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Original article

Breastfeeding and risk of febrile seizures in infants: The Japan Environment and Children's Study

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Abstract

Objective: Our study was conducted to examine the association between breastfeeding and febrile seizures (FS) in the first year of life.

Methods: We used data from a birth cohort study, the Japan Environment and Children's Study (JECS). In a self-administered questionnaire, we asked participants the duration of breastfeeding and whether their children were diagnosed as having FS during their first 12 months. We estimated the association of duration and exclusiveness of breastfeeding with the FS by using multiple logistic regression analysis.

Results: Of 84,082 children, 995 (1.2%) were diagnosed as having FS by the age of 12 months. The prevalence of FS was higher in children who were breastfed for shorter duration. Multiple logistic regression analysis showed that, compared with children breastfed for less than 1 month, those breastfed for 4–6 months and 7–12 months had lower risks of FS (adjusted odds ratio [aOR], 0.65 [95% confidence interval {CI}, 0.42–0.99]; aOR, 0.66 [95% CI: 0.45–0.96], respectively). Moreover, compared with infants who received both breast milk and formula milk for 6 months, infants who were breastfed exclusively for 6 months had lower risk of FS (aOR: 0.78 [95% CI: 0.64–0.95]).

Conclusions: Our results suggest that breastfeeding has a protective effect against FS in the first year of life.

Keywords: Breastfeeding; Febrile seizures; The Japan Environment and Children's Study; JECS

1. Introduction

A febrile seizure (FS) is a seizure accompanied by fever without central nervous system infection, metabolic abnormality, or intoxication. FS is the most common type of seizure in children and occurs in 2%–5% of all infants and children between 6 and 60 months of age, with a peak incidence in the second year of life [1,2]. The reported prevalence of FS in Japan, which is higher than in other countries, ranges between 3.4% and 11% [3–5].

Although the cause of FS remains unknown, both genetic factors and early-life environmental exposures are considered to play important roles in the development of FS. For example, a family history of FS markedly increases the risk of FS in offspring [3]. Most

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etiologic studies on FS have focused on genetic factors, and little is known about environmental risk factors. Among environmental factors, intrauterine factors including fetal growth retardation, low birth weight, and short gestational age are considered to be important [6–8]. However prenatal exposure to maternal smoking, maternal alcohol and coffee consumption, and pre-eclampsia have little or no association with FS [7,9,10].

Breastfeeding provides many health benefits to both babies and mothers. Numerous studies in industrialized countries have shown that extended duration of breastfeeding has a protective effect against common infectious diseases, including respiratory infections, otitis media, and gastrointestinal tract infections [11–14]. Moreover, duration of breastfeeding is considered to be associated with improved cognitive development in children [15–18]. However, currently available data rarely address the preventive effect of breastfeeding on FS [19,20].

In the present study, we hypothesized that breastfeeding is associated with decreased risk of FS. Using data from the Japan Environment and Children's Study (JECS), we assessed the association between the duration of any breastfeeding and FS by 12 months of age.

2. Methods

2.1. Study design

We analyzed a dataset from the JECS, a birth cohort study undertaken to elucidate the influence of environmental factors during the fetal period and early childhood on children's health, with follow-up until age 13. The protocol for and baseline data from this study are available elsewhere [21,22]. JECS was initiated by the Ministry of the Environment, which organized a national research group headed by the National Institute of Environmental Studies in collaboration with the National Center for Child Health and Development and 15 regional centers.

For JECS, pregnant women were recruited between January 2011 and March 2014. Eligibility criteria for participants (expectant mothers) were as follows: 1) residence in the study areas at the time of recruitment and enrolled with collaborating healthcare providers; 2) expected delivery date after August 1, 2011; and 3) capable of comprehending the Japanese language and completing the self-administered questionnaire. Details of the JECS project have been described previously [22].

The JECS protocol was approved by the Institutional Review Board on Epidemiological Studies of the Ministry of the Environment and by the ethics committees of all participating institutions. JECS was conducted in accordance with the Declaration of Helsinki and other internationally valid regulations and guidelines. All participants provided written informed consent.

