PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Early Feeding and Risk of Celiac Disease in a Prospective Birth Cohort

Ketil Størdal, Richard A. White and Merete Eggesbø

Pediatrics 2013;132;e1202; originally published online October 7, 2013;
DOI: 10.1542/peds.2013-1752

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pediatrics.aappublications.org/content/132/5/e1202.full.html

PEDIATRICS is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. PEDIATRICS is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2013 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 0031-4005. Online ISSN: 1098-4275.

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™

Downloaded from pediatrics.aappublications.org at Swets Info Serv 37619198 on November 7, 2013

Early Feeding and Risk of Celiac Disease in a Prospective Birth Cohort

Ketil Størdal, Richard A. White and Merete Eggesbø

Pediatrics 2013;132;e1202; originally published online October 7, 2013;
DOI: 10.1542/peds.2013-1752

Updated Information & Services	including high resolution figures, can be found at: http://pediatrics.aappublications.org/content/132/5/e1202.full.html
Supplementary Material	Supplementary material can be found at: http://pediatrics.aappublications.org/content/suppl/2013/10/02/peds.2013-1752.DCSupplemental.html
References	This article cites 26 articles, 8 of which can be accessed free at: http://pediatrics.aappublications.org/content/132/5/e1202.full.html#ref-list-1
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://pediatrics.aappublications.org/site/misc/Permissions.xhtml
Reprints	Information about ordering reprints can be found online: http://pediatrics.aappublications.org/site/misc/reprints.xhtml

PEDIATRICS is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. PEDIATRICS is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2013 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 0031-4005. Online ISSN: 1098-4275.

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™

Downloaded from pediatrics.aappublications.org at Swets Info Serv 37619198 on November 7, 2013

Early Feeding and Risk of Celiac Disease in a Prospective Birth Cohort

WHAT'S KNOWN ON THIS SUBJECT: Lower risk of early celiac disease (CD) has been observed with breastfeeding and low dose of gluten at introduction. Gluten introduction before 4 or after 6 months has been associated with increased risk. For CD diagnosed after 2 years, the association is unclear.

WHAT THIS STUDY ADDS: Gluten introduction delayed to >6 months as well as breastfeeding >12 months was associated with a modest increase in CD in this first population-based birth cohort study, and gluten introduction under continued breastfeeding was not protective.

abstract

NIH FREE

OBJECTIVES: Timing of gluten introduction has been associated with the risk of celiac disease (CD) in children, but the optimal time window is unknown. We aimed to study the effect of age of gluten introduction on the risk of CD, adjusting for continued breastfeeding.

METHODS: In The Norwegian Mother and Child Cohort Study, a prospective birth cohort including 107 000 children, CD was identified by questionnaires and by linkage to the Norwegian Patient Register. Gluten introduction was reported monthly from 0 to 6 months of age, and breastfeeding from 0 to 18 months.

RESULTS: After exclusion of cases with insufficient information, 324 children with CD in a cohort of 82 167 were used in the analyses. Gluten was introduced before or at 4 months in 8.0%, 5 to 6 months in 45.3%, and after 6 months in 46.6%, whereas continued breastfeeding was stable at ~78% at 6 months age. CD was diagnosed in 3.68/1000 of the infants with gluten introduction at 5 to 6 months compared with 4.15/1000 with late and 4.24/1000 with early gluten introduction. After adjustment for the child's age and gender, breastfeeding, and maternal CD, delayed gluten introduction was associated with an increased risk of CD (adjusted odds ratio, 1.27 [95% confidence interval, 1.01–1.65], P = .045). Breastfeeding >12 months was also associated with increased risk (adjusted odds ratio, 1.49 [95% confidence interval, 1.01–2.21], P = .046).

CONCLUSIONS: We found an increased risk of CD in children introduced to gluten after 6 months and a higher risk in children breastfed after 12 months age. *Pediatrics* 2013;132:e1202–e1209

AUTHORS: Ketil Størdal, MD, PhD,[a,b] Richard A. White, PhD,[a] and Merete Eggesbø, MD, PhD[a]

[a]*Norwegian Institute of Public Health, Oslo, Norway; and* [b]*Østfold Hospital Trust, Fredrikstad, Norway*

KEY WORDS

celiac disease, nutrition, epidemiology, breastfeeding, children

ABBREVIATIONS

aOR—adjusted odds ratio
CD—celiac disease
CI—confidence interval
MoBa—The Norwegian Mother and Child Cohort Study
NPR—The Norwegian Patient Register
OR—odds ratio

Dr Størdal conceptualized the study, drafted the initial manuscript, and performed the main data analysis; Dr White performed the statistical analysis with multiple imputations and drafted the tables for the main outcomes (Table 2 and 3); Dr Eggesbø supervised the writing of the article, with contributions on the methods applied and critically reviewed the drafts, and she has also been involved in the planning of the whole cohort study (The Norwegian Mother and Child Cohort Study); and all authors approved the final manuscript as submitted.

www.pediatrics.org/cgi/doi/10.1542/peds.2013-1752

doi:10.1542/peds.2013-1752

Accepted for publication Aug 23, 2013

Address correspondence to Ketil Størdal, MD, PhD, Norwegian Institute of Public Health, Pb 4404 Nydalen, 0403 Oslo, Norway. E-mail: ketil.stordal@fhi.no

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

Copyright © 2013 by the American Academy of Pediatrics

FINANCIAL DISCLOSURES: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: The Norwegian Mother and Child Cohort Study is supported by the Norwegian Ministry of Health and the Ministry of Education and Research, NIH/NIEHS (contract N01-ES-75558), NIH/NINDS (grant 1 U01 NS 047537-01 and grant 2 U01 NS 047537-06A1), and the Norwegian Research Council/FUGE (grant 151918/S10).

