Early feeding practices seem to have no impact on the risk of developing celiac disease during childhood

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Primary Prevention of Celiac Disease: Environmental Factors with a Focus on Early Nutrition

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Key insights

Previously, the main evidence for the influence of early nutrition practices on the risk of celiac disease came from observational studies. Recently, the results from two large randomized controlled studies (the PREVENTCD and CELIPREV trials) were published. The aim of these studies was to evaluate the effect of the timing of gluten introduction on the risk of celiac disease in at-risk children. Contrary to previous thought, the timing of gluten introduction in an infant's diet does not influence the risk of developing celiac disease.

Current knowledge

Celiac disease is an autoimmune enteropathic disorder in which dietary gluten and related prolamins play a major pathogenic role. Genetically susceptible individuals harbor a background in which variants of human leukocyte antigens (HLA) haplotypes DQ2/DQ8 are the main predisposing factors. The symptoms of celiac disease range from asymptomatic to gastrointestinal and non-gastrointestinal presentations of varying severity. Celiac disease affects around 1% of the general population in Europe, greatly affecting patients' quality of life and incurring a significant cost burden on society. There has always been a great deal of inconsistency in the literature regarding the impact of the timing of gluten introduction on the risk of celiac disease.

Practical implications

The only available treatment for affected individuals is a strict, gluten-free diet. Until recently, special emphasis was placed on early nutrition, namely, the timing and mode of gluten in-

Factor	Supporting evidence
Breastfeeding as a protective factor	No
Timing of gluten introduction	No
Delayed gluten introduction	No
Mode of delivery (cesarean)	No
Genetic background	Yes

Factors influencing the risk of developing celiac disease: an update

roduction as a preventive measure. However, results from the PREVENTCD and CELIPREV trials do not support the current recommendations. The age of the child at gluten introduction (between 4 and 12 months) has no effect on the prevention of celiac disease. Gluten should only be introduced in line with general recommendations for starting infant complementary foods. In children with no genetic predisposition for celiac disease, the timing and mode of gluten introduction does not influence disease risk.

Recommended reading

Szajewska H, Shamir R, Chmielewska A, et al: Systematic review with meta-analysis: early infant feeding and coeliac disease – update 2015. *Aliment Pharmacol Ther* 2015;41:1038–1054.

Primary Prevention of Celiac Disease: Environmental Factors with a Focus on Early Nutrition

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Key Messages

- Celiac disease (CD) is an autoimmune disease caused by gluten, which requires a lifelong gluten-free diet.
- Breastfeeding does not prevent CD.
- The timing of gluten introduction into the infant's diet does not influence the risk of developing CD.
- Genetic predisposition (presence of HLA-DQ2 and/or DQ8) is the main factor influencing the development of CD.

Key Words

Celiac disease · Environment · Gluten · Breastfeeding · Nutrition

Abstract

Celiac disease (CD) is a common autoimmune disorder caused by ingestion of gluten. When diagnosed, it should be treated with a lifelong, strict gluten-free diet. Early infant feeding practices have been suggested as a means of preventing CD. In the last few decades, observational data have suggested that breastfeeding, especially at the time of introducing gluten into the infant's diet, as well as the time and

mode of gluten first being given to a child could prevent or delay the occurrence of CD. As a result, recommendations advised that it is prudent to avoid both early (<4 months) and late (>7 months) introduction of gluten, and to introduce gluten gradually while the infant is still being breastfed, as this may reduce the risk of celiac disease, type 1 diabetes mellitus, and wheat allergy. Recently, the results of two large randomized trials have shown that breastfeeding in general, breastfeeding during gluten introduction, and early or delayed gluten introduction do not influence the total risk of CD in genetically predisposed individuals. Introducing gluten at 4 versus 6 months in very small amounts, or at 6 versus 12 months, resulted in similar rates of CD in these children. Thus, early feeding practices seem to have no impact on the risk of developing CD during childhood. In children without the genetic predisposition, the age and mode of gluten introduction do not influence the risk anyway.

