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Pediatrics

June 2016, VOLUME 137 / ISSUE 6

Breastfeeding and Risk of Kawasaki Disease: A Nationwide Longitudinal Survey in Japan

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Abstract

BACKGROUND AND OBJECTIVES: Kawasaki disease (KD) is the most common cause of childhood-acquired heart disease in developed countries. However, the etiology of KD is not known. Aberrant immune responses are considered to play key roles in disease initiation and breastfeeding can mature immune system in infants. We thus examined the association between breastfeeding and the development of KD.

METHODS: We used a nationwide population-based longitudinal survey ongoing since 2010 and restricted participants to a total of 37 630 children who had data on their feeding during infancy. Infant feeding practice was queried at 6 to 7 months of age, and responses to questions about hospital admission for KD during the period from 6 to 30 months of age were used as outcome. We conducted logistic regression analyses controlling for child and maternal factors with formula feeding without colostrum as our reference group.

RESULTS: A total of 232 hospital admissions were observed. Children who were breastfed exclusively or partially were less likely to be hospitalized for KD compared with those who were formula fed without



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colostrum; odds ratios for hospitalization were 0.26 (95% confidence interval: 0.12–0.55) for exclusive breastfeeding and 0.27 (95% confidence interval: 0.13–0.55) for partial breastfeeding. Although the risk reduction was not statistically significant, feeding colostrum only also provided a protective effect.

CONCLUSIONS: We observed protective effects of breastfeeding on the development of KD during the period from 6 to 30 months of age in a nationwide, population-based, longitudinal survey in Japan, the country in which KD is most common.

- Abbreviations:

CI — confidence interval

KD — Kawasaki disease

OR — odds ratio

What's Known on This Subject:

Kawasaki disease (KD), an acute self-limiting systemic vasculitis, is the most common cause of childhood-acquired heart disease in developed countries, but the etiology of the disease is unknown. Aberrant immune responses are considered to play key roles in disease initiation.

What This Study Adds:

We observed protective effects of breastfeeding on the development of KD during the period from 6 to 30 months of age in Japan, the country in which KD is most common.

Kawasaki disease (KD), an acute self-limiting systemic vasculitis of childhood, is the most common cause of childhood-acquired heart disease in most developed countries.^{1–5} KD mainly occurs in young children⁵; ~88% of cases occurred under 5 years of age during the 2-year period of 2011 through 2012 in Japan.^{6,7} The highest incidence of KD is reported in Japan.⁸ Although the etiology of the disease is unknown,¹ KD may occur in genetically susceptible individuals with an aberrant immune response to some environmental trigger.^{3,4,9}

Breastfeeding, a normative standard for infant feeding and nutrition, is considered to provide protection against infections and contain numerous factors that modulate and promote development of the

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immune system during infancy.¹⁰ Immune maturation may relate to lifelong immunologic disorders¹¹; thus, breastfeeding may be important to the development of the diseases in which the immune system plays a role in disease initiation, including KD. However, as far as we know, no studies have examined the association between breastfeeding and the development of KD.

In the current study, we therefore examined the association in children between breastfeeding and the development of KD from 6 to 30 months of age, using data from a nationwide, population-based, longitudinal survey in Japan, the country in which KD is most common.⁸

Methods

Study Participants

Since 2010, the Japanese Ministry of Health, Labor, and Welfare has conducted an annual survey among newborn infants and their parents, known as the Longitudinal Survey of Babies in the 21st Century.

Questionnaires were sent to all families in Japan who had had an infant (or infants) born between May 10 and 24, 2010, to collect information of infants at 6 months of age. Among the 43 767 questionnaires mailed, 38 554 were completed and returned (response rate of 88.1%).


Follow-up questionnaires were sent to participating families each year (at age 18 months, 30 months). Data from 2010–2012 (ie, the third survey at age 30 months) are currently available from the Ministry of Health, Labor, and Welfare. Birth records from the Japanese vital statistics system are also linked to each child surveyed. Birth record data include birth length; birth weight; gestational age; singleton, twin, or other multiple birth; gender; parity; and parental age at delivery.

