**Title page**

**Title**

Association between maternal antenatal depression and infant development: a hospital-based prospective cohort study

**Names and Affiliations of Authors**

Yuko Otake[a], Sonomi Nakajima[b], Akiko Uno[c], Shizue Kato[c], Seiko Sasaki[c], Eiji Yoshioka[d], Tamiko Ikeno[a], Reiko Kishi[a]

[a]Centre for Environmental and Health Science, Hokkaido University, Sapporo, Japan; [b]Department of Occupational Therapy, Sapporo Medical University School of Sciences, Sapporo, Japan; [c]Department of Public Health, Hokkaido University Graduate School of Medicine, Sapporo, Japan; [d]Division of Community Medicine and Epidemiology, Department of Health Science, Asahikawa Medical University, Asahikawa, Japan.

**Address correspondence to**

Reiko Kishi, Centre for Environmental and Health Science, Hokkaido University, North 12, West 7, Kita-ku, Sapporo, 060-0812, Japan

TEL: +81-(0)11-706-4747, Fax: +81-(0)11-706-4725

E-mail: rkishi@med.hokudai.ac.jp

**Keywords**

Maternal depression, pregnancy, infant development, gestational age, cohort study

## Abstract

**Objective:** To examine the association between antenatal depression and infant development after controlling for sufficient confounders.

**Methods:** A hospital-based prospective cohort study (Hokkaido Study on Environment and Children's Health) was conducted between July, 2002 and October, 2005, in Sapporo, Japan. Out of 309 mothers who delivered at Sapporo Toho Hospital during the study period and who agreed with the assessment of depression, 154 mother-infant pairs were eligible in the final analysis. Antenatal depression was assessed between the $2^{nd}$-$3^{rd}$ trimesters using the Edinburgh Postnatal Depression Scale (EPDS), and infant development was assessed at 6 months by Bayley Scales of Infant Development II (BSID-II). Potential confounders including socioeconomic status, birth complications, postnatal depression and childcare environment were obtained from medical records and self-administered questionnaires. A series of linear regression analyses was conducted using the EPDS total score as an independent variable and BSID-II as dependent variables, adjusting confounders.

**Results:** Nine women (5.8%) were considered antenatally depressed in this cohort. Based on a series of linear regression analyses, the study identified that antenatal EPDS was significantly related to shorter gestational age ($\beta = -0.25$, 95% CI [−1.20, −0.17]), and shorter gestational age was significantly related to lower BSID-II (mental development) score ($\beta =$ 0.23, 95% CI [0.00, 0.00]).

**Conclusions:** Gestational age was an important confounder in the association between maternal antenatal depression and infant development. A delay in infant development may be related to a shorter gestational period caused by maternal depression during pregnancy.

## Text

## Introduction

The relationship between maternal psychological distress during pregnancy and infant development has increasingly been recognised, and various studies have been conducted using animal models, human physiology, and epidemiology.

Animal experiments suggest that maternal stress during pregnancy is associated with alterations in brain function and behaviour in infants. The fetuses of mothers that experience stress show alterations in activation of the hypothalamic-pituitary-adrenal (HPA) axis and in brain function compared to fetuses of non-stressed mothers [1, 2]. According to a review of animal experiments, infants born to rodent mothers exposed to antenatal stress demonstrated more problems in learning behaviour than infants of non-stressed mothers [3].

Physiological mechanisms in humans have been proposed by several researchers [2-4]. Antenatal anxiety appears to raise uterine artery resistance, which can influence fetal development and infant birth weight [3]. The psychological status of pregnant women is known to alter the intrauterine environment and fetal HPA axis function, which influences longitudinal behavioural and psychological development of infants after birth [2,4].

Given these observations, epidemiological studies on human populations have been launched in recent years [5-7]. For example, one report from a large cohort study, the Avon Longitudinal Study of Parents and Children (ALSPAC) [6], indicated that antenatal

depression influences child development independently of postnatal depression. The ALSPAC study also found that anxiety during pregnancy continues to affect child development four years after birth [7]. Another study exploring mothers who were pregnant at the time of a tornado disaster in Canada revealed the impact of strong objective stress during pregnancy on the IQ and language capability of infants [5]. Even though exposures to maternal antenatal depression, stress, and anxiety are supposed to be correlated to one another, our current study focused especially on depression during pregnancy because investigation on antenatal depression in relation to infant development is less common, therefore is more required, than those examining other maternal psychological factors [7-9].

Previous studies examining antenatal depression and infant development have had two important problems: contradictory findings and the omission of confounding factors related to child rearing. Although some studies have insisted that antenatal depression is related to lower infant development scores that indicate a developmental delay [6, 10], others have related antenatal depression to higher performance on infant development tests [11] or have shown no correlation with infant development [12]. The ALSPAC study [6] and the study by DiPietro et al [11]. reported contradictory effects of antenatal depression, despite the fact that both studies were conducted using prospective birth cohorts and applied globally standardised measures, including the Edinburgh Postnatal Depression Scale (EPDS) or the Center for Epidemiologic Studies Depression Scale (CES-D) for maternal depression, and the Denver Developmental

Screening Test (DDST) or the Bayley Scales of Infant Development II (BSID-II) for assessing infant development. Although the study population of the ALSPAC was large (9244 women), the study had limitations, such as the small number of depressed mothers and the use of maternal self-reporting to assess infant development [6]. Even though DiPietro et al. used structured assessment to avoid the problem of self-reporting, the number of participants was much smaller (94), which limited the study's statistical power [11].

In addition, confounding factors were not sufficiently controlled for in previous studies. Previous researchers controlled for diverse maternal and infant factors, including antenatal and postnatal maternal psychological distress, maternal smoking during pregnancy, maternal age, maternal educational level, infant birth weight and gender, and infant age at the time of developmental assessment [6, 10-12]. However, these studies did not consider differences in the rearing attitude of the parents or in the home environment. Infant development is strongly influenced by interactions between the infant and the stimuli surrounding them. For example, mother-child interactions and maltreatment are well-known factors in infant development [13-15]. When infants fail to obtain appropriate stimulation from their care givers, developmental problems typically result. Therefore, examination of child rearing factors as confounders during the postnatal period is necessary.

Given these two principal limitations to previous studies, the purpose of our current study was to examine the association between antenatal depression and infant development while

103 controlling for childcare factors in addition to other confounders considered in previous
104 studies.
105
106 **Methods**
107 *Study design and population*
108 A prospective cohort study was carried out between July, 2002 and October, 2005 at the
109 Sapporo Toho Hospital in Hokkaido, Japan (Hokkaido Study on Environment and Children's
110 Health). Pregnant women who were at 23-35 weeks of gestation during a routine
111 gynaecological check-up in this study period were recruited as study participants. All
112 participants were native Japanese and were residents of Sapporo or surrounding areas. Of
113 1,796 potentially eligible women, 514 agreed to participate in Hokkaido Study (Fig. 1; 30%
114 participation rate).
115 Assessment of depression during pregnancy was conducted between October, 2002 and
116 April, 2004 as a nested cohort study within Hokkaido Study. Pregnant women who were
117 recruited to Hokkaido Study during this period were involved in the assessment of antenatal
118 depression, and 309 women completed questionnaires (60% of initial cohort). Postnatal
119 depression was assessed in 267 mothers between 1 and 4 months after delivery, and infant
120 development was evaluated in 154 mother-infant pairs during the period from 5 months and
121 16 days up to 6 months and 15 days after birth (50 % follow-up rate). Excluded participants

were those who did not complete the protocol due to miscarriage, stillbirth, multiple birth, relocation, death of the infant, or voluntary withdrawal from the study. Statistical analysis was conducted for 154 mother-infant pairs.

*Exposure measure*

The Edinburgh Postnatal Depression Scale (EPDS) was applied to evaluate the incidence of antenatal depression, and pregnant women in 23-35 weeks of gestation were required to fill in the EPDS questionnaire when they were recruited. We assessed maternal depression between the second and third trimesters since it is the period for fetal development and previous studies also collected maternal psychological distress during the same period [6, 11-12]. The EPDS is a widely used self-rating questionnaire [18] and it has been used during the antenatal period even though originally developed as a screening tool for maternal depression following childbirth [6]. Because the validity and reliability of the EPDS in Japanese women has been investigated [19], it has been commonly used for screening of postnatal depression in Japanese community settings. The EPDS is composed of ten questions evaluating depressive symptoms. Women rate their feelings over the previous seven days using a score from 0 to 30. The standardised cutoff of 8/9 for Japanese women was applied (discriminating 9 or higher as depressed [19]), because Japanese women tend to score modestly compared to English women, for whom the suggested cutoff is 12/13 [18].

*Outcome measure*

Infant development was assessed at 6 months after birth using the Bayley Scales of Infant Development II (BSID-II) [20], one of the most widely used and validated assessment tools for preschool children. Because BSID-II is not standardised in Japan, we translated a BSID-II manual in consultation with a manual for BSID, which has been used in the Hokkaido Study [21]. The validity of the BSID-II toward Japanese infants was previously evaluated by referring to the Denver Developmental Screening Test (DDST) [22], and was used in an analysis of the Hokkaido Study to assess the effects of antenatal exposure to PCBs and dioxins on infant development [21]. The BSID-II consists of a mental development index (MDI) for assessing cognitive, language, and personal/social development, and a psychomotor development index (PDI) for assessing fine and gross motor development. MDI and PDI scores range from 50 to 150. In the United States, a mean value of 100 has been established as the cutoff point for each. However, because the cutoff for Japanese infants requires further investigation [23], we used the total PDI and MDI scores in our current study.

