

# BMJ Open Breast feeding and infant development in a cohort with sibling pair analysis: the Japan Environment and Children's Study

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## ABSTRACT

**Objectives** To investigate the association between breast feeding and infant development during the first year of life using sibling comparison.

**Design** Nationwide prospective birth cohort study with sibling pair analysis.

**Setting** 15 regional centres that participated in the Japan Environment and Children's Study.

**Participants** This study included 77 119 children (singleton, term birth and no malformation/severe diseases) whose mothers were registered between January 2011 and March 2014, including 3521 duos or trios of siblings.

**Primary outcome measures** The primary outcome was developmental delay at 6 and 12 months of age, assessed using the Japanese translation of the Ages and Stages Questionnaires, third edition. Multivariable regression analyses adjusted for confounders were performed to estimate the risk ratios of delay associated with any or exclusive breast feeding. Pairs of siblings discordant for statuses were selected, and conditional regression analyses were conducted with a matched cohort design.

**Results** Developmental delay was identified in 6162 (8.4%) and 10 442 (14.6%) children at 6 and 12 months of age, respectively. Any breast feeding continued until 6 months or 12 months old was associated with reduced developmental delay at 12 months of age (adjusted risk ratio (95% CI): 0.81 (0.77 to 0.85) and 0.81 (0.78 to 0.84), respectively). Furthermore, exclusive breast feeding until 3 months was associated with reduced developmental delay at 12 months of age (adjusted risk ratio, 0.86 (95% CI 0.83 to 0.90)). In sibling pair analysis, the association between any breast feeding until 12 months and reduced developmental delay at 12 months of age persisted (adjusted risk ratio, 0.64 (95% CI 0.43 to 0.93)).

**Conclusions** The present study demonstrated the association of continuous breast feeding with reduced developmental delay at 1 year of age using sibling pair analysis, in which unmeasured confounding factors are still present but less included. This may provide an argument to promote breastfeeding continuation.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This study is the largest birth cohort study that investigated the association between breast feeding and infant development.
- ⇒ The association was examined using not only ordinary multivariable regression analysis but also sibling comparison, which strongly controls for sibling-shared factors.
- ⇒ Monthly feeding status was collected at child's age of 1 month, 6 and 12 months, minimising the risk of recall bias.
- ⇒ Developmental delay was determined by a parent-reported screening test and thus may be equivocal.
- ⇒ The results could not eliminate the possibility that the association still could be explained by reverse causation because the reason for cessation of breast feeding was not known.

## INTRODUCTION

Since 1929, the beneficial effects of breast feeding on brain development have been repeatedly demonstrated.<sup>1-4</sup> Many observational studies<sup>5-8</sup> demonstrate that breast feeding is associated with better cognitive outcomes, including neurodevelopment, language and intelligence. In these studies, however, the causation remains unclear because the reason for cessation of breast feeding is not known. Furthermore, this association can be produced by differences in demographic, socioeconomic and environmental factors between mothers who breastfeed and those who do not.<sup>9-12</sup> In high-income countries, mothers with higher levels of education, social position, income and intelligence are more inclined to breastfeed and to do so more exclusively and for a longer duration. Thus, their children are more likely to have higher cognitive functions, which can result in a superficial association between



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breast feeding and better child cognition. In previous studies, the association disappeared or became highly diminished after controlling for confounders, especially maternal intelligence.<sup>9 13 14</sup> Nonetheless, a recent meta-analysis concluded that breast feeding was significantly associated with higher cognitive abilities, even after adjusting for such confounding factors.<sup>3</sup>

After explicitly controlling for these measured factors, unmeasured—even unknown—confounders such as parental characteristics and child-rearing practices remained. To further control for these confounders, previous studies<sup>9 15–17</sup> conducted sibling pair analysis in investigating the association of breast feeding with child cognitive outcomes. These analyses focused on siblings pairs who were discordant for breastfeeding exposure. A sibling pair from the same mother largely shares parental and environmental factors. Thus, the effects of these confounders can be cancelled out when the pair is matched in the analysis. However, on this topic, sibling pair analysis is challenging because little variation in breast feeding often exists between siblings, which may reduce statistical power and erroneously cause null findings.<sup>17</sup> To our knowledge, only three studies<sup>9 15 16</sup> have examined the association between breast feeding and cognitive functions using this method, and these studies all produced statistically null effects. The reason for the null results remains unclear. However, these findings may be accounted for by the study designs: data on feeding status were collected only once within 1 year<sup>9</sup> or 2 years<sup>15</sup> after a child's birth or in adolescence.<sup>16</sup>

The goal of the current study was to investigate the association between breast feeding and child development during the first year of life by using data from the Japan Environment and Children's Study (JECS). This nationwide birth cohort study includes >100 000 children and thus enables sibling pair analysis with a sufficient number of participants. The monthly status of breast feeding was collected repeatedly in the first year of life, thereby minimising the risk of recall bias. The beneficial effects of breast feeding on cognitive development decrease as children age<sup>18</sup>; therefore, investigating the association between breast feeding and cognitive development during early childhood has the advantage of allowing researchers to infer the role of breast feeding on the developing brain.

## METHODS

### Design

The JECS is a nationwide, multicentre, prospective birth cohort study funded by the Ministry of Environment, Japan. The details of the study design have been described elsewhere.<sup>19 20</sup> Briefly, pregnant participants were registered between January 2011 and March 2014 in 15 regional centres covering a wide geographical area in Japan. During the pregnancy, data on demographics, smoking, alcohol, education and socioeconomic statuses were obtained during the first and second/third

trimesters by using self-administered questionnaires. Detailed information regarding the mother and child was obtained from medical records transcripts during the first trimester, at the time of delivery, and when the child was 1 month. After delivery, data on feeding style, use of complementary foods, developmental status and affected diseases were collected at ages 1 and 6 months and every 6 months until the child was 6 years old, and then twice a year thereafter via self-reported questionnaires completed by the parents.

