EARLY DIET AND THE RISK OF COELIAC DISEASE. AN UPDATE 2024 POSITION PAPER BY THE ESPGHAN SPECIAL INTEREST GROUP ON COELIAC DISEASE

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ABSTRACT

This position paper by the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Special Interest Group on Coeliac Disease (SIG-CD) presents an update to the 2016 recommendations concerning early diet and the risk of coeliac disease (CD). The 2024 statements and recommendations are essentially similar to the 2016 recommendations. Breastfeeding, whether any amount, exclusive, or of any duration, does not reduce the risk of developing CD. Introducing gluten into an infant's diet between completed 4 and 12 months of age does not affect the cumulative incidence of CD, although earlier introduction may lead to earlier seroconversion and CD. In observational studies involving cohorts with a known risk for CD, consuming a high amount of gluten compared to a low amount during weaning and in the subsequent childhood years – specifically the first 2 to 3 years, and even up to 5 years in some studies – was associated with an increased risk for CD. However, the specific optimal amounts of gluten consumption remain undetermined due to insufficient evidence on safe thresholds, and the impact of restricting gluten in the diet of healthy children of unknown risk for CD is unknown. Thus, any recommendation on the gluten amount is currently unjustifiable for the general population and infants with known HLA risk types. There is no specific guidance on the type of gluten-containing foods to be introduced at weaning.

Keywords: Coeliac Disease Risk, Gluten Introduction, Gluten Amount, Infant Nutrition, Infant Diet, Infant Feeding.

What is Known

- Previous ESPGHAN position papers have addressed the relationship between breastfeeding, gluten introduction in infants, and the risk of developing coeliac disease (CD) during childhood.
- There is a recognised need for an update considering new evidence.

What is New

- The ESPGHAN Special Interest Group on Coeliac Disease has formulated key questions concerning early feeding practices/diet and the risk of coeliac disease autoimmunity (CDA) and CD.
- Recommendations from previous position papers have been updated or reaffirmed based on the latest published evidence.
- Knowledge gaps were identified, underscoring the need for further research to better understand the impact of early feeding practices on the risk of CDA/CD.

BACKGROUND

In 2016, the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) issued recommendations on early feeding and gluten introduction and the risk of developing coeliac disease (CD) during childhood (1). These recommendations were confirmed in 2017 by the ESPGHAN Committee on Nutrition (2). The recommendations emphasised that while breastfeeding offers numerous health benefits, it does not reduce the risk of CD, whether it overlaps with the introduction of gluten or not. It is also stated that introducing gluten to an infant's diet between 4 and 12 months of age does not affect the risk of developing coeliac disease autoimmunity (CDA) – defined as the presence of anti-transglutaminase or anti-endomysial antibodies – or CD, up to the age of 3 years. However, in children with a known genetic risk of CD, introducing gluten earlier may lead to the earlier onset of CDA and CD without affecting the cumulative incidence of CD. Observational studies suggested that consuming high amounts of gluten (in the upper quartile compared to the lower quartile) during the initial weeks after its introduction and throughout infancy might increase the risk of CD. However, the amount of gluten considered optimal for consumption during weaning was not determined. Even though only individuals carrying one or more of the CD risk alleles can develop CD while on a gluten-containing diet, recommendations were intended for all infants since the genetic risk is typically unknown in infants when introducing solid foods.

With the emergence of new evidence since the 2016/2017 recommendations, a systematic review was carried out in 2023 to assess how early infant feeding practices affect the risk of developing CDA and CD (3). The primary objective of this review was to update the ESPGHAN position paper from 2016 based on this systematic review

and the most recent publications regarding early feeding practices/diet and their impact on CDA and CD risk. This document represents ESPGHAN's current position, which updates or reaffirms previous recommendations in the context of recent findings.

METHODS

Group Composition and Conflict of Interest Disclosure

The group included members from the ESPGHAN Special Interest Group on Coeliac Disease (SIG-CD) and representatives from the ESPGHAN Committees on Nutrition and Allied Health Professionals. The members of the group were physicians and allied health professionals, as well as experts in paediatrics, paediatric gastroenterology, paediatric nutrition, and dietetics. All team members disclosed any potential conflicts of interest, which were reviewed by the ESPGHAN Council.

