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# The Lack of an Association of Breastfeeding with the Development of Childhood Intussusception: A Nationwide Birth Cohort Survey in Japan

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## Abstract

**Background:** This study investigated the association between feeding practices and the development of childhood intussusception.

**Materials and Methods:** We conducted secondary data analyses using the Longitudinal Survey of Newborns in the 21st Century in Japan. We performed multivariable logistic regression analyses to examine the association between feeding practice and intussusception development in children aged between 6 and 18 months. We used the following variables as potential confounders: gender, gestational age, birth weight, singleton or multiple births, parity, maternal age at delivery, maternal smoking status, and paternal smoking status. Furthermore, we performed multivariable logistic regression analyses to examine the association between breastfeeding duration and intussusception development.

**Results:** In total, 31,802 children were analyzed in this study. The annual incidence of intussusception was 1.6 cases per 1,000 children aged between 6 and 18 months. No significant association was found between exclusive breastfeeding and the development of intussusception, compared with exclusive formula feeding (odds ratio, 1.64; 95% confidence interval, 0.32–30.0). Furthermore, no significant association was observed between breastfeeding duration and intussusception development.

**Conclusions:** Our findings demonstrated no association between breastfeeding and the development of childhood intussusception.

**Keywords:** cohort study, feeding practice, incidence, risk factor

## Introduction

Intussusception is the most common cause of intestinal obstruction in children under 2 years of age.<sup>1</sup> The annual incidence of hospitalization for intussusception in children under the age of 5 years has been estimated to be between 8 and 52 per 100,000 children worldwide.<sup>2</sup> This serious medical condition occurs when one part of the intestine slides into another part, leading to venous congestion and edema of the bowel wall, which can lead to bowel infarction or perforation. In severe cases, the condition can be fatal. Although lymph node enlargement resulting from intestinal infection is believed to cause idiopathic intussusception in some cases, no etiology has been identified in >90% of cases.<sup>1,3</sup>

Exclusive breastfeeding is recommended until the age of 6 months, followed by continued breastfeeding with complementary foods until the age of 2 years or older.<sup>4,5</sup> Breast milk contains abundant active immune factors that help establish the mature immune system of infants.<sup>6</sup> Breastfeeding has been shown to reduce the risk of infectious and non-infectious diseases and maintain long-term child health.<sup>4,7</sup> Breastfeeding has been associated with a potential reduction in the incidence of gastrointestinal infections.<sup>8,9</sup>

Several case-control studies have examined whether breastfeeding is a protective or risk factor for the development of intussusception; however, these studies have inconclusive results.<sup>3,10–14</sup> We hypothesized that breast and formula milk would have different effects on the gastrointestinal tract and

intestinal lymph nodes, leading to different risks of the development of intussusception. Therefore, we investigated the association between feeding practices and intussusception development using data from a Japanese national birth cohort study. Furthermore, we compared the risk of intussusception according to breastfeeding duration.

## Materials and Methods

### *Data source and participants*

We conducted secondary data analyses using the Longitudinal Survey of Newborns in the 21st Century (2010 Cohort)—a birth cohort study conducted in Japan by the Ministry of Health, Labour and Welfare. This survey aimed to collect basic data essential for the formulation and implementation of policies to address low fertility rates and improve the health and well-being of children in Japan.<sup>15</sup> This cohort included all babies born in Japan between May 10, 2010, and May 24, 2010, based on birth records from national vital statistics. Questionnaires for the first survey were mailed to all participating families when their infants were aged 6 months ( $N = 43,767$ ). Returning the questionnaires was considered consent to participate in the study. The response rate for the first survey was 88.1% ( $N = 38,554$ ). Follow-up questionnaires were sent annually to eligible children. We used data from three surveys: the first (at the age of 6 months), second (at the age of 18 months), and third (at the age of 30 months) surveys. The response rates for the second and third surveys were 86.6% and 86.2%, respectively. We excluded participants with missing information on feeding practice in the first survey and hospital admission for intussusception in the second survey. This study was approved by the Ethical Committee of the International University of Health and Welfare (No. 23-Io-29). Furthermore, this study was conducted according to the Strengthening the Reporting of Observational Studies in Epidemiology Statement.<sup>16</sup>