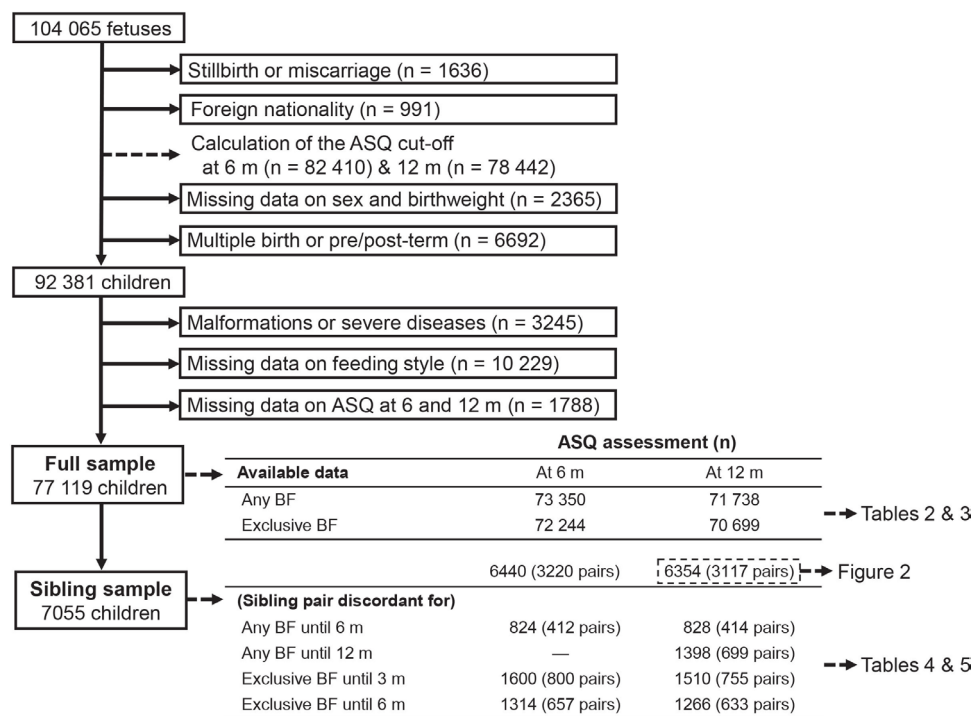
### Participants

In this study, we used the fixed dataset 'jecs-an-20180131' that was released in March 2018. This dataset contains all available data extracted from the aforementioned questionnaires and records until a child was 12 months old. The data for 104 065 fetuses from 103 062 pregnancies were linked to the respective maternal data. The participants selected were 92 381 live-born singleton children, delivered at term ( $\geq 37$  gestational weeks and  $< 42$  gestational weeks), of parents of Japanese nationality and for whom information on sex and birth weight had been recorded (figure 1). Of these children, those who had malformations or severe diseases, or who had missing information on feeding style during the first year of life or development at 6 months and 12 months old were excluded. After these exclusions, the data of 77 119 children were included in our analysis.

### Exposure

The main exposure factor was breast feeding. Mothers were asked to fill in the monthly feeding status of their child by using questionnaires when the child was 1 month, 6 months and 12 months old. This information included whether the child was breastfed, formula fed or both. The questionnaire administered when the child was 12 months old also queried when complementary food was first started. Breastfeeding duration indicated how long a child was breastfed from birth, irrespective of concurrent consumption of formula milk. We also dichotomously assessed whether or not a child continued (1) any breast feeding until 6 months old, (2) any breast feeding until 12 months, (3) exclusive breast feeding until 3 months and (4) exclusive breast feeding until 6 months. Breast feeding was 'exclusive' if the child consumed only breast-milk—and nothing else (no consumption of formula milk or complementary foods) during these periods. To gain more insight into the significance of exclusive breast feeding, we further classified the children who continued breast feeding until 6 months into four categories: (1) children who ingested neither formula milk nor complementary food (exclusive breast feeding), (2) those who ingested formula but not complementary food, (3) those who ingested complementary food but not formula and (4) those who ingested both formula and complementary food, at any time during the period.

For sibling pair analysis, we selected pairs who were discordant on the status of any breast feeding or exclusive



**Figure 1** Flow chart of participant selection. ASQ, Ages and Stages Questionnaires; BF, breast feeding.

breast feeding. When discordance was observed among three siblings (eg, only one of the three children was breastfed), we randomly selected one of the two siblings who were not breastfed and then paired the selected one with the breastfed sibling.

## Outcome

The outcome was developmental delay measured at 6 months and 12 months old, using the Japanese translated version of the Ages and Stages Questionnaires (ASQ): A Parent-Completed Monitoring System, third edition. This version was prepared through a back-translation procedure and was approved by the publisher of the original English version.<sup>21</sup> The ASQ can identify infants or young children who need further developmental assessment to determine whether they are eligible for early intervention. The findings of the questionnaire basically agree with those of professionally administered developmental batteries.<sup>22–23</sup> It has been used in clinical and research settings and translated into several languages.<sup>24–27</sup> The ASQ assesses five developmental domains. For each domain, six skills are described to which parents answer ‘yes,’ ‘sometimes,’ or ‘not yet,’ depending on whether their child is demonstrating the described skill. The responses are converted to points, with ‘yes’ receiving 10 points; ‘sometimes,’ 5 points and ‘not yet,’ 0 points. The child’s score for each developmental domain is the sum of all points received for the items under that domain and ranges from 0 to 60 points. The cut-off score for each domain was defined as 2 SD below the mean score of large standardised samples in the USA. A child was defined as having a developmental delay if a score was at or below the cut-off level in any developmental domain. When

the cut-off scores of the original English version were used in our population, an excessive number of children were classified as having a developmental delay (47.4% and 34.6% for 6 months and 12 months, respectively). Although preliminary cut-off scores of the Japanese translation were recently proposed,<sup>28</sup> these were not recommended to be used with confidence before 24 months old because of very limited sample sizes. Therefore, the cut-off scores were determined by using the same methodologies used in the original version, based on available data at ages 6 months (n=82 410) and 12 months (n=78 442) (figure 1), which would represent the general Japanese population. As a continuous variable, in addition, total score of ASQ was defined as the sum of the scores for the five domains, ranging from 0 to 300 points.