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

Presence of gluten in the diet is the only well-established environmental factor in celiac disease (CD), and is prerequired as indicated in the disease definition (gluten-sensitive enteropathy).[1] A strong genetic predisposition through the presence of HLA antigen types DQ2 or DQ8[2] and detailed understanding of how the HLA-molecules present modified deamidated gluten to reactive T-cells[3] are the pillars of the current understanding of how CD develops. Recently, this knowledge has been supplemented by genome-wide association studies and candidate gene studies, identifying loci with significant but small effects coding for regulatory elements and for genes involved in immunity.[4,5]

Apart from gluten exposure in the diet, lines of evidence point to timing and dose of gluten in the weaning diet during infancy to affect the risk of disease.[6] However, the optimal method and time frame for introduction of gluten has not yet been established. In a prospective birth cohort following genetically susceptible individuals carrying HLA antigen risk alleles, the risk for CD was found to be elevated with gluten introduction <4 months of age, but also increased when introduction was delayed to >6 months as compared with 4 to 6 months.[7] In Sweden, an epidemic of CD has been reported where incidence rates increased rapidly particularly among children <2 years born during 1985–1996.[8] This has been attributed partly to an increased dose of gluten and a delay in the time for gluten introduction in the weaning diet. This was followed by a decline in incidence rates in the young age groups when the amount of gluten again was reduced. The decline in incidence rates could partly be attributed to increased breastfeeding rates during the same period.[9] A protective effect of breastfeeding has been shown in several observational studies and summarized in a metaanalysis.[10] At present, it is unclear whether a protective effect of breast milk is limited to its presence during gluten introduction. It has also been proposed that breastfeeding may delay onset of symptoms and diagnosis of CD rather than offer actual protection against disease.[11]

Tolerance to food antigens is closely controlled by the innate and adaptive immune system. Environmental factors likely to be involved in tolerance development are maternal diet during pregnancy and lactation, the infant's diet, mode of delivery, micronutrients, and gut microbiota.[12] A window effect during a critical period in which the infant's immune system is more likely to adapt to food antigens with development of oral tolerance has been hypothesized.[13]

The aim of the current study was to study the association between timing of gluten introduction modified by breastfeeding and the risk of CD in childhood in a prospective birth cohort.

METHODS

The Norwegian Mother and Child Cohort Study (MoBa) is a prospective population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health.[14] Participants were recruited from all over Norway from 1999 to 2008, and 38.7% of invited women consented to participate. The cohort now includes 109 000 children, 91 000 mothers, and 71 700 fathers. The questionnaires are filled out weeks 17, 22, and 30 of pregnancy, at ages 6 and 18 months, and 3, 5, 7, 8, and 12 years. Core data from the Medical Birth Registry are linked to the study database. The current study is based on version VII of the quality-assured data files released for research in June 2012.

Informed consent was obtained from each MoBa participant upon recruitment. The substudy and linkage to the patient registry was approved by The Regional Committee for Medical Research Ethics in South-Eastern Norway.

The Norwegian Patient Register

The Norwegian Patient Register (NPR) is an administrative database containing activity data from all Norwegian government-owned hospitals and outpatient clinics. Reporting of data to the NPR is mandatory and linked to the governmental reimbursement system for funding of health services. Diagnoses are reported as *International Classification of Diseases, 10th Revision* codes. Individual-level data are available from 2008 onward when the 11-digit personal identification number unique to every Norwegian citizen was included.

Outcome Definition

The diagnostic criteria from the European Society of Pediatric Gastroenterology, Hepatology and Nutrition published in 1991, which were in use during this period, require a small-bowel biopsy for diagnosis of CD. As biopsies are performed in government-owned hospitals only, all children with biopsy-proven CD will have been diagnosed at facilities reporting to the NPR. However, as the registration started on January 1, 2008, there is a possibility that cases diagnosed before this date and not seen biannually in the outpatient clinic as recommended from the guidelines[15] are lost from the patient register. For this study, the NPR provided data from 2008 through 2011 for children participating in MoBa. CD is registered as the entry code in NPR, when children are referred to biopsy due to suspect CD, and this code is not removed if the biopsy does not confirm the diagnosis. To prevent misclassification due to unconfirmed CD, we demanded at least 2 entries of a celiac diagnosis in the NPR. At the age of 7 and

8, the MoBa questionnaire contains a specific question of CD diagnosed in the child. The cases identified from parental questionnaires were added to the ones identified twice in the registry.