### *Feeding practice*

The first survey collected information on feeding practices. The survey included the following questions: “Did you breastfeed your child? (i) breastfed, (ii) never breastfed, or (iii) only colostrum”; “If (i) breastfed, for how many months?” and “Did you feed your child formula milk? (i) formula milk or (ii) never formula milk?”; “If (i) formula fed, for how many months?” Based on previous studies,<sup>17,18</sup> we combined “never breastfed” and “colostrum only” into a category of “exclusive formula feeding.” Subsequently, we categorized feeding practice into three groups: “exclusive breastfeeding,” “partial breastfeeding,” and “exclusive formula feeding.” We further categorized the duration of breastfeeding and formula feeding into four groups: “<1 months,” “1–2 months,” “3–5 months,” and “6–7 months.”

### *Hospital admission for intussusception*

The survey on hospitalization due to intussusception was included as a survey item in the second and third surveys but not in the first survey. The following question was asked to the caregiver: “During the previous 1 year, has your child been hospitalized for the treatment of any of the following illnesses or injuries?” If the respondent checked “intussusception” from the multiple options, which included various

diseases and injuries, the participants were considered to have been hospitalized for intussusception.

### *Covariates*

Based on previous studies,<sup>3,10–14,19</sup> we selected the following variables as covariates: gender (male or female), singleton or multiple births, gestational age (term or preterm), parity at 6 months of age (0 or  $\geq 1$ ), birth weight (normal [ $\geq 2,500$  g] or low birth weight [ $< 2,500$  g]), maternal age at birth ( $< 20$ , 20–34, or  $\geq 35$  years of age), maternal smoking status at 6 months of age (smoking or no smoking), and paternal smoking status at 6 months of age (smoking or no smoking).

### *Statistical analysis*

We first compared baseline characteristics between eligible and analyzed children. For the analyzed children, we compared baseline characteristics between those with and without hospital admission for intussusception.

We performed multivariable logistic regression analyses using complete cases without missing values to investigate the association between feeding practices (reference category, “exclusive formula feeding”) and hospital admission for intussusception between 6 and 18 months of age or between 6 and 30 months of age. Moreover, we performed multivariable logistic regression analysis to examine the association between breastfeeding duration (reference category, “<1 month”) and hospital admission for intussusception between 6 and 18 months of age. We used the following variables as potential confounders: gender, singleton or multiple births, gestational age, parity, birth weight, maternal age at birth, maternal smoking status, and paternal smoking status. All analyses were performed using R (version 4.3.2; R Core Team 2023).

## Results

Of the 38,554 eligible children, 31,802 were analyzed in this study (Supplementary Fig. S1). No differences in baseline characteristics were observed between the eligible and analyzed children (Supplementary Table S1). Table 1 shows the baseline characteristics of the analyzed children according to their intussusception status. The incidence of intussusception in children between 6 and 18 months of age and in those between 6 and 30 months of age was 1.6 cases per 1,000 children (50/31,802) and 2.0 cases per 1,000 children (57/28,104), respectively. The group with hospital admission for intussusception tended to have a higher percentage of male, parity, and mothers who were smokers than the group without hospital admission for intussusception.

Table 2 shows the odds ratios (ORs) and 95% confidence intervals (CIs) for the association between feeding practices and hospital admission for intussusception. No significant association was found between exclusive breastfeeding and hospital admission for intussusception compared with exclusive formula feeding (OR, 1.64; 95% CI, 0.32–30.0 for 6–18 months of age and OR, 1.59; 95% CI, 0.32–28.8 for 6–30 months of age). Furthermore, the association between partial breastfeeding and formula feeding was not significant. As shown in Table 3, no significant association was observed between breastfeeding duration and hospital admission for intussusception.

