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ORIGINAL RESEARCH

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Association of maternal hemoglobin levels during pregnancy with sleep and developmental problems in 1-year-old infants: A cohort study

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Abstract

Background and Aims: Maternal hemoglobin concentration during pregnancy is reported to be associated with various perinatal outcomes and may also be associated with infant development. This study aims to investigate the association between maternal hemoglobin levels during early or mid-pregnancy and sleep and developmental problems in 1-year-old infants.

Methods: We used the data of 66,935 pregnant women who were participants of the Japan Environment and Children's Study, a nationwide cohort study in Japan, between 2011 and 2014. Maternal hemoglobin level was examined at recruitment (mean gestational age, 15.3 weeks; SD, 2.85 weeks; range, 6–22 weeks). Information on infant sleep and development at the age of 1 year was acquired using a questionnaire. Infant development was evaluated using the Ages and Stages Questionnaire (ASQ).

Kazushige Nakahara and Takehiro Michikawa contributed equally to this study.

The Japan Environment and Children's Study Group members are listed at the end of this article.

Results: The mean (SD) maternal hemoglobin level was 12.0 (1.0) g/dl. Maternal hemoglobin levels were not associated with the majority of infant sleep and developmental outcomes. In the group with maternal hemoglobin <10.0 g/dl, the risk ratio (RR) for sleep at 22:00 or later was higher than that in the reference group with 11.0 g/dl ≤ hemoglobin < 14.0 g/dl (RR 1.12, 95% confidence interval = 1.00–1.25). In the analysis with maternal hemoglobin level as a continuous variable, both high and low hemoglobin levels were associated with a higher RR of a late bedtime. In addition, a low maternal hemoglobin level was associated with a higher RR for abnormal fine motor skills in the ASQ.

Conclusion: Our results suggest that a low level of maternal hemoglobin during pregnancy is associated with late bedtime and abnormal fine motor skills in 1-year-old infants. Conversely, a high level of maternal hemoglobin may also be associated with the infant's late bedtime.

KEYWORDS
development, hemoglobin, infant, pregnancy, sleep

1 | INTRODUCTION

Many previous studies have evaluated the association between maternal hemoglobin concentration during pregnancy and perinatal outcomes.[1,2] For example, low maternal hemoglobin levels during pregnancy have been reported to increase the risk of low birthweight (LBW), small for gestational age (SGA), and preterm birth (PTB).[1–10] In contrast, excessively high hemoglobin levels are also reported to be associated with perinatal outcomes such as SGA, pre-eclampsia (PE), and gestational diabetes (GDM).[2–4,8,9,11,12]

Perinatal complications, such as LBW, SGA, PTB, PE, and GDM, are risk factors for developmental disorders,[13,14] which present in children as sleeping problems, including frequent awakening, crying during the night, and short sleep duration due to late bedtime.[15,16] Therefore, maternal hemoglobin levels during pregnancy may be associated with infant sleep and development. Some studies have evaluated the association between maternal hemoglobin levels and infant development.[2] However, most of these studies had small sample sizes, and the influence of the maternal hemoglobin level on the sleep and development of infants remains unclear.

Thus, the aim of this study was to investigate the association between maternal hemoglobin levels during early or mid-pregnancy and sleep and developmental problems in 1-year-old infants using large-scale data.

2 | METHODS

2.1 | Research ethics

The study protocol was reviewed and approved by the Ministry of the Environment's Institutional Review Board on Epidemiological Studies (no. 100910001) and by the Ethics Committees of all participating institutions: the National Institute for Environmental Studies (Programme Office of the Japan Environment and Children's Study [JECS]), the National Centre for Child Health and Development, Hokkaido University, Sapporo Medical University, Asahikawa Medical College, Japanese Red Cross Hokkaido College of Nursing, Tohoku University, Fukushima Medical University, Chiba University, Yokohama City University, University of Yamanashi, Shinshu University, University of Toyama, Nagoya City University, Kyoto University, Doshisha University, Osaka University, Osaka Medical Centre and Research Institute for Maternal and Child Health, Hyogo College of Medicine, Tottori University, Kochi University, University of Occupational and Environmental Health, Kyushu University, Kumamoto University, University of Miyazaki, and University of Ryukyu. Written informed consent for the protocol, which also included a follow-up study of children after birth, was obtained from all participants. All study procedures were performed in accordance with the approved guidelines.

2.2 | Study participants

The data used in this study were obtained from the JECS, an ongoing large-scale cohort study. The JECS was designed to follow children from the prenatal period to the age of 13 years. The detailed protocol of the study and the baseline profile of participants in the JECS have been previously reported.[17,18] The participants underwent a blood test at recruitment (mean gestational age: 15.6 weeks, SD: 3.3 weeks) and answered a questionnaire on lifestyle and behavior twice during pregnancy. Participants also answered a questionnaire about their children 1 year after delivery (C-1y).

