



A prospective cohort study of the association between the Apgar score and developmental status at 3 years of age: the Japan Environment and Children's Study (JECS)

Tetsuya Tsuchida¹ · Satomi Yoshida¹ · Masato Takeuchi¹ · Chihiro Kawakami² · Koji Kawakami¹ · Shuichi Ito^{2,3} · The Japan Environment, Children's Study Group³

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Abstract

Apgar score (AS) is a well-established tool for assessing viability of newborns, and its association with subsequent child development has been suggested. We aimed to assess whether Apgar scores (ASs) ≥ 7 (generally considered normal) are associated with the developmental status at 3 years of age while adjusting for perinatal and socioeconomic confounders. We extracted the data of ASs at 1 and 5 min among participants of the Japan Environment and Children's Study datasets, which were used in this nationwide cohort study. The outcomes comprised developmental status that was less than each cutoff value for the following five domains of the Ages & Stages Questionnaire (Japanese version, 3rd edition): communication, gross and fine motor, problem-solving, and personal-social domains. For this objective, we conducted multivariable logistic regression analyses on the data of 54,716 children. Compared with ASs ≥ 9 at 5 min, the adjusted odds ratios (aOR) for delayed development in children with ASs ≤ 8 were 1.31 (95% confidence interval, 1.11–1.56), 1.20 (1.04–1.38), and 1.16 (1.01–1.34), respectively, for gross and fine motor, and problem-solving domains. Among neonates with ASs ≤ 8 at 1 min, when those with ASs ≤ 8 at 5 min were compared with those with ASs ≥ 9 at 5 min, the aOR for gross motor domain was 1.34 (1.11–1.61).

Conclusion: ASs ≤ 8 compared with those ≥ 9 at 5 min, even considering the change of AS from 1 to 5 min, were associated with increased ORs for developmental delay in 3-year-olds. Even ASs that are considered normal might affect the subsequent development.

What is Known:

- Apgar score is a general tool for evaluating the vitality of newborns. It is also basically measured at 1 minute and 5 minutes after birth and the scores of ≥ 7 are considered normal.
- The Apgar scores at each minute affect clinical findings of neonates after birth and the subsequent long-term development.

What is New:

- Neonates with Apgar scores of ≤ 8 at 5 minutes compared with those of ≥ 9 , including the change in Apgar score from 1 minute to 5 minutes, are associated with increased odds ratios for developmental status at 3 years of age adjusting for perinatal and socioeconomic confounders.

Keywords Asphyxia · Neonatal vitality · Child health care · Developmental disorder · Mental function · Motor function

✉ Koji Kawakami
kawakami.koji.4e@kyoto-u.ac.jp

Tetsuya Tsuchida
tsuchida.tetsuya.57s@st.kyoto-u.ac.jp

Satomi Yoshida
yoshida.satomi.4r@kyoto-u.ac.jp

Masato Takeuchi
takeuchi.masato.3c@kyoto-u.ac.jp

Chihiro Kawakami
chihirok@yokohama-cu.ac.jp

Shuichi Ito
itoshu@yokohama-cu.ac.jp

¹ Department of Pharmacoepidemiology, Graduate School of Medicine and Public Health, Kyoto University, Kyoto, Japan

² Department of Pediatrics, Graduate School of Medicine, Yokohama City University, Yokohama, Japan

³ National Institute for Environmental Studies, Tsukuba, Japan

Abbreviations

aOR	Adjusted odds ratio
aRR	Adjusted rate ratio
AS	Apgar Score
ASQ-3	Ages & Stages Questionnaire, 3rd Edition
ASs	Apgar Scores
J-ASQ-3	Ages & Stages Questionnaire (Japanese version, 3rd Edition)
JECS	Japan Environment and Children's Study
OR	Odds ratio
95% CI	95% Confidence interval

Introduction

Apgar score (AS), an assessment tool to evaluate neonatal vitality based on the perinatal status and effects of resuscitation [1, 2], comprises 5 items: heart rate, respiratory effort, reflex irritability, muscle tone, and color at birth [1]. A neonate is assessed at 1 and 5 min after birth and each item is attributed a score of 0, 1, or 2 (total score range, 0–10 for each assessment) [1]. A population-based study on more than two million children reported the following distribution of Apgar scores (ASs) at 5 min: ≤ 3 , ≤ 6 , 9, and 10 (0.3%, 1.1%, 25.3%, and 67.9%, respectively) [3]. However, interobserver variability, perinatal complications, and interventions delivered to the mother and neonate affect the calculation of an AS [1, 4].

ASs were not originally intended for use as a long-term prognostic tool [1]. However, in recent studies, associations between low ASs and death [5–7], cerebral palsy [7–9], and autism [10–12] have been reported. Findings regarding associations of the ASs with childhood development remain controversial, as studies have used different AS categories and outcome measurements [13–16]. Studies [6, 17] have found that the ASs were associated with neonatal and long-term complications, including child development [6, 18–21]; however, they did not sufficiently adjust for the important perinatal status confounders.

Therefore, we aimed to determine whether ASs ≥ 7 (considered normal) were associated with the child developmental status at 3 years of age and to identify an optimal cutoff value of ASs in relation to the developmental status, including the perinatal confounders. To accomplish these objectives, we used a nationwide cohort dataset in Japan.

Materials and methods

Study design and setting

The Japan Environment and Children's Study (JECS), which is ongoing in 15 Regional Centers in Japan [22], is

a nationwide cohort study that is originally organized to investigate the association between environmental factors and children's health from pregnancy to 13 years of age. 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. The recruitment period was between January 2011 and March 2014; the aim was to register approximately 100,000 pregnant women and their offspring [22]. This population's data were considered comparable to those collected in the national survey [23]. To recruit participants, pregnant women were enrolled at the Co-operating health care providers Regional Centers nearby [24] and written informed consent was obtained from all participants.

The JECS dataset (jecs-ta-20190930) comprised prospectively collected data from regularly submitted self-administered questionnaires [22]. We listed the questionnaires we used (Supplementary Table 1). MT2-food frequency questionnaire provided information on food intake. This questionnaire used in the JECS was based on the Japan Public Health Center-based Prospective Study for the Next Generation [25]. Additionally, DrT1, Dr0m, and Dr1m included transcribed medical records. Program Office collated these questionnaire data to conduct accurate analyses.

Participants

The study population included children without physical anomalies at birth. Accordingly, we excluded children with physical anomalies, or a diagnosis of congenital metabolic disorders based on the Dr0m and Dr1m and also missing values.

Variables

The exposures were the ASs at 1 and 5 min recorded at Dr0m. The outcomes were the developmental status at 3 years of age that was less than the cutoff values for specific domains, assessed using the Ages and Stages Questionnaire (Japanese version, 3rd Edition; J-ASQ-3). The J-ASQ-3, which was based on the original parent-reported Ages and Stages Questionnaire (ASQ-3), was translated into Japanese. The ASQ-3 is a screening tool used to determine the developmental status in early childhood [26]. In total, 30 questions are used to evaluate the following 5 domains: communication, gross and fine motor, problem-solving, and personal-social. Parents were required to select 1 of the following 3 responses: yes, sometimes, and no, corresponding to 10, 5, and 0 points, respectively. In each domain, the scores ranged from 0 to 60 points. If a child's developmental status is less than the J-ASQ-3 cutoff value, the child can be referred to a medical specialist in child development. We

used the previously validated cutoff values for each domain as set in the J-ASQ-3 [27].

We also listed the potential confounders (Supplementary Table 1). These confounders included the following factors: child, maternal, paternal, and family. The child-related factors were, for example, number of children birthed and fetal position. The maternal factors were, for instance, mode of conception, mode of delivery, maternal and obstetric complications, marital status, intimate partner violence, and number of advisers on the child's development. The paternal factors included the active smoking status, and educational level. The family income was obtained from MT2 as the family factor.

Statistical analysis

We categorized ASs at 1 and 5 min into ≤ 6 , 7, 8, 9, and 10, and then into the following groups for comparisons: ≤ 6 vs ≥ 7 , ≤ 7 vs ≥ 8 , ≤ 8 vs ≥ 9 , and ≤ 9 vs 10. We defined delayed development as when a child's developmental score in each domain was less than the cutoff value, which was 29.95, 39.26, 27.91, 30.03, and 29.89 for the communication, gross and fine motor, problem-solving, and personal-social domains, respectively [27].