TABLE 1. CHARACTERISTICS OF THE STUDY PARTICIPANTS ACCORDING TO THEIR INTUSSUSCEPTION STATUS

|                                            | 6–18 months of age (N = 31,802)    |                                           | 6–30 months of age (N = 28,104)    |                                           |
|--------------------------------------------|------------------------------------|-------------------------------------------|------------------------------------|-------------------------------------------|
|                                            | Intussusception<br>(N = 50), n (%) | No intussusception<br>(N = 31,752), n (%) | Intussusception<br>(N = 57), n (%) | No intussusception<br>(N = 28,047), n (%) |
| Gender                                     |                                    |                                           |                                    |                                           |
| Male                                       | 29 (58)                            | 16,383 (52)                               | 38 (67)                            | 14,493 (52)                               |
| Female                                     | 21 (42)                            | 15,369 (48)                               | 19 (33)                            | 13,554 (48)                               |
| Singleton or multiple births               |                                    |                                           |                                    |                                           |
| Singleton                                  | 49 (98)                            | 31,176 (98)                               | 56 (98)                            | 27,547 (98)                               |
| Multiple                                   | 1 (2)                              | 576 (2)                                   | 1 (2)                              | 500 (2)                                   |
| Gestational age                            |                                    |                                           |                                    |                                           |
| Term birth ( $\geq 37$ weeks)              | 48 (96)                            | 30,074 (95)                               | 54 (95)                            | 26,598 (95)                               |
| Preterm birth ( $< 37$ weeks)              | 2 (4)                              | 1,672 (5)                                 | 3 (5)                              | 1,444 (5)                                 |
| Missing                                    | 0                                  | 6                                         | 0                                  | 5                                         |
| Parity at 6 months of age                  |                                    |                                           |                                    |                                           |
| 0                                          | 19 (39)                            | 14,899 (47)                               | 21 (38)                            | 13,142 (47)                               |
| $\geq 1$                                   | 30 (61)                            | 16,537 (53)                               | 35 (63)                            | 14,637 (53)                               |
| Missing                                    | 1                                  | 316                                       | 1                                  | 268                                       |
| Birth weight                               |                                    |                                           |                                    |                                           |
| Normal weight ( $\geq 2,500$ g)            | 45 (90)                            | 28,789 (91)                               | 53 (93)                            | 25,439 (91)                               |
| Low birth weight ( $< 2,500$ g)            | 5 (10)                             | 2,958 (9)                                 | 4 (7)                              | 2,604 (9)                                 |
| Missing                                    | 0                                  | 5                                         | 0                                  | 4                                         |
| Maternal age at birth                      |                                    |                                           |                                    |                                           |
| $< 20$ years of age                        | 1 (2)                              | 174 (1)                                   | 1 (2)                              | 116 (0.4)                                 |
| 20–34 years of age                         | 38 (76)                            | 23,556 (74)                               | 44 (77)                            | 20,631 (74)                               |
| $\geq 35$ years of age                     | 11 (22)                            | 8,022 (25)                                | 12 (21)                            | 7,300 (26)                                |
| Maternal smoking status at 6 months of age |                                    |                                           |                                    |                                           |
| 0                                          | 44 (88)                            | 29,906 (94)                               | 52 (91)                            | 26,592 (95)                               |
| $\geq 1$                                   | 6 (12)                             | 1,774 (6)                                 | 5 (9)                              | 1,399 (5)                                 |
| Missing                                    | 0                                  | 72                                        | 0                                  | 56                                        |
| Paternal smoking status at 6 months of age |                                    |                                           |                                    |                                           |
| 0                                          | 29 (59)                            | 18,730 (60)                               | 35 (64)                            | 16,942 (61)                               |
| $\geq 1$                                   | 20 (41)                            | 12,414 (40)                               | 20 (36)                            | 10,633 (39)                               |
| Missing                                    | 1                                  | 608                                       | 2                                  | 472                                       |
| Feeding practice                           |                                    |                                           |                                    |                                           |
| Exclusive breastfeeding                    | 16 (32)                            | 10,946 (34)                               | 19 (33)                            | 9,774 (35)                                |
| Partial breastfeeding                      | 33 (66)                            | 19,795 (62)                               | 37 (65)                            | 17,429 (62)                               |
| Exclusive formula feeding                  | 1 (2)                              | 1,011 (3)                                 | 1 (2)                              | 844 (3)                                   |
| Breastfeeding duration                     |                                    |                                           |                                    |                                           |
| $< 1$ month                                | 1 (2)                              | 1,011 (3)                                 | 1 (2)                              | 844 (3)                                   |
| 1–2 months                                 | 9 (18)                             | 2,584 (8)                                 | 9 (16)                             | 2,208 (8)                                 |
| 3–5 months                                 | 7 (14)                             | 3,169 (10)                                | 8 (14)                             | 2,703 (10)                                |
| 6–7 months                                 | 33 (66)                            | 24,541 (78)                               | 39 (68)                            | 21,923 (79)                               |
| Missing                                    | 0                                  | 447                                       | 0                                  | 369                                       |
| Formula feeding duration                   |                                    |                                           |                                    |                                           |
| $< 1$ month                                | 16 (33)                            | 10,946 (35)                               | 19 (34)                            | 9,774 (35)                                |
| 1–2 months                                 | 5 (10)                             | 5,963 (19)                                | 9 (16)                             | 5,356 (19)                                |
| 3–5 months                                 | 4 (8)                              | 3,278 (11)                                | 5 (9)                              | 2,842 (10)                                |
| 6–7 months                                 | 24 (49)                            | 10,948 (35)                               | 23 (41)                            | 9,586 (35)                                |
| Missing                                    | 1                                  | 617                                       | 1                                  | 489                                       |