Between January 2011 and March 2014, 103,060 pregnant women were recruited from 15 Regional Centers throughout Japan

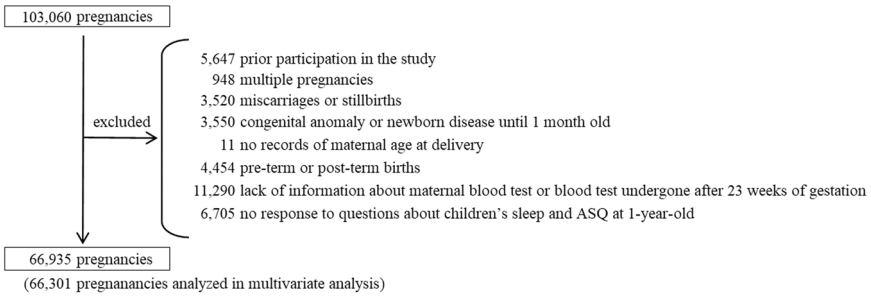

FIGURE 1 Population flowchart Ages and Stages Questionnaire (ASQ)

(Figure 1). Of these, we excluded 36,125 pregnancies due to the following reasons: participation in the JECS study for the second time or more (n = 5647), multiple fetuses (n = 948), miscarriage or stillbirth (n = 3520), congenital anomaly or disease at 1 month of age (n = 3550), missing information on maternal age at delivery (n = 11), deliveries before 37 weeks or after 42 weeks of gestation (n = 4454), blood tests performed after 23 weeks of gestation or lack of information about maternal blood test results (n = 11,290), and no response to questions about children's sleep and development at C-1y (n = 6705). We would like to investigate the effects of hemoglobin level in early pregnancy; however, not many participants underwent blood tests in the first trimester. Therefore, we limited the participants to those who had a blood test before 23 weeks of gestation (because loss of pregnancy until 22 weeks of gestation is considered a miscarriage in Japan). The remaining 66,935 participants were included in the analysis. In a multivariate analysis, we excluded participants lacking information on the covariates (n = 608); therefore, a total of 66,301 participants were included in the multivariate analysis.

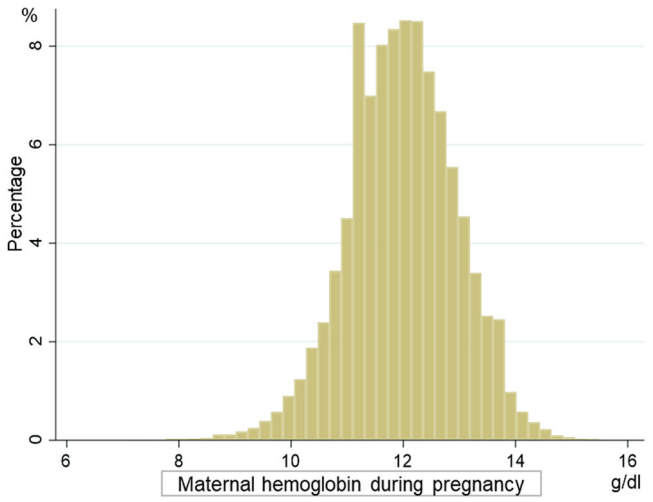

FIGURE 2 The distribution of maternal hemoglobin levels during pregnancy in this study. The horizontal axis indicates maternal hemoglobin levels and the vertical axis indicates the proportion of groups divided by hemoglobin level at intervals of 0.2 g/dl

2.3 | Exposure: Maternal hemoglobin

Maternal blood was obtained intravenously at each institution and stored at 1–10°C until blood analysis within 48 h at a designated laboratory (SRL Inc., a commercial laboratory in Tokyo, Japan). We divided the participants into four groups based on the maternal hemoglobin level during pregnancy as follows: hemoglobin < 10.0 g/dl, 10.0 g/dl ≤ hemoglobin < 11.0 g/dl, 11.0 g/dl ≤ hemoglobin < 14.0 g/dl, hemoglobin ≥ 14.0 g/dl. On the basis of the distribution of maternal hemoglobin levels in this study (Figure 2) and a previous study,[2] we made the above categories and defined the groups with 11.0 g/dl ≤ hemoglobin < 14.0 g/dl as the reference group.

2.4 | Outcome 1: Infant sleeping problems

One year after delivery, information on infant outcomes was collected via a questionnaire named C-1y, which was completed by the caregiver (mother in most cases). The C-1y questionnaire included questions regarding their infant's sleep time in the previous 24 h, in 30 min increments. They were also asked whether their children cried at night, and if so, at what frequency ("rarely," "1–3 times in a month," "1–2 times in a week," "3–4 times in a week," and "5 times in a week or more"). In this analysis, we focused on five points concerning infant night-time sleep because it was reported that children with autism spectrum disorder tend to experience night awakening, have a late bedtime, short sleep duration during the night, and a longer nap than considered normal.[15] First, we determined the number of nocturnal awakenings from maternal responses to questions regarding infants' sleeping periods. We defined ≥ 3 awakenings as too many, because a previous study reported that the upper limit of the number of awakenings during the night for 1-year-old infants was 2.5.[19] Second, we determined whether the infants awoke more than once and whether they stayed awake for more than 1 h during the night. If so, these were defined as unusual. Third, we analyzed the duration of night-time sleep (20:00–07:59). We regarded less than 8 h of sleep as too short, because past studies have reported the mean duration of sleep for this age as 8.3 h.[19] Fourth, we determined the infants' bedtimes. In this study, about 65% of 1-year-old infants slept later than 21:00 and about 20% slept later than 22:00. Therefore, we defined bedtime after 22:00 as too late. Fifth, we obtained information about crying at night in the past month. If the mother answered that her infant cried during the night, and that the frequency of crying at night was more than five times per week, we defined the case as "crying at night."

