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Health-related quality of life in children screened for celiac disease: a pilot study at a pediatric outpatient clinic

Degree Project in Medicine

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Table of Content

ABBREVIATIONS: **4**

1. ABSTRACT **5**

Background: 5
Aim: 5
Methods: 5
Results: 6
Conclusion: 6

2. INTRODUCTION **7**

3. BACKGROUND **7**

Celiac disease *7*
Gluten 7
Pathophysiology of celiac disease 8
Manifestations of celiac disease 9
Diagnosis 9
Treatment 11

Health-related quality of life (HrQoL) *11*
Measuring HrQoL in children 12

Celiac disease screening *12*

4. AIM **14**

5. METHODS AND MATERIALS **15**

Study design and outcome definition *15*

Source population *16*

Participants *16*

Instruments/measures *17*
Kidscreen 17
Gastrointestinal Symptom Rating Scale (GSRS) 20

Statistical methods *20*

Post-hoc power analysis *20*

Ethical considerations *21*

6. RESULTS **22**

Descriptive characteristics *22*

Health-related quality of life (HrQoL) in children with versus without serological evidence of celiac disease *24*

Differences in health-related quality of life according to sex and age *25*

Gastrointestinal symptom rating *27*

7. DISCUSSION 28
Interpretation of findings in light of previous studies 28
Interpretation of health-related quality of life according to sex and age 31
Strengths and weaknesses 32
Conclusion 33
8. POPULÄRVETENSKAPLIG SAMMANFATTNING 34
9. ACKNOWLEDGEMENTS 36
10. REFERENCES 37
11. APPENDIX 41

ABBREVIATIONS:

CD: Celiac disease

CDA: Celiac disease autoimmunity

CSI: Celiac disease index

EMA: Endomysial antibodies

ESPGHAN: European Society for Pediatric Gastroenterology Hepatology and Nutrition

GSRS: Gastrointestinal symptom rating scale

HrQoL: Health-related quality of life

HLA: Human leukocyte antigen

TGA: Transglutaminase autoantibodies

WHO: World Health Organization

1. ABSTRACT

Health-related quality of life in children screened for celiac disease: a pilot study at a pediatric outpatient clinic

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Background: Celiac Disease (CD) is a chronic autoimmune enteropathy that affects some 2-3% of Swedish children. Due to diffuse or subclinical symptoms, many remain undiagnosed. Screening for CD is currently not recommended due to a lack of evidence of its beneficial effects.

Aim: The primary aim was to describe potential differences in health-related quality of life (HrQoL) in children screened for CD. A secondary objective was to compare the participant's HrQoL according to age and sex.

Methods: This study was part of a pilot screening project for CD conducted at the pediatric outpatient clinic in Hisingen, Gothenburg, between November 2019 and March 2020. A total of 496 children were enrolled, out of which 469 children were screened for CD-specific transglutaminase autoantibodies, and 11 received positive screening results. The validated generic questionnaire Kidscreen-27 was administered to all children at study enrollment. Children with positive screening results were compared to children with negative screening results. The children's HrQoL measurements were also compared based on age and sex.

Results: No significant differences in HrQoL were observed in children with positive screening than children with negative screening. No major differences in HrQoL were observed according to sex. Boys scored significantly higher than the girls in the subdimension *Physical wellbeing* (P-value 0.035). Children under the age of eight years scored significantly higher in total raw score (P-value 0.043) as well as the subdimensions; *School Environment* (P-value 0.0006) and *Physical wellbeing* (P-value <0.0001) as compared to older participants.

Conclusion: Using the Kidscreen-27 questionnaire, we found similar HrQoL in children with versus without serological evidence of CD, which may suggest that undetected CD does not significantly impact the HrQoL. However, we cannot rule out that the lack of such association is due to limited statistical power or the use of a generic HrQoL questionnaire, unable to capture CD-specific components of health.

2. INTRODUCTION

This project emanated from a pilot study to investigate the feasibility of implementing celiac disease (CD) screening at a pediatric outpatient department. This project focuses on the health-related quality of life (HrQoL) in children screened for CD as one of the key aspects when assessing the overall potential benefits and harms of CD screening.

Celiac disease (CD) is a chronic immune-mediated autoimmune enteropathy induced by the ingestion of gluten in genetically predisposed individuals (1). The classic presentation of the disease includes diarrhea, abdominal pain, and weight loss. However, the symptoms and their severity vary, and patients can also be asymptomatic (1, 2). The disease is also associated with an increased risk of death (3, 4). The only available treatment is a life-long gluten-free diet for life (1). Sweden has one of the highest prevalence of CD-cases worldwide, and it is estimated that 2-3 % of children in Sweden are affected (5, 6). However, due to diffuse symptoms or lack thereof, many remain undiagnosed (3, 5). Serological markers can be used to detect undiagnosed CD. However, current evidence is insufficient to support the screening of asymptomatic children for CD (7). One of the key aspects in assessing whether the implementation of general screening may be appropriate is its potential impact on the patients' HrQoL (8).

3. BACKGROUND

Celiac disease

Gluten

Gluten is a protein complex and a major storage protein of wheat grains. The composition and the distribution of protein content vary between different varieties of wheat. The main protein components are the prolamins named glutenin and gliadin (9). These prolamins are capable of

inducing CD (10). Hordeins found in barley, and secalins found in rye are prolamins with similar immunogenic properties and also capable of triggering CD (10, 11). Although gluten is technically referred to as the protein complex found in wheat only, the term "gluten" is commonly used to describe all peptides associated with CD (9, 10). Whenever the term gluten is used in this paper, it refers to the latter of the term's two definitions.

Pathophysiology of celiac disease

Gluten is highly resistant to proteolytic degradation in the small intestine due to its rich content of proline and glutamine, which many proteases are unable to cleave (9). In CD, undigested peptide derivates of gluten can be transported from the intestinal lumen into the lamina propria through transcellular or paracellular pathways (12). In the lamina propria, immunogenic epitopes of gluten bind to HLA-DQ2 or HLA-DQ8 molecules on antigen-presenting cells, which in CD leads to the activation of CD4+ T-cells and, in turn, intestinal inflammation (13). In the lamina propria, the enzyme tissue transglutaminase deamidates glutamine to negatively charged glutamate in the undigested peptide fragments, enhancing their affinity for HLA-DQ2 and HLA-DQ8 (10). The increased affinity leads to more efficient immunogenicity for the peptide fragments (10, 14).

The appearance of tissue transglutaminase autoantibodies (TGA) are hallmarks for CD. However, the formation of the TGA is not entirely understood (10). It has been proposed that the antigen-presenting cells initially target gluten peptide residues but inadvertently take up gluten-TGA complexes, which leads to an immune reaction and the formation of antibodies against both TGA and the peptide residues (14). However, there is a controversy in whether the autoantibodies play a significant role in the tissue destruction of the disease or not. Still, they have been suggested to play a role in the extraintestinal manifestations. This is most

notably seen in the CD-associated dermatological condition dermatitis herpetiformis, where lesions are formed in the skin due to TGA expression in the dermal papillae (10). Besides TGA, CD is associated with endomysial antibodies (EMA) (14).

Manifestations of celiac disease

The presentation of CD is diverse and might include a wide range of symptoms, both gastrointestinal and extraintestinal manifestations, and their level of severity vary (15). Some patients may experience subclinical symptoms, and some may even be asymptomatic (12). Children tend to present more "classic" symptoms, including diarrhea, abdominal pain, and a failure to thrive. This is particularly the case of children under the age of three years, where the gastrointestinal manifestations may be more prominent compared to older children and adolescents, who instead more frequently present with extraintestinal manifestations (1). The gastrointestinal symptoms of CD include diarrhea, abdominal pain, anorexia, bloating, constipation, gastroesophageal reflux, weight loss, vomiting, and nausea (1, 15, 16). The extraintestinal manifestations of CD include fatigue, anemia, dermatitis herpetiformis, dental enamel hypoplasia, osteopenia/osteoporosis, delayed puberty, peripheral neuropathy, and psychiatric disorders such as anxiety and depression (15). CD is associated with a slight but statistically significant increase in mortality risk than the general population (4). CD is also associated with an increased risk of gastrointestinal cancer and lymphoma (2). Due to the diverse and diffuse presentation of the disease, many patients remain undiagnosed (1, 15).

Diagnosis

The diagnosis of CD is often based on a combination of serological results, genetic disease markers, and a biopsy-verified gluten-reactive enteropathy (12). If CD is suspected, the measurement of IgA-antibodies against TGA is the recommended first screening test due to

its high sensitivity and specificity (2). Measurement of EMA could be used in inconclusive cases such as those with weakly positive IgA-TGA levels (1, 2). The patient must be on a gluten-containing diet to secure the high sensitivity of the serological test (1). IgA deficiency could lead to false-negative serological screening results. Therefore, it is essential to measure the total IgA concentration in conjunction with the serological test, and in the case of IgA deficiency, IgG-based serological tests should be performed instead (2).

