CD DUX Child version

We would like to know how you feel these days.
Therefore, could you please indicate how you feel in different situations?
You can do that by circling in each question one of the faces that fits you best.
There are no wrong answers; it's about what you feel.

	Please express how you've been feeling lately.
1.	When I think of food containing gluten, I feel … 
2.	When at school I am given food containing gluten, I find it … 
3.	Talking about my coeliac disease with others my age, I find … 
4.	Not being able to eat just everything, I find ... 
5.	When someone offers me food that I can't have, I feel … 
6.	When I have to explain to others what coeliac disease is, I feel … 

Please express how you've been feeling lately.	
7.	Talking about coeliac disease I find … 
8.	Having to follow a lifelong diet, I find … 
9.	Having to pay attention to what I eat, I find … 
10.	Having coeliac disease is … 
11.	Not being able to eat anything I want like other people, I find … 
12.	Following a diet for my coeliac disease is … 

Thanks for filling in this questionnaire!

CD DUX Parent- Girl version

We would like to know how your daughter feels these days.
Therefore, could you please indicate how your daughter feels in different situations?
You can do that by circling in each question one of the faces that fits your daughter's feelings best. There are no wrong answers; it's about what you think your daughter feels.

	Please express how your daughter has been feeling lately.
1.	When your daughter thinks of food containing gluten, she feels … 
2.	When at school your daughter is given food containing gluten, she finds it … 
3.	Talking about celiac disease with others her age, she finds … 
4.	Not being able to eat just everything, she finds … 
5.	When someone offers her food that she can't have, she feels … 
6.	When your daughter has to explain to others what celiac disease is, she feels … 

Please express how your daughter has been feeling lately.	
7.	Talking about celiac disease your daughter finds ... 
8.	Having to follow a lifelong diet, your daughter finds … 
9.	Having to pay attention to what she eats, she finds … 
10.	Having celiac disease your daughter finds … 
11.	Not being able to eat anything she wants like other people, she finds … 
12.	Following a diet for her celiac disease your daughter finds ... 

Thanks for filling in this questionnaire!

CD DUX Parent- Boy version

We would like to know how your son feels these days.
Therefore, could you please indicate how your son feels in different situations? You can do that by circling in each question one of the faces that fits your son's feelings best. There are no wrong answers; it's about what you think your son feels.

Please express how your son has been feeling lately.	
1.	When your son thinks of food containing gluten, he feels … 
2.	When at school your son is given food containing gluten, he finds it … 
3.	Talking about celiac disease with others his age, he finds … 
4.	Not being able to eat just everything, he finds … 
5.	When someone offers him food that he can't have, he feels … 
6.	When your son has to explain to others what celiac disease is, he feels … 

Please express how your son has been feeling lately.	
7.	Talking about celiac disease your son finds ... 
8.	Having to follow a lifelong diet, your son finds … 
9.	Having to pay attention to what he eats, he finds … 
10.	Having celiac disease your son finds … 
11.	Not being able to eat anything he wants like other people, he finds … 
12.	Following a diet for his celiac disease your son finds ... 

Thanks for filling in this questionnaire!

Summary Table of the Revised Literature
ESPGHAN position paper on the management and follow-up of children and adolescents with coeliac disease.

Supplementary material

Question 1. Is follow-up and management of CD needed?

A search was conducted in Medline using the search terms celiac, coeliac, children, adherence and follow-up. The search identified a total of 356 records, of which 12 were included for this question: 8 primary observational studies (7509 children) and 4 systematic reviews (640 studies). As there were insufficient studies in children only, we included 1 study in both adults and children (Kurppa 2012), 1 systematic review until the age of 20 years (Snyder 2016) and another one without an age specification (Valitutti 2017).

Author, country (year)	Study type/ description	Age (years)	Sample size	Objectives	Main findings
Barnea, Israel (2014)	Case-control	Mean diagnosis 6.4 lost to follow up (LTFU) 5.96 controls	50 CD children 52 CD children with LTFU	To characterize LTFU population, and identify compliance barriers to gluten- free diet (GFD) and follow-up.	LTFU is associated with non-adherence to GFD and positive serology.
Bellini, Italy (2011)	Case-control	6-16	156 cases, 353 controls	To determine locus-of-control in coeliacs compared to healthy.	No difference between locus-of-control, to test for adherence to the GFD, in the two groups.
Charalampopoulous, Greece (2013)	Cohort	2-18	90 CD children	To characterize compliance to GFD.	Low compliance rate (44%), worse with age. Parents' education is important.
Hagopian, US/Europe (2017)	Cohort	4.5 months-15	5891 CD children	To determine timing, extent of co-occurrence, and associated genetic and demographic factors.	Early type 1 diabetes (T1D) and coeliac disease (CD) autoimmunity occur together more than expected.
Kurppa,	Interview	<18 ->18	94 CD	To assess	88% Adherence. Younger age at diagnosis,

Finland (2012)			children 749 CD adults	adherence to GFD.	being currently a teenager, and current symptoms were associated with non-adherence to diet.
Ludvigson, Sweden (2016)	Systematic review	Not available (N/A)	190 studies	To propose recommendations for the management in adolescents and young adults, and how to facilitate the transition to adult healthcare.	Diagnosis to be re-evaluated when made outside current European Society of Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) or North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) recommendations or when the patient questions his/her diagnosis.
Myléus, Sweden (2020)	Systematic review	<20	49 studies	To assess adherence to GFD.	Adherence 78% (range 23-98%). Studies varied in design and quality.
Rimárová, Slovakia (2018)	Cross-sectional	9-15	Caregivers to 325 children	To assess adherence to GFD.	Adherence is higher among girls. Younger children and children with family history of CD had significantly higher compliance. Children of parents (especially of mothers) with higher education had better adherence.
Snyder, US (2016)	Systematic review	6 months – 20	N/A	To assess the available evidence in 6 categories associated with CD to develop a set of best practices.	Quality of the data available was often insufficient to provide unequivocal best practices. Using the available data and the clinical experience of the panel, a practical framework for the management of children with CD was created.
Tapsas, Sweden (2014)	Cohort	<1	316 children	To assess adherence to GFD and intake of oats.	97% Adherence, but 83% had occasional transgressions.
Valitutti, Italy (2017)	Systematic review	N/A	401 studies	To summarize the available studies on follow-up of CD in children.	The "best practice" and evidence-based recommendations for follow-up in patients with CD are still awaited. A yearly follow-up visit is advised as the safest approach for children with CD.
Wessels,	Cohort	Mean at	182 CD	To determine the	Investigations for iron, folate, and vitamin B12

Netherlands (2016)		diagnosis 6.3	children	frequency of nutritional deficiencies and thyroid dysfunction in children with CD at diagnosis and during follow-up after initiation of a GFD.	deficiencies are relevant at the time of diagnosis. However, ordering these tests at follow-up visits may be questionable because only mild deficiencies occurred in a minority of the children.

Question 2. Who should do follow-up of which patients and which is the role of the dietician? What is the role of self-care including E-health?

A search was conducted in PubMed using the search terms celiac, coeliac, children, follow-up, gluten-free diet, paediatrician, paediatric expert in the field of celiac, general doctor, dietitian and e-health. The search identified a total of 111 records, of which 4 were included for this question: 2 primary observational studies (381 children) and 2 randomized clinical trials (RTC) in both children and adults (Haass 2017, Vriezinga 2018) (365 patients <25 years).

Author, country (year)	**Study type/ Description**	**Age (years)**	**Sample size**	**Objectives**	**Main findings**
Connan, Canada (2019)	Prospective	Mean 13.5±4.5	18 CD children	To design, develop and refine an interactive E-learning module to educate CD patients/families regarding implementation of a GFD.	Interactive E-learning module is effective in knowledge retention. Mean satisfaction post-module completion was high. Knowledge test scores increased significantly from pre- to post- module completion.
Haas, USA (2017)	RCT	12-24	61 CD children/adults	To determine the impact of Text message intervention on GFD adherence, QoL and patient activation.	Comparing enrolment and three-month follow-up significant improvement in patient activation and QoL in the TEACH intervention group. No statistically significant difference in GFD adherence.

Johansson, Sweden (2019)	Retrospective cohort	Median at diagnosis 7	363 CD patients	To investigate the outcome of different follow up protocols of CD led by either paediatricians or dietitians.	Non-compliance: no difference in prevalence between the different follow-up protocols. anti-tTG IgA reversed equally over time between the three clinics. Total mean cost per patient was less by visits led by dietitian.
Vriezinga, The Netherlands (2018)	RCT multicentre	<25	304 CD children and adults	To evaluate the efficacy of online consultation compared with outpatient clinic follow-up.	Health problems were detected more frequently using online consultation. Results indicate that online consultations for children and young adults with CD are cost saving, increase CD-specific HRQOL, and are satisfactory for the majority.

Question 3: What should be the frequency of follow-up and what should be assessed?

A search was conducted in Pubmed using the search terms celiac, coeliac, children and follow-up. The search identified a total of 382 records, of which 30 were included for this question: 17 primary observational studies (1599387 children) 12 reviews (772 studies) and 1 guideline. As there were insufficient studies in children only, we included 1 guideline in adults (Al Toma 2019), one publication in adults and children (Husby & Murray 2019) and one systematic review (Zingone 2018) in adults. We also included 5 studies published before 2010 (Ansaldi 2003, Elfström 2008, Leonardi 2009, Meloni 2009 and Park 2007), 1 after March 2020 (Lionetti 2021) and 1 narrative review (Anania 2017) since they were considered especially informative.

Author, country (year)	**Study type/ description**	**Age (years)**	**Sample size**	**Objectives**	**Main findings**
Al Toma, Europe (2019)	United European Gastroenterology (UEG) adult guidelines	Adults	N/A	To address the management of gluten-related disorders including CD.	Bone density measurement (DEXA) should be measured in those at high risk of osteoporosis. At diagnosis or not later than the age of 30–35 years and then repeated at 5-year intervals. A shorter interval (2–3 years) in case of low bone density, evidence of ongoing villus atrophy or poor dietary adherence.
Anania, Italy (2017)	Narrative Review	4-17	N/A	A review of vaccination status in CD patients.	Current evidence supports a good immunogenicity of most vaccines with the exception of hepatitis B virus (HBV), that elicits a lower response in CD patients compared to the general population. An evaluation of the response to HBV vaccine should be routinely assessed in newly diagnosed CD children and adolescents who were previously vaccinated for HBV.
Ansaldi,	Cohort	17	343 CD	To establish the	The high frequency of autoimmune thyroid disease

Italy (2003)		months-17	cases, 230 controls	prevalence of autoimmune thyroid involvement in a large series of paediatric patients with CD.	found among patients with CD, even on a GFD, may justify a thyroid status assessment at diagnosis and at follow-up evaluation of children with CD.
Assa, Israel (2017)	Cross-sectional	Mean 17.1	7145 CD cases, 1580896 controls	To investigate the association of a diagnosis of CD with various comorbidities in late adolescence.	Autoimmune diseases were significantly more common in subjects with CD, including insulin dependent diabetes, inflammatory bowel disease, arthritis, thyroid diseases, and psoriatic skin disorders. Further associations included asthma, bile stones, migraine, anaemia and menstrual abnormalities.
Barnea, Israel (2014)	Retrospective case-control	Mean at diagnosis 6.4 in LTFU and 5.96 in control	50 cases (CD with LTFU) 52 controls (CD with FU)	To assess utility of follow up and consequences of not being followed up.	LTFU is associated with non-adherence to GFD and positive serology. Risk factors for LTFU should be identified and addressed in order to improve patient care.
Blansky, USA and Canada (2019)	Retrospective chart review	Mean at diagnosis 9.7	250 CD	To evaluate adherence to guidelines for dietitian consultation and follow-up for children with CD.	Most subjects (83%) consulted a dietitian, with 31% attending both a dietitian-led class and an individual visit. One-fourth of children were lost to follow-up within a year of diagnosis, and 22 (9%) had no gastrointestinal (GI) visits after their diagnostic biopsy. Children lost to follow-up within the first year were older at diagnosis than those who adhered to follow-up for longer.
Canova, Italy, Sweden, and USA (2018)	Longitudinal population-based	0-17	1233 CD cases 6167 controls	To examine the risk of any fracture in CD children compared with references individually using the regional	22 Individuals with CD and 128 reference individuals experienced a fracture, giving an overall HR (hazard ratio) of 0.87 (95% ci 0.55-1.37). There is no evidence of an increased risk of fractures during childhood and youth.

