Association of epidural analgesia during labor with neurodevelopment of children during the first three years: the Japan Environment and Children’s Study

Masayuki Shima1,2*, Narumi Tokuda1, Hideki Hasunuma1,2, Yoshiko Kobayashi1,3, Hiroyuki Tanaka4, Hideaki Sawai3, Hiroaki Shibahara1,4, Yasuhiro Takeshima1,5, Munetaka Hirose1,3 and the Japan Environment and Children’s Study (JECS) Group1

*Correspondence: shima-m@hyo-med.ac.jp
†The study group members are listed in the Acknowledgements.
1Hyogo Regional Center for the Japan Environment and Children’s Study, Hyogo Medical University, Nishinomiya, Japan. 2Department of Public Health, School of Medicine, Hyogo Medical University, Nishinomiya, Japan. 3Department of Anesthesiology and Pain Medicine, School of Medicine, Hyogo Medical University, Nishinomiya, Japan. 4Department of Obstetrics and Gynecology, School of Medicine, Hyogo Medical University, Nishinomiya, Japan. 5Department of Pediatrics, School of Medicine, Hyogo Medical University, Nishinomiya, Japan.

Abstract

Background: Epidural analgesia relieves pain during labor. However, the long-term effects on neurodevelopment in children remain unclear. We explored associations between exposure to epidural analgesia during labor and childhood neurodevelopment during the first 3 years of life, in the Japan Environment and Children’s Study (JECS), a large-scale birth cohort study.

Methods: Pregnant women were recruited between January 2011 and March 2014, and 100,304 live births of singleton children born at full-term by vaginal delivery, and without congenital diseases were analyzed. Data on mothers and children were collected using a self-administered questionnaires and medical record transcripts. The children’s neurodevelopment was repeatedly assessed for five domains (communication, gross motor, fine motor, problem solving, and personal-social), using the Ages and Stages Questionnaires, Third Edition, at six time points from age 6 to 36 months. After adjusting for potential confounders, the associations between exposure to epidural analgesia during labor and children’s neurodevelopment at each time point were assessed.

Results: Of the 42,172 children with valid data at all six time points, 938 (2.4%) were born to mothers who received epidural analgesia during labor. Maternal exposure to epidural analgesia was associated with neurodevelopmental delays during the first 3 years after birth. Delay risks in gross and fine motor domains were the greatest at 18 months (adjusted odds ratio (aOR) [95% confidence interval (CI)]: 1.40 [1.06, 1.84] and 1.54 [1.17, 2.03], respectively), subsequently decreasing. Delay risks in communication and problem-solving domains were significantly high at 6 and 24 months, and remained significant at 36 months (aOR [95% CI]: 1.40 [1.04, 1.90] and 1.28 [1.01, 1.61], respectively). Exposure to epidural analgesia was also associated with the incidence of problem solving and personal-social delays from 18 to 24 months old. Neurodevelopmental delay risks, except for communication, were dominant in children born to mothers aged ≥30 years at delivery.

Conclusions: This study showed that maternal exposure to epidural analgesia during labor was associated with neurodevelopmental delays in children during the first 3 years after birth.

Keywords: Birth cohort study, Children, Epidural analgesia during labor, Japan Environment and Children’s Study (JECS), Maternal age, Neurodevelopment, the Ages and Stages Questionnaires, Third Edition (ASQ-3)

Introduction

Epidural analgesia is an effective and widely accepted method of providing pain relief during labor [1, 2]. Many studies have reported that epidural analgesia provides better pain relief during labor than systemic opioids or other techniques [3, 4]. The use of epidural analgesia during labor has increased internationally in recent years, and is currently used in 20–70% of all deliveries worldwide [3, 5–7]. However, while the proportion of analgesia administered during labor has increased from 4.6% in 2014 to 6.1% in 2016 [8], the level of use is markedly lower in Japan than in other countries, owing to cultural backgrounds and a shortage of obstetric anesthesia providers [9]. Although some studies have shown adverse effects of epidural analgesia during labor, such as low Apgar scores and admissions to the neonatal intensive care unit [7, 10,
been described elsewhere [24]. Each child was followed up mainly through self-administered questionnaires twice during pregnancy: in the first and second/third trimester. The medical records of mothers and children were transcribed by physicians, midwives, nurses, and/or research coordinators immediately after delivery, and 1 month after birth. Children were followed up mainly through self-administered questionnaires completed by their mothers or guardians at 1 month after birth, and thereafter once every 6 months from 6 months to 3 years of age. Each child’s neurodevelopment was assessed using the Japanese translation of the Ages and Stages Questionnaires, Third Edition (ASQ-3) [27, 28], a parent-completed screening tool, at a total of six time points from 6 months to 3 years of age.

Figure 1 shows a flowchart of the inclusion process for this study. Of the 103,060 pregnancies and 104,062 fetuses registered in the JECS, 100,304 were live births. Among these, preterm (<37 weeks of gestation) or post-term (>41 weeks of gestation) births, multiple births, and infants with congenital anomalies, all of which can affect development, were excluded. To investigate the effects of epidural analgesia during labor, as the most common method of painless delivery, we also excluded children delivered by cesarean section, those with missing information about delivery mode or type of painless delivery, and those born by painless delivery using combined spinal-epidural anesthesia or a paracervical block. Furthermore, of the 73,830 children who met the criteria for this study, children without valid data from the ASQ-3 at any of the six time points from 6 months to 3 years were excluded to investigate the progress of neurodevelopment among the same children. Finally, a total of 42,172 children were included in the present analyses. This study is based on the “jecs-ta-20190930” dataset, released in October 2019 and revised in April 2020.

