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Systematic review: early feeding practices and the risk of coeliac disease. A 2022 update and revision

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Summary

Background: The effects of early feeding practices on the risk of coeliac disease (CD) remain debated.

Aims: To update evidence on these practices on the risk of CD and/or CD-related autoimmunity (CDA), defined as anti-transglutaminase or anti-endomysial antibody positivity

Methods: We searched MEDLINE, EMBASE and the Cochrane Library to May 2022 for randomised controlled trials (RCTs) and observational studies.

Results: We included 36 publications (30 studies). In the population at genetic risk of developing CD (HLA DQ2/DQ8-positive), exclusive or any breastfeeding and longer breastfeeding duration did not reduce the risk of developing CD/CDA during childhood. While a meta-analysis of four case–control studies showed a decreased risk for CD when gluten was introduced during breastfeeding, this was not shown in RCTs and cohort studies. Age at gluten introduction was not associated with cumulative CD/CDA risk, although two RCTs suggested that earlier gluten introduction was associated with earlier CDA appearance. Evidence from six observational studies suggests that consumption of a higher amount of gluten at weaning and/or thereafter may increase CD risk. There is insufficient evidence to determine the amount of gluten

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associated with an increased CD/CDA risk. Regarding whether infant feeding practices modulate the risk conferred by different HLA genotypes results were inconsistent.
Conclusions: For the population at genetic risk of CD, breastfeeding and age at gluten introduction have no effect on its cumulative incidence during childhood. There is some evidence for an effect of the amount of gluten consumed at weaning and/or thereafter on CD/CDA risk.

1 | INTRODUCTION

Coeliac disease (CD) is *'an immune-mediated systemic disorder elicited by gluten and related prolamines in genetically susceptible individuals and characterised by the presence of a variable combination of gluten-dependent clinical manifestations, CD specific antibodies, HLA-DQ2 or HLA-DQ8 haplotypes and enteropathy'*.[1] The prevalence in the general population is approximately 1% (ranges from 0.5% to 2%).[2] Untreated CD is a major health burden due to morbidity and mortality associated with the disease,[3,4] and recent evidence suggests that the incidence and prevalence rates of CD are rising in the paediatric age group.[5–7] Thus, preventive strategies targeted at reducing the occurrence of CD should be considered a major priority. Early infant feeding practices have been considered as a risk factor for developing CD. However, recommendations on altering infant feeding practices to reduce the risk of CD in the first decade of the 21st century in Europe and the USA were mainly based on observational studies rather than randomised controlled trials (RCTs), including those analysing the increased prevalence of CD in Sweden.[8] In 2016,[9] based on accumulating evidence from RCTs, revised recommendations related to infant feeding practices in relation to the association between risk of CD and breastfeeding, age at gluten introduction, consumption of gluten while being breastfed, and gluten amounts were published. In 2017,[10] these recommendations were incorporated into a position paper on complementary feeding by the Committee of Nutrition of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN). Since these publications, new evidence has emerged,[11–15] mainly on the association of CD risk with breastfeeding and the amount of gluten when introduced into the infant's diet. Furthermore, more information has become available on the relationship between genetic risk and gluten introduction.[11,12] In addition, the 2016 paper evaluated strategies for reducing the occurrence of CD in high-risk populations; however, strategies for reducing the risk in the general population were neither searched for nor evaluated. In these previous publications, the terms 'high-risk population' and 'general population' were used. However, in the current publication, we use the terms (i) individuals at genetic risk of developing CD (i.e., those who tested positive for the HLA markers DQ2 and/or DQ8) and (ii) individuals with unknown genetic risk for CD (i.e., those not tested for HLA DQ2/DQ8) which are more appropriate. Of note, different HLA DQ2/DQ8 genotypes are associated with different levels of risk of developing CD. In general, individuals who are homozygous for HLA DQ2 have a higher risk of CD development than do heterozygous individuals.[16,17] Importantly, of individuals with unknown HLA risk alleles, only those being positive for HLA DQ2 and/or DQ8 (about a third of the population) are at risk of developing CD, while those not harbouring these HLA markers will not develop CD regardless of preventive measures and early feeding habits, including gluten intake. This implies that results from studies including only participants at genetic risk for CD can be extrapolated to those with unknown genetic risk, although the effect size in the cohort may be smaller because HLA DQ2/DQ8-negative individuals will not contribute.

The aim of this systematic review was to revise and update a 2015 systematic review with a meta-analysis on early infant feeding practices and the risk of CD in individuals at genetic risk of developing CD[18] and to extend the search and include studies evaluating the risk in individuals with unknown genetic risk for CD. The intention is that this updated systematic review and meta-analysis will serve as a basis for revising the ESPGHAN guidelines[9,10] on gluten introduction and the risk of CD and CD autoimmunity (CDA), the latter defined as positivity for anti-transglutaminase (TGA) and/or endomysial antibodies (EMA) in the same subject.

2 | METHODS

The protocol for this systematic review was registered at PROSPERO (CRD42021248583) and previously published.[19] For a summary of the Methods, see Table S1. Below, only the clinical questions are summarised. The Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA)[20] and the Cochrane Collaboration guidance for undertaking and reporting the results of a systematic review and meta-analysis[21] were followed.

2.1 | Clinical questions

The following clinical questions were pre-specified:

1. Breastfeeding and CD. Is the risk of developing CD reduced by exclusive or any breastfeeding? Is the age when CD develops influenced by exclusive or any breastfeeding? Is the risk of developing CD affected by breastfeeding duration?
2. Breastfeeding at the time of gluten introduction and CD. Is the risk of CD reduced if gluten is consumed while the infant is still breastfed?
3. 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?

4. 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?
5. 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?
6. 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 lactation?
7. Genetic predisposition. Does the gluten amount consumed by the infant have different effects in relation to different HLA risk alleles? The latter question differs from one in the published protocol [*Does the risk of developing CD differ between low- and high-risk populations ('genetic load')*]. However, it more accurately reflects the aim of this review.