Data regarding exposure measurement, maternal lifestyle, and other background information were collected by self-administered questionnaires distributed to participants at registration (M-T1) and during the second or third trimester (M-T2) [23]. Information on maternal drug use was obtained through interviews performed by research coordinators at registration (In-T1) and during the second or third trimester (In-T2). Medical histories of past and present pregnancies and the physical status of participating mothers and children were transcribed from their obstetricians' and pediatricians' medical charts at delivery (Dr-0m). Information regarding the children's living environment and past medical history were collected through self-administered questionnaires distributed to participants when their children were 6 and 12 months old (C-6m and C-1y, respectively).

2.2. Sample selection

The present study used the dataset "jecs-an-20180131", which was released in January 2018. In total, records of 104,065 mother–child pairs were included in the dataset, and these mothers gave birth to 102,429 live children. Of the mothers who gave birth to live children, 90,449 answered the C-1y questionnaire. From the 90,449 mother–child pairs, we excluded cases of multiple birth (n = 1,641), those missing data on gestational age (n = 189), cases of preterm or post-term birth (n = 4,236), and those missing data on feeding pattern (n = 301). In total, 84,082 mother–child pairs were included in the final study sample (Fig. 1).

2.3. Assessment of feeding pattern

Information on feeding patterns was obtained through the C-1y questionnaire, which asked how long their infants had received breast milk or formula milk. The duration of breastfeeding obtained from the questionnaire was categorized into 4 groups: (1) less than 1 month; (2) 1 to 3 months; (3) 4 to 6 months; and (4) 7 to 12 months [13,17]. Moreover, in order to assess the duration of exclusive breastfeeding, we used the following 4 categories: (1) received breast milk for less than 1 month ("scarcely breastfed"); (2) received both breast milk and formula milk for 6 months ("partial for 6 months"); (3) breastfed and received no other milk for 6 months ("exclusive breastfeeding for 6 months"); and (4) other scenarios ("others").

2.4. Assessment of FS

Information on FS was obtained from responses to the C-1y questionnaire. In C-1y, mothers checked various boxes to indicate the diseases, including FS, that

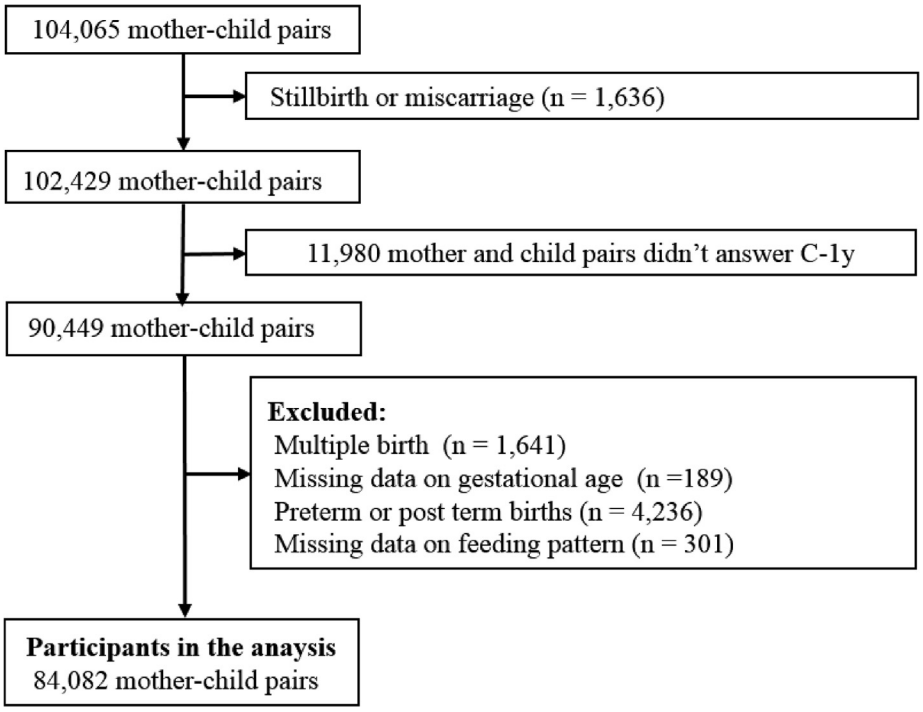

Fig. 1. Flowchart for selection of participants from JECS.

were diagnosed in their children when 12 months of age or younger. Information regarding the number of episodes of FS or type of seizures was not collected.