				medical birth register.	
Deora, Canada (2017)	Retrospective chart review	Median 7.8	140 CD	To examine the prevalence of micronutrient deficiencies at diagnosis, 6 and 18 months following the start of GFD.	Vitamin D is the most common deficient vitamin at diagnosis and should be checked as a part of the annual assessment for these children. Serum ferritin was subnormal in 34.5% with zinc in 18.6% children, but only 10.9% children had iron deficiency anaemia.
Diamanti, Italy (2011)	Cohort	1.9–24	545 cases, 622 controls	To evaluate, in children and adolescents with CD on GFD the prevalence of autoimmune thyroiditis	There was no significant difference in autoimmune thyroiditis prevalence between patients with CD on a GFD (10%) and controls (8.2%).
Fouda, Saudi Arabia and Canada (2013)	Systematic review Position paper	N/A	N/A	To provide recommend-dations on screening, diagnosis, treatment and follow-up of low bone mineral density (BMD) in CD patients.	Current evidence does not support the screening of all CD patients for BMD at diagnosis. Follow-up BMD assessment should be performed 1-2 years after initiation of a GFD.
Gidrewicz, Canada (2017)	Cross-sectional	Mean 10.4	228 CD children	To characterize the normalization of the tissue transglutaminase antibody (TGA) and EMA in children on a strict GFD	In children with the highest serology at diagnosis, 79.7% had an abnormal TGA 12 months after diagnosis. At 2 years, an abnormal TGA persisted in 41.7%. In contrast, only 35% of children with the lowest serology at diagnosis displayed abnormal TGA at 12 months.

Heshin-Bekenstein, Israel (2015)	RCT	1-18	82 CD children	To assess two vaccines, a new pre-s vaccine compared to standard hepatitis b (engerix b) in CD patients.	Good response to two vaccinations for hepatitis B in CD patients. Single booster dose sufficient to raise abs in all. Vaccine response for HBV appears good.
Husby, Denmark and Argentina (2019)	Systematic review	Adults and children	N/A	Review and update on CD.	The follow-up should be problem oriented based on symptoms and signs, rather than a routine screening of malabsorption parameters. Guidelines suggest that patients should be controlled by a multidisciplinary team each 3 to 6 months from diagnosis to stabilization. After substantial improvement, annual evaluation is recommended.
Husby & Murray Denmark and USA (2019)	Systematic review American Gastroenterological Association (AGA)	Adults and children	N/A	To define key modalities in the diagnosis and monitoring of CD in adults as well as in children and adolescents.	The usefulness of serology at follow-up is limited for adults and better for children. A refinement of the TG2-IgA determination utilizing the detectable levels below the upper normal limit may be added in the identification of CD patients with mucosal healing.
Leonardi, Italy (2009)	Retrospective	N/A	60 CD patients	To study if CD patients are less able to respond to the hepatitis B vaccine	CD patients have a lower percentage of response to hepatitis B vaccination than healthy subjects.
Lionetti, Italy (2021)	Case-control	Range 5-11	131 CD cases 131 controls	To evaluate vitamin D status of children with newly diagnosed CD by a large case-control study.	Plasma vitamin D levels were significantly lower in patients than in control subjects. The percentage of children with vitamin D deficiency (<20 ng/ml) was significantly higher in CD children as compared to controls.

Mager, Canada (2012)	Registry	3-17	54 CD children	To determine the relationships between vitamin K/D status and lifestyle variables on BMD in CD children at diagnosis and after 1-year GFD.	43% had suboptimal vitamin D status and 25% had suboptimal vitamin K status at diagnosis all resolved after 1 year. Children CD are at risk for suboptimal bone health likely due in part to suboptimal vitamin D/K status. Strategies to optimize vitamin K/D intake may contribute to improved BMD in CD.
Meloni, Italy (2009)	Retrospective	10 months -18	324 CD children	To study the prevalence of autoimmune thyroiditis in children with CD and the effects of a GFD on thyroid function.	A high prevalence of autoimmune thyroiditis among children with CD (10.5%), compared with the Sardinian paediatric background population (2.92%), was found, and appears to be gluten independent.
Park, USA (2007)	Case-control	9.2 cases, 10.4 controls	26 CD cases, 18 controls	To determine whether children with CD fail to show a response to HBV vaccine more frequently than children without CD.	More than 50% of children with CD do not show a response to standard vaccination regimens for HBV. Given the large number of children with CD throughout the world, this observation suggests that there is a large HBV-susceptible population despite widespread vaccination. Current immunization strategies may need to be reassessed to protect this population and achieve the goal of universal protection.
Petroff, Germany (2018)	Cohort	Mean 8.6	345 CD children	To determine if antibody test could provide valuable information about GFD success after 3 months.	The mean concentration TGA-IgA decreased by a factor of 14 at 3 months of follow-up but remained above 1-fold the upper limit of normal (ULN) in 83.8% of patients.

Rousseff, Belgium (2018)	Multicentre prospective	Mean diagnosis 6.0 Currently Mean 7.3	133 CD children	To evaluate HBV vaccination response in children with CD. Response in initial non-responders after a single booster vaccination as well as factors influencing HBV vaccination response were evaluated.	A single intramuscular booster vaccination is able to induce a serologic response in two thirds of the initial non-responders. Control of HBV vaccination response has to become part of the follow-up in CD patients.
Sansotta, Italy (2020)	Retrospective chart review	Mean at diagnosis 5.1	260 CD children	To compare the performance of TGA by chemiluminescence immunoassay (CLIA) to the standard enzyme-linked immunosorbent assay (ELISA) methods in monitoring CD children after the start of GFD	At 30 months follow-up children tested by CLIA are less likely to normalize TGA levels compared to those tested by ELISA. Younger age at diagnosis and lower baseline TGA are predictors of earlier TGA normalization, regardless of the adopted assay.
Sansotta, USA (2017)	Retrospective chart review	1.28-17.89	260 CD children	To compare the performance of TGA by CLIA to the ELISA methods in monitoring CD children after the start of GFD.	The percentage and the time of the TGA normalization in CD children on GFD should be interpreted according to the utilized assay: at 30 months' follow-up children tested by CLIA are less likely to normalize TGA levels compared to those tested by ELISA. Younger age at diagnosis and lower baseline TGA are predictors of earlier TGA normalization, regardless of the adopted assay.

Snyder, USA (2016)	Systematic review	6 months-20	N/A	To assess the available evidence in 6 categories associated with CD to develop a set of best practices.	Routine screening for bone health at 1 year, alanine aminotransferase (ALT) and aspartate aminotransferase (AST), anaemia if previously abnormal, measure 25-OH vitamin D level if previously abnormal. Routinely obtain complete blood cells (CBC), screening for thyroid disease at follow-up, testing with tTG-IgA antibodies at periodic intervals and assessment of anthropometric measures.
Tuna Kirsaçlioğlu, Turkey (2016)	Retrospective chart review	1.25–16	37 CD cases, 143 controls	To evaluate changes in growth and bone metabolism during GFD.	The BMD of patients was significantly lower than that of control subjects at time of diagnosis, but not after 1 year of follow-up. In the first year of GFD, BMD, BMD z-score, height-for-age z-scores, and weight-for-age z-scores were significantly increased compared with the baseline.
Urganci, Turkey (2013)	Case-control	1-15	30 CD cases, 50 controls	To evaluate the response to hepatitis A and B vaccinations in paediatric patients with CD.	The rate of seroconversion to the hepatitis B virus- and hepatitis A virus (HAV) vaccine is lower in patients with CD than in healthy controls.
Usta, Turkey (2014)	Cohort	Mean 13.2	63 CD	To assess the effect and duration of GFD on bone health in children with CD.	Dietary compliance is important for bone health, and the time needed to normalize the BMD is not known. Patients with positive EMA, poor dietary history and history of bone pain should be evaluated with dual-energy x-ray absorptiometry (DXA) during follow-up.
Wessels, The Netherlands (2016)	Cohort. Retrospective	Median at diagnosis 6.3□4.3	182 CD	To determine the frequency of nutritional deficiencies and thyroid dysfunction in children with CD and during follow-up after initiation of a GFD.	Complementary blood investigations are relevant at the time of diagnosis of CD but have little diagnostic yield during follow-up visits once the patient is placed on a GFD.

Zanoni, Italy (2015)	Case-control	1-18 T1D 1-37 CD 1-43 HC	69 T1D 42 CD 79 HC	To analyse the serological response to HB vaccine and measles-containing vaccines in T1D, patients with CD and healthy control (HC) subjects.	HC subjects showed protective anti-HBs antibodies after vaccination, with no statistically significant difference. A lower statistically significant difference was found in the mean antibodies to Hepatitis B surface antibody (HBsAb) level of T1DM subjects when compared with the other two groups. No correlation between Human Leukocyte Antigen (HLA) DQ2 expression in T1DM and vaccine response was detected.
Zingone Italy (2018)	Systematic review	N/A	328 studies Adults	To examine the data from existing studies in which vitamin D has been assessed in CD patients.	Most of the studies on vitamin D in adult CD report a 25 (OH) vitamin D deficiency at diagnosis that disappears when the patient goes on a GFD, independently of any supplementation. When the active 1,25 (OH) vitamin D form was evaluated, it resulted in the normal range at the time of CD diagnosis. A strict and lifelong GFD can help recover vitamin D level without any supplementation

Question 4. Adherence to the gluten-free diet.

Q4.1. Should the adherence to the GFD be assessed during follow-up and if so, how?

Q4.2. What is the role of detection of Gluten Immunogenic Peptides (GIPs) in the assessment of the compliance to the gluten-free-diet?

Q4.1. Should the adherence to the diet be assessed during follow-up and if so, how?

A search was conducted in Medline using the search terms celiac, coeliac, children, adherence, follow-up, gluten-free diet, dietitian, teenagers, questionnaires, score, E Health/App. The search identified a total of 54 records, of which 9 were included for this question: 6 primary observational studies (306 children) and 3 systematic reviews (15470 studies). As there were insufficient studies in children only, we included studies in adults and children (Comino 2016, Moreno 2017) and in adults (Down 2018 and Harder 2020). We included Harder 2020 published after March 2020 since it was considered especially informative.