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Background

Celiac disease (CD) is an immune-mediated systemic disorder elicited by gluten and related prolamins in genetically susceptible individuals, which is characterized by the presence of a variable combination of gluten-dependent clinical manifestations, CD-specific antibodies,

Table 1. Duration of breastfeeding and risk of CD [adapted from 9, 10]

First author [Ref.], study	Duration of BF	Conclusion
<i>Interventional studies</i>		
Vriezinga [7], PREVENTCD	No significant association between CD and BF duration	
Lionetti [8], CELIPREV	No significant association between CD and BF duration	
<i>Observational studies</i>		
Included in the systematic review by Akobeng [26]		
Auricchio [22]	BF <30 days or bottle-fed vs. BF >30 days	Risk of CD higher if BF shorter
Ascher [37]	No significant association between CD and BF duration	
Falsh-Magnusson [35]	Median BF duration 2.5 months (CD) vs. 4 months (controls)	Risk of CD higher if BF shorter
Greco [23]	BF <90 days or bottle-fed vs. BF >90 days	Risk of CD higher if BF shorter
Ivarsson [36]	Median BF duration 5 months (CD) vs. 7 months (controls)	Risk of CD higher if BF shorter
Peters [24]	CD decreased by 63% for BF duration >2 vs. <2 months	Risk of CD higher if BF shorter
Decker [25]	No significant association between CD and BF duration	
Hummel [33] ^a /Ziegler [59] ^a , BABYDIAB	No significant association between CD autoimmunity and BF duration	
Jansen [31], Generation R Study	No significant association between CD autoimmunity and BF duration	
Norris [27], DAISY Study	No significant association between CD autoimmunization and BF duration	
Roberts [28]	No significant association between CD and BF duration	
Størdal [32], MoBa ^b	No significant association between CD and BF duration	
Welanders [29]	No significant association between CD and BF duration	
Ziegler [30]	No significant association between CD autoimmunity and BF duration	
BF = Breastfeeding. ^a Same population. ^b The Norwegian Mother and Child Cohort Study.		

HLA-DQ2 or HLA-DQ8 haplotypes, and enteropathy [1]. The clinical spectrum of the disease may range from gastrointestinal and non-gastrointestinal symptoms of different intensity to an asymptomatic presentation [1]. CD affects approximately 1% of the general population in Europe, which makes it a relatively common disease of a significant social impact [2]. A lifelong, strict, gluten-free diet remains the only available treatment for affected individuals. The quality of life of people suffering from CD may be decreased, and the disease imposes a significant cost burden on society [3–5]. Due to the above reasons, primary prevention has been advocated and a special emphasis was put on early nutrition, namely breastfeeding, as well as the time and mode of gluten introduction as preventive measures [6]. Until recently, the main body of evidence for the influence of early nutrition practices on the risk of CD was derived from observational studies, the results of which cannot be interpreted as a causality, but rather as associations. Thus, the pursuit of randomized trials was strongly recommended. In October 2014, two large randomized controlled trials (RCTs) performed by two different research teams that were designed to examine the effect of different timings of gluten introduction were published, delivering long-awaited data on the effect of different timings of gluten introduction [7, 8]. One of the 2 studies, the Prevent Coeliac Disease (PREVENTCD;

<http://www.preventcd.com>) project, investigated the hypothesis of possible induction of tolerance to gluten in genetically predisposed children through the introduction of small quantities of gluten during the period of breastfeeding, either at 4 or 6 months of age [7]. The other study, the Risk of CD and Age at Gluten Introduction (CELIPREV) trial, compared the risk of CD immunization and overt CD in children at increased risk in whom dietary gluten had been introduced at 6 months compared to 12 months of age [8]. These 2 studies, a previous systematic review [9], and a recent systematic review [10] that incorporated the results of the 2 RCTs served as the basis for this current review.

Breastfeeding and CD

Breastfeeding is the optimal way of feeding an infant for many health-related reasons, and exclusive breastfeeding for 4–6 months of age is recommended worldwide [11, 12]. There are several mechanisms by which breastfeeding has been linked to the prevention of CD. Given that breast milk is abundant in factors involving passive immunity, such as lysozyme, lactoferrin or IgA antibodies, breastfeeding may prevent gastrointestinal infections that have been linked to CD development [13–15]. Gut permeability, which has been shown to be de-

creased in breastfed infants, is another important player in CD pathogenesis [16, 17]. Additionally, breastfeeding theoretically might help with the development of tolerance to gluten by exposing an infant to some gluten fractions digested with human milk [18, 19]. Moreover, the role of the gut microbiota is also being raised in the context of CD prevention due to significant differences in microbial patterns observed in breastfed infants compared to formula-fed infants [20]. The above-listed factors may be some of the plausible explanations for the protective potential of human milk against CD.

Exclusive or Any Breastfeeding and Duration of Breastfeeding

Previous studies have provided no clear evidence on whether exclusive breastfeeding compared with formula or mixed feeding reduces the risk of CD or only delays the onset of symptoms [21–24]. Contradictory results have been reported on the effect of any breastfeeding compared to no breastfeeding [24, 25]. In the systematic review by Akobeng et al. [26] (involving 6 observational studies), protection against CD with a longer duration of breastfeeding was reported. However, observational studies that followed did not confirm this finding [25, 27–30].