2.5. Covariates

Maternal history of epilepsy was obtained from the M-T1 questionnaire; maternal education, family income, and maternal smoking habits during pregnancy from M-T2; information regarding anticonvulsant use during pregnancy (that is, drug use from week 12 of pregnancy until the In-T2 interview) from In-T2; maternal age and birth outcome, including gestational age and birth weight, from Dr-0m; the sex of the offspring from revised Dr-0m data; information regarding siblings from C-6m; and information regarding daycare attendance and episodes of fever by the age of 12 months from C-1y. Regarding episodes of fever, participants were asked the numbers of episodes of temperature $\geq$38 °C and $\geq$39 °C that their children had experienced since birth.

Mothers were categorized into three groups according to age at their child's delivery: younger than 20 years, 20–34 years, and 35 years or older. Mothers' length of education was categorized as less than 10 years, 10–12 years, 13–16 years, and 17 years or higher. Maternal smoking habits were defined as smoking during pregnancy or others. Family income was categorized as less than 2 million yen, 2 to 3.9 million yen, 4 to 5.9 million yen, 6 to 7.9 million yen, 8 to 9.9 million yen, and 10 million yen or higher. Offspring formed two groups according to birth weight: less than 2,500 g and 2,500 g or more. The number of fever episodes during the first year of life was defined as 0, 1 or 2, 3 or 4, and 5 or more.

2.6. Statistical analyses

First, participants' baseline characteristics were compared according to duration of breastfeeding using the chi-squared test. Second, we performed a logistic regression analysis to determine whether the duration of any breastfeeding or other participants' characteristics were associated with the risk (odds ratio) of developing FS in the first year of life. We also performed logistic regression to calculate the association between exclusive breastfeeding and the risk (odds ratio) of developing FS. In these analyses, we adjusted for baseline characteristics such as maternal age, maternal education, family income, maternal smoking during pregnancy, maternal history of epilepsy, number of siblings, birthweight, and day care attendance. Third, we separately adjusted the logistic regression models for the numbers of fever episodes $\geq$38 °C and $\geq$39 °C to assess whether these factors influenced the association between breastfeeding and FS; for these models, offspring who never had any fever $\geq$38 °C were excluded. Results are pre-

sented as crude odds ratios, adjusted odds ratios (aORs), and means with 95% confidence intervals (95% CIs). All analyses were performed using Stata 13.1 (Stata Corp, College Station, Texas).

3. Results

The characteristics of the enrolled children and mothers are shown in Table 1. Of the 84,082 mothers, 1,940

Table 1
Baseline characteristics and duration of any breastfeeding.