A total of 395 children with CD (245 girls, 62%) were identified from 106 917 live births: 325 children had a minimum of 2 entries in the NPR, and 70 had the diagnosis from questionnaires of whom 27 also had 1 entry in the NPR. Two hundred forty-two children had a single entry in the NPR, which could not be supported by parental reports, and these were not included among the celiac cases.

After exclusion because of missing information on gluten exposure at 6 months' age (n = 22 297) or concerning maternal CD (n = 2453), 324 children with CD and 81 843 cohort controls constituted the complete cases in the analysis (Fig 1).

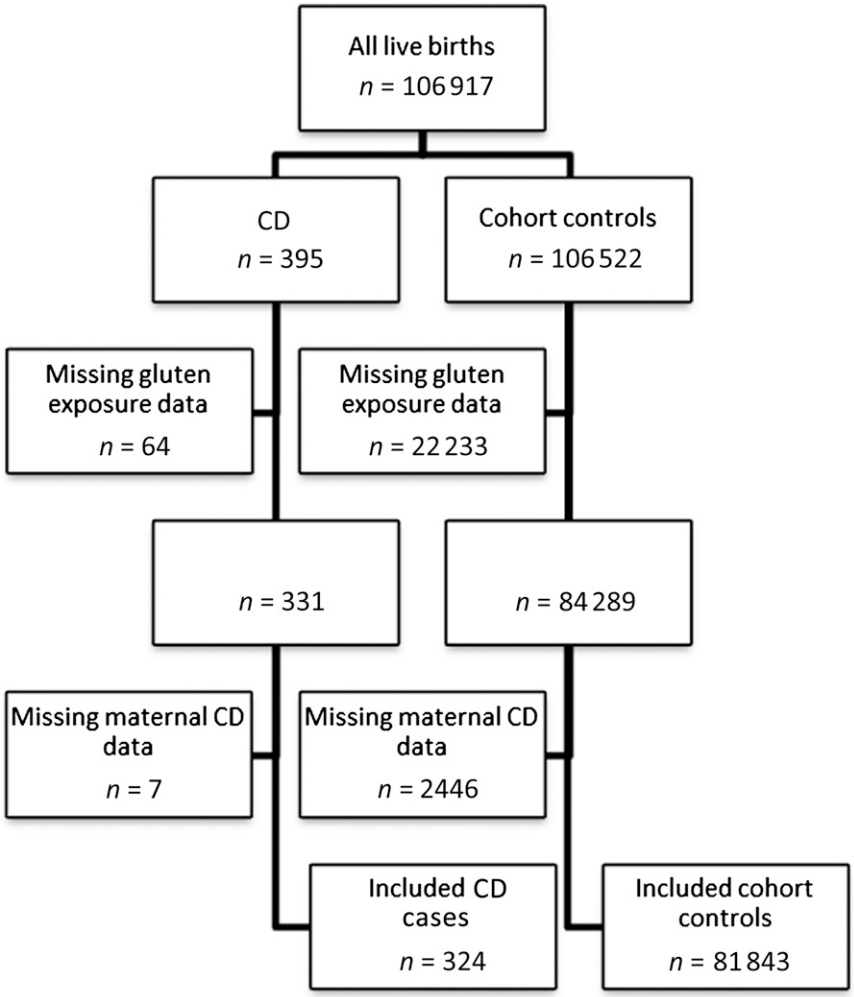

FIGURE 1
Selection of patients for study and causes for exclusion.

Questionnaires

A linkage to The Medical Birth Registry provided maternal age, mode of delivery, birth weight, and gestational age. From questionnaires completed during pregnancy, information concerning maternal CD, education, and smoking was obtained. At 6 months of age, the questionnaire contained information on breastfeeding for each month since birth (yes/no). Introduction of solids (subtypes of cereals, vegetables, and fruits) was similarly reported for each month up to 6 months' age. The questionnaire at 18 months contained separate fields for presence of breastfeeding in 3-month intervals (6–8, 9–11, 12–14, 15–18), and the medians of these intervals were used as fixed numbers when calculating the duration of breastfeeding.

Statistics

Analyses were performed by using the SPSS 19.0 (IBM SPSS Statistics, IBM Corporation) or Stata12 (Stata Corp, College Station, TX) statistical software packages. The main analysis was conducted by using logistic regression analyses. Variables with $P < .1$ in bivariate analyses were included in the adjusted multiple regression model. Unadjusted and adjusted odds ratios (aORs) for complete cases are presented in the main tables.

A sensitivity analysis was conducted by performing multiple imputations on the entire data set, containing 106 917 subjects. Multiple imputation by chained equations were implemented by using Stata 12 (command: mi impute chained), with variables CD, gender, maternal CD, age at which gluten was introduced (continuous), breastfeeding duration (continuous), mothers age, categorical education, birth weight, and caesarean status. Ten imputed data sets were generated with 200 iterations of burn-in each. The main analyses were then rerun on the imputed data sets, and changes in estimates (from the complete case analyses) were observed.

RESULTS

Cases and Cohort Characteristics

Complete information was available up to 6 months for 324 children with CD and 81 843 cohort controls, and up to 18 months for 287 with CD and 67 628 cohort controls.