2.5 | Outcome 2: Infant development

We used the Japanese version of the Ages and Stages Questionnaire (ASQ), third edition, to evaluate infant development.[20,21] The C-1y questionnaire also included the ASQ, which captures developmental delay in five domains: communication, gross motor skills, fine motor skills, problem-solving, and personal–social characteristics. The response to each question is one of the following: "yes," "sometimes," or "not yet," which are scored as 10, 5, and 0 points, respectively. Each ASQ domain was evaluated using six questions, and the total score ranged from 0 to 60. The cut-off point for each domain in the Japanese version was 2 SD below the mean, and all the cut-off points were determined by age groups in a previous study.[21] The cut-off points at 1 year of age were as follows: communication, 4.53; gross motor skill, 9.43; fine motor skill, 25.47; problem-solving, 15.37; and personal–social characteristics, 4.95. The outcomes were defined by scores less than the cut-off point for each ASQ domain and scores less than the cut-off point of any one of the five ASQ domains.

2.6 | Covariates

All information on covariates was collected prospectively. Information on maternal age at delivery, prepregnancy body mass index (BMI), parity, gestational age at birth, infertility treatment, type of delivery, iron agent medication during pregnancy, and infant sex were collected from medical record transcripts completed at delivery. Information about smoking habits, alcohol consumption, educational background, and household income, were collected via self-administered questionnaires completed during pregnancy.

Each covariate was categorized as follows: smoking habit (never smoked, ex-smoker who quit smoking before pregnancy, or smoker during early pregnancy), alcohol consumption (never drank, ex-drinker who quit drinking before pregnancy, or drinker during early pregnancy), pre-pregnancy BMI (<18.5, 18.5–24.9, or ≥25.0 kg/m^2), parity (0 or ≥1), infertility treatment (none, ovulation stimulation/artificial insemination by sperm from husband, or assisted reproductive technology), type of delivery (vaginal or cesarean section), gestational age at birth (37–38 or 39–41 weeks), and infant sex (male or female).

2.7 | Statistical analyses

We used a log-binominal regression model to explore the association of maternal hemoglobin level with each outcome and to estimate the risk ratio (RR) of each outcome and the 95% confidence intervals (CIs). We initially adjusted for maternal age at delivery, and then further adjusted for all covariates. We also used restricted cubic spline (RCS) models with three knots as reference values of hemoglobin 12.0 g/dl (median) to assess the nonlinear association between maternal hemoglobin level as a continuous variable and each outcome.[22] In the RCS models, all data points were used to estimate the dose response association between maternal hemoglobin levels and outcomes; thus, this nonlinear association was expressed as a spline curve.

The covariates to be added to the multivariable model as potential risk factors for developmental disorders were determined by referring to the previous literature.[23,24] We did not complete missing data. As mentioned in Section 2.2, the multivariable analysis was limited to participants with covariate data. However, the proportion of participants excluded from multivariable analysis due to missing information on covariates was only 1%.

In this study, we used a fixed data set "jecs-ta-20190930," which was released in October 2019. Stata version 15 (StataCorp LP) was used for all statistical analyses.

2.8 | Sensitivity analyses

To validate the results of this study, we performed several sensitivity analyses. First, if maternal hemoglobin level during pregnancy was associated with the outcome of an infant bedtime of 22:00 or later, we also analyzed the outcome of an infant bedtime of 23:00 or later. Second, to account for blood sampling timing, we performed a stratified analysis in which the participants were divided according to the timing of their blood sampling (6 to <14 and 14 to <22 gestational weeks). Finally, to consider the influence of maternal socioeconomic status on infant development, we added maternal educational background and household incomes as covariates in the multivariate log-binominal analysis. Information on these was collected by the questionnaire completed by participants during pregnancy. These factors were categorized as follows: maternal education background (<10, 10–12, 13–16, or ≥17 years) and household income (<2, 2 to <4, 4 to <6, 6 to <8, 8 to <10, or ≥10 million Japanese-yen/year). Among the 66,301 participants included in the multivariate model, those lacking this information were excluded (n = 4648), and the remaining 61,635 participants were included in the multivariate analysis involving socioeconomic status factors.

3 | RESULTS

The baseline characteristics of the participants, along with available data on maternal hemoglobin levels during pregnancy, are shown in Table 1. Blood tests were conducted at a mean of 15.3 weeks of gestation (SD: 2.85 weeks, range: 6–22 weeks) in this study population, and the distribution of the gestational weeks at blood tests is shown in Figure S1. The mean (SD) maternal hemoglobin level was 12.0 (1.0) g/dl, and the distribution of maternal hemoglobin levels is shown in Figure 2.

