

# Breast-feeding and Infant Hospitalization for Infections: Large Cohort and Sibling Analysis

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## ABSTRACT

**Objectives:** Breast-feeding may protect against infections, but its optimal duration remains controversial. We aimed to study the association of the duration of full and any breast-feeding with infections the first 18 months of life.

**Methods:** The Norwegian Mother and Child study (MoBa) is a prospective birth cohort which recruited expecting mothers giving birth from 2000 to 2009. We analyzed data from the full cohort (n = 70,511) and sibling sets (n = 21,220) with parental report of breast-feeding and infections. The main outcome measures were the relative risks (RRs) for hospitalization for infections from 0 to 18 months by age at introduction of complementary foods and duration of any breast-feeding.

**Results:** Although we found some evidence for an overall association between longer duration of full breast-feeding and lower risk of hospitalizations for infections, 7.3% of breast-fed children who received complementary foods at 4 to 6 months of age compared to 7.7% of those receiving complementary foods after 6 months were hospitalized (adjusted RR 0.95, 95% confidence interval 0.88–1.03). Higher risk of hospitalization was observed in those breast-fed 6 months or less (10.0%) compared to  $\geq 12$  months (7.6%, adjusted RR 1.22, 95% confidence interval 1.14–1.31), but with similar risks for 6 to 11 months versus  $\geq 12$  months. Matched sibling analyses, minimizing the confounding from shared maternal factors, showed nonsignificant associations and were generally weaker compared with the cohort analyses.

**Conclusions:** Our results support the recommendation to fully breast-feed for 4 months and to continue breast-feeding beyond 6 months, and suggest that protection against infections is limited to the first 12 months.

**Key Words:** human milk, infancy, infectious disease, weaning

(*JPGN* 2017;65: 225–231)

Received August 31, 2016; accepted January 25, 2017.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site ([www.jpjn.org](http://www.jpjn.org)).

The Norwegian Mother and Child Cohort Study is supported by the Norwegian Ministry of Health and Care Services and the Ministry of Education and Research, NIH/NIEHS (contract no. N01-ES-75558), NIH/NINDS (grant no. 1 U01 NS 047537-01 and grant no. 2 U01 NS 047537-06A1). The study was funded by the Norwegian Institute of Public Health. Dr Størdal was supported by an unrestricted grant from Oak Foundation, Geneva, Switzerland.

The authors report no conflicts of interest.

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DOI: 10.1097/MPG.0000000000001539

## What Is Known

- Breast-feeding from birth may protect against infections, but optimal duration of breast-feeding is unclear.
- Delaying introduction of complementary foods may reduce the risk of infections, but may be more important for formula than for solid foods.
- Breast-feeding is associated with a healthy lifestyle in high-income countries, making interpretation of breast-feeding studies difficult.

## What Is New

- Breast-feeding for  $\leq 6$  compared to  $\geq 12$  months was associated with higher risk of infections, but with similar risks for 6 to 11 and  $\geq 12$  months' duration.
- Breast-fed children who received complementary foods at 4 to 6 months of age had similar risk for infection as those receiving complementary foods after 6 months.

There is an ongoing controversy regarding optimal breast-feeding duration and time of weaning (1). The recommendation from the World Health Organization (WHO) (2) to continue full breast-feeding until 6 months of age has been adopted by several industrialized countries (1,3–5). Still, only 1% to 13% of mothers in the UK, the US, and Norway comply with this recommendation (4,6,7). The WHO furthermore recommends to continue partial breast-feeding up to 2 years or beyond (3). There is a need for more studies providing stronger evidence to underpin a revision of current guidelines, as stated by the WHO expert consultation (8).

Protection against infections is one of several causes considered in the breast-feeding recommendations (9,10). These benefits appear particularly in developing countries with a high burden of infectious diseases in infancy (11–13), where the risk of unsafe formula feeding adds to a higher pressure of infections (8). These observations have partly been reproduced in industrialized countries (6,14).

Breast-feeding in wealthy societies is associated with health conscious behavior (15), and consequently, confounding effects of other healthy choices needs to be thoroughly investigated. Furthermore, previous studies have included few infants fully breast-fed for 6 months. Underlying characteristics of this group could possibly confound the results, in addition to uncertainty in the estimates due to limited sample sizes (6,14,16,17). Moreover, few studies have addressed the optimal duration of breast-feeding beyond 6 months regarding infection prevention (6,14).