Depending on the TGA levels, a decision is made whether to proceed with duodenal biopsy sampling or not (17). In children, duodenal biopsies are recommended to confirm CD diagnosis in cases where TGA levels do not exceed ten times the upper limit of normal (1). One or two biopsies from the duodenal bulb and at least four biopsies from the distal duodenum are retrieved via upper endoscopy (12). Histological features of CD include villous atrophy, crypt hyperplasia, and increased intraepithelial lymphocytes. The demonstration of histological changes in duodenal biopsies confirms the diagnosis (2, 12). The histological damage of the duodenal mucosa can be categorized according to the Marsh classification (18).

In 2012, the European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) proposed that symptomatic children with IgA-TGA concentrations higher than ten times the upper limit of normal can obtain CD diagnosis without a duodenal biopsy (7). In 2020, the diagnostic guidelines were updated; since then, all children, irrespective of symptoms or not, with an IgA-TGA level above ten times the upper limit of normal can be diagnosed with CD without a biopsy. Instead, additional laboratory testing of EMA-antibodies or a second TGA-test that confirms high serology titers is needed (17). HLA

haplotype determination can be valuable if there are equivocal serology or histology results or rule out disease in children on a gluten-free diet (1).

Treatment

The only treatment available for patients with CD is a strict gluten-free diet (16). For CD patients, this includes the complete avoidance of wheat, rye, and barley, whereas oats usually are safe for CD patients if there is no cross-contamination (14). Generally, the symptoms improve within days to weeks and precede the recovery of the duodenal villous atrophy and a reduction of autoantibodies levels (2). It is recommended that all patients with newly diagnosed CD visit an expert dietitian to obtain knowledge on how to avoid gluten and to learn about healthy gluten-free substitutes and supplements (1, 2). Despite a prescripted gluten-free diet, about 10-30 % of CD patients suffer from persistent or recurrent symptoms, most commonly caused by inadvertent gluten contamination (1).

Maintaining a strict gluten-free diet is accompanied by difficulties and may cause negative social consequences (19), including social situations involving food such as dining out or birthday parties (15). Additionally, it has been shown that a gluten-free diet can produce stigma experiences for adolescents (20). Moreover, gluten-free foods are expensive and less available than their gluten-containing counterparts, which also adds to the burden of CD (21). Hence, CD and its treatment may significantly affect the everyday life of affected patients (22).

Health-related quality of life (HrQoL)

The World Health Organisation defines the quality of life as: *"an individual's perception of their position in life in the context of the culture and value systems in which they live and in*

relation to their goals, expectations, standards, and concerns" (23). Health-related quality of life (HrQoL) is a concept that includes the aspects of quality of life that are affected by either mental or physical health. The concept of HrQoL has evolved since the 1980s. The measurement of HrQoL can be useful when assessing the burden of a disease (24) and, therefore, an important aspect in the evaluation of the benefits and harms associated with screening programs for diseases(8).

Measuring HrQoL in children

The assessment of HrQoL in children requires that the questionnaire is designed to appropriately account for the age and cognitive level of children (25). The Kidscreen instrument is used to assess the HrQoL in children and adolescents. It was developed simultaneously in several different European countries to obtain cross-cultural validity and facilitate international comparison. It is a self-report measure instrument available in 10-, 27- and 52-item versions and corresponding proxy-versions for parents (26).

Celiac disease screening

It is currently recommended to screen children with CD-associated symptoms, such as gastrointestinal symptoms and signs of malabsorption, including poor growth or weight loss, a practice called active case-finding of CD. Targeted CD-screening is also recommended for individuals at a higher risk of developing CD, including first-degree relatives to CD patients and individuals with CD-associated conditions such as diabetes mellitus type 1, Downs syndrome, autoimmune thyroid disease, Turner syndrome, Williams syndrome, selective IgA deficiency, and autoimmune liver disease (17). However, mass CD-screening of asymptomatic individuals outside these high-risk groups is currently not recommended due to

the lack of evidence needed to assess the harms and benefits of such CD-screening (8). IgA-TGA is generally considered the preferred test for screening since it offers high sensitivity and specificity (1).

There is not enough evidence showing that early CD diagnosis identified through mass screening is beneficial in general or whether it, in particular, improves the HrQoL of those detected. Potential harms with mass screening for CD in children include false positives serology tests causing unnecessary biopsies and anxiety while under investigation. However, some advocate that the implementation of mass screening for CD because early CD diagnosis is difficult, the disease prevalence is high, a serological screening test is available that offers both high sensitivity and specificity, and delayed treatment of CD may potentially lead to complications (27).

4. AIM

The overall purpose of this study is to investigate the health-related quality of life (HrQoL) in children screened for CD at a pediatric outpatient clinic. The primary aim is to describe potential differences in HrQoL using Kidscreen-27 in screened patients with versus without positive CD-screening. The secondary objective is to assess the HrQoL of all participating children and describe potential differences based on age and sex.

5. METHODS AND MATERIALS

Study design and outcome definition

The pilot study, "Serological identification of Celiac disease in Kids (SICK)" was conducted at the pediatric outpatient clinic at Hisingen, Gothenburg. Children visiting the clinic between November 2019 and March 2020 were invited, and some 500 patients gave their consent and were enrolled into the study. The outpatient clinic has five full-time doctors, five full-time nurses, and 36,000 listed children aged 0-17 years old. The overreaching aim of SICK was to test the feasibility of incorporating CD-screening at a pediatric outpatient clinic.

The participating children were screened for CD using TGA measured at the Sahlgrenska University Hospital using Fluorescence Enzyme Immunoassay (Phadia250-Thermo Fisher). All children were also screened for IgA deficiency (< 0,07 g/L). IgA deficient children were screened for IgG-TGA instead of IgA-TGA. Cut-offs for positive TGA were set to ≥7 U/ml since this concentration has shown to have a high predictive value for CD diagnosis verified by biopsies (28). IgA/IgG-TGA concentrations ≥ 7 U/ml were considered as a positive test. Children who received a positive screening result were then invited back for a second confirmatory IgA-TGA test. Participants testing positive on the confirmatory test were considered as persistent TGA-positive cases and, for the purpose of this study, henceforth referred to have CD autoimmunity (CDA). Children with CDA were offered a work-up of CD at a pediatric gastroenterology clinic. The participants that received negative results on the initial screening test are referred to as non-CDA. None of the participants were single TGA-positive.

The validated questionnaire Kidscreen-27 was used to assess the participating children's HrQoL. Participants at the age of eight years or older were asked to answer the survey independently, while the legal guardians were asked to answer for the participating children under the age of eight years. All participating children or their parents were also asked to rate their gastrointestinal symptoms using the instrument Gastrointestinal Symptom Rating Scale (GSRS) and parts of the disease-specific instrument Celiac Symptom Scale (CSI). Data regarding the medical history (defined as conditions where the participants have sought medical attention), numbers of visits to the pediatric outpatient clinic the past year, the reason for the present visit, and if the child previously has been tested for CD-antibodies together with social demographics, was also collected at study enrollment.

Source population

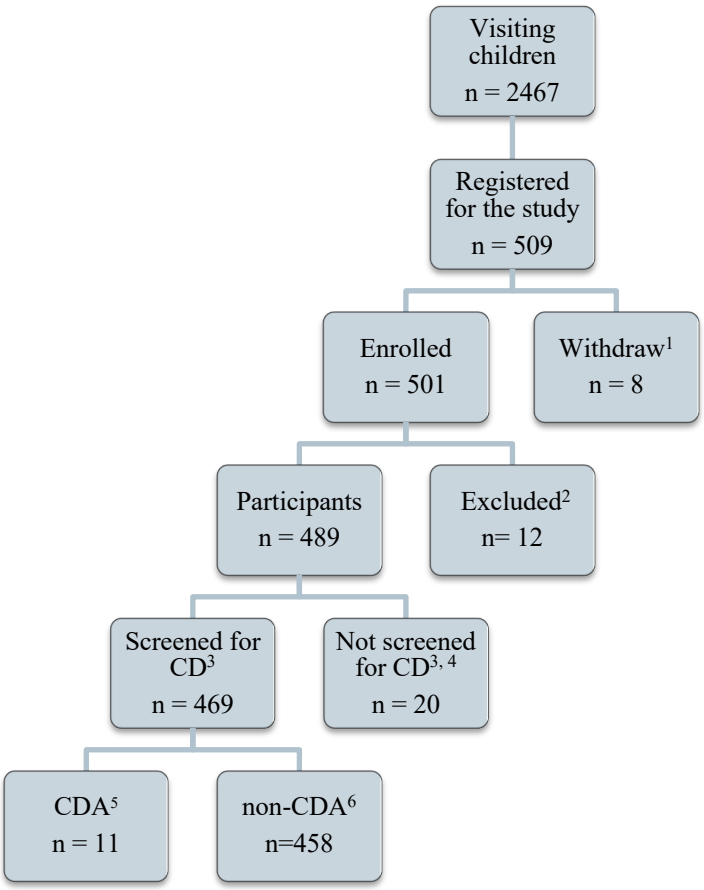
Children between the age of 2 to 17 years who, for any reason, visited the pediatric outpatient department in Hisingen, Gothenburg, between November 2019 and March 2020 were invited into the study. Participants with previous CD diagnosis or type 1 diabetes were excluded from serological screening for CD but could otherwise participate in the study (i.e., survey of symptoms and HrQoL-questionnaire).