For the assessment, infants were brought to the community centre in Sapporo, where they were tested in a quiet private room in the presence of one or both parents. Each evaluation was performed by one of three occupational therapists with clinical experience in the field of developmental disabilities. The examiners were unaware of the antenatal EPDS scores of the

mothers. In all cases, scoring was performed first by the examiner who performed the examination, and then double-checked by the two other examiners based on a video recording of the examination. The final score was decided through discussion and agreement by all three examiners.

*Confounder measures*

*Characteristics of participants.* Participants completed a self-administered questionnaire at the time of recruitment (during 23-35 weeks of gestation). The questionnaire included information related to maternal smoking, caffeine intake, alcohol intake, drug use, working status during pregnancy, educational level of both parents, and household income. Information on the anamnesis of thyroid disease and mental illness was also obtained through the questionnaire. Maternal smoking was categorised as either “no” (non-smokers who did not smoke throughout pregnancy or who quit smoking during the first trimester) or “yes” (smokers who continued to smoke during pregnancy, including women who quit after the first trimester). Modified self-administered questionnaires described by Nagata et al [16, 17]. were used to estimate caffeine and alcohol intake, respectively. Drug use and anamnesis of parents included medication taken at the time of study and complete disease history. Perinatal information was obtained from obstetrical records and included age of parents at childbirth, pregnancy complications, gestational age, and infant sex, parity, disease, birth weight, and

179 birth size (length, head circumference, and chest circumference). Information on maternal
180 working status at 6 months after delivery was inquired based on self-reported questionnaire at
181 6-month infant assessment.

182 *Maternal psychological status before and during pregnancy.* At the time of recruitment,
183 pregnant women were also asked to fill in self-rating questionnaires which were originally
184 developed to ask other psychological status before and during pregnancy. Women gave
185 answers of "yes" or "no" to questions about (a) stressful life events during the year before
186 pregnancy ("Have you experienced stressful life events during the past year?"); (b) maternal
187 neuroses, including past depressive symptoms ("Have you felt continuous depression or
188 unhappiness every day for more than 2 weeks before pregnancy?"), worrying ("Do you think
189 of yourself as a worrier?"), and obsessiveness ("Do you think of yourself as obsessive?"); and
190 (c) readiness for pregnancy, including planned pregnancy ("Did you plan to be pregnant?") as
191 well as wanted pregnancy ("Did you want to be pregnant?").

192 *Maternal postnatal depression.* The EPDS was used to evaluate postpartum depression,
193 and was mailed to mothers at 1 month after delivery and returned by the end of 4 months.

194 *Childcare environment.* The self-rating questionnaire of the Evaluation of Environmental
195 Stimulation (EES) was used to evaluate the childcare environment. Mothers were asked to
196 answer the questionnaire in the 6-month assessment period for infant development. The EES
197 was devised based on the Home Observation for Measurement of the Environment (HOME)

198 [24] and the Home Screening Questionnaire (HSQ) [25] as adapted for Japanese cultural and
199 social contexts of the childcare environment [26]. The EES is composed of 30 items
200 comprising six subscales, including “humanistic involvement” (varied involvement in daily
201 life, scored 0–9), “responsiveness” (maternal response to the child, scored 0–2), “avoidance
202 of restriction and punishment” (avoidance of neglect of infant, scored 0–1), “physical
203 involvement” (appropriate maternal physical stimulus of the infant, scored 0–4), “social
204 involvement” (opportunities for social interaction outside the home, scored 0–6),
205 “organisation of the environment” (organisation of the physical environment, scored 0–3),
206 and “social support” (social support in child rearing, scored 0–5). Higher scores indicate
207 better childcare environments.
208
209 *Statistical analysis*
210 A series of univatriable and multivariable analyses was conducted through the following
211 procedure; (1) in order to detect confounding variables that is possibly correlated to maternal
212 depression during pregnancy, univariable analyses exploring correlation between the antenatal
213 EPDS score and potential confounders (factors adjusted in previous studies including
214 characteristics of mothers, fathers, infants, and childcare environments) were carried out using
215 Spearman’s correlation test, Mann-Whitney U test, and Kraskal-Wallis test, (2) the same
216 nonparametric tests were conducted between BSID-II scores (MDI, PDI) and potential

217 confounders so that confounders possibly in relation to infant development were detected, (3)
218 for the purpose of identifying correlation between maternal antenatal depression and infant
219 development, univariable analyses using Spearman's correlation test and Mann-Whitney U
220 test were carried out, and (4) as a final justification, multivariable analyses entering the
221 antenatal EPDS score as an independent variable and the MDI and PDI scores as outcome
222 variables were conducted with and without adjusting for confounders which indicated a
223 significant association of $p < 0.01$ in univariable analyses in step (1) and (2). In this final
224 process, case-control comparison between depressed and non-depressed women during
225 pregnancy was not available because of only 9 (5.8%) cases in study participants, therefore,
226 we applied linear regression analyses using the total score of antenatal EPDS as continuous
227 variable, which minimized the influence of few depressed women during pregnancy. The
228 MDI and PDI scores were transformed into log 10 scales because the distributions were
229 skewed, whilst the independent variable of the antenatal EPDS score was hypothesized to
230 follow a normal distribution according to the central limit theorem under the condition of over
231 100 sample size [27].

232 As a result of analyses (1)-(4), gestational age and intrauterine growth restriction (IUGR)
233 were supposed to be significant confounders between depression during pregnancy and infant
234 development, therefore, correlation of the antenatal EPDS score with gestational age and
235 IUGR was additionally analyzed. Consequently, further linear regression analyses as well as

236 logistic regression analyses were carried out, entering gestational age and IUGR as outcome
237 variables and the antenatal EPDS score as an independent variable. There was no
238 multicollinearity in a series of regression analyses. The goodness of fit for all regression
239 models was evaluated by using adjusted R square and F-test.
240
241 *Informed consent and ethical review*
242 This study was conducted after obtaining written informed consent from all participants
243 and was approved by the institutional ethics board for epidemiologic studies at the Hokkaido
244 University Graduate School of Medicine.
245
246 **Results**
247 Table 1 presents characteristics of mothers, fathers, infants, and the childcare environment.
248 The mean ± SD maternal age at delivery was 31.4 ± 4.9 years. The number of mothers with a
249 low annual household income (<3,000,000 yen) was 26 (16.9%), the number who smoked
250 during pregnancy was 22 (14.3%), and the number who reported stressful life events during
251 the year before pregnancy was 60 (39.0%). There were 78 male (50.6%) and 76 female
252 (49.4%) infants and 71 first-born infants (46.1%). The mean ± SD gestational age was 275.7 ±
253 8.5 days, and the mean ± SD infant birth weight was 3090.5 ± 361.1 g. The number of infants
254 for preterm birth, small for gestational age (SGA), low birth weight, and intrauterine growth

restriction (IUGR) was five (3.2%), three (1.9%), three (1.9%), and 12 (7.8%), respectively. None of the women assessed had diabetes during pregnancy, however, the cohort included 17 women with pregnancy-induced hypertension, 7 thyroid disease, and two mental disease, one of whom was prescribed minor tranquilizer.

Table 2 presents data for antenatal and postnatal depression of mothers and data for infant development. The EPDS identified 9 depressed mothers during pregnancy (5.8%) and 21 depressed mothers at 1 month after delivery (13.6%). The median MDI score was 90 ($25^{th}$–$75^{th}$ percentile = 88–94), and the median PDI score was 88 ($25^{th}$–$75^{th}$ percentile = 82–97).

Table 3 presents the results of univariable analyses between the antenatal EPDS score, BSID-II scores (MDI, PDI), and potential confounders. Potential confounding variables during pregnancy that showed significant association ($p < 0.10$) with antenatal EPDS included maternal education level ($p = 0.055$), household income ($p = 0.076$), past depressive symptoms ($p < 0.000$), worrying ($p < 0.000$), obsessiveness ($p < 0.000$), father's age ($r = -0.14$, $p = 0.088$), and father's education level ($p = 0.096$). Postnatal EPDS also indicated statistical significant in relation to antenatal EPDS ($r = -0.48$, $p < 0.000$) (Table 4). Potential confounding factors that were significantly associated with MDI included infant sex ($p = 0.067$), IUGR ($p = 0.059$), gestational age ($r = 0.19$, $p = 0.019$), birth weight ($r = 0.15$, $p = 0.068$), infant length ($r = 0.15$, $p = 0.067$), and head circumference ($r = 0.13$, $p = 0.097$).

Potential confounding variables significantly related to PDI included caffeine intake during pregnancy ($r = -0.16$, $p = 0.043$), gestational age ($r = 0.24$, $p = 0.002$), birth weight ($r = 0.14$, $p = 0.079$), infant length ($r = 0.14$, $p = 0.079$), age at 6-month assessment ($r = 0.16$, $p = 0.046$), and "avoidance of restriction and punishment" ($r = 0.18$, $p = 0.025$). Maternal smoking during pregnancy and maternal age that were adjusted in previous studies indicated no statistical significant in correlation with antenatal EPDS, MDI, or PDI.