The most recent data from large cohort studies still brought no clear evidence with regards to the role of breastfeeding and CD prevention. A prospective Generation R cohort including 1,679 Dutch children positive for HLA-DQ2 and/or DQ8 evaluated the possible association of the timing of gluten introduction and breastfeeding duration with CD autoimmunity at 6 years of age. It was shown that breastfeeding for longer than 6 months was not related to a lower risk of CD autoimmunity [31]. Interestingly, the Norwegian Mother and Child Cohort Study (MoBa) involving more than 100,000 children showed that breastfeeding for longer than 12 months was associated with a higher risk of CD [32]. A German cohort study (BABYDIAB) observed more than 1,500 children of parents suffering from type 1 diabetes and measured islet and CD autoimmunity. No association between the duration of breastfeeding and risk of CD autoimmunity was found [33]. In the cross-sectional ETICS study (Exploring the Iceberg of Celiacs in Sweden), 2 birth cohorts were compared [34]. The duration of breastfeeding was longer in the 1997 cohort (9 months) compared to the 1993 cohort (7 months), being similar to that of the Swedish general population. The pooled results for 5 observational studies [22, 23, 25, 28, 33] showed that any breastfeeding compared with no breastfeeding

Fig. 1. No breastfeeding versus any breastfeeding and the risk of CD. Results from the PREVENTCD study (no significant difference between groups). BF = Breastfeeding.

had no effect on the risk of developing CD [odds ratio (OR) 0.69, 95% confidence interval (CI) 0.30–1.59] [10]. The results of breastfeeding duration on the risk of CD are summarized in table 1.

In 2014, the results of the 2 aforementioned interventional trials were published. The PREVENTCD study was a multicenter double-blind placebo-controlled randomized trial, carried out in 8 countries (Croatia, Germany, Hungary, Israel, Italy, The Netherlands, Poland, and Spain), involving 944 children with HLA-DQ2 or HLA-DQ8 positivity who had at least 1 first-degree relative with CD [7]. Children were randomly assigned to receive placebo ($n = 469$) or 100 mg of immunologically active gluten ($n = 475$) daily from 16 to 24 weeks of age. Both groups received increasing amounts of gluten from 6 months onward. The main outcome measure was the frequency of CD, which was confirmed by intestinal biopsy at 3 years of age. The CELIPREV study was a multicenter randomized interventional trial conducted in Italy [8]. Dietary gluten was introduced at 6 months of age ($n = 297$) or at 12 months of age ($n = 256$) in infants at risk for CD, defined by the presence of a first-degree relative with CD and a positive test for HLA-DQ2 or HLA-DQ8 (tested later during the study). The presence of specific CD autoantibodies and overt CD at 5 years of age were the main outcome measures.

The results of both the PREVENTCD (fig. 1) and CELIPREV studies showed that exclusive as well as any breastfeeding did not significantly influence the development of CD. Neither did the duration of breastfeeding (table 1). Despite the above, one needs to cautiously in-

Table 2. Breastfeeding during the introduction of gluten and risk of CD [adapted from 6, 7]

First author [Ref.], study	Conclusion
<i>Interventional studies</i>	
Vriezinga [7], PREVENTCD	No effect
Lionetti [8], CELIPREV	No effect
<i>Observational studies</i>	
Included in a meta-analysis by Szajewska [10]	
Falsh-Magnusson [35]	Protective
Peters [24]	Protective
Ivarsson [36]	Protective
Norris [27], DAISY study	No effect
Aronsson [38], TEDDY study	No effect
Størdal [32], MoBa study	No effect ^a
Ascher [37]	No effect
Pooled	No effect
Hummel [41], BABYDIAB	No effect
Ivarsson [34], ETICS	No effect
^a Breastfeeding predisposing to CD?	

interpret these data, as both trials were designed to evaluate the risk of CD among children who were randomly assigned to the introduction of gluten at various ages, not the effect of breastfeeding on the risk of developing CD.

Breastfeeding at the Time of Gluten Introduction

Previously, a meta-analysis by Akobeng et al. [26] suggested that breastfeeding at the time of gluten introduction might be protective. However, it was unclear whether it provided long-term prevention against CD or only delayed the onset of the disease [24, 35–37]. Results of the recently published cohort studies did not confirm the protective effect of breastfeeding at the time of gluten introduction on developing CD [31, 38]. Also, the pooled results for 7 observational studies showed that breastfeeding at the time of gluten introduction has no effect on the risk of developing CD compared with formula feeding (OR 0.88, 95% CI 0.52–1.51) [10]. The results of both recently published randomized studies, PREVENTCD and CELIPREV, did not show a protective effect of introducing gluten during breastfeeding [7, 8]. Again, caution is needed when interpreting the results, as neither of these 2 RCTs was designed to address directly the effect of breastfeeding on CD. A summary of the studies showing the effect of breastfeeding at the time of gluten introduction is presented in table 2.