Background characteristics of included and excluded participants are found in Table 1.

Early Infant Feeding

Gluten was introduced in the cohort before or at 4 months in 8.0%, at 5 or 6 months in 45.3%, and after 6 months in 46.6%. Breastfeeding was continued by 78.1% of the mothers at 6 months' age (Table 1).

A trend to introduce gluten at a later age during the recruitment period was seen with introduction ≤6 months in 62.0% for the cohort born in 2000 as compared with 16.4% in 2009, whereas breastfeeding rates at 6 months fluctuated at ∼78% for the whole recruitment period (Fig 2).

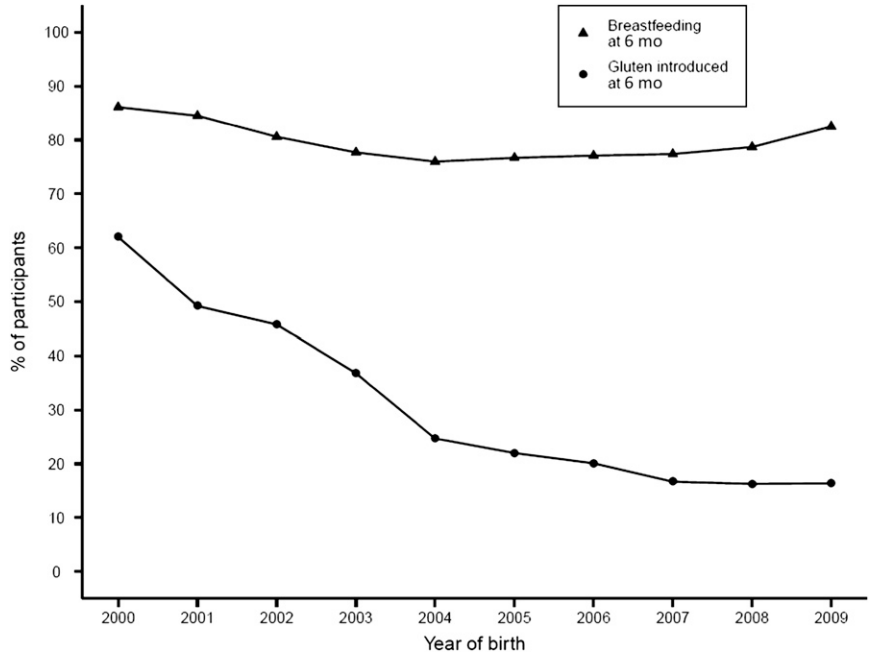

FIGURE 2
Proportion at 6 months of age with gluten introduction and continued breastfeeding during the recruitment period from 2000 to 2009.

Age of Gluten Introduction and Association With Risk of Celiac Disease

CD was diagnosed in 3.68/1000 of the infants who had been introduced to gluten at 5 or 6 months of age. In the early introduction group (≤4 months), the proportion with diagnosed CD was 4.24/1000 and 4.15/1000 in the late introduction group (>6 months).

Significant predictors for CD in univariate analyses were maternal CD, female gender, and age of the child (odds ratio [OR], 1.21 [95% confidence interval (CI), 1.15–1.27]), whereas no significant associations were found with mode of delivery, smoking, birth weight, gestational age, parity, maternal age, and education (Supplemental Table 5).

In a model adjusted for child's age and gender, maternal CD, and breastfeeding (Table 2), an increased risk for CD in the group introduced to gluten after 6 months was found (aOR, 1.27 [95% CI, 1.01–1.65], $P = .045$). Early introduction of gluten was not associated with increased risk for CD in the adjusted analyses (Table 2). In the multiple imputed and adjusted model, similar effect sizes were found (OR, 1.24 [95% CI, 0.98–1.56], for late gluten; OR, 0.97 [95% CI, 0.65–1.45] for early gluten introduction).

In a subanalysis of children breastfed >12 months, the aOR for CD was 1.59 (0.96–2.62) for those introduced to gluten after 6 months.

TABLE 1 Background Characteristics of the Cohort and Early Infant Feeding

	CD		Excluded
	Yes, $n = 324$	No, $n = 81\,843$	$n = 24\,750$
Mean age, y (median, range)	6.8 (7.0, 2–12)	5.9 (6.0, 2–12)	5.8 (6.0, 2–12)
Girl, *n* (%)	201 (62.0)	39 882 (48.7)	12 053 (48.7)
Maternal CD, *n* (%)	13 (4.0)	325 (0.40)	82 (0.47)
Missing, *n*	0	0	7297
Gluten introduction, *n* (%)			
≤4 mo	28 (8.6)	6580 (8.0)	NA
5–6 mo	137 (42.3)	37 107 (45.3)	NA
>6 mo	159 (49.1)	38 156 (46.6)	NA
Breastfeeding, *n* (%)			
<3 mo	36 (11.1)	10 932 (13.4)	NA
3–5 mo	23 (7.1)	6990 (8.5)	NA
≥6 mo	265 (81.8)	63 921 (78.1)	NA

NA, not available. Data represent 324 children with CD, 81 843 cohort controls, and 24 750 excluded from analysis.