TABLE 1 Baseline characteristics of the study population categorized by maternal hemoglobin level during pregnancy

	Total population (n = 66,935)		<10.0		10.0–10.9		11.0–14.0		>14.0	
	n[a]	%	n[a]	%	n[a]	%	n[a]	%	n[a]	%
Maternal characteristics										
Age at delivery (years)										
<25	5684	8.5	97	6.7	561	7.3	4,952	8.7	74	8.0
25–29	18,505	27.7	312	21.5	1869	24.2	16,053	28.3	271	29.2
30–34	24,268	36.3	521	35.8	2819	36.5	20,580	36.2	348	37.5
≥35	18,478	27.6	524	36.0	2481	32.1	15,237	26.8	236	25.4
Smoking habit										
Never smoked	39,923	59.8	855	58.9	4591	59.6	33,954	59.9	523	56.5
Ex-smoker who quit before pregnancy	15,736	23.6	338	23.3	1837	23.8	13,329	23.5	232	25.1
Smoker during early pregnancy	11,092	16.6	259	17.8	1279	16.6	9383	16.6	171	18.5
Alcohol consumption										
Never drank	23,082	34.6	530	36.5	2592	33.6	19,612	34.6	348	37.5
Ex-drinker who quit before pregnancy	12,119	18.1	253	17.4	1330	17.2	10,372	18.3	164	17.7
Drinker during early pregnancy	31,611	47.3	669	46.1	3793	49.2	26,733	47.1	416	44.8
Prepregnancy body mass index (kg/m^2)										
<18.5	10,676	16.0	306	21.1	1545	20.0	8733	15.4	92	9.9
18.5–24.9	49,581	74.1	1,070	73.6	5814	75.2	42,080	74.1	617	66.4
≥25.0	6646	9.9	78	5.4	371	4.8	5977	10.5	220	23.7
Parity										
0	29,308	43.9	509	35.1	3082	40.0	25,217	44.5	500	54.1
≥1	37,391	56.1	942	64.9	4622	60.0	31,402	55.5	425	46.0
Infertility treatment										
No	62,426	93.3	1,370	94.3	7199	93.2	53,025	93.4	832	89.6
Ovulation stimulation/artificial insemination by sperm from husband	2449	3.7	39	2.7	286	3.7	2080	3.7	44	4.7
Assisted reproductive technology	2020	3.0	44	3.0	241	3.1	1682	3.0	53	5.7
Type of delivery										
Vaginal	55,264	82.7	1,157	79.6	6393	82.8	46,981	82.9	733	79.2
Cesarean	11,530	17.3	296	20.4	1326	17.2	9715	17.1	193	20.8
Gestational age (weeks)										
Early term (37–38)	21,824	32.6	507	34.9	2522	32.6	18,483	32.5	312	33.6
Full term (39–41)	45,111	67.4	947	65.1	5208	67.4	38,339	67.5	617	66.4
Educational background (years)										
<10	2584	3.9	77	5.4	319	4.2	2142	3.8	46	5.0
10–12	20,242	30.5	537	37.3	2369	31.0	17,067	30.3	269	29.2
13–16	42,429	64.0	807	56.1	4862	63.5	36,166	64.3	594	64.5
≥17	1016	1.5	18	1.3	103	1.4	883	1.6	12	1.3
Household income (million Japanese-yen/year)										
<2	3122	5.0	94	7.1	391	5.5	2605	4.9	32	3.6

(Continues)

TABLE 1 (Continued)

	Total population (n = 66,935)		<10.0		10.0–10.9		11.0–14.0		>14.0	
	n[a]	%	n[a]	%	n[a]	%	n[a]	%	n[a]	%
2 to <4	21,167	34.0	489	36.8	2380	33.4	17,985	34.0	313	35.2
4 to <6	20,916	33.6	430	32.4	2387	33.5	17,799	33.7	300	33.8
6 to <8	10,145	16.3	188	14.2	1172	16.4	8647	16.4	138	15.5
8 to <10	4181	6.7	74	5.6	499	7.0	3549	6.7	59	6.6
≥10	2666	4.3	53	4.0	298	4.2	2268	4.3	47	5.3
Iron agent medication during pregnancy										
No	38,423	57.4	256	17.6	2377	30.8	34,974	61.6	816	87.8
Yes	28,512	42.6	1198	82.4	5353	69.3	21,848	38.5	113	12.2
Infant characteristics										
Birth weight										
Mean (SD) (g)	3062 (365)		3064 (377)		3071 (363)		3061 (365)		3056 (389)	
Small for gestational age	4820	7.2	121	8.3	530	6.9	4087	7.2	82	8.9
Infant sex										
Male	34,066	50.9	695	47.8	3807	49.3	29,052	51.1	512	55.1
Female	32,869	49.1	759	52.2	3923	50.8	27,770	48.9	417	44.9

Abbreviation: SD, standard deviation.

[a]Numbers in subgroups do not equal overall number because of missing data.