Timing of Gluten Introduction

There has been a considerable deal of inconsistency in the literature with regards to the impact of the timing of gluten introduction on the risk of CD. In 2008, based on the results of observational studies, the best available evidence at that time, the European scientific bodies [the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Food Safety Authority (EFSA)] recommended that it is prudent to avoid both early (<4 months) and late (>7 months) introduction of gluten and to introduce gluten gradually while the infant is still being breastfed [39, 40]. This approach was considered to decrease the risk of CD (also the risk of type 1 diabetes and wheat allergy). Since then, a substantial body of evidence from both cohort studies and, most importantly, large RCTs has become available. Data from both interventional and observational studies are summarized in table 3.

In the previously published prospective cohort study by Norris et al. [27], both early (<3 months of age) and late (>7 months of age) introduction of gluten to children at increased risk of CD and type 1 diabetes was associated with an increased risk of CD autoimmunity. Other studies did not report such effects [24, 29, 30, 35, 36].

Two new large cohort studies [31, 32] reported data comparing the introduction of gluten before and after 6 months of age. The Generation R Study found that later compared to earlier exposure was not significantly associated with CD autoimmunity [31]. The Norwegian Mother and Child Cohort Study (MoBa) showed that later but not earlier exposure to gluten increased the risk of CD, although this difference was of borderline significance (adjusted OR 1.27, 95% CI 1.01–1.65) [32].

In The Environmental Determinants of Diabetes in the Young (TEDDY) study, first exposure to gluten before 17 weeks, between 17 and 26 weeks, or after 26 weeks of age was compared, and no difference was found in the risk of CD autoimmunity or CD between the groups [38]. Another cohort study (BABYDIAB) reported no difference in CD autoimmunity in infants with gluten introduction before or after 3 months of age [33].

The ETICS study of cross-sectional design compared 2 birth cohorts of 12-year-olds and found a significant difference in the total prevalence of CD in children born during the CD epidemic (in 1993, when gluten was introduced from 6 months of age) and those born after the epidemic (in 1997, with gluten introduction involving small amounts given from 4 to 6 months of age) [34].

The results of interventional trials designed to assess the role of the timing of gluten introduction were pub-

Table 3. Time of gluten introduction and risk of CD or CD autoimmunity [adapted from 6, 7]

First author [Ref.], study	Results
<i>Interventional studies</i>	
Vriezinga [7], PREVENTCD	No significant difference in CD risk for different time of gluten introduction (4 vs. 6 months) at 3 years
Lionetti [8], CELIPREV	6 vs. 12 months: RR 2.36 (1.27–4.36) at 2 years – predisposing; no significant difference at 5 years (primary outcome)
Hummel [41] ^a /Beyerlein [42] ^a	No significant difference in CD and CD autoimmunity for different time of gluten introduction (6 vs. 12 months)
Sellitto [43]	No significant difference in CD autoimmunity risk for different time of gluten introduction (6 vs. 12 months)
<i>Observational studies</i>	
Falth-Magnusson [35]	No significant association between CD and time of gluten introduction
Ivarsson [36]	No significant association between CD and time of gluten introduction (different time intervals from 1 to 12 months)
Norris [27], DAISY Study	1–3 vs. 4–6 months: HR 2.94 (95% CI 0.83–10.4) – predisposing to CD; ≥7 vs. 4–6 months: HR 1.78 (95% CI 0.92–3.42) – predisposing
Peters [24]	No significant association between CD and time of gluten introduction (different time intervals from ≤3 to >5 months)
Welander [29]	No significant association between CD and time of gluten introduction (different time intervals from 0 to 12 months)
Ziegler [30]	No significant association between CD and time of gluten introduction (different time intervals from ≤3 to >6 months)
Jansen [31], Generation R Study	No significant association between CD autoimmunity and time of gluten introduction (<6 vs. >6 months)
Størdal [32], MoBa ^b	<6 vs. >6 months: adjusted OR 1.27 (95% CI 1.01–1.65) – borderline significance for CD risk
Hummel 2007 [33], BABYDIAB	No significant association between CD autoimmunity and time of gluten introduction (<3 or >3 months)
Aronsson [38], TEDDY	No significant association between CD or CD autoimmunity and time of gluten introduction (<17 vs. 17–26 vs. >26 weeks)
Ivarsson [34], ETICS	More CD in children born during the CD epidemic (1993; gluten introduction from 6 months of age) than after the epidemic (1997; gluten introduction in small amounts from age 4–6 months)
HR = Hazard ratio; RR = relative risk. ^a Same population. ^b The Norwegian Mother and Child Cohort Study.	