Breastfeeding and Risk of Celiac Disease

Mean duration of breastfeeding in cases and controls was 10.4 and 9.9 months, respectively ($P = .031$). In the analysis adjusted for maternal CD, age and gender of the child and age at introduction of gluten, we observed a positive association between duration of breastfeeding and the risk for CD (aOR, 1.49 [95% CI 1.01–2.21], $P = .046$) for infants breastfed >12 months as compared with <6 months. In the multiple imputed and adjusted model,

TABLE 2 Unadjusted and Adjusted Associations Between Age at Introduction of Gluten Into the Diet and the Risk of a Diagnosis of CD in the Norwegian Mother and Child Birth Cohort Study (324 With CD and 81 843 Cohort Controls)

Age at Gluten Introduction	Unadjusted	Adjusted[a]	95% CI	*P*
≤4 mo	1.15	1.05	0.69–1.58	.89
5–6 mo	Reference	Reference	Reference	Reference
≥7 mo	1.13	1.27	1.01–1.65	.045

[a] Adjusted for maternal CD, breastfeeding, and gender and age of the child.

the association was similar (aOR, 1.46 [95% CI, 1.06–2.02], $P = .02$). For intermediate duration of breastfeeding (6–12 months) no significant association was found (Table 3), and the association was nonlinear with indications of a threshold effect after 12 months age (Fig 3).

Gluten Introduction During Breastfeeding

During the first 6 months of life, continued breastfeeding for 1 month beyond the first gluten exposure was defined as "gluten introduced during breastfeeding," and borderline overlapping breastfeeding as gluten introduction from 1 month before to 1 month after cessation of breastfeeding. Details on first gluten exposure were stated only in the questionnaire at 6 months' age. The effect of gluten introduction during breastfeeding could thus be assessed only for the group where gluten had been introduced at 6 months of age (170 with CD and 44 986 cohort controls). In this subgroup, the risk of CD was highest in those breastfed >1 month after gluten introduction, but the difference was not statistically significant (aOR, 1.17 [95% CI, 0.74–1.87], $P = .50$) (Table 4).

DISCUSSION

Timing of Gluten Introduction

The study indicates that introduction of gluten later than 6 months of age is associated with an increased risk of CD. This finding is well in accordance with a previous prospective birth cohort study following high-risk individuals with either known HLA antigen risk alleles for CD or first degree relatives with type 1 diabetes.[7] The reported effect size was smaller in the current study. This could be due to a selected high-risk cohort compared with our population-based study. Systematic screening was not performed in the current study, a different approach from the comparable study where annual screening for CD was done and a relatively high number of asymptomatic individuals were detected. Another prospective study of high-risk individuals for type 1 diabetes and CD could not confirm an association between timing of gluten introduction and CD, but was inadequately powered to detect differences.[16]

Early introduction of gluten, usually defined as before 4 months' age, has been hypothesized as a trigger for CD.[17–19] We could not confirm previous findings of a similarly increased risk in the group with early gluten introduction. However, in our cohort only 8% of the infants were introduced to gluten before 5 months, and 0.9% started gluten ingestion before 4 months. Thus, the power to assess a possible association with early introduction was low.

From the Swedish epidemic, timing of gluten introduction has been assessed as a risk factor without clear evidence in the case-control study.[20] A high amount of gluten in the weaning diet was associated with an increased risk, and suggested as a contributing factor from the peak epidemic years.[21] A striking difference between pediatric CD in Norway and Sweden is the age at diagnosis. Whereas a study in Norway revealed <10% to be diagnosed before the age of 2 years with the highest incidence rates from 2 to 5 years of age (abstract; Stordal et al, WCPGHN 2012)[22], the Swedish registry recorded during the years of highest incidence the majority (up to 67%) diagnosed before age 2 and the highest incidence rates before 2 years of age.[23]

Our data add evidence to the hypothesis of a window effect for introduction of food antigens.[13] An important on-going randomized control trial is expected to provide further evidence for the optimal age to introduce gluten in the diet.[24]

The trend to delay gluten introduction during the recruitment period was in accordance with a change in national recommendations for infant feeding. Similar to the World Health Organization guidelines, solitary breastfeeding and avoidance of solid feeds up to 6 months' age was recommended in new guidelines from 2001.[25] A potential adverse effect of delayed introduction of solids may have consequences for future guidelines for infant feeding.

Breastfeeding and Risk of Celiac Disease

The association between breastfeeding prolonged beyond 12 months' age and an increased risk for CD is, to our

TABLE 3 Unadjusted and Adjusted Associations Between Duration of Breastfeeding and the Risk of a Diagnosis of CD in the Norwegian Mother and Child Birth Cohort Study

Duration of Breastfeeding	Unadjusted	Adjusted[a]	95% CI	*P*
<6 mo	Reference	Reference	Reference	Reference
6–12 mo	1.26	1.27	0.85–1.86	.24
≥13 mo	1.52	1.49	1.01–2.21	.046

Analyzed for complete cases (287 with CD and 67 628 cohort controls).

[a] Adjusted for maternal CD, gender, and age of child and age at gluten introduction.