The main objective of the present study was to assess whether the risk of hospitalization for infections before the age of 18 months was different in infants introduced to complementary foods from 4 to 6 months compared to the recommended 6 months. Secondary objectives were to study whether duration of any breast-feeding was associated with hospitalization and with infections in general. In addition to a traditional cohort analysis, we assessed whether breast-feeding predicted risk of infections in a matched sibling design.

## METHODS

### Cohort Formation

The Norwegian Mother and Child Cohort Study (MoBa) is a population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health (18). Participants were recruited from all over Norway (rural/urban) from 1999 to 2008, and 95,200 mothers (40.6% of eligible) participated with 1 or more pregnancies. Written informed consent was obtained. The MoBa study was approved by The Regional Committee for Medical Research Ethics in South-Eastern Norway. The present study is based on version VII of the quality-assured data files released for research in June 2012.

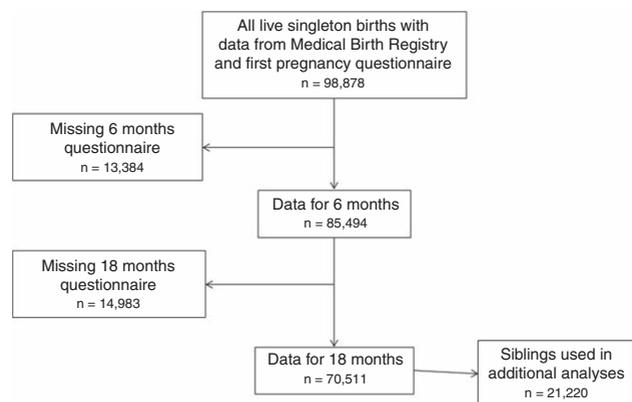
Follow-up is conducted by mailed questionnaires. We use information from the baseline questionnaire completed around week 17 of pregnancy and 2 follow-up questionnaires at infant age 6 and 18 months (available at [www.fhi.no/moba](http://www.fhi.no/moba)).

Only singletons whose parents returned questionnaires at 6 and 18 months of age ( $n = 70,511$ , flow chart Fig. 1) were included (Supplemental Digital Content 1, Table, <http://links.lww.com/MPG/A903>, for characteristics of included and nonincluded participants). Children with missing data for any of the study variables were excluded from the analysis.

In order to reduce bias that may occur due to differences in self-reporting of infections and confounding maternal effects, siblings in the cohort were studied in a secondary analysis.

### Main Exposure: Infant Feeding

In the 6 months' questionnaire, ongoing breast-feeding or formula feeding from the first week in monthly intervals and age at introduction of solids was specified up until completion (median 27 weeks). From 6 to 18 months of age, the mothers reported



**FIGURE 1.** Subjects included in the analyses. Siblings were part of the full cohort and also included in sibling analyses. MBR = Medical Birth Registry. \*Two hundred twenty-five of the 13,384 were lost due to deaths in the observation period. †Twenty-one of the 14,983 were lost due to deaths in the observation period.

whether they were breast-feeding in 4 intervals (6–8, 9–11, 12–14, and 15–18 months). The median value of each interval was used as a fixed value in calculations of breast-feeding duration. For the regression analyses, duration of any breast-feeding was categorized into 6 intervals (no breast-feeding, 0.1–3, 4–6, 6.1–8, 9–11, and  $\geq 12$  months). Full breast-feeding was defined as breast-feeding from birth without any formula or solids. This allows for water and vitamins, different from the strict definition of exclusive breast-feeding.

To assess whether partial breast-feeding was associated with different risk of infections than full breast-feeding, age at introduction of complementary foods (formula or solid foods) in infants breast-fed  $>6$  months was analyzed in categories  $<1$ , 1 to 3, and 4 to 5 months with full breast-feeding for 6 months as the reference category. We performed subanalyses for the age at introduction of formula or solids, all adjusted for the duration of any breast-feeding.

### Main Outcome Definitions: Infections

The primary outcome was hospitalization due to infection by maternal report from 0 to 18 months. In additional analyses hospitalization was separated in age 0 to 6 and 6 to 18 months. We assessed the validity of this outcome from the questionnaires by comparing it to hospital statistics in a subsample from one major hospital, in which 197 of 212 admissions were correctly reported in questionnaires (sensitivity 93%).

