

# Systematic Review With Meta-analysis of the Health-related Quality of Life in Children With Celiac Disease

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## ABSTRACT

**Objectives:** The aim of this article is to systematically review and meta-analyze the published data on the comparison of the health-related quality of life (HRQOL) in children and adolescents with celiac disease (CD) and healthy children. Moreover, the meta-analysis was performed to compare the parent proxy-report and child self-report of HRQOL.

**Methods:** The databases of PubMed, Embase, Scopus, and Cochrane library were searched from inception to April 2019 to identify observational studies that evaluated the HRQOL in children with CD. Studies comparing the HRQOL in celiac patients and healthy children, and also comparing the parent's proxy-report and child self-report of HRQOL were included. Comprehensive meta-analysis software was used for statistical analysis.

**Results:** Through our systematic search, 26 articles met our predefined inclusion criteria. The result of our meta-analysis on studies using the PedsQL questionnaire showed that the total score of HRQOL was not significantly different between celiac patients and healthy controls (SMD (95% confidence interval; CI):  $-0.11[-0.45 \text{ to } 0.23]$ ,  $P = 0.52$ ). The result of our meta-analysis showed that the parents reported the child's diet and communication scores lower than that of children. Only 4 out of 11 studies showed a significant correlation between HRQOL and gluten-free diet (GFD) compliance and 2 of 4 studies showed a significant negative association between HRQOL and age at diagnosis.

**Conclusions:** The results of the present study showed that there was no significant difference between children with CD and healthy controls regarding HRQOL. Moreover, the parental perception of their children's HRQOL was lower than the children's perception.

**Key Words:** adolescents, celiac disease, children, health-related quality of life

(JPGN 2020;70: 468–477)

Received October 1, 2019; accepted December 15, 2019.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site ([www.jpgn.org](http://www.jpgn.org)).

This study was funded by Research Center for Evidence Based Medicine (RCEBM), Tabriz University of Medical Sciences, Tabriz, Iran.

Ethical approval: This article does not contain any studies with human participants or animals performed by any of the authors.

The authors report no conflicts of interest.

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DOI: 10.1097/MPG.0000000000002604

## What Is Known

- Different studies evaluated the quality of life in children with celiac disease and compared it with that of healthy children.
- There is no systematic review and meta-analysis to summarize the quality of life data in children.

## What Is New

- The total score of health-related quality of life was not significantly different between celiac patients and healthy controls.
- The parents reported the child's diet and communication scores lower than that of children.
- Only 4 out of 11 studies showed a significant correlation between quality of life and gluten-free diet compliance.
- Two of the 4 studies showed a significant negative association between quality of life and age at diagnosis.

Celiac disease (CD) is an autoimmune, lifelong enteropathy caused by the ingestion of cereals containing gluten protein, such as wheat, barley, and rye in genetically predisposed individuals (1). Its prevalence is up to 1% (2) and is associated with various clinical presentations including malabsorption, steatorrhea, weight loss, or growth failure (1). At present, the only treatment for celiac disease is strict compliance to the gluten-free diet (exclusion of wheat, rye and barley, and other gluten-containing food products from the diet) for life (3). In this diet, all sources of gluten (apparent and hidden) should be avoided, which resulted in the disappearance of the symptoms and improvement of nutritional status (3). Due to several limitations of the gluten-free diet, strict compliance to diet is challenging and could affect the patient's quality of life. Improvement in health-related quality of life (HRQOL) is considered to be an essential primary outcome and determinant of therapeutic benefit in chronic diseases like celiac disease (4).

HRQOL measures both physical and mental health. Different general and disease-specific questionnaires were developed and validated in this regard and numerous studies investigated the HRQOL in children and adults. A recent meta-analysis in adult celiac patients concluded that compliance with the gluten-free diet partially improves the HRQOL in this population (5). Different studies compared the HRQOL status of celiac children with that of healthy ones. Although some studies reported the same HRQOL score in celiac children and healthy population (6–9), others showed significantly lower HRQOL in children with CD (10–14). Moreover, some studies compared the report of children and parent proxy-report and

providing mixed results. In some studies, parent reports are found to be similar to child reports (15,16), however, it is far different from children's reports in other studies (17,18). To the best of our knowledge, there has been not any systematic review and meta-analysis to summarize these studies. Thus, in the present study, we systematically reviewed the studies assessing the HRQOL in children with celiac disease. Additionally, the meta-analysis was performed for the following outcomes: comparison of the HRQOL between children with celiac disease and healthy controls; comparison of the parent proxy report with child self-report.