**Exposure and outcomes**

In this study, epidural analgesia administered during labor and delivery was used as the exposure variable. Information on delivery mode and whether mothers experienced a painless delivery were obtained from medical record transcripts just after delivery. When painless delivery was performed, the type of anesthesia used (epidural anesthesia, combined spinal-epidural anesthesia, or paracervical block) was confirmed.

Neurodevelopmental delays in the child were assessed using the ASQ-3, a parent-completed developmental screening tool designed for children from 1 to 66 months of age [29–31]. The ASQ-3 comprises 30 questions across five developmental domains (communication, gross motor, fine motor, problem-solving, and personal-social). For each question, the parent answers “yes,” “sometimes,” or “not yet.” These answers are allocated scores of 10, 5, or 0 points, respectively, and the sum of individual scores is calculated. If the score for each domain is less than the cutoff, the child is referred for further assessment. Details of the ASQ-3 were provided by Squires et al [27]. The present study used the Japanese translation of the ASQ-3 (J-ASQ-3), which has been validated using adjusted cut-off scores for Japanese children [28]. When the score for each domain was below the Japanese cutoff, the child was considered to have a neurodevelopmental delay in that domain.

**Covariates**

Covariates were chosen based on findings derived from previous studies into the effects of epidural analgesia dur-
Data on covariates were obtained from responses to the self-administered questionnaires and medical record transcripts. Maternal characteristics included maternal age at delivery, parity, delivery mode, duration of labor, comorbidity (diabetes and hypertension), body mass index before pregnancy, occupation in the first trimester, smoking status, alcohol consumption, educational level, annual household income, and marital status at 6 months after childbirth. In addition, the children’s characteristics included sex, birth weight, Apgar score at 5 min after birth, feeding methods in infancy, nursery attendance at 6 and 12 months, screen time at 12 months, and sibling cohabitations [25, 32]. The study area was included as a covariate to consider geographical variations in the use of epidural analgesia during labor.

**Statistical analysis**

The characteristics of mothers and children were compared between the groups exposed and unexposed to epidural analgesia during labor. For understanding children’s neurodevelopment, scores in each J-ASQ-3 domain at each time point were first compared between the exposed and unexposed groups. Next, children below and above the cut-off score for each domain at each time point were termed “delayed” and “normal,” respectively, and proportions were compared between groups. Subsequently, multiple logistic regression analyses were performed to estimate associations between epidural analgesia during labor and neurodevelopment, after adjusting for the above covariates. Results were shown as adjusted odds ratios (aORs) and 95% confidence intervals (CIs) of risk of neurodevelopmental delay in the group exposed to epidural analgesia. Additionally, associations between epidural analgesia and the incidence of neurodevelopmental delay at every 6 months after 18 months old were estimated. In these analyses, we examined neurodevelopmental delays after 18 months old, because the ASQ-3 may not be accurate for children under 13 months old [33]. Neurodevelopmental delay at 24 months onset in children without delay at 18 months indicated delay onset during 18–24 months. Similarly, neurodevelopmental delay onset at 30 and 36 months was assessed in children without delay at 24 and 30 months, respectively. Moreover, we examined the relationship between epidural analgesia and neurodevelopmental delays after stratifying by maternal age at delivery (<30 years/≥30 years), because the epidural analgesia administration was higher among older mothers; older maternal age was associated with decreased ASQ-3 scores [34]. Furthermore, we also performed stratified analyses by parity to address differences in the effects of epidural analgesia between primiparas and multiparas.

We applied a multiple imputation method for missing variables to reduce potential non-response bias from missing data and to improve the precision of estimates. The 20 datasets for each imputed variable were created and merged to estimate aORs and 95% CIs [35, 36]. For sensitivity analyses, we also estimated associations between epidural analgesia and neurodevelopment without a multi-
Results

Characteristics of participants and scores for each J-ASQ-3 domain

The characteristics of mothers and children are shown in Table 1. Of the 42,172 children included in this study, 938 (2.2%) were born to mothers who received epidural analgesia during labor. This percentage was similar to the 2.1% among those excluded from this analysis because of missing J-ASQ-3 scores from 6 to 36 months old (Table S1). Mothers who received epidural analgesia were associated with higher frequencies of induced delivery, vacuum or forceps delivery, and longer duration of labor. Regarding the characteristics of children, the proportion of children living with siblings was lower in the group exposed to epidural analgesia.
epidural analgesia than in the unexposed group. The children’s sex and the proportion of 5-min Apgar scores <7 did not differ between the groups. The characteristics of the children included in this analysis were similar to those of the excluded children (Table S1).

The mean scores for each J-ASQ-3 domain at each time are shown in Table S2. All scores were lower in the group exposed to epidural analgesia than in the unexposed group, and most of the differences were significant (p < .05 for ≥4 time points for all 5 domains). The numbers and proportions of children below the cut-off score for each J-ASQ-3 domain at each time point are shown in Table 2. The proportions of children with these scores were higher in the exposed group than in the unexposed group, except scores for the personal-social domain at 6 months. These proportions were broadly similar between children included and excluded in this analysis (Table S3).

