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# Neurological development in 36-month-old children conceived via assisted reproductive technology: The Japan Environment and Children's Study

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## Abstract

**Purpose:** This study aimed to investigate neurodevelopment in children conceived via *in vitro* fertilization (IVF) or intracytoplasmic sperm injection (ICSI) with several types of embryo transfers.

**Methods:** We analyzed data for 77 928 children and their mothers included in a Japanese birth cohort study. Among the included children, 4071 were conceived via IVF, while 1542 were conceived via ICSI. Neurodevelopmental delay at the age of 3 years was assessed using the Japanese version of the Ages and Stages Questionnaires, 3rd edition.

**Results:** In the crude model, the odds ratios for developmental delay in 1–4 domains were higher among children conceived via IVF, ICSI, and non-ART (ovulatory induction or intrauterine insemination) than in spontaneously conceived children. After adjusting for parental background factors and the child's sex, there were no differences in the risk of developmental delay when comparing singletons conceived by IVF, ICSI, or non-ART and those conceived spontaneously. Higher odds ratios for developmental delay in one domain were observed in singleton girls conceived via IVF when compared with those who were spontaneously conceived.

**Conclusion:** Most cases of developmental delay may be associated with multiple pregnancies and factors related to infertility, such as parental age, irrespective of the use of ART.

KEYWORDS
assisted reproductive technology, children, embryo transfer, fertility, neurodevelopment

Takao Miyake and Midori Yamamoto contributed equally to this work.

The Japan Environment and Children's Study (JECS) Group are listed in Appendix.

## 1 | INTRODUCTION

Worldwide, the use of assisted reproductive technologies (ART) such as *in vitro* fertilization (IVF) and intracytoplasmic sperm injection (ICSI) continues to increase annually, with ICSI accounting for over 50% of ART cycles in many countries.[1,2] As of 2017, the percentage of conceptions associated with ART in Japan had increased to 6%.[3] Pregnancies conceived via ART are generally associated with increased risks of adverse obstetric and perinatal outcomes when compared with spontaneous conception (SC).[4,5] Additionally, there are concerns regarding its possible negative effect on children's health outcomes.

Adverse obstetric and perinatal outcomes have primarily been reported in patients with multiple pregnancies following the transfer of multiple embryos.[6-8] As the success rates of frozen embryo transfer have recently improved, single embryo transfer (SET) rates are increasing worldwide.[9] In 2008, the Japan Society of Obstetrics and Gynecology issued a recommendation for SET, following which rates of multiple pregnancy in the country decreased considerably, thus relatively improving perinatal outcomes.[10] Although the incidence of adverse obstetric and perinatal outcomes in patients with single ART-associated pregnancies is lower than that in patients with multiple pregnancies, it remains higher than that in those with spontaneous pregnancies.[11-15] This difference may be linked to technical issues related to IVF/ICSI with ovulation induction/culturing, or to the inherent characteristics and genetic features of subfertility. However, the direct relationship between ART and children's health outcomes remains poorly understood.[11,16-18]

Most studies on neurological development have reported no risk associations in children conceived via ART after adjustment for multiple births.[11] However, the Danish National Birth Cohort reported an association between ICSI and mild delay in several developmental milestones,[19] and the Finnish Population-Based Register Study reported a slightly higher rate of psychiatric diagnoses in singleton children born after ART than in those born after SC.[20] However, there is limited evidence concerning the effects of ART and frozen embryo transfer on child development, warranting further large-scale epidemiological studies.

Initiated in 2011, the Japan Environment and Children's Study (JECS) is a nationwide birth cohort study that aims to elucidate the effects of environmental factors on child health and development. Several studies have analyzed JECS data to investigate ART. Among them, Nagata et al. reported that women who conceived via ART were at higher risk of placenta previa, morbidly adherent placenta, pregnancy-induced hypertension, blood transfusion, intensive care unit (ICU) admission, and preterm delivery than those who conceived naturally, even after controlling for potential confounders.[21] Yoshimasu et al. reported that the use of ART was not associated with maternal psychological distress during pregnancy, although it associated with a slight increase in lack of affection for the child.[22,23] Additional studies have investigated prenatal factors associated with neurodevelopment in children, reporting negative associations between maternal blood levels of manganese and cadmium and neurodevelopment in children up to 3 and 2 years of age, respectively.[24,25] Maternal exposure to formalin or formaldehyde during pregnancy has also been associated with an increased risk of neurodevelopmental delay in children at 1 year of age,[26] while maternal sleep quality and physical activity during pregnancy have been associated with a decreased risk.[27,28]

Given the relative scarcity of evidence mentioned above, we aimed to clarify the relationships between ART and children's neurodevelopment using JECS data. To achieve this aim, we investigated the association between fertility treatments (including ART) and developmental delay in all children and singletons at 3 years of age, considering the child's sex and differences in parental background. We also analyzed the association between transferred embryos and children's development.

## 2 | MATERIALS AND METHODS

### 2.1 | Study population

The study design of the JECS has been described previously.[29] Briefly, the JECS is a nationwide, government-funded birth cohort study aiming to evaluate the effects of environmental factors on children's health and development. In total, 103 060 pregnancies were registered at 15 regional centers located throughout Japan between January 2011 and March 2014. This study used the jecs-ta-20190930 dataset, which was released in October 2019.

The JECS protocol was reviewed and approved by the Ministry of the Environment's Institutional Review Board on Epidemiological Studies and the Ethics Committees of all participating institutions. This study was conducted in accordance with the Helsinki Declaration and other nationally valid regulations and guidelines. Written informed consent was obtained from all parents regarding their children's participation in the study.

### 2.2 | Assessment of neurodevelopment

The children's neurodevelopment at the age of 3 years was assessed using the Japanese version of the Ages and Stages Questionnaires, Third Edition (J-ASQ-3),[30,31] which was completed by parents or primary guardians between 34 months, 16 days and 38 months, 30 days after childbirth. The ASQ-3 is used to screen for developmental delay across five domains: communication, gross motor, fine motor, problem solving, and personal–social. There are six questions for each domain, and their total scores add up to 0–60 points. Mezawa et al. verified the validity of the J-ASQ-3 and reported the cut-off scores for developmental delay at the age of 3 years as follows: communication (29.95), gross motor (39.26), fine motor (27.91), problem solving (30.03), and personal–social (29.89).[31]

## 2.3 | Conception information

The method of conception and potential confounders were identified through medical record transcripts and self-administered questionnaires filled out by mothers during pregnancy. The former items were transcribed by doctors, nurses, midwives, hospital staff, or Research Coordinators involved in the JECS. When discrepancies occurred, data with notes on more advanced treatment were selected, in the following descending order of priority: (1) ICSI, (2) IVF, (3) artificial insemination by husband (AIH), (4) ovulation induction, and (5) SC. AIH and ovulation induction were grouped together as “Non-ART” for analysis. Embryo transfers were further classified as follows when the relevant information was available in medical record transcripts: (1) fresh embryo transfer, (2) frozen embryo transfer, and (3) blastocyst transfer. If this information was unavailable in medical record transcripts, the data were used when mothers reported “blastocyst transfer” on the questionnaire.