lished recently. In the PREVENTCD study, the risk of CD at 3 years of age was similar in the group receiving 100 mg of immunologically active gluten daily from 16 to 24 weeks of age compared to the placebo group. The cumulative incidence of CD was 5.2% (95% CI 3.6–6.8) [7]. Introduction of gluten at 6 months was compared to 12 months in 3 other studies. In the CELIPREV trial, the earlier introduction of gluten increased the risks of CD autoimmunity (16 vs. 7%, $p = 0.002$) and overt CD (12 vs. 5%, $p = 0.01$) at 2 years, but it had no effect on either risk at 5 years of age, which was the primary outcome of the study [8]. Thus, the later introduction of gluten delayed the onset of the disease without influencing the overall risk. The results for PREVENTCD and CELIPREV are presented in figure 2. Other interven-

tional studies also reported no difference between groups in the risk of CD and/or CD autoimmunity [41–43] (table 3).

Amount of Gluten at Introduction

A study from Sweden analyzed the amount of gluten ingested by children. In children younger than 2 years of age, the risk of developing CD was greater when gluten was introduced into the diet in ‘large’ amounts compared to ‘small’ or ‘medium’ amounts without quantification in grams per day (adjusted OR 1.5, 95% CI 1.1–2.1). The effect was not observed in older children [36]. The above data come from the Swedish epidemic of CD. During the 1980s, Sweden experienced a fourfold increase in the

Fig. 2. Timing of gluten introduction and the risk of CD: data from the PREVENTCD (no significant difference between groups) and CELIPREV trials [a significant difference between groups at 2 years but not at 5 years (primary outcome)]. NS = Not significant.

number of CD cases. This phenomenon was preceded by the change in infantile dietary habits: increasing daily gluten intake and postponing the timing of gluten introduction. The number of new CD cases decreased significantly after the nutritional recommendations were modified and the amount of gluten ingested was reduced. Data from the Swedish epidemic suggest that ingestion of large amounts of gluten at introduction, and possibly large amounts later on, increase the risk for the early onset of CD. However, whether other elements, such as specific products given in Sweden or other environmental factors, played a role in the epidemic cannot be ruled out.

Lastly, the risk of CD development in HLA-DQ2.5 homozygous and HLA-DQ2.2/2.5 heterozygous individuals was reported to be significantly higher than that in HLA-DQ2.5/non-DQ2 heterozygous individuals. The dose of the HLA-DQ2 gene might be related to gluten epitope diversity and the risk of CD [44]. It is plausible that the amount of gluten needed for CD development is different in subjects of different genetic risk.

The PREVENTCD study reported that the amount of gluten at weaning was not related to the development of CD. This conclusion was based on the mean daily gluten intake after the intervention in a subset of participants [7]. However, of note, it was not a preplanned study outcome.

Other Environmental Factors

Genetic predisposition and exposure to gluten are the two undeniable factors necessary for CD to develop. However, most of the individuals positive for HLA-DQ2

and/or HLA-DQ8 who are exposed to gluten do not develop the disease. Predisposing genes are carried by 30% of general population [45], while CD occurs only in 1% [1]. Apart from early nutrition, other environmental factors must play a role. Repeated gastrointestinal infections have been reported to increase the risk of CD [13, 14]. Increased intestinal permeability might be causative, allowing proteins, such as gliadin, to enter the lamina propria and activate the autoimmune reaction. Evidence, however, is not clear. Some studies have found infections at the time of gluten introduction not to be associated with increased risk of CD [46, 47].

The intestinal microbiota has also been investigated as a potential pathogenetic factor in CD. Duodenal and fecal microbiota have been reported to be imbalanced in children with CD, with increased proportions of *Bacteroides* species and a reduction of *Bifidobacterium* species. A more favorable pattern was only partially restored after introducing a gluten-free diet [48, 49]. Administering *Bifidobacterium* together with a gluten-free diet in children with CD was investigated in a randomized placebo-controlled trial [50]. A decrease in both the numbers of the *Bacteroides fragilis* group and the content of secretory IgA in stools was found, which might further confirm the role of microbiota in the pathogenesis of CD. However, it still remains unclear whether the differences in microbial patterns between celiac and non-celiac individuals are a causative factor or rather a consequence of the disease. Interestingly, a possible interaction between genotype and gut microbiota predisposing to CD development has been raised in some studies and is being further explored [20]. In infants at a high genetic risk of developing CD,

the bacterial pattern is significantly different from that in infants at moderate or low risk [51–53]. Further studies on the potential role of altered microbiota in infants genetically predisposed to CD might provide more insight [20].