3 | RESULTS

3.1 | Characteristics of included studies

For the process of study selection, see Figure S1 (flow diagram). Thirty-six publications (6 RCTs, 8 cohort studies in 15 publications, and 16 case–control studies in 15 publications) were included. Among them, compared with our last review, 1 RCT and 17 observational studies in 16 publications were newly identified. Through searching ClinicalTrials.gov, we identified two ongoing studies, that is, Prevention of Celiac Disease in Skåne (PreCiSe) (NCT03562221) and Gluten Reduction and Risk of Celiac Disease (GRAIN) (NCT04593888). As these studies are still ongoing, they will not be discussed. The characteristics of all studies are summarised in Tables S2. For the overall summary of findings, see Table 1.

3.1.1 | RCTs

In addition to previously included RCTs,[22–26] only one new RCT (The Enquiring About Tolerance [EAT] Study[27]), was identified. This was an open-label study that enrolled 1303 infants from the population with unknown genetic CD risk in England and Wales. Children (n = 1303) were randomly allocated to: (i) an early introduction group, in which participants consumed six allergenic foods (including wheat) in addition to breastfeeding from the age of 4 months, or (ii) a standard introduction group, in which participants avoided allergenic foods and followed the recommendations of exclusive breastfeeding until 6 months of age. CD was a prespecified secondary outcome measure of the EAT study. However, the study had major limitations. It was not designed to assess the prevalence of CD. Neither the type of serological test used nor cutoff values were described. Family history of CD was not assessed. Age at gluten introduction (range 4–33 months in the early introduction group) and weekly gluten intake of those diagnosed with CD were not reported. ESPGHAN guidelines for CD diagnosis were not followed for all cases. Finally, participants with low positive antibodies titers were not referred for biopsies, and the analysis involved only 1004 of 1303 (77%) enrolled children who were tested for TGA at 3 years of age with only seven of them diagnosed with CD.[28]

3.1.2 | Observational studies

Eight prospective cohort studies (PreventCD, TEDDY, DAISY, Generation R, BABYDIAB, DIABIMMUNE, MoBA and ABIS) reported in 15 publications were included.[11–15,29–38] Eight new publications of five cohort studies (PreventCD, TEDDY, DAISY, DIABIMMUNE and MoBA) were identified.[11–15,29,37,38] The PreventCD cohort includes children who continued follow-up for the PreventCD randomised controlled trial.[12,15] In this review, we assessed separately cohorts of individuals at genetic risk of developing CD (12 publications)[11,12,14,15,29,30,32,33,35–38] and individuals of unknown genetic risk for CD (ABIS and MoBA).[13,31,34] One study (DIABIMMUNE)[37] was assessed as a cohort study, but, with a matched control group selected retrospectively.

Sixteen case–control studies were identified,[13,39–53] including eight new studies.[13,39–41,44,48,52,53] Four of the case–control studies included sub-cohorts of interventional and non-interventional cohort studies (TEDDY, PreventCD, MoBA and ABIS).[13,41,44,52] Three case–control studies published before February 2015[44,48,53] were not identified by the previous review. One publication[13] reported results from two studies (MoBA cohort and nested case–control study including children with genotype data available). Excluded studies with reasons for exclusion are summarised in Table S5.

3.2 | Risk of bias in included studies

3.2.1 | RCTs

Risk of bias for RCTs is reported in Figure S2. Two publications[25,26] based on the same BABYDIET study were assessed jointly. Only one trial was assessed as having a low risk of bias in all domains.[22] Other trials had methodological limitations in at least one domain. The weakest domain across the included trials was the randomisation process (three [reported in four publications] out of five trials were assessed as having some concern or high risk of bias).[23,24,26,35]

3.2.2 | Observational studies

The risk of bias in observational studies is reported in the online Tables S6. The NOS total score for cohort studies (Table S6) ranged from five (one study)[36] to nine (maximum score, one study).[13] Of note, one of the items was the representativeness of the exposed cohort, with the inclusion of only at-risk populations. The results from at-risk

TABLE 1 Summary of findings

Intervention/ exposure	Population	RCTs	Cohort studies	Case–control studies
Breastfeeding (Any or exclusive)	With genetic risk	No difference in CD/CDA risk (1 RCT) for any and exclusive breastfeeding	No difference in CDA risk (2 studies) for any and exclusive breastfeeding	No difference in CD risk (meta-analysis of 4 studies) for any and exclusive breastfeeding
	With unknown risk	NR	NR	NR
Breastfeeding duration	With genetic risk	No difference in CD risk (2 RCTs) for duration of any and exclusive breastfeeding No difference in CDA risk (2 RCTs) for duration of any or exclusive breastfeeding	No difference in CD risk (1 study) for duration of any or exclusive breastfeeding No difference in CDA risk (4 studies) for duration of any or exclusive breastfeeding (*except for 1 study using propensity score*)	No difference in CD risk (5 studies) for duration of any breastfeeding (*except for 1 study*)
	With unknown risk	NR	No difference in CD risk (2 studies) for any or exclusive breastfeeding	NR
Breastfeeding during gluten introduction	With genetic risk	No difference in CD risk (2 RCTs) No difference in CDA risk (1 RCT)	No difference in CD risk (1 study) for breastfed ≤1 and >1 month during gluten introduction Mixed results for CDA risk (2 studies)	Decreased CD risk (5 studies, including meta-analysis of 4 studies)
	With unknown risk	NR	No difference in CD risk (1 study)	NR
Age of gluten introduction	With genetic risk	No difference in CD risk (4 RCTs) for any time point comparison Mixed results for CDA risk (4 RCTs): a difference only at 12 vs. 6 months at 1 year (1 RCT) and at 2 years of age (meta-analysis of 2 RCTs)	No difference in CD risk for 4 vs. 4–6 vs. >6 months (meta-analysis of 2 studies), and mean age of gluten introduction (one study) No difference in CDA risk (4 studies)	No difference in CD risk (5 studies) with 2 exceptions: a difference only in 2 of 6 comparisons (≤3 and at 7–12 months)
	With unknown risk	No difference in CD and CDA risk (1 RCT)	No difference in CD risk for <4 vs. ≥6; <4 vs. 4–6; and ≤4 vs. 5–6 months (2 studies), but a decreased CD risk for 4–6 vs. ≥6 months (1 study)	NR
Amount of gluten intake	With genetic risk	NR	Increased risk of CD associated with higher consumption of gluten (3 studies) and CDA (1 study)	Increased risk of CD associated with higher consumption of gluten (3 studies)
	With unknown risk	NR	Increased risk for CD at the age of 18 months, limited to the 2nd and 4th quartiles of gluten intake (one study)	NR
Type of introduced gluten-containing food	With genetic risk	NR	Increased risk of CD/CDA with high daily bread intake (>18.3 g/day) vs.no bread intake at 12 months; and for CDA only for low daily porridge intake (≤158 g/day) at 9 month (1 study) No difference in CDA risk for cow's milk, gluten-free solid foods or gluten-containing solid foods (1 study)	Increased risk of CD when gluten was introduced with follow-up formula, but not with solid foods (meta-analysis of 2 studies) Increased risk for CD when gluten introduced with wheat cereals, but not for barley and oat (1 study) No difference in CD risk for follow-up formula and porridge (1 study)
	With unknown risk	NR	NR	NR
Gluten during lactation	Any	NR	NR	NR