## Statistical analysis

To assess the association of breast feeding with child development, we conducted multivariable quasi-Poisson regression analyses for dichotomous dependent variables, and multiple linear regression analyses for continuous dependent variables. The adjusted covariates were (1) sex, (2) gestational age, (3) birth weight, (4) mother’s age, (5) maternal smoking status during pregnancy, as recorded in the first trimester, (6) maternal alcohol consumption during pregnancy, as recorded in the second trimester, (7) maternal and (8) paternal education level (junior high school, high school and university or graduate school), (9) annual family income (<¥4 000 000; ¥4 000 000–¥5 999 999; ≥¥6 000 000), (10) introduction of complementary foods before 6 months old and (11) home speech stimulation at 1 month (whether a mother did or did not talk to her baby habitually: yes/



no). The 'home speech stimulation' covariate was used instead of the Home Observation for Measurement of the Environment scale,<sup>29</sup> which is not employed in the JECS.

For sibling pair analysis, we conducted conditional logistic regression analyses with 1:1 matched cohort data of sibling pairs whose dichotomous statuses of breast feeding were discordant.<sup>30</sup> We reported adjusted relative risks (aRRs) with 95% CIs that were converted from ORs using an established method.<sup>31 32</sup> We also used a longitudinal linear mixed model, in which fixed effects were age of ASQ assessment (6 vs 12 months old), duration of breast feeding and the interaction term between them, with random intercept for sibling. The adjusted covariates were as follows: (1) sex, (2) gestational age, (3) birth weight, (4) order of siblings in the discordant pair, (5) maternal smoking status, (6) maternal alcohol consumption, (7) complementary food introduction and (8) home speech stimulation at 1 month old. All statistical analyses were conducted using R software (V.3.5.0). In the R package, we used 'survival' (V.3.2.7) for conditional logistic regression model and 'lme4' for longitudinal linear mixed model. The level of significance was  $p=0.05$ .

### Patient and public involvement

No participants were involved in creating the research question or the outcome measures, nor were they involved in developing plans for recruitment, design or implementation of the study. No participants were asked to provide advice on the interpretation or writing up of the results. There are plans to disseminate the results of the research to study participants and the general public. Participants were thanked in the acknowledgements.

### RESULTS

The baseline characteristics of 77 119 children are summarised in table 1. Nearly all (76 167, 98.8%) children were started on any breastmilk during their first month of life. Any breast feeding was continued until ages 6 and 12 months in 82.1% and 64.4% of children, respectively. Exclusive breast feeding was continued until ages 3 and 6 months in 39.6% and 20.3% of children, respectively. Developmental delay was identified in 8.4% and 14.6% of children at 6 months and 12 months old, respectively. The sibling cohort included 3521 sibling sets (7055 children) in total: 3508 duos (7016 children) and 13 trios (39 children). The characteristics of the sibling sample were substantially similar to those of the full sample. Nevertheless, the sibling sample appeared to have weak tendencies towards younger maternal age, lower paternal education, lower family income, lower rates for any breast feeding until 12 months old and higher rates for exclusive breast feeding until 3 months.

For the full sample ( $n=77\,119$ ), we conducted multivariable regression analyses, while adjusting for confounders, to examine developmental delay in relation to various types of breastfeeding exposures. When breast feeding was treated as dichotomous variables, quasi-Poisson

models revealed that any breast feeding continued until 6 months was associated with reduced developmental delay at ages 6 months (aRR (95% CI): 0.81 (0.76 to 0.86)) and 12 months (0.81 (0.77 to 0.85)) (table 2A). Any breast feeding until 12 months was similarly associated with reduced developmental delay at age 12 months (0.81 (95% CI 0.78 to 0.84)). Any breast feeding was similarly continued until 12 months old between children with (77.4%) and without developmental delay (78.6%) at 6 months old (online supplemental figure S1), arguing against the possibility that developmental delay per se interrupted the continuation of breast feeding. When developmental delay was not observed at 6 months old, it is more likely to occur newly at 12 months in children who discontinued breast feeding by 12 months old than those continued it while delay at 6 months resolved more often in children who continued breast feeding (online supplemental figure S2). Furthermore, exclusive breast feeding that continued until 3 months old, but not until 6 months, was associated with developmental delay at age 12 months (0.86 (95% CI 0.83 to 0.90)), table 2B). Among the children who continued breast feeding until 6 months old and had the information on complementary food, the effects of formula milk and complementary food was estimated, referenced to exclusive breast feeding (table 2C). The risk of developmental delay at 6 months was reduced in children who concomitantly ingested complementary food, irrespective of formula feeding. The risk of developmental delay at 12 months was increased in those who concurrently ingested formula milk without complementary food, but was reduced in those who ingested complementary food with no formula. When breast feeding duration was treated as a continuous variable, multiple linear regression model demonstrated that duration of any or exclusive breast feeding was positively associated with increased total ASQ scores at 6 and 12 months old (table 3).