### Association between epidural analgesia during labor and the prevalence of neurodevelopmental delay

The results of logistic regression analyses for associations between epidural analgesia during labor and each J-ASQ-3 domain at each time point are shown in Fig. 2. For communication, children born to mothers who received epidural analgesia during labor displayed significantly increased risks of neurodevelopmental delays at 6, 24, and 36 months old (aOR [95%CI]: 1.95 [1.01, 3.80], 1.39 [1.03, 1.89], and 1.40 [1.04, 1.90], respectively). Concerning fine and gross motor development, neurodevelopmental delay risks were significantly higher at 18 months (aOR [95%CI]: 1.40 [1.06, 1.84] and 1.54 [1.17, 2.03], respectively). Thereafter, aORs in both domains gradually decreased; however, gross motor delay risk remained significantly high at 24 months (aOR [95%CI]: 1.37 [1.06, 1.76]). Neurodevelopmental delay risks in problem solving were significantly higher at 6, 24, and 36 months, although no clear trend was apparent during the first 3 years. Personal-social delay risks were significantly high at 12 and 24 months.

The results were similar in sensitivity analyses without the multiple imputation method (Table S4). In stratified analyses by maternal age at delivery, the associations between epidural analgesia during labor and neurodevelopmental delay, except communication delay, were dominant in children born to mothers aged ≥30 years (Fig. 3). Conversely, stratified analyses by parity revealed that personal-social delay risks were similar in primiparas and multipartas, and other domains’ delay risks were larger in multipartas (Table S5).

### Association between epidural analgesia during labor and the incidence of neurodevelopmental delay

The results of logistic regression analyses for associations between epidural analgesia during labor and the incidence of neurodevelopmental delay are shown in Fig. 4. Risks of the incidence of problem solving and personal-social delays were significantly high from 18 to 24 months old (aOR [95%CI]: 1.53 [1.10, 2.13] and 1.97 [1.35, 2.87], respectively). The incidence of neurodevelopmental delay from 24 to 36 months old was not significant in any domain. Analyses without the multiple imputation method showed similar results (Table S6). In stratified analyses by maternal age at delivery, the incidence of gross motor, problem solving and personal-social delay risks was significantly high from age 18 to 24 months in children born to mothers aged ≥30 years. Delay onset during 30–36 months for problem solving was also significant. In contrast, no significant association was observed in children born to mothers aged <30 years (Fig. 5). Conversely, in stratified analyses by parity, associations between epidural

| Table 2 | Neurodevelopmental delay in each domain of the J-ASQ-3 among children, with or without epidural analgesia |
|---------|----------------------------------------------------------------------------------------------------------|
| Domain             | Cut-off scores for each item* | Unexposed to epidural analgesia during labor (n = 41,234) | Exposed to epidural analgesia during labor (n = 938) |
|                   |                             | n (%)              | n (%)              |
| Communication      |                               |                     |                     |
| 6 months           | 22.93                        | 231 (0.6)           | 10 (1.1)            |
| 12 months          | 4.53                         | 42 (0.1)            | 2 (0.2)             |
| 18 months          | 5.82                         | 831 (2.0)           | 29 (3.1)            |
| 24 months          | 14.33                        | 1,474 (3.6)         | 50 (5.3)            |
| 30 months          | 26.01                        | 1,844 (4.5)         | 49 (5.2)            |
| 36 months          | 29.95                        | 1,498 (3.6)         | 50 (5.3)            |
| Gross motor        |                               |                     |                     |
| 6 months           | 15.12                        | 4,091 (9.9)         | 112 (1.9)           |
| 12 months          | 9.43                         | 2,156 (5.2)         | 59 (6.3)            |
| 18 months          | 37.59                        | 1,702 (4.1)         | 61 (6.5)            |
| 24 months          | 39.13                        | 2,174 (5.3)         | 72 (7.7)            |
| 30 months          | 38.36                        | 1,574 (3.8)         | 46 (4.9)            |
| 36 months          | 39.26                        | 1,636 (4.0)         | 42 (4.5)            |
| Fine motor         |                               |                     |                     |
| 6 months           | 16.24                        | 2,021 (4.9)         | 49 (5.2)            |
| 12 months          | 25.47                        | 2,187 (5.3)         | 54 (5.8)            |
| 18 months          | 26.76                        | 1,663 (4.0)         | 61 (6.5)            |
| 24 months          | 33.48                        | 782 (1.9)           | 25 (2.7)            |
| 30 months          | 30.13                        | 2,275 (5.5)         | 65 (6.9)            |
| 36 months          | 27.91                        | 2,910 (7.1)         | 77 (8.2)            |
| Problem solving    |                               |                     |                     |
| 6 months           | 26.27                        | 4,281 (10.4)        | 123 (13.1)          |
| 12 months          | 15.37                        | 2,039 (4.9)         | 54 (5.9)            |
| 18 months          | 15.93                        | 1,601 (3.9)         | 48 (5.1)            |
| 24 months          | 29.38                        | 1,585 (3.8)         | 55 (5.9)            |
| 30 months          | 25.78                        | 2,177 (5.3)         | 65 (6.9)            |
| 36 months          | 30.03                        | 2,851 (6.9)         | 85 (9.1)            |
| Personal-social    |                               |                     |                     |
| 6 months           | 22.53                        | 1,424 (3.5)         | 32 (3.4)            |
| 12 months          | 20.93                        | 447 (1.1)           | 17 (1.8)            |
| 18 months          | 34.87                        | 943 (2.3)           | 33 (3.5)            |
| 24 months          | 34.30                        | 1,017 (2.5)         | 46 (4.9)            |
| 30 months          | 39.95                        | 1,275 (3.1)         | 44 (4.7)            |
| 36 months          | 40.27                        | 1,219 (3.0)         | 37 (3.9)            |

*Cut-off scores for Japanese children [28] were used.