Results of univariable analyses for the MDI and PDI scores in relation to the antenatal and postnatal EPDS scores were indicated in Table 4. Maternal antenatal EPDS was tend to be significantly correlated to MDI ($r = -0.15$, $p = 0.057$), while there was no significant association between maternal postnatal depression and infant development.

We conducted linear regression analyses between the antenatal EPDS score and the MDI and PDI scores, and adjusted for any factors with an association of $p < 0.10$ in univariable analyses (Table 5, Table 6). Model 1 was adjusted for infant factors: infant sex, IUGR, gestational age, birth weight, length, head circumference, and age at 6-month assessment. Model 2 was adjusted using these same parameters as well as maternal caffeine intake during pregnancy and the childcare factor "avoidance of restriction and punishment". Model 3 was a full model that adjusted for all covariants with a significant association of $p < 0.10$ in the univariable analyses, namely, father's age and father's educational level in addition to factors adjusted in Model 2. In linear regression analyses, $p < 0.05$ was considered to be a significant

association.

Table 5 presents the MDI score in relation to the antenatal EPDS score and confounding variables based on the crude model (the goodness of fit: adjusted $R^2$ = 0.007, $F$=2.07, $p$=0.153), model 1 (adjusted $R^2$ = 0.087, $F$=2.81, $p$=0.006), model 2 (adjusted $R^2$ = 0.080, $F$=2.34, $p$=0.014), and model 3 (adjusted $R^2$ = 0.069, $F$=1.94, $p$=0.034). Even though the validity of all statistical models except the crude model was assured at the level of $p < 0.05$, adjusted $R^2$ was highest in model 1. A significant association between antenatal EPDS and MDI was not found in the crude model or in any of the adjusted models (Crude: β = −0.00, 95% CI [−0.00, 0.00], $p$ = 0.153; Model 1: β = −0.05, 95% CI [−0.00, 0.00], $p$ = 0.500; Model 2: β = −0.05, 95% CI [−0.00, 0.00], $p$ = 0.552, Model 3: β = −0.05, 95% CI [−0.00, 0.00], $p$ = 0.585). On the other hand, gestational age indicated significant relation to MDI with consistently larger regression coefficients than those of the other factors even though the statistical model was changed (Model 1: β = 0.23, 95% CI [0.00, 0.00], $p$ = 0.013; Model 2: β = 0.22, 95% CI [0.00, 0.00], $p$ = 0.019, Model 3: β = 0.23, 95% CI [0.00, 0.00], $p$ = 0.018). IUGR, similarly, showed significant relation to MDI in all models (Model 1: β = 0.19, 95% CI [0.00, 0.04], $p$ = 0.020; Model 2: β = 0.21, 95% CI [−0.00, 0.04], $p$ = 0.015, Model 3: β = 0.21, 95% CI [0.00, 0.04], $p$ = 0.017).

Table 6 presents the PDI score in relation to the antenatal EPDS score and confounding variables based on the crude model (the goodness of fit: adjusted $R^2$ = −0.007, $F$ = 0.01, $p$ =

312 0.927), model 1 (adjusted $R^2$ = 0.092, $F$=2.93, $p$ = 0.005), model 2 (adjusted $R^2$ = 0.133, $F$ =
313 3.34, $p$ = 0.001), and model 3 (adjusted $R^2$ = 0.141, $F$ = 3.09, $p$ = 0.001). Each adjusted model
314 was validated at the level of $p < 0.01$, however, model 3 indicated the highest value of
315 adjusted $R^2$. Whilst there was no significant correlation between antenatal EPDS and PDI in
316 all models, PDI did show association with gestational age (Model 1: β = 0.28, 95% CI [0.00,
317 0.00], $p$ = 0.003; Model 2: β = 0.25, 95% CI [0.00, 0.03], $p$ = 0.006; Model 3: β = 0.23, 95%
318 CI [0.00, 0.00], $p$ = 0.012), infant age at 6-month assessment (Model 1: β = 0.25, 95% CI
319 [0.00, 0.00], $p$ = 0.002; Model 2: β = 0.24, 95% CI [0.00, 0.00], $p$ = 0.003; Model 3: β = 0.24,
320 95% CI [0.00, 0.00], $p$ = 0.002), and "avoidance of restriction and punishment" (Model 2: β =
321 0.20, 95% CI [0.01, 0.07], $p$ = 0.010; Model 3: β = 0.23, 95% CI [0.02, 0.08], $p$ = 0.004).
322 Despite no significant relation of antenatal EPDS to MDI or PDI in linear regression
323 analysis, Spearman's correlation test detected the trend of correlation between antenatal EPDS
324 and MDI ($r$ = −0.15, $p$ = 0.057) (Table 3). On the other hand, antenatal EPDS was
325 significantly associated to gestational age in Spearman's correlation ($r$ = 0.22, $p$ = 0.006)
326 (Table 3), moreover, gestational age and IUGR was significantly related to MDI or PDI in
327 linear regression analyses. In order to explore association between all of those variables in
328 detail, we conducted further multiple linear regression analyses on gestational age and logistic
329 regression analyses on IUGR in relation to antenatal EPDS (Table 7), adjusting for all
330 potential confounders before delivery: maternal factors (age, education level, household

income, worked during pregnancy, smoked during pregnancy, caffeine intake during pregnancy, alcohol intake during pregnancy, stressful life events before pregnancy, past depressive symptoms, worrying, obsessiveness, planned pregnancy, wanted pregnancy), paternal factors (age and education level), and infant factors (sex and parity).

As a consequence, antenatal EPDS was significantly correlated to gestational age in the crude model (β = −0.18, 95% CI [−0.92, −0.06], $p = 0.026$; the goodness of fit: adjusted $R^2 = 0.026$, $F = 5.07$, $p = 0.026$), and not to IUGR (OR = 0.96, 95% CI [0.78, 1.19], $p = 0.697$; the goodness of fit: nagelkerke $R^2 = 0.003$, $\chi^2 = 0.16$, $p = 0.686$). This trend did not change even confounders were adjusted. Especially in the adjusted model analysing association between antenatal EPDS and gestational age, the regression coefficient of antenatal EPDS was highest of all variables (β = −0.25, 95% CI [−1.20, −0.17], $p = 0.010$; the goodness of fit: adjusted $R^2 = 0.123$, $F = 2.19$, $p < 0.000$).

## Discussion

### *Summary of study findings*

In our current study, the hypothesis that maternal depression during pregnancy has an adverse relationship with infant development was evaluated using improved adjustments for confounding variables. Although the trend of association between maternal antenatal depression and infant development was found in the univariable analysis, the correlation was

lost in multivariable analyses. However, after all regression analyses, the study highlighted the fact that depression during pregnancy was significantly related to shorter gestational age, and shorter gestational age was in significant relation to developmental delay in infant cognitive fanction. Therefore, gestational age was considered to be an important confounder in the association between maternal antenatal depression and infant mental development. This is the first study to investigate the relationship between maternal depression during pregnancy and infant development with a proper control for gestational age, and it thus offers new insight into the seemingly inconsistent results from previous studies.

*Prevalence of maternal depression and scoring of infant development*

The prevalence of maternal depression during pregnancy, defined using a cutoff of 8/9 on the EPDS, was 5.8% in the current study, which was relatively low in comparison with reports generated in Europe and the United States. Previous studies evaluating maternal depression during the second or third trimester reported prevalence levels of 7.0% in the USA [6], 13.9% in England [28], and 17.4% in Sweden [29] using the EPDS, and 8.7% in Hong Kong using the Beck Depression Scale [30]. However, the prevalence of depression during pregnancy based on the DSM-III-R Major Depressive Episode in Japan was reported to be 5.6% [31]. In addition, according to a report of meta-analyses regarding perinatal depression in developed countries [32]., the prevalence for major and minor depression during pregnancy ranged from

6.5% to 12.9% (minor depression ranged from 1.0% to 12.9%), and maternal depression in one to two months after delivery was estimated to be from 10% to 15%. The prevalence of antenatal and postnatal maternal depression in our study was within those ranges. These may endorse the credibility of our study results.

The BSID-II score was applied to evaluate infant development in this study. The median MDI and PDI scores were 90 and 88, respectively, which were both lower than standardised scores (mean score 100). Because both cultural and language differences exist between Japan and the United States, the BSID-II must be used with care in Japan. However, the first BSID edition was previously used in Japan for developmental assessment of infants [33], and a high correlation was reported between BSID-II and the Kyoto Developmental Test, which was standardised in Japan. Furthermore, a study in Taiwan revealed high reproducibility using BSID-II despite cultural differences [34]. To improve reliability, evaluation of development was limited to 6-month-old infants, and every examiner scored each infant. Therefore, the BSID-II scores of the participants in this study were directly comparable with each other.