Secondary outcomes were infections regardless of hospitalization from 0 to 18 months indicated from a specified list. Lower respiratory tract infections (LRTIs = pneumonia/bronchiolitis), gastroenteritis (GE), and acute otitis media were dichotomized (none vs any). Upper respiratory tract infections (URTI) and frequent infections (total number of the 4 types of infections) were dichotomized corresponding to the upper quintile of the distribution in the whole sample (URTI  $>8$  or “frequent infections”  $>10$ , respectively).

### Other Covariates

Information regarding maternal age, birth weight, gestational age, parity, mode of delivery, and sex was obtained from the Medical Birth Registry. The first questionnaire provided information on smoking during pregnancy, paternal smoking, and duration of maternal education in 4 categories. Duration of child day care outside home was categorized into 4 groups (Supplemental Digital Content 1, Table, <http://links.lww.com/MPG/A903>, for covariates and categorization).

### Statistical Analyses

Analyses were performed using the SPSS 20.0 statistical software package (IBM SPSS Inc, Chicago, IL) and Stata version 13 (StataCorp LP, College Station, TX). The main analysis was conducted using binary regression models to obtain relative risks (RRs), with robust variance to correct for potential clustering within families. Confounders reported from previous studies were pre-selected. Other covariates associated with any of the outcomes with 95% confidence intervals for RR not including 1.00 in unadjusted analyses were assessed for inclusion in the multiple regression models, but removed from the final model if the estimates changed  $<10\%$ .

As sensitivity analyses to assess robustness of findings, we explored the potential effect of using different cut-offs for the total number of URTI and total infections, and fitted Poisson regression models for number of infectious episodes. Sensitivity analyses were consistent with our main analyses (data not shown).

Finally, we estimated the odds ratio for infections in siblings (matched sets conditioned on the maternal origin), using conditional logistic regression models. In this model, covariates that are identical within sibling sets will not contribute to the final estimates. Thus, only sibling sets with different duration of breast-feeding can potentially change the odds ratio from 1. We included as covariates potential confounders that could differ among siblings, comparing an unmatched design to the sibling analysis.

**RESULTS**

The mean duration of any breast-feeding was 10.0 months (SD 4.5), 80.8% were breast-fed >6 months. Fourteen percent were fully breast-fed for 6 months; 0.9% was never breast-fed. Longer duration of any breast-feeding was strongly associated with higher maternal age and parity, education, nonsmoking status, vaginal delivery, and day care at home (all *P* < 0.001; Supplemental Digital Content 2, Table, <http://links.lww.com/MPG/A903>).

Before the age of 18 months, 8.0% were admitted to hospital for infections. GE or LRTI accounted for 68% (Supplemental Digital Content 3, Fig., <http://links.lww.com/MPG/A903>, which demonstrates that the age at admission was evenly distributed during the period from 0 to 18 months). The frequency of all infections increased gradually with age (Supplemental Digital Content 4, Table, <http://links.lww.com/MPG/A903>).

**Age at Introduction of Complementary Foods and Infections**

Age at introduction of complementary foods was a significant predictor for hospitalization for infections among infants who were breast-fed for a minimum of 6 months (adjusted RR 0.98 per month delay, 95% confidence interval 0.97–1.00, *P* for trend 0.01). This association was driven by a higher risk for hospitalization in those with introduction of complementary foods at <4 months of

age (Fig. 2). In categorical analyses, hospitalization for infections was reported in 7.7% of infants fully breast-fed for 6 months compared to 7.3% of those introduced to complementary foods at 4 to 6 months (aRR 0.95, 0.88–1.03, Fig. 2, Supplemental Digital Content 5, Table, <http://links.lww.com/MPG/A903>).

The risk was significantly lower when formula introduction was delayed (aRR 0.96 per month, 0.93–0.98), but formula introduction from 4 months was not associated with increased risk of hospitalization. For solids introduction, we found a nonsignificant trend in the opposite direction (aRR 1.03 per month, 1.00–1.07, Fig. 2).