Descriptive statistics were used to report the frequencies and proportions of variables. Multivariable logistic regression analyses were performed to accomplish the objectives of this study. We categorized several continuous variables such as pre-pregnancy maternal body mass index (BMI) and maternal age at childbirth. The effect size in the results was described using odds ratios (ORs) with point estimates and 95% confidence intervals (CIs). Moreover, to explore the association of the change of ASs from 1 to 5 min with the child development, we conducted a subgroup analysis. Sensitivity analysis was performed to assess the robustness of this study because a diagnosis of cerebral palsy or chromosomal abnormality after birth up to 3 years of age is likely to over-estimate the effect size of ORs. After excluding children with these diagnoses up to 3 years of age based on C1y, C2y, and C3y from the study population, we performed the same analyses. Two-tailed statistical tests were performed, and the statistical significance was set at 0.05. We used R (version 3.6.1; R Foundation, Vienna, Austria) statistical software for this study.

Results

Participants

The JECS collected 104,062 fetal records (Fig. 1). After excluding 49,346 children, the study population comprised

54,716 children (females, 26,900; males, 27,816) (Supplementary Table 2). We presented the number of children with ASs in the ≤ 6 , 7, 8, 9, and 10 categories at 1 and 5 min (Table 1). The proportion of children with AS of 9 at 1 and 5 min is the highest of all categories. We also showed the number of outcomes in communication, gross and fine motor, problem-solving, and personal-social domains (Table 1). The frequency in the fine motor domain was the largest of all domains. Furthermore, the occurrence in AS of 9 was the largest of any other ASs. The higher the ASs at 1 and 5 min, the lower the proportion of maternal perinatal complications (Supplementary Table 3). We also indicated missing data in Fig. 1.

Main results

In terms of AS at 1 min, adjusted OR (aOR) for the problem-solving domain when ASs ≤ 6 were compared with those ≥ 7 was 1.34 (1.08–1.67). Similarly, aORs of gross motor and problem-solving domains comparing ASs ≤ 7 with those ≥ 8 were 1.38 (1.15–1.66) and 1.26 (1.08–1.47), respectively (Table 2). In contrast, when compared with ASs ≥ 9 at 1 min, ASs ≤ 8 were not associated with the five domains (Table 2). Moreover, we found the associations between ASs at 5 min and several domains: aORs were 1.31, 1.20, and 1.16 (1.11–1.56, 1.04–1.38, and 1.01–1.34) for gross and fine motor, and problem-solving domains, respectively (Table 2).

Subgroup analysis

We focused on the subgroup of ASs ≤ 8 at 1 min to investigate the association of the changes in the ASs from 1 to 5 min with child development. There were 19,913 participants in this subgroup analysis. Compared with ASs ≥ 9 at 5 min, aOR of gross motor for ASs ≤ 8 was 1.34 (1.11–1.61) (Table 3). The aOR of gross motor for an AS of 9 at 5 min was 0.74 (0.62–0.89) and that for an AS of 10 was 0.82 (0.62–1.08), compared with ASs ≤ 8 at 5 min (Table 3).

Sensitivity analysis

The number of children in this sensitivity analysis was 54,687 (Fig. 1). The frequencies of the exposures and outcomes were shown in (Supplementary Table 4). The aOR for communication domain when ASs ≤ 6 at 5 min were compared with scores ≥ 7 showed the change in the direction of effect: 0.99 (0.54–1.83) (Supplementary Table 5). In contrast, aORs of any other domains at 1 and 5 min indicated the same direction

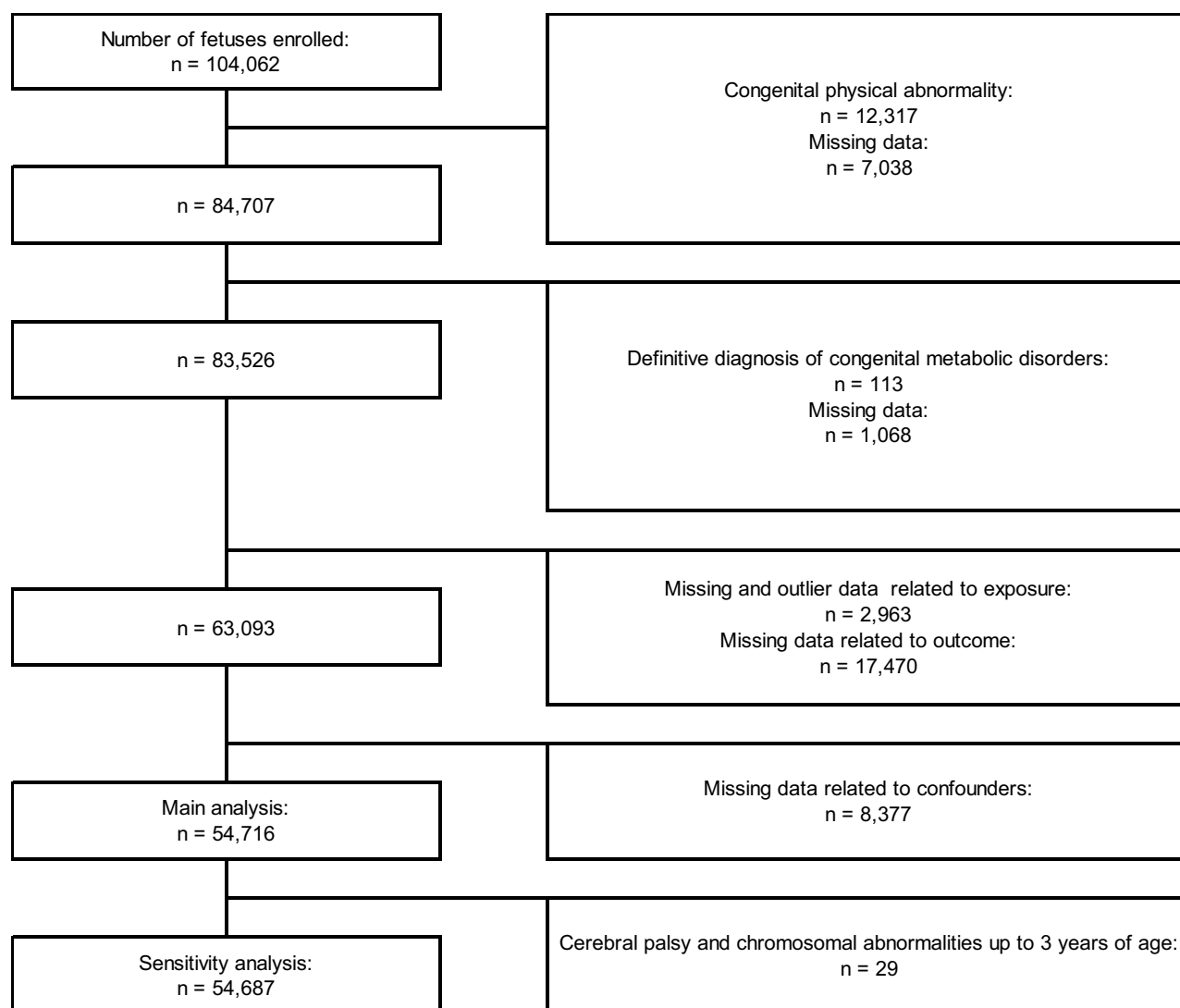


Fig. 1 Flowchart detailing the selection of the study population

of effect as the main analysis (Supplementary Table 5; Supplementary Table 6; Supplementary Table 7).

Discussion

We evaluated the association between AS and developmental status at 3 years of age, adjusting for perinatal and socioeconomic confounders. The proportions of neonates with the ASs ≤ 7 at 5 min who meet developmental delay at 3 years of age on the scale of the current study were as follows: 1.39% for the communication domain, 1.63% for the gross motor domain, 1.46% for the fine motor domain, 1.34% for the problem-solving domain, and 1.67% for the personal-social domain. In AS at 1 min, ASs ≤ 8 were not associated with five domains of the outcome, compared with those ≥ 9 ;

whereas at 5 min, also considering the change of ASs from 1 to 5 min, ASs ≤ 8 were associated with an increased aOR for the developmental delay of gross motor domain. Additionally, we confirmed the same direction of effect in the sensitivity analysis.