*Antenatal depression, gestational age, and infant mental development*

In previous studies examining the association of antenatal depression with infant development, Deave et al [6]. used the EPDS and reported that antenatal depression has an adverse impact on infant development, whereas DiPietro et al [11]. used the BSID-II and

388 reported a positive impact. Surprisingly, our results were inconsistent with both of these
389 studies and successfully added new findings into them. There are several reasons that may
390 explain why our results were different from earlier reports especially in terms of controlling
391 confounders. First of all, there were differences in the confounding factors entered into
392 statistical analyses as well as the credibility of those information. Although many potential
393 confounders were considered by Deave et al [6]., all but four (antenatal tobacco use, maternal
394 age, postnatal life events, and postnatal depression) were removed through a conceptual
395 framework. The confounder of gestational age was also removed in the final analyses of
396 DiPietro et al [11]. Moreover, the latter report does not describe how information on
397 gestational age was obtained. In our study, all perinatal information was obtained from
398 medical records, ensuring reliability of the data. Second, there were differences in childcare
399 factors and in infant age at assessment. In our study, childcare environment was taken into
400 account as a considerable confounder, in addition, infant development was evaluated at 6
401 months to minimise the influence of other confounding factors after birth. In the Deave and
402 DiPietro studies [6, 11], child assessments were conducted much later (18 and 24 months,
403 respectively), and childcare factors were not controlled for through all steps of analysis.
404 DiPietro et al [11]. reported a high level of maternal educational (median, 17 years), but
405 Deave et al [6]. provided no information on maternal education. Higher education levels can
406 counteract negative influences that come into play during the perinatal period [35]. It is likely

that other aspects of the childcare environment positively or negatively affect infant development [36]. In our study, education levels of both parents were also analysed statistically as confounding variables. Third, there were differences in the measures used. Deave et al. [6] applied the DDST, which evaluates similar developmental abilities as the BSID-II, but depends on parental reporting. Depressed mothers may possibly perceive their children's abilities as being lower. Such a reporter bias would lead to the apparent statistical association between antenatal depression and child development in that study. In contrast, reporter bias in infant assessment was avoided in our study by using an objective and blinded assessment, providing improved credibility.

In our current study, gestational age was identified to be a considerable confounding variable; that is, infants of depressed mothers tended to be delivered earlier and suffer cognitive developmental delays as a consequence. Severer score of EPDS during pregnancy was related to shorter gestational age (β = −0.25, 95% CI [−1.20, −0.17], $p = 0.010$), and shorter gestational age was related to lower scores of mental (β = 0.23, 95% CI [0.00, 0.00], $p = 0.013$) as well as psychomotor (β = 0.23, 95% CI [0.00, 0.00], $p = 0.012$) development in adjusted linear regression analysis (Table 5, Table6), supporting the notion that the developmental delays were a consequence of early delivery brought by maternal depression during pregnancy. Several studies endorse the impact of maternal depression on the length of gestation by showing that antenatal depression is associated with either a reduced gestational

age [37] or a greater incidence of preterm birth among severely depressed women compared to non-depressed women [38, 39]. The influence of antenatal depression on gestational age may be explained by a potential biological pathway. According to recent studies, cortisol increases the release of placental corticotropin-releasing hormone (CRH) [39, 40], which plays a key role in triggering parturition [40-43]. Depression in pregnant women is related to a greater incidence of premature delivery and to elevated antenatal cortisol levels compared to non-depressed women [38]. Higher levels of cortisol and CRH were also detected in women who delivered preterm compared with those who delivered at term [40]. In our current study, it was not available to analyse relation of preterm birth to maternal depression during pregnancy due to only 5 (3.2%) preterm birth. However, it will be important to explore the association between gestational age, preterm birth, and maternal antenatal depression in greater detail in further studies.

*Childcare factors and infant psychomotor development*

Infant PDI was related not only to gestational age but also to "avoidance of restriction and punishment" in this study. The positive association of "avoidance of restriction and punishment" with PDI in our study does agree with earlier studies. Some studies have reported that infants exposed to maltreatment show lower PDI scores than control groups [44, 45], confirming our findings. However, they also detected an impact of maltreatment on MDI

445 scores [44, 45], which we did not see. The reason for this difference may be due to the
446 difference in infant age at the time of assessment. Previous studies involved infants between 2
447 and 30 months, whereas our study involved infants at the age of 6 months. The reported
448 impact of maltreatment on MDI appeared only after 14 months of age [46]; thus, the lack of
449 association at an earlier age is consistent with our results.
450
451 *Study strengths and limitations*
452 This study constitutes a prospective cohort study, which minimises recall bias. We
453 collected infant development scores through constructed assessment by examiners blinded to
454 other data, enabling us to control for reporting bias and observer bias. We also collected
455 perinatal information on mothers and infants (such as disease history, pregnancy conditions,
456 and birth weight and size) from medical records written by obstetricians, not from maternal
457 reports, which further increased data reliability. Moreover, diverse confounding variables
458 were controlled for during a series of statistical analyses.
459 Nonetheless, this study has the following limitations. First, our sample size was relatively
460 small for representatives of the general population, even larger sample size than several
461 previous studies [10-12]. However, despite small sample size, the goodness of fit in all
462 adjusted models of linear regression analyses indicated statistical significances ($p < .05$),
463 endorsing the validity of the study results. Second, our study may have several selection bias

because it was based on a cohort from one regional hospital treating pregnant women in Sapporo and the surrounding areas, and the participant rate in our study was low (30%). There were several reasons of the low participant: of all potential participants who we approached, the women who decided to enrol in the Japanese cord blood bank (22% of those who were approached), and the women who decided to deliver the baby at another hospital (3% of those who were approached) were excluded from the cohort. Some of the women we approached did not express interest in our study, and some were unable or unwilling to participate, therefore, there was a possibility that depressed women may have been less likely to be involved in this study. The follow-up rate was also slightly low in our cohort study (50%). Out of 298 women with single birth (96 % of all study participants), those who did not completed or returned the mailed EPDS questionnaire between 1 and 4 months after delivery (10 % of those of single birth), and those who did not show up to the infant assessment during the period from 5 months and 16 days up to 6 months and 15 days after birth (42% of those who were assessed the postnatal EPDS), were excluded from the study. Because BSID-II is not standardized for use in Japan, we strictly limited the period of assessment, which may have introduced the low follow-up rate. In our current study, the prevalence of small for gestational age (SGA) was also very small (1.9%). Pregnant women may possibly have avoided participating in or dropped out from our cohort study through the follow-up period because of depression itself, causing a selection bias that may slightly lower the prevalence of

483 depressive symptoms as well as that of SGA. These may limit extrapolation of our results to
484 the general population. However, there was no remarkable difference between the prevalence
485 of antenatal depression for all participants at the beginning (309 women, 5.2%) and that for
486 analysed women (154 women, 5.8%), therefore, the low follow-up rate was unlikely to have a
487 significant influence on the study results. Finally, information on antenatal psychological
488 distress may have been insufficient, because maternal depression was not based on clinical
489 diagnosis, and the experience of stressful events and the other maternal psychological status
490 were collected using yes/no questions based on unstandardized questionnaires. However, the
491 EPDS is thought to be a well-validated scale and was used in the previous study by Deave et
492 al. in the absence of clinical diagnosis [6].

493 In conclusion, our current study suggests that the delay in infant mental development may
494 be related to a shorter gestational period resulting from maternal depression during pregnancy.
495 Because impaired cognitive and motor functions present at 6 months can be reversed by
496 school age, further follow-up monitoring should continue at least until school age and
497 additional studies are required to clarify this issue.

498

499 **Acknowledgments**

500 This study was supported by a Grant-in-Aid for Health Scientific Research from the Japan
501 Ministry of Health, Labour and Welfare, and by a Grant-in-Aid for Scientific Research from

502 the Japan Society for the Promotion of Science. There are no financial and other conflicts of
503 interest that might bias our work. We are also extremely grateful to all families who took part
504 in this study, to the obstetricians and nurses who helped recruit them and provided medical
505 data, and to the occupational therapists who performed the infant assessments.

506 **Conflict of interest**

507 There are no conflicts of interest, including competing financial interest and financial

508 relationship with the funding organizations, with regard to this manuscript.

509 **References**


510 1 Fameli M, Kitraki E, Stylianopoulou F. Effects of hyperactivity of the maternal
511 hypothalamic-pituitary-adrenal (HPA) axis during pregnancy on the development of the
512 HPA axis and brain monoamines of the offspring. Int J Dev Neurosci 1994;12(7):651-9.
513 2 Welberg LA, Seckl JR. Prenatal stress, glucocorticoids and the programming of the brain.
514 J Neuroendocrinol 2001;13(2):113-28.
515 3 Teixeira JM, Fisk NM, Glover V. Association between maternal anxiety in pregnancy and
516 increased uterine artery resistance index: cohort based study. BMJ 1999;318(7177):153-7.
517 4 Weinstock M. Alterations induced by gestational stress in brain morphology and
518 behaviour of the offspring. Prog Neurobiol 2001;65(5):427-51.
519 5 Wadhwa PD. Psychoneuroendocrine processes in human pregnancy influence fetal
520 development and health. Psychoneuroendocrinology 2005;30(8):724-43.
521 6 Deave T, Heron J, Evans J, Emond A. The impact of maternal depression in pregnancy on
522 early child development. BJOG 2008;115(8):1043-51.
523 7 O'Connor TG, Heron J, Glover V. Antenatal anxiety predicts child behavioral/emotional
524 problems independently of postnatal depression. J Am Acad Child Adolesc Psychiatry
525 2002;41(12), 1470-7.
526 8 Laplante DP, Brunet A, Schmitz N, Ciampi A, King S. Project Ice Storm: prenatal
527 maternal stress affects cognitive and linguistic functioning in 5 1/2-year-old children. J

528 Am Acad Child Adolesc Psychiatry 2008;47(9), 1063-72.

529 9 Laplante DP, Barr RG, Brunet A, Galbaud du Fort G, Meaney ML, Saucier JF, et al. Stress
530 during pregnancy affects general intellectual and language functioning in human toddlers.
531 Pediatr Res 2004;56(3), 400-10.