Author, country (year)	**Study type/ description**	**Age (years)**	**Sample size**	**Objectives**	**Main findings**
Comino, Spain (2016)	Cohort	1-72 CD cases	N/A	To evaluate the measurement of GIP in stools as a	No association was found between faecal GIP and dietary questionnaire or TGA.

				marker of GFD adherence in CD patients and compare it with traditional methods of GFD monitoring.	
Dowd, Canada (2018)	Prospective	Mean 39.25	118 CD adults	To design, develop and pilot test a smartphone app to promote effective self-management of CD and promote gut health.	MyHealthyGut is the first evidence-based app that may be helpful in empowering users to effectively self-manage CD and promote general gut health.
Gerasimidis, Scotland (2018)	Prospective	New diagnosed 10 Previously diagnosed 9.3	90 CD children	Recent gluten intake measured by GIP in children with CD and compared to routine clinical measures to evaluate GFD compliance.	Compared to GIP, the Biagi score, TGA, and clinical assessment presented sensitivity of 17%, 42%, and 17%, respectively. A combination of methods did not improve identification of patients who were noncompliant and more than 50% of the patients noncompliant on GFD still remained undetected. Interestingly, the specificity and positive predictive validity of TGA was very low.
Harder, Italy (2020)	Retrospective	Adults	273 CD adults	To develop a scoring system to stratify CD patients on a GFD according to their risk of having persistence of villous atrophy (VA).	A four-level score (0·5, 1·5, 3, 4) was obtained. Patients on a strict GFD and with good clinical conditions (4) have a very low risk of persistence of VA. Conversely, the risk is very high in patients with poor adherence to a GFD and unsatisfactory clinical response (0·5). A score of 1·5 is linked with a high risk. Risk is intermediate in patients scoring 3 (strict GFD and no/partial clinical improvement).
Ludvigsson, Sweden (2018)	Systematic review	N/A	10062 CD	To review the literature on CD therapeutic trials and issue recommendations for outcome measures.	Careful evaluation and reporting of outcome measures will increase transparency and comparability of CD therapeutic trials, and will benefit patients, healthcare and the pharmaceutical industry.
Ludvigsson,	Systematic	N/A	N/A	To review the	This paper presents the Oslo definitions for CD-

Sweden (2013)	review			literature on the use of terms related to CD and gluten.	related terms.
Moreno, Spain (2017)	Case-control	3-64 CD cases 3-57 controls	65 children, 69 adults 58 CD cases, 76 controls	To develop a method to determine gluten intake and monitor GFD compliance in patients with CD and to evaluate its correlation with mucosal damage.	GIPs are detected in urine after gluten consumption, enabling a new and non-invasive method to monitor GFD compliance and transgressions. The method was sensitive, specific and simple enough to be convenient for clinical monitoring of patients with CD as well as for basic and clinical research applications including drug development.
Silvester, Canada (2017)	Systematic review	N/A	26 studies	To assess the sensitivity and specificity of TG IgA and serum EMA immunoglobulin A (IgA) assays in identifying patients with CD who have persistent villous atrophy despite a GFD.	In a meta-analysis of patients with biopsy-confirmed CD undergoing follow-up biopsy on a GFD, we found that tests for serum TG IgA and EMA IgA levels had low sensitivity in detection of persistent villous atrophy. We need more-accurate non-invasive markers of mucosal damage in children and adults with CD who are following a GFD.
Wessels, The Netherlands (2018)	Cohort	Mean 11.3 Mean at diagnosis 4.9	151 children and young adults	To compare GFD compliance in CD children, measured by a short dietary questionnaire against a long questionnaire similar to a dietary interview and correlation between both questionnaires and CD antibodies and identifying variables predicting noncompliance.	Compared to the long questionnaire, short dietary questionnaires and TG2 antibodies serology failed to detect dietary transgressions in CD children, wherein adolescents were shown to be at highest risk. Long questionnaires specific for children may be useful to assess diet compliance, especially in settings with no dietitian consultation available.

Q4.2. What is the role of detection of Gluten Immunogenic Peptides (GIPs) in the assessment of the compliance to the gluten-free diet?

A search was conducted in Medline using the search terms celiac, coeliac, children, adherence, follow-up, gluten immunogenic peptides, gluten free diet, compliance, adherence, diet, monitor, aftercare, secondary care and health-care. The search identified a total of 28 records, of which 7 were included for this question: 5 primary observational studies (1 in children, 2 in both adults and children and 2 in adults) (129 children) and 2 systematic reviews (990 publications). As there were insufficient studies in children only, we included studies in adults (Stefanolo 2021 and Sylvester 2020) both adults and children (Comino 2016 and Moreno 2017) and children (Comino 2019). We included Silvester 2020 and Stefanolo 2021 studies published after March 2020 since they were considered especially informative.

Author, country (year)	Study type/ description	Age (years)	Sample size	Objectives	Main findings
Comino, Spain (2016)	Multicentre prospective	1–72 cases, 0–66 controls	188 CD cases 84 controls	To evaluate the measurement of GIP in stools as a marker of GFD adherence in CD patients and compare it with traditional methods of GFD monitoring.	Detection of GIP in stools reveals limitations of traditional methods for monitoring GFD in CD patients. The GIP ELISA enables direct and quantitative assessment of gluten exposure early after ingestion and could aid in the diagnosis and clinical management of nonresponsive CD and refractory CD.
Comino, Spain (2019)	Multicentre prospective	Median 4	64 CD children	To evaluate the usefulness of faecal GIP to support the diagnosis and to determine the adherence to the GFD in CD children.	Faecal GIP testing may guide treatment of CD prior to diagnosis and during the assessment diet adherence. Further studies could determine if early identification of gluten exposure reduces the need for expensive/invasive investigations for non-responsive CD.
Ludvigsson, Sweden (2018)	Systematic review	N/A	10062 CD	To review the literature on CD therapeutic trials and issue recommendations for outcome measures.	A strong correlation has been demonstrated between the absence of GIP in urine and healing of the intestinal epithelium.
Myléus, Sweden (2020)	Systematic review	N/A	49 studies, 7850 children	To investigate the rate of adherence to a GFD in children with CD, risk factors that affect adherence, and outcomes of non-	The GIP assays reported the lowest adherence rate, suggesting that it also finds those with occasional involuntary gluten exposure. The highest median adherence was found for biopsies, followed by self-report, structured dietary interview, and serology test.

				adherence.	
Moreno, Spain (2017)	Prospective	3–64 CD cases 3–57 controls	69 adults 65 children 58 CD cases 76 controls	To develop a method to determine gluten intake and monitor GFD compliance in patients with CD and to evaluate its correlation with mucosal damage.	GIPs are detected in urine after gluten consumption, enabling a new and non-invasive method to monitor GFD compliance and transgressions. The method was sensitive, specific and simple enough to be convenient for clinical monitoring of patients with CD as well as for basic and clinical research applications including drug development.
Stefanolo, Argentina (2021)	Prospective cohort	Median 46 (IQR 34-55)	53 CD adults	To evaluate how often patients who are on GFD are still exposed to gluten.	Patients with CD on a long-term GFD still frequently are exposed to gluten. Assays to detect GIP in stool and urine might be used to assist dietitians in assessment of GFD compliance.
Silvester, Canada (2020)	Prospective	Mean 41	18 CD adults	To detect gluten in food ingested and stool and urine excreted by CD patients endeavouring to follow a strict GFD.	8% of food samples from 9 participants with detectable gluten had a median concentration of 11 ppm, 40% contained >20 ppm, and 20% contained >200 ppm. GIPs were detected in 30 urine samples from 8 participants and 8 stool samples from 5 participants. Two thirds of those with a positive sample result had persistent VA.

Question 5. Common issues during follow-up and management of CD

Q5.1. When to expect catch-up growth? Q5.2. Is a lactose-free diet necessary? Q5.3. Chronic tiredness in well controlled in coeliac disease? Q5.4. Irritable bowel syndrome (IBS) in CD? Q5.5. How to treat anaemia and/or sideropenia?

A search was conducted in Medline using the search terms celiac, coeliac, children, follow-up, catch up, growth and development, lactose intolerance, chronic tiredness, fatigue, irritable bowel syndrome, anaemia and iron deficiency. The search identified a total of 58 records, of which 18 were included for this question: all primary observational studies (1590861 children). We included studies in children (Comba 2018, Soliman 2019, Tuna Kirsaclioglu 2016, Zung 2012, Basso 2012, Terrone 2013, Saps 2017, Assa 2017, Çatal 2015, Kivelä 2017, Nestares 2020, Radlović 2009, Rajalaht 2017 and Wessels 2016). Two especially informative papers on adults and children were also included (Jericho 2017, Burger 2018).

Q5.1. When to expect catch-up growth?

Author, country (year)	Study type/description	Age (years)	Sample size	Objectives	Main findings

Comba, Turkey (2018)	Retrospective cohort	2-17	73 CD	To evaluate the relation between age at diagnosis and adherence to the GFD on growth in children with CD.	Late CD diagnosis (> 6 years) negatively affected both the height and weight and BMI. Adherence to a GFD was shown to have significantly positive effects on weight and BMI z scores. No difference was found between the two groups in terms of height z-scores.
Soliman, Qatar (2019)	Case-control	7,4 ± 2,6 cases and controls	30 CD cases 30 controls	To evaluate the effect of GFD on growth of children with CD on long-term GFD (>2 years).	The change in the Ht-SDS was significantly higher in the CD group. 50% of children with CD on GFD were still increasing their Ht-SDS even after an average of 2 years or more after the beginning of GFD. No difference in Ht-SDS between CD children on GFD and normal controls. Daily weight gain was significantly lower in the control versus CD children on a GFD.
Tuna Kirsaclioglu, Turkey (2016)	Retrospective cohort	8.8 ± 4.6	37 CD	To evaluate changes in growth and bone metabolism during GFD in children with CD.	Significant improvements in WAZs and HAZs after 1 year on a GFD. 21.4% of the patients remained short statured after 3 years on a GFD. All patients with low weight at presentation had normal weight ranges after 2 years on a GFD. No difference in WAZ, HAZ and lab data due to adherence to the GFD.
Zung, Israel (2012)	Retrospective cohort	4,5 ± 2,4	55 CD	To assess the significance of seroconversion in predicting height and weight gain during the first year of GFD in children with CD.	Early catch-up growth occurs without seroconversion: mean Ht-SDS and Wt-SDS after 6 months GFD were higher than those at baseline, both in seropositive TGA and seronegative patients. No difference in Ht-SDS and Wt-SDS between those who reversed to seronegative TGA and those who remained seropositive.

Q5.2. Is a lactose-free diet necessary?

Author, country (year)	Study type/description	Age (years)	Sample size	Objectives	Main findings
Basso, Italy (2012)	Case-control	Mean 11,8 cases 13.5 controls	92 CD cases 188 controls	To evaluate the association of Primary Lactase Deficiency (PLD) and CD by comparing the prevalence of PLD in CD subjects and in a control population.	More than 70% of all subjects positive for the cytosine (C)/C polymorphism at C/Thymine (T)-13910 and for the Guanosine (G)/G polymorphism at G/Adenine (A)-22018 (genetic markers of hypolactasia), without significant differences between CD patients and controls.
Kuchay, India (2015)	Case-control	5-10	52 CD cases 102 controls	To assess the association between CD and SNPs leading to adult type hypolactasia (AtH) in children.	No significant correlation between C/T -13910 or G/A -22018 SNPs of AtH and CD. Children with C/C or G/G genotype of AtH may not be at greater risk of CD.

Q5.3. Chronic tiredness in well-controlled in coeliac disease?

Author, country (year)	Study type/description	Age (years)	Sample size	Objectives	Main findings
Jericho, USA (2017)	Retrospective cohort	Median 8.8	157 CD children	To characterize prevalence of extraintestinal symptoms at time of diagnosis and after GFD.	Children had greater improvements on a GFD as compared to adults. Chronic fatigue improved in 81% of children on strict GFD.
Terrone, Italy (2013)	Prospective cohort	Median 10.2	139 CD: 54 newly diagnosed, 54 in remission after GFD, 45 potential CD.	To screen for neurological and behavioural disorders in a paediatric cohort of patients with CD to detect possible differences related	Statically significant decrease of chronic fatigue at remission in comparison to diagnosis. GFD had a positive impact on neuropsychiatric symptoms.

				to adherence to GFD.	

Q5.4. Irritable bowel syndrome (IBS) in CD?

Author, country (year)	Study type/description	Age (years)	Sample size	Objectives	Main findings
Saps, Italy and USA (2017)	Case- control	4-18	96 CD cases, 97 unrelated controls.	To test the hypothesis that CD children on a GFD are at risk of abdominal pain (AP) and abdominal pain related functional GI disorders (AP-FGDI).	Subjects with CD and controls (8,2%) have a similar prevalence of chronic AP and AP-FGIDs.

Q5.5. How to treat anaemia and/or sideropenia?

Author, Country (year)	Study type/description	Age (years)	Sample size	Objectives	Main findings
Assa, Israel (2017)	Case-control	Mean 17.1 cases and controls	7145 CD cases, 1580896 controls	To investigate the associations between CD and various medical conditions.	Anaemia was significantly more common in subjects with CD (OR = 1.7, 95% CI 1.5–1.9, p <0.0001) than in controls.
Burger, The Netherlands (2018)	Retrospective cohort	9	250 CD children and adults	To evaluate the yield of routine laboratory tests and DEXA scans in CD.	At diagnosis: anaemia in 24.4%, iron deficiency in 38% of all 250 patients. All deficiencies recovered within 2 years of GFD with or without supplements. Data on children not presented separately.
Çatal, Turkey (2015)	Retrospective cohort	8.1 ± 4.21	91 CD	To determine the hematologic manifestations at diagnosis and the effects of a GFD.	Anaemia is 24.2% at diagnosis. Anaemia was less common in patients on a strict GFD (5.8% vs 25.6%).