## Discussion

In this study, we investigated whether breastfeeding is a protective or risk factor for the development of childhood intussusception in Japanese children. However, there was little evidence of an association between feeding practices and intussusception development. The point estimate for exclusive breastfeeding with the development of intussusception was  $> 1.0$ ; however, breastfeeding was not a likely risk factor because no dose-dependent relationship was

observed between breastfeeding duration and intussusception development. The results of this study provide little evidence to suggest changes in the currently recommended infant feeding practices. Breastfeeding remains the recommended method of infant feeding because of its many health benefits.<sup>4,5</sup>

As shown in Table 4, the association between infant feeding practices and intussusception development has been controversial.<sup>3,10–14</sup> Three studies<sup>10,11,14</sup> have reported that

TABLE 2. ASSOCIATION BETWEEN FEEDING PRACTICES AND INTUSSUSCEPTION STATUS

|                           | 6–18 months of age |                  | 6–30 months of age |                  |
|---------------------------|--------------------|------------------|--------------------|------------------|
|                           | No. of cases (‰)   | aOR (95% CI)     | No. of cases (‰)   | aOR (95% CI)     |
| Feeding practice          |                    |                  |                    |                  |
| Exclusive breastfeeding   | 16 (1.5)           | 1.64 (0.32–30.0) | 19 (1.9)           | 1.59 (0.32–28.8) |
| Partial breastfeeding     | 33 (1.7)           | 1.83 (0.38–32.7) | 37 (2.1)           | 1.76 (0.37–31.4) |
| Exclusive formula feeding | 1 (1.0)            | 1 (reference)    | 1 (1.2)            | 1 (reference)    |

aOR, adjusted Odds Ratio; CI, confidence interval; No., number.

breastfeeding was a protective factor for intussusception development, whereas other studies have reported a risk factor or no association. Our results were consistent with those of the latter group of studies. Three studies involving children who received the rotavirus vaccine have shown the protective effect of breastfeeding on the development of intussusception. In 2006, two live-attenuated oral rotavirus vaccines were licensed: a monovalent rotavirus vaccine (Rotarix<sup>®</sup>) and a pentavalent rotavirus vaccine (RotaTeq<sup>®</sup>). In 2009, the World Health Organization recommended that rotavirus vaccination programs be implemented worldwide. Further research on the interaction between feeding practice and rotavirus vaccination and the development of intussusception may be required.

When interpreting the results, note that this study was conducted in Japanese children born during a period when the polio vaccine was administered orally and the rotavirus vaccine was not yet licensed. In September 2012, the polio vaccine was replaced by an inactivated vaccine administered by subcutaneous injection instead of the traditional oral live vaccine. Voluntary rotavirus vaccination programs began in Japan with the approval of the monovalent rotavirus vaccine (Rotarix) in November 2011, followed by the pentavalent rotavirus vaccine (RotaTeq) in July 2012.