532 10 Sugawara M, Kitamura T, Aoki M, Shima S. Maternal depression during pregnancy and
533 newborn's behavioral characteristics J child health. 1988;47(5), 577-81.

534 11 DiPietro JA., Novak MF, Costigan KA, Atella LD, Reusing SP. Maternal psychological
535 distress during pregnancy in relation to child development at age two. Child Dev
536 2006;77(3), 573-87.

537 12 Kaplan LA, Evans L, Monk C. Effects of mothers' prenatal psychiatric status and
538 postnatal caregiving on infant biobehavioral regulation: can prenatal programming be
539 modified? Early Hum Dev 2008;84(4), 249-56.

540 13 Mash EJ, Johnston C. A comparison of the mother-child interactions of younger and older
541 hyperactive and normal children. Child Dev 1982;53(5), 1371-81.

542 14 Gardner FE. The quality of joint activity between mothers and their children with
543 behaviour problems. J Child Psychol Psychiatry 1994;35(5), 935-48.

544 15 Famularo R, Kinscherff R, Fenton T. Psychiatric diagnoses of maltreated children:
545 preliminary findings. J Am Acad Child Adolesc Psychiatry 1992;31(5), 863-7.

546 16 Nagata C, Kabuto M, Shimizu H. Association of coffee, green tea, and caffeine intakes

547 with serum concentrations of estradiol and sex hormone-binding globulin in
548 premenopausal Japanese women. Nutr Cancer 1998;30, 21-4.
549 17 Nagata C, Kabuto M, Takatsuka N, Shimizu H. Associations of alcohol, height, and
550 reproductive factors with serum hormone concentrations in postmenopausal Japanese
551 women. Steroid hormones in Japanese postmenopausal women. Breast Cancer Res Treat
552 1997;44(3), 235-41.
553 18 Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the
554 10-item Edinburgh Postnatal Depression Scale. Br J Psychiatry 1987;150, 782-6.
555 19 Okano T, Murata M, Masuji F, Tamaki R, Nomura J, Miyaoka H, et al. Validation and
556 reliability of Japanese version of EPDS (Edinburgh Postnatal Depression Scale). Archives
557 of psychiatric diagnosis and clinical evaluation 1996;7(4), 525-33.
558 20 Bayley N. Manual for the Bayley scales of infant development,2nd ed. New York:
559 Psychological corporation; 1993.
560 21 Nakajima S, Saijo Y, Kato S, Sasaki S, Uno A, Kanagami N, et al. Effects of prenatal
561 exposure to polychlorinated biphenyls and dioxins on mental and motor development in
562 Japanese children at 6 months of age. Environ Health Perspect 2006;114(5), 773-8.
563 22 Nakamura Y, Nakajima S, Yanagiya S, Sengoku Y, Tachi N, Kishi R. Developmental
564 assessment for 6 months infants by the Bayley scales of infant development. 2nd ed. Part
565 III: A validation study by using JDDST. The Journal of Japanese Occupational Therapy

566 Association 2004;23, 392.

567 23 Nakajima S, Nakamura Y, Yanagiya S, Sengoku Y, Tachi N, Kishi R. Developmental
568 assessment for 6 months infants by the Bayley scales of infant development. 2nd ed. Part I:
569 Results of mental and psychomotor development. The Journal of Japanese Occupational
570 Therapy Association 2004;23, 390.

571 24 Bradley RH, Caldwell BM. Home observation for measurement of the environment: A
572 validation study of screening efficiency. Am J Ment Defic 1977;81(5), 417-20.

573 25 Frankenburg WK, Coons CE. Home Screening Questionnaire: its validity in assessing
574 home environment. J Pediatr 1986;108(4), 624-6.

575 26 Anme T. Child support and evaluation and child care environment in the era of low
576 birthrates. Tokyo: Kawashima Shoten; 1996.

577 27 Mitchell H. Katz. Multivariable Analysis: A Practical Guide for Clinicians, Second
578 Edition. Cambridge: Cambridge University Press; 2006.

579 28 Evans J, Heron J, Francomb H, Oke S, Golding J. Cohort study of depressed mood during
580 pregnancy and after childbirth. BMJ 2001;323(7307), 257-60.

581 29 Josefsson A, Berg G, Nordin C, Sydsjö G. Prevalence of depressive symptoms in late
582 pregnancy and postpartum. Acta Obstet Gynecol Scand 2001;80(3), 251-5.

583 30 Chung TK, Lau TK, Yip AS, Chiu HF, Lee DT. Antepartum depressive symptomatology is
584 associated with adverse obstetric and neonatal outcomes. Psychosom Med 2001;63(5),

585 830-4.

586 31 Kitamura T, Yoshida K, Okano T, Kinoshita K, Hayashi M, Toyoda N, et al. Multicentre
587 prospective study of perinatal depression in Japan: incidence and correlates of antenatal
588 and postnatal depression. Arch Womens Ment Health. 2006;9(3):121-30.

589 32 Gavin NI, Gaynes BN, Lohr KN, Meltzer-Brody S, Gartlehner G, Swinson T. Perinatal
590 depression: a systematic review of prevalence and incidence. Obstet Gynecol. 2005;106(5
591 Pt 1):1071-83.

592 33 Oka T, Suzuki K, Nakai K, Hosokawa T, Satoh H. A trial to apply Bayley Scales of Infant
593 Development second edition to Japanese children. J Clin Exp Med 2005;212, 259-63.

594 34 Huang HL, Chuang SF, Jong YJ, Yu L, Shieh YL. Applicability of BSID-II in diagnosing
595 developmental delay at Kaohsiung area. Kaohsiung J Med Sci 2000;16, 197-202.

596 35 Wang LW, Wang ST, Huang CC. Preterm infants of educated mothers have better outcome.
597 Acta Paediatr 2008;97(5), 568-73.

598 36 Weisglas-Kuperus N, Baerts W, Smrkovsky M, Sauer PJ. Effects of biological and social
599 factors on the cognitive development of very low birth weight children. Pediatrics
600 1993;92(5), 658-65.

601 37 Van Dijk AE, Van Eijsden M, Stronks K, Gemke RJ, Vrijkotte TG. Maternal depressive
602 symptoms, serum folate status, and pregnancy outcome: results of the Amsterdam Born
603 Children and their Development study. Am J Obstet Gynecol 2010;203(6), 563-7.

604 38 Diego MA, Field T, Hernandez-Reif M, Schanberg S, Kuhn C, Gonzalez-Quintero VH.
605 Prenatal depression restricts fetal growth. Early Hum Dev 2009;85(1), 65-70.
606 39 Dayan J, Creveuil C, Marks MN, Conroy S, Herlicoviez M, Dreyfus M, et al. Prenatal
607 depression, prenatal anxiety, and spontaneous preterm birth: A prospective cohort study
608 among women with early and regular care. Psychosom Med 2006;68(6), 938-46.
609 40 Sandman CA, Glynn L, Schetter CD, Wadhwa P, Garite T, Chicz-DeMet A, et al. Elevated
610 maternal cortisol early in pregnancy predicts third trimester levels of placental
611 corticotropin releasing hormone (CRH): priming the placental clock. Peptides 2006;27(6),
612 1457-63.
613 41 Majzoub JA, Karalis KP. Placental corticotropin-releasing hormone: function and
614 regulation. Am J Obstet Gynecol 1999;180(1 Pt 3), S242-6.
615 42 Pike IL. Maternal stress and fetal responses: evolutionary perspectives on preterm delivery.
616 Am J Hum Biol 2005;17(1), 55-65.
617 43 McLean M, Bisits A, Davies J, Woods R, Lowry P, Smith R. A placental clock controlling
618 the length of human pregnancy. Nat Med 1995;1(5), 460-3.
619 44 Appelbaum AS. Developmental retardation in infants as a concomitant of physical child
620 abuse. J Abnorm Child Psychol 1977;5(4), 417-23.
621 45 Koski MA, Ingram EM. Child abuse and neglect: effect on Bayley Scale scores. J Abnorm
622 Child Psychol 1977;5(1), 79-91.

623 46 Allen R, Wasserman GA. Origins of language delay in abused infants. Child Abuse Negl
624 1985;9(3), 335-40.