(Continues)

TABLE 1 (Continued)

Intervention/ exposure	Population	RCTs	Cohort studies	Case–control studies
genetic predisposition	With genetic risk	NR	No association between different HLA DQ2 genotypes (2 studies), with one exception, HLA DQ2.2/DQ7 (1 study)	No difference in CD risk between HLA haplotypes (heterozygotes and homozygotes) (1 study) An association between higher gluten intake and risk of CD for DR3-DQ2 homozygotes and heterozygotes, but no difference in tertiles distribution and different HLA risk genotypes (1 study)

Abbreviations: CD, celiac disease; CDA, celiac disease autoimmunity; NR, not reported; RCT, randomised controlled trial.

groups can be extrapolated to the general population (i.e., those with unknown genetic risk for CD), although the effect size may be smaller because it is based only on the subgroup of participants testing positive for HLA DQ2/DQ8. A weak item was completeness of the follow-up as part of the exposure domain (eight publications without a star). Age (selected by the review team as the main important factor) was not considered as a confounder in 10 included public ations.[11,12,14,15,29,30,33–36] Furthermore, two studies in three publications did not adjust data for any confounding factors.[34–36] The NOS total score for case–control studies (Table S7) ranged from five (one study)[42] to nine (maximum score).[13] The weakest item was definition of controls (nine studies did not achieve a star).[39,42,44–46,49–51,53] The main reason was not reporting a history of CD in the control group. The lack of history of CD may not be informative without screening of the relatives. However, having a known member with CD in the core family may have an influence on the age of gluten introduction and the amount of gluten intake.

Assessment of exposure was done using other than recommended methods (i.e., secure records) in seven studies.[39,40,42,46,48,50,53] Five studies did not make any adjustment of effect measures for any confounding factors.[40,41,43,47,48] The same method of ascertainment for cases and controls was used in all studies.

4 | BREASTFEEDING (ANY OR EXCLUSIVE) AND CD/CDA RISK

4.1 | RCTs

In the previous review, based on the findings from the PreventCD study,[22] in a population at genetic risk of developing CD, no difference in risk for CD/CDA was found between children who were ever breastfed or exclusively breastfed compared to those who were never breastfed.[18] No new RCTs that evaluated this risk were identified for the current review.

4.2 | Cohort studies

Two cohort studies included in the previous review reported on breastfeeding and CDA risk in newborns at-risk of T1DM or CD (BABYDIAB).[35,36] In the first cohort study,[35] we found no difference in CDA development between groups who received any breastfeeding compared to those who were never breastfed (OR 1.73, 95% CI, 0.77–3.86) (Figure S3). Similarly, no difference in CDA risk was noted between children exclusively breastfed versus those who were not breastfed in the second cohort study (OR 0.96, 95% CI, 0.41–2.27)[36] (Figure S3). Among other cohort studies, none evaluated if any breastfeeding influences CDA risk in the population with unknown genetic risk for CD. Likewise, the effect of any or exclusive breastfeeding on CD development, either in populations at genetic risk or in unknown genetic risk populations, was not assessed in any cohorts.

4.3 | Case–control studies

The meta-analysis of four case–control studies, including two newly identified studies,[39,42,43,48] found no difference in CD risk between children with any/exclusive breastfeeding and children who were never breastfed (OR 0.99, 95% CI, 0.62 to 1.58) (Figure S4).

5 | BREASTFEEDING DURATION AND CD/CDA RISK

5.1 | RCTs

No new trial assessing the association between the duration of any or exclusive breastfeeding and CD/CDA risk was identified. However, the effect of breastfeeding duration on CD development in the population at genetic risk of developing CD was reported in three RCTs included in the previous review.[22,23,25]

The duration of any and exclusive breastfeeding did not significantly affect CD risk in the PreventCD study.[22] In the CELIPREV study,[23] there was no difference in mean breastfeeding duration in months between the group of children with CD compared to the control group without CD (MD 0.20, 95% CI, −1.23 to 1.63) or between groups with and without CDA (MD -0.2, 95% CI, −1.46 to 1.06) (Figure S5). In the BABYDIET study,[25] only the median duration of exclusive breastfeeding was reported for the groups with gluten introduction at 6 months (median, 2 weeks; range: 0–25) and 12 months (median, 10 weeks; range, 0–25). However, no association between exclusive breastfeeding duration and CDA was reported.

5.2 | Observational studies

5.2.1 | Duration of any breastfeeding and CDA in population at genetic risk of developing CD (cohort studies)

Four cohort studies (in six publications)[11,29,32,33,35,36] reported on the association between any breastfeeding duration and CDA development in populations at genetic risk of developing CD. The current analysis includes new findings of the TEDDY Study[29] and includes not previously reported effect measures for older studies.

The TEDDY study showed no decreased CDA risk for any breastfeeding >6 months compared to ≤6 months (adjusted HR 1.08, 95% CI, 0.95 to 1.23).[29] Likewise, in two other cohort studies, there was no difference in CDA risk between any breastfeeding for ≤6 months compared to >6 months (BABYDIAB)[35] and between <6 months compared to ≥6 months (GENERATION R)[33] (see Figure S6).

The DAISY study[32] reported data as a continuous outcome. There was no difference in mean duration of breastfeeding between groups of children with CDA compared to those without CDA (MD, 1.6 months, 95% CI, −0.84 to 4.04) (Figure S7). Although a more recent report of the same cohort was available,[14] data on the control group were not provided and, therefore, this study could not be included in the analysis.