3.1 | Association of maternal hemoglobin levels with sleep problems in 1-year-old infants

There were no significant associations between maternal hemoglobin level and infant sleeping problems, with the exception of late bedtime in the log-binominal regression model. In the group with maternal hemoglobin < 10.0 g/dl, the RR for sleep at 22:00 or later was significantly higher than the reference group with 11.0 g/dl ≤ hemoglobin < 14.0 g/dl (RR: 1.12, 95% CI: 1.00–1.25) (Table 2).

In the RCS model, the association between maternal hemoglobin level and sleep at 22:00 or later showed a U-shaped relationship. In addition, a higher level of maternal hemoglobin was associated with a higher RR for infant sleep of less than 8 h during the night (Figure 3). Each figure of the RCS model for infant sleep problems is presented separately in Figures S2–S6.

In the sensitivity analysis, in which the infant bedtime outcome changed to 23:00 or later, a high hemoglobin level (>14.0 g/dl) was associated with a late bedtime (RR: 1.39, 95% CI: 1.07–1.80, Table S1). In the RCS model, both low and high levels of maternal hemoglobin were associated with an infant bedtime of 23:00 or later, similar to the findings of the analysis using the outcome of an infant bedtime of 22:00 or later (Figures S5 and S7). However, in the subanalysis including maternal socioeconomic status as covariates, an association between maternal hemoglobin level and late infant bedtime was not found (Table S2). The stratified analysis according to the timing of blood sampling showed that there was little difference in the RR value compared to the overall analysis (Table S3).

3.2 | Association of maternal hemoglobin with development in 1-year-old infants

Similar to infant sleeping problems, there were few significant associations between maternal hemoglobin level and abnormal ASQ scores in the log-binominal regression model (Table 2). Only in the domain of fine motor skills, a slightly low hemoglobin level (10.0–10.9 g/dl) was associated with a higher RR for an abnormal score compared to the reference group (RR: 1.10, 95% CI: 1.00–1.21). This association was also found in the sensitivity analysis adjusted for maternal socioeconomic status (RR: 1.13, 95% CI: 1.01–1.25, Table S2). We did not find any significant difference in the association when accounting for the timing of blood sampling in the stratified analysis (Table S3). Additionally, in the RCS model (Figure 4), a lower maternal hemoglobin level was associated with a higher RR for abnormal scores only in the fine motor skills of the ASQ. Each figure of the RCS model for ASQ abnormality is presented separately in Figures S8–S13.

TABLE 2 Association between hemoglobin level during pregnancy, and sleep and Ages and Stages Questionnaire (ASQ) at 1 year of age

Hemoglobin (g/dl)	No. of participants	No. of outcomes	%	Maternal age-adjusted model RR	95% CI		Multivariable model[a] RR	95% CI	
Sleeping problems									
Awakening ≥ 3 times in a night									
<10.0	1441	28	1.9	**0.78**	0.54	1.13	**0.78**	0.54	1.13
10.0–10.9	7674	194	2.5	**1.02**	0.88	1.18	**1.01**	0.87	1.17
11.0–14.0	56,459	1379	2.4	**Ref**			**Ref**		
>14.0	924	23	2.5	**1.02**	0.68	1.53	**1.07**	0.71	1.60
Total analytical sample	66,498	1624	2.4						
Awakening ≥ 1 time and staying awake for more than 1 h									
<10.0	1441	93	6.5	**1.14**	0.94	1.39	**1.16**	0.94	1.42
10.0–10.9	7674	438	5.7	**1.01**	0.92	1.12	**1.03**	0.93	1.14
11.0–14.0	56,459	3165	5.6	**Ref**			**Ref**		
>14.0	924	65	7.0	**1.26**	0.99	1.60	**1.21**	0.94	1.54
Total analytical sample	66,498	3761	5.7						
Night sleep of <8 h (20:00 – 07:59)									
<10.0	1441	87	6.0	**1.14**	0.93	1.41	**1.17**	0.94	1.44
10.0–10.9	7674	391	5.1	**0.97**	0.88	1.08	**0.99**	0.89	1.10
11.0–14.0	56,459	2924	5.2	**Ref**			**Ref**		
>14.0	924	56	6.1	**1.18**	0.91	1.52	**1.14**	0.88	1.49
Total analytical sample	66,498	3458	5.2						
Sleep at 22:00 or later									
<10.0	1441	319	22.1	**1.12**	1.01	1.23	**1.12**	1.00	1.25
10.0–10.9	7674	1546	20.2	**1.02**	0.97	1.07	**1.03**	0.97	1.08
11.0–14.0	56,459	11,171	19.8	**Ref**			**Ref**		
>14.0	924	203	22.0	**1.12**	0.99	1.27	**1.08**	0.94	1.24
Total analytical sample	66,498	13,239	19.9						
Crying at night for ≥ 5 days in a week									
<10.0	1454	118	8.1	**1.10**	0.92	1.31	**1.10**	0.93	1.32
10.0–10.9	7730	587	7.6	**1.03**	0.95	1.12	**1.02**	0.94	1.11
11.0–14.0	56,796	4198	7.4	**Ref**			**Ref**		
>14.0	928	59	6.4	**0.86**	0.67	1.10	**0.87**	0.68	1.12
Total analytical sample	66,908	4962	7.4						
Development									
Communication									
<10.0	1322	0	0.0	**n.a**			**n.a**		
10.0–10.9	7027	9	0.1	**1.34**	0.66	2.74	**1.38**	0.67	2.82
11.0–14.0	51,931	48	0.1	**Ref**			**Ref**		
>14.0	859	1	0.1	**1.26**	0.17	9.11	**1.21**	0.17	8.80
Total analytical sample	61,139	58	0.1						