## 2.4 | Statistical analyses

Characteristics of children and parents were compared between SC and the various types of infertility treatment (ICSI, IVF, and non-ART [ovulatory induction or intrauterine insemination]) using the Mann–Whitney *U*-test or Fisher's exact test. Bonferroni correction was used to compensate for Type I error in multiple comparisons. Associations between the child's development and the method of conception or embryo transfer were analyzed via binomial logistic regression with three models. The crude model was not adjusted for any covariates. Adjusted Model 1 was adjusted for the sex of the child and parental background factors including parental age and education; household income; parity; maternal body mass index; pre-existing conditions (chronic hypertension, hyperthyroidism, hypothyroidism, autoimmune disease, and kidney disease); folic acid supplementation; smoking; drinking; maternal history of developmental disorders, epilepsy, and mental disease; method of feeding, and residential area. Obstetric and perinatal factors were not included in Adjusted Model 1 because they may act as intermediate variables, although they were added as covariates in Adjusted Model 2. These variables included complications during pregnancy (diabetes mellitus, gestational diabetes mellitus, and pregnancy-induced hypertension), delivery mode, fetal presentation, and intrauterine growth restriction. Small for gestational age was determined according to Japanese neonatal anthropometric charts for gestational age[32,33] and defined as a birthweight below the 10th percentile. The missing values for covariates were complemented by multiple imputations. In the process, each missing value was replaced with a series of substituted plausible values by creating 10 filled-in complete datasets using conception methods, outcomes, covariates, and variables related to conception methods/child development (singleton/multiple births, gestational week, birthweight, the presence of physical anomalies, Apgar score, and umbilical arterial blood pH). For sensitivity analysis, complete case analyses were performed by excluding missing data for covariates. SPSS ver. 27 (IBM Corp) was used for statistical analyses.

## 3 | RESULTS

The flowchart of participant inclusion is shown in Figure 1. Of 104 062 fetal records, the following were excluded: 591 cases with missing data related to conception; 65 cases with missing data related to the details of ART; 1259 miscarriages; 295 stillbirths; 1702 cases in which miscarriage or stillbirth status was unknown; 2183 cases involving the death of the mother/child or termination of follow-up due to unknown address; 1418 withdrawals; 87 chromosomal abnormalities; 18 534 cases with inadequate completion of the J-ASQ-3 at 3 years. Finally, 70 924 children born through SC, 4071 children born after non-ART, 1391 children born after IVF, and 1542 children born after ICSI were included in the analysis set. Notably, the rate of inadequate J-ASQ-3 completion was 18.4% in the SC group, which was higher than that for the other conception methods (9.5%–13.0%; Table S1).

Table 1 shows a comparison of child and parent characteristics between children conceived via SC and those conceived via non-ART, IVF, or ICSI. Higher rates of multiple births, preterm births, and cesarean sections as well as lower birthweight and rates of physical anomalies were observed in children born after non-ART, IVF, and ICSI than in children born after SC. Parents who underwent infertility treatment had a higher proportion of primiparas; higher age, educational attainment, and income; and lower maternal smoking and drinking rates during pregnancy than those who did not undergo such treatment. Table 2 presents a comparison of perinatal characteristics between singleton children conceived spontaneously and those conceived via non-ART, IVF, or ICSI. In singletons, the rates of preterm birth, lower birthweight, and cesarian section were still higher in children born after non-ART, IVF, and ICSI than in children born after SC.

Table 3 displays the results of the logistic regression analysis for the relationship between infertility treatment and developmental delay at 3 years. In the analysis including all children without adjusting for covariates (crude model), children conceived via IVF had higher odds ratios (ORs) for delay in gross motor, fine motor, problem solving, and personal–social domains of development than those conceived spontaneously. Children born after ICSI also had higher ORs for delays in the gross motor domain, while children conceived via non-ART had high ORs for communication, gross motor, fine motor, and personal–social domains. After adjusting for parental background factors and sex of the child (Adjusted Model 1), the higher ORs for delay in the gross motor domain disappeared in the ICSI group. After adjusting for obstetric and perinatal factors (Adjusted Model 2), all increased ORs disappeared except for those related to the fine motor domain in the non-ART group. In an analysis restricted to singletons, the results for the crude model were similar