To conduct sibling pair analysis, we extracted data from pairs of siblings who both underwent a developmental assessment at 6 months old (3220 pairs) and 12 months old (3117 pairs). Among these children, we further selected sibling pairs who were discordant for various breastfeeding statuses (figure 1 and table 4). Few variations existed in the statuses between pairs; therefore, the number of selected pairs was relatively small, varying from 412 pairs (824 children) to 800 pairs (1600 children), based on age (3 months, 6 months, or 12 months) and type (any breast feeding or exclusive breast feeding). Among these combinations, the adjusted conditional regression model for 699 sibling pairs (1398 children) revealed that any breast feeding until 12 months was significantly associated with reduced developmental delay at this age (0.64 (95% CI 0.43 to 0.93)). The mean breast feeding duration was 12 months in the sibling who was continuously breastfed and  $7.8\pm 2.9$  months in the sibling who was not. Moreover, exclusive breast feeding was not significantly associated with reduced developmental delay at any age. In sibling pairs discordant for any breast

**Table 1** Baseline characteristics of the children

	Full sample (n=77 119)	Missing	Sibling sample (n=7055)	Missing	Effect size*
Boy, no. (%)	39 350 (51.0)	0	3552 (50.3)	0	0.00
Gestational age (weeks), mean (SD)	39.5 (1.1)	0	39.5 (1.1)	0	0.00
Birth weight (g), mean (SD)	3062 (365)	0	3079 (360)	0	0.01
Maternal age (years), mean (SD)	31.3 (4.9)	4	29.8 (4.6)	0	0.09
Maternal smoking during pregnancy, no (%)	12 424 (16.3)	858	1062 (15.2)	58	0.01
Maternal alcohol during pregnancy, no (%)	2080 (2.7)	875	231 (3.3)	71	0.01
Maternal education, no. (%)		700		49	0.02
Junior high school	3029 (4.0)		310 (4.4)		
High school	56 180 (73.5)		5264 (75.1)		
University/graduate school	17 210 (22.5)		1432 (20.4)		
Paternal education, no (%)		1111		62	0.03
Junior high school	4960 (6.5)		541 (7.7)		
High school	44 973 (59.2)		4381 (62.6)		
University/graduate school	26 075 (34.3)		2071 (29.6)		
Family income, no (%)		5454		427	0.03
Low (<¥4 000 000)	28 012 (39.1)		2836 (42.8)		
Middle (¥4 000 000–¥5 999 999)	24 070 (33.6)		2189 (33.0)		
High (≥¥6 000 000)	19 583 (27.3)		1603 (24.2)		
Complementary food before 6 months, no (%)	34 126 (44.9)	1175	3194 (45.9)	95	0.01
Home speech stimulation at 1 month, no (%)	62 400 (81.1)	214	5611 (79.7)	17	0.01
Any breast feeding until 1 month, no (%)	76 167 (98.8)	0	6976 (98.9)	0	0.00
Any breast feeding until 6 months, no (%)	63 296 (82.1)	0	5713 (81.0)	0	0.01
Any breast feeding until 12 months, no (%)	49 672 (64.4)	0	4148 (58.8)	0	0.04
Exclusive breast feeding until 3 months, no (%)	30 049 (39.6)	1175	3031 (43.5)	95	0.03
Exclusive breast feeding until 6 months, no (%)	15 447 (20.3)	1175	1507 (21.7)	95	0.01
Neurodevelopmental delay at 6 months, no (%)	6162 (8.4)	3769	559 (8.3)	322	0.00
Neurodevelopmental delay at 12 months, no (%)	10 442 (14.6)	5381	888 (13.4)	443	0.01

Effect sizes are calculated as phi/Cramer's V and r, using  $\chi^2$  and Student's t-tests for the categorical and numerical variables, respectively.

\*The difference between sibling samples versus the rest (n=70 064).

feeding until 12 months, when the first-born children continued breast feeding, the second born, who discontinued it, had a tendency for developmental delay at 12 months; when the first born discontinued breast feeding, the second showed a reduced tendency (online supplemental figure S3). In sibling pairs who were discordant for maternal smoking, a proxy for socioeconomical status at that time, any breast feeding was similarly continued until 12 months old between children whose mothers had smoking (52.9%) vs no smoking (54.5%) during the pregnancy (online supplemental figure S4). When breast feeding was treated as continuous variables, longitudinal linear mixed model revealed that duration of any, but not exclusive, breast feeding was associated with increased total ASQ score (table 5).

To clarify how differently siblings were breastfed during the first year of life, we classified 3117 pairs whose developmental assessment at 12 months old was recorded into

three groups: 'both' (both children were breastfed), 'discordant' (only one child was breastfed) and 'neither' (neither child was breastfed) (figure 2). The number of discordant pairs increased from 43 (1.4%) pairs at the first month of life to 389 (12.5%) pairs at 6 months and 666 (21.4%) pairs at 12 months.

## DISCUSSION

The present study investigated the relationship between breast feeding and child development during the first year of life. Ordinary multivariable regression analyses demonstrated that any breast feeding continued until 6 or 12 months old, and exclusive breast feeding until 3 months were significantly associated with reduced developmental delay. In the sibling pair analysis, only the association between any breast feeding until 12 months old and reduced developmental delay at 12 months old remained