Delivery by cesarean section and associated alterations in the development of the enteric homeostasis during the neonatal period have been suggested to influence the incidence of CD [54]. However, more recent large cohort studies have found no association between the mode of delivery and the incidence of CD [55, 56]. Vaccinations, due to modulation of immunity, have been proposed to be involved in the process of developing autoimmune diseases [57]. Scarce data available with regards to CD fail to support this hypothesis [58].

Conclusion

The results of recently published interventional studies did not confirm previous findings from observational studies and did not support current recommendations. Neither the specific timing of gluten introduction nor breastfeeding protect against CD in genetically predisposed individuals. Therefore, there is a need to update

current recommendations to suggest that since the age of gluten introduction (anywhere between 4 and 12 months) has no effect on the prevention of CD, gluten should be introduced only as part of recommendations for introducing complementary foods in general. It is worth emphasizing that in children with no genetic predisposition for CD, the timing and mode of gluten introduction does not influence the risk anyhow. Furthermore, breastfeeding for 6 months and beyond should be promoted due to its many positive effects on health, but CD prevention should not be used as a reason to do so; there is no need to introduce gluten while the infant is still being breastfed. In regard to the mode of delivery, even though it was once suggested to be related to CD, there seems to be no support for such an association. Finally, the gut microbiota may play a greater role in the pathogenesis of CD than previously appreciated. The role of other environmental factors such as infections or vaccinations remains unclear.

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References

- Husby S, Koletzko S, Korponay-Szabo IR, et al: Guidelines for the diagnosis of coeliac disease. *J Pediatr Gastroenterol Nutr* 2012; 54:136–160.
- Mustalahti K, Catassi C, Reunanen A, et al: The prevalence of celiac disease in Europe: results of a centralized, international mass screening project. *Ann Med* 2010;42:587–595.
- Kurppa K, Collin P, Mäki M, et al: Celiac disease and health-related quality of life. *Expert Rev Gastroenterol Hepatol* 2011;5:83–90.
- Shamir R, Hernell O, Leshno M: Cost-effectiveness analysis of screening for celiac disease in the adult population. *Med Decis Making* 2006;26:1–12.
- Hershcovici T, Leshno M, Goldin E, et al: Cost effectiveness of mass screening for celiac disease is determined by time-delay to diagnosis and quality of life on a gluten free diet. *Aliment Pharmacol Ther* 2010;31:901–910.
- Troncone R, Ivarsson A, Szajewska H, Mearín ML; Members of European Multistakeholder Platform on CD (CDEUSSA): Review article: future research on coeliac disease – a position multistakeholder platform on celiac disease (CDEUSSA). *Aliment Pharmacol Ther* 2008;27:1030–1043.
- Vriezinga SL, Auricchio R, Bravi E, et al: Randomized feeding intervention in infants at high risk for celiac disease. *N Engl J Med* 2014;371:1304–1315.
- Lionetti E, Castellana S, Francavilla R, et al: Introduction of gluten, HLA status, and the risk of celiac disease in children. *N Engl J Med* 2014;371:1295–1303.
- Szajewska H, Chmielewska A, Piścik-Lech M, et al: Systematic review: early infant feeding and coeliac disease prevention. *Aliment Pharmacol Ther* 2012;36:607–618.
- Szajewska H, Shamir R, Chmielewska A, et al: Systematic review with meta-analysis: early infant feeding and coeliac disease – update 2015. *Aliment Pharmacol Ther* 2015;41: 1038–1054.
- World Health Organization: The optimal duration of exclusive breastfeeding: report of an expert consultation. Geneva, World Health Organization, 2001. http://www.who.int/nutrition/publications/optimal_duration_of_exc_bfeeding_report_eng.pdf (accessed September 4, 2012).
- ESPGHAN Committee on Nutrition; Agostoni C, Braegger C, Decsi T, Kolacek S, Koletzko B, Michaelsen KF, Mihatsch W, Moreno LA, Puntis J, Shamir R, Szajewska H, Turck D, van Goudoever J: Breast-feeding: a commentary by the ESPGHAN Committee on Nutrition. *J Pediatr Gastroenterol Nutr* 2009;49:112–125.
- Stene LC, Honeyman MC, Hoffenberg EJ, et al: Rotavirus infection frequency and risk of celiac disease autoimmunity in early childhood: a longitudinal study. *Am J Gastroenterol* 2006;101:2333–2340.
- Troncone R, Auricchio S: Rotavirus and celiac disease: clues to the pathogenesis and perspectives on prevention. *J Pediatr Gastroenterol Nutr* 2007;44:527–528.
- Solid LM: Breast milk against celiac disease. *Gut* 2002;51:767–768.