Jericho, USA (2017)	Retrospective cohort	8.8	157 CD	To characterize prevalence of extra-intestinal symptoms at diagnosis and recovery on GFD.	12% Anaemia at diagnosis. It improved in 84% after 24 months on a GFD, including 1 patient who received a blood transfusion.
Kivelä, Finland (2017)	Retrospective cohorts	Screen-detected 7.0 Clinically detected 8.0	504 CD	To compare the baseline and follow-up characteristics of patients detected by screening and due to clinical suspicion.	Anaemia present in 22.9% (P < .001) of clinically detected patients and 7.1% of screen-detected patients (p<0.001); low MCV 10.6% vs 13.4%, ferritin 20.5% vs 20.0% and increased TfR 31.3% vs 22.2%. Clinical response was similar in both groups? 97.5% vs 96.2%, (P = .766).
Nestares, Spain (2020)	Case-control	Mean 8.5 cases 10.3 controls	68 CD cases 43 controls	To assess whether the use of a GFD is sufficient for maintaining correct iron status in children with CD.	CD children on a GFD had lower iron intake and nutritionally less balanced diet than the controls.
Radlović, Serbia (2009)	Retrospective cohort	0.5-7.5	90 CD	To evaluate the effect of GFD on the nutritional status of children with the classical form of CD. Sub-analysis about the effects of the GFD duration and the patients' compliance.	86 (95.56%) Had normal Hb values and 4 anaemia on a GFD after a median of 3.03 (range 1.08-8.75) years.
Rajalahti, Finland (2017)	Retrospective cohort	Anaemic 8.5 Non-anaemic 7.4	455 CD	To compare clinical, serological, and histological manifestations between CD children with and without anaemia at diagnosis.	Anaemia in 18.0% at diagnosis. Children with anaemia had higher values for TGA, were less often screen-detected and had more severe histological damage 92% Recovered from anaemia after a median of 1 year on a GFD, but Hb remained lower compared with the non-anaemic group.

Repo, Finland (2017)	Prospective cohorts	Potential CD with partial or subtotal villous atrophy (P/SVA), CD and controls, respectively: 6.3, 7.5, 6.1, 6.0	19 potential CD cases, 83 CD cases, 23 controls	To investigate the prevalence of anaemia and iron deficiency in children with potential and established CD.	Prevalence of anaemia in controls, potential CD, P/SVA, and TVA: 0%, 15%, 22%, and 63% respectively. Low ferritin 0%, 21%, 35%, and 87%. After a median of 7 months on a GFD.
Wessels, The Netherlands (2016)	Retrospective cohort	6.3 (±4.3)	182 CD	To determine the frequency of nutritional deficiencies in children with CD at diagnosis and during follow-up on a GFD.	At diagnosis: iron deficiency (28%) and anaemia (9%). At follow-up (mean 3.1 (±3.1 years): iron deficiency i8% and iron deficiency anaemia 2%.

Question 6. Specific issues during follow-up and management. Q6.1. How to approach persistent high serum levels of antibodies against tissue transglutaminase (TGA)? Q6.2. When is it necessary to (re)biopsy? Q6.3. Refractory coeliac disease in children: does it exist?

Q6.1. How to approach persistent high serum levels of antibodies against tissue transglutaminase (TGA)?

A search was conducted in PubMed using the search terms celiac, coeliac, children, follow-up, persistent or elevated transglutaminase, antibody and gluten-free diet. The search identified a total of 167 records, of which 17 were included for this question: all primary observational studies (2128 children). Since it was considered especially informative, we included one article published after March 2020 (Sansotta 2020).

Author, country (year)	**Study type/ description**	**Age (years)**	**Sample size**	**Objectives**	**Main findings**
Bannister, Australia (2014)	Retrospective cohort	Mean 7.5	150 CD	To evaluate the accuracy of anti-TGA-IgA and IgG against anti-deamidated gliadin peptide (DGP) during follow-up.	Sensitivity and specificity of combined TGA-IgA and DGP IgG was 75% and 85%, with positive predictive value (PPV) and a negative predictive value (NPV) of 22% and 98%, respectively.
Benelli, Italy (2016)	Prospective cohorts	Mean group 1 2.1. Mean group 2 2.4.	143 CD	To evaluate the clinical and laboratory response to GFD of patients	The percentage of children whose TGA IgA became negative after diagnosis was 51-55% at 6 months, 19-21% at 12 months, 5-6% at 24 months and 7% at 36 months.

				who received a diagnosis without a biopsy compared with those who underwent a biopsy.	
Bufler, Germany (2014)	Retrospective cohort	Mean 5.6	91 CD	To compare performance of DGP IgG, DGP IgA and TGA IgA during follow-up on a GFD.	DGP decreased sooner than TGA IgA. Non-adherence was best indicated by TGA IgA. At 18 months on GFD, 30% of children still showed positive TGA IgA for three different assay tests and 15%t for only one assay.
Candon, France (2012)	Retrospective cohort	Mean 6.6	80 CD	To compare the quantitative radio binding assay for TGA (RBA-TGA) to one of the second generation commercial ELISA at diagnosis and during follow-up.	RBA is likely responsible for higher TGA positivity rates during GFD than previously reported with ELISA. Decreasing trend in TGA levels rather than absolute levels may be used as a surrogate marker of adherence to GFD.
Chow, USA (2012)	Retrospective cohort	N/A	26 CD	To determine the prevalence and significance of IgA deficiency and partial deficiency in patients with CD.	In patients who are IgA deficient, IgG serologies may be persistently elevated despite histologic recovery.
Comino, Spain (2019)	Multicentre prospective cohort	Mean 4	64 CD	To evaluate TGA IgA, DPG IgA, GIP and dietary compliance at 6, 12 and 24 months after diagnosis.	Dietitian assessment was only moderately correlated with GIP detection but performed better in compliance evaluation than antibody assessment.
Dahlbom, Hungary-Sweden (2010)	Multicentre prospective cohorts	Group 1 52 children mean 1.6 Group 2 59 children mean 8.1	111 CD	To evaluate quantitative detection of IgA-TGA and IgG-TGA in serum for the prediction of the mucosal condition.	IgG-TGA declined slower than IgA-TGA. The initial levels of IgA-TGA correlated with the normalization time. Longer normalization time attains older children with milder clinical symptoms.
Ghazzawi,	Retrospective	Mean 8.5	40 CD	To assess the rate of	The mucosal healing rate was 64% in a selected

USA (2014)	cohort			mucosal healing in treated children with CD within a median time on GFD of 24 months.	group of treated children with mean time for follow-up biopsy of 24 months.
Gidrewicz, Canada (2017)	Retrospective cohort	Mean 10.4	228 CD	To characterize the normalization of the TGA and IgA EMA in children on a strict GFD.	Normalization of coeliac serology took >1 year in approximately 75% of GFD-compliant children with the highest coeliac serology or most severe mucosal injury at diagnosis.
Hogen Esch, The Netherlands (2011)	Retrospective multicentre cohort	Mean 5.6	129 CD	To determine the dynamics of TGA and EMA in children with CD after starting a GFD.	80% Will be seronegative for EMA and TGA after 2 years of GFD, and the mean concentration of TGA will show a 74% decrease after 3 months of diet.
Isaac, Canada (2017)	Retrospective cohort	Mean 9.3	487 CD	To evaluate time to normalization of TGA in the local paediatric CD population post diagnosis.	Good dietary compliance and lower anti-TG at diagnosis are predictors of earlier anti-TG normalization. Patients with T1DM are less likely to normalize anti-TG levels, with longer normalization time.
Leonard, USA (2017)	Retrospective cohort	Mean 10.6	103 CD	To determine whether IgA TGA correlates with mucosal damage at the time of a repeat endoscopy with duodenal biopsy in these patients.	19% Of paediatric patients treated with a GFD had persistent enteropathy. At the time of the repeat biopsy, TGA was elevated in 43% of cases with persistent enteropathy and 32% of cases in which there was mucosal recovery.
Lund, Sweden-Denmark (2016)	Multicentre retrospective cohort	Mean 9	34 CD	To measure the reduction of CD antibodies (IgA-TG and IgG DGP) in children with CD after initiation of GFD.	After 3.6 months on GFD 15% of children had normalized IgA-TG values and 26% had normalized IgG DGP values. After 7.6 months on GFD 39% had normalized IgA-TG values and 57% had normalized IgG DGP values.
Mehta, USA (2018)	Retrospective cohort	Mean 11	66 CD	To determine the association between serum TGA and	A negative TGA value was not associated with good adherence.

				dietitian-assessed adherence	
Sansotta, Italy (2020)	Retrospective cohort	Median ELISA 5.1 Chemiluminescence: 7.7	130 CD	Comparison of TGA IgA ELISA Vs Chemiluminescence titers during follow-up.	TGA normalization takes longer in children tested by chemiluminescence as compared to ELISA. Higher baseline TGA and older age at diagnosis predict a longer TGA normalization time.
Vécsei, Austria (2014)	Prospective cohort	Median: 7.8	53 CD	To compare the performance of up-to-date antibody tests in predicting mucosal status in children with untreated CD vs. children after GFD (18 months follow-up biopsy).	Only negative EMA had a likelihood ratio (LR) < 0.1 thus being an informative and clinically useful marker of mucosal healing in CD.
Webb, Sweden (2014)	Sub-study of a cross-sectional CD screening	Median: 13	193 CD	To evaluate GFD adherence after 1 year of follow-up in children with screening-detected CD in a general population.	After 1 year, 85% had normalized TG2-IgA levels. Those with the highest markers at diagnosis had the lowest proportion (75%) of normalized TG2-IgA levels after 1 year, but for most of them their initial values were more than halved.

Q6.2. When is it necessary to (re)biopsy?

A search was conducted in PubMed using the search terms celiac, coeliac, children, follow-up, repeated, biopsy and follow-up biopsy. The search identified a total of 225 records, of which 8 were included for this question: 6 primary observational studies (592 children) and 2 Meta-analysis (87 studies). As there were insufficient studies in children only, we included studies in both adults and children (Osman 2014, Sylvester 2017 and Szakács 2017).