ASs at 1 min were associated with an increased aOR for delayed development in a few domains of outcome. Previous studies [1, 2] reported ASs of 0, 1, 2, and 3 at 1 min would just assess early neonatal status but not predict a child's developmental status. However, recent studies have shown the association of ASs at 1 min with neonatal complications [6] and the developmental status at 5 years of age [21]. Other previous studies [6] have reported ASs of 7, 8, and 9 in term infants were associated with increased aORs for neonatal complications, compared with AS of 10. Moreover, ASs of ≤ 9 in term singletons, compared with a score of 10, were

Table 1 Outcomes for Apgar score in the main analysis

Apgar score at 1 min						
Score	Frequencies (n = 54,716)	Communication (n = 1,944)	Gross motor (n = 2,267)	Fine motor (n = 3,960)	Problem-solving (n = 3,803)	Personal-social (n = 1,619)
0	6	0	1	1	0	0
1	56	5	7	8	8	7
2	74	7	8	8	10	5
3	89	9	10	16	16	5
4	160	6	7	15	11	8
5	197	13	24	24	21	14
6	381	21	21	43	44	17
7	1,088	52	78	100	102	46
8	17,862	667	757	1,367	1,298	559
9	30,406	1,016	1,187	2,073	1,998	824
10	4,397	148	167	305	295	134
Apgar score at 5 min						
0	47	1	1	6	0	2
1	4	0	0	0	0	0
2	4	0	0	0	0	0
3	11	0	2	3	0	1
4	36	3	3	6	4	3
5	40	1	5	3	5	1
6	85	9	10	13	11	6
7	204	13	16	27	31	14
8	2,149	96	135	203	187	74
9	27,118	979	1,103	1,994	1,915	761
10	25,018	842	992	1,705	1,650	757

associated with an increased adjusted rate ratio (aRR) for developmental vulnerability and special needs at 5 years of age using Early Development Instrument [21]. However, we found no association between ASs ≤ 8 and ≥ 9 at 1 min in all domains. The reasons for different results might be affected by sample size and the number of events about statistical power. In addition, the association of AS at 1 min with child development can depend on each setting such as the age when the outcome was measured.

ASs ≤ 8 at 5 min compared with those ≥ 9 were associated with increased aORs for gross and fine motor domains. The association between AS and subsequent motor development was shown [18, 19]. For example, a large-scale cohort study found in newborns with gestational ages ≥ 37 weeks, ASs ≤ 3 at 5 min, compared to those ≥ 7 , were associated with increased aORs for motor impairments in school [18]. We showed ASs at 5 min were associated with increased aOR for motor development at 3 years of age and had a larger association with gross motor than fine motor development. The J-ASQ-3 uses the same formats in each domain but, in terms of estimating the developmental status, the motor domains are likely to be more noticeable and easier to assess than others. Moreover, the J-ASQ-3 is a screening tool that assesses development in five domains such as communication, gross motor, fine motor,

problem-solving and personal-social [27]. Depending on the domain being evaluated, the effect from associated factors might vary. In this study, the ASs at 5 min were associated with gross and fine motor and problem-solving domains but were not associated with communication and personal-social domains. This may be because the maternal higher educational background affects the better infantile socioemotional status [28], while child exposed to intimate partner violence was directly associated with socioemotional problems and these problems might be mediated by the strength of mother–child attachment, overall family functioning and level of mother’s emotional support, although these results are shown from the exploratory research [29]. In this study, we conducted the analysis adjusting for these confounders mentioned above, and these factors might be much more strongly associated with the communication and personal-social domains than ASs.

The temporal change in AS, from 1 to 5 min or from 5 to 10 min was demonstrated as useful in assessing neonatal vitality [2]. ASs of 9 at both 5 and 10 min compared with ASs of 9 and 10 at 5 and 10 min, respectively, were associated with increased aORs for neonatal complications in term infants [6]. Moreover, a previous study identified term singletons with AS of 9 at both 1 and 5 min compared with ASs of 9 and 10 at 1 and 5 min, respectively, increased aRRs

Table 2 Association between the Apgar scores at 1 min and at 5 min and each domain in the J-ASQ-3

Score	Communication		Gross motor		Fine motor		Problem-solving		Personal-social	
	Crude OR (95%CI)	aOR* (95%CI)	Crude OR (95%CI)	aOR* (95%CI)	Crude OR (95%CI)	aOR* (95%CI)	Crude OR (95%CI)	aOR* (95%CI)	Crude OR (95%CI)	aOR* (95%CI)
1 min										
≤ 6	1.86 (1.43–2.42)	1.31 (0.97–1.76)	2.08 (1.64–2.63)	1.26 (0.97–1.65)	1.76 (1.44–2.14)	1.22 (0.98–1.52)	1.75 (1.43–2.14)	1.34 (1.08–1.67)	2.06 (1.57–2.71)	1.33 (0.98–1.81)
≥ 7	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference
≤ 7	1.62 (1.33–1.97)	1.20 (0.97–1.49)	1.97 (1.66–2.33)	1.38 (1.15–1.66)	1.53 (1.32–1.77)	1.14 (0.97–1.33)	1.58 (1.36–1.82)	1.26 (1.08–1.47)	1.76 (1.44–2.17)	1.23 (0.98–1.54)
≥ 8	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference
≤ 8	1.18 (1.07–1.29)	1.03 (0.94–1.14)	1.19 (1.09–1.29)	1.03 (0.94–1.12)	1.18 (1.10–1.26)	1.04 (0.97–1.12)	1.16 (1.09–1.24)	1.05 (0.98–1.13)	1.21 (1.10–1.34)	1.03 (0.92–1.14)
≥ 9	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference
5 min										
≤ 6	1.79 (1.04–3.08)	1.17 (0.66–2.07)	2.37 (1.51–3.72)	1.34 (0.82–2.19)	2.04 (1.39–2.98)	1.33 (0.89–2.00)	1.30 (0.82–2.05)	0.90 (0.56–1.46)	2.00 (1.14–3.51)	1.20 (0.66–2.17)
≥ 7	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference
≤ 7	1.83 (1.23–2.70)	1.21 (0.79–1.86)	2.19 (1.56–3.08)	1.25 (0.85–1.82)	2.01 (1.52–2.65)	1.35 (1.00–1.83)	1.81 (1.35–2.43)	1.33 (0.97–1.83)	2.21 (1.49–3.28)	1.37 (0.89–2.11)
≥ 8	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference
≤ 8	1.38 (1.15–1.67)	1.10 (0.90–1.34)	1.71 (1.45–2.00)	1.31 (1.11–1.56)	1.47 (1.29–1.68)	1.20 (1.04–1.38)	1.38 (1.21–1.59)	1.16 (1.01–1.34)	1.36 (1.11–1.67)	1.03 (0.83–1.28)
≥ 9	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference

*adjusted according to sex of the child; mother's age at birth; painless delivery; medication use during pregnancy; supplements taken during pregnancy; maternal complications during pregnancy; mode of delivery; gravidity; gestational age; birth weight; obstetric complications; number of children birthed; fetal position; maternal and paternal active smoking habits; maternal passive smoking; maternal alcohol consumption; maternal and paternal educational background; family income; number of advisers required for the pregnancy; maternal BMI; mode of pregnancy; marital status; frequency of intimate partner violence

J-ASQ-3, Ages and Stages Questionnaire (Japanese version, 3rd edition); CI, confidence interval; BMI, body mass index; OR, odds ratio; aOR, adjusted odds ratio

for developmental vulnerability at 5 years of age [21]. These studies showed the improvement of AS according to time flow resulted in the better neonatal and future developmental status. We also found the same direction of effect regardless of the developmental measurements and ages. Thus, changes in AS could be important variables in subsequent childhood development.

Previous studies used original categories of AS such as '0–3', '4–6', and '7–10' [7, 18, 19, 30], or related scores [5, 6, 8, 10]. If ASs are ≤ 6 at 5 min, repeated assessment of neonates is recommended [2]. However, the reliability of AS is limited due to interobserver variability [1, 2, 4]; therefore, we changed the cutoff value for AS by 1 point for the category of '7–10', although ASs ≥ 7 are generally considered normal. Similar to previously reported distributions [6], we found that the higher the AS, the lower the prevalence of children with less than the cutoff value in all domains. Additionally, most of the outcomes occurred in ASs 8 and 9 at 1 min, and 9 and 10 at 5 min. Therefore, we considered these analyses might have been less reliable and that the direction of communication domain in the J-ASQ-3

could change inversely if the cutoff value for the AS was set in 7 at 5 min.

Strength

This study has some strengths. The JECS had a large sample size and many variables for the adjustment of confounders. The quality of this dataset was also strictly maintained, which facilitated precise analysis. Moreover, to our knowledge, this is the first study in an Asian population to report an association between AS and developmental status at 3 years of age. This finding might assist clinical practices in terms of predicting future child development.