Participants

A number of 2467 children visited the outpatient clinic during the time of the study, between November 2019 and March 2020. A total of 501 children aged 2-17 years were enrolled in the study, out of whom 12 were later excluded from analyses due to missing or incorrect data. Of the participating children, 469 were screened for CD, whereas 20 participants were excluded from serological testing due to an established CD diagnosis. Out of the 469 screened children,

11 (2,3 %) were repeatedly positive for TGA (i.e., CDA), and 458 children had negative results ("non-CDA-group").

Figure 1 - Participants Flowchart



[1] Withdraw due to missing consent and other reasons, including not having enough time
[2] Excluded due missing or incorrect information, legal guardians under the age of 18 years
[3] Celiac Disease (CD)
[4] 20 children were not screened for Celiac Disease (CD) due to previous CD diagnosis and other
[5] Children with positive screening results are referred to as CDA (celiac disease autoimmunity)
[6] Children with negative screening results are referred to as non-CDA (non-celiac disease autoimmunity)

Instruments/measures

Kidscreen

The self-report version of the 27-item Kidscreen questionnaire was used to assess the HrQoL of the participating children. The Kidscreen-27 is derived from the original 52-item Kidscreen questionnaire that was simultaneously developed in several European countries to provide a cross-cultural HrQoL instrument aimed at children and adolescents aged 8-18 years (29).

Kidscreen-27 is grouped into 5 HrQoL dimensions: "*Physical Wellbeing"* (5 items), "*Psychological Wellbeing"* (7 items), "*Autonomy & Parent Relations*" (7 items), "*Social Support & Peers"* (5 items), and "*School Environment"* (4 items). Each item is scored on a 5-point scale ranging from "never"/"not at all" to "always" based on self-perceived HrQoL during the last week.

The Kidscreen-27 is scored on the Rasch scales since it fulfills the assumptions of the Rasch model (26). Higher Kidscreen-score indicates a higher HrQoL (negatively formulated items are therefore, first re-coded). Items were summed up for each subscale, creating scale raw scores. These scale raw scores were transformed into Rasch person parameter estimates and T-values, which were used for the statistical analyzes (26).

Each subdimension examines an aspect of children's self-perceived HrQoL as presented in table 1 below. The complete Kidscreen-27 questionnaire is presented in appendix 1.

Table 1, Overview of Kidscreen-27 subdimensions

Subdimension:	Content:	A high score indicates that:	A low score indicates that:
Physical wellbeing	The child's physical activity, energy level, fitness, and overall perceived health.	The child is physically fit, active, energetic, and healthy.	The child has low energy, is physically unwell and exhausted, and feeling unfit.
Psychological wellbeing	The child's emotions and satisfaction with life.	The child is happy, has an optimistic life view, and is satisfied with life.	The child is feeling unhappy and depressed, having low self-esteem, and no pleasure in life.
Autonomy and parent relations	The parents' interaction, family support, perceived autonomy, and financial resources.	The child is positive about the parent relationship, has enough freedom to choose, satisfied with financial resources.	The child feels restricted, overlooked, not appreciated, and feels finances are restricting.
Social support and peers	The interaction with friends and peers as well as the perceived support.	The child feels accepted, supported, and included.	The child is feeling excluded and not accepted by peers.
School environment	Includes the cognitive capacity, learning, concentration, and feelings about school as well as the relationship with teachers.	The child feels happy at school and doing well.	The child dislikes school and is not doing well.

The psychometric properties of the Kidscreen-27 measure were tested in a cross-cultural study across 13 European countries that showed acceptable construct validity (29), which refers to what extent the questionnaire measures what it is intended to measure. Also, the reliability of the Kidscreen-27 instrument is satisfactory with an internal consistency value with a range between 0.76-0.89 (Cronbach's Alpha), which reflects to what extent the different items are inter-correlated where a value of 0 indicates no correlation and ≥ 0.9 indicates possible redundancy in items. The test-retest value for Kidscreen-27 varied between

0.56-0.77, reflecting the extent to which the individual response remains consistent across repeated administration of the same questionnaire. Higher values indicate that measurement error is less likely to account for individual change in response over time (26, 30).

Gastrointestinal Symptom Rating Scale (GSRS)

Gastrointestinal Symptom Rating Scale (GSRS) consists of 15 items divided into five subscales for common gastrointestinal syndromes: *"Pain Syndrome," "Reflux Syndrome," "Indigestion syndrome," "Constipation Syndrome,"* and *"Diarrhea Syndrome".* Each item is scored on a 7-graded Likert scale. A score of 1 equates to having no symptoms and a score of 7 equates to having the most severe symptoms (31, 32). The instrument was initially developed for irritable bowel syndrome and peptic ulcer disease (33).

Statistical methods

Between-group differences were estimated between children with CDA versus non-CDA and, for our secondary aim, according to age (< 8 years and ≥ 8 years) and sex. The Mantel-Haenszel chi-square test was used to test the trend of categorial ordered data, and the chi-square test was used for non-ordered variables. Mann-Whitney U-test was used for continuous data. P-values less than 0.05 or a 95% confidence interval not including 1.00 was regarded as statistically significant.

Post-hoc power analysis

Below power analysis is based on the sample size detailed in Table 1 and assumes a common standard deviation between groups and a two-sided significance level of 0.05. Based on these assumptions, we have 80% power to detect a minimum 11.1 difference in Kidscreen-27 total

raw score in children with versus without CDA. The power analysis was conducted using STATA version 16 (StataCorp LP, TX, USA).

Ethical considerations

This study is in accordance with the Helsinki declaration and has been approved by the Swedish Ethical Review Authority, diary number, 2019-01950. Informed consent was retrieved from all participants after being thoroughly informed of the scope and purpose of the study. Data were pseudonymized before statistical analyzes.

6. RESULTS

Descriptive characteristics

Characteristics of the participants are summarized in table 2. Mean age (+SD) was 9.29 years (4.31) for the children with negative screening (non-CDA) and 5.71 (3.58) for the children with positive screening (CDA). P-value 0.0057 using the Mann-Whitney U-test. Sex was evenly distributed between groups, 240 girls (50.2%) and five girls (45.5%) in the CDA-group. The most common reason for visiting the pediatric outpatient clinic was *"Allergy/Asthma"* (35.0%), followed by *"Gastrointestinal disorders"* (23.5%).

The most common condition in medical history was asthma affecting 28.9% of all participants. The most common conditions in children with CDA (%) were asthma (36.4%) and food allergies (36.4%). Also, long-term constipation or diarrhea (27.3%), pollen allergies (27.3%), and eczema (27.3%) were common in children with CDA. The corresponding frequencies of these conditions in non-CDA children were asthma (28.7%), food allergies (16.8%), long-term constipation/diarrhea (24.2 %), pollen allergies (19.2%), and eczema (17.2%). Poor growth was affecting 15.5% of the non-CDA participants, but none of the children with CDA. Generally, participants had made at least 1(36.2 %) or 2 (25.4 %) previous visits during the last year; in the CDA-group, all children had at least one previous visit before study enrollment.