- 16 Heyman M, Abed J, Lebreton C, et al: Intestinal permeability in coeliac disease: insight into mechanisms and relevance to pathogenesis. *Gut* 2012;61:1355–1364.
- 17 Shulman RJ, Schanler RJ, Lau C, et al: Early feeding, antenatal glucocorticoids, and human milk decrease intestinal permeability in preterm infants. *Pediatr Res* 1998;44:519–523.
- 18 Chirido FG, Rumbo M, Anon MC, et al: Presence of high levels of non-degraded gliadin in breast milk from healthy mothers. *Scand J Gastroenterol* 1998;33:1186–1192.
- 19 Verhasselt V: Neonatal tolerance under breastfeeding influence. *Curr Opin Immunol* 2010;22:623–630.
- 20 Verdu EF, Galipeau HJ, Jabri B: Novel players in coeliac disease pathogenesis: role of the gut microbiota. *Nat Rev Gastroenterol Hepatol* 2015;12:497–506.
- 21 Nash S: Does exclusive breast-feeding reduce the risk of coeliac disease in children? *Br J Community Nurs* 2003;8:127–132.
- 22 Auricchio S, Folio D, de Ritis G, et al: Does breast feeding protect against the development of clinical symptoms of coeliac disease in children? *J Pediatr Gastroenterol Nutr* 1983;2:428–433.
- 23 Greco L, Auricchio S, Mayer M, et al: Case control study on nutritional risk factors in coeliac disease. *J Pediatr Gastroenterol Nutr* 1988;7:395–399.
- 24 Peters U, Schneeweiss S, Trautwein EA, et al: A case-control study of the effect of infant feeding on coeliac disease. *Ann Nutr Metab* 2001;45:135–142.
- 25 Decker E, Engelmann G, Findeisen A, et al: Cesarean delivery is associated with coeliac disease but not inflammatory bowel disease in children. *Pediatrics* 2010;125:e1433–e1440.
- 26 Akobeng AK, Ramanan AV, Buchan I, et al: Effect of breast feeding on risk of coeliac disease: a systematic review and meta-analysis of observational studies. *Arch Dis Child* 2006;91:39–43.
- 27 Norris JM, Barriga K, Hoffenberg EJ, et al: Risk of coeliac disease autoimmunity and timing of gluten introduction in the diet of infants at increased risk of disease. *JAMA* 2005;293:2343–2351.
- 28 Roberts SE, Williams JG, Meddings D, et al: Perinatal risk factors and coeliac disease in children and young adults: a record linkage study. *Aliment Pharmacol Ther* 2009;29:222–231.
- 29 Welander A, Tjernerberg AR, Montgomery SM, et al: Infectious disease and risk of later coeliac disease in childhood. *Pediatrics* 2010;125:e530–e536.
- 30 Ziegler AG, Schmid S, Huber D, et al: Early infant feeding and risk of developing type 1 diabetes-associated autoantibodies. *JAMA* 2003;290:1721–1728.
- 31 Jansen MA, Tromp II, Kiefte-de Jong JC, et al: Infant feeding and anti-tissue transglutaminase antibody concentrations in the Generation R Study. *Am J Clin Nutr* 2014;100:1095–1101.
- 32 Størdal K, White RA, Eggesbø M: Early feeding and risk of coeliac disease in a prospective birth cohort. *Pediatrics* 2013;132:1202–1209.
- 33 Hummel S, Hummel M, Banholzer J, et al: Development of autoimmunity to transglutaminase C in children of patients with type 1 diabetes: relationship to islet autoantibodies and infant feeding. *Diabetologia* 2007;50:390–394.
- 34 Ivarsson A, Myléus A, Norström F, et al: Prevalence of childhood coeliac disease and changes in infant feeding. *Pediatrics* 2013;131:e687–e694.
- 35 Falth-Magnusson K, Franzen L, Jansson G, et al: Infant feeding history shows distinct differences between Swedish coeliac and reference children. *Pediatr Allergy Immunol* 1996;7:1–5.
- 36 Ivarsson A, Hernell O, Stenlund H, et al: Breast-feeding protects against coeliac disease. *Am J Clin Nutr* 2002;75:914–921.
- 37 Ascher H, Krantz I, Rydberg L, et al: Influence of infant feeding and gluten intake on coeliac disease. *Arch Dis Child* 1997;76:113–117.
- 38 Aronsson CA, Lee H-S, Liu E, et al: Age at gluten introduction and risk of coeliac disease. *Pediatrics* 2015;135:239–245.