5.2.2 | Duration of exclusive breastfeeding and CDA in population at genetic risk of developing CD (cohort studies)

The association between the duration of exclusive breastfeeding and CDA risk was reported in two cohorts (TEDDY[29] and BABYDIAB[36]). The TEDDY study found no difference in CDA (TGA) risk between the group exclusively breastfed for longer than 3 months compared to the group exclusively breastfed for 3 months or less (adjusted HR 1.8, 95% CI, 0.94–1.24); however, by using a propensity score, there was an increased risk of CDA in relation to longer exclusive breastfeeding duration (adjusted HR 1.08, 95% CI, 1.03–1.14).[29] Likewise, in the BABYDIAB study, there was no difference in CDA risk between groups exclusively breastfed for 3 months or longer compared to those breastfed for 3 months or less (OR 1.15, 95% CI, 0.42–3.12).[36]

5.2.3 | Duration of breastfeeding (any or exclusive) and CD in population at genetic risk of developing CD (cohort studies)

In the PreventCD cohort study,[15] there was no difference at ages 12, 24, 36, 48 and 60 months between any reported duration of any or exclusive breastfeeding and CD risk (Figure S8,S9). In the DIABIMMUNE cohort study,[37] any breastfeeding duration was reported as a continuous outcome (mean with 95% CI). However, no SD or MD were reported.

5.2.4 | Duration of breastfeeding (any or exclusive) and CD in the population with unknown genetic risk for CD (cohort studies)

In the population with unknown CD risk, the association between the duration of any breastfeeding and the development of CD was reported in two cohorts (ABIS and MoBA).[31,34] There was no difference in the number of children with CD in relation to breastfeeding duration in both studies (Figure S10).

5.2.5 | Duration of breastfeeding (any or exclusive) and CD (case–control studies)

Duration of any breastfeeding was reported in five case–control studies as dichotomous outcomes, including one new study and one not previously identified.[39,46,50,51,53] There was no association between the duration of any breastfeeding and risk of CD in any of six meta-analyses performed for dichotomic measures (Figure S11).

In four studies, the duration of breastfeeding was reported as a continuous measure, or only OR was reported; thus, it could not be included in the meta-analysis. An effect measure (OR) for the association between breastfeeding duration and the risk of CD was reported only in two studies,[39,41]; for another two,[40,46] the MD between groups was calculated (Table S8). In only one study,[46] there was a difference in mean duration of exclusive (MD −0.60 months, 95% CI, −1.16 to −0.04) and partial (MD −2.0 months, 95% CI, −3.1 to −0.9) breastfeeding between CD and control groups. Other studies[39–41] reported no difference in breastfeeding duration between groups of children with and without CD.

6 | BREASTFEEDING DURING GLUTEN INTRODUCTION AND CD/CDA RISK

6.1 | Interventional trials (in population at genetic risk of developing CD)

No new RCTs reported this outcome. However, we calculated not previously reported RRs for the CELIPREV study.[23] The association between breastfeeding during gluten introduction and risk of CD

was reported in two RCTs.[22,23] In both studies, there was no effect of breastfeeding at the time of gluten introduction on CD development. For the PreventCD,[22] OR 1.34, 95% CI, 0.75–2.40, as reported in the previous review;[18] and for the CELIPREV study, OR 1.03, 95% CI, 0.59–1.80.[23] (Figure S12).

Only the CELIPREV study reported on the association between breastfeeding during gluten introduction and CDA development.[23] There was no difference in the number of children breastfed during gluten introduction between groups with CDA and without CDA (OR 0.98, 95% CI, 0.59–1.64) (Figure S13).[23]

6.2 | Observational studies

6.2.1 | Breastfeeding vs. discontinued breastfeeding during gluten introduction and CD in population at genetic risk of developing CD (cohort study)

No increased risk of CD between children breastfed for ≤1 month (adjusted for country, HLA, gender, family history of CD and age at gluten introduction, HR 1.07, 95% CI, 0.69–1.67) or >1 month (adjusted HR 1.13, 95% CI, 0.88–1.46) during gluten introduction as compared to discontinued breastfeeding before gluten introduction was reported in a single study (TEDDY).[30]

6.2.2 | Breastfeeding vs. discontinued breastfeeding during gluten introduction and CDA in population at genetic risk of developing CD (cohort studies)

The association between breastfeeding during gluten introduction and CDA development was reported in two studies.[30,32] In the TEDDY study,[30] a trend of increased CDA risk was reported when breastfeeding lasted for ≤1 month (adjusted HR 1.08, 95% CI, 0.82–1.44), which turned out to be significantly increased when breastfeeding continued >1 month during gluten introduction (adjusted HR 1.23, 95% CI, 1.05–1.44), as compared to discontinued breastfeeding before gluten introduction. However, in the DAISY study,[32] there was no difference in CDA risk between children exposed to wheat, barley and rye while still being breastfed compared to those not being breastfed at the time of gluten introduction (OR 1.20, 95% CI, 0.69 to 2.10) (Figure S14).

6.2.3 | Breastfeeding during gluten introduction and CD in the population with unknown CD risk (cohort study)

In the MoBA cohort,[31] breastfeeding (in relation to discontinuation of breastfeeding) at the time of gluten introduction was not associated with later CD development (adjusted OR 1.17; 95% CI, 0.74–1.87).[31]

6.2.4 | Breastfeeding during gluten introduction and CD (case–control studies)

Five case–control studies reported on the association between breastfeeding during gluten introduction and CD risk. In a meta-analysis of four studies,[45–47,49] there was a decreased risk of CD in the group of children breastfed during gluten introduction compared to the control group (OR 0.51, 95% CI, 0.34–0.77, $n = 1959$) (Figure S15). In one study,[40] including only children with the HLA-DQ2 genotype, the authors reported that children were *more* frequently breastfed in the control group compared to the CD group (OR 0.11, 95% CI, 0.01 to 0.8, $n = 235$) (Table S9).

7 | AGE AT GLUTEN INTRODUCTION AND CD/CDA RISK

7.1 | Interventional trials

7.1.1 | Age at gluten introduction and CD (population at genetic risk of developing CD)

In the previous review,[18] no effect of time of gluten introduction on the development of CD was reported in any of the four identified RCTs in populations at genetic risk of developing CD.[22–25] No new trials evaluating this outcome were identified by the current review. Compared to our 2015 analysis, we report more time comparisons. However, as previously reported, similar rates of CD were found in children introduced to gluten at earlier versus later time points (Figure S16).