# Tables

**Table 1.** Characteristics of mothers, fathers, infants, and childcare environments

| Characteristic | Mean ± SD, *n* (%) |
|---|---|
| Maternal characteristics | |
| Age (years) | 31.4 ± 4.9 |
| Education level (years) | |
| ≤9 | 5 (3.2) |
| 10–12 | 54 (35.1) |
| 13–16 | 92 (59.7) |
| ≥17 | 3 (1.9) |
| Household income (yen/year) | |
| <3,000,000 | 26 (16.9) |
| 3,000,000–5,000,000 | 68 (44.2) |
| 5,000,000–7,000,000 | 40 (26.0) |
| >7,000,000 | 20 (13.0) |
| Worked during pregnancy | 23 (14.9) |
| Smoked during pregnancy | 22 (14.3) |
| Caffeine intake during pregnancy (mg/day) | 123.4 (80.2−183.1)[a] |
| Alcohol intake during pregnancy (g/day) | 0.0 (0.0−0.9)[a] |
| Stressful life events before pregnancy | 60 (39.0) |
| Self-reported psychological status | |
| Past depressive symptoms | 18 (11.7) |
| Worrying | 70 (45.5) |
| Obsessiveness | 45 (29.2) |
| Readiness for pregnancy | |
| Planned pregnancy | 77 (50.0) |
| Wanted pregnancy | 131 (85.1) |
| Worked at 6 months postpartum | 17 (11.0) |
| Paternal characteristics | |
| Age (years) | 33.2 ± 5.8 |
| Education level (years) | |
| ≤9 | 4 (2.6) |
| 10–12 | 53 (34.4) |
| 13–16 | 80 (51.9) |
| ≥17 | 17 (11.0) |
| Infant characteristics | |
| Male | 78 (50.6) |
| First born (parity = 0) | 71 (46.1) |

| | |
|---|---|
| Preterm birth | 5 (3.2) |
| SGA | 3 (1.9) |
| Low birth weight | 3 (1.9) |
| IUGR | 12 (7.8) |
| Gestational age (days) | 275.7 ± 8.5 |
| Birth weight (g) | 3090.5 ± 361.1 |
| Length (cm) | 48.3 ± 1.7 |
| Head circumference (cm) | 33.3 ± 1.3 |
| Chest circumference (cm) | 31.5 ± 1.4 |
| Age at 6-month assessment (days) | 190.3 ± 8.7 |
| Childcare environment | |
| EES subscores at 6 months | |
| Humanistic involvement | 7 (7−8)[a] |
| Responsiveness | 2 (2−2)[a] |
| Avoidance of restriction and punishment | 1 (1−1)[a] |
| Physical involvement | 3 (2−3)[a] |
| Social involvement | 4 (3−5)[a] |
| Organisation of environment | 2 (2−3)[a] |
| Social support | 5 (4−5)[a] |

[a]Median (25th−75th); EES, Evaluation of Environmental Stimulation; IUGR, intrauterine growth restriction; SGA, small for gestational age.

3

**Table 2.** Antenatal and postnatal maternal depression and infant development

| Maternal depression | Median (25th−75th), *n* (%) |
|---|---|
| Antenatal EPDS[a] | |
| Total score | 1 (0−3) |
| ≤8 | 145 (94.2) |
| ≥9 | 9 (5.8) |
| Postnatal EPDS[b] | |
| Total score | 3 (1−6) |
| ≤8 | 133 (86.4) |
| ≥9 | 21 (13.6) |
| Infant development[c] | |
| BSID-II Mental Development Index: MDI | 90 (88−94) |
| BSID-II Psychomotor Development Index: PDI | 88 (82−97) |

[a]Maternal depression between the second and the third trimesters (23 – 35 gestational weeks); [b]Maternal depression after delivery (1 – 4 months); [c]Infant development at 6 months (from 5 months and 16 days to 6 months and 15 days after birth); BSID-II, Bayley Scales of Infant Development II; EPDS, Edinburgh Postnatal Depression Scale.

**Table 3.** Maternal antenatal depression (EPDS) and infant development (BSID-II, MDI & PDI) in relation to potential confounding variables[a]

| | | Antenatal EPDS[b] | | MDI[c] | | PDI[c] | |
|---|---|---|---|---|---|---|---|
| | *n* | Mean ± SD | *p* | Mean ± SD | *p* | Mean ± SD | *p* |
| Maternal characteristics | | | | | | | |
| Age (years)[d] | | $r = -0.11$ | 0.184 | $r = 0.01$ | 0.867 | $r = 0.01$ | 0.865 |
| Education level (years)[e] | | | | | | | |
| ≤12 | 55 | 3.07 ± 3.70 | 0.055[†] | 91.39 ± 4.96 | 0.147 | 90.80 ± 10.95 | 0.492 |
| ≥13 | 87 | 2.02 ± 2.67 | | 90.95 ± 5.98 | | 89.73 ± 10.41 | |
| Household income (yen/year)[f] | | | | | | | |
| <3,000,000 | 26 | 3.85 ± 3.87 | 0.076[†] | 89.38 ± 5.25 | 0.415 | 89.15 ± 11.18 | 0.807 |
| 3,000,000–5,000,000 | 68 | 2.18 ± 2.68 | | 91.69 ± 5.25 | | 90.76 ± 10.27 | |
| 5,000,000–7,000,000 | 40 | 1.78 ± 2.57 | | 90.10 ± 5.12 | | 90.05 ± 11.19 | |
| >7,000,000 | 20 | 2.42 ± 3.14 | | 91.45 ± 7.16 | | 89.45 ± 10.42 | |
| Worked during pregnancy[e] | | | | | | | |
| No | 131 | 2.58 ± 3.32 | 0.342 | 90.63 ± 5.37 | 0.301 | 90.16 ± 10.41 | 0.754 |
| Yes | 23 | 1.52 ± 1.59 | | 92.13 ± 6.81 | | 90.00 ± 11.89 | |
| Smoked during pregnancy[e] | | | | | | | |
| No | 132 | 2.34 ± 2.97 | 0.913 | 90.83 ± 5.64 | 0.856 | 90.33 ± 10.55 | 0.619 |
| Yes | 22 | 2.91 ± 4.05 | | 90.05 ± 5.59 | | 89.00 ± 11.09 | |
| Caffeine intake during pregnancy (mg/day)[d] | | $r = 0.18$ | 0.827 | $r = -0.04$ | 0.662 | $r = -0.16$ | 0.043[*] |
| Alcohol intake during pregnancy (g/day)[d] | | $r = 0.11$ | 0.160 | $r = -0.07$ | 0.383 | $r = -0.04$ | 0.671 |
| Stressful life events before pregnancy[e] | | | | | | | |
| No | 94 | 2.27 ± 3.14 | 0.220 | 91.14 ± 5.22 | 0.450 | 89.34 ± 11.47 | 0.162 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Yes | 60 | 2.67 ± 3.16 | | 90.42 ± 6.19 | | 90.38 ± 9.03 | |
| Self-reported psychological status | | | | | | | |
| Past depressive symptoms[e] | | | | | | | |
| No | 136 | 1.96 ± 2.58 | < 0.000** | 90.75 ± 5.73 | 0.337 | 90.17 ± 10.68 | 0.861 |
| Yes | 18 | 5.94 ± 4.56 | | 91.67 ± 4.67 | | 89.89 ± 10.31 | |
| Worrying[e] | | | | | | | |
| No | 84 | 1.29 ± 1.74 | < 0.000** | 91.21 ± 5.67 | 0.383 | 89.37 ± 10.13 | 0.387 |
| Yes | 70 | 3.79 ± 3.84 | | 90.43 ± 5.56 | | 91.06 ± 11.15 | |
| Obsessiveness[e] | | | | | | | |
| No | 109 | 1.76 ± 2.29 | 0.001** | 90.66 ± 5.85 | 0.686 | 89.84 ± 10.49 | 0.556 |
| Yes | 45 | 4.02 ± 4.21 | | 91.33 ± 5.03 | | 90.84 ± 10.94 | |
| Readiness for pregnancy | | | | | | | |
| Planned pregnancy[e] | | | | | | | |
| No | 77 | 2.66 ± 3.44 | 0.677 | 90.92 ± 6.28 | 0.880 | 90.12 ± 11.52 | 0.912 |
| Yes | 77 | 2.18 ± 2.81 | | 90.79 ± 4.90 | | 90.16 ± 9.68 | |
| Wanted pregnancy[e] | | | | | | | |
| No | 23 | 3.39 ± 4.20 | 0.238 | 91.65 ± 6.78 | 0.945 | 91.22 ± 10.04 | 0.548 |
| Yes | 131 | 2.25 ± 2.90 | | 90.72 ± 5.40 | | 89.95 ± 10.72 | |
| Worked at 6 months[e] | | | | | | | |
| No | 137 | 2.48 ± 3.27 | 0.988 | 90.92 ± 5.62 | 0.772 | 89.92 ± 10.52 | 0.504 |
| Yes | 17 | 1.94 ± 1.89 | | 90.35 ± 5.71 | | 91.88 ± 11.43 | |
| Paternal characteristics | | | | | | | |
| Age (years)[d] | | $r = -0.14$ | 0.088† | $r = -0.02$ | 0.845 | $r = -0.09$ | 0.273 |
| Education level (years)[e] | | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ≤12 | 57 | 2.79 ± 2.21 | 0.096† | 90.65 ± 5.74 | 0.891 | 91.19 ± 9.62 | 0.167 |
| ≥13 | 97 | 2.21 ± 3.15 | | 90.98 ± 5.56 | | 89.52 ± 11.14 | |
| Infant characteristics | | | | | | | |
| Sex[e] | | | | | | | |
| Male | 78 | 2.31 ± 2.82 | 0.617 | 91.72 ± 5.71 | 0.067† | 90.81 ± 10.03 | 0.337 |
| Female | 76 | 2.54 ± 3.45 | | 89.97 ± 5.61 | | 89.45 ± 11.12 | |
| Parity[e] | | | | | | | |
| 0 | 71 | 2.61 ± 3.49 | 0.963 | 91.17 ± 5.62 | 0.725 | 89.82 ± 10.99 | 0.553 |
| ≥1 | 83 | 2.27 ± 2.82 | | 90.59 ± 5.63 | | 90.41 ± 10.31 | |
| Preterm birth | | | | | | | |
| No | 149 | 2.37 ± 3.06 | 0.725 | 90.87 ± 5.67 | 0.992 | 90.09 ± 10.49 | 0.890 |
| Yes | 5 | 4.00 ± 5.15 | | 90.40 ± 3.85 | | 91.40 ± 15.13 | |
| SGA[e] | | | | | | | |
| No | 151 | 2.43 ± 3.16 | 0.957 | 90.88 ± 5.66 | 0.659 | 90.18 ± 10.70 | 0.803 |
| Yes | 3 | 2.00 ± 2.65 | | 89.67 ± 2.08 | | 88.00 ± 3.00 | |
| Low birth weight[e] | | | | | | | |
| No | 151 | 2.38 ± 3.13 | 0.165 | 90.83 ± 5.63 | 0.757 | 90.24 ± 10.61 | 0.351 |
| Yes | 3 | 4.33 ± 3.51 | | 92.00 ± 5.29 | | 85.00 ± 10.39 | |
| IUGR[e] | | | | | | | |
| No | 142 | 2.45 ± 1.42 | 0.859 | 90.62 ± 5.55 | 0.059* | 90.32 ± 10.84 | 0.477 |
| Yes | 12 | 2.08 ± 2.28 | | 93.67 ± 5.77 | | 88.00 ± 7.12 | |
| Gestational age (days)[d] | | $r = 0.22$ | 0.006** | $r = 0.19$ | 0.019* | $r = 0.24$ | 0.002** |
| Birth weight (g)[d] | | $r = 0.06$ | 0.479 | $r = 0.15$ | 0.068† | $r = 0.14$ | 0.079† |
| Length (cm)[d] | | $r = 0.15$ | 0.065† | $r = 0.15$ | 0.067† | $r = 0.14$ | 0.079† |