- 39 ESPGHAN Committee on Nutrition; Agostoni C, Decsi T, Fewtrell M, et al: Complementary feeding: a commentary by the ESPGHAN Committee on Nutrition. *J Pediatr Gastroenterol Nutr* 2008;46:99–110.
- 40 EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA): Scientific opinion on the appropriate age for introduction of complementary feeding of infants. <http://www.efsa.europa.eu/en/efsajournal/doc/1423.pdf> (accessed June 9, 2015).
- 41 Hummel S, Pfluger M, Hummel M, et al: Primary dietary intervention study to reduce the risk of islet autoimmunity in children at increased risk for type 1 diabetes: the BABYDIET study. *Diabetes Care* 2011;34:1301–1305.
- 42 Beyerlein A, Chmiel R, Hummel S, et al: Timing of gluten introduction and islet autoimmunity in young children: updated results from the BABYDIET study. *Diabetes Care* 2014;37:e194–e195.
- 43 Sellitto M, Bai G, Serena G, et al: Proof of concept of microbiome-metabolome analysis and delayed gluten exposure on coeliac disease autoimmunity in genetically at-risk infants. *PLoS One* 2012;7:e33387.
- 44 Vader W, Stepniak D, Kooy Y, et al: The HLA-DQ2 gene dose effect in coeliac disease is directly related to the magnitude and breadth of gluten-specific T cell responses. *Proc Natl Acad Sci USA* 2003;100:12390–12395.
- 45 Kagnoff MF: Celiac disease: pathogenesis of a model immunogenetic disease. *J Clin Invest* 2007;117:41–49.
- 46 Welander A, Tjernerberg AR, Montgomery SM, et al: Infectious disease and risk of later coeliac disease in childhood. *Pediatrics* 2010;125:e530–e536.
- 47 Lebowitz B, Green PHR, Murray JA: Season of birth in a nationwide cohort of coeliac disease patients. *Arch Dis Child* 2013;98:48–51.
- 48 Collado MC, Donat E, Ribes-Koninckx C, et al: Imbalances in faecal and duodenal Bifidobacterium species composition in active and nonactive coeliac disease. *BMC Microbiol* 2008;8:232.
- 49 Collado MC, Donat E, Ribes-Koninckx C, et al: Specific duodenal and faecal bacterial groups associated with paediatric coeliac disease. *J Clin Pathol* 2009;62:264–269.
- 50 Olivares M, Castillejo G, Varea V, et al: Double-blind, randomised, placebo-controlled intervention trial to evaluate the effects of Bifidobacterium longum CECT 7347 in children with newly diagnosed coeliac disease. *Br J Nutr* 2014;112:30–40.
- 51 De Palma G, Capilla A, Nadal I, et al: Interplay between human leukocyte antigen genes and the microbial colonization process of the newborn intestine. *Curr Issues Mol Biol* 2010;12:1–10.
- 52 Sánchez E, De Palma G, Capilla A, et al: Influence of environmental and genetic factors linked to coeliac disease risk on infant gut colonization by Bacteroides species. *Appl Environ Microbiol* 2011;77:5316–5323.
- 53 De Palma G, Capilla A, Nova E, et al: Influence of milk-feeding type and genetic risk of developing coeliac disease on intestinal microbiota of infants: the PROFICEL study. *PLoS One* 2012;7:e30791.
- 54 Decker E, Engelmann G, Findeisen A, et al: Cesarean delivery is associated with coeliac disease but not inflammatory bowel disease in children. *Pediatrics* 2010;125:e1433–e1440.
- 55 Emilsson L, Magnus MC, Størdal K: Perinatal risk factors for development of coeliac disease in children, based on the prospective Norwegian Mother and Child Cohort Study. *Clin Gastroenterol Hepatol* 2015;13:921–927.
- 56 Sevelsted A, Stokholm J, Bønnelykke K, et al: Cesarean section and chronic immune disorders. *Pediatrics* 2015;135:e92–e98.
- 57 Wraith DC, Goldman M, Lambert PH: Vaccination and autoimmune disease: what is the evidence? *Lancet* 2003;362:1659–1666.
- 58 Myléus A, Stenlund H, Hernell O, et al: Early vaccinations are not risk factors for coeliac disease. *Pediatrics* 2012;130:e63–e70.
- 59 Ziegler AG, Schmid S, Huber D, et al: Early infant feeding and risk of developing type 1 diabetes-associated autoantibodies. *JAMA* 2003;290:1721–1728.