In the current study, we used data from the first (age 6 months), second (age 18 months), and third surveys (age 30 months) because information on feeding practices during infancy was queried only in the first survey, and hospital admission for KD during the previous year was queried in the second and third surveys (ie, hospitalizations between the ages of 6 and 18 months and between 18 and 30 months). Children with information missing about feeding practices during infancy ($n = 924$) were excluded, leaving a total of 37 630 participants for the analysis (**Fig 1**). We then excluded 3702 participants who lacked information from the second and third surveys on hospital admission owing to KD.


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W Slusser et al., *Pediatr Rev*, 1997

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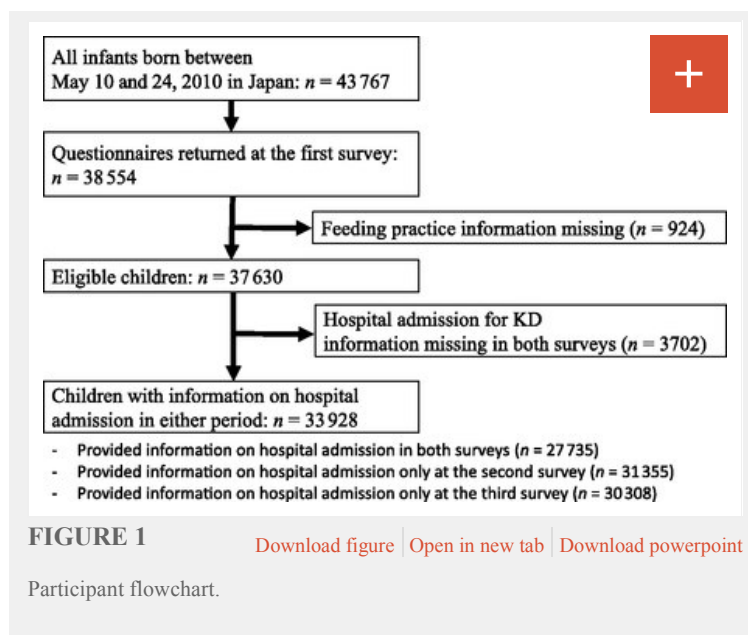
William T. Basco, Jr., MD, Medscape, 2011

Maternity Practices, Breastfeeding Among Adolescent Mothers 

Oluwatosin Olaiya et al., Medscape, 2016

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Among the remaining 33 928 participants, 27 735 had information on hospital admission for KD from both surveys: 31 355 participants only at the second survey, and 30 308 only at the third survey.



Infant Feeding Practices

The first survey at 6 months of age included questions on breastfeeding practices (infant was breastfed, only fed colostrum, or never breastfed) and formula feeding practices (infant was fed formula or never fed formula). Using information on both breastfeeding and formula feeding practices, we established the categories of “formula feeding without colostrum (and never breastfed),” “formula feeding (only) with colostrum,” “partial breastfeeding,” and “exclusive breastfeeding.” We used category as a main exposure of interest.

Additionally, the duration (months) of breastfeeding and formula feeding was queried. We divided the category of “partial breastfeeding” based on breastfeeding duration (breastfeeding for 1–2 months, 3–5 months, or 6–7 months) in an additional analysis. Although the first survey was conducted at 6 months of age, children breastfed up to age 7 months were included owing to the timing of the survey.

Hospital Admission for KD

Hospital admission for KD during the previous 1 year was queried at the second and third surveys (ie, hospitalizations between the ages of 6 and 18 months and between 18 and 30 months). We used hospital admission at least once from age 6 to 30 months as the outcome of interest. We targeted KD incidence between age 6 and 30 months, owing to a high

incidence of the disease during this period⁷ and the availability of data. The diagnostic criteria for KD has not changed in Japan since 2002.^{12,13}

Statistical Analyses

To evaluate the impact of loss to follow-up (**Fig 1**), we first compared baseline characteristics between children with information on breastfeeding (eligible children), children who were included in the analysis, and children who lacked information on hospital admission owing to KD at both surveys. We then compared baseline characteristics between the participants who were admitted for KD and those who were not.