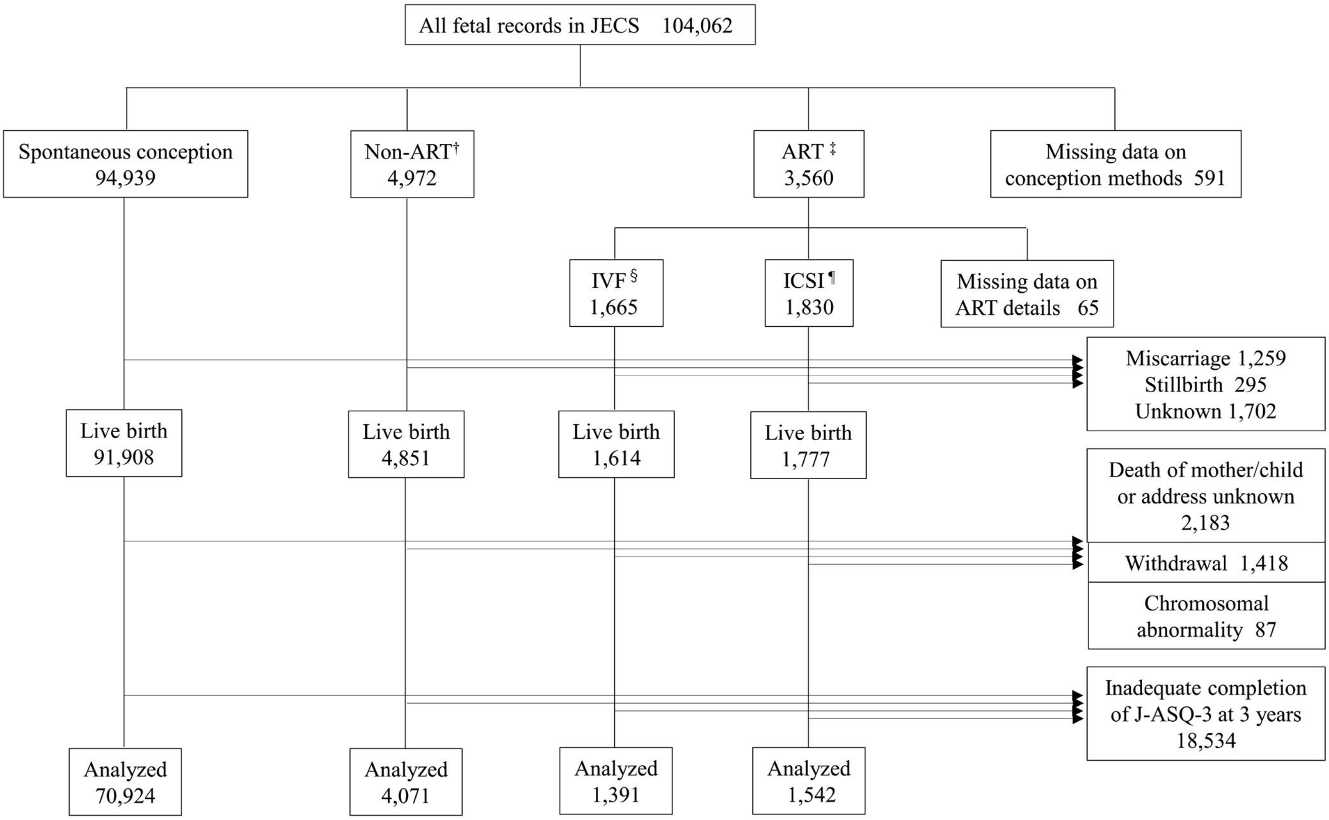


**FIGURE 1** Flowchart of the inclusion process for participating children. †Non-ART, without assisted reproductive technologies (ovulatory induction or intrauterine insemination); ART, assisted reproductive technologies; IVF, *in vitro* fertilization; ICSI, intracytoplasmic sperm injection

to those observed among all children. After adjusting for parental background factors and sex of the child, all increased ORs for children conceived via non-ART, IVF, and ICSI disappeared. The result did not change in Adjusted Model 2. Furthermore, when the analysis was restricted to term-birth singletons, higher ORs were observed in only three domains among children conceived via IVF and one domain among children conceived via non-ART and ICSI in the crude model, whereas all high ORs disappeared in the adjusted models.

An analysis was performed by sex to investigate the relationships between infertility and developmental delay in singletons at 3 years of age (Table 4). In all domains, the rate of developmental delay was higher in boys than in girls. In boys, high ORs for gross motor delay were observed in children conceived via IVF or ICSI in the crude model, which also revealed high ORs in three developmental domains among those conceived via non-ART; however, the higher ORs disappeared in the adjusted models. The OR for the personal–social domain decreased in boys conceived via ICSI (OR [95% confidence interval], 0.68 [0.48–0.96]). In girls, high ORs were observed for all domains in children conceived via IVF and for the personal–social domain in those conceived via ICSI in the crude model. After adjusting for covariates, the ORs for fine motor delay remained high (OR [95% confidence interval], 1.64 [1.17–2.31] in Adjusted Model 2). The high OR for the fine motor domain remained when the analysis was restricted to term-birth singleton girls (Table S2).

Table 5 presents the relationship between embryo transfer and developmental delay at 3 years in singletons. Among the 2708 total singletons born after IVF or ICSI, we analyzed the relationship between embryo transfer and child development in 1947 children with available information related to embryo transfer. Although the data only represented a small number of fresh embryo transfers, the ORs for delays in the fine motor, problem solving, and personal–social domains were high in the crude model. The OR for fine motor development was high for children born after IVF/ICSI in cases of frozen embryo transfer, while the OR for gross motor development was high for children born after IVF/ICSI in cases of blastocyst transfer; however, the high ORs disappeared in the adjusted models.

A complete case model was used to perform sensitivity analysis after excluding missing values for covariates ($n = 66\,733$ for all children). Similar to the multiple imputation model overall, no increase in the risk of developmental delay was observed for singletons or term-birth singletons born after ART in the adjusted model (Table S3).

## 4 | DISCUSSION

This study investigated the relationships between ART and development at 3 years of age using data from a large birth cohort study involving children born in Japan between 2011 and 2014. The analysis revealed the following findings: (1) The risk of developmental

**TABLE 1** Characteristics of children and parents in the spontaneous conception, non-ART[a], IVF, and ICSI groups ($N$ = 77 928)

| Characteristics | Spontaneous | Non-ART[a] | IVF | ICSI | Missing, % |
|---|---|---|---|---|---|
| Number | 70 924 | 4071 | 1391 | 1542 | |
| Child characteristics | | | | | |
| Boys, % | 51.3 | 50.3 | 53.3 | 49.3 | 0 |
| Multiple birth, % | 1.2 | **7.6** | **7.9** | **7.5** | 0 |
| Twin | 1.2 | **7.1** | **7.7** | **7.5** | |
| Triplet | 0.0 | **0.5** | **0.2** | **0 (none)** | |
| Gestational age at birth (weeks), mean (SD) | 38.8 (1.6) | **38.6 (2.0)** | **38.4 (2.2)** | **38.6 (2.1)** | 0.2 |
| Preterm birth (<37 weeks), % | 4.9 | **9.2** | **10.4** | **10.2** | 0.2 |
| Birthweight (g), mean (SD) | 3017.9 (417.7) | **2928.4 (494.0)** | **2939.7(514.0)** | 2975.6 (500.8) | 0.2 |
| Low birthweight (<2500 g), % | 8.0 | **13.0** | **12.9** | **12.3** | 0.2 |
| Very low birthweight (<1500 g), % | 0.5 | **1.5** | **1.7** | **1.5** | |
| Small for gestational age, % | 7.7 | **10.3** | 8.7 | 8.0 | 2.9 |
| Cesarean section, % | 18.5 | **25.9** | **39.9** | **40.4** | 0.4 |
| Physical anomaly at birth, % | 6.0 | **7.5** | 7.4 | **7.7** | 2.3 |
| Neonatal asphyxia, % | 0.5 | 0.6 | **1.3** | 1.0 | 5.1 |
| Mothers' characteristics | | | | | |
| Age at delivery (years), mean (SD) | 31.2 (4.9) | **33.0 (4.2)** | **36.1 (3.8)** | **36.1 (4.0)** | 0.0 |
| Education, % | | | | | |
| Junior or senior high | 34.7 | **23.2** | **23.1** | **21.4** | 1.0 |
| Junior college or vocational | 42.6 | **48.1** | **46.4** | **47.2** | |
| Undergraduate or above | 22.7 | **28.7** | **30.5** | **31.4** | |
| Annual household income (million Japanese Yen), % | | | | | |
| <400 | 40.1 | **26.7** | **20.6** | **17.7** | 6.9 |
| 400-<600 | 33.4 | **36.9** | **35.7** | **33.7** | |
| ≥600 | 26.4 | **36.4** | **43.7** | **48.5** | |
| Primiparous, % | 41.3 | **61.9** | **68.3** | **70.0** | 0.0 |
| BMI before pregnancy (kg/m$^2$), mean (SD) | 21.1(3.2) | 21.3(3.6) | 21.3(3.1) | **21.3(3.1)** | |
| Smoking during pregnancy, % | 17.6 | **9.5** | **6.3** | **4.9** | 0.3 |
| Drinking during pregnancy, % | 50.5 | **46.6** | **38.3** | **39.0** | 0.2 |
| Fathers' characteristics | | | | | |
| Age at 6 months after delivery (years), mean (SD) | 33.5 (5.8) | **35.3 (5.0)** | **38.1 (4.8)** | **38.9 (5.5)** | 3.5 |
| Education, % | | | | | |
| Junior or senior high | 42.8 | **31.7** | **32.6** | **31.8** | 1.5 |
| Junior college or vocational | 23.1 | **22.9** | **20.0** | **21.7** | |
| Undergraduate or above | 34.1 | **45.5** | **47.5** | **46.5** | |