Duration of breastfeeding (months)	<1 n (%) 1,940 (2.3%)	1–3 n (%) 10,007 (11.9%)	4–6 n (%) 7,623 (9.1%)	7–12 n (%) 64,512 (76.7%)	*p* value
Maternal age (years)					
<20	26 (4.5%)	193 (33.4%)	78 (13.5%)	281 (48.6%)	<0.001
20–35	1,322 (2.2%)	7,254 (12.0%)	5,522 (9.1%)	46,488 (76.7%)	
≥35	592 (2.6%)	2,559 (11.2%)	2,023 (8.8%)	17,740 (77.4%)	
Smoking during pregnancy					
No	1,658 (2.1%)	8,791 (11.0%)	7,045 (8.8%)	62,204 (78.1%)	<0.001
Yes	238 (7.3%)	1,022 (31.5%)	448 (13.8%)	1,541 (47.4%)	
Maternal education (years)					
<10	256 (7.4%)	948 (27.5%)	397 (11.5%)	1,849 (53.6%)	<0.001
10–12	916 (3.6%)	4,499 (17.7%)	2,858 (11.2%)	17,224 (67.6%)	
13–16	720 (1.4%)	4,337 (8.2%)	4,186 (7.9%)	43,664 (82.5%)	
≥17	12 (0.9%)	72 (5.5%)	82 (6.3%)	1,146 (87.4%)	
Family income (million yen)					
<2.0	206 (5.1%)	847 (20.9%)	499 (12.3%)	2,494 (61.6%)	<0.001
2.0–3.9	735 (2.8%)	3,737 (14.0%)	2,612 (9.8%)	19,541 (73.4%)	
4.0–5.9	496 (1.9%)	2,681 (10.3%)	2,247 (8.6%)	20,643 (79.2%)	
6.0–7.9	177 (1.4%)	1,037 (8.2%)	939 (7.4%)	10,503 (83.0%)	
8.0–9.9	63 (1.2%)	426 (8.2%)	393 (7.6%)	4,319 (83.0%)	
≥10	46 (1.4%)	259 (7.7%)	271 (8.1%)	2,783 (82.9%)	
Maternal history of epilepsy					
No	1,891 (2.3%)	9,863 (11.9%)	7,517 (9.0%)	63,853 (76.8%)	<0.001
Yes	39 (8.5%)	78 (16.9%)	47 (10.2%)	297 (64.4%)	
Anticonvulsants use during pregnancy					
No	1,908 (2.3%)	9,983 (11.9%)	7,611 (9.1%)	64,449 (76.8%)	<0.001
Yes	32 (24.4%)	24 (18.3%)	12 (9.2%)	63 (48.1%)	
Sex of offspring					
Male	992 (2.3%)	5,131 (12.0%)	3,867 (9.0%)	32,856 (76.7%)	0.9
Female	948 (2.3%)	4.876 (11.8%)	3,756 (9.1%)	31,656 (76.8%)	
Birthweight (g)					
<2,500	150 (3.3%)	709 (15.7%)	457 (10.1%)	3,203 (70.9%)	<0.001
≥2,500	1,789 (2.3%)	9,294 (11.7%)	7,162 (9.0%)	61,273 (77.1%)	
Day care attendance					
No	1,330 (2.2%)	6,582 (10.8%)	4,702 (7.7%)	48,555 (79.4%)	<0.001
Yes	592 (2.6%)	3,374 (15.0%)	2,881 (12.8%)	15,714 (69.7%)	
Number of fever episodes (≥38.0 °C)					
0	285 (2.2%)	1,497 (11.5%)	1,123 (8.6%)	10,157 (77.8%)	<0.001
1–2	869 (2.1%)	4,595 (11.1%)	3,382 (8.2%)	32,672 (78.7%)	
3–4	330 (2.2%)	1,744 (11.6%)	1,405 (9.3%)	11,573 (76.9%)	
≥5	265 (2.7%)	1,458 (15.0%)	1,227 (12.6%)	6,778 (69.7%)	
Number of fever episodes (≥39.0 °C)					
0	514 (2.1%)	2,777 (11.4%)	2,042 (8.4%)	18,984 (78.1%)	<0.001
1–2	811 (2.1%)	4,410 (11.7%)	3,438 (9.1%)	29,205 (77.1%)	
3–4	144 (2.5%)	691 (12.2%)	620 (10.9%)	4,216 (74.3%)	
≥5	59 (3.0%)	341 (17.2%)	274 (13.8%)	1,311 (66.1%)	

Data were missing on maternal age (n = 4), smoking during pregnancy (n = 1,135), maternal education (n = 916), family income (n = 6,128), siblings (n = 1,117), birthweight (n = 45), day care attendance (n = 352), number of fever episodes (≥38.0 °C) (n = 4,722), and number of fever episodes (≥39.0 °C) (n = 14,245).
Differences between groups were compared by using chi-squared tests.

(2.3%) breastfed their children for less than 1 month; 10,007 (11.9%) for 1 to 3 months; 7,623 (9.1%) for 4 to 6 months; and 64,512 (76.7%) for 7 to 12 months (Table 1). The rate of continued breastfeeding at 1 year was 57.1% (n = 47,998). Older mothers, those who didn't smoke during pregnancy, those with more education, those with higher family income, those who had no history of epilepsy, and those who didn't use anticonvulsants during pregnancy tended to breastfeed their children for longer durations (Table 1). In addition, children who were breastfed for longer tended to have fewer fever episodes and were unlikely to attend day care (Table 1).

Of the 84,082 total children, 995 children (1.2%) were diagnosed as having FS by the age of 12 months (Table 2). The prevalence of FS was higher in children who were breastfed for shorter durations. In the multiple logistic regression analysis, compared with children breastfed for less than 1 month as a reference, those breastfed for 4 to 6 months and 7 to 12 months had lower risks of FS (aOR: 0.65 [95% CI: 0.42–0.99], aOR: 0.66 [95% CI: 0.45–0.96], respectively) (Table 2).