**Table 2** Association between any or exclusive BF and developmental delay for the full sample (n=77 119)

Developmental delay at 6 months			Developmental delay at 12 months		
No	cRR(95% CI)	aRR (95% CI)*†	No	cRR (95% CI)	aRR (95% CI)*†
(A) Any BF					
Until 6 months					
No	1263/12 967 (9.7%)	1 (reference)	2091/12 735 (16.4%)	1 (reference)	1 (reference)
Yes	4899/60 383 (8.1%)	<b>0.83 (0.79 to 0.88)</b>	8351/59 003 (14.2%)	<b>0.86 (0.82 to 0.90)</b>	<b>0.81 (0.77 to 0.85)</b>
Until 12 months					
No	—	—	4061/25 303 (16.0%)	1 (reference)	1 (reference)
Yes	—	—	6381/46 435 (13.7%)	<b>0.86 (0.83 to 0.89)</b>	<b>0.81 (0.78 to 0.84)</b>
Developmental delay at 6 months			Developmental delay at 12 months		
No	cRR(95% CI)	aRR(95% CI)*	No	cRR (95% CI)	aRR (95% CI)*
(B) Exclusive BF					
Until 3 months					
No	3794/43 558 (8.7%)	1 (reference)	6637/42 648 (15.6%)	1 (reference)	1 (reference)
Yes	2273/28 685 (7.9%)	<b>0.91 (0.87 to 0.96)</b>	3664/28 050 (13.1%)	<b>0.84 (0.81 to 0.87)</b>	<b>0.86 (0.83 to 0.90)</b>
Until 6 months					
No	4768/57 508 (8.3%)	1 (reference)	8228/56 374 (14.6%)	1 (reference)	1 (reference)
Yes	1299/14 735 (8.8%)	1.06 (1.00 to 1.13)	2073/14 324 (14.5%)	0.99 (0.95 to 1.04)	0.97 (0.92 to 1.01)
Developmental delay at 6 months			Developmental delay at 12 months		
No	cRR (95% CI)	aRR (95% CI)*	No	cRR (95% CI)	aRR (95% CI)*
(C) BF until 6 months					
FF(−), CF(−) (=exclusive BF)	1299/14 735 (8.8%)	1 (reference)	2073/14 324 (14.5%)	1 (reference)	1 (reference)
FF(+), CF(−)	1713/18 482 (9.3%)	1.05 (0.98 to 1.13)	2935/17 985 (16.3%)	<b>1.13 (1.07 to 1.19)</b>	<b>1.09 (1.03 to 1.15)</b>
FF(−), CF(+)	631/9960 (6.3%)	<b>0.72 (0.66 to 0.79)</b>	1087/9857 (11.0%)	<b>0.76 (0.71 to 0.82)</b>	<b>0.82 (0.77 to 0.88)</b>
FF(+), CF(+)	1184/16 314 (7.3%)	<b>0.82 (0.76 to 0.89)</b>	2145/16 000 (13.4%)	<b>0.93 (0.88 to 0.98)</b>	0.97 (0.91 to 1.03)
*Adjusted for sex, gestational age, birth weight, mother's age, maternal smoking and alcohol, maternal and paternal education, family income and home speech stimulation at 1 month.					
†Adjusted further for the introduction of complementary food. Boldface represents statistical significance (p<0.05).					
aRR, adjusted risk ratio; BF, breast feeding; CF, complementary food; cRR, crude risk ratio; FF, formula feeding.					

\*Adjusted for sex, gestational age, birth weight, mother's age, maternal smoking and alcohol, maternal and paternal education, family income and home speech stimulation at 1 month.

†Adjusted further for the introduction of complementary food. Boldface represents statistical significance (p&lt;0.05).

aRR, adjusted risk ratio; BF, breast feeding; CF, complementary food; cRR, crude risk ratio; FF, formula feeding.

**Table 3** Association between duration of any or exclusive BF and total ASQ score for the full sample (n=77 119)

	Increase of score at 6 months per BF month		Increase of score at 12 months per BF month	
	crude B (95% CI)	adjusted B (95% CI)*†	crude B (95% CI)	adjusted B (95% CI)*†
Duration of any BF (0–6 months)	<b>1.04 (0.79 to 1.28)</b>	<b>1.32 (1.06 to 1.58)</b>	<b>0.94 (0.66 to 1.22)</b>	<b>1.48 (1.18 to 1.78)</b>
Duration of any BF (0–12 months)	—	—	<b>0.47 (0.36 to 0.57)</b>	<b>0.77 (0.65 to 0.88)</b>
	Increase of score at 6 months per BF month		Increase of score at 12 months per BF month	
	crude B (95% CI)	adjusted B (95% CI)*	crude B (95% CI)	adjusted B (95% CI)*
Duration of exclusive BF (0–6 months)	<b>0.63 (0.51 to 0.76)</b>	<b>0.54 (0.41 to 0.67)</b>	<b>0.91 (0.77 to 1.05)</b>	<b>0.90 (0.75 to 1.04)</b>

\*Adjusted for sex, gestational age, birth weight, mother's age, maternal smoking and alcohol, maternal and paternal education, family income and home speech stimulation at 1 month.

†Adjusted further for the introduction of complementary food. Boldface represents statistical significance (p<0.05).

ASQ, Ages and Stages Questionnaires; BF, breast feeding.

significant. The null association of any breast feeding until 6 months might be explained by failure to detect less developmental variations at 6 months compared with those at 12 months, or involvement of other environmental factors that child had experienced after 6 months.

The association that we observed between breast feeding and brain functions has repeatedly been reported in observational, meta-analysis and randomised controlled studies.<sup>3 4 7 8 33</sup> In these studies, the results were heterogeneously adjusted for various parental and environmental confounders. However, no matter how many measured confounders are included, unmeasured confounding factors always exist. Hence, we opted for sibling pair analysis, which controls for all factors shared by siblings from the same mother.<sup>17</sup> We observed a significant association between breast feeding and development at 12 months. Our findings further support the WHO's recommendations concerning continued breast feeding beyond 6 months old.<sup>2</sup> The reason for our significant results is unlikely to be explained simply by the sufficient number of our discordant pairs of siblings (1398 children), which is comparable to the number in previous studies<sup>9 15 16</sup> reporting null findings (1046, 1090 and 1773 children). A possible explanation is that we assessed child's development in the first year of life, whereas the previous studies assessed it at 4–14 years. A randomised control study showed that the beneficial effects of breast-milk on cognitive development decrease with advancing age; thus, other environmental and genetic factors may become more important as children age.<sup>18</sup>

The mechanisms underlying the association between breast feeding and brain development are unclear but may be attributable to its nutrients such as long-chain polyunsaturated fatty acids, hormones and cytokines.<sup>34 35</sup> Another probable mechanism is mother–infant interaction produced by breast feeding behaviours.<sup>36</sup> A series of Family Nurture Intervention study have repeatedly

demonstrated the importance of early nurturing activities that engage the mother and infant reciprocally in physical, sensory and emotional experiences in infant development.<sup>37–43</sup> Such nurturing activities via breast feeding may enhance the connection between social motivation and mother–infant relational health,<sup>44</sup> leading to better development.