Table 2 – Baseline characteristics of study participants

	All children n=489	Non-CDA[1] n= 478	CDA[2] n=11
Age[3]:	9.21 (4.32)	9.29 (4.31)	5.71 (3.58)
Sex[4]:			
Girls	245 (50.1%)	240 (50.2%)	5 (45.5%)
Boys	244 (49.9%)	238 (49.8%)	6 (54.5%)
Reason for visit[5]:			
Gastrointestinal disorders	90 (23.5%)	87 (23.4%)	3 (27.3%)
Respiratory tract infection	18 (4.7%)	17 (4.6%)	1 (9.1%)
Neurologic disorders incl. headache	28 (7.3%)	28 (7.5%)	0 (0.0%)
Kidney- or urinary tract disease	8 (2.1%)	7 (1.9%)	1 (9.1%)
Mental illness	3 (0.8%)	3 (0.8%)	0 (0.0%)
Allergy, asthma	134 (35.0%)	129 (34.7%)	5 (45.5%)
Eczema or other skin condition	13 (3.4%)	13 (3.5%)	0 (0.0%)
Overweight, puberty or metabolism	36 (9.4%)	36 (9.7%)	0 (0.0%)
Growth	25 (6.5%)	25 (6.7%)	0 (0.0%)
Other	28 (7.3%)	27 (7.3 %)	1 (9.1%)
Medical history[6]:			
Asthma	139 (28.9%)	135 (28.7%)	4 (36.4%)
Diarrhea or constipation (long-term)	117 (24.3%)	114 (24.2%)	3 (27.3%)
Failure to thrive	73 (15.1%)	73 (15.5%)	0 (0.0%)
Eczema	83 (17.2%)	80 (17.0%)	3 (27.3%)
Food allergy	83 (17.2%)	79 (16.8%)	4 (36.4%)
Respiratory tract infection	48 (10.0%)	46 (9.8%)	2 (18.2%)
Abdominal pain	125 (26.0%)	123 (26.1%)	2 (18.2%)
Pollen allergies	93 (19.4%)	90 (19.2%)	3 (27.3%)
Other[7]	440	436	4
The number of previous visits at the pediatric outpatient clinic over the last year[8]:			
0	23 (4.8%)	23 (4.9%)	0 (0.0%)
1	174 (36.2%)	169 (36.0%)	5 (45.5%)
2	122 (25.4%)	119 (25.3%)	3 (27.3%)
3	76 (15.8%)	75 (16.0%)	1 (9.1%)
4	25 (5.2%)	24 (5.1%)	1 (9.1%)
5	24 (5.0%)	24 (5.1%)	0 (0.0%)
≥ 6	37 (7.5%)	36 (7.7%)	1 (9.1%)
Previous screened for CD antibodies (prior to this study)[9]:			
Yes	91 (19.8%)	91 (20.3%)	0 (0.0%)
Established CD diagnosis[10]:			

Yes	19 (4.0%)	19 (4.1%)	0 (0.0%)
No	460 (96.0%)	449 (95.9%)	11 (100%)

[1]CDA (Celiac Disease Autoimmunity), the group of children with positive screening results
[2]Non-CDA (Non-Celiac disease Autoimmunity), the participants with negative screening results
[3] Age is presented as mean (+SD) in CDA-, Non-CDA and total, respectively.
[4] Sex is presented as number (%) of girls and boys in CDA, Non-CDA, and total.
[5] The reason for the participant's visit to the pediatric outpatient clinic is presented as the number (%) of children in each reason-category for the respective groups CDA, Non-CDA, and total.
[6] Medical history is defined by conditions in which the participants visited a doctor for presented as number (%) of children for each condition.
[7] Other conditions are presented as the number of cases and include (number of cases in all participants): ADHD (20), autism (19), anemia (18), fracture (47), epilepsy (19), pubertal delay (8), heart condition (12), headache/migraine (46), incontinence (27), Dwarfism (18), congenital syndrome (2), urticaria (39), mental illness (41), rheumatic disorder (6), thyroid disorder (10), syncope (12), urinary tract infection (36), development delay (15), Overweight/obesity (45).
[8] The number of times each participant has been visiting the clinic before study enrolment divided by CDA and non-CDA during the past year.
[9]Number of participants with previous CD screening test by CDA and Non-CDA
[10] Number of participants (%) with CD diagnosis prior to study enrolment.

Health-related quality of life (HrQoL) in children with versus without serological evidence of celiac disease

The HrQoL was assessed by the generic questionnaire Kidscreen-27, and the results are presented in Table 3. Higher scores are indicative of a higher HrQoL. The median of the total raw score was 114 in non-CDA and 118.5 in CDA participants (P-value 0.42). There were also no significant differences found in the separate subdimensions of Kidscreen. The highest mean score was observed in the subdimension *"Autonomy and parent relations"* in which the parent interaction, family support, and autonomy of the child is being examined, with a mean (SD) score of 55.8 (9.9) in non-CDA children and 58.6 (11.6) in children with CDA (P-value 0.51). The child's level of physical activity and energy and perceived overall health is represented in the subdimension *"Physical wellbeing*," the mean (SD) score of this dimension was 49.0 (10.5) in non-CDA and 51.6 (13.8) in CDA children (P-value 0.79). The lowest mean scores were found in *"Psychological wellbeing,"* which examines the child's emotions and satisfaction with life. For non-CDA children, the mean (SD) score was 45.5 (6.1) and in

CDA children 47.6 (9.4) (P-value 0.70). See Supplementary Table 1 for complete responses by each individual item of Kidscreen-27.

Table 3 – Kidscreen-27 measure of HrQoL in the Non-CDA- vs CDA-group of participating children

Kidscreen-27 dimension:	**Non-CDA[1]** (n = 478) Mean (SD)	**CDA[2]** (n = 11) Mean (SD)	**P-value[3]**
Total raw score	114 (105;123)[4]	118.5 (105;122) [4]	0.42
Physical wellbeing	49.0 (10.5)	51.6 (13.8)	0.79
Psychological wellbeing	45.5 (6.1)	47.6 (9.4)	0.70
Autonomy and parent relations	55.8 (9.9)	58.6 (11.6)	0.51
Social support and Peers	51.7 (10.5)	52.4 (9.4)	0.91
School environment	55.1 (9.9)	60.0 (11.3)	0.13

[1] The children with negative screening are referred to as Non-CDA (Celiac disease autoimmunity)
[2] The children with positive screening, CDA (Celiac Disease Autoimmunity)
[3] P-values was calculated using the Mann-Whitney U-test
[4] Total raw score presented as median (Q1; Q3)

Differences in health-related quality of life according to sex and age

The total median of raw score of Kidscreen-27 was similar for girls 114 (interquartile range, IQR: 104;122) and boys 114 (105;123). Boys scored higher in the subdimension *"physical wellbeing"* compared to girls with a mean (SD) of 49.8 (10.2) respectively 48.2 (10.7), P-value 0.035. The subdimension of *"Psychological wellbeing"* had the lowest score of 45.9 (5.7) in girls and 45.2 (6.7) in boys, P-value 0.097. Instead, the highest mean score was found in *"Parent relations and autonomy,"* 55.9 (10.5) in girls and 55.7 (9.4) in boys, P-value 0.93. All subdimensions are presented in Table 4.

Table 4 - Kidscreen-27 measure of HrQoL in girls vs. boys

Kidscreen-27 dimension:	Boys (n = 244) Mean (SD)	Girls (n = 245) Mean (SD)	P-value[1]
Total raw score	114 (105; 123)[2]	114 (104;122)[2]	0.62
Physical wellbeing	49.8 (10.2)	48.2 (10.7)	**0.035**
Psychological wellbeing	45.9 (5.7)	45.2 (6.7)	0.097
Parent relations and autonomy	55.9 (10.5)	55.7 (9.4)	0.93
Social support and Peers	51.1 (11.4)	52.3 (9.5)	0.39
School environment	54.5 (10.1)	55.7 (9.9)	0.38

[1] P-value was calculated using the Mann-Whitney U-test
[2] The total raw score is presented as median (Q1; Q3)

The younger participants scored higher in total raw score, (median) 116 compared to the older children and adolescents 112.5, P-value 0.043. The younger children did also score higher in *"Physical wellbeing,"* (mean) 51.6 (SD: 10.2) compared to 47.9 (10.3) in the older children, P-value < 0.0001 and in the subdimension of *"School environment"* 56.9 (10.7) in the younger children-group and 53.9 (9.3) in the group with older children, P-value 0.0006. No significant differences were observed in other dimensions. All subdimensions are presented in table 5.

Table 5 - Kidscreen-27 measure of HrQoL in children aged < 8 years vs. older

Kidscreen-27 dimension:	Children < 8 years (n=213) Mean (SD)	Children ≥ 8 years n=276 Mean (SD)	P-value[1]
Total raw score	116 (107; 123)[2]	112.5 (103;121)[2]	**0.043**
Physical wellbeing	51.6 (10.2)	47.0 (10.3)	**< 0.0001**
Psychological wellbeing	51.9 (9.0)	51.2 (10.6)	0.62
Parent relations and autonomy	56.1 (10.8)	55.6 (9.2)	0.70
Social support and Peers	51.4 (11.1)	51.9 (10.0)	0.31
School environment	56.9 (10.7)	53.9 (9.3)	**0.0006**

[1] P-value was calculated using the Mann-Whitney U-test
[2] The total raw score is presented as median (Q1; Q3)

Gastrointestinal symptom rating

The total mean (SD) score on GSRS was 1.58 (0.67) in children with CDA and 1.52 (0.45) in non-CDA children (P-value 0.91). No significant difference was observed between CDA and non-CDA children in any of GSRS subscales *"Diarrhea syndrome," "Indigestion syndrome," "Constipation syndrome," "Abdominal pain,"* and *"Reflux syndrome"* (table 6).