Author, country (year)	**Study type/ Instrument**	**Age (years)**	**Sample size**	**Objectives**	**Main findings**
Bannister, Australia (2014)	Prospective longitudinal	Mean at diagnosis 7.5.	150 CD	To determine whether TGA IgA and anti-DGP IgG are sensitive and specific markers of mucosal recovery in	5.3% of follow-up duodenal biopsies had persistent villous abnormalities. The sensitivity and specificity of serology as a marker of significant mucosal pathology was 75 and 85%, PPV 22% NPV 98%.

				children with CD on a GFD for at least 12 months	
Belei, Romania (2018)	Prospective cohort	Mean age: 4.6	105 CD	To assess the rate and timing of histologic recovery among children with CD on a GFD.	86 children enrolled with Marsh type III lesions, histologic remission was observed in 81.4% after 1 year, 91.8% within 2–3 years and 97.6% in long-term follow up (≥ 3 years). Histologic recovery in CD after starting a GFD in children takes at least 1 year and might be incomplete in a small proportion of children, mainly associated with IgA immunodeficiency.
Ghazzawi, Minnesota (2014)	Retrospective cohort	Average at diagnosis 8.5	40 CD	To assess the rate of mucosal healing and indications for repeat small bowel (SB) biopsy in children with CD.	Histology on the second biopsy showed complete healing (n=25), intraepithelial lymphocytes (n=9), and persistent villous atrophy (n=6). Average time between biopsies was 24 months.
Leonard, USA (2017)	Retrospective cohort	Mean at diagnosis 10.6	103 CD	To determine the rate of mucosal recovery in paediatric patients with CD on a GFD. To determine whether IgA TGA correlates with mucosal damage at the time of a repeat endoscopy with duodenal biopsy.	5 CD children may have persistent enteropathy despite adherence to a GFD for at least 1 year. 45% of patients with persistent enteropathy were asymptomatic at the time of the repeat endoscopy. IgA TGA was a poor predictor of Marsh 3 histology at repeat biopsy as sensitivity 43%, specificity 68%, PPV 25%, and NPV was 83%. TGA IgA may not be an accurate marker of mucosal recovery in these patients.
Osman, Malaysia (2014)	Prospective cohorts	Mean 15	78 CD 46 children 32 adults	To assess the serological and histological recovery profiles of CD patients, in children and adults after commencing a GFD for at least 1 year ± 1 month.	Complete histological remission was seen in 29 of 46 treated CD children, 5 showed Marsh 3a changes and 2 showed Marsh 3b after GFD. After 1 year of follow-up, 15.2% of children patients with CD still had at least partial VA.
Silvester, USA	Systematic review	Children/Adults	26 studies	To assess the sensitivity and	Tests for serum TGA IgA and EMA IgA levels had low sensitivity in detection of persistent VA. Few studies

(2017)				specificity of TGA IgA and EMA IgA assays in identifying patients with CD who have persistent VA despite a GFD.	have specifically examined the relationship between serum antibody testing and mucosal damage in patients who are trying to follow a GFD.
Szakács, Hungary (2017)	Systematic review	Children/Adults	61 studies	To address the question whether CD children on a GFD display higher mucosal recovery ratios than adults.	Children show higher complete recovery and disappearance of VA ratios as compared to adults. There is considerable heterogeneity across studies concerning complete mucosal recovery ratios achieved by a GFD in CD. Younger age on diagnosis, less severe initial histologic damage and male gender predisposes for achieving mucosal recovery.
Vécsei, Austria (2014)	Prospective cohort	Mean 11.3	148 CD	To compare the performance of up-to-date antibody tests in predicting mucosal status in children with untreated CD vs. children on GFD.	Negative EMA most reliably predicts mucosal healing. In general antibody tests, especially DGP-IgA, are of limited value in predicting the mucosal status in the early years post-diagnosis but may be sufficient after a longer period of time.

Q6.3. Refractory coeliac disease in children: does it exist?

A search was conducted in PubMed using the search terms celiac, coeliac, children, follow-up, unresponsive, refractory, non-responsive and nonresponsive. The search identified a total of 69 records, of which 7 were included for this question: 6 observational studies (252 children) and 1 meta-analysis (5 studies in children). As there were insufficient studies in children only, we included studies in both adults and children (Jericho 2017, Schmitz 2013, Silvester 2017 and Van Leeuwen 2013).

Author, country (year)	**Study type/ description**	**Age (years)**	**Sample size**	**Objectives**	**Main findings**
Comino, Spain (2019)	Multicenter prospective cohort	Mean 4	64 CD	To evaluate the usefulness of faecal GIP to support the diagnosis and to determine the adherence to the GFD in CD children. Faecal GIP, IgA-TG and anti-DGP analysed at	97% Of the children had detectable GIP at diagnosis. On a GFD, the rate of GIP increased from 13% at 6 months to 25% at 24 months. Mean estimated gluten exposure dropped from 5543 mg/d at diagnosis to 144 mg/d at 6 months, then increased to 606 mg/d by 24 months. DGP normalized and only 20% had elevated TG by 24 months. The elevation of IgA-TG was more prolonged in patients with detectable GIP.

				diagnosis, and 6, 12 and 24 months thereafter.	
Janczyk, Poland/ The Netherlands (2015)	Case reports	Patients 1/ 2: 7 Patient 3: 1	3 CD	To describe clinical and laboratory data of children with biopsy-proven CD who did not respond to GFD.	Patient 1 showed no refractory CD, responded to Enteral Nutrition (EN) and on long-term follow-up symptoms, pathology and serology resolved completely on GFD. Patient 2 showed no refractory CD, responded to EN after 5 years of follow-up remains asymptomatic on GFD but with high EMA. Patient 3 did not respond to EN, partially responded to immunosuppressive treatment, had to remain indefinitely on total parenteral nutrition (TPN).
Jericho, USA (2017)	Retrospective cohorts	Children (≤18) and adults (>18) Mean diagnosis 8.8	328 CD 157 children	To assess the prevalence of extra-intestinal symptoms in children vs adults and the effect of the GFD on their resolution.	Extraintestinal manifestations of CD occur at similar rates in children and adults. However, children on a GFD resolve their symptoms more completely and faster than the adults. No refractory CD identified in the whole series.
Salvestrini, Italy and UK (2014)	Laboratory investigation	Children	23 5 archival jejunal biopsies 9 CD cases 9 controls	To verify if VA in CD represents a disorder of pathological matrix expansion. Staining for sulphated GAGs, heparan sulphate proteoglycans (HSPG), short-chain HSPG (D-HSPG) and the proteoglycan syndecan-1 (CD138), which is expressed on epithelium and plasma cells.	HSPG expression was lost in the epithelial compartment but contrastingly maintained within an expanded lamina propria. Matrix expansion, through syndecan-1+ cell recruitment and lamina propria GAG increase, underpins VA in CD. As in other matrix expansion disorders, IL-6 is upregulated and represents a target for immunotherapy in patients with CD refractory to GFD.

Schmitz, The Netherlands (2013)	Laboratory investigation	Children and adults	N/A	To identify the physiological counterpart of the aberrant intraepithelial lymphocytes (IELs) displaying an atypical $CD3^{-}CD7^{+}icCD3^{+}$ phenotype seen in refractory CD type II.	RCDII cell lines were transcriptionally distinct from T-cell receptor positive Intraepithelial lymphocytes (T-IEL) and expressed higher levels of multiple NK (Natural Killer) cell receptors. The authors speculate that this Interleukin-15 (IL-15) responsive population of cells represents the physiological counterpart of the aberrant T cells expressed in RCDII.
Silvester, USA (2017)	Systematic review	Children and adults	26 studies	To assess the sensitivity and specificity of TGA IgA and EMA IgA in identifying patients with CD who have persistent villous atrophy despite a GFD.	The analysis excluded subjects with refractory CD. TGA and EMA detected VA with specificity, respectively, of 0.83 and 0.91; sensitivity was 0.50 and 0.45. Thus, authors conclude that most persons with VA on a GFD had normal levels of TGA or EMA.
Van Leeuwen, The Netherlands (2013)	Laboratory investigation	Children and adults; Children mean 5.9	36 children	To find out whether alterations occur in the frequency of natural CD62L (+) transcription factor forkhead box P3 (Foxp3) (+) regulatory T cell (Treg) or mucosally-imprinted CD62L(neg) CD38(+) Foxp3(+) Treg in peripheral blood of CD patients, comparing children with adults.	In children, the percentages of peripheral blood CD4+ Foxp3+ Treg were comparable between CD patients and healthy age-matched controls. In adultS on GFD and in refractory CD, increased percentages of circulating natural CD62L+ Foxp3+ Treg, normal mucosally-imprinted CD62LnegCD38+ Foxp3+ Treg frequencies were observed. Significant numeric deficiency of mucosally-imprinted or natural Foxp3+ Treg could explain the effector responses in CD.

Question 7. Should the quality of life (QOL) be assessed during the follow-up and if yes, how?

A search was conducted in Medline using the search terms celiac, coeliac, children, follow-up and quality of life/QoL. The search identified a total of 89 records, of which 18 were included for this question: 16 primary observational studies (16043 children) and 2 systematic reviews (39 studies). As the study from Nikniaz 2020, published after March 2020, was considered especially informative, we have included it.

Author country year	Study type/ Instrument	Age (years)	Sample size	Objectives	Main findings
Altobelli, Italy (2013)	Cross-sectional	Mean 14.2	140 CD	To assess health-related quality of life (HRQOL) and effect of demographic, clinical characteristics and GFD adherence on perceived health status.	Only the mental component summary score (MCS12) was lower in CD patients. More than one third of CD reported feeling angry "always" or "most of the time" about having to follow the GFD, and nearly 20% reported feeling different from others and misunderstood because of the CD.
Barrio, Spain (2018)	Cross-sectional	Mean 12.4	434 CD	To assess the impact of CD in HRQOL.	CD had no substantial negative impacts on the children's quality of life (QOL).
Barrio, Spain (2016)	Cross-sectional	Mean 12.4	480 CD	To assess HRQOL in CD.	Overall, both children and parents reported the HRQOL of the children as ''neutral". Significantly worse HRQOL scores were recorded in children showing a non-classical clinical presentation, in those not adhering to treatment and in those reporting difficulties in following the diet.
Bellini, Italy (2011)	Case-control	Mean Cases 10 Controls 12	156 CD cases, 353 controls	To verify whether subjects with CD have a different LoC compared with healthy subjects, and to evaluate the relationship with adherence to a prescribed GFD and QOL.	No difference in LoC values between patients with CD and controls. Good dietary compliance was associated with a more internal LoC. Patients with a satisfactory QOL had a more internal LoC.
Benelli, Italy (2016)	Prospective cohort	Mean 5.9	143 CD	To evaluate consequences on QOL of the application of the	Patients diagnosed according to the no-biopsy approach have the same QOL as patients diagnosed with duodenal biopsies.

				new ESPGHAN guidelines for the diagnosis of CD.	
Biagetti, Italy (2015)	Case-control	Mean Cases 8.7 Controls 9.5	73 CD cases, 143 controls	To investigate the impact of the GFD on the psycho-physical well-being of CD children.	No significant differences in QOL between CD patients and controls. Children with diet-difficulties or comorbidities (allergy, asthma and autoimmune thyroiditis) showed the lowest QOL scores.
Biagetti, Italy (2013)	Cross-sectional	Mean 8.7	76 CD	To investigate the impact of CD and the GFD on the HRQOL and the social and emotional world of children with CD.	Children with CD experience strong emotions related to the GFD, involving several aspects of everyday life. There were no significant differences between symptomatic and asymptomatic patients.
Mager, Canada (2018)	Case control multisite	Mean Cases 10.4 Controls 10.9	243 CD cases, 148 controls	To determine sociodemographic and socioeconomic factors influencing HRQOL.	Child-parent perceptions of HRQOL in a multi-ethnic population with CD are comparable to healthy reference populations, but significantly higher than in parent/child with mild gastrointestinal complaints (GI-CON). Adherence to the GFD in ethnically diverse youth with CD was related to GI symptoms, age of the child, and ethnicity of the parent-child.
Meyer, Israel (2017)	Development and validation of the CD Children's Activities Report (CD-Chart)	Mean 8.33	126 CD cases, 30 controls	To establish the CD-Chart's reliability and validity.	CD-Chart showed adequate internal consistency. CD group required significantly more pre-preparation for food-related activities than controls ($p < 0.001$).
Myléus, Sweden (2014)	Cross-sectional multicentre	12	328 CD cases, 12037 controls	To investigate QoL in 1. undetected CD; 2. diagnosed CD; 3. without CD.	HRQOL was similar in the 3 groups.
Nikniaz, Iran (2020)	Systematic review	<18	26 studies	To report the published data on HRQOL assessed by CD-specific and	Mean HRQOL score using CD-specific CDDUX was 58.81, which is neutral. The result using the generic PedsQL showed similar HRQOL in CD patients and in healthy controls. Parents reported the child's diet and

				by generic questionnaires.	communication scores lower than that of children.
Nordyke, Sweden (2013)	Cross-sectional	12 -13	103 CD cases 483 controls	To investigate QOL of adolescents with screening-detected CD before and one year after diagnosis and treatment.	QOL in CD was similar to the referents, both before and one year after, except in the dimension of pain at follow-up, in which fewer cases reported > problems than referents (12.6% and 21.9% respectively, adjusted odds ratio (OR) 0.50).
Simsek, Turkey (2015)	Case-control	Mean 11.84	25 CD cases, 25 controls	To assess QOL in children with newly diagnosed CD and in healthy controls, both at diagnosis and after 1 year on GFD.	Total scores and scores of the emotional well-being subscale were significantly lower in patients with CD compared with the control group. No differences in QOL were found between before and after GFD recommendations in children with CD, indicating a persistent decreased QOL the first year of follow-up.
Skjernin, Denmark (2017)	Enquiry	Mean 11.12	77 CD	To assess HRQOL in children/adolescents with mean CD duration 4.05 +/- 3.43 years and compare it with the one of 345 adults with CD (mean age 39.03 +/-13.75 years; mean CD duration 9.12+/- (11.88 years).	Respondents reported being mainly satisfied with their QOL when assessed by generic items. In comparison to adults, children perceived a larger burden of following a GFD and were more negatively affected by thoughts of desired gluten-containing food and by feelings of exclusion or difference from peers.
Vriezinga, The Netherlands (2017)	Prospective cohort	Mean 12.5	78 CD	Agreement between physician reported and patient reported HRQOL at a follow-up visit.	Reports were discrepant in 40 of 70 (self-reported a poor HRQOL & physicians good). Discrepancies occurred more frequently in patients with a disease duration <9 y and in females. Both factors were predictors of a poorer HRQOL.