Limitation

In contrast, this study has several limitations. First, we used many variables to adjust for confounders; however, we could not adjust for unmeasurable confounders such as specific clinical findings including fever and laboratory

Table 3 Association with the temporal change of Apgar scores from ≤ 8 at 1 min to ≤ 8 , 9, and 10 at 5 min of the J-ASQ-3

Communication				
At 5 min	Subjects	Events	Crude OR (95%CI)	aOR (95%CI)*
n = 19,913				
≥ 9	17,423	658	reference	reference
≤ 8	2,490	122	1.31 (1.08–1.60)	1.11 (0.90–1.37)
≤ 8	2,490	122	reference	reference
9	15,599	602	0.78 (0.64–0.95)	0.92 (0.74–1.13)
10	1,824	56	0.61 (0.45–0.85)	0.74 (0.53–1.03)
Gross motor				
≥ 9	17,423	745	reference	reference
≤ 8	2,490	168	1.62 (1.36–1.93)	1.34 (1.11–1.61)
≤ 8	2,490	168	reference	reference
9	15,599	661	0.61 (0.51–0.73)	0.74 (0.62–0.89)
10	1,824	84	0.67 (0.51–0.87)	0.82 (0.62–1.08)
Fine motor				
≥ 9	17,423	1,336	reference	reference
≤ 8	2,490	246	1.32 (1.14–1.52)	1.14 (0.98–1.32)
≤ 8	2,490	246	reference	reference
9	15,599	1,211	0.77 (0.66–0.89)	0.89 (0.76–1.04)
10	1,824	125	0.67 (0.54–0.84)	0.79 (0.62–1.00)
Problem-solving				
≥ 9	17,423	1,276	reference	reference
≤ 8	2,490	234	1.31 (1.13–1.52)	1.16 (1.00–1.35)
≤ 8	2,490	234	reference	reference
9	15,599	1,144	0.76 (0.66–0.88)	0.86 (0.74–1.00)
10	1,824	132	0.75 (0.60–0.94)	0.87 (0.69–1.09)
Personal-social				
≥ 9	17,423	563	reference	reference
≤ 8	2,490	98	1.23 (0.99–1.53)	1.01 (0.80–1.27)
≤ 8	2,490	98	reference	reference
9	15,599	492	0.79 (0.64–0.99)	0.97 (0.77–1.22)
10	1,824	71	0.99 (0.72–1.35)	1.23 (0.89–1.70)

*adjusted according to sex of the child; mother's age at birth; painless delivery; medication use during pregnancy; supplements taken during pregnancy; maternal complications during pregnancy; mode of delivery; gravidity; gestational age; birth weight; obstetric complications; number of children birthed; fetal position; maternal and paternal active smoking habits; maternal passive smoking; maternal alcohol consumption; maternal and paternal educational background; family income; number of advisers required for the pregnancy; maternal BMI; mode of pregnancy; marital status; frequency of intimate partner violence

J-ASQ-3, Ages and Stages Questionnaire (Japanese version, 3rd edition); CI, confidence interval; BMI, body mass index; OR, odds ratio; aOR, adjusted odds ratio

data related to systemic infection of newborns, and post-natal treatment procedures such as intubation for the child. However, we performed the sensitivity analysis excluding participants such as cerebral palsy which caused developmental delay over the post-natal course and indicated

the same direction as results of the main analysis. Second, we excluded missing data, which might affect the study population in terms of selection bias. Third, applying the AS to assess the vitality of neonates after birth involves interobserver variability; however, we adjusted the cut-off values for ASs associated with child development to reduce the effect of this limitation. Moreover, AS is likely to be suggested to have the internal validity in monitoring trends over time and will provide additional information on newborn health [3]. Therefore, we consider that AS is a simple and effective method which can assess not only the vitality of neonates immediately after birth but also the long-term development. Lastly, we used the J-ASQ-3 for the developmental status, but this scale was measured by parents/caregivers [26, 27]. Therefore, there might be under-reporting or over-reporting assessments due to the parents' attachment to their children. However, we considered it was reasonable to use this scale because pediatricians conduct their decision making based on medical interviews with parents/caregivers.

Conclusion

The current study showed an association between the ASs and developmental status at 3 years of age. Compared with neonates with ASs ≥ 9 at 5 min, scores ≤ 8 were associated with gross and fine motor, and problem-solving domains. In neonates with ASs ≤ 8 at 1 min, delayed development in gross motor domain was larger in those with ASs ≤ 8 at 5 min than with ASs ≥ 9 . These results may provide guidance in improving clinical practices concerning child development follow-up and in detecting delayed development at an earlier age regardless of the complications and interventions in the perinatal period.

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1007/s00431-021-04249-y>.

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Authors' contributions Conceptualization: Tetsuya Tsuchida, Satomi Yoshida, Masato Takeuchi, and Koji Kawakami; Data curation: Tetsuya Tsuchida, Chihiro Kawakami, and Shuichi Ito; Methodology: Tetsuya Tsuchida, Satomi Yoshida, and Masato Takeuchi; Formal analysis and investigation: Tetsuya Tsuchida; Writing – original draft preparation: Tetsuya Tsuchida; Writing – review and editing: Satomi Yoshida, Masato Takeuchi, Chihiro Kawakami, Koji Kawakami, and Shuichi Ito; Funding acquisition: Chihiro Kawakami and Shuichi Ito; Resources: Chihiro Kawakami and Shuichi Ito; Supervision: Satomi Yoshida, Masato Takeuchi, Chihiro Kawakami, Koji Kawakami, and Shuichi Ito.

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Availability of data and material Data are unsuitable for public deposition due to ethical restrictions and legal framework of Japan. It is prohibited by the Act on the Protection of Personal Information (Act No. 57 of 30 May 2003, amendment on 9 September 2015) to publicly deposit the data containing personal information. Ethical Guidelines for Medical and Health Research Involving Human Subjects enforced by the Japan Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare also restricts the open sharing of the epidemiologic data. All inquiries about access to data should be sent to: jecs-en@nies.go.jp. The person responsible for handling enquiries sent to this e-mail address is Dr Shoji F. Nakayama, JECS Program Office, National Institute for Environmental Studies.

Code availability N/A.

Declarations

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ministry of the Environment's Institutional Review Board on Epidemiological Studies and the Ethics Committees of all participating institutions.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent for publication The participant has consented to the submission to this journal.

Conflict of interest The authors have no conflicts of interest to disclose.

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Supplementary Table 1 The kinds of self-administered questionnaires in the JECS

Names	Subjects	Respondents	Timings	Variables
C1y	Child	Parents or Caregivers	1 year after birth	Chromosomal abnormality (sensitivity analysis), Cerebral palsy (sensitivity analysis)
C2y	Child	Parents or Caregivers	2 years after birth	Chromosomal abnormality (sensitivity analysis)
C3y	Child	Parents or Caregivers	3 years after birth	J-ASQ-3, Cerebral palsy (sensitivity analysis)
DrT1	Mother	Medical doctors	The first trimester	Pre-pregnancy maternal BMI; Mode of conception; Gravidity
Dr0m	Mother and Child	Medical doctors	At birth	Apgar score; Age at childbirth; Gestational age; Sex of the child; Painless delivery; Birth weight; Fetal position; Medication use during pregnancy, such as steroid therapy, antibiotic therapy, iron, folic acid, ritodrine and magnesium; Maternal complications during pregnancy; Obstetric complications
Dr1m	Mother and Child	Medical doctors	1 month after birth	Congenital metabolic disorders
MT1	Mother	Mother	The first trimester	Marital status

MT2	Mother	Mother	The second trimester	Intimate partner violence during pregnancy; Supplement use during pregnancy; Maternal and paternal active smoking during pregnancy; Maternal passive smoking during pregnancy; Maternal and paternal educational levels; Family income; Number of pregnancy advisers
MT2-FFQ	Mother	Mother	The second trimester	Alcohol consumption during pregnancy

Abbreviations: JECS, Japan Environment and Children's Study; FFQ, Food Frequency Questionnaire; J-ASQ-3, Ages and Stages Questionnaire (Japanese version, 3rd edition); BMI, Body Mass Index

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Affiliation and E-mail address of the Corresponding Author:

Department of Pharmacoepidemiology

Kyoto University Graduate School of Medicine and Public Health

kawakami.koji.4e@kyoto-u.ac.jp

Supplementary Table 2 Baseline characteristics

	Apgar score at 1 minute (54,716)				Apgar score at 5 minutes (54,716)			
	≤6	7	8	≥9	≤6	7	8	≥9
	(963)	(1,088)	(17,862)	(34,803)	(227)	(204)	(2,149)	(52,136)
Child sex	429	483	8,767	17,221	89	95	1,027	25,689
Female, n (%)	(44.5)	(44.4)	(49.1)	(49.5)	(39.2)	(46.6)	(47.8)	(49.3)
Number of children birthed	906	1,030	17,370	34,557	214	190	2,043	51,416
Single, n (%)	(94.1)	(94.7)	(97.2)	(99.3)	(94.2)	(93.1)	(95.1)	(98.6)
Fetal position	830	1,002	17,005	33,961	207	184	2,000	50,407
Cephalic, n (%)	(86.2)	(92.1)	(95.2)	(97.6)	(91.2)	(90.2)	(93.1)	(96.7)
Breech, n (%)	112	68	725	744	18	16	119	1,496
	(11.6)	(6.3)	(4.1)	(2.1)	(7.9)	(7.8)	(5.5)	(2.9)
Others*, n (%)	21	18	132	98	2	4	30	233
	(2.2)	(1.7)	(0.74)	(0.28)	(0.88)	(2.0)	(1.4)	(0.45)
Gestational age (weeks)	279	154	1,105	868	71	73	297	1,965
Preterm (<37), n (%)	(29.0)	(14.2)	(6.2)	(2.5)	(31.3)	(35.8)	(13.8)	(3.8)
Term (37 to ≤41)	682	929	16,717	33,850	155	131	1,846	50,046
n (%)	(70.8)	(85.4)	(93.6)	(97.3)	(68.3)	(64.2)	(85.9)	(96.0)
Post-term (≥42)	2	5	40	85	1		6	125
n (%)	(0.21)	(0.46)	(0.22)	(0.24)	(0.44)	0	(0.28)	(0.24)