| | | | | | | |
|---|---|---|---|---|---|---|
| Head circumference (cm)[d] | $r = 0.14$ | 0.094[†] | $r = 0.13$ | 0.097[†] | $r = 0.07$ | 0.365 |
| Chest circumference (cm)[d] | $r = 0.07$ | 0.391 | $r = 0.13$ | 0.113 | $r = 0.09$ | 0.294 |
| Age at 6-month assessment (days)[d] | $r = 0.07$ | 0.385 | $r = 0.09$ | 0.275 | $r = 0.16$ | 0.046[*] |
| Childcare environment | | | | | | |
| EES subscores at 6 months | | | | | | |
| Humanistic involvement[d] | $r = 0.20$ | 0.018[*] | $r = 0.04$ | 0.610 | $r = -0.04$ | 0.958 |
| Responsiveness[d] | $r = 0.05$ | 0.530 | $r = 0.10$ | 0.200 | $r = 0.03$ | 0.705 |
| Avoidance of restriction and punishment[d] | $r = -0.56$ | 0.491 | $r = 0.93$ | 0.252 | $r = 0.18$ | 0.025[*] |
| Physical involvement[d] | $r = -0.11$ | 0.165 | $r = -0.04$ | 0.667 | $r = -0.09$ | 0.251 |
| Social involvement[d] | $r = 0.20$ | 0.018[*] | $r = -0.03$ | 0.740 | $r = -0.13$ | 0.120 |
| Organisation of environment[d] | $r = 0.10$ | 0.242 | $r = -0.07$ | 0.378 | $r = -0.02$ | 0.821 |
| Social support[d] | $r = -0.21$ | 0.011[*] | $r = -0.06$ | 0.474 | $r = 0.03$ | 0.694 |

[a]Potential confounding variables including characteristics of mothers, fathers, infants, and childcare environments; [b]Maternal antenatal depression between the second and the third trimesters (23 – 35 gestational weeks); [c]Infant mental and psychomotor development at 6 months (from 5 months and 16 days to 6 months and 15 days after birth); Statistical analyses: [d]Spearman correlation, [e]Mann-Whitney U test, [f]Kruskal-Wallis test; [**]$p < 0.10$, [*]$p < 0.05$, [†]$p < 0.01$; EES, Evaluation of Environmental Stimulation; EPDS, Edinburgh Postnatal Depression Scale; IUGR, intrauterine growth restriction; MDI, Mental Development Index; PDI, Psychomotor Development Index; SGR, small for gestational age.

**Table 4.** Infant development (BSID-II, MDI & PDI) in relation to antenatal and postnatal maternal depression (EPDS)

| | | Antenatal EPDS[a] | | MDI[b] | | PDI[b] | |
|---|---|---|---|---|---|---|---|
| | *n* | Mean ± SD | *p* | Mean ± SD | *p* | Mean ± SD | *p* |
| Maternal characteristics | | | | | | | |
| Antenatal EPDS | | | | | | | |
| Total score[c] | | | | $r = -0.15$ | 0.057[†] | $r = -0.1$ | 0.881 |
| ≤8[d] | 145 | | | 90.88 ± 5.71 | 0.756 | 90.06 ± 10.51 | 0.841 |
| ≥9 | 9 | | | 90.44 ± 3.92 | | 91.33 ± 12.57 | |
| Postnatal EPDS at 1 month | | | | | | | |
| Total score[c] | | $r = -0.48$ | < 0.000[**] | $r = -0.16$ | 0.679 | $r = -0.03$ | 0.216 |
| ≤8[d] | 133 | 1.88 ± 2.54 | < 0.000[**] | 90.96 ± 5.80 | 0.302 | 89.71 ± 10.68 | 0.798 |
| ≥9 | 21 | 5.86 ± 4.30 | | 90.19 ± 4.33 | | 92.81 ± 9.94 | |

[a]Maternal antenatal depression between the second and the third trimesters (23 – 35 gestational weeks); [b]Infant mental and psychomotor development at 6 months (from 5 months and 16 days to 6 months and 15 days after birth); Statistical analyses: [c]Spearman correlation, [d]Mann-Whitney U test; [**]$p < 0.10$, [*]$p < 0.05$, [†]$p < 0.01$; EPDS, Edinburgh Postnatal Depression Scale; MDI, Mental Development Index; PDI, Psychomotor Development Index.

**Table 5.** Infant mental development (BSID-II, MDI) in relation to maternal antenatal depression (EPDS) and confounding variables

| | Crude model[a] adjusted $R^2 = 0.007$ $F = 2.07$, $p = 0.153$ | | | Model 1 adjusted $R^2 = 0.087$ $F = 2.81$, $p = 0.006$ | | | Model 2 adjusted $R^2 = 0.080$ $F = 2.34$, $p = 0.014$ | | | Model 3 adjusted $R^2 = 0.069$ $F = 1.94$, $p = 0.034$ | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | β | 95% CI | *P* | β | 95% CI | *P* | β | 95% CI | *p* | β | 95% CI | *p* |
| Antenatal EPDS | −0.00 | [−0.00, 0.00] | 0.153 | −0.05 | [−0.00, 0.00] | 0.500 | −0.05 | [−0.00, 0.00] | 0.552 | −0.05 | [−0.00, 0.00] | 0.585 |
| Infant factors | | | | | | | | | | | | |
| Sex | | | | −0.14 | [−0.02, 0.00] | 0.107 | −0.14 | [−0.02, 0.00] | 0.105 | −0.14 | [−0.02, 0.00] | 0.105 |
| IUGR | | | | 0.19 | [0.00, 0.04] | 0.020* | 0.21 | [−0.00, 0.04] | 0.015* | 0.21 | [0.00, 0.04] | 0.017* |
| Gestational age | | | | 0.23 | [0.00, 0.00] | 0.013* | 0.22 | [0.00, 0.00] | 0.019* | 0.23 | [0.00, 0.00] | 0.018* |
| Birth weight | | | | 0.04 | [0.00, 0.00] | 0.790 | 0.05 | [0.00, 0.00] | 0.725 | 0.05 | [0.00, 0.00] | 0.730 |
| Length | | | | 0.01 | [0.00, 0.00] | 0.928 | 0.02 | [−0.00, 0.00] | 0.864 | 0.02 | [−0.00, 0.00] | 0.878 |
| Head circumference | | | | 0.08 | [0.00, 0.01] | 0.408 | 0.07 | [−0.00, 0.01] | 0.505 | 0.07 | [−0.00, 0.01] | 0.522 |
| Age at 6-month assessment | | | | 0.09 | [0.00, 0.00] | 0.233 | 0.09 | [0.00, 0.00] | 0.252 | 1.00 | [0.00, 0.00] | 0.230 |
| Childcare factor | | | | | | | | | | | | |
| Avoidance of restriction and punishment | | | | | | | 0.08 | [−0.01, 0.03] | 0.349 | 0.07 | [−0.01, 0.03] | 0.384 |
| Maternal factor | | | | | | | | | | | | |
| Caffeine intake during pregnancy | | | | | | | −0.20 | [0.00, 0.00] | 0.841 | −0.02 | [0.00, 0.00] | 0.849 |
| Paternal factors | | | | | | | | | | | | |
| Age | | | | | | | | | | 0.00 | [−0.00, 0.00] | 0.980 |
| Education level | | | | | | | | | | 0.04 | [−0.01, 0.01] | 0.627 |

Statistical analyses: multiple linear regression analyses; $n = 154$; $^{*}p < 0.05$, $^{**}p < 0.01$; Model 1 adjusted for infant factors (sex, IUGR, gestational age, birth weight, length, head circumference, and age at 6-month assessment); Model 2 adjusted as in Model 1 *and* for childcare factor (avoidance of restriction and punishment) and maternal factor (caffeine intake during pregnancy); Model 3 adjusted as in Model 2 *and* for paternal factors (age and education level); EPDS, Edinburgh Postnatal Depression Scale; IUGR, intrauterine growth restriction; PDI, Psychomotor Development Index.