We hypothesized that breast and formula milk would have different effects on the intestinal lymph nodes and different risks for intussusception development. Several studies have shown that recent intestinal infections are a risk factor for intussusception development.<sup>10,11,20</sup> Although the etiology of intussusception remains incompletely elucidated, hyperplasia of intestinal-associated lymphoid tissue is hypothesized to be a

significant contributor to its pathogenesis. Both breast and formula milk have been found to affect intestinal immunity. Breast milk has been shown to affect the gut microbiota of infants.<sup>21</sup> Breast milk contains many immune components, such as secretory immunoglobulin A, and breastfeeding has been shown to reduce the risk of intestinal infections and allergic diseases. However, this study provided little evidence for a protective or even a risk effect of breastfeeding on intussusception development.<sup>8,9,21</sup>

The strengths of this study include a large sample size and a nationally representative birth cohort design.<sup>15</sup> However, this study has several limitations. First, there was a potential for outcome misclassification of the diagnosis of intussusception, considering that it was based on self-reported questionnaires about the history of hospital admission for intussusception. If there is potential for outcome misclassification, nondifferential misclassification of diseases typically biases the estimated associations toward the null.<sup>22</sup> However, because the outcomes of this study were limited to cases of intussusception requiring inpatient treatment, it is unlikely that such misclassification would occur in Japan. The prevalence of intussusception estimated in this study is similar to that reported in previous studies<sup>23,24</sup> in Japan. Second, the onset of intussusception before the age of 6 months was not included. In the Western Pacific region, the median age of hospital admission for intussusception was 70 weeks (interquartile range, 42–126 weeks), and the median proportion of cases with intussusception onset by the age of 15 weeks was 2.4%.<sup>2</sup> This study could be considered to include most childhood intussusception cases. Third, feeding practices after the age of 6 months were not investigated. However, the influence of breast or formula milk feeding may be small because this is the time when solid foods are introduced. A previous study<sup>13</sup> showed that formula feeding is positively associated with intussusception development before the introduction of solid foods, although no significant difference was observed between breastfeeding and formula feeding with regard to intussusception development after the introduction of solid foods. Future research on the association between feeding practices and intussusception development may be required, considering the timing of the introduction and content of solid foods.

## Conclusions

Our study found little evidence of an association between breastfeeding and the development of childhood intussusception. Although we could not conclude that breastfeeding is a protective or risk factor for intussusception development, we

TABLE 3. ASSOCIATION BETWEEN BREASTFEEDING OR FORMULA FEEDING DURATION AND INTUSSUSCEPTION STATUS

|                          | No. of cases (‰) | aOR (95% CI)     |
|--------------------------|------------------|------------------|
| Breastfeeding duration   |                  |                  |
| <1 month                 | 1 (1.0)          | 1 (reference)    |
| 1–2 months               | 9 (3.5)          | 3.37 (0.63–62.3) |
| 3–5 months               | 7 (2.2)          | 1.98 (0.34–37.5) |
| 6–7 months               | 33 (1.3)         | 1.42 (0.30–25.5) |
| Formula feeding duration |                  |                  |
| <1 month                 | 16 (1.5)         | 1 (reference)    |
| 1–2 months               | 5 (0.8)          | 0.61 (0.20–1.56) |
| 3–5 months               | 4 (1.2)          | 0.84 (0.24–2.31) |
| 6–7 months               | 24 (2.2)         | 1.49 (0.77–2.93) |

aOR, adjusted Odds Ratio; CI, confidence interval; No., number.