Birth weight (g)	305	198	1,871	1,954	73	73	374	3,808
<2,500, n (%)	(31.7)	(18.2)	(10.5)	(5.6)	(32.2)	(35.8)	(17.4)	(7.3)
2,500 to <4,000	651	877	15,828	32,582	152	130	1,753	47,903
n (%)	(67.6)	(80.6)	(88.6)	(93.6)	(67.0)	(63.7)	(81.6)	(91.9)
≥4,000	7	13	163	267	2	1	22	425
n (%)	(0.73)	(1.2)	(0.91)	(0.77)	(0.88)	(0.49)	(1.0)	(0.82)
Age at childbirth (years)	8	2	58	147	2	1	7	205
<20, n (%)	(0.83)	(0.18)	(0.32)	(0.42)	(0.88)	(0.49)	(0.33)	(0.39)
20 to <35	636	703	12,360	25,214	159	130	1,416	37,208
n (%)	(66.0)	(64.6)	(69.2)	(72.4)	(70.0)	(63.7)	(65.9)	(71.4)
≥35	319	383	5,444	9,442	66	73	726	14,723
n (%)	(33.1)	(35.2)	(30.5)	(27.1)	(29.1)	(35.8)	(33.8)	(28.2)
Maternal pre-pregnancy BMI	159	159	2,750	5,647	35	39	318	8,323
<18.5, n (%)	(16.5)	(14.6)	(15.4)	(16.2)	(15.4)	(19.1)	(14.8)	(16.0)
18.5 to <25	672	769	13,022	26,205	157	141	1,511	38,859
n (%)	(69.8)	(70.7)	(72.9)	(75.3)	(69.2)	(69.1)	(70.3)	(74.5)
≥25	132	160	2,090	2,951	35	24	320	4,954
n (%)	(13.7)	(14.7)	(11.7)	(8.5)	(15.4)	(11.8)	(14.9)	(9.5)
Gravidity	375	407	5,767	10,524	76	84	708	16,205
0, n (%)	(38.9)	(37.4)	(32.2)	(30.2)	(33.5)	(41.2)	(32.9)	(31.1)

Mode of conception	839	933	16,324	32,557	201	171	1,905	48,376
Spontaneous, n (%)	(87.1)	(85.8)	(91.4)	(93.5)	(88.5)	(83.8)	(88.6)	(92.8)
Mode of delivery	317	388	9,200	22,069	79	81	877	30,937
Spontaneous, n (%)	(32.9)	(35.7)	(51.5)	(63.4)	(34.8)	(39.7)	(40.8)	(59.3)
Caesarean	395	351	4,633	4,520	101	82	724	8,992
n (%)	(41.0)	(32.3)	(25.9)	(13.0)	(44.5)	(40.2)	(33.7)	(17.2)
Induced	140	212	2,912	6,303	37	28	394	9,108
n (%)	(14.5)	(19.5)	(16.3)	(18.1)	(16.3)	(13.7)	(18.3)	(17.5)
Others**	111	137	1,117	1,911	10	13	154	3,099
n (%)	(11.5)	(12.6)	(6.3)	(5.5)	(4.4)	(6.4)	(7.2)	(5.9)
Marital status	928	1,041	17,248	33,817	214	200	2,080	50,540
Married, n (%)	(96.4)	(95.7)	(96.6)	(97.2)	(94.3)	(98.0)	(96.8)	(96.9)
Maternal active smoking	31	29	699	1,111	13	3	74	1,780
Yes, n (%)	(3.2)	(2.7)	(3.9)	(3.2)	(5.7)	(1.5)	(3.4)	(3.4)
Paternal active smoking	385	494	8,166	15,101	105	79	937	22,975
Yes, n (%)	(40.0)	(45.4)	(45.4)	(43.4)	(46.3)	(38.7)	(43.6)	(44.1)
Maternal passive smoking	314	369	6,524	12,014	74	69	757	18,321
Yes, n (%)	(32.6)	(33.9)	(36.5)	(34.5)	(32.6)	(33.8)	(35.2)	(35.1)
Maternal alcohol intake	17	23	497	935	5	6	53	1,408
Yes, n (%)	(1.8)	(2.1)	(2.8)	(2.7)	(2.2)	(2.9)	(2.5)	(2.7)

Maternal educational level	324	352	6,288	11,101	78	74	710	17,203
≤12 years Yes, n (%)	(33.6)	(32.4)	(35.2)	(31.9)	(34.4)	(36.3)	(33.0)	(33.0)
Paternal educational level	402	459	7,751	14,369	103	85	930	21,863
≤12 years Yes, n (%)	(41.7)	(42.2)	(43.4)	(41.3)	(45.4)	(41.7)	(43.3)	(41.9)
Family income	695	787	12,928	25,232	158	144	1,576	37,764
<6 million yen** Yes, n (%)	(72.2)	(72.3)	(72.4)	(72.5)	(69.6)	(70.6)	(73.3)	(72.4)

*including transverse and others; **including vacuum and forceps; ***\$ 1 = ¥103 in 2013

Abbreviation: BMI, body mass index

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Affiliation and E-mail address of the Corresponding Author:

Department of Pharmacoepidemiology

Kyoto University Graduate School of Medicine and Public Health

kawakami.koji.4e@kyoto-u.ac.jp

Supplementary Table 3 Detailed baseline characteristics

	Apgar score at 1 minute (54,716)				Apgar score at 5 minutes (54,716)			
	≤6	7	8	≥9	≤6	7	8	≥9
	(963)	(1,088)	(17,862)	(34,803)	(227)	(204)	(2,149)	(52,136)
Gestational age (weeks)	39	5	3	1	15	9	10	14
≤28, n (%)	(4.0)	(0.46)	(0.017)	(0.0029)	(6.6)	(4.4)	(0.47)	(0.027)
29 to ≤30, n (%)	31	7	17	4	9	10	17	23
	(3.2)	(0.64)	(0.095)	(0.011)	(4.0)	(4.9)	(0.79)	(0.044)
31 to ≤32, n (%)	44	15	72	12	12	10	35	86
	(4.6)	(1.4)	(0.40)	(0.034)	(5.3)	(4.9)	(1.6)	(0.16)
33 to ≤34, n (%)	45	31	204	46	10	13	72	231
	(4.7)	(2.8)	(1.14)	(0.13)	(4.4)	(6.4)	(3.4)	(0.44)
35 to ≤36, n (%)	120	96	809	805	25	31	163	1,611
	(12.5)	(8.8)	(4.5)	(2.3)	(11.0)	(15.2)	(7.6)	(3.1)
Birth weight (g)	29	4	3	1	10	8	10	9
<1000, n (%)	(3.0)	(0.37)	(0.017)	(0.0029)	(4.4)	(3.9)	(0.47)	(0.017)
1000 to <1500, n (%)	57	19	45	8	19	12	32	66
	(5.9)	(1.7)	(0.25)	(0.023)	(8.4)	(5.9)	(1.5)	(0.13)
1500 to <2500, n (%)	219	175	1823	1,945	44	53	332	3,733
	(22.7)	(16.1)	(10.2)	(5.6)	(19.4)	(26.0)	(15.4)	(7.2)