We conducted logistic regression analyses to evaluate the relationships among the 4 infant feeding practice categories (formula feeding without colostrum, formula feeding with colostrum, partial breastfeeding, and exclusive breastfeeding) and hospital admission from age 6 to 30 months. We first estimated a crude odds ratio (OR) and a 95% confidence interval (CI) for the main outcome (model 1). We then examined the OR and 95% CI after controlling for child factors (model 2) and both child and maternal factors, in addition to residential information (model 3). Throughout the analyses, we used the formula feeding without colostrum category as our reference group.

Child factors included gender (dichotomous), singleton birth or not (dichotomous), term or preterm birth (<37 weeks' gestation; dichotomous), parity (0 and >1 birth; dichotomous). Maternal factors included maternal age at delivery (<30, 30–34, ≥35 years; categorical), maternal smoking habits (dichotomous), and maternal educational level (categorical). Residential information included the residential area where the participant was born (ward, city, and town or village; categorical). The child's gender, singleton birth or not, gestational age, parity, and maternal age at delivery were listed in the birth record. Maternal smoking status was ascertained at the first survey. Maternal educational level was used an indicator of socioeconomic status and obtained from the second survey (age 18 months). We reclassified the original 8 education categories into 3, as follows: university (4 years) or higher, junior college (2 years) or vocational school, and high school or less. Residential information was obtained from the national census conducted in 2010. We selected these potential confounders based on previous studies or previous knowledge of the association between breastfeeding and some allergic diseases.^{14–16} We excluded cases with

missing data and conducted our analyses with complete cases.

In further analyses, we divided the category “partial breastfeeding” based on breastfeeding duration (breastfeeding for 1–2 months, 3–5 months, or 6–7 months) and used the following categories: formula feeding without colostrum, formula feeding with colostrum, partial breastfeeding for 1 to 2 months, partial breastfeeding for 3 to 5 months, partial breastfeeding for 6 to 7 months, and exclusive breastfeeding to 6 to 7 months of age. We then examined the association between infant feeding practices and hospital admission for KD.

Because of small numbers in the categories “formula feeding without colostrum” and “formula feeding with colostrum,” we also combined these categories into 1 category designated “formula feeding” and repeated the analyses.

Furthermore, we stratified by gender and examined the association between infant feeding practices and hospital admission from age 6 to 30 months.

In the sensitivity analyses, we further adjusted for the following variables in addition to the same set of covariates as in model 3 because of possible potential confounding¹⁷: paternal annual income during the year the child was born as another indicator of socioeconomic status, obtained at the second survey (as a continuous variable), and day-care attendance. Persons who took care of the children during the daytime were queried at the first survey; children cared for by preschool teachers were classified as attending day care. Furthermore, most participants were considered to be of Japanese origin. We restricted participants to those whose father and mother are both Japanese and repeated the analyses because of high occurrence of KD among children of Japanese origin.¹⁸

In the additional analysis, to explore the possible mechanism between breastfeeding and the development of KD, we conducted logistic regression analyses to evaluate the relationships between breastfeeding and hospital admission for any cause excluding injuries, burn injuries, and fractures from 6 to 30 months of age. We adjusted for the same set of potential confounders.

All CIs were calculated at the 95% level. Stata statistical software Release 13 (StataCorp LP, College Station, TX) was used for all

analyses. This study was approved by the Institutional Review Board at Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences (No. 1506-073).

Results

Among eligible children, >34% were in the category of exclusive breastfeeding (**Table 1**). Children who lacked information on hospital admission for KD at the second and third surveys were more likely to be multiple births, preterm births, formula fed, and to have young mothers, mothers who smoked, mothers with lower educational level, and mothers who lived in rural areas (towns or villages) compared with children included in the analyses.

TABLE 1

[View inline](#)

Demographic Characteristics of Eligible Children With or Without KD Hospital Admission Data ($n = 37\,630$)

We show the baseline characteristics between the participants who were admitted for KD during the period of 6 to 30 months of age and those who were not in **Table 2**. Among 27 735 participants, a total of 232 admissions for KD were observed, that is, the incidence proportion of 0.84% for 2 years. The participants who were admitted tended to have more siblings, been formula fed, and older mothers compared with those who were not admitted. The same information among participants with information on hospital admission either at the second or third survey is shown in **Supplemental Tables 5 and 6**.