				Patient variables predicting a discrepancy between reports, or a lower HRQOL.	
Wagner, Austria-Germany (2015)	Case-control	10–20	259 CD cases, 53 controls	To assess QOL and eating disorders (ED) in young females with CD adhering to GFD since at least 1 year. * ED assessed using Eating Disorder Inventory 2 and Eating Disorder Examination (EDE).	32 CD patients (15.5%) suffered from ED. HRQOL of CD patients without ED was similar to the one in healthy controls with a higher Joy of life. QOL was significantly lower in CD patients with ED, both in comparison to CD patients without CD disorders as in health controls. The authors suggest early identification of ED in patients with CD.
White, UK (2016)	Systematic review	N/A <18	Adolescents	To assess burdens associated with following a GFD and the factors associated with adherence.	Adolescents with CD face stigmatisation and feel isolated in social situations and at school. Additional burdens are a lack of knowledge regarding CD and GFD difficulties in interpreting food labels, as well as dissatisfaction with the organoleptic properties of GF products.
Wolf, USA (2018)	Prospective cohort	Mean 15.7	30	To examine the associations of QOL with adherence to GFD.	The overall mean CDPQOL score was 70.1 which corresponds to a good QOL without significant differences by level of dietary vigilance.

Q8. Should the follow-up of children with special situations be different from the one in the average CD patient? Q8.1 In cases of unclear diagnosis? Q8.1.1. How to perform a gluten-challenge? Q8.2 8.2. In children with associated type 1 diabetes (T1D)? Q8.3 In children with IgA deficiency? Q8.4 In cases of potential CD?

Q8.1 In cases of unclear diagnosis? Q8.1.1. How to perform a gluten-challenge?

A search was conducted in Pubmed using the search terms celiac, coeliac, children, follow-up and gluten-challenge. The search identified a total of 850 records, of which 20 were included for this question: 9 RCT (1 in children: 23 children) and 8 primary observational studies (2 in children: 194 children). As there were insufficient studies in children only, we included 14 studies in adults (Daveson 2020, Goel 2020, Kelly 2020, Lahdeaho 2011, Lahdeaho 2014, Lahdeaho 2019, Leffler 2012, Leffler 2013, Mansikka 2019, Sankari 2020, Sarna 2018, Taavela 2019, Tye-Din 2019, Leonard 2021) and 2 studies in both adults and children (Husby 2020 and Van Overbeek). We included 4 studies published before 2010 (Van Overbeek 1997, Korponay-Szabo 1997, Holm 2006 and Kurppa 2008) and 1 after March 2020 (Leonard 2021) since they were especially informative.

Author, country (year)	Study type/ description	Age (years)	Sample size	Objectives	Main findings
Daveson, Australia (2020)	RTC: 6g/day masked gluten challenge (GC) versus Sham challenge Time course: 4 hours	18-70	36 CD adults	To assess serum immunological markers Interleukin 2 (IL-2) as reaction to GC.	CD Patient Reported Outcome (CeD PRO) scores increased, mainly nausea. IL2 serum levels increase 4 hours after the GC median fold change of 20. No increase in IL2 serum levels in the sham challenge group.
Goel, Australia (2020)	Dietary intervention/ 6g/day gluten Time course: 6 hours	18-70	50 CD adults	To assess a wide spectrum of serum cytokines (IL2, IL6, Interferon gamma (IFNγ) ,tumor necrosis factor alpha (TNFα), chemokine ligand 9,8,20, Interleukin-22 (IL22), Interleukin-10 (IL10), C-C Motif Chemokine Ligand 2 (CCL2), amphiregulin) as response to short term GC.	Serum cytokine showed an increased level after short term GC, peak concentration 4 hours after GC. Serum cytokines were correlated with symptoms.

Hardy Italy, Australia, USA (2015)	Dietary intervention/ 1-3 slices of wheat bread/day	Median 9	41 CD children	To compare the T-cell response to gluten in children and adults.	GI symptoms in 71% of the patients after the gluten challenge. Isolation and measurement of T-cell clones in blood samples showed similar gluten-specific T-cell receptor (TRC) repertoires, similar clone response in children and adults.
Holm, Finland (2006)	Dietary intervention 14 g/day gluten, (range 7-19g/day)	Median 13	10 CD children	To assess the response to gluten and oats respectively	4 Patients had gastrointestinal symptoms concurrent with the duodenal mucosal deterioration. Both TGA and EMA showed elevated levels after one month of gluten challenge in all patients. Histological relapse was shown within 3-12 months after starting the GC.
Husby, Europe (2020)	Systematic review Evidence based guidelines	N/A	61 Studies Children and Adults	To guide physicians in accurately diagnosing CD and permit omission of duodenal biopsies in selected cases	CD diagnosis can be accurately established with or without duodenal biopsies if given recommendations are followed
Kelly, USA (2013)	Exploratory, RTC: 2.7g/day gluten (900 mg three times/day) vs placebo. Time course: 6 weeks	Median 50.3	43 CD adults	To assess gluten-induce response in symptoms, serology, urinary lactulose-mannitol ratio (LAMA).	GI symptoms increased in the first 3 weeks up to a mean of 0.3-0.4 units maintained in plateau in the last 3 weeks. Psychological General Well Being Index (PGWBI) lower scores in the last 2 weeks. Urinary LAMA ratio increased from 1.0 to 2.3-2.4 at 4 weeks of GC. 30% of the patients in the GC group seroconverted to positive antibodies (TGA-IgA).
Korponay-Szabo, Hungary (1997)	Dietary intervention gluten 5-10 g/day	Median: 5.09 3.31 8.63	153 CD children	To assess EMA accuracy	Serological relapse (EMA positivity) as early as 6 weeks; 66% of 134 pts at 3 months of challenge and 90% at 6 months respectively. Histological relapse at 6 months of gluten challenge

Kurppa, Finland (2008)	Case report/ N/A	6, 10 months 16 years	3 CD children	To evaluate if periods of gluten intake and gluten withdrawal may have an impact on disease expression, and the phenotype may vary in the same person over time	The phenotype of CD can change from intestinal disorder to extraintestinal manifestations over time.
Lahdeaho, Finland (2011)	Dietary intervention: Low amount GC (1-3 g/day) OR Moderate amount GC (3-5 g/day) Time-course: 12 weeks/84 days (Range 29-103)	Median 49	25 CD adults	To assess the amount and duration of GC intervention to produce SB mucosal deterioration.	1-3g/day Gluten for 12 weeks is proposed to induce measurable SB mucosal deterioration.

Lahdeaho, Finland (2014)	Dietary intervention: Low dose GC: 1.5g/day Medium dose GC: 3g/day High dose GC: 6g/day Time course: 6 weeks Part 2: 2g/day Gluten Time course: 6 weeks	Part 1 Low dose: Median 55 Medium dose: Median 52 High dose: Median 59 Part 2: Median 50	Part 1 47 CD adults Part 2 21 CD adults	To establish the optimal daily dose of gluten for a 6-week GC.	"Gluten dose optimization": 1.5g/day gluten induces mucosal deterioration, even if clinically tolerated, however the change of villous height/crypt ratio (VH:CrD) from baseline was not sufficiently consistent and was too close to the baseline readout. GC in the placebo drug arm: 2g/day gluten for 6 weeks-time course induces measurable, clear injury to the SBl mucosa.
Lahdeaho, Finland (2019)	Dietary intervention: 2-4 g/day gluten Time course of GC: 10 weeks	Median 55.8	19 CD adults Per protocol: 15 CD adults	To assess gluten-induce response in symptoms, serology, small bowel mucosal histology.	Worsening of symptoms (increase in mean weekly CeD PRO and Gastrointestinal Symptom Rating Scale (GSRS) scores). Seroconversion to positivity for TGA-IgA and DGP antibodies. 2-4 g/day Gluten induces clinical, serological and histological relapse in the majority of patients.
Leffler, USA (2012)	Dietary intervention: 2.4 g/day gluten (800 mg capsules- three times/day during meals) Time course:14 days	Median 46.3	14 CD adults	To assess gluten-induce response in the placebo arm in symptoms, serology, urinary lactulose-mannitol ratio.	GI symptoms according to GSRS increased in severity, especially "indigestion" 64.3% pts. Experienced symptoms of "gluten toxicity". Urinary LAMA ratios increased in the GC group, but not statistically significant'. Antibody titers with no significant mean changes from baseline to day 21.
Leffler, USA (2013)	RCT Low amount GC (3g/day gluten). High amount GC (7.5g/day gluten).	Median 43.3	20 CD adults	To assess duration of GC	GI symptoms increased by day 3 and returned to baseline by day 28. Antibody titers increased slightly from baseline to day 14 of GC but markedly by day 28. No changes in LAMA. Reduction in VH:CrD ratio and increase in intraepithelial lymphocyte (IEL) density. 3g/day for at least 2 and up to 8 weeks is proposed to obtain gluten-induced response in serology and histology.
Leonard USA	Dietary intervention	Adults	14 CD adults	Assessment of the response to	Significant changes in gut-homing CD8 T cells, enzyme-linked immune absorbent spot and HLA-DQ2 restricted

(2021)	RCT: Lower dose GC: 3g/day Higher dose GC: 10g/day Time course: 14 days			dose and duration of the GC, assessment of new biomarkers	gluten-specific CD4 T cells after higher dose (10 g Gluten/day) Symptoms and IL2 significant or near significant changes after lower dose (3g Gluten/day)
Sankari, Finland (2020)	Dietary intervention Case-control/ 200g/day commercially available wheat bread Time course: 3 days followed by the same amount for 1 year time course	Treated Dermatitis herpetiformis (DH) Median 58 Treated CD Median 48 Untreated CD Median 50	16 DH adults 15 CD adults 18 untreated CD adults	To assess the response to dose and duration of the GC in terms of clinical, serological and histological parameters.	Clinical, serological and histological remission (non-VA in the duodenal mucosa).12/16 developed Dermatitis Herpetiformis (DH) rash, 12/16 seroconverted to positive EMA, 14/16 and 10/16 showed positive serum anti transglutaminase 3 (TG3) and transglutaminasa 2 (TG2), decrease in VH:CrD ratio,10/16 showed presence of TG2-IgA deposits in SB mucosa, 10/16 showed TG3-IgA deposits in the skin.
Sarna, Norway, (2018)	Dietary intervention/ 5.7 g/day gluten Time course: 2 weeks	41.6	19 CD adults	To assess response to 2 weeks of GC in CD individuals.	2 weeks of GC is not enough to detect gluten induced histological changes by conventional histology. HLA-DQ: gluten tetramers detection by flow-cytometry is proposed as surrogate biomarkers after short gluten-challenge
Taavela, Finland (2019)	Dietary intervention/ 4g/day gluten. Time course: 10 weeks	N/A	15 CD adults	To assess SB deterioration in GC Assessment of new immunohistochemical (IHC) markers of SB mucosal response of GC; comparison of the studied IHC markers with	Marsh class worsened in 80% of cases. Good correlation coefficient between APOA4:Ki67 messenger RNA (mRNA) ration and crypt depth (VH:CrD) ratio. Good correlation coefficient between Apolipoprotein A4:Ki-67 protein (APOA4:Ki67) mRNA ratio with CD3+IELs densities. CD138+ lamina propria strongly increased during GC.

				morphometric measurements.	
Tye-Din, Australia (2019)	Dietary intervention Case-control/ 6g/day gluten Time course: 6 hours	N/A	25 CD adults 25 not CD adults	To assess serum immunological markers IL2 as reaction to GC.	IL2 serum levels increase after 2,4, and 6 hours of GC. Peak IL2 levels correlated with symptoms severity (mainly with vomiting and nausea). No increase in serum IL2 levels among the control group.
Van Overbeek The Netherlands, (1997)	Retrospective Questionnaires/ N/A	2-57	55 FDR children and adults	To investigate the pattern of gluten consumption in the general Dutch population for different age and sex groups and for different product groups, and to investigate the daily gluten intake of first-degree relatives of CD patients	The gluten intake of first-degree relatives (FDR) of CD patients was the same as that of the general population. A low gluten intake apparently does not explain the specific presentation and prevalence of CD in first-degree relatives of CD patients

Q8.2. In children with associated type 1 diabetes (T1D)?