Table 6 – GSRS in CDA and Non-CDA

	Non-CDA[1] n = 468 Mean (SD)	**CDA**[2] n = 11 Mean (SD)	**Total** n = 479 Mean (SD)	**P-value**[3]
GSRS total score	1.58 (0.67)	1.52 (0.45)	1.58 (0.66)	0.91
Diarrhea syndrome	1.50 (0.86)	1.64 (0.78)	1.5 (0.86)	0.50
Indigestion syndrome	1.76 (0.94)	1.52 (0.66)	1.75 (0.94)	0.42
Constipation syndrome	1.67 (1.07)	1.91 (0.97)	1.68 (1.06)	0.36
Abdominal pain syndrome	1.69 (0.90)	1.45 (1.01)	1.69 (0.91)	0.13
Reflux syndrome	1.27 (0.68)	1.09 (0.30)	1.27 (0.68)	0.34

[1] The children with negative screening are referred to as Non-CDA (Celiac disease autoimmunity)
[2] The children with positive screening, CDA (Celiac Disease Autoimmunity)
[3] Between-group comparison was performed using the Mann-Whitney U-test

7. DISCUSSION

This project is a part of the pilot study *"Serological Identification of Celiac disease in Kids (SICK),"* which examines the feasibility of serological screening for CD at a pediatric outpatient clinic. This study set out with the primary aim of assessing HrQoL measured with the generic questionnaire Kidscreen-27 in the 496 participating children. No significant differences in HrQoL were observed in children with positive CD-screening compared to those with negative results. The HrQoL also seemed largely similar between boys and girls, respectively, between children younger than eight and children eight years or older.

Interpretation of findings in light of previous studies

Our results are in line with several previous studies, supporting the argument that there is no, or only a minimal decrease in HrQoL in paucisymptomatic individuals with undetected CD. Two previous Swedish studies by Myléus A et al. and Nordycke K et al., found no differences in HrQoL between children with screening-detected CD versus children without CD, respectively, as compared with children with an established diagnosis of CD (34, 35). Similar results have also been shown in adult patients with CD (8). However, to our knowledge, only one previous study, by van Koppen EJ et al., including children aged 2-4 years, has found a poorer HrQoL in children screening-detected CD compared to a healthy reference group of children at the same age. However, the decreased HrQoL was restricted to children with gastrointestinal symptoms of CD, while children without symptoms of disease scored similar HrQoL as their peers without CD (36). Similar results have been observed in adults in a UK population-based longitudinal study by Violato M et al. on CD where the number of symptoms was inversely associated with the HrQoL (37). The connection between the

severity of gastrointestinal symptoms and poorer HrQoL has also been shown in a previous prospective study by Nachman F et al. from Argentina (38).

In our study, gastrointestinal symptoms as measured by the validated GSRS were largely similar between children with positive celiac screening than with negative celiac screening. While a formal interaction analysis between HrQoL and symptom score in CDA was outside the scope of this study, our data suggest that the lack of association found between self-reported HrQoL and CDA might be explained by the few symptoms of this study population. Another possible explanation why our study did not show significant differences in HrQoL could be the lack of statistical power, or, simply, is that there is no actual difference in HrQoL between children with versus without positive CD-screening. However, we cannot rule out the possibility that a CD-specific HrQoL questionnaire might have captured differences in HrQoL that our generic questionnaire was not able to detect since a CD-specific instrument elicits the aspects of HrQoL that might be influenced by the disease (39).

In CD, HrQoL may be affected by the diagnosis itself, its follow-up, and the strict dietary treatment. Some studies have shown poorer HrQoL in patients with CD, particularly in dimensions regarding their spare time and especially among adolescents (22, 39, 40). However, other studies have found no significant differences in HrQoL between individuals with CD and comparators (36, 41, 42). In contrast, other studies have shown an improvement of CD-associated symptoms after installing a gluten-free diet, which parallels better HrQoL (36, 37). The HrQoL of children and adolescents with CD diagnosis is influenced by the age at diagnosis, the presence and severity of symptoms before treatment, and the number of years on a gluten-free diet (43, 44).

Our results are well in line with those of a large, general population-based Swedish study by Berman AH et al. on Kidscreen-27 measured HrQoL. The median of total raw scores (interquartile range) in our study was 114 (105; 123) in non-CDA and 118.5 (105; 122) in CDA children compared with 115 (105-121) in the random sample population of the previous Swedish study (45). The most significant difference between ours and Berman et al. was between the subdimension score for psychological wellbeing: mean (SD) score of 53.4 (10.93) in the study by Berman AH et al. compared to a mean (SD) score of 45.5 (6.1) (non-CDA) (45). One explanation for this inconsistency between our study and Berman et al. regarding "Psychological Wellbeing" might be that we included children from a pediatric outpatient clinic and many of the participating children suffered from other chronic conditions that may affect their HrQoL (45).

A meta-analysis, by Silva N et al., investigating HrQoL impairments in children and adolescents with chronic health conditions using the Kidscreen questionnaires found statistical but not clinically significant differences in the subdimensions *"Physical wellbeing"* and *"Psychological wellbeing"* when compared to healthy control groups (46). However, this meta-analysis study includes a broad range of physical chronic health conditions, for example, CD, epilepsy, cerebral palsy, asthma, obesity, and Duchenne muscular dystrophy, which complicates the comparison with our study. In a Spanish study by Murillo M et al. assessing HrQoL using Kidscreen-10 in children with type I diabetes, it was found that children with type 1 diabetes have slightly worse *"Physical wellbeing"* than the general population (47). A Polish study by Manczak M et al., used Kidscreen-52 to assess the HrQoL in children suffering from Juvenile idiopathic arthritis and found lower scores in children with Juvenile idiopathic arthritis in *"Physical wellbeing"* but also in other dimensions not as predictable

such as *"Autonomy," "Social support and peers*," and *"School environment"* (48). Although it is difficult to compare different chronic health conditions with their respective impact on HrQoL, the fact that the studies mentioned above have shown that chronic diseases can negatively influence the HrQoL, provides a strong argument for the importance of HrQoL assessment.

Interpretation of health-related quality of life according to sex and age

A secondary objective in this study was to describe possible differences in HrQoL according to sex and age. No significant difference was observed in the total raw score according to sex. However, younger children (< 8 years) scored significantly higher in total raw score as well as in "*Physical Wellbeing"* and "*School Environment"* compared to older children (≤ 8 years). It has previously been demonstrated that older children and adolescents tend to score lower HrQoL than younger children (45, 49, 50). In the above-mentioned Swedish study by Berman AH et al., of children aged 11- 18 years (45), the younger age-groups scored significantly higher than the older age-groups in the total raw score and in all subdimensions except for "*Social Support and Peers".* Similar findings have also been shown in a larger pan-European study by Bisegger et al. (50). Our study could not observe such major differences between ages. A possible explanation might be that the sample size is too small. Another important aspect is that the Kidscreen questionnaire was developed for children aged eight years and older. At the same time, our study included younger children whose parents reported for them (without the formal use of a Kidscreen proxy-version). Given the relatively small sample size of our study (n=489), age was dichotomized into younger children (< 8 years) and older children and adolescents (≥ 8 years). We cannot rule out that the use of smaller age bands

might have revealed a more substantial age-related heterogenicity of HrQoL similar to what has been found in other studies (45, 50).

In the present study, no major differences according to sex were observed. This finding is consistent with the Swedish validation study by Berman AH et al. on Kidscreen, which showed no sex differences neither overall nor in any subdimensions of Kidscreen-27 measured HrQoL (45). However, those findings are contrary to previous studies including, the above-mentioned large pan-European study by Bisegger et al. based on Kidscreen-52, where adolescent females scored lower in *"Self-perception," "Physical wellbeing," "Psychological wellbeing,"* and *"Mood and emotions"* (49-51). Furthermore, another Swedish study by Svedberg P et al. found that boys scored higher compared to girls in the Kidscreen-52 dimensions: *"Physical wellbeing," "Psychological wellbeing," "Moods and emotions," "Self-perception," "Autonomy,"* and *"School environment"* (51). There are several possible explanations for this inconsistency between our study and the studies mentioned above regarding sex-related HrQoL differences, including methodological differences in study design, source population studied, and version of Kidscreen used. Also, we cannot rule out that our limited study size may, due to insufficient study power or chance, have prevented us from identifying a difference in HrQoL between sexes.

Strengths and weaknesses

A strength of this study is that the HrQoL was assessed prior to the screening result since it allows a fairer evaluation since the diagnosis itself may influence the self-perceived HrQoL. Another strength is the comprehensive baseline data collected at study enrollment, including demographic data, medical history, etc. Kidscreen-27, with its excellent psychometric

properties, provides a valid, reliable, and sensitive measurement of HrQoL in children yet reduces the time of completion compared to the more extended 52-item long version of Kidscreen. Another advantage is that Kidscreen is an internationally validated questionnaire that facilitates the comparison with similar studies worldwide (52). On the other hand, the comparison with other studies in this field is complicated by the fact that our study population consisted of children (≥ 8 years) who themselves could fill out the survey and children too young to do so. Kidscreen is validated in children aged 8 to 18 years. An important limitation of this study is our small sample size and corresponding study power, which increase the risk of committing a type II error (i.e., false negative).