(Continues)

TABLE 2 (Continued)

Hemoglobin (g/dl)	No. of participants	No. of outcomes	%	Maternal age-adjusted model RR	95% CI		Multivariable model[a] RR	95% CI	
Gross motor skills									
<10.0	1322	69	5.2	**0.91**	0.72	1.14	**0.89**	0.70	1.12
10.0–10.9	7029	396	5.6	**1.00**	0.90	1.11	**1.00**	0.90	1.10
11.0–14.0	51,932	2855	5.5	**Ref**			**Ref**		
>14.0	859	49	5.7	**1.04**	0.79	1.37	**1.03**	0.78	1.35
Total analytical sample	61,142	3369	5.5						
Fine motor skills									
<10.0	1323	84	6.4	**1.11**	0.90	1.36	**1.11**	0.90	1.37
10.0–10.9	7029	431	6.1	**1.09**	0.99	1.20	**1.10**	1.00	1.21
11.0–14.0	51,901	2859	5.5	**Ref**			**Ref**		
>14.0	859	55	6.4	**1.16**	0.90	1.51	**1.15**	0.89	1.48
Total analytical sample	61,112	3429	5.6						
Problem solving									
<10.0	1320	71	5.4	**1.03**	0.82	1.29	**1.08**	0.86	1.36
10.0–10.9	7019	373	5.3	**1.04**	0.93	1.15	**1.07**	0.96	1.19
11.0–14.0	51,855	2582	5.0	**Ref**			**Ref**		
>14.0	858	34	4.0	**0.80**	0.57	1.11	**0.72**	0.52	1.01
Total analytical sample	61,052	3060	5.0						
Personal–social characteristics									
<10.0	1321	15	1.1	**0.96**	0.58	1.60	**0.92**	0.55	1.54
10.0–10.9	7011	88	1.3	**1.07**	0.86	1.34	**1.07**	0.85	1.34
11.0–14.0	51,803	592	1.1	**Ref**			**Ref**		
>14.0	855	11	1.3	**1.13**	0.62	2.04	**1.14**	0.63	2.08
Total analytical sample	60,990	706	1.2						
Total (abnormal score for any 1 of the 5 domains)									
<10.0	1323	182	13.8	**0.98**	0.86	1.13	**0.99**	0.86	1.13
10.0–10.9	7030	994	14.1	**1.03**	0.97	1.10	**1.04**	0.98	1.11
11.0–14.0	51,952	6964	13.4	**Ref**			**Ref**		
>14.0	859	118	13.7	**1.02**	0.87	1.21	**1.00**	0.84	1.18
Total analytical sample	61,164	8258	13.5						

Note: The values of RR are shown in bold.

Abbreviations: ASQ, Ages and Stages Questionnaire; CI, confidence interval; Ref, reference; RR, risk ratio.

[a]Adjusted for maternal age at delivery, smoking habits, alcohol consumption, pre-pregnancy body mass index, gestational age at birth, parity, infertility treatment, infant sex, and type of delivery.

4 | DISCUSSION

This study used nationwide large-scale data to investigate the associations between maternal hemoglobin levels during early pregnancy and the development and sleep of 1-year-old children. In this study, maternal hemoglobin levels were not associated with the majority of the infant sleep and developmental outcomes. However, both low and high levels of maternal hemoglobin during early pregnancy were associated with a higher risk of late bedtime at 1 year of age. A higher maternal hemoglobin level was also associated with a higher risk of short sleep duration at night in infants. Among developmental parameters at 1 year of age, only fine motor skills were associated with a low level of maternal hemoglobin.

To the best of our knowledge, this is the first study to investigate the association between maternal hemoglobin levels during