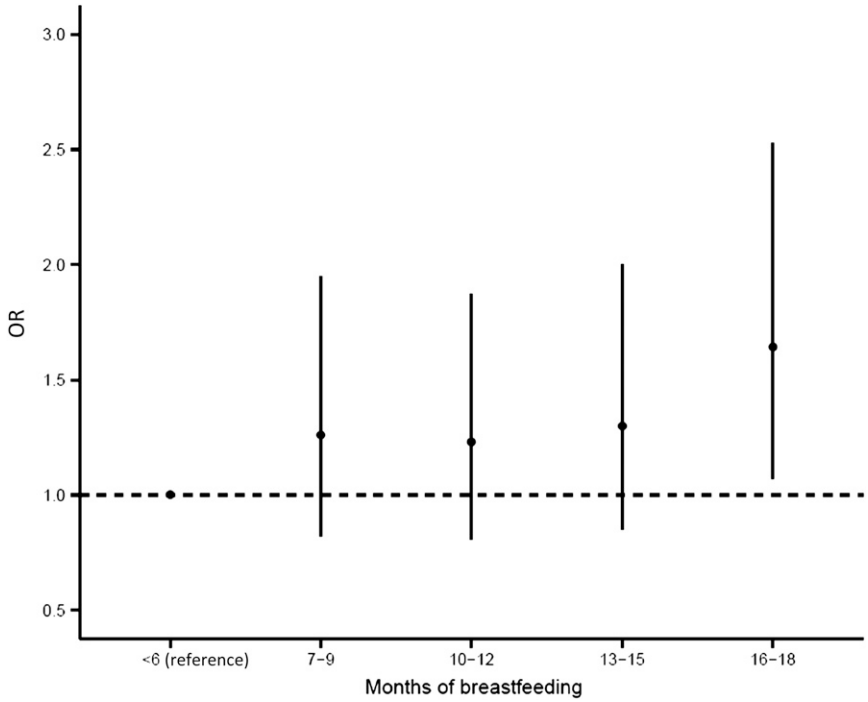

FIGURE 3
aOR (95% CI) for CD and duration of breastfeeding. Adjusted for maternal CD, gender, and age of child and age at gluten introduction.

knowledge, not previously reported. The association was nonlinear, with a significantly higher risk when comparing duration <6 months with >12 months. However, the borderline significance found after adjustment for confounding factors, calls for caution in the interpretation.

Breastfeeding may be continued for reasons unrecorded in our data (ie, hereditary risks for CD not present in the mother or because of perceived symptoms of food sensitivity in the infant). Because of the observational design of the study, we cannot rule out the possibility of reverse causation.

Nonetheless, the finding contradicts former observations of a protective effect of breastfeeding.[10,20] The breastfeeding rate at 6 months of 78% in our cohort is markedly higher than in comparable studies, typically ranging from 34% to 63%.[16,26] Thus, potential protective effects of breastfeeding could have reached a ceiling effect in our cohort. Alternatively, protective effects could be limited to early onset disease, as the association found in previous studies between early onset CD and breastfeeding has not been observed for those diagnosed >2 years of age.[6,20]

In the current study, the association remained statistically significant after adjusting for gluten introduction before or after 6 months. However, the actual age of gluten introduction after 6 months and the amount of gluten in the infant diet from 6 to 18 months has not been recorded. Thus, we hypothesize that the higher risk observed in those breastfeeding beyond 12 months could be driven by underlying differences in gluten introduction, as this group could have an even more delayed gluten introduction. Delayed introduction could also be associated with higher amounts of gluten at introduction, impacting on the risk for CD.

An umbrella effect of continued breastfeeding when gluten is introduced in the diet has been suggested based on epidemiologic data.[20,27,28] The hypothesis of a protective effect of breastfeeding during gluten introduction could not be supported by our data, but the sample size in this part was too small to draw firm conclusions.

The strength of our study is the prospective design, which prevents the recall bias encountered in case-control studies. Questionnaires were completed close to the actual exposures of interest and before the CD was diagnosed. The external validity of the study is ensured with a population-based design. Breastfeeding duration and time of gluten introduction is similar to the general Norwegian population.[29,30] A known selection of mothers in the study has not been found to influence on the association between several exposures and outcomes.[29]

The diagnosis of CD in this study is based on the national patient register or parental reports. We do not have access to patient files and clinical data for details regarding biopsy results and

TABLE 4 Gluten Exposure Under Continued Breastfeeding, With Borderline Overlapping Breastfeeding (Continued ±1 mo After Gluten Introduction) and Absent Breastfeeding at Gluten Introduction, and the Risk for CD ("Umbrella Effect")

Continued Breastfeeding at Time of Gluten Introduction	All, *n* = 45 156	CD, *n* (%), *n* = 170 (0.38)	Unadjusted OR (95% CI)	aOR[a] (95% CI)	*P*
Yes	26 413	118 (0.45)	1.22 (0.77–1.95)	1.17 (0.74–1.87)	.50
Borderline: +/− 1 mo overlap	12 993	31 (0.24)	0.65 (0.38–1.14)	0.65 (0.37–1.14)	.13
No	5750	21 (0.37)	Reference	Reference	Reference

Included in the analysis are only those where gluten had been introduced at or before 6 mo age (*n* = 45 326).
[a] Adjusted for maternal CD, gender, and age of child.

serological markers to validate the diagnosis. The relatively strict case definition with 2 or more entries in the NPR was chosen to avoid false-positives among the celiac cases at the expense of false-negatives in the cohort as a whole. We expect some undiagnosed as well as misclassified celiac patients in the cohort both due to our relatively strict criteria for classifying disease and because of the well-known high rate of undiagnosed compared with diagnosed cases in screening studies.[26,27] However, CD has been found to be undiagnosed in 1% to 2% of the population in screening studies.[26–28] This could potentially reduce the size of the observed associations, with ORs closer to 1 if the risk factors are similar in the diagnosed and undiagnosed group of patients with CD.