*Note*: Bold text indicates $p < 0.0167$ when compared with spontaneous conception after Bonferroni correction.
Abbreviations: BMI, body mass index; ICSI, intracytoplasmic sperm injection; IVF, *in vitro* fertilization; SD, standard deviation.
[a]Non-ART, without assisted reproductive technologies (ovulatory induction or intrauterine insemination).

delay in an analysis unadjusted for covariates was higher in children conceived via IVF, ICSI, and non-ART than in children conceived spontaneously; (2) the risk of developmental delay was not higher in singletons born after IVF, ICSI, or non-ART than in children born after SC after adjusting for parental background factors and the sex of the child; (3) singleton girls born after IVF were at a higher risk of fine motor delay than those born after SC, even after adjusting for covariates; (4) the risk of developmental delay was not higher in singletons conceived via frozen embryo or blastocyst transfer than in children born after SC after adjusting for covariates; and (5) singletons conceived via fresh embryo transfer had a higher rate of developmental delay than those conceived spontaneously.

**TABLE 2** Perinatal characteristics of singleton children in the spontaneous conception, non-ART[a], IVF, and ICSI groups ($N = 76\ 537$)

| Characteristics | Spontaneous | Non-ART[a] | IVF | ICSI | missing, % |
|---|---|---|---|---|---|
| Number | 70 067 | 3762 | 1281 | 1427 | |
| Child characteristics | | | | | |
| Gestational age at birth (weeks), mean (SD) | 38.9 (1.5) | 38.8 (1.7) | 38.7 (1.9) | 38.7 (1.9) | 0.2 |
| Preterm birth (<37 weeks), % | 4.4 | **5.4** | **7.6** | **6.9** | 0.2 |
| Birthweight (g), mean (SD) | 3027.2 (408.7) | **2988.9 (443.6)** | 3002.5 (461.7) | 3028.8 (468.6) | 0.2 |
| Low birthweight (<2500 g), % | 7.3 | **8.8** | **9.4** | **8.4** | 0.2 |
| Very low birthweight (<1500 g), % | 0.5 | **0.9** | **0.9** | **1.2** | |
| Cesarean section, % | 17.7 | **21.1** | **35.8** | **36.1** | 0.4 |

*Note*: Bold text indicates $p < 0.0167$ when compared with spontaneous conception after Bonferroni correction.

Abbreviations: BMI, body mass index; ICSI, intracytoplasmic sperm injection; IVF, *in vitro* fertilization; SD, standard deviation.

[a]Non-ART, without assisted reproductive technologies (ovulatory induction or intrauterine insemination).

According to the crude analysis, the risk of developmental delay was higher in four domains among children conceived via IVF and in one domain among those conceived via ICSI than in children conceived spontaneously. However, the increased risk of developmental delay was not unique to ART and was also observed in children conceived by non-ART. After adjusting for parental background factors, including parental age and parity (Adjusted Model 1), the increase in the risk of developmental delay in children conceived via non-ART/IVF/ICSI disappeared, except for narrowed ORs in communication, gross motor, and fine motor domains for non-ART/IVF. The remaining high ORs disappeared almost completely after adjusting for obstetric and perinatal factors (Adjusted Model 2). These results suggest that the higher risk of developmental delay observed in children conceived via ART and non-ART was linked to parental factors, such as parental age and obstetric history, as well as to obstetric and perinatal outcomes. In the adjusted models, increased maternal and paternal ages were independently associated with developmental delay (data not shown). Decreases in oocyte quality and fertility have been associated with age and pathological as well as genetic factors.[17,34] In their inter-sibling analysis, Seggers et al. reported that higher subfertility rates and maternal characteristics such as age, rather than IVF treatment itself, were associated with low birthweight.[35] For ICSI, which is primarily indicated for male infertility, the genetic effects of abnormal sperm on children's health and development have been discussed in addition to its invasiveness.[11,36] However, in our study, ICSI was not associated with an increased risk of developmental delay when compared with IVF.

The rate of multiple births was 7.5%–7.9% among children conceived after infertility treatment, which was higher than that among those conceived spontaneously. At commencement of the survey, the Japan Society of Obstetrics and Gynecology had already recommended SET; therefore, the rate of multiple births had decreased dramatically since 1995 (20% at the time). However, double-embryo transfer was permitted for women aged 35 years or older and for women who could not become pregnant after multiple embryo transfer attempts; thus, it is not yet possible to entirely avoid multiple-birth pregnancies. In the current study, the ORs for developmental delay in the gross motor and fine motor domains were higher in children conceived via IVF after adjusting for parental background factors, but higher ORs were not observed in singletons. These results suggest that the higher rates of developmental delay in children conceived via IVF were associated with adverse perinatal outcomes related to multiple births. Furthermore, in the crude model, the high OR for developmental delay in the fertility treatment group was similar to that for all children when the analysis was restricted to singletons. However, the high ORs in the IVF and non-ART groups partially disappeared in the full-term singleton-only analysis, indicating that developmental delays in children conceived via fertility treatment may be partially mediated by preterm birth.

The results of our study on 3-year-old children support the findings of multiple studies reporting only mild or no delay in psychomotor development in children born after ART.[11,37-39] However, a sex-specified analysis on singletons indicated that the risk of developmental delay in the fine motor domain was higher only in girls conceived via IVF after adjusting for covariates. The same result was observed for full-term singleton infants. While the precise cause remains unknown, such findings indicate that there may be a sex difference in the effect of infertility treatment on development.