Conclusion

This study aimed to assess the HrQoL in children screened for CD at a pediatric outpatient clinic. No significant differences in HrQoL were observed in children with a positive screening result compared to the children with a negative outcome, which suggests that undetected CD does not significantly impact the HrQoL of affected children. However, we cannot rule out that the lack of such association is due to limited statistical power or our use of a generic HrQoL questionnaire, unable to capture CD-specific components of health. Further work is needed to fully understand the impact on the HrQoL in children with undetected CD in order to enable a proper assessment of whether or not the benefits outweigh the harms of CD screening.

8. POPULÄRVETENSKAPLIG SAMMANFATTNING

Hälsorelaterad livskvalitet hos barn screenade för celiaki – en pilotstudie på en pediatrisk öppenvårdsmottagning.

Ungefär 2-3 % av barn i Sverige har celiaki, det vill säga glutenintolerans. Vid celiaki leder glutenintag från vete och liknande sädesslag till att tarmen blir inflammerad och kan ge symptom i form av magbesvär såsom diarré eller gaser men kan också ge mer diffusa symptom såsom trötthet och viktnedgång. Symptomen kan variera mycket och några har inga eller väldigt få och milda symptom vilket leder till att många förblir odiagnosticerade.

Med hjälp av ett blodprov går det att mäta koncentrationen av antikroppar som är kopplade till celiaki och på sätt kan man upptäcka sjukdomen via så kallad screening. Denna studie fokuserar på den hälsorelaterade livskvaliteten hos barn som blivit screenade för celiaki vid en öppenvårdsmottagning för barn. I samband med screeningen fick barnen fylla i en enkät om deras upplevda hälsorelaterade livskvalitet den senaste veckan. Livskvaliteten hos de barn med påvisbara celiaki-antikroppar (förmodad odiagnosticerad celiaki) jämfördes sedan mot de barn med negativ screening, alltså utan sådana antikroppar. I studien gjordes också jämförelser av livskvaliteten baserat på kön och ålder hos de medverkande barnen.

Studien fann inga signifikanta skillnader i hälsorelaterad livskvalitet mellan barnen med celiaki-associerade antikroppar jämfört med barnen utan sådana antikroppar. Inga större skillnader i hälsorelated livskvalitet sågs heller mellan könen eller med avseende på ålder (under 8 år versus 8 år eller äldre). Deltagarna i studien fick förutom att skatta hälsorelaterad livkvalitet också skatta deras mag- och tarmbesvär. Inga signifikanta skillnader hittades mellan barnen med celiaki-associerade antikroppar jämfört med barnen utan sådana

antikroppar avseende mag-och tarmbesvär. Det faktum att barnen med celiaki-associerade antikroppar inte hade mer besvär från mage-tarm skulle kunna förklara varför de inte skattade lägre hälosorelaterade livskvalitet än barnen utan sådana antikroppar. Denna pilotstudie hade relativt få deltagare vilket också gör det svårare att hitta signifikanta skillander mellan studiegrupper. Den enkät som användes för att mäta livskvalitet är främst utformad för barn i åldrarna 8-18 år men i denna studien ingick även yngre barn (från 2 års ålder) vilket möjligen också kan ha påverkat resultatet.

Sammantaget visar denna pilotstudie för celiaki-screening inga större skillnader i hälsorelaterad livskvalitet mellan barn med respektive utan. Studien begränsades dock av ett relativt litet studiematerial. Eftersom livskvalitet är en central aspekt i att kunna värdera för och nackdelarna med celiaki-screening hos barn krävs större studier på detta område för att kunna utesluta också mindre, men fortsatt betydelsefulla skillnader i livskvalitet hos barn med respektive utan odiagnosticerad celiaki.

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10. REFERENCES

1. Al-Bawardy B, Codipilly DC, Rubio-Tapia A, Bruining DH, Hansel SL, Murray JA. Celiac disease: a clinical review. Abdom Radiol (NY). 2017;42(2):351-60.
2. Lebwohl B, Sanders DS, Green PHR. Coeliac disease. Lancet. 2018;391(10115):70-81.
3. Rubio-Tapia A, Kyle RA, Kaplan EL, Johnson DR, Page W, Erdtmann F, et al. Increased prevalence and mortality in undiagnosed celiac disease. Gastroenterology. 2009;137(1):88-93.
4. Lebwohl B, Green PHR, Söderling J, Roelstraete B, Ludvigsson JF. Association Between Celiac Disease and Mortality Risk in a Swedish Population. Jama. 2020;323(13):1277-85.
5. Myléus A, Ivarsson A, Webb C, Danielsson L, Hernell O, Högberg L, et al. Celiac disease revealed in 3% of Swedish 12-year-olds born during an epidemic. J Pediatr Gastroenterol Nutr. 2009;49(2):170-6.
6. Singh P, Arora A, Strand TA, Leffler DA, Catassi C, Green PH, et al. Global Prevalence of Celiac Disease: Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol. 2018;16(6):823-36.e2.
7. Husby S, Koletzko S, Korponay-Szabó IR, Mearin ML, Phillips A, Shamir R, et al. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease. J Pediatr Gastroenterol Nutr. 2012;54(1):136-60.
8. Bibbins-Domingo K, Grossman DC, Curry SJ, Barry MJ, Davidson KW, Doubeni CA, et al. Screening for Celiac Disease: US Preventive Services Task Force Recommendation Statement. Jama. 2017;317(12):1252-7.
9. Biesiekierski JR. What is gluten? J Gastroenterol Hepatol. 2017;32 Suppl 1:78-81.
10. Kupfer SS, Jabri B. Pathophysiology of celiac disease. Gastrointest Endosc Clin N Am. 2012;22(4):639-60.
11. Ludvigsson JF, Leffler DA, Bai JC, Biagi F, Fasano A, Green PH, et al. The Oslo definitions for coeliac disease and related terms. Gut. 2013;62(1):43-52.
12. McAllister BP, Williams E, Clarke K. A Comprehensive Review of Celiac Disease/Gluten-Sensitive Enteropathies. Clin Rev Allergy Immunol. 2019;57(2):226-43.
13. Schuppan D, Junker Y, Barisani D. Celiac disease: from pathogenesis to novel therapies. Gastroenterology. 2009;137(6):1912-33.
14. Barker JM, Liu E. Celiac disease: pathophysiology, clinical manifestations, and associated autoimmune conditions. Adv Pediatr. 2008;55:349-65.
15. Guandalini S, Assiri A. Celiac disease: a review. JAMA Pediatr. 2014;168(3):272-8.
16. Leonard MM, Sapone A, Catassi C, Fasano A. Celiac Disease and Nonceliac Gluten Sensitivity: A Review. Jama. 2017;318(7):647-56.
17. Husby S, Koletzko S, Korponay-Szabó I, Kurppa K, Mearin ML, Ribes-Koninckx C, et al. European Society Paediatric Gastroenterology, Hepatology and Nutrition Guidelines for Diagnosing Coeliac Disease 2020. J Pediatr Gastroenterol Nutr. 2020;70(1):141-56.

18. Marsh MN. Gluten, major histocompatibility complex, and the small intestine. A molecular and immunobiologic approach to the spectrum of gluten sensitivity ('celiac sprue'). Gastroenterology. 1992;102(1):330-54.
19. Di Sabatino A, Corazza GR. Coeliac disease. Lancet. 2009;373(9673):1480-93.
20. Olsson C, Lyon P, Hörnell A, Ivarsson A, Sydner YM. Food that makes you different: the stigma experienced by adolescents with celiac disease. Qual Health Res. 2009;19(7):976-84.
21. Lee AR, Wolf RL, Lebwohl B, Ciaccio EJ, Green PHR. Persistent Economic Burden of the Gluten Free Diet. Nutrients. 2019;11(2).
22. Black JL, Orfila C. Impact of coeliac disease on dietary habits and quality of life. J Hum Nutr Diet. 2011;24(6):582-7.
23. The World Health Organization Quality of Life assessment (WHOQOL): position paper from the World Health Organization. Soc Sci Med. 1995;41(10):1403-9.
24. Centers of Disease Control and Prevention. Measuring Healthy Days Atlanta, Georgia: CDC, November, 2000.
25. Ravens-Sieberer U, Gosch A, Abel T, Auquier P, Bellach BM, Bruil J, et al. Quality of life in children and adolescents: a European public health perspective. Soz Praventivmed. 2001;46(5):294-302.
26. Ravens-Sieberer U, Gosch A. The kidscreen questionnaires : handbook-quality of life questionnaires for children and adolescents: Lengerich : Pabst; 2006.
27. Aggarwal S, Lebwohl B, Green PH. Screening for celiac disease in average-risk and high-risk populations. Therap Adv Gastroenterol. 2012;5(1):37-47.
28. Werkstetter KJ, Korponay-Szabó IR, Popp A, Villanacci V, Salemme M, Heilig G, et al. Accuracy in Diagnosis of Celiac Disease Without Biopsies in Clinical Practice. Gastroenterology. 2017;153(4):924-35.
29. Ravens-Sieberer U, Auquier P, Erhart M, Gosch A, Rajmil L, Bruil J, et al. The KIDSCREEN-27 quality of life measure for children and adolescents: psychometric results from a cross-cultural survey in 13 European countries. Qual Life Res. 2007;16(8):1347-56.
30. Tsang S, Royse CF, Terkawi AS. Guidelines for developing, translating, and validating a questionnaire in perioperative and pain medicine. Saudi J Anaesth. 2017;11(Suppl 1):S80-s9.
31. Dimenäs E, Glise H, Hallerbäck B, Hernqvist H, Svedlund J, Wiklund I. Quality of life in patients with upper gastrointestinal symptoms. An improved evaluation of treatment regimens? Scand J Gastroenterol. 1993;28(8):681-7.
32. Dimenäs E, Glise H, Hallerbäck B, Hernqvist H, Svedlund J, Wiklund I. Well-being and gastrointestinal symptoms among patients referred to endoscopy owing to suspected duodenal ulcer. Scand J Gastroenterol. 1995;30(11):1046-52.
33. Svedlund J, Sjödin I, Dotevall G. GSRS--a clinical rating scale for gastrointestinal symptoms in patients with irritable bowel syndrome and peptic ulcer disease. Dig Dis Sci. 1988;33(2):129-34.
34. Myléus A, Petersen S, Carlsson A, Hammarroth S, Högberg L, Ivarsson A. Health-related quality of life is not impaired in children with undetected as well as diagnosed celiac disease: a large population based cross-sectional study. BMC Public Health. 2014;14:425.