When the exclusiveness of breastfeeding was taken into account, 33,935 (40.0%) mothers exclusively breastfed their children for 6 months (Table 3). The risk of FS was lower in infants who were breastfed exclusively for 6 months compared with those who received breast milk and formula milk for the same duration (aOR: 0.78 [95% CI: 0.64–0.95]) (Table 3).

In addition, the prevalence of FS was higher in children whose mothers were younger, less educated, and less affluent and who smoked during pregnancy. However, the association between FS and smoking habit disappeared after the model was adjusted for the other variables.

The number of fever episodes during the first year of life was associated with both FS and duration of breastfeeding (Tables 1 and 2). However, adjustment for the number of fever episodes (≥38 °C) only slightly influenced the association between FS and either breastfeeding duration or exclusiveness of breastfeeding (compare the aORs in the last 2 columns in Tables 2 and 3). Similarly, adjustment for the number of high-fever episodes (≥39 °C) only slightly influenced these associations (Tables S1 and S2). Overall, these results suggest that number of fever episodes did not influence associations between FS and either breastfeeding duration or exclusiveness.

4. Discussion

The present study revealed a negative, dose-responsive, and duration-responsive association of breastfeeding with FS in the first year of life in a large-scale, prospective birth cohort. Past studies focused on the association between breastfeeding and FS are very scarce [19,20]. Greenwood showed an association between failure of breastfeeding and FS after the model was adjusted for birth weight and neonatal problems [19]. However, the authors did not report any influence of the duration of breastfeeding, and they stated the need for confirmation of this association from other studies [19]. Mahyar reported that the mean duration of breastfeeding was significantly shorter in children with FS than in healthy children, but these authors did not adjust for confounding factors [20].

We also found a negative association between duration of breastfeeding and number of fever episodes, thus suggesting a protective effect of breastfeeding on common infectious diseases. Moreover, the number of fever episodes was positively associated with increased risk of FS. This finding is consistent with several previous studies, although Visser showed that frequent fever episodes were not associated with the risk of FS in infants 6 to 12 months old [24–26]. Contrary to our hypothesis, the number of fever episodes had little effect on the association between the duration of breastfeeding and the risk of FS. This result suggests that the effect through which breast feeding reduces the risk of FS occurs through mechanism other than its reduction of the number of febrile episodes. However, the number of fever episodes may be associated independently with FS.

The protective effect of breastfeeding on common infections is considered to be due to several factors in human breast milk, including epidermal growth factor, immunoglobulin A, and oligosaccharides [13]. In addition, human milk is high in docosahexaenoic acid, a major n-3 long-chain polyunsaturated fatty acid (n-3 LC-PUFA), and the positive effect of breastfeeding on pediatric neurodevelopment seems to be due in part to the levels of n-3 LC-PUFAs in breast milk [17]. Moreover, n-3 LC-PUFAs may reduce neuronal excitability and exert an anti-convulsive effect [27]. Although the mechanisms underlying the protective effect of breastfeeding on FS remain to be clarified, n-3 LC-PUFAs in human breast milk may be associated with the protective effect on FS.

Mothers who had a history of epilepsy and mothers who answered that they had taken anticonvulsants during pregnancy both were likely to have breastfed for a shorter duration. The shorter duration of breastfeeding of mothers who had a history of epilepsy may be related to their anticonvulsant treatment. Family history of epilepsy has not been reported to be a risk of onset of FS itself, although it is an important factor related to the subsequent onset of epilepsy [3]. In the current study, however, we found that a maternal history of epilepsy

Table 2
Duration of any breastfeeding and other baseline characteristics of participants with and without febrile seizures.