Maternal pre-pregnancy BMI	100	110	1,552	2,384	23	19	236	3,868
25 to <30, n (%)	(10.4)	(10.1)	(8.7)	(6.8)	(10.1)	(9.3)	(11.0)	(7.4)
30 to <35, n (%)	26	41	392	458	8	5	60	844
	(2.7)	(3.8)	(2.2)	(1.3)	(3.5)	(2.5)	(2.8)	(1.6)
35 to <40, n (%)	5	4	114	85	4		18	186
	(0.52)	(0.37)	(0.64)	(0.24)	(1.8)	0	(0.84)	(0.36)
≥40, n (%)	1	5	32	24			6	56
	(0.10)	(0.46)	(0.18)	(0.069)	0	0	(0.28)	(0.11)
Gravidity	588	681	12,095	24,279	151	120	1,441	35,931
≥1, n (%)	(61.1)	(62.6)	(67.7)	(69.8)	(66.5)	(58.8)	(67.1)	(68.9)
Maternal complications	197	224	3,049	4,369	46	41	418	7,334
Yes, n (%)	(20.5)	(20.6)	(17.1)	(12.6)	(20.3)	(20.1)	(19.5)	(14.1)
Obstetric complications	652	660	8,927	14,637	156	138	1,251	23,331
Yes, n (%)	(67.7)	(60.7)	(50.0)	(42.1)	(68.7)	(67.6)	(58.2)	(44.8)
Painless delivery	24	45	424	725		7	46	1,165
					0			
Yes, n (%)	(2.5)	(4.1)	(2.4)	(2.1)		(3.4)	(2.1)	(2.2)
Steroid use	75	69	662	826	14	21	122	1,465
Yes, n (%)	(7.8)	(6.3)	(3.7)	(2.4)	(6.2)	(10.3)	(5.7)	(2.8)
Antibiotics use	227	266	3,717	7,490	58	55	467	11,120
Yes, n (%)	(23.6)	(24.4)	(20.8)	(21.5)	(25.6)	(27.0)	(21.7)	(21.3)

Iron medication use	351	425	6,752	15,853	90	78	770	22,443
Yes, n (%)	(36.4)	(39.1)	(37.8)	(45.6)	(39.6)	(38.2)	(35.8)	(43.0)
Folic acid use	39	26	441	700	8	14	62	1,122
Yes, n (%)	(4.0)	(2.4)	(2.5)	(2.0)	(3.5)	(6.9)	(2.9)	(2.2)
Ritodrine use	337	374	5,001	9,565	91	81	684	14,421
Yes, n (%)	(35.0)	(34.4)	(28.0)	(27.5)	(40.0)	(39.7)	(31.8)	(27.7)
Magnesium use	80	57	398	678	20	20	88	1,085
Yes, n (%)	(8.3)	(5.2)	(2.2)	(1.9)	(8.8)	(9.8)	(4.1)	(2.1)
Supplement use	414	484	7,702	14,914	89	95	895	22,435
Yes, n (%)	(43.0)	(44.5)	(43.1)	(42.9)	(39.2)	(46.6)	(41.6)	(43.0)
Intimate partner violence	955	1,083	17,685	34,441	225	202	2,123	51,614
None, n (%)	(99.2)	(99.5)	(99.0)	(99.0)	(99.1)	(99.0)	(98.8)	(99.0)
Rarely, n (%)	7	3	136	257	2	2	18	381
	(0.73)	(0.28)	(0.76)	(0.74)	(0.88)	(0.98)	(0.84)	(0.73)
Sometimes, n (%)	1	2	38	83	0	0	8	116
	(0.10)	(0.18)	(0.21)	(0.24)			(0.37)	(0.22)
Often, n (%)	0	0	3	22	0	0	0	25
			(0.017)	(0.063)				(0.048)
Number of pregnancy advisers	6	12	155	300	3		23	447
0, n (%)	(0.62)	(1.1)	(0.87)	(0.86)	(1.3)	0	(1.1)	(0.86)

	348	433	6,914	12,993	83	78	825	19,642
1-2, n (%)	(36.1)	(39.8)	(38.7)	(37.2)	(36.6)	(38.2)	(38.4)	(37.7)
	609	643	10,793	21,570	141	126	1,301	32,047
≥3, n (%)	(63.2)	(59.0)	(60.4)	(62.0)	(62.1)	(61.8)	(60.5)	(61.5)
Marital status	29	39	513	817	10	4	60	1,324
Unmarried, n (%)	(3.0)	(3.6)	(2.9)	(2.3)	(4.4)	(2.0)	(2.8)	(2.5)
	6	8	100	165	3		9	267
Divorced, n (%)	(0.62)	(0.74)	(0.56)	(0.47)	(1.3)	0	(0.42)	(0.51)
			1	4				5
Bereavement, n (%)	0	0	(0.0056)	(0.011)	0	0	0	(0.0096)
Maternal passive smoking	103	120	2,124	4,178	27	22	235	6,241
1 day / week, n (%)	(10.7)	(11.0)	(11.9)	(12.0)	(11.9)	(10.8)	(10.9)	(12.0)
	79	93	1,382	2,693	17	20	182	4,028
2 - 3 days / week, n (%)	(8.2)	(8.5)	(7.7)	(7.7)	(7.5)	(9.8)	(8.5)	(7.7)
	44	56	835	1,569	8	8	100	2,388
4 - 6 days / week, n (%)	(4.6)	(5.1)	(4.7)	(4.5)	(3.5)	(3.9)	(4.7)	(4.6)
	88	100	2,183	3,574	22	19	240	5,664
7 days / week, n (%)	(9.1)	(9.2)	(12.2)	(10.3)	(9.7)	(9.3)	(11.2)	(10.9)

Abbreviation: BMI, body mass index

Article Title:

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and Children's Study Group

Affiliation and E-mail address of the Corresponding Author:

Department of Pharmacoepidemiology

Kyoto University Graduate School of Medicine and Public Health

kawakami.koji.4e@kyoto-u.ac.jp

Supplementary Table 4 Outcomes for each Apgar score in the sensitivity analysis

Apgar score at 1 minute

Score	Frequencies (n = 54,687)	Communication (n = 1,929)	Gross motor (n = 2,249)	Fine motor (n = 3,940)	Problem-solving (n = 3,785)	Personal-social (n = 1.604)
0	6	0	1	1	0	0
1	55	4	6	7	7	6
2	72	5	7	6	8	4
3	89	9	10	16	16	5
4	160	6	7	15	11	8
5	197	13	24	24	21	14
6	381	21	21	43	44	17
7	1,084	49	74	96	99	43
8	17,849	661	749	1,358	1,290	552
9	30,398	1,013	1,184	2,070	1,995	821
10	4,396	148	166	304	294	134

Apgar score at 5 minutes

0	47	1	1	6	0	2
1	4	0	0	0	0	0
2	4	0	0	0	0	0
3	11	0	2	3	0	1
4	35	2	2	5	3	2

5	40	1	5	3	5	1
6	84	8	10	12	10	6
7	204	13	16	27	31	14
8	2,146	94	133	200	184	72
9	27,100	971	1,092	1,983	1,906	752
10	25,012	839	988	1,701	1,646	754

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Kyoto University Graduate School of Medicine and Public Health

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Supplementary Table 5 Association between the Apgar scores at 1 minute and at 5 minutes and each domain in the J-ASQ-3 (sensitivity analysis)

[illegible]

5 minutes

≤6	1.54	0.99	2.29	1.28	1.91	1.24	1.17	0.81	1.87	1.12
	(0.86-2.77)	(0.54-1.83)	(1.44-3.63)	(0.77-2.13)	(1.29-2.83)	(0.82-1.89)	(0.72-1.90)	(0.49-1.34)	(1.04-3.35)	(0.60-2.08)
≥7	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference
≤7	1.70	1.13	2.15	1.23	1.95	1.31	1.74	1.28	2.15	1.34
	(1.13-2.55)	(0.72-1.75)	(1.53-3.04)	(0.84-1.81)	(1.47-2.58)	(0.96-1.78)	(1.29-2.35)	(0.93-1.77)	(1.44-3.21)	(0.86-2.07)
≥8	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference
≤8	1.35	1.07	1.69	1.31	1.45	1.18	1.36	1.15	1.33	1.01
	(1.11-1.63)	(0.88-1.32)	(1.44-1.99)	(1.10-1.56)	(1.27-1.66)	(1.03-1.36)	(1.18-1.56)	(0.99-1.33)	(1.08-1.64)	(0.81-1.27)
≥9	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference

*adjusted according to sex of the child; mother's age at birth; painless delivery; medication use during pregnancy; supplements taken during pregnancy; maternal complications during pregnancy; mode of delivery; gravidity; gestational age; birth weight; obstetric complications; number of children birthed; fetal position; maternal and paternal active smoking habits; maternal passive smoking; maternal alcohol consumption; maternal and paternal educational background; family income; number of advisers required for the pregnancy; maternal BMI; mode of pregnancy; marital status; frequency of intimate partner violence

Abbreviations: J-ASQ-3, Ages and Stages Questionnaire (Japanese version, 3rd edition); CI, confidence interval; BMI, body mass index; OR, odds ratio; aOR, adjusted odds ratio

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Department of Pharmacoepidemiology

Kyoto University Graduate School of Medicine and Public Health

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Supplementary Table 6 Association with the temporal change of Apgar scores from ≤ 8 at 1 minute to ≤ 8 , 9, and 10 at 5 minutes of the J-ASQ-3 (sensitivity analysis)