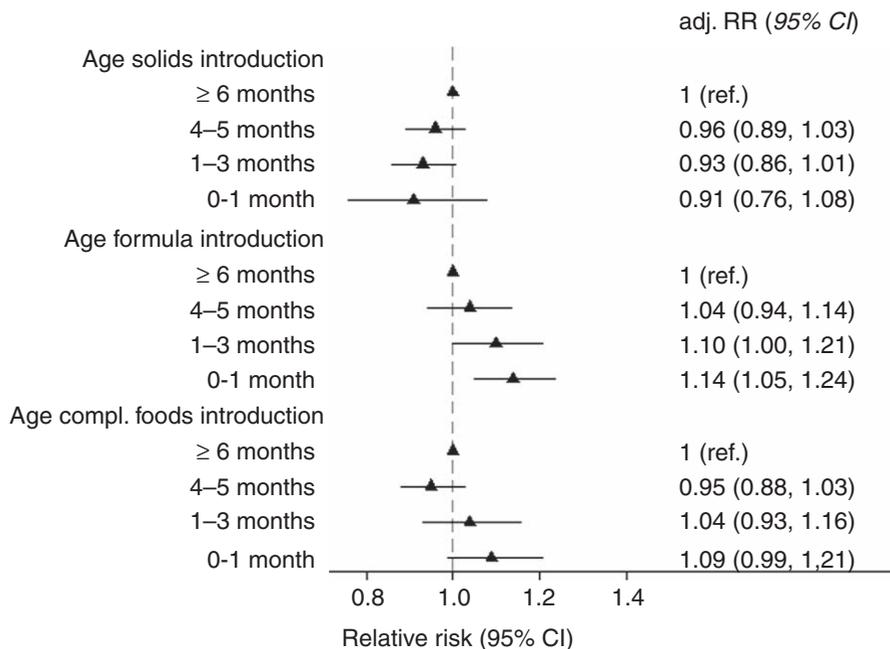
We also performed subanalyses separating the main outcome in time periods of 0 to 6 months and 6 to 18 months. The point estimates did not change substantially, but the confidence intervals became wider due to the lower proportion with events (Supplemental Digital Content 5, Table, <http://links.lww.com/MPG/A903>).

When we analyzed all infections regardless of hospitalization, introduction of complementary foods <4 months was associated with an increased risk for GE, URTI, and frequent infections but not for LRTI (Supplemental Digital Content 5, Table, <http://links.lww.com/MPG/A903>).

**Duration of Any Breast-feeding and Infections**

Compared with infants breast-fed ≥12 months, infants breast-fed for <6 months had an increased risk for hospitalization. The association was primarily driven by GE (Fig. 3A). Breast-feeding <6 months was in general associated with an increased risk for infectious outcomes regardless of hospitalization (Fig. 3B).

Infants breast-fed for 6 to 11 months did not differ significantly from those breast-fed ≥12 months regarding hospitalization (Fig. 3A), but with a slightly reduced risk of GE, otitis media, and frequent infections if breast-fed up to 9 months (Fig. 3B, Supplemental Digital Content 6, Table, <http://links.lww.com/MPG/A903>).



**FIGURE 2.** Relative risk of hospital admission for infections the first 18 months of life by age at introduction of complementary foods, solid foods, and formula in infants breast-fed >6 months age (n = 57,007). Relative risks were adjusted for maternal age and parity (3 categories), caesarean section, maternal smoking, education, birth weight (<2500, 2500–3499, 3500–4499, >4500 g), gestational age (</>37 weeks), sex, day care outside home, and duration of any breast-feeding. Adj.RR = adjusted relative risk; CI = confidence interval.

TABLE 1. Duration of full breast-feeding and infections in the first 18 months of life in a sibling and full cohort analysis

Endpoint	Model	Number of children with endpoint (%)	Odds ratio (95% CI) per month before introduction of complementary foods
Hospitalization for any infection	Siblings matched (n = 12,495)	1012 (8.1)	0.975 (0.924–1.029)
	Full cohort (n = 56,993)	4315 (7.6)	0.978 (0.963–0.994)
Any lower respiratory tract infection	Siblings matched (n = 12,147)	1674 (13.8)	0.994 (0.952–1.038)
	Full cohort (n = 55,301)	7124 (12.9)	0.990 (0.978–1.003)
Any gastroenteritis	Siblings matched (n = 11,739)	7008 (59.7)	0.981 (0.950–1.013)
	Full cohort (n = 53,226)	31,651 (59.5)	0.974 (0.965–0.983)
Upper respiratory tract infections ( $\geq 9$ )	Siblings matched (n = 11,988)	2581 (21.5)	0.982 (0.943–1.022)
	Full cohort (n = 54,437)	11,236 (20.6)	0.968 (0.957–0.978)
Frequent infections ( $\geq 11$ )	Siblings matched (n = 11,988)	2312 (19.3)	0.973 (0.933–1.015)
	Full cohort (n = 54,437)	10,190 (18.7)	0.959 (0.949–0.970)

CI = confidence interval.