A search was conducted in PubMed using the search terms celiac, coeliac, children, follow-up and diabetes. The search identified a total of 151 records, of which 10 were included for this question: all primary observational studies, 7 studies in children (3295 children) and 3 studies in both adults and children (Kurien 2016, Molazadegan 2013, Reilly 2016).

Author, country (year)	**Study type/ description**	**Age (years)**	**Sample size**	**Objectives**	**Main findings**
Craig, Australia	Multicentric, multi continent.	Median 8.1	1835 children	To analyse outcomes (Haemoglobin A1c	CD is a common comorbidity in youth with T1DM. Differences in CD prevalence may reflect international

(2017)	Cross sectional			(HbA1c), Ht-SDS, overweight/obesity) between T1DM and CD.	variation in screening and diagnostic practices, and/or CD risk. Although glycaemic control was not different, the lower Ht-SDS supports close monitoring of growth and nutrition in this population.
Gopee, Australia (2013)	Cohort children with T1DM and CD 1 year after GFD	N/A Children	24 children	Renal involvement in T1DM and CD	Lower degree of renal involvement in T1DM and CD compared to T1DM alone.
Isaac, Canada (2017)	Retrospective	Mean 9.3	487 CD children with T1DM	Follow-up of patients with T1DM and CD.	Seroconversion in patients with CD and T1DM is three times as long as in DC patients compliant with the diet. Compliance of T1DM and CD patients was lower than the one of patients with only CD.
Kivelä, Finland (2018)	Retrospective	Clinically detected 8.7 Screen detected 11.7	236 CD children	Long term outcomes of CD patients diagnosed in childhood.	Long term outcomes as measured by Psychological General Well-Being (PGWB) and GI symptoms GSRS, of screen-detected (including T1DM) patients do not differ from clinically detected cases, suggesting that there is no need to recommend different follow-up practices in these two groups.
Kurien, Sweden (2016)	Population based cohort	Median at diagnosis T1DM 9 Median at diagnosis CD 12 Adults/children	960 CD adults/children with T1DM	Development of thyroid disorders in T1DM and CD	CD patients with T1DM have an increased risk of developing autoimmune thyroid disease than isolated T1DM patients. Thyroid disorders should be actively assessed in T1DM and CD patients. Individuals diagnosed with T1DM early in childhood had lower risk for AI thyroid disease.
Laitinen, Finland (2017)	Retrospective	Mean 7.3	42 Children with T1DM	Clinical characteristic of CD detected by screening in T1DM and by diagnosis of clinical cases. Dietary adherence.	CD patients detected during T1DM surveillance have similar signs of malabsorption and mucosal damage as clinical cases. Similar recommendations on follow-up for screening detected CD in T1DM and clinical CD. The compliance is comparable in both groups; thus, no additional monitoring is suggested in screen-detected cases.
Mollazadegan,	Retrospective	Adults	566	Diabetic retinopathy	Risk of retinopathy is not increased in T1DM and CD. It

Sweden (2013)	registry based	/Children N/A	children with CD and T1DM 261 (age 10-20)	in T1DM and CD compared to T1DM alone.	is lower within the first 0-5 and neutral within the 5-10 years of follow-up. Risk progressively increases after 10 years and is the highest after >=15 years of follow-up.
Reilly, Sweden (2016)	Nationwide registry	Median at T1DM diagnosis 9 Median at CD diagnosis 12 Adults/Children	958 adults/children with T1DM and CD	Fracture risk in T1DM and CD patients.	Compared to T1DM patients with T1DM and CD do not have increased fracture risk. This risk does not change with the follow-up time. HR for fracture is progressively increasing by time after CD diagnosis but it doesn't reach significant levels. Overall number of fractures are very low.
Tsouka, Canada (2015)	Retrospective	Median 8.83	41 CD children with T1DM	To evaluate complication screening and follow-up patterns in a population with T1DM/CD in relation to a matched cohort with CD.	Increased number of thyroid diseases after 2 years of follow-up in 15% of the T1DM and CD group. No differences in pathological findings between the two groups. Patients with both T1DM and CD had higher BMI, weight and height.
Williams, USA (2018)	Cohort	At T1DM diagnosis 8.1 strongly positive; 7.4 weakly positive	64 children with T1DM and CD	Long term renal involvement in patients with T1DM and CD autoimmunity	Patients with T1DM and CD have lower blood pressure (BP) and cholesterol levels at 25 years of diabetes duration. Risk of microalbuminuria in these patients is also lower in this group compared to T1DM only patients. Only 8 known CD patients. Conclusion coeliac autoimmunity in patients with T1DM does not increase the risk of renal disease.

Q8.3 In children with associated IgA deficiency?

A search was conducted in PubMed using the search terms celiac, coeliac, children, follow-up and IgA deficiency. The search identified a total of 24 records, of which 2 were included for this question: 2 primary observational studies (191 children), one of them prospective. Since it was especially informative, we used one article published after March 2020 (López 2020).

Author, country (year)	**Study type/ description**	**Age (years)**	**Sample size**	**Objectives**	**Main findings**

Belei, Romania (2018)	Prospective cohort	Mean 4.6 +/- 1.2.	105 CD children; 2 with IgA deficiency	Histology recovery after one year of GFD in children.	Incomplete recovery of intestinal mucosa might take longer in patients with IgA deficiency. Only two such patients.
López, Spain (2020)	Multicentric retrospective cohort	Biopsy group median 4.4 No biopsy group 4.2	86 CD children with IgA deficiency	Diagnosis and follow-up practices in IgA deficient patients after 2012 ESPGHAN guidelines.	After 2 years half of patients with IgA deficiency remain seropositive. Substantial number of patients diagnosed with no-biopsy approach in IgA deficient patients, which is not in accordance with the 2012 guidelines.

Q8.4. In cases of potential CD?

A search was conducted in PubMed using the search terms celiac, coeliac, children, follow-up and potential celiac disease. The search identified a total of 80 records, of which 9 were included for this question: 8 performed in children (835 children) and 1 in both adults and children (Kondola 2016).

Author, country (year)	**Study type/description**	**Age (years)**	**Sample size**	**Objectives**	**Main findings**
Auricchio, Italy (2014)	Prospective cohort	Median 6.4	210 Potential CD children	Natural history potential CD.	Control every 6 months. Biopsy repeated after 1-2-years. Antibodies: 20% negative, 37% fluctuating, 43% persistently positive. Still potential: 86% at 3 years, 73% at 6 years, 67% at 9 years.
Auricchio, Italy (2019)	Prospective cohort	Range 2-18	280 Potential CD children	Natural history of potential CD.	Controls every 6 months, biopsies every 2 years. At 12 years follow-up: 89 antibodies negative. Age>3 years, density of gamma delta intestinal IELs, presence of intestinal anti-tTG antibodies predictive VA.
Fernandez, Spain (2019)	Prospective cohort	2-3 First screening, 10-12 second screening	262 children first screening, 185 children second screening	Evolution of a cohort genetically at-risk for CD.	First screening by 3 years of age: 5 potential CD + 6 antibody positive. After 10 years follow-up: 2 still potential and 1 CD.
Kondola, India (2016)	Prospective cohorts	Mean 28.7	57 adults/children with potential CD	Natural history of potential CD.	Controls every 6 month. 22 History of diarrhoea, 9 anaemia. 57 Followed-up:12 antibody: negative, 41 persistently positive, 4 become CD.
Kurppa, Finland	Dietary intervention	Median 6	76 Children	Effect of dietary intervention GFD in	Follow-up available in 13 patients with potential CD disease. Disease exacerbated in those who continued

(2010)			with potential CD	potential CD.	gluten consumption (n=8): developed VA: 5 after 1 year and 2 after 2 years. In those on GFD (n=5): disappearance of symptoms and antibodies.
Lionetti, Italy (2012)	Prospective cohort	Mean 29 ± 12 months	96 children with potential CD	Natural history of potential CD in a cohort of first-degree relatives followed since birth.	Controls every 6 months. Biopsy repeated after 1-2 years. 21 Followed-up: 18 antibodies negative, 12 fluctuating antibodies, 1 become CD.
Lionetti, Italy (2019)	Prospective cohort	Median 24 months	96 children with potential CD	Natural history of potential CD in a cohort of first-degree relatives followed since birth.	26 potential CD, 23 followed up on gluten containing diet: after 10 years follow up 19 antibodies negative (83%), 1 fluctuating antibodies (4%), 3 become CD (13%).
Mandile, Italy (2018)	Prospective cohort	Median 7.27	65 children with potential CD	Effect of GFD.	Controls every 6 months. 47 Followed up, response evaluated in 35: 19 positive response to GFD, 2 partial response, 14 no response. After GFD no changes of immunohistochemical parameters in biopsies.
Tosco, Italy, (2011)	Prospective cohort	Median 6 years and 8 months	106 children with potential CD	To determine the natural history of potential CD in children.	Most children with potential CD remain healthy. After 3 years, approximately 33% of patients develop VA. Intestinal deposits of anti-TGA-IgA identify children at risk for VA.

Q9. How to improve the communication: To parents? To patients?

A search was conducted in Medline using the search terms celiac, coeliac, children, follow-up, gluten-free diet, communication, patient satisfaction, caregivers/education, education, consultants/education, consultants/organization and administration. The search identified a total of 46 records. Further publications were identified from other searches. In total, of which 14 publications were included for this question:12 primary observational studies (638 children), 2 literature reviews (34 studies). Since there weren't enough studies in children, we included 4 studies in adults (Halmos 2018, Paganizza 2019, Ukkola 2011 and Ukkola 2012) and 1 in both adults and children (Sainsbury 2018). We included two articles published before 2010 (Gardiner 1999 and Cahill 2007) since they were considered especially informative.