Communication				
At 5 minutes	Subjects	Events	Crude OR (95%CI)	aOR (95%CI)*
n = 19,893				
≥ 9	17,408	650	reference	reference
≤ 8	2,485	118	1.29 (1.05-1.57)	1.10 (0.89-1.35)
≤ 8	2,485	118	reference	reference
9	15,584	594	0.79 (0.65-0.97)	0.93 (0.75-1.15)
10	1,824	56	0.64 (0.46-0.88)	0.76 (0.54-1.06)
Gross motor				
≥ 9	17,408	734	reference	reference
≤ 8	2,485	165	1.62 (1.36-1.92)	1.34 (1.12-1.61)
≤ 8	2,485	165	reference	reference
9	15,584	650	0.61 (0.51-0.73)	0.74 (0.61-0.89)
10	1,824	84	0.68 (0.52 -0.89)	0.83 (0.63-1.10)
Fine motor				
≥ 9	17,408	1,325	reference	reference
≤ 8	2,485	241	1.30 (1.13-1.51)	1.12 (0.96-1.31)
≤ 8	2,485	241	reference	reference
9	15,584	1,200	0.78 (0.67-0.90)	0.90 (0.77-1.05)

10	1,824	125	0.69 (0.55-0.86)	0.80 (0.63-1.01)
Problem-solving				
≥9	17,408	1,267	reference	reference
≤8	2,485	229	1.29 (1.12-1.50)	1.15 (0.98-1.34)
≤8	2,485	229	reference	reference
9	15,584	1,135	0.77 (0.67-0.90)	0.87 (0.75-1.02)
10	1,824	132	0.77 (0.61-0.96)	0.88 (0.70-1.11)
Personal-social				
≥9	17,408	554	reference	reference
≤8	2,485	95	1.21 (0.97-1.51)	1.00 (0.79-1.26)
≤8	2,485	95	reference	reference
9	15,584	483	0.80 (0.64-1.01)	0.97 (0.77-1.23)
10	1,824	71	1.02 (0.74-1.39)	1.26 (0.91-1.74)

*adjusted according to sex of the child; mother's age at birth; painless delivery; medication use during pregnancy; supplements taken during pregnancy; maternal complications during pregnancy; mode of delivery; gravidity; gestational age; birth weight; obstetric complications; number of children birthed; fetal position; maternal and paternal active smoking habits; maternal passive smoking; maternal alcohol consumption; maternal and paternal educational background; family income; number of advisers required for the pregnancy; maternal BMI; mode of pregnancy; marital status; frequency of intimate partner violence

Abbreviations: J-ASQ-3, Ages and Stages Questionnaire (Japanese version, 3rd edition); CI, confidence interval; BMI, body mass index; OR, odds ratio; aOR, adjusted odds ratio

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Department of Pharmacoepidemiology

Kyoto University Graduate School of Medicine and Public Health

kawakami.koji.4e@kyoto-u.ac.jp

Supplementary Table 7 Association between the Apgar scores (≤9 and 10) at 1 minute and at 5 minutes and each domain in the J-ASQ-3

Score	Communication		Gross motor		Fine motor		Problem-solving		Personal-social	
	Crude OR	aOR*	Crude OR	aOR*	Crude OR	aOR*	Crude OR	aOR*	Crude OR	aOR*
	(95%CI)	(95%CI)	(95%CI)	(95%CI)	(95%CI)	(95%CI)	(95%CI)	(95%CI)	(95%CI)	(95%CI)
1 minute										
≤9	1.06	0.97	1.10	1.00	1.05	0.98	1.04	0.97	0.97	0.87
	(0.90-1.26)	(0.81-1.15)	(0.94-1.30)	(0.85-1.18)	(0.93-1.19)	(0.86-1.11)	(0.92-1.18)	(0.85-1.09)	(0.81-1.16)	(0.72-1.04)
10	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference
5 minutes										
≤9	1.11	0.99	1.09	0.97	1.12	1.02	1.11	1.02	0.96	0.83
	(1.01-1.21)	(0.90-1.09)	(1.10-1.18)	(0.89-1.06)	(1.05-1.20)	(0.96-1.10)	(1.04-1.18)	(0.95-1.09)	(0.87-1.06)	(0.75-0.92)
10	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference

1 minute (sensitivity analysis)

	1.05	0.96	1.10	1.00	1.05	0.98	1.04	0.97	0.96	0.86
≤9	(0.89-1.25)	(0.81-1.14)	(0.94-1.29)	(0.85-1.18)	(0.93-1.18)	(0.86-1.11)	(0.92-1.18)	(0.85-1.10)	(0.80-1.15)	(0.72-1.03)
10	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference
5 minutes (sensitivity analysis)										
	1.10	0.98	1.08	0.97	1.12	1.02	1.10	1.01	0.95	0.82
≤9	(1.00-1.20)	(0.90-1.08)	(0.99-1.17)	(0.89-1.06)	(1.05-1.19)	(0.95-1.09)	(1.03-1.18)	(0.95-1.09)	(0.86-1.05)	(0.74-0.91)
10	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference

*adjusted according to sex of the child; mother's age at birth; painless delivery; medication use during pregnancy; supplements taken during pregnancy; maternal complications during pregnancy; mode of delivery; gravidity; gestational age; birth weight; obstetric complications; number of children birthed; fetal position; maternal and paternal active smoking habits; maternal passive smoking; maternal alcohol consumption; maternal and paternal educational background; family income; number of advisers required for the pregnancy; maternal BMI; mode of pregnancy; marital status; frequency of intimate partner violence

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Department of Pharmacoepidemiology

Kyoto University Graduate School of Medicine and Public Health

kawakami.koji.4e@kyoto-u.ac.jp

Supplementary Table 8 Association between the Apgar scores at 1 minute and at 5 minutes as continuous variables and each domain in the J-ASQ-3

n = 54,716	Communication		Gross motor		Fine motor		Problem-solving		Personal-social	
	Crude OR	aOR*	Crude OR	aOR*	Crude OR	aOR*	Crude OR	aOR*	Crude OR	aOR*
	Apgar scores									
	(95%CI)	(95%CI)	(95%CI)	(95%CI)	(95%CI)	(95%CI)	(95%CI)	(95%CI)	(95%CI)	(95%CI)
1 minute	0.88	0.96	0.86	0.95	0.89	0.97	0.90	0.96	0.87	0.97
	(0.84-0.92)	(0.91-1.01)	(0.83-0.89)	(0.91-0.99)	(0.87-0.92)	(0.93-1.01)	(0.87-0.93)	(0.92-0.99)	(0.83-0.91)	(0.91-1.02)
5 minutes	0.91	1.00	0.89	0.98	0.89	0.96	0.92	0.99	0.96	1.08
	(0.86-0.97)	(0.94-1.07)	(0.84-0.94)	(0.92-1.04)	(0.85-0.92)	(0.91-1.00)	(0.88-0.96)	(0.94-1.04)	(0.89-1.02)	(1.00-1.16)

*adjusted according to sex of the child; mother's age at birth; painless delivery; medication use during pregnancy; supplements taken during pregnancy; maternal complications during pregnancy; mode of delivery; gravidity; gestational age; birth weight; obstetric complications; number of children birthed; fetal position; maternal and paternal active smoking habits; maternal passive smoking; maternal alcohol consumption; maternal and paternal educational background; family income; number of advisers required for the pregnancy; maternal BMI; mode of pregnancy; marital status; frequency of intimate partner violence

Abbreviations: J-ASQ-3, Ages and Stages Questionnaire (Japanese version, 3rd edition); CI, confidence interval; BMI, body mass index; OR, odds ratio; aOR, adjusted odds ratio

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Supplementary Table 9 Association between the Apgar scores at 1 minute and at 5 minutes as continuous variables and each domain in the J-ASQ-3

(adjusted by maternal age at birth and maternal BMI as continuous variables)

n = 54,716	Communication		Gross motor		Fine motor		Problem-solving		Personal-social	
	Crude OR	aOR*	Crude OR	aOR*	Crude OR	aOR*	Crude OR	aOR*	Crude OR	aOR*
	(95%CI)	(95%CI)	(95%CI)	(95%CI)	(95%CI)	(95%CI)	(95%CI)	(95%CI)	(95%CI)	(95%CI)
	Apgar scores									
1 minute	0.88	0.96	0.86	0.95	0.89	0.97	0.90	0.96	0.87	0.97
	(0.84-0.92)	(0.91-1.01)	(0.83-0.89)	(0.91-1.00)	(0.87-0.92)	(0.94-1.01)	(0.87-0.93)	(0.92-0.99)	(0.83-0.91)	(0.91-1.02)
5 minutes	0.91	1.00	0.89	0.98	0.89	0.96	0.92	0.99	0.96	1.08
	(0.86-0.97)	(0.94-1.07)	(0.84-0.94)	(0.92-1.04)	(0.85-0.92)	(0.91-1.00)	(0.88-0.96)	(0.94-1.04)	(0.89-1.02)	(1.00-1.17)