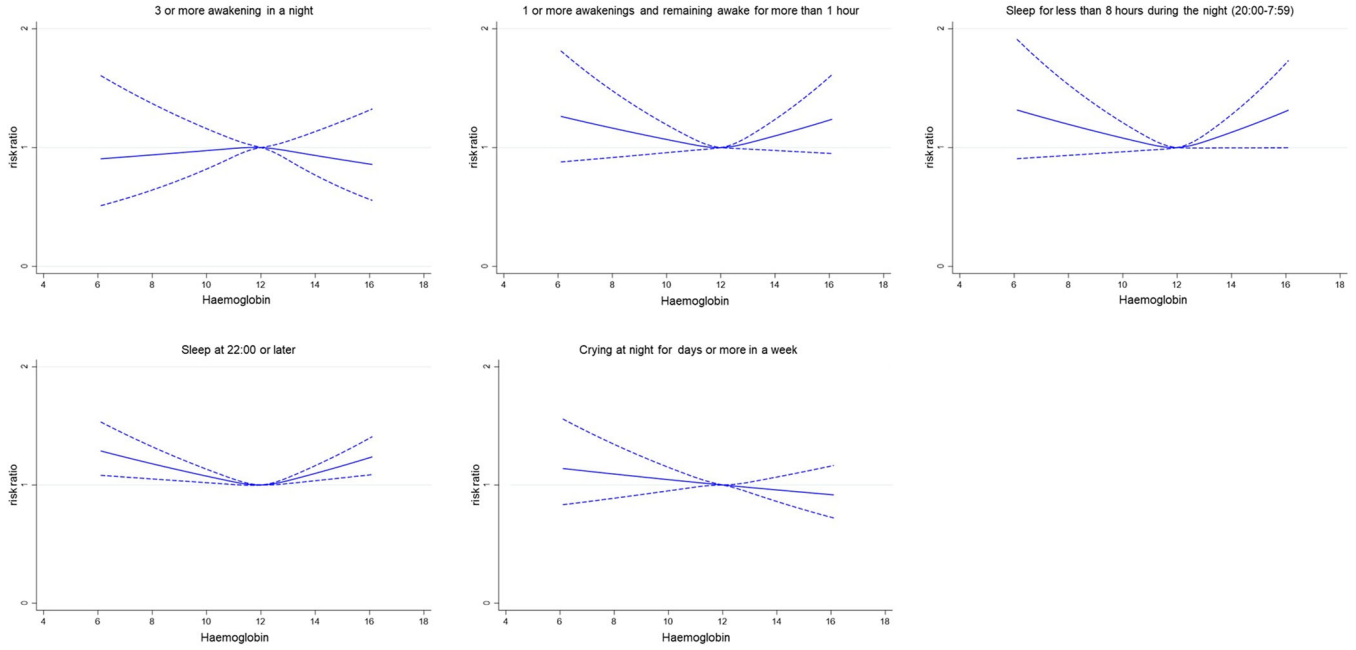

FIGURE 3 Association between maternal hemoglobin levels and infants' sleep outcomes in the restricted cubic spline models. The solid line indicates the risk ratio (RR) and the dotted line indicates the 95% confidence interval. The reference was set at a hemoglobin level of 12.0 g/dl

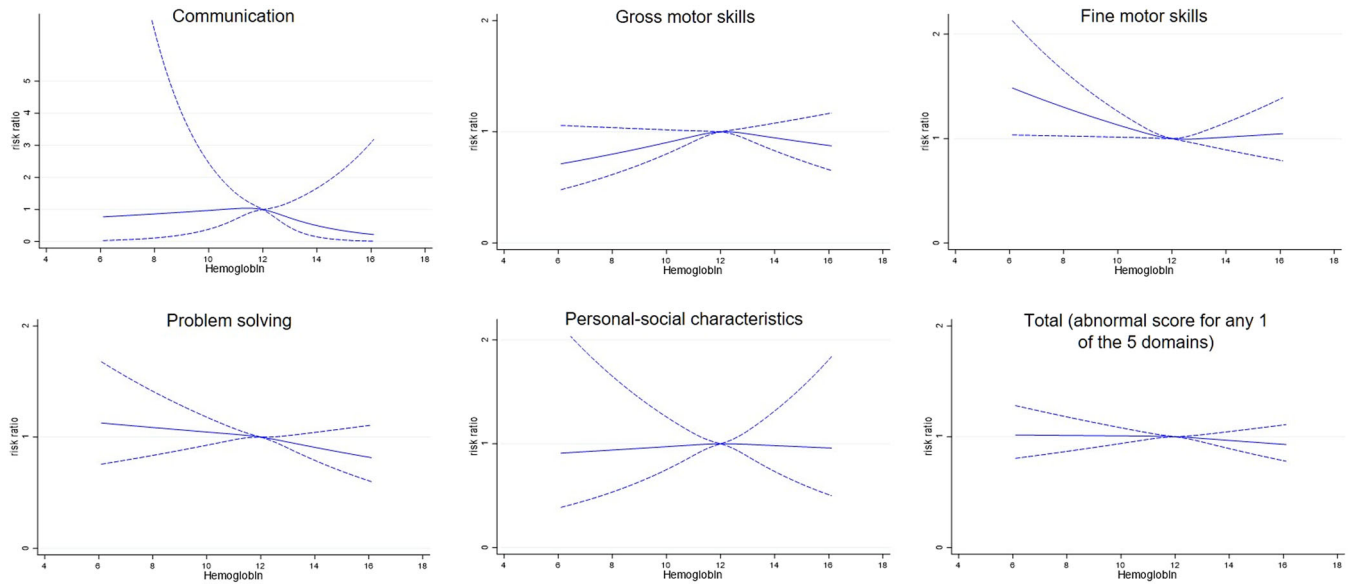

FIGURE 4 Association between maternal hemoglobin levels and infants' abnormal scores in the Ages and Stages Questionnaire in the restricted cubic spline models. The solid line indicates the risk ratio (RR) and the dotted line indicates the 95% confidence interval. The reference was set at a hemoglobin level of 12.0 g/dl

pregnancy and sleep problems in offsprings. Maternal hemoglobin levels during pregnancy have been reported to be associated with those of children at 3–5 years of age.[25] Anemia has also been associated with sleep patterns in infancy.[26,27] Thus, maternal hemoglobin may affect infant sleep through infant hemoglobin levels.