In the backdrop of technological advancements in embryo cryopreservation, the "freeze-all" technique and SET to avoid ovarian hyperstimulation syndrome and multiple birth pregnancies have been recommended.[40] Our analysis of singletons revealed a marked increase in the rate of developmental delay across three domains in children conceived via fresh embryo transfer. No association was observed for IVF/ICSI-frozen embryo transfer or IVF/ICSI-blastocyst transfer after adjusting for covariates. We cannot draw definitive conclusions from our survey results alone given the large amount of unavailable data. However, our findings regarding the high prevalence of developmental delay in the fresh embryo transfer group were similar to those of a randomized controlled trial in which ASQ-3 scores for the fine motor and problem solving domains were lower in the fresh embryo transfer group than in the freeze-only group among children at 2–3 years of age.[41] Previous meta-analyses have reported improved live birth rates via frozen embryo transfer when compared with fresh embryo transfer, along with lower risks of preterm birth, fetal growth restriction, and ovarian hyperstimulation

**TABLE 3** Association between conception and children's developmental delay at the age of 3 years among all children and singletons

| | | | Spontaneous | | Non-ART[a] | | IVF | | ICSI | |
|---|---|---|---|---|---|---|---|---|---|---|
| Population | Analysis model | Domain | % of cases | Odds ratio [95% CI] | % of cases | Odds ratio [95% CI] | % of cases | Odds ratio [95% CI] | % of cases | Odds ratio [95% CI] |
| All children (*n* = 77 928) | Crude | Communication | 4.0 | 1.00 reference | 4.9 | **1.22 [1.05, 1.41]** | 4.9 | 1.23 [0.96, 1.57] | 4.8 | 1.20 [0.95, 1.52] |
| | | Gross motor | 4.5 | 1.00 reference | 5.9 | **1.35 [1.18, 1.54]** | 7.6 | **1.76 [1.44, 2.16]** | 6.5 | **1.48 [1.21, 1.82]** |
| | | Fine motor | 7.6 | 1.00 reference | 9.3 | **1.23 [1.10, 1.37]** | 10.5 | **1.42 [1.19, 1.68]** | 7.8 | 1.03 [0.85, 1.24] |
| | | Problem solving | 7.4 | 1.00 reference | 8.0 | 1.08 [0.96, 1.22] | 9.8 | **1.35 [1.13, 1.62]** | 8.3 | 1.13 [0.94, 1.36] |
| | | Personal–Social | 3.3 | 1.00 reference | 4.4 | **1.34 [1.14, 1.56]** | 5.2 | **1.62 [1.27, 2.05]** | 3.7 | 1.12 [0.86, 1.47] |
| | Adjusted 1 | Communication | 4.0 | 1.00 reference | 4.9 | **1.18 [1.01, 1.37]** | 4.9 | 1.04 [0.81, 1.35] | 4.8 | 1.04 [0.81, 1.33] |
| | | Gross motor | 4.5 | 1.00 reference | 5.9 | **1.16 [1.01, 1.33]** | 7.6 | **1.27 [1.03, 1.57]** | 6.5 | 1.07 [0.86, 1.32] |
| | | Fine motor | 7.6 | 1.00 reference | 9.3 | **1.19 [1.06, 1.33]** | 10.5 | **1.21 [1.01, 1.45]** | 7.8 | 0.91 [0.75, 1.10] |
| | | Problem solving | 7.4 | 1.00 reference | 8.0 | 1.03 [0.91, 1.16] | 9.8 | 1.14 [0.94, 1.37] | 8.3 | 0.96 [0.80, 1.16] |
| | | Personal–Social | 3.3 | 1.00 reference | 4.4 | 1.17 [1.00, 1.38] | 5.2 | 1.13 [0.88, 1.45] | 3.7 | 0.80 [0.61, 1.06] |
| | Adjusted 2 | Communication | 4.0 | 1.00 reference | 4.9 | 1.15 [0.99, 1.34] | 4.9 | 1.00 [0.77, 1.29] | 4.8 | 1.00 [0.78, 1.28] |
| | | Gross motor | 4.5 | 1.00 reference | 5.9 | 1.12 [0.98, 1.29] | 7.6 | 1.19 [0.97, 1.47] | 6.5 | 1.00 [0.81, 1.24] |
| | | Fine motor | 7.6 | 1.00 reference | 9.3 | **1.16 [1.03, 1.30]** | 10.5 | 1.16 [0.97, 1.39] | 7.8 | 0.87 [0.71, 1.05] |
| | | Problem solving | 7.4 | 1.00 reference | 8.0 | 1.01 [0.89, 1.14] | 9.8 | 1.10 [0.91, 1.32] | 8.3 | 0.93 [0.77, 1.12] |
| | | Personal–Social | 3.3 | 1.00 reference | 4.4 | 1.13 [0.96, 1.33] | 5.2 | 1.07 [0.83, 1.38] | 3.7 | 0.76 [0.57, 1.00] |
| Singletons (*n* = 76 537) | Crude | Communication | 4.0 | 1.00 reference | 4.4 | 1.11 [0.94, 1.30] | 4.6 | 1.16 [0.89, 1.51] | 4.8 | 1.22 [0.95, 1.56] |
| | | Gross motor | 4.4 | 1.00 reference | 5.3 | **1.21 [1.05, 1.41]** | 7.3 | **1.68 [1.36, 2.09]** | 6.6 | **1.52 [1.23, 1.88]** |
| | | Fine motor | 7.6 | 1.00 reference | 8.5 | **1.14 [1.01, 1.28]** | 10.1 | **1.38 [1.15, 1.65]** | 7.9 | 1.05 [0.86, 1.27] |
| | | Problem solving | 7.4 | 1.00 reference | 7.4 | 1.00 [0.88, 1.14] | 9.4 | **1.31 [1.08, 1.58]** | 8.3 | 1.14 [0.95, 1.38] |
| | | Personal–Social | 3.3 | 1.00 reference | 4.0 | **1.24 [1.04, 1.46]** | 4.6 | **1.42 [1.09, 1.85]** | 3.7 | 1.13 [0.86, 1.49] |
| | Adjusted 1 | Communication | 4.0 | 1.00 reference | 4.4 | 1.07 [0.91, 1.27] | 4.6 | 0.99 [0.75, 1.30] | 4.8 | 1.06 [0.82, 1.37] |
| | | Gross motor | 4.4 | 1.00 reference | 5.3 | 1.05 [0.90, 1.21] | 7.3 | 1.21 [0.97, 1.51] | 6.6 | 1.09 [0.88, 1.36] |
| | | Fine motor | 7.6 | 1.00 reference | 8.5 | 1.10 [0.97, 1.24] | 10.1 | 1.18 [0.97, 1.43] | 7.9 | 0.93 [0.76, 1.14] |
| | | Problem solving | 7.4 | 1.00 reference | 7.4 | 0.96 [0.84, 1.09] | 9.4 | 1.10 [0.90, 1.34] | 8.3 | 0.98 [0.80, 1.19] |
| | | Personal–Social | 3.3 | 1.00 reference | 4.0 | 1.09 [0.92, 1.30] | 4.6 | 1.00 [0.76, 1.31] | 3.7 | 0.82 [0.61, 1.09] |
| | Adjusted 2 | Communication | 4.0 | 1.00 reference | 4.4 | 1.06 [0.90, 1.26] | 4.6 | 0.97 [0.74, 1.27] | 4.8 | 1.03 [0.80, 1.33] |
| | | Gross motor | 4.4 | 1.00 reference | 5.3 | 1.04 [0.89, 1.20] | 7.3 | 1.16 [0.93, 1.45] | 6.6 | 1.05 [0.84, 1.31] |
| | | Fine motor | 7.6 | 1.00 reference | 8.5 | 1.09 [0.97, 1.23] | 10.1 | 1.15 [0.95, 1.39] | 7.9 | 0.90 [0.74, 1.10] |
| | | Problem solving | 7.4 | 1.00 reference | 7.4 | 0.95 [0.83, 1.08] | 9.4 | 1.08 [0.88, 1.31] | 8.3 | 0.95 [0.78, 1.16] |
| | | Personal–Social | 3.3 | 1.00 reference | 4.0 | 1.08 [0.91, 1.28] | 4.6 | 0.96 [0.59, 1.27] | 3.7 | 0.79 [0.59, 1.05] |