In contrast to any breast feeding, exclusive breast feeding had no significant association with developmental delay in our study. Research on the association between exclusive breast feeding and cognitive development is relatively scarce and has yielded inconsistent results: some studies report positive effects of exclusive breast feeding on neurodevelopment,<sup>45 46</sup> whereas other studies report limited or rather negative effects.<sup>47–49</sup> The reason for the reduced effects of exclusive breast feeding versus that of any breast feeding is not well understood. Our results showed that concomitant ingestion of complementary food, but not formula milk, was associated with reduced developmental delay in the children who continued breast feeding until 6 months old (table 2C). Thus, breastmilk without supplementation of complementary food may not meet the full requirements for energy and micronutrients such as iron and zinc, which all have important roles in the developing brain,<sup>50</sup> of the average infant at 6 months old, as some researchers suggested.<sup>51</sup> Withholding complementary food until age 6 months may negate the beneficial effects of breast feeding. Alternatively, such withholding might reflect some unmeasured confounders that adversely related to infant development.

In this study, a number of pairs who were discordantly breastfed in the first year of life increased with age, with the least discordance being at 1 month old, at which point 98.2% of the sibling pairs were both breastfed. This finding suggests that most mothers breastfeed their children in early infancy but discontinue later at different

**Table 4** Selective analysis of sibling pairs discordant for any or exclusive BF among sibling sample (n=7055)

Developmental delay at 6 months				Developmental delay at 12 months			
No	Age diff., median (range)	cRR (95% CI)	aRR (95% CI)*†	No	Age diff., median (range)	cRR (95% CI)	aRR (95% CI)*†
<b>Any BF</b>							
Until 6 months							
No	36/412 (8.7%)	22 months	1 (reference)	65/414 (15.7%)	21 months	1 (reference)	1 (reference)
Yes	29/412 (7.0%)	(10–38 months)	0.80 (0.49 to 1.28)	55/414 (13.3%)	(10–38 months)	0.81 (0.54 to 1.17)	0.87 (0.55 to 1.34)
Until 12 months							
No	–	–	–	100/699 (14.3%)	22 months	1 (reference)	1 (reference)
Yes	–	–	–	78/699 (11.2%)	(10–38 months)	0.74 (0.54 to 1.01)	<b>0.64 (0.43 to 0.93)</b>
Developmental delay at 6 months				Developmental delay at 12 months			
No	Age diff., median (range)	cRR (95% CI)	aRR (95% CI)*	No	Age diff., median (range)	cRR (95% CI)	aRR (95% CI)*
<b>Exclusive BF</b>							
Until 3 months							
No	60/800 (7.5%)	24 months	1 (reference)	96/755 (12.7%)	24 months	1 (reference)	1 (reference)
Yes	62/800 (7.8%)	(10–38 months)	1.04 (0.72 to 1.47)	97/755 (12.8%)	(10–39 months)	1.01 (0.74 to 1.37)	0.99 (0.69 to 1.38)
Until 6 months							
No	51/657 (7.8%)	24 months	1 (reference)	70/633 (11.1%)	24 months	1 (reference)	1 (reference)
Yes	49/657 (7.5%)	(12–38 months)	0.95 (0.63 to 1.42)	83/633 (13.1%)	(12–38 months)	1.23 (0.88 to 1.69)	1.12 (0.74 to 1.65)

\*Adjusted for sex, gestational age, birth weight, sibling order, maternal smoking and alcohol, and home speech stimulation at 1 month.

†Adjusted further for the introduction of complementary food. Boldface represents statistical significance ( $p < 0.05$ ).

Age diff., age difference between sibling pair; aRR, adjusted risk ratio; cRR, crude risk ratio.



**Table 5** Association between duration of any or exclusive BF and total ASQ score for sibling sample (n=7055)

	Increase of score per BF month	
	Crude B (95% CI)	Adjusted B (95% CI)*†
ASQ age (6 months (0) vs 12 months (1))	<b>12.8 (11.7 to 14.0)</b>	<b>12.9 (11.8 to 14.1)</b>
Duration of any BF (0–6 months)	<b>2.57 (1.38 to 3.75)</b>	<b>2.23 (1.05 to 3.41)</b>
ASQ age × duration of any BF	−0.57 (−1.69 to 0.55)	−0.40 (−1.53 to 0.73)
	Increase of score per BF month	
	Crude B (95% CI)	Adjusted B (95% CI)*
ASQ age (6 months (0) vs 12 months (1))	<b>12.9 (11.7 to 14.0)</b>	<b>12.9 (11.8 to 14.1)</b>
Duration of exclusive BF (0–6 months)	1.00 (−0.15 to 2.15)	1.14 (−0.01 to 2.28)
ASQ age × duration of exclusive BF	0.65 (−0.48 to 1.77)	0.65 (−0.48 to 1.78)