CONCLUSIONS

We observed a higher risk of CD with delayed gluten introduction as well as with prolonged breastfeeding >12 months, though the effects were of modest sizes. Gluten introduction <4 months was uncommon in the population, and the study was not powered to assess this association. Development of tolerance may be facilitated by timely introduction of gluten, but factors involved in loss of tolerance needs further studies.

ACKNOWLEDGMENTS

We are grateful to all the participating families in Norway who take part in this ongoing cohort study.

REFERENCES

1. Koning F, Schuppan D, Cerf-Bensussan N, Sollid LM. Pathomechanisms in celiac disease. *Best Pract Res Clin Gastroenterol*. 2005;19(3):373–387
2. Sollid LM, McAdam SN, Molberg O, et al. Genes and environment in celiac disease. *Acta Odontol Scand*. 2001;59(3):183–186
3. Molberg O, Mcadam SN, Körner R, et al. Tissue transglutaminase selectively modifies gliadin peptides that are recognized by gut-derived T cells in celiac disease. *Nat Med*. 1998;4(6):713–717
4. Trynka G, Hunt KA, Bockett NA, et al; Spanish Consortium on the Genetics of Coeliac Disease (CEGEC); PreventCD Study Group; Wellcome Trust Case Control Consortium (WTCCC). Dense genotyping identifies and localizes multiple common and rare variant association signals in celiac disease. *Nat Genet*. 2011;43(12):1193–1201
5. Maurano MT, Humbert R, Rynes E, et al. Systematic localization of common disease-associated variation in regulatory DNA. *Science*. 2012;337(6099):1190–1195
6. Szajewska H, Chmielewska A, Pieścik-Lech M, et al; PREVENTCD Study Group. Systematic review: early infant feeding and the prevention of coeliac disease. *Aliment Pharmacol Ther*. 2012;36(7):607–618
7. Norris JM, Barriga K, Hoffenberg EJ, et al. Risk of celiac disease autoimmunity and timing of gluten introduction in the diet of infants at increased risk of disease. *JAMA*. 2005;293(19):2343–2351
8. Olsson C, Stenlund H, Hörnell A, Hernell O, Ivarsson A. Regional variation in celiac disease risk within Sweden revealed by the nationwide prospective incidence register. *Acta Paediatr*. 2009;98(2):337–342
9. Carlsson A, Agardh D, Borulf S, Grodzinsky E, Axelsson I, Ivarsson SA. Prevalence of celiac disease: before and after a national change in feeding recommendations. *Scand J Gastroenterol*. 2006;41(5):553–558
10. Akobeng AK, Ramanan AV, Buchan I, Heller RF. Effect of breast feeding on risk of coeliac disease: a systematic review and meta-analysis of observational studies. *Arch Dis Child*. 2006;91(1):39–43
11. Ashabani A, Abushofa U, Abusrewill S, Abdelazez M, Tucková L, Tlaskalová-Hogenová H. The prevalence of coeliac disease in Libyan children with type 1 diabetes mellitus. *Diabetes Metab Res Rev*. 2003;19(1):69–75
12. Calder PC, Krauss-Etschmann S, de Jong EC, et al. Early nutrition and immunity - progress and perspectives. *Br J Nutr*. 2006;96(4):774–790
13. Prescott SL, Smith P, Tang M, et al. The importance of early complementary feeding in the development of oral tolerance: concerns and controversies. *Pediatr Allergy Immunol*. 2008;19(5):375–380
14. Magnus P, Irgens LM, Haug K, Nystad W, Skjaerven R, Stoltenberg C; MoBa Study Group. Cohort profile: the Norwegian Mother and Child Cohort Study (MoBa). *Int J Epidemiol*. 2006;35(5):1146–1150
15. Norwegian Paediatric Association. *Guidelines for Coeliac Disease*. Oslo, Norway: Norwegian Paediatric Association; 2011
16. Ziegler AG, Schmid S, Huber D, Hummel M, Bonifacio E. Early infant feeding and risk of developing type 1 diabetes-associated autoantibodies. *JAMA*. 2003;290(13):1721–1728
17. Kelly DA, Phillips AD, Elliott EJ, Dias JA, Walker-Smith JA. Rise and fall of coeliac disease 1960-85. *Arch Dis Child*. 1989;64(8):1157–1160
18. Logan RF, Rifkind EA, Busuttil A, Gilmour HM, Ferguson A. Prevalence and "incidence" of celiac disease in Edinburgh and the Lothian region of Scotland. *Gastroenterology*. 1986;90(2):334–342
19. Stevens FM, Egan-Mitchell B, Cryan E, McCarthy CF, McNicholl B. Decreasing incidence of coeliac disease. *Arch Dis Child*. 1987;62(5):465–468
20. Ivarsson A, Hernell O, Stenlund H, Persson LA. Breast-feeding protects against celiac disease. *Am J Clin Nutr*. 2002;75(5):914–921
21. Ivarsson A, Myléus A, Norström F, et al. Prevalence of childhood celiac disease and changes in infant feeding. *Pediatrics*. 2013;131(3). Available at: Available at: www.pediatrics.org/cgi/content/full/131/3/e687
22. Stordal K, Beitnes ACR, Vikskjold PF, et al. High cumulative incidence of clinically diagnosed coeliac disease in Norway [Abstract 10053]. *World Congress of Pediatrics Gastroenterology, Hepatology and Nutrition*. 2012
23. Olsson C, Hernell O, Hörnell A, Lönnberg G, Ivarsson A. Difference in celiac disease risk between Swedish birth cohorts suggests an opportunity for primary prevention. *Pediatrics*. 2008;122(3):528–534
24. Hogen Esch CE, Rosén A, Auricchio R, et al; PreventCD Study Group. The PreventCD Study design: towards new strategies for the prevention of coeliac disease. *Eur J Gastroenterol Hepatol*. 2010;22(12):1424–1430