## Sibling Analyses

The median difference in duration of full and any breast-feeding within sibling sets discordant for duration of breast-feeding was 1.5 and 3.0 months, respectively, and 41% had identical duration of any breast-feeding. The first-born sibling had a mean shorter duration of both full and any breast-feeding of 0.4 months. Infants with a matched sibling control with difference in duration of full breast-feeding (n = 12,495) or any breast-feeding (n = 11,149) contributed in the sibling analysis.

In the conditional logistic regression analysis of siblings we found no significant associations for age for introduction of complementary foods with hospital admission for infections, and with risk for infections regardless of hospitalization (Table 1). Similarly, duration of any breast-feeding was not a significant predictor (Table 2). The odds ratios per month were generally closer to 1 in the conditional analysis compared to the unconditional full cohort analysis (Tables 1 and 2).

Significant predictors for infections in the sibling model were birth order, birth weight <2500 g, male sex, and day care outside home (data not shown).

## DISCUSSION

In this large birth cohort, we found a small but significant trend for lower risk for hospitalizations for infections for each

month of delaying complementary foods in breast-fed infants. Breast-fed children who, however, received complementary foods at 4 to 6 months of age had a similar risk as those delaying complementary foods to after 6 months, suggesting a threshold effect for duration of full breast-feeding. Breast-feeding for  $\leq 6$  months compared to  $\geq 12$  months was associated with an increased risk, whereas infants breast-fed for 6 to 11 months had risks of hospitalization similar to those breast-fed  $\geq 12$  months. The estimated associations were weaker and nonsignificant in the sibling analysis compared with the full cohort analysis. The present study is the first in this field to include a discordant sibling analysis, an analysis that studies differences within sibling sets and thereby reduces the potential confounding from shared maternal factors.

The similar hospitalization risk for infants introduced to complementary foods from 4 to 6 compared to  $\geq 6$  months parallels 2 previous cohort studies (6,17) and the recent randomized controlled EAT trial (19). In contrast, others have found a reduced risk of lower respiratory tract infections with 6 months of full breast-feeding (16,20). It should be noted that the sample sizes were smaller in these studies, and additionally, fewer confounding factors could be assessed.

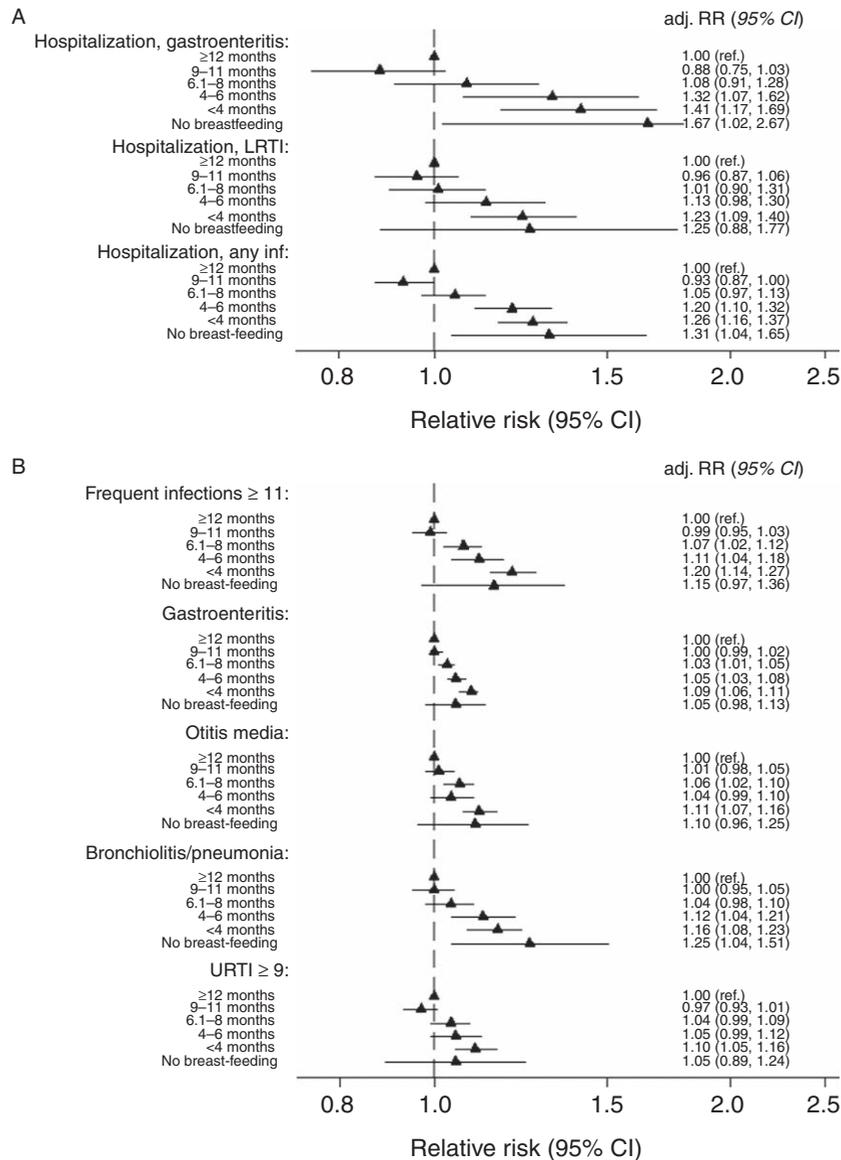
In our study, infants introduced to formula in addition to breast milk before 4 months had increased risk for infections, which was not found for later formula introduction or for solid foods. The difference between formula and solids as regards infection risk is in accordance with observations from the UK Millennium Cohort