Abbreviations: J-ASQ-3, the Japanese translation of the Ages and Stages Questionnaires, Third Edition.
analgesia during labor and incidence of personal-social delay were strong in primiparas; however, associations with gross and fine motor and problem-solving delays were strong in multiparas (Table S7).

**Discussion**

This study investigated the progress of neurodevelopment for children born to mothers who received epidural analgesia during labor. Maternal exposure to epidural analgesia was associated with neurodevelopmental delays in five domains of the J-ASQ-3 during the first 3 years after birth. The findings suggested that epidural analgesia during labor may affect the neurodevelopment of children and that the effects may persist up to 36 months old. This is the first study to report the longitudinal characteristics of neuro-

|                | 6 months | 12 months | 18 months | 24 months | 30 months | 36 months |
|----------------|----------|-----------|-----------|-----------|-----------|-----------|
| **Communication** |          |           |           |           |           |           |
|                | 1.95 (1.01, 3.80) | 1.82 (0.41, 8.04) | 1.28 (0.86, 1.89) | 1.39 (1.03, 1.89) | 1.10 (0.81, 1.49) | 1.40 (1.04, 1.90) |
| **Gross motor** | 1.22 (0.99, 1.50) | 1.12 (0.85, 1.48) | 1.40 (1.06, 1.84) | 1.37 (1.06, 1.76) | 1.18 (0.87, 1.61) | 1.02 (0.74, 1.41) |
| **Fine motor**  | 1.13 (0.84, 1.52) | 1.08 (0.81, 1.44) | 1.54 (1.17, 2.03) | 1.27 (0.84, 1.93) | 1.20 (0.92, 1.57) | 1.12 (0.88, 1.43) |
| **Problem solving** | 1.26 (1.03, 1.53) | 1.09 (0.82, 1.45) | 1.21 (0.90, 1.65) | 1.41 (1.05, 1.87) | 1.22 (0.94, 1.60) | 1.28 (1.01, 1.61) |
| **Personal-social** | 1.03 (0.72, 1.49) | 1.80 (1.08, 3.01) | 1.41 (0.98, 2.03) | 1.84 (1.34, 2.53) | 1.33 (0.96, 1.84) | 1.27 (0.90, 1.80) |

Fig. 2 Association of epidural analgesia during labor with neurodevelopmental delay among children

Adjusted odds ratios (95% confidence intervals) for neurodevelopmental delay in each domain of the J-ASQ-3 among children born to mothers who received epidural analgesia during labor are shown from age 6 to 36 months. Adjusted for maternal age at delivery, parity, delivery mode, duration of labor, comorbidity (diabetes and hypertension), body mass index before pregnancy, occupation in the first trimester, smoking status, alcohol consumption, educational level, annual household income, marital status at 6 months after childbirth, child’s sex, birth weight, Apgar score at 5 min after birth, feeding methods in infancy, nursery attendance, screen time at 12 months old, siblings cohabiting with the child, and study area. A multiple imputation method was used to reduce potential selection bias from missing variables.

Abbreviations: J-ASQ-3, the Japanese translation of the Ages and Stages Questionnaires, Third Edition.

Environmental Health and Preventive Medicine (2022) 27:37
development in children born to mothers who received epidural analgesia during labor.

 Associations between exposure to epidural analgesia during labor and neurodevelopmental outcomes in children have been investigated, mostly in retrospective studies. While many studies have found no adverse effects of epidural analgesia on children [1, 3, 12–15], other studies have reported associations between exposure to epidural analgesia and outcomes in children [7, 10, 11]. However, most previous studies have investigated only peri- and
neonatal outcomes among children born to mothers who received epidural analgesia during labor, and findings about the potential long-term effects of epidural analgesia on neurodevelopment in childhood have been limited [3, 37]. One animal study reported that epidural analgesia during labor altered the normal course of behavioral development in rhesus monkeys [38]. Conversely, a human study found that the use of neuraxial analgesia during labor was not associated with learning disabilities in childhood [39]. In a retrospective birth cohort study, Qiu et al. [21] reported that maternal epidural analgesia during labor increased the risk of ASD in children. Recently, Hanley et al. [19] has also reported that epidural analgesia was associated with a small increased risk of ASD; however, two other studies found no association between epidural analgesia and ASD incidence in children [20, 21]. Thus, consensus remains lacking on long-term neurodevelopment in children born to mothers who received epidural analgesia during labor, and study designs, outcomes analyzed, and follow-up periods have differed markedly between studies.