TABLE 4. LIST OF PREVIOUS STUDIES ON THE ASSOCIATION BETWEEN BREASTFEEDING AND INTUSSUSCEPTION DEVELOPMENT

| <i>Author (year)</i>          | <i>Country</i> | <i>Study period</i>           | <i>Study design</i> | <i>OR (95% CI)</i> | <i>Effect of breastfeeding</i> | <i>Breastfeeding versus reference</i>                         | <i>Covariate</i>                                                                                                                                                                      |
|-------------------------------|----------------|-------------------------------|---------------------|--------------------|--------------------------------|---------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Pisacane (1993) <sup>12</sup> | Italy          | 1989–1990                     | Case–control        | 6.0 (1.8–20.4)     | Risk factor                    | Exclusive breastfeeding versus no breastfeeding               | Matched by gender, age, and hospitalization during the same period in the same surgical ward<br>Stratified by gender, social class, birth order, birth weight, and household crowding |
| Bines (2006) <sup>3</sup>     | Australia      | 2002–2004                     | Case–control        | 0.62 (0.06–3.3)    | No association                 | Exclusive breastfeeding versus no exclusive breastfeeding     | Matched by age, gender, and region                                                                                                                                                    |
|                               | Vietnam        | 2002–2003                     | Case–control        | 0.65 (0.35–1.2)    | No association                 | Exclusive breastfeeding versus no exclusive breastfeeding     | Matched by age, gender, and region                                                                                                                                                    |
| Johnson (2010) <sup>13</sup>  | United States  | 1998–1999                     | Case–control        | 0.83 (0.63–1.11)   | No association                 | Breast milk for most feedings versus cow's milk-based formula | Matched by age and hospital of birth                                                                                                                                                  |
|                               |                | Subgroup, >5 weeks before ISF |                     | 1.16 (0.67–2.0)    | No association                 | Breast milk for most feedings versus cow's milk-based formula | Matched by age and hospital of birth<br>Adjusted for receipt of Rotashield <21 days, sex, race/ethnicity, level of education, and insurance status                                    |
|                               |                | Subgroup, <5 weeks before ISF |                     | 1.33 (0.59–3.33)   | No association                 | Breast milk for most feedings versus cow's milk-based formula | Matched by age and hospital of birth<br>Adjusted for receipt of Rotashield <21 days, sex, race/ethnicity, level of education, and insurance status                                    |
|                               |                | Subgroup, no ISF              |                     | 0.43 (0.26–0.71)   | Protective factor              | Breast milk for most feedings versus cow's milk-based formula | Matched by age and hospital of birth<br>Adjusted for receipt of Rotashield <21 days, sex, race/ethnicity, level of education, and insurance status                                    |

(continued)

TABLE 4. (CONTINUED)

| <i>Author (year)</i>         | <i>Country</i> | <i>Study period</i> | <i>Study design</i> | <i>OR (95% CI)</i> | <i>Effect of breastfeeding</i> | <i>Breastfeeding versus reference</i>                                               | <i>Covariate</i>                                                                                                                                                                                                                                                       |
|------------------------------|----------------|---------------------|---------------------|--------------------|--------------------------------|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Restivo (2018) <sup>11</sup> | Italy          | 2016–2017           | Case–control        | 0.48 (0.23–0.99)   | Protective factor              | Exclusive breastfeeding $\geq 2$ months versus exclusive breastfeeding $< 2$ months | Matched by age, gender, and gestational age<br>Adjusted for birth order, gastroenteritis for the last 30 days of hospitalization, antibiotic drugs in the last 30 days                                                                                                 |
| Fotso (2019) <sup>10</sup>   | France         | 2008–2012           | Case–control        | 0.42               | Protective factor              | Exclusive breastfeeding versus exclusive formula feeding                            | Matched by age, gender, and gestational age                                                                                                                                                                                                                            |
|                              |                |                     |                     | 0.36 (0.15–0.91)   | Protective factor              | Breastfeeding alone versus Infant formula alone or with breast                      | Matched by age, gender, admission period, and center<br>Adjusted for gestational term, medication before hospitalization, weight at admission, height at admission, and height at admission, gastroenteritis within 15 days, and concomitant diseases before admission |
| Oberle (2020) <sup>14</sup>  | Germany        | 2010–2014           | Case–control        | 0.54 (0.33–0.88)   | Protective factor              | Breastfeeding versus no breastfeeding                                               | Matched by gender, date of birth, federal state, and place of residence<br>Adjusted for Rotavirus life vaccine dose 1 and family history of intussusception                                                                                                            |
| Kuniyoshi (this article)     | Japan          | 2010 at birth       | Cohort              | 1.64 (0.32–30.0)   | No association                 | Exclusive breastfeeding versus exclusive formula feeding                            | Adjusted for gender, gestational age, birth weight, singleton or multiple births, parity, maternal age at delivery, maternal smoking status, and paternal smoking status                                                                                               |

CI, confidence interval; ISF, introduction of solid food; OR, odds ratio.

believe that it should continue to be recommended considering the overall benefits of breastfeeding.

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### Author Contribution

Y.K.: Writing—original draft, writing—review and editing, data curation, formal analysis, investigation, and visualization.

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### Supplementary Material

Supplementary Figure S1  
Supplementary Table S1

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