. Eval.* 1996; **7**: 525–553.
40. Sakurai K, Nishi A, Kondo K, Yanagida K, Kawakami N. Screening performance of K6/K10 and other screening instruments for mood and anxiety disorders in Japan. *Psychiatry Clin. Neurosci.* 2011; **65**: 434–441.
41. Levada OA, Troyan AS. Insulin-like growth factor-1: A possible marker for emotional and cognitive disturbances, and treatment effectiveness in major depressive disorder. *Ann. Gen. Psychiatry* 2017; **16**: 38.
42. Sharma AN, da Costa e Silva BF, Soares JC, Carvalho AF, Quevedo J. Role of trophic factors GDNF, IGF-1 and VEGF in major depressive disorder: A comprehensive review of human studies. *J. Affect. Disord.* 2016; **197**: 9–20.
43. Kondo M, Koyama Y, Nakamura Y, Shimada S. A novel 5HT3 receptor–IGF1 mechanism distinct from SSRI-induced antidepressant effects. *Mol. Psychiatry* 2018; **23**: 833–842.
44. Pan W, Kastin AJ. Interactions of IGF-1 with the blood-brain barrier in vivo and in situ. *Neuroendocrinology* 2000; **72**: 171–178.
45. Nagaraja TN, Patel P, Gorski M, Gorevic PD, Patlak CS, Fenstermacher JD. In normal rat, intraventricularly administered insulin-like growth factor-1 is rapidly cleared from CSF with limited distribution into brain. *Cerebrospinal Fluid Res.* 2005; **2**: 5.
46. Trotter A, Maier L, Pohlandt F. Management of the extremely preterm infant: Is the replacement of estradiol and progesterone beneficial? *Paediatr. Drugs* 2001; **3**: 629–637.
47. Garcia-Segura LM, Arevalo MA, Azcoitia I. Interactions of estradiol and insulin-like growth factor-I signalling in the nervous system: New advances. *Prog. Brain Res.* 2010; **181**: 251–272.
48. Munive V, Santi A, Torres-Aleman I. A concerted action of estradiol and insulin like growth factor 1 underlies sex differences in mood regulation by exercise. *Sci. Rep.* 2016; **6**: 1–10.
49. El-Den S, O'Reilly CL, Chen TF. A systematic review on the acceptability of perinatal depression screening. *J. Affect. Disord.* 2015; **188**: 284–303.
50. Bloch M, Schmidt PJ, Danaceau M, Murphy J, Nieman L, Rubinow DR. Effects of gonadal steroids in women with a history of postpartum depression. *Am. J. Psychiatry* 2000; **157**: 924–930.
51. de Rezende MG, Garcia-Leal C, de Figueiredo FP *et al*. Altered functioning of the HPA axis in depressed postpartum women. *J. Affect. Disord.* 2016; **193**: 249–256.
52. Parry BL, Meliska CJ, Sorenson DL *et al*. Plasma melatonin circadian rhythm disturbances during pregnancy and postpartum in depressed women and women with personal or family histories of depression. *Am. J. Psychiatry* 2008; **165**: 1551–1558.
53. Lucas A, Pizarro E, Granada ML, Salinas I, Sanmartí A. Postpartum thyroid dysfunction and postpartum depression: Are they two linked disorders? *Clin. Endocrinol. (Oxf)* 2001; **55**: 809–814.
54. Völzke H, Friedrich N, Schipf S *et al*. Association between serum insulin-like growth factor-I levels and thyroid disorders in a population-based study. *J. Clin. Endocrinol. Metab.* 2007; **92**: 4039–4045.

Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1 Comparison of characteristics between the enrolled and excluded mothers.

Table S2. Odds ratios for having psychological distress (K6 ≥ 5) during the first trimester of pregnancy (n = 7545).

Table S3. Comparison of the pregnant women included and excluded in the cross-sectional multivariable analysis.

Table S4. Characteristics of postpartum women according to the Edinburgh Postnatal Depression Scale (EPDS) score at 1 month after childbirth.

Table S5. Comparison of mothers included and excluded in the longitudinal multivariable analysis.

Table S6. Odds ratios for developing postpartum depression (Edinburgh Postnatal Depression Scale score ≥ 13) at 1 month after childbirth in 7264 mothers, including participants with severe psychological distress in the first trimester.