We found neurodevelopmental delays during the first 3 years after birth in children exposed to epidural analgesia during labor. The mechanisms through which epidural analgesia increases neurodevelopmental delay risk remain unknown. Although epidural analgesia is known to prolong the duration of labor [40], prolonged labor has not been demonstrated to be associated with increased risk of ASD [41–43]. Qiu et al. [21] therefore suggested that prolonged exposure to anesthesia may be a risk factor for ASD. In the present study, there was no significant association between duration of epidural analgesia and children’s neurodevelopment (data not shown). However, stratified analyses by parity, which is considered to result in differences in the progress of labor, revealed that personal-social delay and other delays associated with epidural analgesia were prominent among primiparas and multiparas, respectively.

In this study, the progress of neurodevelopmental delays in children exposed to epidural analgesia during delivery differed among the five domains of J-ASQ-3. The number of children with communication delay was very small at 18-24 months.

**Fig. 4** Association of epidural analgesia during labor with the incidence of neurodevelopmental delay among children

Adjusted odds ratios (95% confidence intervals) for the incidence of neurodevelopmental delay in each domain of the J-ASQ-3 among children born to mothers who received epidural analgesia during labor are shown, every 6 months after 18 months. Adjusted for maternal age at delivery, parity, delivery mode, duration of labor, comorbidity (diabetes and hypertension), body mass index before pregnancy, occupation in the first trimester, smoking status, alcohol consumption, educational level, annual household income, marital status at 6 months after childbirth, child’s sex, birth weight, Apgar score at 5 min after birth, feeding methods in infancy, nursery attendance, screen time at 12 months old, siblings cohabiting with the child, and study area. A multiple imputation method was used to reduce potential selection bias from missing variables.

Abbreviations: J-ASQ-3, the Japanese translation of the Ages and Stages Questionnaires, Third Edition.

| Communication | 18-24 months | 1.31 (0.90, 1.91) |
|---------------|--------------|-------------------|
|               | 24-30 months | 1.04 (0.66, 1.65) |
|               | 30-36 months | 1.46 (0.80, 2.66) |

**Gross motor**

| 18-24 months | 1.23 (0.89, 1.69) |
|--------------|-------------------|
| 24-30 months | 1.01 (0.61, 1.66) |
| 30-36 months | 0.97 (0.58, 1.62) |

**Fine motor**

| 18-24 months | 1.18 (0.68, 2.05) |
|--------------|-------------------|
| 24-30 months | 1.22 (0.89, 1.66) |
| 30-36 months | 1.01 (0.72, 1.43) |

**Problem solving**

| 18-24 months | 1.53 (1.10, 2.13) |
|--------------|-------------------|
| 24-30 months | 1.26 (0.91, 1.75) |
| 30-36 months | 1.29 (0.92, 1.80) |

**Personal-social**

| 18-24 months | 1.97 (1.35, 2.87) |
|--------------|-------------------|
| 24-30 months | 1.26 (0.82, 1.94) |
| 30-36 months | 1.06 (0.59, 1.92) |

Adjusted odds ratio (95% confidence interval)
and 12 months old; this might have resulted from the considerably lower cut-off score for the domain at each time point for Japanese children than the original score [23, 28]. In addition, Yue et al. [33] pointed out that the ASQ-3 may not be accurate for children aged below 13 months. The delay risks in gross and fine motor domains were the greatest at 18 months, but decreased to become insignificant with the growth of the child. In contrast, the delay risks in communication and problem-solving domains remained significantly high at 36 months, and a significant delay risk in the personal-social domain persisted from 12 to 30 months of age. These results suggest that the effects on delays in these domains may persist until the children are at least 3 years old. The incidence of neurodevelopmental delay risks from age 18 to 24 months were also significant for the problem-solving and personal-social domains. The ASQ-3 is used as a screening tool to detect neurodevelopmental disorders in children [29–31]. Delays in the communication domain have been reported to indicate an initial concern for ASD [44]. Delays in the problem-solving and personal-social domains are also likely to be associated with developmental disorders.

Increased maternal age has been reported to be associated with decreased gross motor and personal-social scores [34]. Conversely, epidural analgesia administration was higher among older mothers in this study. In stratified analyses by maternal age at delivery, the association between epidural analgesia and neurodevelopmental delays was dominant in children born to mothers aged ≥30 years. In addition, the incidence of gross motor, problem solving, and personal-social delay risks from age 18 to 24 months was observed in children born to mothers aged ≥30 years, consistent to the previous report [34].

The main strength of this study was that we were able to examine associations between the neurodevelopment of
developmental outcomes were evaluated during the for a large-scale epidemiological study. Finally, neurode-
neurodevelopment delays in children, and is appropriate for communication, were dominant in children born to moth-
ers aged $\geq$30 years at delivery. These findings suggest that epidural analgesia during labor affects the neurodevelopment of children and that the effects may persist up to 36 months of age.

Abbreviations
\text{aOR:} adjusted odds ratio; \text{ASD:} autism spectrum disorders; \text{ASQ-3:} Ages and Stages Questionnaires, Third Edition; CI: confidence interval; J-ASQ-3: the Japanese translation of the Ages and Stages Questionnaires, Third Edition; JECS: Japan Environment and Children’s Study.

Supplementary information
The online version contains supplementary material available at https://doi.org/10.1265/ehpm.22-00088.