TABLE 2

[View inline](#)

Demographic Characteristics of Eligible Children With Data of KD Hospital Admission From 6 to 30 Months of Age ($n = 27\,735$)

Children who were breastfed were less likely to be hospitalized for KD from 6 to 30 months of age (**Table 3**). Even after adjusting for all covariates (model 3), protective associations remained for exclusive and partial breastfeeding; ORs for hospitalization were 0.26 (95% CI: 0.12–0.55) for exclusive breastfeeding and 0.27 (95% CI: 0.13–0.55) for partial breastfeeding. Although not statistically significant, a protective association was observed even for the category of formula feeding with colostrum: OR 0.39 (95% CI: 0.14–1.09). When we divided the

category of “partial breastfeeding” based on breastfeeding duration, the ORs reached a plateau at a point estimate of around 0.26 for the category of breastfeeding for 3 to 5 months.

TABLE 3[View inline](#)

Breastfeeding and KD Hospital Admission From 6 to 30 Month of Age

Even after we combined the categories of “formula feeding without colostrum” and “formula feeding with colostrum” into 1 category of “formula feeding,” we obtained similar findings. Protective associations remained for exclusive and partial breastfeeding ([Table 4](#)).

TABLE 4[View inline](#)

Associations Between Breastfeeding Duration and KD Hospital Admission From 7 to 30 Months of Age, Using the Category of Formula Feeding (Both With and Without Colostrum) as a Reference

When stratified by sex, protective associations between breastfeeding and the development of KD did not change substantially between male and female participants; however, exclusive breastfeeding was more protective among male children ([Supplemental Table 7](#)).

In the sensitivity analyses, even after further adjusting for paternal income or day-care attendance, the main findings did not change substantially (data not shown). Among the 33 928 eligible children, the parents of 32 783 children (96.7%) were both Japanese. The results did not change even after restricting the analysis to these children, and ORs for hospitalization for KD were 0.27 (95% CI: 0.12–0.59) for exclusive breastfeeding and 0.27 (95% CI: 0.13–0.60) for partial breastfeeding, compared with the category of formula feeding without colostrum.

When we examined the relationships between breastfeeding and hospital admission for any cause in the additional analysis, exclusive breastfeeding and partial breastfeeding for longer months were protective for the risk of hospital admission ([Supplemental Table 8](#)).

Discussion

In the current study, we examined the association in children between breastfeeding and the development of KD from 6 to 30 months of age, using data from a nationwide, population-based, longitudinal survey in

Japan. We then observed that children who were breastfed exclusively or partially were less likely to be hospitalized for KD compared with those who were formula fed. Although the risk reduction was not statistically significant, feeding colostrum only also provided a protective effect. The protective associations did not change even after adjusting for an extensive list of potential confounders or in the sensitivity analyses. This is the first study examining the association between breastfeeding and development of KD.

We consider there to be at least 2 reasons for the protective effects of breastfeeding on development of KD. First, the mother may provide her own immunologic memory (ie, antimicrobial factors such as secretory immunoglobulin A, oligosaccharides, lactoferrin, nucleotides) to her infant via breast milk,^{19,20} which may prevent the infant from contracting infections that trigger abnormal immune responses. Second, breastfeeding may support the maturation of immune system (ie, programming of the system),¹⁷ which may limit potential damage from an uncontrolled inflammatory response.¹⁹ Breast milk contains numerous factors, including allergens, which modulate and promote immune system development.^{10,11,21} Moreover, breast milk is considered to mature the immune system through the establishment of intestinal microbiota.^{10,11} We observed protective effects of breastfeeding on the risk of hospital admission excluding injuries, burn injuries, and fractures, which may indicate that breastfeeding has a generic effect rather than a specific effect on KD. The protective effects of breastfeeding on KD may be related to broad antiinfective functions of breast milk. In addition, a previous US cohort study suggested an increased risk of hospitalization for any cause among children who subsequently developed KD.⁹ Although it is impossible to draw a definite conclusion as to the underlying mechanism, these observations may support the preceding theories.