10 **Table 6.** Infant psychomotor development (BSID-II, PDI) in relation to maternal antenatal depression (EPDS) and confounding variables

| | Crude model[a] adjusted $R^2 = -0.01$, $F = 0.01$, $p = 0.927$ | | | Model 1 adjusted $R^2 = 0.09$, $F = 2.93$, $p = 0.005$ | | | Model 2 adjusted $R^2 = 0.13$, $F = 3.34$, $p = 0.001$ | | | Model 3 adjusted $R^2 = 0.14$, $F = 3.09$, $p = 0.001$ | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | β | 95% CI | *p* | β | 95% CI | *p* | β | 95% CI | *p* | β | 95% CI | *p* |
| Antinatal EPDS | −0.01 | [−0.00, 0.00] | 0.927 | 0.03 | [−0.00, 0.00] | 0.709 | 0.05 | [−0.00, 0.00] | 0.533 | 0.04 | [−0.00, 0.00] | 0.659 |
| Infant factors | | | | | | | | | | | | |
| Sex | | | | −0.09 | [−0.03, 0.01] | 0.284 | −0.10 | [−0.03, 0.00] | 0.219 | −0.10 | [−0.03, 0.01] | 0.217 |
| IUGR | | | | −0.02 | [−0.04, 0.03] | 0.769 | 0.01 | [−0.03, 0.01] | 0.924 | −0.00 | [−0.03, 0.03] | 0.957 |
| Gestational age | | | | 0.28 | [0.00, 0.00] | 0.003** | 0.25 | [0.00, 0.03] | 0.006** | 0.23 | [0.00, 0.00] | 0.012* |
| Birth weight | | | | 0.01 | [0.00, 0.00] | 0.928 | 0.04 | [0.00, 0.00] | 0.752 | 0.03 | [0.00, 0.00] | 0.832 |
| Length | | | | 0.03 | [−0.01, 0.01] | 0.795 | 0.06 | [−0.01, 0.01] | 0.609 | 0.07 | [−0.01, 0.01] | 0.557 |
| Head circumference | | | | −0.04 | [−0.01, 0.01] | 0.695 | −0.09 | [−0.01, 0.00] | 0.385 | −0.07 | [−0.01, 0.01] | 0.477 |
| Age at 6-month assessment | | | | 0.25 | [0.00, 0.00] | 0.002** | 0.24 | [0.00, 0.00] | 0.003** | 0.24 | [0.00, 0.00] | 0.002** |
| Childcare factor | | | | | | | | | | | | |
| Avoidance of restriction and punishment | | | | | | | 0.20 | [0.01, 0.07] | 0.010* | 0.23 | [0.02, 0.08] | 0.004** |
| Maternal factor | | | | | | | | | | | | |
| Caffeine intake during pregnancy | | | | | | | −0.09 | [0.00, 0.00] | 0.254 | −0.09 | [0.00, 0.00] | 0.262 |
| Paternal factors | | | | | | | | | | | | |
| Age | | | | | | | | | | −0.14 | [−0.00, 0.00] | 0.082 |
| Education level | | | | | | | | | | −0.03 | [−0.20, 0.01] | 0.662 |

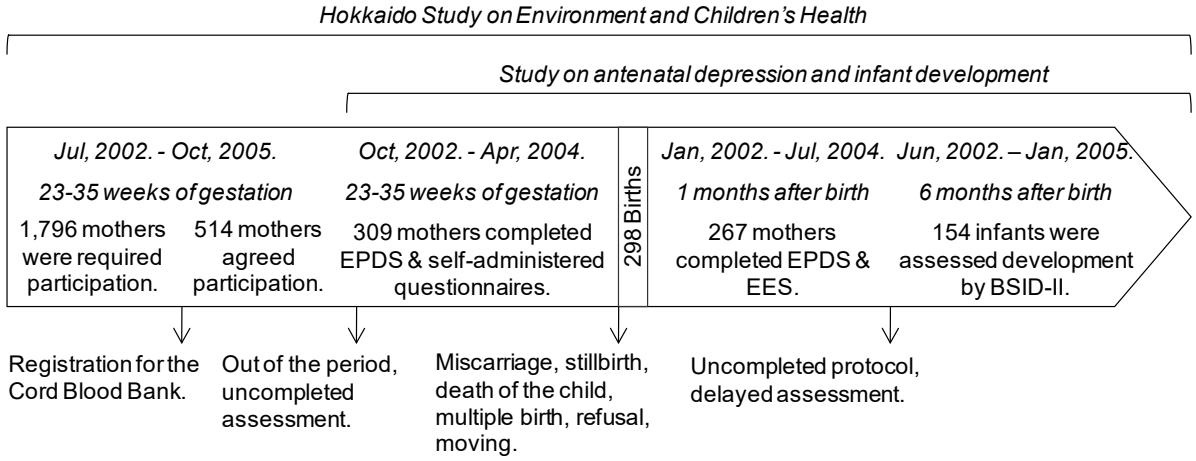
Statistical analyses: multiple linear regression analyses; $n = 154$; $^{*}p < 0.05$, $^{**}p < 0.01$; Model 1 adjusted for infant factors (sex, IUGR, gestational age, birth weight, length, head circumference, and age at 6-month assessment); Model 2 adjusted as in Model 1 *and* for childcare factor (avoidance of restriction and punishment) and maternal factor (caffeine intake during pregnancy); Model 3 adjusted as in Model 2 *and* for paternal factors (age and education level); EPDS, Edinburgh Postnatal Depression Scale; IUGR, intrauterine growth restriction; PDI, Psychomotor Development Index.

**Table 7.** Gestational age and IUGR in relation to maternal antenatal depression (EPDS) and confounding variables

| | Gestational age[a] | | | IUGR[b] | | |
|---|---|---|---|---|---|---|
| | β | 95% CI | *p* | OR | 95% CI | *p* |
| Crude | | adjusted $R^2 = 0.03$, $F = 5.07$, $p = 0.026$ | | | Nagelkerke $R^2 = 0.003$, $\chi^2 = 0.16$, $p = 0.686$ | |
| Antenatal EPDS | −0.18 | [−0.92, −0.06] | 0.026* | 0.96 | [0.78, 1.18] | 0.697 |
| Adjusted[c] | | adjusted $R^2 = 0.12$, $F = 2.19$, $p = 0.006$ | | | Nagelkerke $R^2 = 0.27$, $\chi^2 = 18.24$, $p = 0.571$ | |
| Antenatal EPDS | −0.25 | [−1.20, −0.17] | 0.010* | 0.81 | [0.59, 1.11] | 0.199 |
| Confounding variables | | | | | | |
| Stressful life events before pregnancy | −0.18 | [−5.91, −0.30] | 0.030* | 2.75 | [0.61, 12.322] | 0.186 |
| Planned pregnancy | 0.20 | [0.26, 6.43] | 0.034* | 0.80 | [0.15, 4.38] | 0.795 |
| Infant sex; female | 0.17 | [0.02, 5.57] | 0.048* | 0.43 | [0.08, 2.38] | 0.333 |
| First born | −0.23 | [−6.84, −1.11] | 0.007** | 1.14 | [0.23, 5.77] | 0.875 |

Statistical analyses: [a]multiple linear regression analyses, [b]logistic regression analyses; $n = 154$; $^*p < 0.05$, $^{**}p < 0.01$ (Table 6 indicates factors which were statistically significant in relation to gestational age or IUGR.); [c]Adjusted for maternal factors (age, education level, household income, worked during pregnancy, smoked during pregnancy, caffeine intake during pregnancy, alcohol intake during pregnancy, stressful life events before pregnancy, past depressive symptoms, worrying, obsessiveness, planned pregnancy, wanted pregnancy), paternal factors (age and education level), and infant factors (sex and parity); EPDS, Edinburgh Postnatal Depression Scale; IUGR, intrauterine growth restriction.

1 **Figure**




EPDS, Edinburgh Postnatal Depression Scale; EES, Evaluation of Environmental Stimulation; BSID-II, Bayley Scales of Infant Development II

2 Fig. 1, Yuko OTAKE

3 **Fig 1.** Selection process for participant eligibility in Hokkaido Study

**Figure Legend**

**Fig 1.** Selection process for participant eligibility in Hokkaido Study.

The prospective cohort study was performed between July, 2002 and October, 2005, based on Toho Hospital (Hokkaido Study on Environment and Children's Health). A total of 1,796 pregnant women were required to participate in the study during a routine gynaecological checkup and 514 women agreed. Women who registered for the Cord Blood Bank were excluded from the eligible participants. Assessment of depression during pregnancy was conducted between October, 2002 and April, 2004; 309 women were involved in the assessment and completed questionnaires (60% of the initial cohort). Pregnant women who were out of the period or failed to complete the assessment were eliminated from the cohort. Postnatal depression was assessed in 267 mothers between 1 and 4 months, and infant development was assessed in 154 mother-infant pairs at during the period from 5 months and 16 days up to 6 months and 15 days after birth (50 % follow-up rate). Excluded participants were those who did not complete the protocol due to miscarriage, stillbirth, multiple birth, relocation, death of the infant, or voluntary withdrawal from the study. Statistical analysis was conducted for 154 mother-infant pairs.