	without FS n n = 83,037	with FS n (%) n = 995 (1.2%)	cOR (95% CI)	aOR (95% CI)*	aOR (95% CI)**
Duration of any breastfeeding (months)					
<1	1,900	40 (2.1%)	1 (Reference)	1 (Reference)	1 (Reference)
1–3	9,855	152 (1.5%)	0.73 (0.52–1.04)	0.81 (0.55–1.21)	0.80 (0.53–1.20)
4–6	7,527	96 (1.3%)	0.61 (0.42–0.88)	0.66 (0.44–1.01)	0.65 (0.42–0.99)
7–12	63,805	707 (1.1%)	0.53 (0.38–0.73)	0.68 (0.47–0.99)	0.66 (0.45–0.96)
p-for trend			<0.001	0.04	0.03
Maternal age (years)					
<20	558	20 (3.5%)	1 (Reference)	1 (Reference)	1 (Reference)
20–35	59,839	747 (1.2%)	0.35 (0.22–0.55)	0.48 (0.25–0.92)	0.53 (0.27–1.02)
≥35	22,686	228 (1.0%)	0.28 (0.18–0.45)	0.39 (0.20–0.76)	0.45 (0.23–0.89)
p-for trend			<0.001	0.003	0.03
Smoking during pregnancy					
No	78,776	922 (1.2%)	1 (Reference)	1 (Reference)	1 (Reference)
Yes	3,193	56 (1.7%)	1.50 (1.14–1.97)	1.11 (0.82–1.51)	1.06 (0.78–1.44)
Maternal education (years)					
<10	3,378	72 (2.1%)	1 (Reference)	1 (Reference)	1 (Reference)
10–12	25,169	328 (1.3%)	0.61 (0.47–0.79)	0.69 (0.51–0.92)	0.69 (0.51–0.92)
13–16	52,338	569 (1.1%)	0.51 (0.40–0.65)	0.66 (0.49–0.88)	0.66 (0.49–0.88)
≥17	1,297	15 (1.1%)	0.54 (0.31–0.95)	0.65 (0.35–1.21)	0.61 (0.32–1.16)
p-for trend			<0.001	0.03	0.02
Family income (million yen)					
<2.0	3,969	77 (1.9%)	1 (Reference)	1 (Reference)	1 (Reference)
2.0–3.9	26,299	326 (1.2%)	0.64 (0.50–0.82)	0.74 (0.57–0.96)	0.74 (0.57–0.96)
4.0–5.9	25,781	286 (1.1%)	0.57 (0.44–0.74)	0.68 (0.52–0.89)	0.67 (0.51–0.88)
6.0–7.9	12,514	142 (1.1%)	0.58 (0.44–0.77)	0.73 (0.54–0.99)	0.73 (0.54–0.99)
8.0–9.9	5,155	46 (0.9%)	0.46 (0.32–0.66)	0.55 (0.37–0.81)	0.54 (0.36–0.80)
≥10	3,318	41 (1.2%)	0.64 (0.43–0.93)	0.83 (0.55–1.23)	0.86 (0.58–1.29)
p-for trend			0.005	0.13	0.21
Maternal history of epilepsy					
No	82,151	973 (1.2%)	1 (Reference)	1 (Reference)	1 (Reference)
Yes	446	15 (3.3%)	2.84(1.69–4.77)	2.48 (1.39–4.44)	2.53 (1.40–4.54)
Siblings					
0	35,716	312 (0.9%)	1 (Reference)	1 (Reference)	1 (Reference)
≥1	46,277	660 (1.4%)	1.63 (1.43–1.87)	1.64 (1.42–1.90)	1.23 (1.06–1.43)
Birthweight (g)					
<2500	4,465	54 (1.2%)	1 (Reference)	1 (Reference)	1 (Reference)
≥2500	78,577	941 (1.2%)	0.99 (0.75–1.30)	0.89 (0.67–1.19)	0.85 (0.63–1.13)
Day care attendance					
No	60,601	568 (0.9%)	1 (Reference)	1 (Reference)	1 (Reference)
Yes	22,141	420 (1.9%)	2.02 (1.78–2.30)	1.95 (1.71–2.24)	1.15 (0.99–1.34)
Number of fever episodes (≥38.0 °C)					
0	13,061	1 (0.0%)			
1–2	41,126	392 (0.9%)	1 (Reference)		1 (Reference)
3–4	14,774	278 (1.9%)	1.97 (1.69–2.30)		1.86 (1.58–2.20)
≥5	9,435	293 (3.0%)	3.26 (2.80–3.80)		2.80 (2.34–3.35)
p-for trend			<0.001		<0.001

Data were missing on maternal age (n = 4), smoking during pregnancy (n = 1,135), maternal education (n = 916), family income (n = 6,128), siblings (n = 1,117), birthweight (n = 45), day care attendance (n = 352), number of fever episodes (≥38.0 °C, n = 4,722).

* Adjusted for all variables presented without number of fever episodes.

** Additional adjustment for number of fever episodes (≥38.0 °C). Cases who never had any fever (≥38 °C) episodes were excluded in this model.

was associated with the risk of FS in their offspring. Whether this association is limited to an early onset of FS is unclear, because infants as old as one year were eligible for this study. To clarify the association between a family history of epilepsy and the risk of FS in offspring, further study is needed.