Additional file 1: Table S1. Comparison of characteristics between partici-
pants included in and excluded from this study. Table S2. Scores in each domain of the J-ASQ-3 among children born to mothers who received epidural analgesia during labor, from 6 to 36 months old, without multiple imputation method. Table S3. Comparison of numbers and proportions of neurodevelopmental delay in each domain of the J-ASQ-3 between participants included in and excluded from this study. Table S4. Adjusted odds ratios for neurodevelopmental delay in each domain of the J-ASQ-3 among children born to mothers who received epidural analgesia during labor, from 6 to 36 months old, without multiple imputation method. Table S5. Adjusted odds ratios for neurodevelopmental delay in each domain of the J-ASQ-3 among children born to mothers who received epidural analgesia during labor, from 6 to 36 months old, stratified by parity. Table S6. Adjusted odds ratios for the incidence of neurodevelopmental delay in each domain of the J-ASQ-3 among children born to mothers who received epidural analgesia during labor, every 6 months after 18 months old, without multiple imputation method. Table S7. Adjusted odds ratios for the incidence of neurodevelopmental delay in each domain of the J-ASQ-3 among children born to mothers who received epidural analgesia during labor, every 6 months after 18 months old, stratified by parity.

Declarations
Ethics approval and consent to participate
The JECS protocol was reviewed and approved by the Institutional Review Board on Epidemiological Studies of the Ministry of the Environment, and by the ethics committees of all participating institutions. The JECS is being conducted in accordance with the Declaration of Helsinki and other internationally recognized regulations. Written informed consent was obtained from all participants.

Consent for publication
Not applicable.

Availability of data and materials
The JECS data are not publicly available due to ethical restrictions and the legal framework of Japan. All inquiries about access to the data should be sent to the JECS Programme Office, National Institute for Environmental Studies (jecs-en@nies.go.jp).

Competing interest
The authors declare that they have no competing interests.

Funding
The JECS was funded by the Ministry of the Environment, Japan. The findings and conclusions of this article are solely the responsibility of the authors and do not represent the official views of the Ministry.
References

1. Jones L, Othman M, Dowswell T, Alfrez Z, Gates S, Newburn M, et al. Pain management for women in labour: an overview of systematic reviews. Cochrane Database Syst Rev. 2012. https://doi.org/10.1002/14651858.CD009234.pub2.

2. Poole JH. Analgesia and anaesthesia during labor and birth: implications for mother and fetus. J Obstet Gynecol Neonatal Nurs. 2003;32:780–93. https://doi.org/10.1111/j.1552-6909.2003.tb00740.x.

3. Anim-Somuah M, Smyth RM, Cyna AM, Cuthbert A. Epidural versus non–epidural or no analgesia for pain management in labour. Cochrane Database Syst Rev. 2018;5:CD000331. https://doi.org/10.1002/14651858.CD000331.pub4.

4. Hawkins JL. Epidural analgesia for labor and delivery. N Engl J Med. 2010;362:1503–10. https://doi.org/10.1056/NEJMct0909254.

5. Hung TH, Hsieh TT, Liu HP. Differential effects of epidural analgesia on modes of delivery and perinatal outcomes between nulliparous and multiparous women: a retrospective cohort study. PLoS One. 2015;10:e0129007. https://doi.org/10.1371/journal.pone.0129007.

6. Martinez AH, Almagro JRF, Garcia-Suelto MM, Barjonon MU, Alaniz MM, Gomez-Salgado J. Epidural Analgesia and Neonatal Morbidity: A Prospective Cohort Study. Int J Environ Res Public Health. 2018;15;https://doi.org/10.3390/ijerph15102092.

7. Törnell S, Elekis C, Hutlin M, Håkansson S, Thunberg J, Högbom U. Low Aggar score, neonatal encephalopathy and epidural analgesia during labour: a Swedish registry-based study. Acta Anaesthesiol Scand. 2015;59:486–95. https://doi.org/10.1111/aas.12477.

8. Kurakazu M, Umehara N, Nagata C, Yamashita Y, Sato M, Sago H. Delivery mode and maternal and neonatal outcomes of combined spinal–epidural analgesia compared with no analgesia in spontaneous labor: A single-center observational study in Japan. J Obstet Gynaecol Res. 2020;46:425–33. https://doi.org/10.3390/jog1411494.

9. Fujita N, Cole NM, Nagasaka Y. Challenges and hurdles for patient safety in obstetric anesthesia in Japan. J Anesth. 2018;32:901–7. https://doi.org/10.1007/s10540-018-2571-7.

10. Altman M, Sandstrom A, Petersson G, Frisell T, Craufurd S, Stephansson O. Prolonged second stage of labor is associated with low Aggar score. Eur J Epidemiol. 2015;30:1209–15. https://doi.org/10.1007/s10654-015-0043-4.

11. Heitoff D, Maimburg RD. Epidural analgesia during birth and adverse neonatal outcomes: A population-based cohort study. Women Birth. 2020. https://doi.org/10.1016/j.wombi.2020.05.012.

12. Halpern SH, Leighton BL, Ohlsson A, Barrett JF, Rice A. Effect of epidural vs parenteral opioid analgesia on the progress of labor: a meta-analysis. JAMA. 1998;280:2105–10. https://doi.org/10.1001/jama.1988.03430310015013.

13. Wang K, Cao L, Deng Q, Sun LQ, Gu TY, Song J, et al. The effects of epidural/spinal opioids in labour analgesia on neonatal outcomes: a meta-analysis of randomized controlled trials. Can J Anaesth. 2014;61:695–709. https://doi.org/10.1007/s12310-014-0185-y.