35. Nordyke K, Norström F, Lindholm L, Carlsson A, Danielsson L, Emmelin M, et al. Health-related quality-of-life in children with coeliac disease, measured prior to receiving their diagnosis through screening. J Med Screen. 2011;18(4):187-92.
36. van Koppen EJ, Schweizer JJ, Csizmadia CG, Krom Y, Hylkema HB, van Geel AM, et al. Long-term health and quality-of-life consequences of mass screening for childhood celiac disease: a 10-year follow-up study. Pediatrics. 2009;123(4):e582-8.
37. Violato M, Gray A. The impact of diagnosis on health-related quality of life in people with coeliac disease: a UK population-based longitudinal perspective. BMC Gastroenterol. 2019;19(1):68.
38. Nachman F, Mauriño E, Vázquez H, Sfoggia C, Gonzalez A, Gonzalez V, et al. Quality of life in celiac disease patients: prospective analysis on the importance of clinical severity at diagnosis and the impact of treatment. Dig Liver Dis. 2009;41(1):15-25.
39. van Doorn RK, Winkler LM, Zwinderman KH, Mearin ML, Koopman HM. CDDUX: a disease-specific health-related quality-of-life questionnaire for children with celiac disease. J Pediatr Gastroenterol Nutr. 2008;47(2):147-52.
40. de Lorenzo CM, Xikota JC, Wayhs MC, Nassar SM, de Souza Pires MM. Evaluation of the quality of life of children with celiac disease and their parents: a case-control study. Qual Life Res. 2012;21(1):77-85.
41. Barrio J, Cilleruelo ML, Román E, Fernández C. Health-related quality of life in Spanish coeliac children using the generic KIDSCREEN-52 questionnaire. Eur J Pediatr. 2018;177(10):1515-22.
42. Kolsteren MM, Koopman HM, Schalekamp G, Mearin ML. Health-related quality of life in children with celiac disease. J Pediatr. 2001;138(4):593-5.
43. Byström IM, Hollén E, Fälth-Magnusson K, Johansson A. Health-related quality of life in children and adolescents with celiac disease: from the perspectives of children and parents. Gastroenterol Res Pract. 2012;2012:986475.
44. Wagner G, Berger G, Sinnreich U, Grylli V, Schober E, Huber WD, et al. Quality of life in adolescents with treated coeliac disease: influence of compliance and age at diagnosis. J Pediatr Gastroenterol Nutr. 2008;47(5):555-61.
45. Berman AH, Liu B, Ullman S, Jadbäck I, Engström K. Children's Quality of Life Based on the KIDSCREEN-27: Child Self-Report, Parent Ratings and Child-Parent Agreement in a Swedish Random Population Sample. PLoS One. 2016;11(3):e0150545.
46. Silva N, Pereira M, Otto C, Ravens-Sieberer U, Canavarro MC, Bullinger M. Do 8- to 18-year-old children/adolescents with chronic physical health conditions have worse health-related quality of life than their healthy peers? a meta-analysis of studies using the KIDSCREEN questionnaires. Qual Life Res. 2019;28(7):1725-50.
47. Murillo M, Bel J, Pérez J, Corripio R, Carreras G, Herrero X, et al. Health-related quality of life (HRQOL) and its associated factors in children with Type 1 Diabetes Mellitus (T1DM). BMC Pediatr. 2017;17(1):16.
48. Mańczak M, Rutkowska-Sak L, Raciborski F. Health-related quality of life in children with juvenile idiopathic arthritis - child's and parent's point of view. Reumatologia. 2016;54(5):243-50.
49. Michel G, Bisegger C, Fuhr DC, Abel T. Age and gender differences in health-related quality of life of children and adolescents in Europe: a multilevel analysis. Qual Life Res. 2009;18(9):1147-57.

50. Bisegger C, Cloetta B, von Rueden U, Abel T, Ravens-Sieberer U. Health-related quality of life: gender differences in childhood and adolescence. Soz Praventivmed. 2005;50(5):281-91.
51. Svedberg P, Eriksson M, Boman E. Associations between scores of psychosomatic health symptoms and health-related quality of life in children and adolescents. Health Qual Life Outcomes. 2013;11:176.
52. Robitail S, Ravens-Sieberer U, Simeoni MC, Rajmil L, Bruil J, Power M, et al. Testing the structural and cross-cultural validity of the KIDSCREEN-27 quality of life questionnaire. Qual Life Res. 2007;16(8):1335-45.

11. APPENDIX

Supplementary table 1:

Variable:		Non-CDA (n=478)[1]	CDA (n=11)[1]	P-value[2]
27item Physical international T-values based on RASCH PP		48.9 (10.4) 47.1 (25.1; 73.2) (48.0; 49.9) n=467	51.6 (13.8) 49.6 (36.6; 73.2) (42.4; 60.9) n=11	0.77
27item Psychological Wellbeing international T-values based on RASCH PP		51.5 (10.0) 50.6 (28; 73.5) (50.6; 52.4) n=468	51.8 (7.9) 53.1 (39.1; 64.4) (46.5; 57.1) n=11	0.78
27item Parents international T-values based on RASCH PP		55.8 (9.9) 53.3 (1.7; 74.4) (54.9; 56.7) n=462	58.6 (11.6) 53.3 (42.9; 74.4) (50.8; 66.4) n=11	0.51
27item Peers international T-values based on RASCH PP		51.7 (10.5) 49.8 (11.2; 66.3) (50.7; 52.7) n=462	52.4 (9.4) 46.9 (42.1; 66.3) (46.1; 58.7) n=11	0.91
27item School international T-values based on RASCH PP		55.1 (10.0) 54.4 (16.3; 71) (54.2; 56.0) n=462	60.0 (11.3) 60.5 (38.7; 71) (52.0; 68.1) n=10	0.13
[1]Continuous variables are presented as Mean (SD) / Median (Min; Max) / (95% CI for Mean) / n= is presented. [2]The Mann-Whitney U-test was used for between-group comparison				
Variable:	**Item label:**	**Non-CDA (n=478)[3]**	**CDA (n=11)[3]**	**p-value[4]**
K27PHY1	**In general, how would you say your health is?**			0.84
	Poor	11 (2.3%)	0 (0.0%)	
	Fair	37 (7.9%)	0 (0.0%)	
	Good	133 (28.3%)	5 (45.5%)	
	Very good	164 (34.9%)	3 (27.3%)	
	Excellent	125 (26.6%)	3 (27.3%)	

