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, 8,791 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.

http://onlinelibrary.wiley.com/doi/10.1111/pcn.13200/full

Postpartum depression is common with an approximate occurrence rate of 10% in new mothers.1–3 Postpartum depression can become prolonged4 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.7 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, 9–10 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, 14

Increased insulin-like growth factor-1 (IGF-1) levels have been reported in persons with severe depression15–16; 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), 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. 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 87,91 pregnant women with available Kessler Psychological Distress Scale (K6) scores 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, was collected using a self-administered questionnaire during the first trimester. The K6 performs well in detecting mood and anxiety disorders. We dichotomized the pregnant women into groups with (K6 ≥12) and without (K6 <12) severe psychological distress. The following factors possibly associated with serum IGF-1 levels or depression 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]/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) score was collected using a questionnaire. Subsequently, the mothers were classified into the postpartum depression group (EPDS ≥13) 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.

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.
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 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)    |                                     |         |
| Q1 (17–97 ng/mL)                   | 59 (23.0)                           | 2130 (25.0) | 0.587   |
| 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/m²                        | 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 χ²-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.
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 \( \geq 13 \) and \( \leq 12 \), 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 \( \geq 5 \) for \( \geq 13 \) 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 \( \geq 13 \) was significantly lower within higher quartiles of serum IGF-1 levels (Table 3). Additionally, the proportion of women with an EPDS score \( \geq 9 \) 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 \( \geq 13 \) and \( \geq 9 \) 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 \( \geq 5 \) 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 \( \geq 13 \) and \( \geq 9 \) (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 2. Odds ratios for having severe psychological distress (K6 \( \geq 13 \)) during the first trimester of pregnancy (n = 7545)

| Quartile of serum IGF-1 (range) | Crude OR (95% CI) | P-value | Adjusted OR (95% CI) | P-value |
|--------------------------------|------------------|--------|----------------------|--------|
| 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 \( \geq 13 \) or \( \geq 9 \)) according to the quartile of serum IGF-1 in longitudinal analyses (n = 8042)

| Quartile of serum IGF-1 (range) | EPDS \( \geq 13 \) \( \leq 12 \) (n = 199) | EPDS \( \geq 13 \) \( \leq 12 \) (n = 7843) | EPDS \( \geq 9 \) \( \leq 8 \) (n = 917) | EPDS \( \leq 8 \) \( n = 7125 \) | P-value |
|--------------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|--------|
| Q1 (17–97 ng/mL)               | 56 (2.8)                       | 1957 (97.2)                    | 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)                    |        |

\(^\dagger\)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.
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. Levada and Troyan reviewed 23 articles on the association between serum IGF-1 levels and major depression. 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. 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. 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. 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. 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. 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. 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. 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 regulates IGF-1 binding to the IGF-1 receptor. Although serum IGFBP-1 levels are known to increase during pregnancy, 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. Moreover, there have been several reports indicating the antidepressant-like effects of subcutaneous or

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

| Quartile of serum IGF-1 (range) | EPDS ≥13 |  | EPDS ≥9 |  |
|-------------------------------|---------|---|---------|---|
| Crude OR (95% CI) | Adjusted OR (95% CI) | P-value | Crude OR (95% CI) | Adjusted OR (95% CI) | P-value |
| Q1 (17–97 ng/mL) | Reference | 1.02 (0.68–1.53) | 0.932 | 0.784 | 0.395 |
| Q2 (98–116 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 |
| Q3 (117–138 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 |
| Q4 (139–299 ng/mL) | 5.84 (4.17–8.17) | <0.001 | 5.50 (3.91–7.73) | <0.001 | 4.36 (3.74–5.08) | <0.001 |
| K6 score at first-trimester (≥5/≤4) | 0.95 (0.90–1.00) | 0.045 | 0.94 (0.89–0.98) | 0.011 | 0.98 (0.96–1.00) | 0.106 |
| Serum IGF-1 concentration (per 10 ng/mL increase) | 5.84 (4.17–8.17) | <0.001 | 5.55 (3.95–7.79) | <0.001 | 4.36 (3.74–5.08) | <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.
intraarrestocentral administration of IGF-1 in mice. However, IGF-1 can cross the blood–brain barrier and is rapidly cleared from cerebrospinal fluid. 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. The neurobiological effect of such steroid withdrawal could predispose one to postpartum depression development. Treatment with estrogen has been found to have a biphasic effect on IGF-1 levels in females. In the central nervous system, interactions between estrogen and IGF-1 signaling have been observed in various neural functions. 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. Munive et al. recently reported that mood regulation through exercise is involved in the interaction between estrogen and IGF-1 in mice. 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 study was limited to include only 8,791 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 were not reported 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. 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, corticosteroid, melatonin, thyroid hormone, and growth hormone. 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 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.

Acknowledgments
The authors would like to express our gratitude to all participants and cooperating health care providers in the JECS. Members of the JECS Group as of 2020: Michihiro Kamiijima (principal investigator, Nagoya City University, Nagoya, Japan), Shin Yamazaki (National Institute for Environmental Studies, Tsukuba, Japan), Yukihiro Ohya (Nagoya City University, Nagoya, Japan), Keiichi Kishii (Hokkaido University, Sapporo, Japan), Nobuo Yagashii (Takane University, Sendai, Japan), Koichi Hashimoto (Fukuoka Medical University, Fukuoka, Japan), Chisato Mori (Chiba University, Chiba, Japan), Shinzo Itsuori (Yokohama City University, Yokohama, Japan), Zentaro Yamagata (University of Yamanashi, Chuo, Japan), Hidekuni Inadera (University of Toyama, Toyama, Japan), Takeo Nakayama (Kanto University, Japan), Hiroe Iso (Osaka University, Suita, Japan), Masayuki Shima (Hyogo College of Medicine, Nishinomiya, Japan), Youichi Kurozawa (Tottori University, Tottori, Japan), Narufumi Suganuma (Kochi University, Nankoku, Japan), Koichi Kusuhara (University of Occupational and Environmental Health, Kitakyushu, Japan), and Takahiko Kata (Kumamoto University, Kumamoto, Japan). The JECS was funded by the Ministry of the Environment of Japan. The findings and conclusions of this article are solely the responsibility of the authors and do not represent the official views of the above organization.

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.

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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.