Research Questions

The systematic review published earlier (3) guided the development of this document. With one exception, the same research questions as in the review were considered (Table 1).

Literature Search

The initial review was conducted in May 2022, using the databases PubMed, EMBASE, and the Cochrane Library (3). Additional searches were performed from May 2022 to June 2023 to include new findings. The group reached a consensus that a targeted search in PubMed would be sufficient. A list of newly identified publications is available upon request. In the sections below, only those considered relevant were cited.

Evidence and Recommendations

The modified Delphi process was used to establish consensus on the recommendations. In the first round, each group member was asked to vote next to each recommendation, choosing from the following options: strongly agree, agree, neither agree nor disagree, disagree, or strongly disagree. Members were also given the opportunity to comment or suggest alternative wording for each recommendation. Voting was kept anonymous. At least 80% agreement from the team was needed on each recommendation. If a recommendation did not get enough agreement, it was revised based on the team's feedback and was sent back for a second round of voting. In this second round, team members knew the overall group scores and comments from the first round, which helped them reconsider their positions. Voting was again anonymous. Once everyone agreed, the recommendation made it into the final document.

ESPGHAN and Public Consultation

The ESPGHAN SIG-CD, the Committee on Nutrition, and the Gastroenterology Committee reviewed the draft to ensure the inclusion of their expert insights. Additionally, the draft was posted on the ESPGHAN website for public consultation, inviting ESPGHAN members and the wider community to provide written feedback.

STATEMENTS & RECOMMENDATIONS

Table 1 summarises the clinical questions, the 2024 statements and recommendations. For a concise summary of the recommendations and practical tips for introducing gluten-containing foods, please refer to Table S1. Below, detailed

explanations are provided to clarify any modifications or reaffirmations of the recommendations initially made in 2016.

Q1. Breastfeeding (BF) and CD. Is the risk of developing CD reduced by exclusive or any BF? Is the age when CD develops influenced by exclusive or any BF? Is the risk of developing CD affected by BF duration?

The 2023 systematic review (3) found that for individuals at genetic risk of developing CD (those with HLA DQ2/DQ8 alleles), neither exclusive nor any BF, nor the duration of BF, was associated with a reduced risk of developing CDA or CD during childhood.

Seven newly identified articles were considered relevant, and full papers were retrieved (4-13). Among these, the only study contributing new data was a retrospective case-control study from Iran (10). This study compared 186 children diagnosed with CD (mean age: 4.8 years) from a single centre with 186 non-CD controls (mean age: 4.1 years). The two groups exhibited significant differences in several critical aspects, including the prevalence of birth weight below 2500 g (35.5% in the CD cohort vs. 7% in controls), maternal education, urban versus rural residency, and caesarean section rates (28% vs. 15.6%, respectively). These factors are known to influence the rates of both any and exclusive BF. Infant diet in the first 6 months of life was reported for both the CD cohort (cases) and controls: 65.1% of cases were exclusively breastfed compared to 83.3% of controls, BF in combination with formula feeding occurred in 28% of cases versus 12.9% of controls, and 7% of cases were not breastfed in contrast to 3.8% of controls ($P<0.001$). Due to the inadequate matching of cases and controls, the retrospective character of the study, a high percentage of

mothers being illiterate, and potential recall bias, we did not consider this study relevant to the data or conclusions drawn from the 2023 systematic review (3).

The 2023 systematic review by Alotiby et al. (11) on the role of BF in the development of immune-mediated diseases, with CD being one of them, examined a different time frame, and several recent important publications from large birth cohort studies were not included. In addition, no methodology to explore the evidence based on the quality of the included studies was applied in contrast to the 2023 review by Szajewska et al. (3). Therefore, we decided to base our statements and recommendations on the more robust review findings by Szajewska et al. (3). Compared to the 2016 position paper, the statements and recommendations have remained the same (refer to Table 1).

Q2. BF at the time of gluten introduction and CD. Is the risk of CD reduced if gluten is consumed while the infant is still being breastfed?