7.1.2 | Age at gluten introduction and CDA (population at genetic risk of developing CD)

Four trials (in five publications)[22–26] assessed the effect of time of gluten introduction on CDA risk. In a meta-analysis of two trials,[23,24] we found a difference in CDA risk at 2 years of child's age between groups of children with later (at 12 months) versus earlier (at 6 months) gluten introduction (RR 0.40, 95% CI, 0.24 to 0.65, $n = 573$) (Figure S17).[23,24] Likewise, one trial found a lower number of children with CDA only at 1 year of child's age with later (at 12 months) versus earlier (at 6 months) gluten introduction (RR 0.06, 95% CI, 0.00 to 0.99, $n = 25$); however, no difference was found at 1.5 and 2 years of child's age.[24] No difference in CDA risk between groups with later (at 12 months of age) compared to earlier (at 6 months of age) time of gluten introduction was found in individual studies at 1.5, 3, 5 and up to 13 years (median, 8.1 years) of age. Similarly, with our previous review, in one study (PreventCD),[22] no difference in CDA risk was found between groups with gluten introduction at 4 versus at 6 months of age at child's ages 1–5 years (Figure S17).

7.1.3 | Age at gluten introduction and CD/CDA (population with unknown genetic risk for CD)

Only the EAT study[27] assessed the effect of time of gluten introduction on the development of CDA and CD in individuals with unknown genetic risk for CD. The authors reported a difference in risk for developing CD between early (4 months) and standard (6 months) wheat introduction groups (the risk difference, 1.4%, 95% CI, 0.6%–2.6%). However, based on our calculations, there was no difference in risk of CD (RR 0.07, 95% CI, 0.00–1.23) or CDA (RR 0.30, 95% CI, 0.06–1.45) between groups with early compared to standard time of wheat introduction (Figure S18).

7.2 | Observational studies

7.2.1 | Age at gluten introduction and CD in population at genetic risk of developing CD (cohort studies)

None of three meta-analyses performed (based on TEDDY and DAISY studies)[14,30] showed a difference in CD risk between groups with gluten introduction at <4, at 4–6, and >6 months. (Figure S19). One study (TEDDY) also reported a continuous outcome. There was a difference in the mean age at gluten introduction between children with CD and without CDA (5.9 ± 1.9 vs. 6.2 ± 1.9 months, MD −0.30, 95% CI, −0.48 to −0.12) (Figure S20).[11]

7.2.2 | Age at gluten introduction and CD in the population with unknown genetic risk for CD (cohort studies)

Based on the analysis of new results from the MoBA cohort,[13] lower CD risk was observed when gluten was introduced to infants at 4–6 months as compared to ≥6 months (OR 0.68, 95% CI, 0.56–0.83) (see Figure S21). In contrast, a meta-analysis of two studies (new results from the MoBA cohort and ABIS) showed no differences in CD risk between infants introduced to gluten at <4 months versus ≥6 months of age.[13,34] Likewise, no differences in CD risk were observed between infants with gluten introduction either at <4 versus at 4–6 months or ≤4 months versus at 5–6 months in individual studies (Figure S21).

7.2.3 | Age at gluten introduction and CD in case–control studies

Five case–control studies (including two not previously included studies)[39,45,50,51,53] reported data on the association between age at gluten introduction and CD as a dichotomic measure. With two exceptions, no difference in risk of CD for most analysed ages of gluten introduction between children with CD and controls was found (Figure S22). A meta-analysis of four studies[39,50,51,53] found a higher number of children with gluten introduction at ≤3 months of age in the group with CD compared to group without CD (OR 1.88, 95% CI, 1.30–2.71). Furthermore, in a meta-analysis of three studies,[39,45,51] there was a lower number of children introduced to gluten at 7–12 months in the group with CD compared to controls (OR 0.74, 95% CI, 0.58–0.93).

Only two case–control studies[39,41] reported the ORs of continuous measures for the association between age at gluten introduction and CD risk, and for an additional one,[46] MD was calculated. However, there was no association between age at gluten introduction and CD in any of these three included studies[39,41,46] (Table S10).

7.2.4 | Age at gluten introduction and CDA in population at genetic risk of developing CD (cohort studies)

The association between age at gluten introduction and CDA development was reported in four studies (TEDDY, BABYDIAB, GENERATION R and DAISY [new results]).[14,30,33,35] Three pooled analyses assessing different timing of gluten introduction (at <4 months, 4–6 months, and ≥6 months) showed no differences in CDA risk between groups (Figure S23). Similarly, in the most recent publication of the TEDDY study,[11] no difference in the mean age at gluten introduction between groups with CDA versus without CDA (MD 0.10 months, 95% CI, −0.01 to 0.21) was reported. However, this was an unadjusted analysis based on baseline characteristics.

8 | AMOUNT OF GLUTEN INTAKE AT WEANING (AND LATER) AND CD/CDA RISK

8.1 | Interventional trials

8.1.1 | Mean gluten intake and CD in population at genetic risk of developing CD (RCTs)

The mean amount of gluten intake in populations at risk of CD was assessed only in two RCTs (CELIPREV and PreventCD); however, neither reported that as an outcome.[22,23] In the CELIPREV study, no difference in mean gluten intake (g/day), at 15 months of age, between the CD and control groups (MD -0.20, 95% CI, −0.65 to 0.25) and between the CDA and control groups (MD -0.20, 95% CI, −0.61 to 0.21) was found (Figure S24). However, data were included only as variables of population characteristics. Data from the PreventCD cohort are reported in the observational studies (cohort study).

8.2 | Observational studies

8.2.1 | Amount of gluten intake and CD/CDA in population at genetic risk of developing CD (cohort studies)

Four new publications of three cohort studies (TEDDY, PreventCD and DAISY),[11,12,14,15] reporting on the association between the amount of gluten intake and risk of CD development were identified. For PreventCD, two analyses were reported. In the first analysis of the PreventCD cohort,[12] the quantity of early (between 18 and 36 months) gluten intake was not related to CD development during the first 5 years of life. However, in a recently updated analysis (of longer follow-up, and with a higher number of children with CD and different statistical approach),[15] an increased risk of CD development in relation to the amount of early gluten intake (HR 1.07/g increase in daily gluten intake) was found (95% CI was not reported). Similar results were reported by two other cohort studies (TEDDY and DAISY). In the TEDDY study,[11] higher daily gluten intake was associated with increased CD risk (adjusted HR 1.50, 95% CI, 1.35–1.66) and CDA risk (adjusted HR 1.30, 95% CI, 1.22–1.38) for every 1 g/day of additional gluten intake. Consistently, in the DAISY study,[14] the risk of CD development was increased in relation to a higher amount of gluten intake throughout childhood (adjusted HR 1.15 per SD of higher gluten intake at 6 years of age, 95%CI, 1.00–1.32).