14. Wang Q, Zheng SX, Ni YF, Lu YY, Zhang B, Lian QQ, et al. The effect of labor epidural analgesia on maternal-fetal outcomes: a retrospective cohort study. Arch Gynecol Obstet. 2018;298:89–96. https://doi.org/10.1007/s00404-018-7777-4.

15. Yin H, Hu R. A cohort study of the impact of epidural analgesia on maternal and neonatal outcomes. J Obstet Gynaec Res. 2019;45:1435–41. https://doi.org/10.1111/jo.13968.

16. Loftus JR, Hill H, Cohen SE. Placental transfer and neonatal effects of epidural sufentanil and fentanyl administered with bupivacaine during labor. Anesthesiology. 1995;83:300–8. https://doi.org/10.1097/00000542-199508000-00010.

17. Moore A, el-Bahrawy A, Hatzakorzian R, Li-Pi-Shan W. Maternal epidural fentanyl administered for labor analgesia is found in neonatal urine 24 hours after birth. Breastfeed Med. 2016;11:40–1. https://doi.org/10.1089/fmb.2015.0173.

18. Spann MN, Serino D, Bansal R, Hao X, Nat G, Toth Z, et al. Morphological features of the neonatal brain following exposure to regional anesthesia during labor and delivery. Magn Reson Imaging. 2015;33:213–21. https://doi.org/10.1016/j.mri.2014.08.033.

19. Hanley GE, Bickford C, Ip A, Lanphear N, Lanphear B, Weikum W, et al. Association of Epidural Analgesia During Labor and Delivery With Autistic Spectrum Disorder in Offspring. JAMA. 2021;326:1176–85. https://doi.org/10.1001/jama.2021.14486.

20. Mikkelsen AP, Greiber IK, Scheller NM, Lidgaard O, Jepsen LS. Association of epidural labor analgesia with offspring risk of autism spectrum disorder in children. JAMA. 2022;326:1170–7. https://doi.org/10.1001/jama.2022.12655.

21. Qiu C, Lin JC, Shi JM, Chow T, Desai VN, Nguyen VT, et al. Association between epidural analgesia during labor and risk of autism spectrum disorders in offspring. JAMA Pediatr. 2020;174:1168–75. https://doi.org/10.1001/jamapediatrics.2020.3231.

22. Weil-Wieler E, Bøtaanen BT, Hanlon-Deerman A, Roos LL, Bubel AJ. Association of epidural labor analgesia with offspring risk of autism spectrum disorders. JAMA Pediatr. 2021;175:698–705. https://doi.org/10.1001/jamapediatrics.2021.0376.

23. Kobayashi Y, Tokuda N, Adachi S, Takehashi Y, Hirose M, Shimada M, et al. Association between surgical procedures under general anesthesia in infancy and developmental outcomes at 1 year: the Japan Environment and Children’s Study. Environ Health Prev Med. 2020;25:104. https://doi.org/10.1186/s12199-020-00873-6.

24. Kawamoto T, Nitta H, Murata K, Toda E, Tsukamoto N, Hayase M, et al. Rationale and study design of the Japan environment and children’s study (JECS). BMC Public Health. 2014;14:25. https://doi.org/10.1186/1471-2458-14-25.

25. Michikawa T, Nitta H, Nakayama SF, Yamazaki S, Isobe T, Tamura K, et al. Baseline Profile of Participants in the Japan Environment and Children’s Study (JECS). J Epidemiol. 2018;28:99–104. https://doi.org/10.2188/jea.JE20170018.

26. Squires J, Twombly E, Bricker D, Potter L. ASQ-3 Ages & Stages Questionnaires/ASQ-3 User’s Guide: Brookes Publishing, Baltimore; 2009.

27. Kerstjens JM, Bos AF, ten Vergert EM, de Meer G, Butcher PR, Reijnveld SA. Support for the global feasibility of the Ages and Stages Questionnaire.

Authors' contributions
MS and YK conceptualized the study, MS and YK analyzed the data and drafted the initial article. MS, NT, HT, Hsa, HST, and YT collected and verified the data. MS, NT, HH, YK, and MH interpreted the data. MS prepared the final version of the article. All authors reviewed and approved the final version.

Acknowledgements
We would like to express our gratitude to all participants and Co-operating health care providers in the Japan Environment and Children’s Study (JECS). Members of the JECS Group as of 2022: Michiro Kamiyama (principal investigator), Nagoya City University, Nagoya, Japan, Shin Yamazaki (National Institute for Environmental Studies, Tsukuba, Japan), Yuichiro Ohyama (National Center for Child Health and Development, Tokyo, Japan), Reiko Kishi (Hokkaido University, Sapporo, Japan), Nobuo Yagashii (Tokoh University, Sendai, Japan), Koichi Hashimoto (Fukushima Medical University, Fukushima, Japan), Chisato Mori (Chiba University, Chiba, Japan), Shuichi Ito (Yokohama City University, Yokohama, Japan), Zenkoro Yamagata (University of Yamanashi, Chuo, Japan), Hidekuni Inadera (University of Toyama, Toyama, Japan), Takanori Nakayama (Kyoto University, Kyoto, Japan), Hiroyasu Ito (Osaka University, Suita, Japan), Masayuki Shima (Kyogo College of Medicine, Nishinomiya, Japan), Hiroshiie Nakamura (Tottori University, Yonago, Japan), Narufumi Suganuma (Kochi University, Nankoku, Japan), Koichi Kusuhara (University of Occupational and Environmental Health, Kitakyushu, Japan), and Takahiko Katoh (Kumamoto University, Kumamoto, Japan).