K27PHY2	**Have you felt fit and well?**			0.95
	Not at all	10 (2.1%)	1 (9.1%)	
	Slightly	29 (6.2%)	0 (0.0%)	
	Moderately	106 (22.6%)	3 (27.3%)	
	Very	207 (44.1%)	3 (27.3%)	
	Extremely	117 (24.9%)	4 (36.4%)	
K27PHY3	**Have you been physically active (e.g., running, climbing, biking?)**			0.94
	Not at all	35 (7.5%)	0 (0.0%)	
	Slightly	68 (14.5%)	4 (36.4%)	
	Moderately	93 (19.8%)	2 (18.2%)	
	Very	182 (38.8%)	1 (9.1%)	
	Extremely	91 (19.4%)	4 (36.4%)	
K27PHY4	**Have you been able to run well?**			0.56
	Not at all	24 (5.1%)	0 (0.0%)	
	Slightly	25 (5.4%)	1 (9.1%)	
	Moderately	99 (21.2%)	2 (18.2%)	
	Very	186 (39.8%)	4 (36.4%)	
	Extremely	133 (28.5%)	4 (36.4%)	
K27PHY5	**Have you felt full of energy?**			0.38
	Never	10 (2.1%)	0 (0.0%)	
	Seldom	38 (8.1%)	1 (9.1%)	
	Quite often	120 (25.6%)	2 (18.2%)	
	Very often	197 (42.0%)	4 (36.4%)	
	Always	104 (22.2%)	4 (36.4%)	
KY27PWB1	**Have your life been enjoyable?**			0.50
	Not at all	1 (0.2%)	0 (0.0%)	
	Slightly	15 (3.2%)	0 (0.0%)	
	Moderately	59 (12.6%)	1 (9.1%)	
	Very	207 (44.2%)	5 (45.5%)	
	Extremely	186 (39.7%)	5 (45.5%)	
KY27PWB2	**Have you been in a good mood?**			0.20
	Never	2 (0.4%)	0 (0.0%)	
	Seldom	14 (3.0%)	0 (0.0%)	
	Quite often	76 (16.2%)	1 (9.1%)	

	Very often	274 (58.5%)	6 (54.5%)	
	Always	102 (21.8%)	4 (36.4%)	
KY27PWB3	**Have you had fun?**			0.60
	Never	1 (0.2%)	0 (0.0%)	
	Seldom	12 (2.6%)	0 (0.0%)	
	Quite often	71 (15.2%)	2 (18.2%)	
	Very often	256 (54.7%)	5 (45.5%)	
	Always	128 (27.4%)	4 (36.4%)	
KY27PWB4	**Have you felt sad?**			0.69
	Always	0 (0.0%)	0 (0.0%)	
	Very often	15 (3.2%)	0 (0.0%)	
	Quite often	137 (29.3%)	5 (45.5%)	
	Seldom	186 (39.7%)	3 (27.3%)	
	Never	130 (27.8%)	3 (27.3%)	
KY27PWB5	**Have you felt so bad that you didn't want to do anything?**			0.51
	Always	2 (0.4%)	0 (0.0%)	
	Very often	20 (4.3%)	0 (0.0%)	
	Quite often	58 (12.4%)	1 (9.1%)	
	Seldom	111 (23.7%)	3 (27.3%)	
	Never	277 (59.2%)	7 (63.6%)	
KY27PWB6	**Have you felt lonely?**			0.94
	Always	2 (0.4%)	0 (0.0%)	
	Very often	12 (2.6%)	0 (0.0%)	
	Quite often	45 (9.6%)	0 (0.0%)	
	Seldom	88 (18.8%)	5 (45.5%)	
	Never	321 (68.6%)	6 (54.5%)	
KY27PWB7	**Have you been happy with the way you are?**			0.78
	Never	17 (3.6%)	1 (9.1%)	
	Seldom	17 (3.6%)	0 (0.0%)	
	Quite often	55 (11.8%)	1 (9.1%)	
	Very often	156 (33.3%)	4 (36.4%)	
	Always	223 (47.6%)	5 (45.5%)	
KY27PAR1	**Have you had enough time for yourself?**			0.43
	Never	2 (0.4%)	1 (9.1%)	

	Seldom	26 (5.6%)	0 (0.0%)	
	Quite often	54 (11.6%)	0 (0.0%)	
	Very often	201 (43.1%)	3 (27.3%)	
	Always	183 (39.3%)	7 (63.6%)	
KY27PAR2	**Have you been able to do the things that you want to do in your free time?**			0.75
	Never	4 (0.9%)	0 (0.0%)	
	Seldom	18 (3.9%)	1 (9.1%)	
	Quite often	65 (13.9%)	2 (18.2%)	
	Very often	220 (47.2%)	2 (18.2%)	
	Always	159 (34.1%)	6 (54.5%)	
KY27PAR3	**Have you parent(s) had enough time for you?**			0.79
	Never	2 (0.4%)	0 (0.0%)	
	Seldom	12 (2.6%)	0 (0.0%)	
	Quite often	59 (12.7%)	2 (18.2%)	
	Very often	207 (44.4%)	4 (36.4%)	
	Always	186 (39.9%)	5 (45.5%)	
KY27PAR4	**Have your parent(s) treated you fairly?**			0.77
	Never	2 (0.4%)	0 (0.0%)	
	Seldom	3 (0.6%)	0 (0.0%)	
	Quite often	24 (5.2%)	0 (0.0%)	
	Very often	162 (34.8%)	6 (54.5%)	
	Always	275 (59.0%)	5 (45.5%)	
KY27PAR5	**Have you been able to talk to your parent(s) when you wanted to?**			0.77
	Never	2 (0.4%)	0 (0.0%)	
	Seldom	6 (1.3%)	0 (0.0%)	
	Quite often	23 (4.9%)	0 (0.0%)	
	Very often	126 (27.0%)	4 (36.4%)	
	Always	309 (66.3%)	7 (63.6%)	
KY27PAR6	**Have you had enough money to do the same things as your friends?**			0.39
	Never	11 (2.4%)	0 (0.0%)	
	Seldom	7 (1.5%)	0 (0.0%)	
	Quite often	26 (5.6%)	1 (9.1%)	

	Very often	113 (24.5%)	1 (9.1%)	
	Always	305 (66.0%)	9 (81.8%)	
KY27PAR7	**Have you had enough money for your expenses?**			0.65
	Never	6 (1.3%)	0 (0.0%)	
	Seldom	6 (1.3%)	0 (0.0%)	
	Quite often	19 (4.1%)	1 (9.1%)	
	Very often	93 (20.1%)	1 (9.1%)	
	Always	338 (73.2%)	9 (81.8%)	
KY27SOC1	**Have you spent time with your friends?**			0.80
	Never	12 (2.6%)	0 (0.0%)	
	Seldom	21 (4.5%)	1 (9.1%)	
	Quite often	82 (17.6%)	1 (9.1%)	
	Very often	224 (48.2%)	6 (54.5%)	
	Always	126 (27.1%)	3 (27.3%)	
KY27SOC2	**Have you had fun with your friends?**			0.94
	Never	9 (1.9%)	0 (0.0%)	
	Seldom	7 (1.5%)	0 (0.0%)	
	Quite often	27 (5.8%)	0 (0.0%)	
	Very often	175 (37.8%)	7 (63.6%)	
	Always	245 (52.9%)	4 (36.4%)	
KY27SOC3	**Have you and your friends helped each other?**			0.81
	Never	9 (1.9%)	0 (0.0%)	
	Seldom	6 (1.3%)	0 (0.0%)	
	Quite often	42 (9.1%)	0 (0.0%)	
	Very often	185 (40.0%)	7 (63.6%)	
	Always	221 (47.7%)	4 (36.4%)	
KY27SOC4	**Have you been able to rely on your friends?**			0.66
	Never	12 (2.6%)	0 (0.0%)	
	Seldom	10 (2.2%)	0 (0.0%)	
	Quite often	56 (12.1%)	0 (0.0%)	
	Very often	162 (35.1%)	7 (63.6%)	
	Always	222 (48.1%)	4 (36.4%)	
KY27SCH1	**Have you been happy at school?**			0.41

	Not at all	11 (2.4%)	0 (0.0%)	
	Slightly	11 (2.4%)	1 (10.0%)	
	Moderately	64 (13.8%)	0 (0.0%)	
	Very	226 (48.8%)	4 (40.0%)	
	Extremely	151 (32.6%)	5 (50.0%)	
KY27SCH2	**Have you got on well at school?**			0.31
	Not at all	7 (1.5%)	0 (0.0%)	
	Slightly	7 (1.5%)	0 (0.0%)	
	Moderately	62 (13.4%)	1 (10.0%)	
	Very	226 (48.8%)	4 (40.0%)	
	Extremely	161 (34.8%)	5 (50.0%)	
KY27SCH3	**Have you been able to pay attention?**			0.18
	Never	7 (1.5%)	0 (0.0%)	
	Seldom	16 (3.5%)	0 (0.0%)	
	Quite often	76 (16.5%)	1 (10.0%)	
	Often	219 (47.4%)	4 (40.0%)	
	Always	144 (31.2%)	5 (50.0%)	
KY27SCH4	**[ks54] 4. Kom Du bra överens med dina lärare?**			0.47
	Never	5 (1.1%)	0 (0.0%)	
	Seldom	2 (0.4%)	0 (0.0%)	
	Quite often	32 (6.9%)	1 (10.0%)	
	Often	174 (37.6%)	2 (20.0%)	
	Always	250 (54.0%)	7 (70.0%)	
	[3] Categorical variables are presented as number (%). [4] Comparison between groups was performed using the Mantel-Haenszel Chi-Square test for ordered categorical variables			