\*Adjusted for sex, gestational age, birth weight, sibling order, maternal smoking and alcohol, and home speech stimulation at 1 month.  
†Adjusted further for the introduction of complementary food. Boldface represents statistical significance (p<0.05).  
ASQ, Ages and Stages Questionnaires; BF, breast feeding.

times for each sibling. Thus, the association between breast feeding and development is likely related more to breast feeding late into year 1 rather than breast feeding early. By contrast, a previous randomised controlled trial<sup>33</sup> in which participants were randomly assigned to a breast-feeding promotion intervention group demonstrated that discordance in breast feeding between an intervention group and control group was larger in early infancy than later in the first year of life. Late discordance such as that in the present study may be common in studies with an observational design. The brain is more sensitive to environmental factors earlier in life; therefore, the discordance later in life may produce less divergent impacts on brain development between siblings. This factor may explain, at least partially, the null results of sibling comparison in previous observational studies.<sup>9 15 16</sup>

### Strengths and limitations

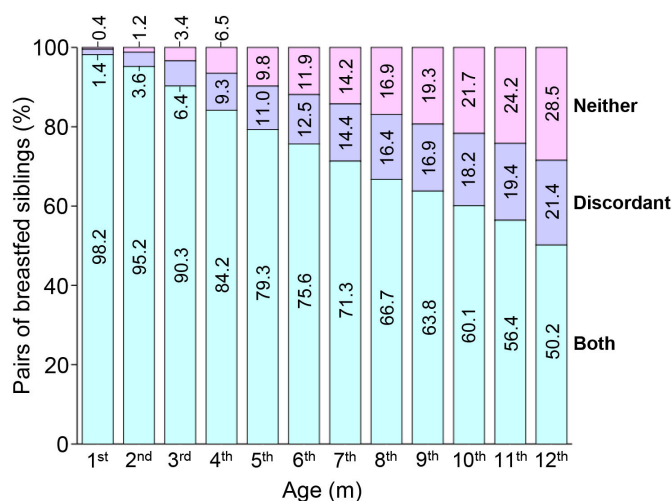
To our knowledge, this study is the largest birth cohort study examining the association between breast feeding and brain

function. We conducted sibling pair analyses with a sufficient number of participants from this large cohort, which enabled us to have strong control over sibling-shared parental and environmental factors. Monthly information on feeding methods was precisely obtained *via* successive questionnaires at 1 month, 6 months and 12 months old, which yielded a much smaller risk of recall bias than that of previous sibling pair studies.<sup>9 15 16</sup>

The current study does have several limitations. The information was largely obtained from self-administered questionnaires. In particular, the identified developmental delay may be somewhat equivocal because it relied solely on responses on the parent-reported screening test of Japanese version of ASQ. Furthermore, even in sibling pair analysis, other confounding factors such as environmental factors may be responsible for the differences because siblings do not share all environmental factors and shared environments may not always be stable.<sup>17</sup> Finally, there were no data on what factors have contributed to cessation of breast feeding. Even within a pair of sibling, there could be difference in socioeconomical status, which might alter parent's rearing behaviours and then affect the child's development. If an infant at potential risk of developmental disorders has less preference to breast feeding, a superficial association can be produced between breast feeding and better development. Indeed, a meta-analysis demonstrated altered feeding habits in children with attention-deficit/hyperactivity disorder.<sup>52</sup> Although our supplementary analyses rather argued against such possibility, the association between breast feeding and a reduced risk of developmental delay in our study still could be explained by such reverse causation.

### CONCLUSION

The present study demonstrated for the first time, by using sibling pair analysis, an association of continuous breast feeding with reduced developmental delay at 1 year. Although causal inference should be cautious in observational studies, both the prospective longitudinal and family-based matched analyses presented may provide a



**Figure 2** Pairs of siblings who were both breastfed, discordantly breastfed or neither breastfed with respect to each month of life (n=3117).

more persuasive argument for public health practitioners and policy-makers to promote breastfeeding continuation, at least during the first year of life. The ongoing JECS cohort may reveal how long the observed beneficial effects will persist in later life.

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**Contributors** MSa conceived, designed the study, analysed the data, interpreted the results and wrote the manuscript. AS, MSh and MO interpreted the results and critically reviewed the manuscript. YSo, MT, YI, RS and YSa critically reviewed the manuscript. SH analysed the data, interpreted the results and critically reviewed the manuscript. KK and SO directed the study and critically reviewed the manuscript.

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**Patient consent for publication** Not required.

**Ethics approval** The JECS protocol was reviewed and approved by the Ministry of Environment's Institutional Review Board for Epidemiological Studies and by the ethics committees of all participating institutions (No.100910001). The ethical approval for this study was an extension of the ethical approval for the JECS protocol. Written informed consent was obtained from all parents.

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**Data availability statement** Data are unsuitable for public deposition due to ethical restrictions and legal framework of Japan. For details, see <http://www.env.go.jp/chemi/ceh/en/>. 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 Programme Office, National Institute for Environmental Studies. No data are available. For details, see <http://www.env.go.jp/chemi/ceh/en/>.