8.2.2 | Amount of gluten intake and CD/CDA in the population with unknown genetic risk for CD (cohort study)

Only the new results of the MoBA cohort study[13] reported on the association between the amount of gluten intake and CD in the general paediatric population. There was a higher risk of CD development per one standard deviation (SD) increase in daily gluten amount at the age of 18 months. In children in the 4th quartile of gluten intake compared with the 1st quartile, the adjusted RR was 1.29, 95% CI, 1.06–1.58. The following cutoff for quartiles were used: 1st quartile: <6.22 g/d; 2nd quartile: 6.22–8.16 g/d; 3rd quartile: 8.16–10.68 g/d; and 4th quartile: 10.68 g/d (≈above 4.1 slices of bread). For each slice of bread (≈ 2.6 g of gluten,) the adjusted RR for CD was 1.07 (95% CI, 1.02–1.13).

8.2.3 | Amount of gluten intake and CD (case–control studies)

Three case–control studies (including two new studies)[41,45,52] reported on the association between the amount of gluten intake and CD risk. In the nested case–control study from the Italian PreventCD cohort,[52] there was an increased risk of CD in relation to the highest quartile of gluten intake (>5.53 g/day, adjusted OR 4.82, 95% CI, 1.1–21) and higher mean gluten intake at 12, 18, 24 and 36 months in the CD group compared with the control group (Figure S25). Likewise, the Swedish nested case–control study in a population at genetic risk of developing CD[41] found an increased CD risk in relation to both total gluten intake before TGA seroconversion (OR 1.05, 95% CI, 1.01–1.10) and gluten intake measured at the last visit before TGA seroconversion (OR 1.28, 95% CI, 1.13–1.46). A population-based Swedish study[45] also found an increased risk of CD development in groups with large versus small-to-medium amounts of gluten intake in the 2 weeks after gluten introduction (OR, 1.4, 95% CI, 1.1–1.9; amount of gluten defined as small, medium or large was not reported).

9 | TYPE OF INTRODUCED GLUTEN-CONTAINING FOOD AND CD/CDA RISK

9.1 | Interventional trials

No RCTs reported the effect of type of gluten-containing food used for gluten introduction.

9.2 | Observational studies

9.2.1 | Type of gluten-containing foods and CD in population at genetic risk of developing CD (cohort study)

Only one study of Swedish children who have genetically known risk of CD (TEDDY cohort) reported the association between intake of eight groups of gluten-containing foods and CD development.[38] Increased risk of CD was found only for high daily bread intake (>18.3 g/d) compared to no bread intake at 12 months (adjusted HR 1.79, 95% CI, 1.10 to 2.91).

9.2.2 | Type of gluten-containing foods and CDA in population at genetic risk of developing CD (cohort studies)

The association between the type of gluten-containing foods and risk of CDA was reported in two cohorts (BABYDIAB and the Swedish part of TEDDY cohort).[35,38] The BABYDIAB study found no association between CDA risk and the introduction of food supplements during the first 3 months of life, including cow's milk formula, gluten-free solid foods or gluten-containing solid foods (HR 1.5, 95% CI, 0.2–10.9).[35] In contrast, in the TEDDY cohort of Swedish genetically at-risk children, an increased risk of CDA was related to low daily intake of porridge (≤158 g/day) at 9 months compared to no porridge intake (adjusted HR 1.53, 95% CI, 1.05–2.23), as well as to high daily intake of bread (>18.3 g/day) at 12 months compared to no bread intake (adjusted HR 1.47, 95% CI, 1.95–2.05).[38]

9.2.3 | Type of gluten-containing foods and CD (case–control studies)

No new relevant case–control study was identified; however, new analyses were performed of previously identified studies. Four case–control studies[45,48,49,53] reported on the association between the type of foods used for gluten introduction and CD risk. A meta-analysis of two Swedish studies[45,49] found an increased risk of CD when gluten was introduced with follow-up formula (OR 1.46, 95% CI, 1.18–1.80) (Figure S26). However, there was no difference between groups with and without CD in relation to gluten introduction with solid foods (OR 0.56, 95% CI, 0.29–1.07). One of these studies[49] also found no difference between groups with and without CD in regard to gluten introduction with follow-up formula and porridge (OR 1.09, 95% CI, 0.54–2.20).

A single study (including children from the United Kingdom)[48] reported on the association between gluten introduction with the use of wheat cereals, rusks or commercial baby foods and CD risk. There was a difference between children with CD versus those without CD only when gluten was introduced with wheat cereals (OR 3.09, 95% CI, 1.19–8.00), but not with rusks or commercial baby foods. In another study (also from the United Kingdom),[53] there was no difference between groups of children with CD and healthy controls introduced to gluten with different types of cereals (wheat, barley, oat) (Table S11).

10 | GLUTEN INTAKE DURING LACTATION

The association between a gluten-free diet compared to a gluten-containing diet of the mother during lactation was not reported in any of the included studies. The PreventCD study[22] reported a maternal diet (gluten-free diet compared to a normal diet) during pregnancy and lactation as a factor unrelated to the development of CD.

11 | GENETIC RISK AND GLUTEN AMOUNT

Four observational studies,[11,13,15,35] including two new cohort studies and one case–control study, reported ambiguous results on the association between feeding practices in children carrying different HLA genotypes.

11.1 | Cohort studies

A recent analysis of the PreventCD cohort[12] showed no association between gluten consumption patterns and risk of CD in relation to different HLA risk alleles and, except for those with the DQ2.2/DQ7 haplotype (HR 5.81, 95% CI, 1.18–28.74). In the DAISY study,[14] no association was found between gluten intake at 1 year and child's HLA genotype (HR not reported, $p > 0.15$).