Interestingly, both exclusive and partial breastfeeding had beneficial effects on the development of KD. In the category of partial breastfeeding for 3 to 5 months, the magnitude of these effects reached a plateau, which means that breastfeeding for at least 3 to 5 months, even together with formula feeding, may provide some benefits. Moreover, although not statistically significant, feeding colostrum only also provided a protective effect. Colostrum, the mammary secretion during the first few days postpartum, also contains immunoglobulins and facilitates establishment of the intestinal microbiota,²² which may

provide some benefits in children.

The strength of the current study is that we had a nationally representative sample, and roughly one-twentieth of the children born in 2010 were included in this survey. We thus had a relatively large number of KD cases, which allowed us to examine the dose-response relationship between breastfeeding and development of KD. In addition, the very high response rate at baseline (88.1%) strengthens the validity of our findings. The type and duration of feeding practices should be accurate because information on feeding was collected at the first survey, when children were 6 to 7 months old. However, we could not evaluate the effect of breastfeeding that continued beyond 6 to 7 months of age.

We have relatively smaller participants in the categories of “formula feeding without colostrum” and “formula feeding with colostrum” to the breastfed group, which may explain relatively wide 95% CIs. However, even after we combined the categories of “formula feeding without colostrum” and “formula feeding with colostrum” into 1 category (“formula feeding”), we obtained the similar findings ([Table 4](#)).

We cannot exclude the possibility of misclassification of hospital admission for KD because of the subjective nature of the questions used to assess this outcome. We could not directly confirm the admission by direct communication with the hospitals because the data set obtained from the Ministry was anonymized data that cannot be linked to any individual. However, the diagnostic criteria for KD in Japan has not changed since 2002^{12,13}; therefore, the diagnostic method used by physicians would be similar throughout the country during the study period. Japan has a universal health insurance system that covers all of its citizens, so most patients with KD would have seen their physicians and then been hospitalized. Indeed, the incidence proportions of hospitalization for KD from 6 to 18 months (0.51%) and from 18 to 30 months (0.37%) ([Supplemental Tables 5 and 6](#)) are close to or slightly higher than the age-specific incidences reported by the Nationwide Survey for KD in Japan: 0.33% to 0.41% from 6 to 17 months and 0.24% to 0.30% from 18 to 29 months of age.^{6,7} The lower proportions in the Nationwide Survey may be due to its incomplete coverage. Even if there remain some misclassifications (eg, incomplete cases), they would be nondifferential, moving effect estimates toward the null.²³

Loss to follow-up might be a concern. Because loss was more common

among higher risk groups such as children who were formula fed and mothers who were smokers (**Table 1**), we may be underestimating the protective effects of breastfeeding on the development of KD.

There is the possibility of a biased association owing to residual confounding factors. However, we extensively adjusted for potential confounders in the main analyses. Furthermore, we examined other potential confounders (ie, paternal income and day-care attendance) in the sensitivity analyses, and the findings did not change substantially. Although familial susceptibility to KD has been reported,²⁴ we had no information on parental KD history. However, the possible number of parents with a past history of KD is considered insufficient to affect the present findings. Therefore, it is unlikely that our findings can be fully explained by residual confounding.

Finally, we only included the admissions for KD from age 6 to 30 months of age because of data availability, which may limit the generalizability of the finding. However, ~50% of the KD cases occurred during this age-group during the 2-year period of 2011 to 2012 in Japan.^{6,7}

Conclusions

We observed protective effects of breastfeeding on the development of KD from age 6 to 30 months in children using data of a nationwide longitudinal survey in Japan, where KD is most prevalent. Given the accumulated evidence on its short- and long-term protective advantages for other diseases,²⁵ breastfeeding should be recommended until such time as further confirmation on the association between breastfeeding and KD is obtained.

Acknowledgment

The authors thank Saori Irie for her help in data collection.

Footnotes

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- **FINANCIAL DISCLOSURE:** The authors have indicated they have no financial relationships relevant to this article to disclose.
- **FUNDING:** Supported in part by a grant for Strategies for Efficient Operation of the University (2007030201).
- **POTENTIAL CONFLICT OF INTEREST:** The authors have indicated they have no potential conflicts of interest to disclose.

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