Author, country (year)	**Study type/ Description**	**Age (years)**	**Sample size**	**Objectives**	**Main findings**
Barnea, Israel (2014)	Telephone questionnaire	At diagnosis <18	50 LTFU 52 controls	To characterize LTFU population, and thus identify compliance	LTFU is associated with non-adherence to GFD and positive serology. Risk factors for LFTU should be identified and addressed in order to improve

				barriers to GFD and follow-up	patient care
Cahill, UK (2007)	Systematic review	6-12	21 Studies	To ascertain the evidence available on the amount and type of involvement that children in the 6–12-year age group have in their primary care consultations when the consultation was held with a child, a general practitioner (GP), and an adult.	Children in the 6–12 age group have little meaningful involvement in their consultations.
Connan, Canada (2019)	Qualitative semi-structured interviews	Mean 13.5 ± 4.5	18 CD children with T1DM	To develop and test the usability of an E-learning module aimed at educating patients and caregivers regarding implementation of the GFD in children with concurrent CD and T1DM.	A multifaceted user-cantered usability approach demonstrated that an innovative, interactive E-learning module is effective in knowledge retention and can provide comprehensive and accessible information in the implementation of the GFD teaching in children with CD and T1D.
Gardiner, UK (1999)	Letter to editor	N/A	N/A	Pointing out that well done patient information on internet may be superior to paper-based information	Information on internet may be superior to paper-based information.
Germini, Italy (2018)	Case-control	25-54 Bartter syndrome (BS) 25-64 CD	26 mothers of children with BS or with CD	To elucidate how the diagnosis of a rare disease, as compared to a common, chronic condition, may influence maternal experiences of childhood illness.	Maximization of both emotional and instrumental social support, through provision of appropriate information or establishment of disease-specific support groups, could greatly contribute to rare disease families' efforts to cope with childhood illness and regain a sense of normality.
Halmos,	Online survey	>36	5310	To comprehensively	Poor knowledge of a GFD and psychological

Australia and New Zealand (2018)			CD adults	assess the patient factors that influence GFD adherence in patients with CD.	wellbeing were independent modifiable risk factors for inadequate adherence to the diet in patients with CD. Involvement of a dietitian and mental health care professional, in the presence of psychological distress, is likely to be necessary to improve adherence and health outcomes.
Kinos, Finland (2012)	Prospective cohort	1-16	222 CD children	To assess health and well-being and the effect of a 1- year GFD in children with CD detected by screening in at-risk groups.	Screen-detected children with CD can attain satisfactory dietary adherence and benefit from treatment similarly to symptom-detected patients. The results support intensified screening for coeliac disease in at-risk children.
Nordyke, Sweden (2014)	Qualitative written narratives	Median 14.6	153 CD adolescents	To describe adolescents´ experience living with screening-detected CD five years after diagnosis with the aim to explore how their perceptions, practices, and beliefs evolved.	Maintenance and evolution in the perceptions, practices, and beliefs of the adolescents after 5 years. Some have adjusted to the disease and adapted new habits and coping strategies to deal with the GFD, while others still doubt they have CD or that being detected was beneficial.
Paganizza, Italy (2019)	Questionnaire	18-45 ≥45	104 CD adults	To investigate adherence to a GFD and potentially associated factors, focusing on the relationship between adherence and knowledge of the gluten content of foods and of CD in general.	The more patients know about their disease and their required diet, the better they are able to adhere to the diet. Supporting and informing patients should be an integral part of the management of CD, and our findings point to ways in which adherence to a GFD might be improved by healthcare practitioners
Rosen, Sweden (2011)	Qualitative follow-up	Median 14.6	117 CD adolescents	To explore how screening-detected CD impacts adolescents' quality of life, as perceived by themselves and their parents.	Screening-detected CD has varying impact on adolescents' quality of life, where their perceived change in health has to be balanced against the social sacrifices the diagnosis may cause.
Sainsbury,	Online survey	Mean 50.2	5573	To evaluate an	Screening-detected CD has varying impact on

Australia and New Zealand (2018)			CD adults/children	expanded collection of theoretical constructs specifically relevant to the maintenance of behaviour change, in the understanding and prediction of GFD adherence.	adolescents' quality of life, where their perceived change in health has to be balanced against the social sacrifices that the diagnosis may cause. This needs to be taken into account in any future suggestion for CD mass screening and in the management of these patients.
Ukkola, Finland (2011)	Prospective	N/A	698 CD adults	To investigate the impact of a GFD on self-perceived health and well-being in symptomatic and asymptomatic patients with CD.	Self-perceived health and well-being were low among patients at the time they were diagnosed with CD. Most patients benefited from a GFD. Perception of health decreased among asymptomatic cases, which discourages population-based screening.
Ukkola, Finland (2012)	Prospective	N/A	698 CD adults	To investigate patients' perceptions of their disease, dietary treatment and self-rated healthcare needs.	Established doctor-patient communication is essential in minimizing the disease burden. Particularly young and screen-detected asymptomatic patients and those with extraintestinal manifestations require extensive support.
White, UK (2016)	Narrative review	Focused on adolescents	13 Studies	To review current literature on the burdens associated with following a GFD and the factors associated with adherence	Poor adherence in adolescence associated with older age, absence of immediate symptoms, poor palatability of GF foods. Emotional support and organisation skills associated with superior adherence. Associations have been reported between HRQoL measures and adherence.

Q10: How to organize the transition from paediatric care to adult health-care?

A search was conducted in PubMed using the search terms celiac, coeliac, children, follow-up, childhood celiac and transition of care. The search identified a total of 85 records, of which 7 were included for this question:4 primary observational studies (17172 children) and 3 reviews/guidelines (Crowley 2011(10 studies), Ludvigsson 2016 and Nagra 2015). Two studies on adults were included since they were considered especially informative (Kivelä 2020 and Reilly 2020).

Author, country (year)	**Study type/ description**	**Age (years)**	**Sample size**	**Objectives**	**Main findings**

Crowley, UK (2011)	Systematic review	11-25	10 studies	To systematically review the evidence of effectiveness of transitional care programmes in young people aged 11-25 with chronic illness (physical or mental) or disability and identify their successful components.	The most commonly used strategies in successful programmes were patient education and specific transition clinics. It is not clear how generalisable these successful studies in DM will be to other conditions.
Kivelä, Finland (2020)	Retrospective, mail questionnaire	Adults	235 CD adults	To evaluate the implementation and significance of long-term follow-up.	75% in follow-up not associated with health or dietary adherence. Non-adherent patients were without follow-up.
Ludvigsson, UK (2016)	Systematic review	N/A	N/A	To help healthcare personnel manage CD in the adolescent and young adult and provide optimal care and transition into adult healthcare.	CD adolescents should gradually assume exclusive responsibility for their care, parental support still important. Biopsy may be considered where paediatric diagnostic criteria have not been fulfilled.
McManus, USA (2013)	Survey	12-18	17114 Children (Youth) with Special Health Care Needs (YSHCN)	To examine current United States (US) performance on transition from paediatric to adult health care and discuss strategies for improvement.	Most youth with YSHCN are not receiving transition preparation. There have been no discernible improvements since this transition outcome was measured in the 2005-2006 National Survey of Children with Special Health Care Needs.
Nagra, UK (2015)	Ready Steady Go program	>11	N/A	To set out some of the obstacles that have delayed the implementation of effective transition and report on a successful transition programme	Successful generic transition programme 'Ready Steady Go' that has been implemented within a large National Health Service teaching hospital in the UK, with secondary and tertiary paediatric services, where it is now established as part of routine care
Reilly, USA and Sweden (2020)	Retrospective, anonymous online survey	18 -25	98 CD adults	To discern rates and predictors of successful transition of care for young adults with childhood diagnosed CD.	Transition of care is inconsistent, particularly among asymptomatic patients. Referral for an adult provider is significantly useful.

Zingone, Italy (2018)	Questionnaire	Mean 14.5	58 CD children	To assess adherence to GFD, CD knowledge, QoL, relationship with caregivers.	A good CD knowledge is positively related to dietary compliance and QOL. TRANSIT-CD disk is proposed.

Abbreviations

A: Adenine
AGA: American Gastroenterological Association
ALT: Alanine Aminotransferase
AP: Abdominal Pain
AP-FGDI: Abdominal Pain related Functional GI disorders
APOA4:Ki67: Apolipoprotein A4:Ki-67 protein
AST: Aspartate Aminotransferase
AtH: Adult type Hypolactasia
BL: Randomized Baseline
BMD: Bone Mineral Density
BMI: Body Mass Index
BMI-SDS: Standardised Body Mass
BP: Blood Pressure
BS: Bartter Syndrome
C: Cytosine
CBC: Complete Blood Cells
CCL2: C-C Motif Chemokine Ligand 2
CD: Coeliac Disease
CD138: Proteoglycan syndecan-1
CD3+: Cluster of differentiation 3+ cells
CD-Chart: CD Children's Activities Report
CDDUX: CD-specific Coeliac Disease DUX
CDPQOL: CD-specific quality of life
CeD PRO: Coeliac Disease Patient Reported Outcome
CLIA: Chemiluminescence Immunoassay
DEXA: Bone density measurement
DGP: Deamidated Gliadin Peptide
DH: Dermatitis Herpetiformis
D-HSPG: short-chain HSPG
DM: Diabetes Mellitus
DXA: Dual-energy x-ray absorptiometry
ED: Eating Disorders
EDE: Eating Disorder Examination
ELISA: Standard enzyme-linked immunosorbent assay
IEL: Intraepithelial lymphocyte
IFNγ: Interferon gamma
IgA: Immunoglobulin A
IgG: Immunoglobulin G
IHC: Immunohistochemical
IL10: Interleukine-10
IL-15: Interleukin-15
IL-2: Interleukin-2
IL22: Interleukin-22
IL-6: Interleukin 6
LAMA: Urinary Lactulose-Mannitol ratio
LCT: Lactase
LoC: Locus of Control
LR: Likelihood Ratio
LTFU: Lost to Follow Up
MCS12: Mental Component Summary score
mRNA: Messenger RNA
N/A: Not Available
NASPGHAN: North American Society for Paediatric Gastroenterology, Hepatology and Nutrition
NK: Natural Killer
NPV: Negative Predictive Value
OR: Odds Ratio
P/SVA: Partial or Subtotal Villous Atrophy
PGWB: Psychological General Well-Being
PGWB: Psychological General Well-Being
PGWBI: Psychological General Well Being Index
PLD: Primary Lactase Deficiency
POC: Point Of Care
PPV: Positive Predictive Value
QOL: Quality Of Life
RBA-Anti-TGA: Radio Binding Assay of anti-tissue Transglutaminase Antibodies
RCDII: Type II refractory CD

EMA: Anti-Endomysial Antibody
EN: Enteral Nutrition
EOS: End of study
ESPGHAN: European Society of Paediatric Gastroenterology Hepatology and Nutrition
FDR: First-Degree Relatives
Foxp3: Transcription factor forkhead box P3
G: Guanosine
GAG: Glycosaminoglycan
GC: Gluten Challenge
GFD: Gluten Free Diet
GGS: Gastrointestinal Symptom Scale
GI: Gastrointestinal
GI-CON: Parent/child with mild gastrointestinal complaints
GIP: Gluten Immunogenic Peptides
GP: General Practitioner
GSRS: Gastrointestinal Symptom Rating Scale
HAV: Hepatitis A Virus
HAZ: Height for Age Z score
HbA1c: Haemoglobin A1c
HBsAb: Hepatitis B surface Antibody
HBV: Hepatitis B Virus
HC: Healthy Control
HLA: Human Leukocyte Antigen
HR: Hazard ratio
HRQOL: Health-related quality of life
HSPG: Heparan sulphate proteoglycan
Ht-SDS: Height growth velocity
Ht-SDS: Height standard deviation score
RCT: Randomized Clinical Trial
SB: Small Bowel
SD: Standard Deviation
SF-12: Form Health Survey 12
SNPs: Single nucleotide polymorphisms
T: Thymine
T1D: Type 1 Diabetes
T1DM: Type 1 Diabetes Mellitus
TEACH: Text Message Educational Automated Compliance Help
TG: Transglutaminase
TG2: Transglutaminasa 2
TG3: Transglutaminase 3
TGA: Antibodies to Transglutaminase
T-IEL: T-cell receptor positive Intraepithelial Lymphocytes
TNFα: Tumor Necrosis Factor alpha
TPN: Total Parenteral Nutrition
TRC: T-Cell Receptor
Treg: Regulatory T cell
tTG: Tissue Transglutaminase
tTG-IgA: tissue transglutaminase-immunoglobulin A
TVA: Total Villous Atrophy
UEG: United European Gastroenterology
ULN: Upper Limit of Normal
US: United States
VA: Villous Atrophy
VH:CrD: Villous Height/Crypt ratio
WAZ: Weight for age Z score
Wt-SDS: Weight Standard Deviation Score
YSHCN: Youth with Special Health Care Needs