The 2023 systematic review (3) concluded that, based on a meta-analysis of four case-control studies, there is a suggested decreased risk of CD when gluten is introduced during BF. However, this association was not supported by randomised controlled trials (RCTs) and cohort studies. No new studies were identified. Compared to the 2016 position paper, there have been no major changes in the statements and recommendations (refer to Table 1).

Q3. Timing of gluten introduction: Is the risk of developing CD influenced by the timing of gluten introduction? Does the age at gluten introduction affect the age when CD develops?

No new studies have emerged since the 2023 systematic review (3). The timing of gluten introduction between completed 4 to 12 months of life has not been linked to a higher overall risk of developing CDA or CD. One RCT indicated that introducing small amounts of gluten at 6 months of age could lead to an earlier onset of CDA compared to later age (12 months) (14). This finding aligns with the biological expectation due to earlier exposure. Despite this, early gluten introduction did not result in a reduced cumulative incidence of CD after the age of 3 years (14). Results from some observational cohort studies suggest that gluten introduction before 6 months was associated with a lower risk of later CD, whereas other cohort studies observed similar risks (3). In summary, no substantial revisions have been necessary for the statements and recommendations previously outlined in the 2016 position paper (refer to Table 1).

Q4. Amount of gluten at weaning (and later) and CD. Is the amount of gluten consumed an independent risk factor for CD development in early childhood? Is there a threshold level for the amount of gluten consumption for this risk?

No new studies have emerged since the 2023 systematic review (3). This review concluded that both cohort and case-control studies suggest that consuming a higher amount of gluten at weaning and thereafter may increase the risk for CDA and CD in genetically predisposed children (**Table S2**). Cohort studies also indicated that a higher daily gluten intake during the first 5 years of life is associated with an increased risk for CDA and CD. The variations in specific daily amounts reported in these studies are possibly due to differences in dietary habits, but also very likely due to different dietary assessment methods as well as statistical analyses used (**Table S2**).

Importantly, all the studies identified a dose-dependent risk association, indicating that higher gluten intake is correlated with an increased risk of CD. However, whether there

is a safe threshold or optimal amount for gluten consumption has not yet been established, and there is currently no evidence to suggest that gluten restriction can prevent the development of CD. Furthermore, most children will not develop CD regardless of their gluten intake, and the nutritional and psychosocial consequences of gluten restriction in healthy children are not well understood. Therefore, it is not possible to make a general recommendation about gluten intake at the population level. Additionally, it is not yet feasible to determine a specific gluten threshold for children with a known risk for CD or to define a group of children who may benefit from gluten restriction.

A 2023 mini-review by Aronsson et al (9) provided an overview of ongoing or completed RCTs that focused on dietary interventions during early childhood to prevent CD. This review introduced two ongoing RCTs involving infants. First, the PreCiSe study (ClinicalTrials.gov Identifier NCT03562221), evaluating the effect of gluten introduction after 3 years of age compared to no dietary restrictions with/without probiotics in children with known risk for CD. Second, the GRaIn study (ClinicalTrials.gov Identifier: NCT04593888), investigating the effect of a gluten-reduced diet versus no gluten restriction up to age 3 years. In the future, the results of these studies will hopefully provide evidence supporting more detailed recommendations about the optimal gluten amount in early childhood and risk for later CD.

Key differences between previous (2016) and current (2024) recommendations include:

- The 2016 recommendation focused on the period just after introducing gluten, whereas the 2024 version extends the period of concern to up to 5 years of life.

- The 2024 recommendation emphasises genetic predisposition and details the types of studies (observational, case-control, and cohort) that contribute to the development of the guidelines.
- The 2024 recommendation emphasises the lack of evidence for an optimal amount or safe threshold of gluten intake, the potential nutritional, economic and psychosocial consequences of a gluten-free or gluten-restricted diet in healthy children at both known and unknown risk (population level), and the challenges in limiting guidance to only those at known risk of developing CD.
- The 2024 recommendation suggests that for children with a known risk for CD, avoiding large amounts of gluten during the first 5 years of life may be beneficial. However, a detailed recommendation on the optimal amount of gluten cannot currently be given.