On the other hand, some studies have reported an association between maternal hemoglobin levels during pregnancy and neurodevelopment in early infancy. A cohort study of 418 Vietnamese mothers and children reported that maternal anemia (Hemoglobin < 11.0 g/dl) during late pregnancy was associated with 6-month motor development.[28] Another study with 636 pairs of mothers and children in Benin also reported that both low and high hemoglobin levels were negatively associated with gross motor skills at the age of 1 year.[29] Although the timing of examination of maternal hemoglobin and the method and age of evaluation of infant development were different among these previous studies and from this study, maternal anemia during pregnancy is likely to be

negatively associated with infant motor skill development. In contrast, a high level of maternal hemoglobin was not associated with infant development, and further research should be done to investigate the association between maternal hemoconcentration during early pregnancy and infant development.

Iron deficiency has been reported to account for 75% of maternal anemia cases during pregnancy.[30] Iron has been shown to play an important role in brain development in both animals and in vitro studies.[31] However, there is no consensus on whether maternal iron deficiency or iron supplementation during pregnancy are associated with neurodevelopment or developmental disorders in children, despite numerous human studies.[31,32] One reason may be that anemia tests and iron agent medication are widely conducted through prenatal checkup in developed countries. Furthermore, in this study, 42.6% of the total population took iron agents during pregnancy, and this may have alleviated the negative effects of iron deficiency in early pregnancy. Maternal anemia can also be caused by a deficiency of other micronutrients such as folic acid and chronic inflammation.[30,33] Both folic acid intake and maternal inflammation during pregnancy are associated with developmental disorders such as autism.[34–36] In addition, both low and high levels of maternal hemoglobin are associated with perinatal complications such as PE, GDM, and LBW.[1,2] These perinatal complications also increase the risk of developmental disorders.[13,14] Therefore, in addition to iron deficiency, maternal hemoglobin may affect children's neurodevelopment through perinatal complications and the various causes of anemia.

Children diagnosed with developmental disorders tend to have sleeping problems in early infancy.[15,16] The association between maternal hemoglobin levels and infant sleeping problems in this study may reflect the association between maternal hemoglobin and developmental disorders. Further, follow-up research is needed to investigate the association between maternal hemoglobin levels and developmental disorders in children.

There are several limitations to this study. First, because we investigated the association between maternal hemoglobin level and many different outcomes, the significant associations found in this study might be chance findings. Furthermore, the observed RR values were generally small, and the association between maternal hemoglobin level and late infant bedtime became less significant when the effects of maternal socioeconomic status were adjusted for. Even if maternal hemoglobin level affects infant sleep and development, the effect is considered to be small compared to other factors. Second, this was an observational study, so there could be unmeasured confounding factors such as parental life rhythm or sleep cycle. Third, the information on outcomes (infant sleep problems and ASQ scores) was evaluated using a questionnaire filled by mothers. In particular, the sleep questionnaire is not validated, and the last 24 h sleep period reported in the questionnaire may not be representative of the infants' daily sleep. Caution is therefore required when interpreting the result of this study. Fourth, the range of the timing of blood tests was wide (6–22 weeks of gestation). A narrow range is preferable because maternal hemoglobin levels are known to decrease physiologically due to an increase in maternal plasma volume after the second trimester of pregnancy.[2,3,6] Although we performed a stratified analysis based on the timing of blood sampling (first trimester or second trimester), it was not possible to determine in which period the hemoglobin level was important for the infant outcome.

However, the strength of this study is that it is a large-scale study focusing on the association between maternal hemoglobin levels during early pregnancy and infant development. Furthermore, we performed statistical analyses with many covariates. In conclusion, both low and high levels of maternal hemoglobin may be associated with sleeping and developmental problems in early infancy.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Study conception and design: Seiichi Morokuma. *Statistical analyses*: Takehiro Michikawa. *Drafting of the manuscript and approval of final content*: Kazushige Nakahara, Seiichi Morokuma, and Takehiro Michikawa. *Critical revision of the manuscript for important intellectual content and manuscript review*: Kazushige Nakahara, Takehiro Michikawa, Seiichi Morokuma, Norio Hamada, Masanobu Ogawa, Kiyoko Kato, Masafumi Sanefuji, Eiji Shibata, Mayumi Tsuji, Masayuki Shimono, Toshihiro Kawamoto, Shouichi Ohga, Koichi Kusuhara, and JECS group members.

DATA AVAILABILITY STATEMENT

The data of this study are unsuitable for public deposition due to ethical restrictions and the legal framework of Japan. It is prohibited by the Act on the Protection of Personal Information (Act No. 57 of May 30, 2003, amendment on September 9, 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 regarding t 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 Programme Office, National Institute for Environmental Studies.

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SUPPORTING INFORMATION

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

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APPENDIX

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