TABLE 2. Duration of any breast-feeding and infections in the first 18 months of life in a sibling and full cohort analysis

Endpoint	Model	Number of children with endpoint (%)	Odds ratio (95% CI) per month before introduction of complementary foods
Hospitalization for any infection	Siblings matched (n = 13,420)	1107 (8.3)	0.994 (0.965–1.024)
	Full cohort (n = 70,487)	5669 (8.0)	0.985 (0.979–0.992)
Any lower respiratory tract infection	Siblings matched (n = 13,043)	1854 (14.2)	0.999 (0.973–1.026)
	Full cohort (n = 68,322)	9030 (13.2)	0.990 (0.985–0.995)
Any gastro-enteritis	Siblings matched (n = 12,582)	7542 (59.9)	0.994 (0.975–1.013)
	Full cohort (n = 65,852)	39,393 (59.8)	0.990 (0.986–0.994)
Upper respiratory tract infections ( $\geq 9$ )	Siblings matched (n = 12,857)	2806 (21.8)	0.983 (0.960–1.007)
	Full cohort (n = 67,249)	13,862 (20.6)	0.996 (0.992–1.001)
Frequent infections ( $\geq 11$ )	Siblings matched (n = 12,857)	2542 (19.8)	0.980 (0.955–1.005)
	Full cohort (n = 67,249)	12,787 (19.0)	0.990 (0.985–0.994)

For each outcome, 2 models were run: a conditional logistic regression within sibling sets, and an unconditional logistic regression analysis in the full cohort with robust variance to correct for potential clustering within families. All models were adjusted for parity, gestational age (<37/ $\geq 37$  weeks), sex, caesarean section, birth weight category, day care outside home, maternal age, maternal education, and maternal smoking.

Only sibships discordant for endpoint contributed to this analysis, that is, sibships in which 1 child had the endpoint and at least 1 sibling did not. CI = confidence interval.



**FIGURE 3.** Relative risk of (A) hospital admission for infection and (B) any infection from 0 to 18 months by duration of any breast-feeding (n = 70,511). Relative risks were adjusted for maternal age and parity (3 categories), caesarean section, maternal smoking, education, birth weight (<2500, 2500–3499, 3500–4500, >4500 g), gestational age (</>37 weeks), sex, and day care outside home. Adj.RR = adjusted relative risk; CI = confidence interval; LRTI = lower respiratory tract infection.

Study (6). In the EAT trial, the main difference between the 2 intervention arms was early introduction of solids, with no difference found for infections except for URTI (19). We speculate that the observed difference in our study could be due to a relatively higher effect on the volume of breast milk given when formula was introduced at an early age, but our data do not provide the granularity to study this in more detail.