Q5. Type of gluten: Is CD risk influenced by the type of cereal (wheat, rye, barley) consumed at gluten introduction or later during childhood? Does the type of gluten-containing products (bread, porridge, follow-on formula) at gluten introduction influence CD risk?

The 2023 systematic review (3) found that no RCTs reported on the risk of CDA or CD in relation to the intake of different types of gluten-containing products. The review included one observational study from Sweden, focusing on a population with a known CD risk (TEDDY cohort), which reported an increased risk of CD associated with a daily bread intake of more than about half a slice of bread compared to no bread intake, but with an equal amount of gluten from other foods at 12 months (15). Additionally, a meta-analysis of two Swedish case-control studies (16, 17) suggested an increased

risk of CD when gluten was introduced with gluten-containing, cereal-based follow-up formula, as opposed to introducing gluten with solid foods.

In the Swedish sub cohort of the TEDDY observational birth cohort study (18) involving children from the general population who are genetically predisposed to type 1 diabetes and CD, 3-day food records up to age 2 years were analysed. This analysis revealed that specific gluten-containing foods consumed at different ages were associated with an increased risk of CDA when adjusting for the total daily gluten intake. Notably, at 9 months, consuming up to one portion of porridge daily was linked to a higher risk of CDA (HR 1.53; 95% CI: 1.05, 2.23; p=0.026) compared to no porridge intake. Similarly, at 12 months, a daily intake of more than half a slice of bread compared with no bread intake was associated with increased risks of CDA (HR: 1.47; 95% CI: 1.05, 2.05; p= 0.023) and CD (HR: 1.79; 95% CI: 1.10, 2.91; p = 0.019). At 18 months, each bottle of daily intake of cereal-based follow-up formula consumed was linked to a heightened risk of CD (HR: 1.16; 95% CI: 1.00, 1.33; p = 0.047). However, the study found no association between the type of gluten-containing grain (wheat or rye) consumed up to 24 months and the risk of CDA or CD, when also considering the total gluten intake. This study did not investigate the type of gluten at the time of its introduction into the diet. Overall, compared to the 2016 position paper, no changes have been made in the statements and recommendations on the type of gluten (refer to Table 1).

Q6. Gluten intake by the mother during lactation. Is CD risk in the offspring influenced by consumption of a gluten-free diet vs. a gluten-containing diet during pregnancy and lactation?

The 2023 systematic review (3) found no reported data on whether the risk of CD in offspring is affected by the mother's consumption of either a gluten-free or a gluten-containing diet during lactation. There have been no subsequent publications that address this specific topic. The impact of maternal gluten intake during pregnancy on the offspring's CD risk remains uncertain. The TEDDY study found no association (19), while the MoBa study indicated that low gluten and high fibre intake during pregnancy might reduce the risk of CD in children (20).

Q7. Genetic predisposition. Does the amount of gluten consumed by the infant have different effects on risk for CDA and CD development in relation to different HLA risk alleles?

As described in the 2023 systematic review (3), four observational studies, including two cohort studies and one case-control study, presented inconclusive results on the link between feeding practices and the risk of CD in children with various HLA genotypes. Since then, no new studies have been identified.

The PreventCD cohort (21) found no significant association between the amounts of gluten consumption and the development of CD by age 5, except in children with the DQ2.2/DQ7 haplotype (HR 5.81, 95% CI, 1.18–28.74). For this group, the increased risk was related only to the initial increase in gluten consumption between 11-18 months of age, not to the overall daily gluten intake or any other parameters. The DAISY study (22) observed no association between gluten intake at 1 year and the development of CDA/CD, considering the child's HLA genotype (HR not reported, $p > 0.15$). Similarly, a nested case-control study within the Norwegian Mother and Child cohort (23) indicated that the association between gluten intake at 18 months and the