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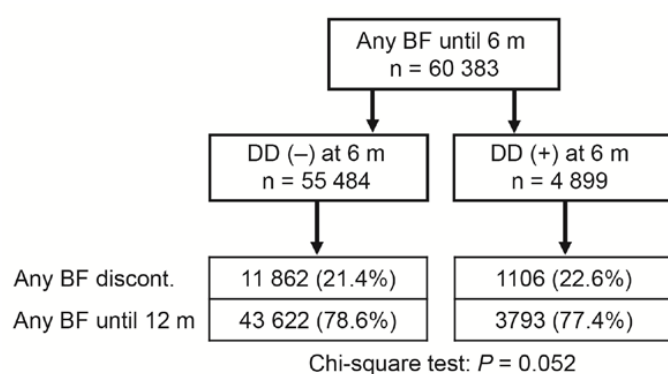
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**Supplementary Information on**

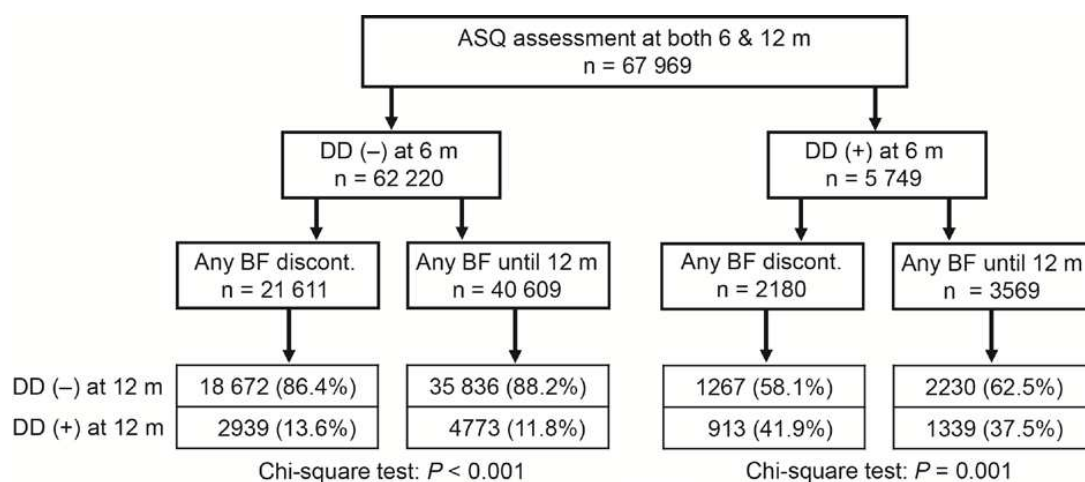
Breastfeeding and infant development in a cohort with sibling pair analysis: the Japan Environment and Children's Study

Masafumi Sanefuji, Ayako Senju, Masayuki Shimono, Masanobu Ogawa, Yuri Sonoda, Michiko Torio, Yuko Ichimiya, Reiko Suga, Yasunari Sakai, Satoshi Honjo, Koichi Kusuhara, Shouichi Ohga, Japan Environment and Children's Study Group

**Supplementary Figures**

**Figure S1. Continuation of any breastfeeding until 12 months in children with vs. without developmental delay at 6 months.**

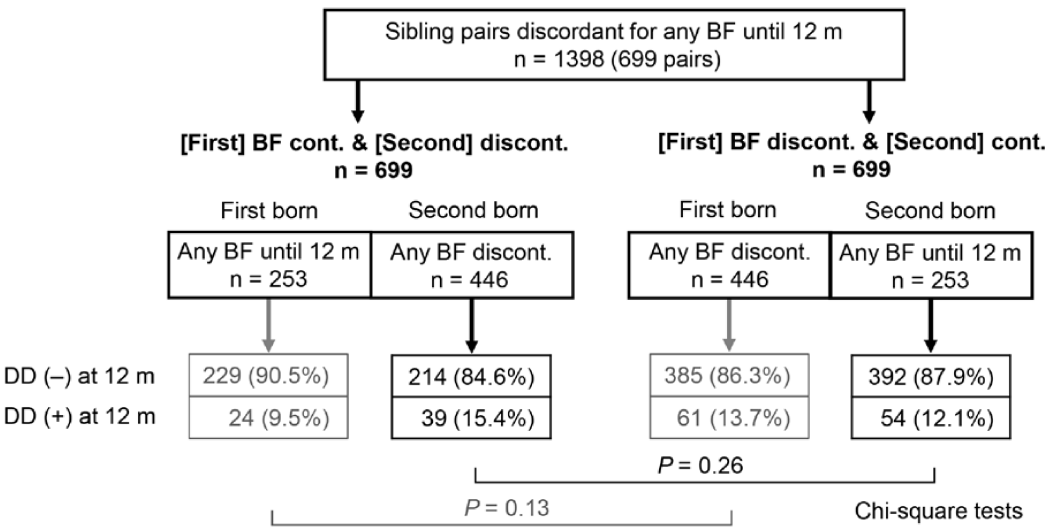
BF, breastfeeding; discontin., discontinuation; DD, developmental delay



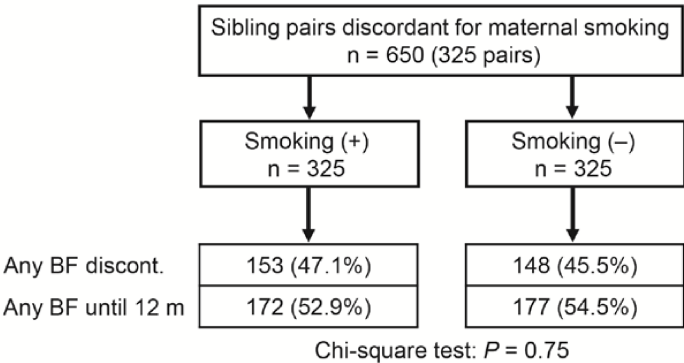
**Figure S2. Developmental prognosis in children who continued any breastfeeding until 12 months vs. discontinued.**

ASQ, Ages and Stages Questionnaires; BF, breastfeeding; discontin., discontinuation; DD, developmental delay.





**Figure S3. The risk of developmental delay of the second born sibling when the first born sibling continued any breastfeeding until 12 months vs. discontinued.**  
BF, breastfeeding; cont., continuation; discont., discontinuation; DD, developmental delay



**Figure S4. Continuation of any breastfeeding until 12 months in siblings whose mothers smoked during pregnancy vs. not.**  
BF, breastfeeding; discont., discontinuation