Received: 1 April 2022, Accepted: 10 August 2022
Published online: 28 September 2022
as developmental screener. Early Hum Dev. 2009;85:443–7. https://doi.org/10.1016/j.eahumdev.2009.03.001.

30. Schonhaut L, Armoj I, Schönstedt M, Alvarez J, Cordero M. Validity of the ages and stages questionnaires in term and preterm infants. Pediatrics. 2013;131:e1468–74. https://doi.org/10.1542/peds.2012-3313.

31. Schonhaut L, Pérez M, Armijo I, Maturana A. Comparison between Ages & Stages Questionnaire and Bayley Scales, to predict cognitive delay in school age. Early Hum Dev. 2020;141:104933. https://doi.org/10.1016/j.earlhumdev.2019.104933.

32. Kushima M, Kojima R, Shinohara R, Horiuchi S, Otawa S, Ookata T, et al. Association Between Screen Time Exposure in Children at 1 Year of Age and Autism Spectrum Disorder at 3 Years of Age: The Japan Environment and Children’s Study. JAMA Pediatr. 2022;176:384–91. https://doi.org/10.1001/jamapediatrics.2021.5778.

33. Yue A, Jiang G, Wang B, Abbey C, Shi Y, et al. Concurrent validity of the Ages and Stages Questionnaire and the Bayley Scales of Infant Development III in China. PLoS One. 2019;14:e0221675. https://doi.org/10.1371/journal.pone.0221675.

34. Little RJ, D’Agostino R, Cohen ML, Dickersin K, Emerson SS, Farrar JT, et al. The prevention and treatment of missing data in clinical trials. N Engl J Med. 2012;367:1355–60. https://doi.org/10.1056/NEJMbt1203730.

35. O’Neill RT, Temple R. The prevention and treatment of missing data in clinical trials: an FDA perspective on the importance of dealing with it. Clin Pharmacol Ther. 2012;91:550–4. https://doi.org/10.1038/clpt.2011.340.

36. Bilic N, Djakovikic I, Kikan-Jakic K, Rudman SS, Ivancic Z. Epidural Analgesia in Labor - Controversies. Acta Clin Croat. 2015;54:330–6.

37. Golub MS, Gemmann SL. Perinatal bupivacaine and infant behavior in rhesus monkeys. Neurotoxicol Teratol. 1998;20:29–41. https://doi.org/10.1016/s0895-069x(97)00089-8.

38. Flick RP, Lee K, Hofer RE, Beinborn CW, Hambel EM, Klei MK, et al. Neuromuscular blockade for vaginal delivery and its effects on childhood learning disabilities. Anesth Analg. 2011;112:1424–31. https://doi.org/10.1213/ANE.0b013e31821f2cdd.

39. Lim G, Facco FL, Nathan N, Waters JH, Wong CA, Eltzschig HK. A Review of the Impact of Obstetric Anesthesia on Maternal and Neonatal Outcomes. Anesthesiology. 2018;129:192–215. https://doi.org/10.1097/ALN.0000000000002182.

40. Gardener H, Spiegelman D, Buka SL. Perinatal and neonatal risk factors for autism: a comprehensive meta-analysis. Pediatrics. 2011;128:344–55. https://doi.org/10.1542/peds.2010-1036.

41. Guinchat V, Thorsen P, Laurent C, Cans C, Bodeau N, Cohen D. Perinatal risk factors for autism. Acta Obstet Gynecol Scand. 2012;91:287–300. https://doi.org/10.1111/j.1600-0412.2011.01325.x.

42. Smallwood M, Sareen A, Baker E, Hamilton R, Kwee E, Williams T. Increased Risk of Autism Development in Children Whose Mothers Experienced Birth Complications or Received Labor and Delivery Drugs. ASN Neuro. 2016;8. https://doi.org/10.1177/1759014116659742.

43. Hard S, Hasley L, Manning C, Fein D. Can Screening with the Ages and Stages Questionnaire Detect Autism? J Dev Behav Pediatr. 2015;36:536–43. https://doi.org/10.1097/DBP.0000000000000201.

44. Sultan P, David AL, Fernando R, Ackland GL. Inflammation and Epidural-Related Maternal Fever: Proposed Mechanisms. Anesth Analg. 2016;122:1546–53. https://doi.org/10.1213/ANE.0000000000001195.

45. Greenwell EA, Wyshak G, Ringer SA, Johnson LC, Rivkin MJ, Lieberman E. Intrapartum temperature elevation, epidural use, and adverse outcome in term infants. Pediatrics. 2012;129:e447–54. https://doi.org/10.1542/peds.2010-2301.

46. Segal S, Pancaro C, Bonney J, Marchand JE. Perinatal Inflammation in the Near-Term Pregnant Rat Induces Fetal Brain Inflammation: A Model for the Consequences of Epidural-Associated Maternal Fever. Anesth Analg. 2017;125:2134–40. https://doi.org/10.1213/ANE.0000000000002479.