development of CD was not dependent on the child's HLA genotype. The nested case-control study of the Swedish TEDDY cohort (24) investigated the effect of high gluten intake (defined as in the upper tertile, e.g., > 5 g/d) prior to seroconversion in relation to three different HLA risk types: high-risk group (DR3-DQ2 homozygotes), moderate risk group (DR3-DQ2 heterozygotes), and low-risk group (only DR4-DQ8 without DR3-DQ2). More cases than controls were found in the upper tertile of gluten intake, but the hazard ratio was not significantly different between the three HLA risk groups. This indicated that the risk-increasing effect of high gluten intake is unrelated to the HLA risk alleles. These association studies do not provide evidence to give specific recommendations concerning gluten intake during infancy and the first years of life based on HLA risk type (refer to Table 1). It can be hypothesised that for infants at high HLA risk, the inherent genetic risk is so pronounced that the amount of gluten consumed (within the ranges typically seen at the population level) may not contribute measurably to the actual risk.

RESEARCH GAPS

We have identified several key areas where further research is needed. These gaps highlight the potential for advancing our understanding of early diet and the risk of CD. Addressing these areas will be crucial in developing more precise guidelines and interventions. The primary research gaps identified include:

- Conducting RCTs to determine if a safe threshold for daily gluten consumption exists at different ages for children with known risk for CD.
- Evaluating gluten-restricted diets in young children should include assessing these diets' nutritional effects on fibre and whole grain intake and wider nutritional and psychological impacts in the children. This assessment should also consider the

economic aspects of choosing gluten-free or gluten-low alternatives, as well as the societal implications.

- Further evaluating the relationship between HLA genotypes, the amount of gluten at introduction and early childhood, and the subsequent risk of CD.
- Until now, research has primarily focused on introducing gluten at 12 months; therefore, it is crucial to evaluate the effects of further delaying its introduction. Such a delay might be justified by the age-related development of immunity and reduced susceptibility to gastrointestinal infections.
- Conducting RCTs to investigate the impact of introducing gluten in natural quantities from age 4 months, which may be considered a controversial practice, as opposed to after 6 months, on the cumulative risk of CD.
- Assessing the impact of different dietary sources and types of foods containing gluten, including those with different textures and in combination with other foods, at food introduction and in early childhood.
- Further exploring the effects of maternal gluten consumption during pregnancy and lactation in various populations.
- Exploring the effects of prenatal and early life dietary exposures in addition to gluten intake, including micronutrients, other dietary components, foods, and dietary patterns.

380 Table 1: 2024 Statements and Recommendations on Early Diet and The Risk Of
381 Coeliac Disease
382

QUESTION	STATEMENTS	RECOMMENDATIONS
Q1. BF and CD.	• Any BF compared with no BF has not been shown to reduce the risk of developing CD during childhood or to delay the development of CD. • Exclusive BF up to age 6 months compared to a shorter duration has not been shown to reduce the risk of CD during childhood.	• Recommendations on BF for infants with known or unknown genetic risk should not be modified due to considerations regarding prevention of CD.
Q2. BF at the time of gluten introduction and CD.	• Breastfeeding at the time of gluten introduction, as compared to gluten introduction after weaning from BF, has not been shown to reduce the risk of developing CD during childhood.	• Introducing gluten while the infant is being breastfed cannot be recommended as a means of reducing the risk of developing CD.
Q3. Timing of gluten introduction.	• The age of gluten introduction between completed 4 and 12 months of age does not seem to influence the absolute risk of developing CDA or CD during childhood.	• Gluten can be introduced into the infant's diet between completed 4 and 12 months of age without affecting the cumulative risk of CDA or CD development during childhood.
Q4. Amount of gluten at weaning (and later) and CD.	• Observational and case-control studies suggest that the consumption of a higher amount of gluten at weaning and/or thereafter may increase the risk of CDA and CD in genetically at-risk children.	• No recommendation can be made regarding the amount of gluten intake at weaning and up to 2-3 years of age for infants of unknown risk for CD. • For infants with a known CD risk, we recommend awaiting the results of ongoing intervention studies before any guidance can be given on the consumption of gluten amounts during the first 2 or 3 years of life.
	• In birth cohort studies, a higher and dose-dependent daily gluten intake during the first years of life (specifically the first 2 to 3 years, and even 5 years in some studies) was found to increase the risk of CDA and CD. However, the daily gluten amounts varied significantly across studies, reflecting different feeding	