The strongest association observed in the full cohort analysis was the increased risk of hospitalization for GE in infants not breast-fed or breast-fed for ≤6 months compared to ≥12 months. Observational studies elsewhere have found lower risk for GE early in life among breast-fed infants (17,21), also supported by the randomized trial from the Belarus (22).

For lower respiratory tract infections, observational studies report conflicting results (14,17,21). The only randomized

controlled trial from an industrialized country did not find any difference in risk for LRTI or hospital admission between the group promoted to breast-feeding compared with controls (22). The full cohort analysis in our study suggests a higher risk of hospitalization for LRTI if breast-feeding lasts ≤4 compared to ≥12 months.

The novel sibling analysis suggested that the associations observed in the full cohort could be biased by residual or unobserved confounding from shared maternal factors. In principle, this matched design eliminates confounding from factors fully shared by the siblings, such as maternal genotype, and reduces confounding from factors likely to be highly correlated among siblings such as rearing practices and parental reporting bias of the infections. The reduced sample size in the cohort belonging to siblings, however, implies wider confidence intervals in the sibling analyses. A matched design has inherent limitations, with the possibility of

increasing bias by nonshared confounders (23). Therefore, we cannot automatically conclude that the sibling design produces a less biased result. Nevertheless, our interpretation of the findings among siblings is that the mother may be more important for the infection risk than the feeding mode, consistent with another recent sibling study on breast-feeding and a multitude of other long-term outcomes (24). This study did not assess the risk of infections.

Few studies have assessed the potential benefit of the WHO recommended breast-feeding after 12 months with regard to infections (3), the observation period has been limited to 6 to 12 months (14,17,20–22,25). We found similar risk for hospitalization in infants breast-fed for 6 to 11 months compared to  $\geq 12$  months. This finding suggests that breast-feeding plays a minor role in infection prevention after 12 months.

Our study is the largest prospective birth cohort of infant feeding and infections to date, with the potential of more precise estimates as compared to previous studies. Data collected in the present study allowed for the assessment of multiple potential confounders, which reduce the risk of overestimating the potential effects of breast-feeding due to the associated healthy behaviors.

The data collection of exposures and outcomes in a recall time period limited to 6 to 12 months reduces the risk of bias, and other studies have shown good agreement with retrospective breast-feeding data and 24-hour recall (26,27). Infectious symptoms occurring close to changes in diet could be more likely to be notified by the parents. Because infections occurred and infant feeding were given in the same time intervals, reverse causation with infections influencing on breast-feeding cannot be ruled out. A serious infection could lead to interruption of breast-feeding and thus overestimate the apparent benefits of breast-feeding. Alternatively, motivation for breast-feeding could be increased with frequent infections, potentially underestimating the benefits.

A potential limitation of our study is that the difference in adjacent groups for duration of breast-feeding may be too small to induce detectable associations. Comparing full breast-feeding for 3 to 4 months against 6 months (omitting 5 months), however, led to essentially the same conclusions (data not shown). The time of infection within each interval was not specified in the questionnaires, leading to an inability to determine this more accurately.

Our results are likely generalizable to industrialized countries with a similar burden of infectious disease and breast-feeding coverage. A higher background risk of infections in low- and middle-income countries could explain differing results in less resourced populations (11–13,28,29). Participants in our cohort study tend to have a higher level of education and age than the general population, and the participants lost during the study similarly were younger and less educated. In general, the associations between exposures and outcomes have been shown to be robust to selection bias (30). A more heterogeneous cohort will also be more prone to confounding effects of socioeconomic differences.

The recommendations for infant feeding need to take all aspects of the health of the child and the mother into account. Health outcomes later in life as allergies, asthma, autoimmune diseases, neurodevelopment, and obesity are important considerations and may be associated to the duration of breast-feeding. Our findings, supported by the sibling analysis, suggest that effects of prolonged breast-feeding may be overestimated by the healthy behavior among mothers who follow the official recommendations for infant feeding.

To conclude, introduction of complementary foods from 4 to 6 months as compared to introduction  $\geq 6$  months of age in breast-fed infants was not a significant risk factor for hospitalization due to infections. Infections thus do not seem to be of major importance for these 2 alternative recommendations for introduction of complementary foods in a high-income society. Our results, however, do support the recommendation to fully breast-feed for 4 months

and to continue breast-feeding beyond 6 months, and suggest that protection against infections is limited to the first 12 months.

**Acknowledgments:** The authors are grateful to all the participating families in Norway who take part in this ongoing cohort study.

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