A major strength of our study is its large sample size, which enabled us to include diverse confounding factors,

Table 3
Duration of exclusive breastfeeding with and without febrile seizures.

	without FS n n = 83,037	with FS n (%) n = 995 (1.2%)	cOR (95% CI)	aOR (95% CI)*	aOR (95% CI)**
Duration of exclusive breastfeeding					
Never	2,283	49 (2.1%)	1.70 (1.24–2.34)	1.23 (0.85–1.78)	1.25 (0.86–1.82)
Partial for 6 mo	14,194	179 (1.3%)	1 (Reference)	1 (Reference)	1 (Reference)
Exclusive for 6 mo	33,578	357 (1.1%)	0.84 (0.70–1.01)	0.80 (0.66–0.97)	0.78 (0.64–0.95)
Others	33,032	410 (1.2%)	0.98 (0.82–1.17)	0.89 (0.74–1.07)	0.87 (0.72–1.05)

Data were missing on maternal age (n = 4), smoking during pregnancy (n = 1,135), maternal education (n = 916), family income (n = 6,128), siblings (n = 1,117), birthweight (n = 45), day care attendance (n = 352), number of fever episodes (≥39.0 °C) (n = 14,245).
* Adjusted for all variables presented without number of fever episodes.
** Additional adjustment for number of fever episodes (≥38.0 °C). Cases who never had any fever (≥38 °C) episodes were excluded in this model.

including prenatal and postnatal environmental factors, in our analyses. To our knowledge, this study is the largest to have assessed the association of breastfeeding with FS and is the first report to show both dose-responsive and duration-responsive relationships of breastfeeding with decreased risk of FS. We asked mothers about their duration of breastfeeding when their children were only 12 months old, thus perhaps reducing recall bias. These factors also enabled us to assess breastfeeding properly. Bauchner indicated that most past studies on breastfeeding have methodological flaws, and they proposed four methodological standards to assess internal validity: (1) avoidance of detection bias; (2) adjustment for confounding variables, such as socioeconomic status, size of family, smoking by the mother, and the mother's level of education; (3) a definition of infant feeding; and (4) a definition of outcome events [28]. Our study meets all four of these criteria. As previous studies have shown, longer duration of breastfeeding was associated with older maternal age and higher educational level. In contrast, maternal smoking during pregnancy and early return to work were associated with shorter duration of breastfeeding [29,30].

Several study limitations should be considered. Residual confounding factors may affect both breastfeeding and FS, although we assessed numerous potential confounding factors. Recall bias regarding the number of fever episodes might exist, particularly among mothers whose children had fevers frequently. Furthermore, mothers whose children experienced FS may have been more aware of their children's fevers than mothers whose children were free of FS. The underreported number of fever episodes in children without FS would result in the overestimated OR. However, the dose-responsive relationship between number of fever episodes and FS imply that the association among them is robust.

Regarding genetic factors, although we adjusted for maternal history of epilepsy, we were unable to obtain information regarding the family history of FS, despite the importance of genetic factors in FS. In addition, we collected information about FS not from medical records but from self-administered questionnaires provided to caregivers. Moreover, mothers who missed answering the questionnaire about FS might have answered as though their children had not been diagnosed as having FS. However, the prevalence of FS at 12 months of age in the current study was similar to that in a previous study conducted in Japan [4]. The prevalence of FS in Japan in children younger than 1 year of age is reported to be 1% [4]. Because details regarding FS, including frequency and duration or type of seizures, were unavailable for our study population, we could not assess whether breastfeeding might be a protective factor against recurrent FS or prolonged seizures.

5. Conclusions

In the current study, longer duration of breastfeeding and exclusive breastfeeding were associated with decreased risk of FS in Japanese infants. Further studies that evaluate the duration of the protective effect against FS after the termination of breastfeeding and those that investigate the protective effect of breastfeeding on recurrent or prolonged seizures are needed.

Contribution to authorship

Study concept and design: NM. Analysis of data: NM and ME. Interpretation of data: NM, ME, TH, MF, and NS. Drafting of the manuscript: NM. Critical revision of the manuscript: ME, TH, MF, NS, and the JECS group.

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Appendix A

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Appendix B. Supplementary data

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