	patterns and dietary habits among countries, as well as various dietary assessment methods used.	
	• The optimal amounts of gluten for introduction at weaning and throughout childhood to reduce the risk for CDA and CD cannot be established from the current data.	
	• There is no evidence that a safe amount of gluten intake exists that can prevent CDA and CD development with a high degree of certainty.	
Q5. Type of gluten at introduction and after weaning.	• The type of gluten at introduction was not shown to modify the risk for developing CD.	• No recommendation can be made regarding the source and type of gluten-containing food to be used at food introduction or after weaning.
Q6. Gluten intake by the mother during pregnancy & lactation.	• There is inconclusive evidence on the link between maternal gluten intake during pregnancy and the risk of CD in the offspring, and no evidence regarding the impact of maternal gluten intake during lactation.	• There is no evidence to give specific recommendations on gluten intake by the mother during pregnancy and lactation.
Q7. Genetic predisposition.	• Observational studies, including cohort and case-control studies, do not provide evidence that the effect of high gluten intake on CD and CDA development is related to different HLA risk types.	• There is not enough evidence to give differentiated recommendations on gluten consumption for various HLA risk types.

BF, breastfeeding; CD, coeliac disease; CDA, coeliac disease autoimmunity

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Table S1. A concise one-page summary of the recommendations and practical tips for introducing gluten-containing foods.

Summary of Recommendations

Breastfeeding	Continue breastfeeding following the recommendations for the general population, regardless of genetic risk for coeliac disease.
Breastfeeding during gluten introduction	No specific guidance since breastfeeding during gluten introduction has not been shown to reduce the risk of coeliac disease.
Timing of gluten introduction	Introduce gluten-containing foods at any age after completing 4 months of age. For tips, refer to the box below.
Gluten amount at weaning & beyond	No specific guidance for infants of unknown risk for coeliac disease. Further research is needed for those at known risk.
Type of gluten after weaning (and later)	No specific guidance on types of gluten at the time of introduction and thereafter
Maternal gluten intake during pregnancy & lactation	No specific guidance on maternal gluten intake during pregnancy and lactation.
Genetic predisposition	No specific dietary guidance in infants at known risk for coeliac disease based on their genetic HLA risk types.

Tips for Introducing Gluten-Containing Foods (Adapt to Local Customs)

Food	**How to introduce to infants**
Gluten-containing baby cereals (with wheat, rye, or barley)	Mix with human milk, formula, or water, depending on the instructions given by the manufacturer.
Bread	Different kinds may be used at introduction, based on wheat and/or rye. Serve in small cubes for younger infants, and larger pieces possible for the older infants to grab and self-serve.
Pasta	Use softly cooked pasta in small shapes or mashed for younger infants. Larger pieces may be used for older infants who can self-feed.
Home-made cereals/porridge	Cook wheat/semolina/barley flour or rolled flakes to an appropriate desired texture for the infant. Match with purees if desired.
Cracker/crisp bread	Use pieces of wheat/rye-based variants. Serving with a soft spread will make swallowing easier.
Couscous/bulgur	Use cooked couscous. If needed, mix with puree/sauce/broth/oil for softer texture.

485 **Table S2. Summary of cohort studies reporting on gluten intake amount in early childhood and associations with the risk of**
486 **developing coeliac disease autoimmunity and coeliac disease.**
487