11.2 | Case–control study

Two case–control studies[13,41] reported on the association between different genetic risk variants and CD risk. In one nested case–control study in children out of the Norwegian MoBA cohort,[13] the association between gluten intake at 18 months and development of CD was not influenced by HLA genotype at-risk for CD.

Likewise, the Swedish nested case–control study[41] reported no difference in gluten intake at the visit before seroconversion between DR3-DQ2 homozygotes and heterozygotes, or those without the DR3-DQ2 genotype. An association between higher gluten intake compared to lower gluten intake and risk of CD was found for both DR3-DQ2 homozygotes (for 5.9 g/day; OR, 3.19; 95% CI, 1.61–6.30) and heterozygotes (for 6.3 g/day; OR, 2.24; 95% CI, 1.08–4.62). However, no difference between gluten intake in relation to tertials distribution and different HLA risk genotypes was noted.

12 | DISCUSSION

The main finding of this systematic review is the accumulating evidence that the amount of gluten introduced into the infant's diet at weaning and/or thereafter may be a risk factor in the development of early age manifestation of CD and CDA. The occurrence of CD and CDA in infants harbouring the HLA risk alleles DQ2 and/or DQ8 is regardless of whether these infants were recruited from the general population with unknown genetic risk for CD or from families with members having CD or type 1 diabetes. Lastly, this systematic review provides current information on the importance of breastfeeding and the introduction of gluten while the infant is being breastfed, as well as information about the age at gluten introduction, the amount and type of gluten, and the interaction of early feeding practices with different degrees of risk based on the different HLA risk allele combinations.

12.1 | Breastfeeding

Exclusive breastfeeding for at least 4 months (17 weeks) and exclusive or predominant breastfeeding for the first 6 months of life is the preferred option and constitutes the optimal nutrition for young infants.[10] This recommendation should not be influenced by our 2015 results,[18] extended to the current report, showing that breastfeeding (any or exclusive) does not change the risk of developing CD or CDA. Regarding breastfeeding duration, we found no new evidence, even if indirect, from RCTs. However, new evidence from a single observational study may suggest that any breastfeeding >6 months or exclusive breastfeeding >3 months compared to a shorter duration was associated with an increased risk of CDA.[29] Nevertheless, caution must be exercised in the interpretation of that report,[29] firstly, because of the lack of adjusting for amount of gluten intake, and, secondly, because this difference was only reported in analysis with use of the propensity score. Third, all other studies, either RCTs, cohort or case–control studies, were unable to show any effect of longer any or exclusive breastfeeding duration

on CD and CDA risk, which this review being the first to systematically review these data. Longer breastfeeding may not be an independent variable, since longer breastfeeding may be associated with later gluten introduction and lower gluten consumption. Finally, concerning breastfeeding during gluten introduction, this evaluation produced inconsistent results. On one hand, most studies (including all RCTs) reported no association between breastfeeding during gluten introduction and the risk for CD or CDA.[31] However, when continued breastfeeding was compared to discontinued breastfeeding during gluten introduction in two cohort studies, there were conflicting results. While the TEDDY study (the Swedish sub-cohort)[30] suggested that there is an increased CDA risk when breastfeeding continues for more than a month after gluten introduction, this was not found in the DAISY[32] study. In addition, a meta-analysis of four case–control studies[45–47,49] showed a decreased risk of CD in the group of children breastfed during gluten introduction compared to the control group.

12.2 | Age at gluten introduction

Overall, our systematic review supports our previous findings that age at gluten introduction does not influence the cumulative risk for CD and CDA.[18] However, as previously shown and is plausible in the context of the pathophysiology of CD, earlier introduction of gluten was associated with earlier appearance of CDA in the population with known CD risk at some time points in a meta-analysis of two[25,26] of five included RCTs.[22–26] Our evaluation of the only (new) RCT (EAT study)[27] conducted in the population with unknown genetic risk for CD suggests that time of gluten introduction does not influence the risk of CD or CDA. The authors of the original study reported a difference in risk for developing CD between early and late wheat introduction groups. However, the study limitations (summarised under *Characteristics of included studies*) preclude the drawing of firm conclusions. Several observational studies also assessed this outcome. In the population with unknown genetic risk for CD, there was one study, MoBA, demonstrating a reduced CD risk with 'standard' (4–6 months) versus 'late' (≥6 months) introduction of gluten,[13] but a meta-analysis of the two available studies, MoBA and ABIS, did not find any such effect.[13,34] Thus, some available data suggest that the age at gluten introduction does influence when CD and/or CDA will occur. However, in the long run, it does not influence the cumulative incidence of CD. A word of caution is required in the interpretation of these results, as available data are limited to practices ranging from introduction during early infancy up to 1 year of age and there is a question as to whether later introduction (beyond 1 year) or avoidance during inflammation (e.g., acute gastroenteritis) in infancy may also have an effect.

12.3 | Amount of gluten

The main change from our previous review in 2015 is the impact of the amount of gluten intake during the first 2 years of life on the risk of CD. For infants at high genetic risk of developing CD, evidence from 6 observational studies suggests that consumption of a higher amount of gluten at weaning and/or thereafter may increase CD risk in childhood. New analysis from the PREVENTCD cohort,[15] as well as data from the TEDDY[11] and DAISY[14] studies, suggest that higher amounts of gluten introduced into the infant's diet increases the risk for CD and CDA. This is consistent with findings from two case–control studies from Sweden[41,45] and one from Italy, evaluating PreventCD participants from Italy.[52] For infants with unknown genetic risk for CD, the information is limited to one cohort study (the MoBA study[13]) showing an increased risk for CD, limited to the 4th quartile of gluten intake, at the age of 18 months. Since CD is a gluten-induced disease, higher amounts of gluten may accelerate seroconversion at an early age or clinical manifestation at any age in so far asymptomatic persons with CD.

12.4 | Type of gluten-containing food

No RCTs reported risk of CDA or CD in relation to intake of different types of gluten-containing foods. Information from one observational study from Sweden regarding the type of gluten in a population with known CD risk (TEDDY cohort) reported an increased risk of CD with high daily bread intake compared to intake of an equal amount of gluten from other foods at 12 months.[38] A meta-analysis of two Swedish case–control studies[46,50] suggested increased risk of CD when gluten was introduced with a follow-up formula but not solid foods.[45,49]

12.5 | Genetic risk & gluten amount

The results from observational (cohort and case–control) studies suggest that the effect of infant feeding practices on the risk of developing CD may be modified by HLA risk alleles (genetic risk groups).[11,13,15,35] However, the results are inconsistent.