(Continues)

TABLE 3 (Continued)

| Population | Analysis model | Domain | Spontaneous | | | Non-ART[a] | | | IVF | | | ICSI | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | % of cases | Odds ratio [95% CI] | | % of cases | Odds ratio [95% CI] | | % of cases | Odds ratio [95% CI] | | % of cases | Odds ratio [95% CI] | |
| Term-birth singletons (≥37 weeks) (*n* = 72 943) | Crude | Communication | 3.8 | 1.00 | reference | 4.0 | 1.06 | [0.89, 1.26] | 4.1 | 1.06 | [0.80, 1.42] | 4.7 | 1.25 | [0.97, 1.62] |
| | | Gross motor | 4.2 | 1.00 | reference | 4.9 | **1.17** | **[1.00, 1.37]** | 6.4 | **1.56** | **[1.23, 1.97]** | 6.4 | **1.55** | **[1.24, 1.97]** |
| | | Fine motor | 7.3 | 1.00 | reference | 8.0 | 1.11 | [0.98, 1.25] | 9.4 | **1.32** | **[1.08, 1.60]** | 7.6 | 1.05 | [0.85, 1.28] |
| | | Problem solving | 7.2 | 1.00 | reference | 6.9 | 0.96 | [0.84, 1.10] | 8.8 | **1.25** | **[1.02, 1.53]** | 8.1 | 1.14 | [0.93, 1.39] |
| | | Personal–Social | 3.1 | 1.00 | reference | 3.6 | 1.17 | [0.98, 1.40] | 4.0 | 1.28 | [0.95, 1.72] | 3.7 | 1.19 | [0.89, 1.58] |
| | Adjusted 1 | Communication | 3.8 | 1.00 | reference | 4.0 | 1.02 | [0.86, 1.22] | 4.1 | 0.91 | [0.67, 1.23] | 4.7 | 1.09 | [0.84, 1.43] |
| | | Gross motor | 4.2 | 1.00 | reference | 4.9 | 1.01 | [0.86, 1.19] | 6.4 | 1.13 | [0.89, 1.44] | 6.4 | 1.13 | [0.90, 1.43] |
| | | Fine motor | 7.3 | 1.00 | reference | 8.0 | 1.07 | [0.94, 1.22] | 9.4 | 1.12 | [0.91, 1.38] | 7.6 | 0.93 | [0.75, 1.14] |
| | | Problem solving | 7.2 | 1.00 | reference | 6.9 | 0.92 | [0.80, 1.05] | 8.8 | 1.05 | [0.85, 1.29] | 8.1 | 0.97 | [0.79, 1.20] |
| | | Personal–Social | 3.1 | 1.00 | reference | 3.6 | 1.03 | [0.86, 1.25] | 4.0 | 0.90 | [0.66, 1.22] | 3.7 | 0.86 | [0.63, 1.15] |
| | Adjusted 2 | Communication | 3.8 | 1.00 | reference | 4.0 | 1.02 | [0.85, 1.22] | 4.1 | 0.90 | [0.67, 1.22] | 4.7 | 1.08 | [0.83, 1.41] |
| | | Gross motor | 4.2 | 1.00 | reference | 4.9 | 1.01 | [0.86, 1.18] | 6.4 | 1.10 | [0.86, 1.40] | 6.4 | 1.09 | [0.87, 1.38] |
| | | Fine motor | 7.3 | 1.00 | reference | 8.0 | 1.07 | [0.94, 1.21] | 9.4 | 1.10 | [0.90, 1.35] | 7.6 | 0.91 | [0.73, 1.12] |
| | | Problem solving | 7.2 | 1.00 | reference | 6.9 | 0.91 | [0.80, 1.05] | 8.8 | 1.04 | [0.84, 1.28] | 8.1 | 0.96 | [0.78, 1.18] |
| | | Personal–Social | 3.1 | 1.00 | reference | 3.6 | 1.03 | [0.86, 1.24] | 4.0 | 0.88 | [0.65, 1.19] | 3.7 | 0.84 | [0.62, 1.13] |

*Note*: Adjusted Model 1was adjusted for parental background factors and sex of the child. Adjusted Model 2 was adjusted for obstetric and perinatal factors in addition to the covariates of Adjusted Model 1. Bold text indicates $p < 0.05$.

Abbreviations: CI, confidence interval; ICSI, intracytoplasmic sperm injection; IVF, *in vitro* fertilization.

[a]Non-ART, without assisted reproductive technologies (ovulatory induction or intrauterine insemination).

**TABLE 4** Association between conception and children's developmental delay at the age of 3 years in singletons stratified by children's sex