Study population	Dietary assessment method	Conversion factor to estimate gluten intake	Mean gluten intake (SD), g/day	Statistical analysis, gluten intake modelled	Adjustment factors included	Risk of CDA n events included in analyses	Risk of CD n events included in analyses
TEDDY (Aronsson, 2019) n=6605 At genetic risk: USA, Finland, Sweden, Germany Follow-up: median age 9 years (range 1.0, 13.0 years).	Prospective, 3-day food records at age 6, 9, 12, 18, 24, 30, 36, 42, 48, 54 and 60 months including all consumed foods and drinks, as well as amounts consumed.	Protein intake from wheat, rye, barley x 0.8	Cohort, age 2 years: 3.7. Age 1 years: USA: 1.7 (1.2), Fin: 2.1 (1.4), Swe: 2.9 (1.4), Ger: 3.1 (1.9). Age 2 years: US: 3.2 (1.7), Fin: 4.0 (1.8), Swe: 3.9 (1.5), Ger: 5.2 (2.2). Age 5 years: US: 5.1 (2.2), Fin: 6.4 (2.2), Swe: 5.6 (1.9), Ger: 8.6 (3.3).	Joint modelling, longitudinally, absolute intake (g/day), energy and age adjusted, as well as g/10 kg bodyweight.	HLA genotype, country, sex, FDR with CD, energy intake. Reported per 1-unit increase/day.	n=1216 aHR = 1.30 (95%CI, 1.22, 1.38, *P*<0.001) per 1-g increase/day.	n=447 aHR=1.50 (95%CI, 1.35, 1.66, *P*<0.001) per 1-g increase/day.
DAISY (Marild 2019) n=1875 At genetic risk: USA Follow-up 13 years.	Retrospective, semi-quantitative FFQ annually from age 1 years, reflecting the previous year. Frequency of foods including pizza, hamburgers, pasta, cereals, bakery products, breads, crackers, cookies, candy.	Protein intake from wheat, rye, barley x 0.75	Age 12-24 months: 10.9 (1.2).	Cox proportional hazards model, fixed intake at age 1-2 years, g/day. Joint modelling, longitudinal (cumulative intake), g/day.	Sex, FDR with CD, parent-reported race-ethnicity, maternal age at time of delivery, HLA genotype, breastfeeding duration, age at gluten introduction, total energy intake, timing of islet autoimmunity**.**	n=161 aHR 1.05 (95%CI, 1.00, 1.09, *P*=0.04) per 1-g increase/day. aHR 1.00 (95%CI 1.00, 1.01), P=0.11 per 1-g increase/day.	n=85 aHR 1.96, (95%CI, 0.90, 4.24, P=0.09**)** per 1-g increase/day. aHR 1.01 (95%CI 1.00, 1.01), P=0.04, per 1-g increase/day.
PreventCD (Crespo-Escobar 2017) n=715 Children with FDR and at genetic risk:	Prospective, 7-day food records or retrospective semi-quantitative FFQ reflecting 1 week's intake.	Protein intake from wheat, rye, barley x 0.8	Age 1 year: Spa: 3.1 (1.5), Ger: 4.3 (2.1), Neth: 6.4 (2.5), Hun: 7.1 (3.9), Ita: 5.4 (2.9). Age 2 years: Spa: 4.4 (1.9), Ger: 6.9 (3.0), Neth: 8.1 (2.7), Hun:	Cox proportional hazards model, 3 categories: a) increase in intake age 11-18 months (ref) b) intake at age 18 months	Sex, intervention group, HLA risk group, country.	ND	n=95 Intake at age 18 months aHR 0.98 (95%CI 0.89, 1.09), increase in intake