12.6 | Strengths and limitations

The methodology of this systematic review was robust. Our search strategy was developed to ensure a thorough literature search, with no restrictions based on language. All analyses were defined a priori. The risk of bias in the included studies was assessed. For non-RCTs (i.e., cohort and case–control studies), we used NOS. However, there are more than 80 tools for assessing the risk of bias in non-RCTs.[54] By itself, this number indicates that none of these scales is ideal. Another strength of this review is the inclusion of the data from the long follow-up of the large PreventCD cohort,[15] which represents the RCT with the lowest risk of bias.

Nonetheless, some methodological issues should be taken into consideration. Only RCTs, if properly designed and conducted, provide the best evidence to prove causality. However, only some of the

questions asked could be answered via RCTs. For example, it would be unethical to randomly assign infants to any or a certain duration of breastfeeding. Even if RCTs were available, they had some limitations. For example, as commented on earlier by some members of our group,[28] the EAT study,[27] reporting as a secondary analysis on gluten intake and the risk of CD in the population with unknown genetic risk for CD, did not report how many enrolled infants came from CD families, to which groups subjects were randomised, whether they dropped out or whether they adhered to a diet with early high-gluten intake. As the study was carried out in a population with unknown genetic risk for CD, there was a mixture of genetic risks. Lack of genotyping and a follow-up period of only 3 years further limit possible conclusions. The TGA test used, and its cutoff value, were not reported. Without reporting the used test, its cutoff value, the number of TGA-positive children and whether all TGA-positive children underwent duodenal biopsies to prove or disprove a diagnosis of CD, the results are not interpretable. Consequently, caution is needed before drawing conclusions on advisable gluten intake in infancy to prevent CD in the population with unknown genetic risk for CD.

Likewise, some of the earlier identified RCTs have some limitations. For example, as described in our earlier review, the PreventCD was not designed nor powered sufficiently to demonstrate the effects of environmental factors that may contribute to the development of CD, such as infections or rotavirus vaccination, even if these were evaluated (but anyway were not among our research questions). Furthermore, sample sizes in two other RCTs included in our review were small, and none of these trials was designed to assess the effect of gluten introduction on the risk of CD/CDA as the primary outcome.

Well-known limitations of observational studies also should be considered. For example, regarding the effects of breastfeeding, limitations include the risk of selection bias (if losses to follow-up are high and related to breastfeeding) and the risk of recall bias (in studies that use self-reporting). The latter is less likely to occur in prospective cohort studies in which mothers are asked for information upon joining the study. However, it is more likely to occur in retrospective cohort studies and case–control studies and occurs when mothers do not remember breastfeeding details accurately. The validity of observational studies can be threatened by confounding, suggesting an association when it does not exist. While confounding had been adjusted for in many of the observational studies included in our review, residual confounding, which occurs when a confounder has not been adequately adjusted for, cannot be excluded. For breastfeeding, examples include additional environmental factors such as a diabetic mother, mode of delivery, infections and the use of antibiotics (or other drugs), which can alter the gut microbiota. Finally, breastfeeding in itself may also be a confounding factor for gluten intake, since the composition of meals and thus, of gluten content may be different for a child with or without breastfeeding, if gluten was not administered as a fixed amount of study material. Another limitation is that CDA was not defined in all studies in the same way. For example, in the TEDDY study, two consecutive blood samples needed to be positive, while in others only one positive result was sufficient for a diagnosis of CDA. For our review, IgG antibodies were only considered as indicative of CDA in cases with IgA deficiency. This assumed that total IgA was measured. However, if not, and/or if combined IgA/IgG tests were used, these tests give false positive results for CDA.[55]

One of the clinical review questions related to the amount of gluten at weaning and later and the risk of CD. In the included studies, various levels of exposure were compared, usually using one category as a reference. However, different studies reported different categories of the exposure variable and exposure was differently assessed (i.e. using a food diary or food frequency questionnaire). Moreover, there were differences in the assessment within one study performed in different countries. We abstained from comparing the lowest and highest categories, as the categories (lowest versus highest) differ across studies. Moreover, the findings may differ depending on the statistical methods used, as documented by discordant results reported for the PreventCD study. The findings by Crespo-Escobar et al.[12] suggested that the amount of gluten, as well as gluten consumption patterns, in early life have no impact on CD development at approximately 6 years of age. Only in children with HLA-DQ2.2/-DQ7 genotypes did high intakes of gluten increase the risk of CD. In contrast, Meijer et al.[15] showed in the same cohort that the quantity of early gluten intake is associated with a significantly higher risk of CD development, with an increased hazard ratio of 1.07 per gram increase in daily gluten intake. The latter study used landmark prediction models to avoid immortal time bias[56] (caused "when a cohort study is designed so that follow-up includes a period of time when participants in the exposed group cannot experience the outcome and are essentially 'immortal'"). Taken together, the true effect of the amount of gluten at weaning remains uncertain and may only be clarified by RCTs.

13 | CONCLUSIONS

This updated review confirms that breastfeeding (any or exclusive, its duration and occurrence during gluten introduction) and time of gluten introduction have no effect on the cumulative incidence of CD during childhood. As expected from biology, earlier introduction of gluten was associated with earlier CDA development, but not with a lower cumulative incidence of CD from 3 years onwards. It seems that the amount of gluten consumed at weaning and thereafter has an impact on CD/CDA risk, but the ambiguity related to the type of gluten introduced and the effect of continued exposure over time diminishes our ability to determine a valid effect. These findings must be considered in the context of limitations of the included studies and do not allow us to provide recommendations for children with known (HLA DQ2/DQ8 positive) or unknown (HLA genotype not known) genetic risk of developing CD.

AUTHOR CONTRIBUTIONS

Hania Szajewska: Conceptualization (lead); data curation (supporting); formal analysis (supporting); methodology (lead); supervision (equal); writing – original draft (lead); writing – review and editing (lead). **Raanan Shamir:** Conceptualization (equal); formal analysis

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CONFLICTS OF INTEREST

The authors declare no conflict of interest related to this review.

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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