| Population | Analysis model | Domain | Spontaneous | | | Non-ART[a] | | | IVF | | | ICSI | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | % of cases | Odds ratio [95% CI] | | % of cases | Odds ratio [95% CI] | | % of cases | Odds ratio [95% CI] | | % of cases | Odds ratio [95% CI] | |
| Boys (*n* = 39 229) | Crude | Communication | 5.9 | 1.00 | reference | 7.2 | **1.23** | **[1.03, 1.48]** | 5.7 | 0.95 | [0.69, 1.32] | 7.4 | 1.27 | [0.95, 1.69] |
| | | Gross motor | 5.1 | 1.00 | reference | 6.1 | 1.20 | [0.99, 1.46] | 8.6 | **1.73** | **[1.32, 2.27]** | 8.5 | **1.73** | **[1.32, 2.26]** |
| | | Fine motor | 11.2 | 1.00 | reference | 12.9 | **1.18** | **[1.02, 1.35]** | 13.2 | 1.20 | [0.96, 1.50] | 11.5 | 1.03 | [0.81, 1.30] |
| | | Problem solving | 9.7 | 1.00 | reference | 10.8 | 1.13 | [0.97, 1.31] | 11.3 | 1.19 | [0.93, 1.50] | 11.2 | 1.18 | [0.93, 1.49] |
| | | Personal–Social | 5.1 | 1.00 | reference | 6.6 | **1.31** | **[1.09, 1.59]** | 6.1 | 1.21 | [0.89, 1.67] | 5.1 | 1.01 | [0.72, 1.42] |
| | Adjusted 1 | Communication | 5.9 | 1.00 | reference | 7.2 | 1.16 | [0.97, 1.40] | 5.7 | 0.83 | [0.59, 1.16] | 7.4 | 1.07 | [0.80, 1.43] |
| | | Gross motor | 5.1 | 1.00 | reference | 6.1 | 1.00 | [0.82, 1.21] | 8.6 | 1.20 | [0.91, 1.59] | 8.5 | 1.19 | [0.90, 1.57] |
| | | Fine motor | 11.2 | 1.00 | reference | 12.9 | 1.09 | [0.95, 1.26] | 13.2 | 1.02 | [0.81, 1.28] | 11.5 | 0.86 | [0.68, 1.09] |
| | | Problem solving | 9.7 | 1.00 | reference | 10.8 | 1.05 | [0.90, 1.22] | 11.3 | 0.99 | [0.78, 1.27] | 11.2 | 0.96 | [0.75, 1.23] |
| | | Personal–Social | 5.1 | 1.00 | reference | 6.6 | 1.13 | [0.93, 1.37] | 6.1 | 0.86 | [0.62, 1.19] | 5.1 | **0.70** | **[0.50, 0.99]** |
| | Adjusted 2 | Communication | 5.9 | 1.00 | reference | 7.2 | 1.16 | [0.96, 1.39] | 5.7 | 0.81 | [0.58, 1.14] | 7.4 | 1.05 | [0.78, 1.41] |
| | | Gross motor | 5.1 | 1.00 | reference | 6.1 | 0.99 | [0.81, 1.21] | 8.6 | 1.15 | [0.87, 1.53] | 8.5 | 1.14 | [0.86, 1.51] |
| | | Fine motor | 11.2 | 1.00 | reference | 12.9 | 1.09 | [0.95, 1.26] | 13.2 | 0.99 | [0.79, 1.25] | 11.5 | 0.84 | [0.66, 1.07] |
| | | Problem solving | 9.7 | 1.00 | reference | 10.8 | 1.04 | [0.89, 1.21] | 11.3 | 0.96 | [0.75, 1.23] | 11.2 | 0.94 | [0.74, 1.20] |
| | | Personal–Social | 5.1 | 1.00 | reference | 6.6 | 1.12 | [0.92, 1.36] | 6.1 | 0.83 | [0.60, 1.15] | 5.1 | **0.68** | **[0.48, 0.96]** |
| Girls (*n* = 37 308) | Crude | Communication | 2.0 | 1.00 | reference | 1.6 | 0.80 | [0.55, 1.16] | 3.4 | **1.72** | **[1.09, 2.70]** | 2.4 | 1.18 | [0.73, 1.92] |
| | | Gross motor | 3.7 | 1.00 | reference | 4.6 | 1.24 | [0.99, 1.56] | 5.8 | **1.58** | **[1.11, 2.24]** | 4.7 | 1.27 | [0.90, 1.81] |
| | | Fine motor | 3.7 | 1.00 | reference | 4.1 | 1.09 | [0.86, 1.38] | 6.6 | **1.82** | **[1.31, 2.53]** | 4.4 | 1.19 | [0.83, 1.71] |
| | | Problem solving | 4.9 | 1.00 | reference | 3.9 | **0.79** | **[0.62, 1.00]** | 7.3 | **1.52** | **[1.11, 2.08]** | 5.5 | 1.13 | [0.82, 1.57] |
| | | Personal–Social | 1.4 | 1.00 | reference | 1.5 | 1.05 | [0.71, 1.53] | 2.9 | **2.04** | **[1.25, 3.33]** | 2.4 | **1.66** | **[1.02, 2.70]** |
| | Adjusted 1 | Communication | 2.0 | 1.00 | reference | 1.6 | 0.80 | [0.55, 1.16] | 3.4 | 1.52 | [0.95, 2.42] | 2.4 | 1.09 | [0.66, 1.80] |
| | | Gross motor | 3.7 | 1.00 | reference | 4.6 | 1.12 | [0.89, 1.41] | 5.8 | 1.21 | [0.84, 1.73] | 4.7 | 0.97 | [0.68, 1.39] |
| | | Fine motor | 3.7 | 1.00 | reference | 4.1 | 1.11 | [0.87, 1.41] | 6.6 | **1.70** | **[1.21, 2.40]** | 4.4 | 1.16 | [0.80, 1.69] |
| | | Problem solving | 4.9 | 1.00 | reference | 3.9 | **0.77** | **[0.61, 0.98]** | 7.3 | 1.33 | [0.96, 1.84] | 5.5 | 1.02 | [0.73, 1.42] |
| | | Personal–Social | 1.4 | 1.00 | reference | 1.5 | 0.94 | [0.64, 1.39] | 2.9 | 1.49 | [0.90, 2.48] | 2.4 | 1.27 | [0.76, 2.12] |
| | Adjusted 2 | Communication | 2.0 | 1.00 | reference | 1.6 | 0.79 | [0.54, 1.15] | 3.4 | 1.46 | [0.92, 2.34] | 2.4 | 1.04 | [0.63, 1.72] |
| | | Gross motor | 3.7 | 1.00 | reference | 4.6 | 1.11 | [0.88, 1.39] | 5.8 | 1.16 | [0.80, 1.66] | 4.7 | 0.93 | [0.65, 1.33] |
| | | Fine motor | 3.7 | 1.00 | reference | 4.1 | 1.10 | [0.86, 1.40] | 6.6 | **1.64** | **[1.17, 2.31]** | 4.4 | 1.11 | [0.77, 1.61] |
| | | Problem solving | 4.9 | 1.00 | reference | 3.9 | **0.77** | **[0.60, 0.98]** | 7.3 | 1.32 | [0.95, 1.82] | 5.5 | 1.01 | [0.72, 1.41] |
| | | Personal–Social | 1.4 | 1.00 | reference | 1.5 | 0.92 | [0.62, 1.36] | 2.9 | 1.44 | [0.86, 2.40] | 2.4 | 1.21 | [0.73, 2.03] |

*Note*: Adjusted Model 1 was adjusted for parental background factors. Adjusted Model 2 was adjusted for obstetric and perinatal factors in addition to the covariates of Adjusted Model 1. Bold text indicates $p < 0.05$.

Abbreviations: CI, confidence interval; ICSI, intracytoplasmic sperm injection; IVF, *in vitro* fertilization.

[a]Non-ART, without assisted reproductive technologies (ovulatory induction or intrauterine insemination).