Spain, Germany, Netherlands, Hungary, Italy Follow-up to minimum age 5 years.	At age 11, 12, 14, 16, 18, 20, 22, 24, 28, 30, 36 months.		11.3 (4.1), Ita: 10.1 (3.9). Age 3 years: Spa: 4.4 (1.9), Ger: 7.8 (3.9), Neth: 9.2 (2.9), Hun: 11.5 (3.3), Ita: 12.1 (3.2).	c) increase in intake between age 18-36 months.			between 18-36 months aHR 1.17 (95%CI 0.59, 2.31) compared with the increase in intake at age 11-18 months.
PreventCD (Meijer 2022) n=433 (1y) n=412 (2y) n=391 (3y) Children with FDR and at genetic risk: Spain, Germany, Netherlands, Hungary, Italy Follow-up to minimum age 8.4 years.	Prospective, 7-day food records or retrospective semi-quantitative FFQ reflecting 1 week's intake. At age 11, 12, 14, 16, 18, 20, 22, 24, 28, 30, 36 months	Protein intake from wheat, rye, barley x 0.8	Age 1 year: IQR 2.6 (CV 0.5) Age 2 years: IQR 2.7 (CV 0.5) Age 3 years: IQR 2.8 (CV 0.5)	Information available at the landmark time point was used. Models backward elimination based on Akaike Information Criterion was used.	Sex, intervention group, HLA risk group, country.	ND	N=135 12 months: HR 1.28 (95%CI 1.09, 1.50); 24 months: HR 1.41 (95%CI 1.15, 1.72); 36 months: HR 1.43 (95%CI 1.13, 1.82). per 1-g increase/day. Overall, till 36 months HR 1.07 per 1-g increase/day
Neapolitan Cohort NEOCEL **+ subgroup of local Prevent CD cohort** (Auricchio 2022) N=83, Infants with known genetic risk for CD and a FDR with CD Follow-up median age: 44.2 months	Matched case control study (27 with later CD and 56 with no later CD matched for age, sex) Prospective, one-day food records at age 9, 12, 18, 24, 36 months including all consumed foods and drinks, as well as the amounts consumed.	Protein intake from wheat, rye, barley x 0.8	From 12 to 24 months of age, CD cases mean intake 5.31 (95%CI 3.76–6.87) vs. controls' mean intake 2.61 (95%CI 1.88–3.35).	Logistic regression to estimate the odds associated with the increments of gluten intake over the 2nd year of life.	HLA risk class, relative affected by CD, serum cytokines production.	ND	N=27 OR = 6.37 (95%CI 1.55, 26.1) $\chi 2$ 7.22; *P*=0.007., per 1.75 g increase/day
MoBa (Lund-Blix 2019) n=67,608	Retrospective, semi-quantitative FFQ at age 18 months	Protein from wheat, rye, barley x 0.75	Age 18 months: 8.8 (3.6)	Binary regression Absolute amount g/day and quartiles	Age at gluten introduction, breastfeeding duration, parental CD, sex, age at the end of the study	ND	n=738 aRR 1.29 (95%CI 1.03,

General population: Norway Follow-up to mean age 11.5 (range 7.5-15.5) years.	Frequency of food intake including bread, pasta, pancakes, baby cereals, cakes and cookies						1.18) per SD increase/day aRR 1.29 (95%CI 1.06, 1.58) highest vs lowest Q.

Abbreviations: aHR; adjusted hazard ratio, aRR; adjusted relative risk, CD; coeliac disease, CDA; coeliac disease autoimmunity, CI; confidence interval, CV; coefficient of variation, DAISY; The Diabetes Auto Immunity Study in the Young, FDR; first-degree relative, FFQ; food frequency questionnaire, g; grams, HLA; human leukocyte antigen, HR; hazard ratio, IQR; interquartile range, MoBA; Norwegian Mother, Father and Child Cohort Study, OR; odds ratio, Q; quartile, TEDDY; The Environmental Determinants of Diabetes in the Young, SD; standard deviation

Gluten content in different foods

In publications on gluten amounts and the risk of coeliac disease, a conversion factor of either 0.75 or 0.8 was used to calculate the amount of gluten from the protein content in wheat, rye, and barley. The protein content of these grains differs between varieties, including the content of whole grain, and the growing conditions. The calculations below are based on a protein content of 10% in the flour and a conversion factor of 0.8 (100 grams of wheat = 8 grams of gluten).

Gluten-containing food, approximate serving size for age 1-3 years	**Approximate content of gluten/serving[1]**
1 slice of bread (ca 30 grams)	2 grams
1 serving of cooked pasta (about 70 grams, 100 ml)	2.5 grams
1 serving of cooked couscous (about 60 grams, 100 ml)	2 grams
1 serving of bulgur (about 70 grams, 100 ml)	1.5 grams
1 crêpe/pancake (about 70 grams)	1 gram
1 serving of cooked semolina (100 grams, 100 ml)	1 gram
1 slice of pizza (about 100 grams, crust about 2/3)	4 grams
1 crisp bread (10 grams)	1 gram
1 biscuit/cracker/wafer (5 grams)	0.5 gram

[1] Rounded to nearest 0.5 gram

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