25. Hay G, Lande B, Grønn M, et al. *Anbefalinger for spedbarnsernæringen*. Oslo, Norway: Helsedirektoratet; 2001
26. Myléus A, Ivarsson A, Webb C, et al. Celiac disease revealed in 3% of Swedish 12-year-olds born during an epidemic. *J Pediatr Gastroenterol Nutr*. 2009;49(2): 170–176
27. Mäki M, Mustalahti K, Kokkonen J, et al. Prevalence of Celiac disease among children in Finland. *N Engl J Med*. 2003;348(25):2517–2524
28. Mustalahti K, Catassi C, Reunanen A, et al; Coeliac EU Cluster, Project Epidemiology. The prevalence of celiac disease in Europe: results of a centralized, international mass screening project. *Ann Med*. 2010;42(8):587–595
29. Nilsen RM, Vollset SE, Gjessing HK, et al. Self-selection and bias in a large prospective pregnancy cohort in Norway. *Paediatr Perinat Epidemiol*. 2009;23(6): 597–608
30. Øverby NC, Kristiansen AL, Andersen LF, Lande B. Spedkost 6 måneder. Oslo, Norway: Helsedirektoratet; 2008

Supplemental Information

SUPPLEMENTAL TABLE 5 Maternal Characteristics, Pregnancy Data, Smoking, Birth Weight, and Mode of Delivery (324 Children With CD, 81 843 Cohort Controls, and 24 750 Excluded From Analysis)

	CD		Excluded
	Yes, *n* = 324	No, *n* = 81 843	*n* = 24 750
Parity, *n* (%)			
0	145 (44.8)	37 972 (46.4)	14 882 (60.1)
1	116 (35.8)	28 622 (35.0)	6260 (25.3)
2+	63 (19.4)	15 249 (18.6)	3608 (14.6)
Maternal age, mean (median, range)	30.1 (30, 19–43)	30.2 (30, 14–47)	30.0 (30, 16–47)
< 25 y, *n* (%)	37 (11.4)	8390 (10.3)	3622 (14.7)
25–35 y, *n* (%)	240 (74.1)	59 376 (72.5)	16 455 (66.5)
> 35 y, *n* (%)	47 (14.5)	14 077 (17.2)	4673 (18.8)
Maternal education, *n* (%)			
≤12 y	91 (28.1)	24 465 (29.9)	6884 (27.8)
13–16 y	139 (42.9)	34 708 (42.4)	6250 (25.3)
≥17 y	87 (26.9)	21 073 (25.7)	3839 (15.5)
Unknown	7 (2.2)	1597 (2.0)	7777 (31.4)
Smoking during pregnancy, *n* (%)			
Yes	21 (6.5)	6492 (7.9)	1644 (6.6)
Missing	11 (3.4)	4180 (5.1)	12 021 (48.6)
Birth weight in g, mean (median)	3582 (3580)	3593 (3610)	3477 (3540)
<2500, *n* (%)	7 (2.2)	2641 (3.2)	1858 (7.5)
2500–3499, *n* (%)	131 (40.4)	30 776 (37.6)	9726 (39.3)
3500–4499, *n* (%)	173 (53.4)	44 712 (54.7)	12 169 (49.2)
>4500, *n* (%)	13 (4.0)	3668 (4.5)	978 (4.0)
Missing	0	46 (0.1)	19
Caesarean delivery, *n* (%)	42 (13.0)	11 568 (14.1)	4511 (18.2)
Elective	13 (4.0)	4209 (5.1)	1646 (6.7)
Emergency	28 (8.6)	6419 (7.8)	2517 (10.2)
Not specified	1 (0.31)	940 (1.1)	348 (1.4)