**TABLE 5** Association between transferred ovum and children's developmental delay at the age of 3 years in singletons

| | | Spontaneous ($n$ = 70 067) | | | IVF/ICSI: Fresh embryo ($n$ = 29) | | | IVF/ICSI: Frozen embryo ($n$ = 407) | | | IVF/ICSI: Blastocyst($n$ = 1511) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Analysis model | Domain | % of cases | Odds ratio [95% CI] | | % of cases | Odds ratio [95% CI] | | % of cases | Odds ratio [95% CI] | | % of cases | Odds ratio [95% CI] | |
| Crude | Communication | 4.0 | 1.00 | reference | 10.3 | 2.77 | [0.84, 9.15] | 4.2 | 1.05 | [0.64, 1.70] | 4.4 | 1.11 | [0.87, 1.43] |
| | Gross motor | 4.4 | 1.00 | reference | 10.3 | 2.48 | [0.75, 8.20] | 5.9 | 1.35 | [0.89, 2.04] | 6.5 | **1.49** | **[1.21, 1.84]** |
| | Fine motor | 7.6 | 1.00 | reference | 24.1 | **3.88** | **[1.66, 9.09]** | 10.3 | **1.40** | **[1.02, 1.93]** | 8.5 | 1.14 | [0.95, 1.37] |
| | Problem solving | 7.4 | 1.00 | reference | 20.7 | **3.28** | **[1.33, 8.06]** | 9.8 | 1.37 | [0.99, 1.90] | 8.5 | 1.16 | [0.97, 1.40] |
| | Personal–Social | 3.3 | 1.00 | reference | 10.3 | **3.38** | **[1.02, 11.19]** | 3.4 | 1.04 | [0.61, 1.78] | 4.0 | 1.23 | [0.95, 1.60] |
| Adjusted 1 | Communication | 4.0 | 1.00 | reference | | NA | | 4.2 | 0.92 | [0.56, 1.50] | 4.4 | 0.94 | [0.73, 1.22] |
| | Gross motor | 4.4 | 1.00 | reference | | NA | | 5.9 | 0.99 | [0.65, 1.50] | 6.5 | 1.07 | [0.86, 1.33] |
| | Fine motor | 7.6 | 1.00 | reference | | NA | | 10.3 | 1.27 | [0.91, 1.76] | 8.5 | 0.98 | [0.81, 1.18] |
| | Problem solving | 7.4 | 1.00 | reference | | NA | | 9.8 | 1.17 | [0.84, 1.64] | 8.5 | 0.98 | [0.81, 1.18] |
| | Personal–Social | 3.3 | 1.00 | reference | | NA | | 3.4 | 0.77 | [0.45, 1.32] | 4.0 | 0.87 | [0.66, 1.13] |
| Adjusted 2 | Communication | 4.0 | 1.00 | reference | | NA | | 4.2 | 0.89 | [0.54, 1.46] | 4.4 | 0.92 | [0.71, 1.19] |
| | Gross motor | 4.4 | 1.00 | reference | | NA | | 5.9 | 0.94 | [0.62, 1.43] | 6.5 | 1.03 | [0.83, 1.27] |
| | Fine motor | 7.6 | 1.00 | reference | | NA | | 10.3 | 1.23 | [0.89, 1.71] | 8.5 | 0.95 | [0.78, 1.15] |
| | Problem solving | 7.4 | 1.00 | reference | | NA | | 9.8 | 1.15 | [0.82, 1.60] | 8.5 | 0.96 | [0.79, 1.16] |
| | Personal–Social | 3.3 | 1.00 | reference | | NA | | 3.4 | 0.73 | [0.43, 1.27] | 4.0 | 0.84 | [0.64, 1.10] |

*Note*: Cases without information on transplanted embryos were excluded ($n$ = 761). Results of Non-ART (ovulatory induction or intrauterine insemination) were omitted ($n$ = 3762). Adjusted Model 1was adjusted for parental background factors and sex of the child. Adjusted Model 2 was adjusted for obstetric and perinatal factors in addition to the covariates of Adjusted Model 1. Bold text indicated $p < 0.05$.

Abbreviations: CI, confidence interval; ICSI, intracytoplasmic sperm injection; IVF, *in vitro* fertilization; NA, not analyzed due to small number.

syndrome.[40,42] A child's developmental delay may also be due to the adverse endometrial environment caused by ovarian hyperstimulation, and the results of our study may support "freeze-all" strategies performed with good-quality embryos under controlled ovarian stimulation.

Differences in the risk of developmental delay between children born after ART and non-ART may be linked primarily to infertility-related factors. Fertility decreases with age, and our findings reaffirmed that those who underwent infertility treatment were also more susceptible to various adverse perinatal outcomes. However, it is uncertain that the general population is aware of these medical findings. Japanese couples are getting married and having children later, and this progressive trend can be traced to women's changing attitudes about their careers and personal goals as well as increasing socioeconomic pressure.[43] Lower fertility with age may drive women to undergo more advanced infertility treatment. In this context, educating the general population thoroughly about the health risks associated with pregnancy at older age and encouraging reforms for more accessible and affordable parenting support programs, such as universal daycare and paid parental leave, would be conducive to better health outcomes of the children to be born.

This study analyzed the relationships between infertility treatments (including ART) and development using data from a large-scale birth cohort study after adjusting for numerous covariates related to parental background and perinatal factors. However, there are several limitations to this study. First, data on the insemination method and embryo transfer were obtained from transcripts of medical records, in some cases by Research Coordinators who were not physicians or obstetrical staff, resulting in some missing data. Furthermore, some supplemental data provided by parents on the self-administered questionnaires may have been misclassified (e.g., data regarding embryo transfer). Second, there may have been observation bias in the assessment of child neurodevelopment owing to parental completion of the J-ASQ-3. Finally, although this study was a large-scale cohort study conducted across 15 locations in Japan, it is not exhaustive and relies on the data of participants enrolled by select obstetricians/gynecologists. Therefore, the collected data may contain biases, and the generalizability of these results should be approached with caution.

In conclusion, although this study discovered an increased risk of developmental delay in certain domains in children born after ART, parental age and factors that influence infertility and multiple births were suggested as the main risk factors. ARTs such as IVF, ICSI, and frozen embryo transfer did not exhibit a significant effect on children's development.

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## CONFLICT OF INTEREST

Takao Miyake, Midori Yamamoto, Kenichi Sakurai, Akifumi Eguchi, Masashi Yoshida, and Chisato Mori declare that they have no conflicts of interests.

## ETHICAL APPROVAL

The JECS protocol was reviewed and approved by the Ministry of the Environment's Institutional Review Board on Epidemiological Studies and the Ethics Committees of all participating institutions.

## HUMAN RIGHTS STATEMENTS AND INFORMED CONSENT

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and its later amendments. Informed consent was obtained from all participants for being included in the study.

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## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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## APPENDIX

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