*adjusted according to sex of the child; mother's age at birth as a continuous variable; painless delivery; medication use during pregnancy; supplements taken during pregnancy; maternal complications during pregnancy; mode of delivery; gravidity; gestational age; birth weight; obstetric complications; number of children birthed; fetal position; maternal and paternal active smoking habits; maternal passive smoking; maternal alcohol consumption; maternal and paternal educational background; family income; number of advisers required for the pregnancy; maternal BMI as a continuous variable; mode of pregnancy; marital status; frequency of intimate partner violence

Abbreviations: J-ASQ-3, Ages and Stages Questionnaire (Japanese version, 3rd edition); CI, confidence interval; BMI, body mass index; OR, odds ratio; aOR, adjusted odds ratio

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Supplementary Table 10 Association between the Apgar scores at 1 minute and at 5 minutes and each domain in the J-ASQ-3

(adjusted by maternal age at birth and maternal BMI as continuous variables)										
Score	Communication		Gross motor		Fine motor		Problem-solving		Personal-social	
	Crude OR	aOR*	Crude OR	aOR*	Crude OR	aOR*	Crude OR	aOR*	Crude OR	aOR*
	(95%CI)	(95%CI)	(95%CI)	(95%CI)	(95%CI)	(95%CI)	(95%CI)	(95%CI)	(95%CI)	(95%CI)
1 minute (n = 54,716)										
≤6	1.86	1.30	2.08	1.26	1.76	1.22	1.75	1.33	2.06	1.32
	(1.43-2.42)	(0.97-1.74)	(1.64-2.63)	(0.96-1.64)	(1.44-2.14)	(0.98-1.52)	(1.43-2.14)	(1.07-1.66)	(1.57-2.71)	(0.97-1.80)
≥7	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference
≤7	1.62	1.20	1.97	1.38	1.53	1.13	1.58	1.25	1.76	1.22
	(1.33-1.97)	(0.97-1.48)	(1.66-2.33)	(1.14-1.66)	(1.32-1.77)	(0.97-1.33)	(1.36-1.82)	(1.07-1.46)	(1.44-2.17)	(0.97-1.52)
≥8	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference
≤8	1.18	1.03	1.19	1.03	1.18	1.04	1.16	1.05	1.21	1.03
	(1.07-1.29)	(0.93-1.13)	(1.09-1.29)	(0.94-1.12)	(1.10-1.26)	(0.97-1.12)	(1.09-1.24)	(0.98-1.13)	(1.10-1.34)	(0.92-1.14)

≥9	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference
5 minutes (n = 54,716)										
≤6	1.79	1.14	2.37	1.33	2.04	1.33	1.30	0.89	2.00	1.19
	(1.04-3.08)	(0.64-2.02)	(1.51-3.72)	(0.81-2.17)	(1.39-2.98)	(0.89-1.99)	(0.82-2.05)	(0.55-1.45)	(1.14-3.51)	(0.65-2.16)
≥7	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference
≤7	1.83	1.20	2.19	1.25	2.01	1.35	1.81	1.32	2.21	1.36
	(1.23-2.70)	(0.78-1.84)	(1.56-3.08)	(0.86-1.82)	(1.52-2.65)	(1.00-1.83)	(1.35-2.43)	(0.97-1.81)	(1.49-3.28)	(0.89-2.10)
≥8	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference
≤8	1.38	1.10	1.71	1.31	1.47	1.20	1.38	1.16	1.36	1.03
	(1.15-1.67)	(0.90-1.34)	(1.45-2.00)	(1.11-1.56)	(1.29-1.68)	(1.04-1.38)	(1.21-1.59)	(1.00-1.34)	(1.11-1.67)	(0.82-1.28)
≥9	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference

*adjusted according to sex of the child; mother's age at birth as a continuous variable; painless delivery; medication use during pregnancy; supplements taken during pregnancy; maternal complications during pregnancy; mode of delivery; gravidity; gestational age; birth weight; obstetric complications; number of children birthed; fetal position; maternal and paternal active smoking habits; maternal passive smoking; maternal alcohol consumption; maternal and paternal educational background; family income; number of advisers required for the pregnancy; maternal

BMI as a continuous variable; mode of pregnancy; marital status; frequency of intimate partner violence

Abbreviations: J-ASQ-3, Ages and Stages Questionnaire (Japanese version, 3rd edition); CI, confidence interval; BMI, body mass index; OR, odds ratio; aOR, adjusted odds ratio

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Department of Pharmacoepidemiology

Kyoto University Graduate School of Medicine and Public Health

kawakami.koji.4e@kyoto-u.ac.jp

Supplementary Table 11 Distribution of the difference between the Apgar score at 1 minute and 5 minutes based on the Apgar score at 1 minute

n = 54,716	The difference of Apgar scores between at 1 minute and 5 minutes over time																				
(negative change: n = 159)	-10	-9	-8	-7	-6	-5	-4	-3	-2	-1	0	1	2	3	4	5	6	7	8	9	10
Apgar score at 1 minute	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0	4
Apgar score at 1 minute	1	0	0	0	0	0	0	0	0	0	3	0	2	8	7	7	4	11	11	3	0
Apgar score at 1 minute	2	0	0	0	0	0	0	0	0	0	1	4	11	4	12	13	14	14	1	0	0
Apgar score at 1 minute	3	0	0	0	0	0	0	0	0	1	0	1	6	20	15	17	21	8	0	0	0
Apgar score at 1 minute	4	0	0	0	0	0	1	0	0	0	7	5	20	31	27	60	9	0	0	0	0
Apgar score at 1 minute	5	0	0	0	0	0	0	1	1	1	3	10	30	64	71	16	0	0	0	0	0
Apgar score at 1 minute	6	0	0	0	0	1	0	0	0	2	8	55	147	143	25	0	0	0	0	0	0
Apgar score at 1 minute	7	0	0	0	0	0	1	1	4	3	30	354	614	81	0	0	0	0	0	0	0
Apgar score at 1 minute	8	0	0	6	1	1	0	4	3	21	1,481	14,665	1,677	0	0	0	0	0	0	0	0
Apgar score at 1 minute	9	0	19	0	0	3	3	6	1	5	32	11,506	18,831	0	0	0	0	0	0	0	0
Apgar score at 1 minute	10	19	0	0	0	0	0	0	0	2	13	4,363	0	0	0	0	0	0	0	0	0

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Supplementary Table 12 Association between the Apgar scores at 1 minute and at 5 minutes as continuous variables and each domain in the J-ASQ-3

n = 54,716	Communication		Gross motor		Fine motor		Problem-solving		Personal-social	
	Crude OR	aOR*	Crude OR	aOR*	Crude OR	aOR*	Crude OR	aOR*	Crude OR	aOR*
	Apgar scores									
	(95%CI)	(95%CI)	(95%CI)	(95%CI)	(95%CI)	(95%CI)	(95%CI)	(95%CI)	(95%CI)	(95%CI)
Difference	1.11	1.05	1.13	1.05	1.05	1.00	1.09	1.05	1.19	1.11
(5 minutes – 1 minute)	(1.05-1.18)	(0.99-1.12)	(1.07-1.19)	(1.00-1.11)	(1.00-1.09)	(0.96-1.04)	(1.04-1.14)	(1.01-1.10)	(1.12-1.26)	(1.05-1.18)

*adjusted according to sex of the child; mother's age at birth; painless delivery; medication use during pregnancy; supplements taken during pregnancy; maternal complications during pregnancy; mode of delivery; gravidity; gestational age; birth weight; obstetric complications; number of children birthed; fetal position; maternal and paternal active smoking habits; maternal passive smoking; maternal alcohol consumption; maternal and paternal educational background; family income; number of advisers required for the pregnancy; maternal BMI; mode of pregnancy; marital status; frequency of intimate partner violence

Abbreviations: J-ASQ-3, Ages and Stages Questionnaire (Japanese version, 3rd edition); CI, confidence interval; BMI, body mass index; OR, odds ratio; aOR, adjusted odds ratio

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Tetsuya Tsuchida, Satomi Yoshida, Masato Takeuchi, Chihiro Kawakami, Koji Kawakami, Shuichi Ito, and the Japan Environmental and Children's Study Group

Affiliation and E-mail address of the Corresponding Author:

Department of Pharmacoepidemiology

Kyoto University Graduate School of Medicine and Public Health

kawakami.koji.4e@kyoto-u.ac.jp