## METHODS

The Preferred Reporting Items for Systematic review and Meta-analysis (PRISMA) was used for reporting of this systematic review and meta-analysis.

### Search Strategy

We searched databases of PubMed, Embase, Scopus, and Cochrane library from inception to April 2019. The following keywords were selected based on population (P) and outcomes (O): ("Celiac disease" OR "coeliac disease" OR "celiac sprue" OR "gluten-sensitive enteropathy") AND ("Health-related quality of life" OR "life quality"). The detail of the search strategy is presented in Supplemental Table S1 (Supplemental Digital Content, <http://links.lww.com/MPG/B765>). Manual citation searching was used to identify additional relevant sources.

The duplicate data were excluded by 1 reviewer (Z.N.). Then 2 reviewers (Z.N. and L.N.) independently screened the remaining records according to study aim, population, outcomes, and inclusion/exclusion criteria. Full papers were obtained for these records and were assessed for relevance independently by 2 reviewers (L.N. and Z.N.). Any discrepancies were resolved through discussion and by consulting a third reviewer (M.A.F.). Studies were included if they evaluated the HRQOL with a valid questionnaire in CD children and adolescents (ages <18 years). Interventional studies and studies published only in abstract form were excluded. There was no restriction on languages and publication date.

### Assessment of Risk of Bias

Two investigators (Z.N. and M.A.F.) independently rated the methodological quality of selected studies using HRQOL assessment tool adapted for celiac disease (5). The following domains were assessed: HRQOL assessment, study population, study design, and results. This tool has 15 questions and if the criterion met, 1 point was allocated for each question. If a study scored more than 80% of the total score, it was considered of high quality. Studies scoring 60% to 80% of the total score were considered to be moderate quality and studies scoring lower than 60% were considered as low quality (5).

### Data Extraction

The following information was extracted independently by 2 authors (Z.N. and L.N.) using an extraction table: the surname of the first author and publication date, country, demographic information, HRQOL assessment tool, sample size, and outcomes. Any discrepancies were resolved through discussion and by consulting a third reviewer (M.A.F.).

### Statistical Analysis

The comprehensive meta-analysis (CMA) software version 2.0 (19) was used for statistical analysis. The studies compared the

HRQOL of celiac patients and healthy controls and also compared the parent's and children's perspectives about HRQOL of children were selected for meta-analysis. For each study, the mean and standard deviation of HRQOL, *P*-value, and sample size were extracted and entered into the software's effect size data entry (comparison of the mean of 2 unmatched groups). The pooled results were expressed as the standard mean difference (SMD) with 95% confidence intervals (CI) and the effect size was calculated. In the forest plot, an SMD greater than 0 indicates a higher score of quality of life. Cochran *Q* and *I*<sup>2</sup> tests were used to identify between-study heterogeneity; *I*<sup>2</sup> < 25%, no heterogeneity; *I*<sup>2</sup> = 25–50%, moderate heterogeneity; *I*<sup>2</sup> > 50% large heterogeneity. The random-effects model or fixed-effects model was performed for meta-analysis based on the heterogeneity results. The random-effect model was used if either *I*<sup>2</sup> > 50% and the Cochran *Q* statistic *P* value of <0.10 (20). The publication bias was tested according to Egger's regression (21).

## RESULTS

Through our systematic search, 26 articles (6–18,22–34) met our predefined inclusion criteria. Figure 1 depicts detailed information for study selection. All studies were full peer-reviewed publications and all had cross-sectional design except 1 that conducted prospectively (14). Ten studies used the CD-specific questionnaires including CDDUX and CDQOL (15,18,24–27,29,31,32,34), others used valid general health-related quality of questionnaires including PedsQL (6,7,12,13,16,23,30), KINDL (14,22), TNO-AZL (8,9), Dux-25 (32), SF-12 (10), and AUQEI (11). The definitions of questionnaires are provided in Table 1.

The results of the risk of bias assessment are presented in Supplemental Table S2 (Supplemental Digital Content, <http://links.lww.com/MPG/B765>). The methodological quality of studies varied; in 9 studies the methodological quality was high, in 10 studies, it was medium, and 7 studies had low methodological quality. Only 30.7% of studies reported the presence or absence of comorbidities. Duration on gluten-free diet (GFD) and the rate of adherence to GFD were reported in only 34.6% and 42% of studies, respectively.

### Participant

Twenty-six studies included in this review represent 2774 children and adolescents with celiac disease. Sample sizes ranged from 22 to 510. Seventeen studies conducted in both children and adolescents (6,7,9,12,14,15,17,18,22–27,29–31), 4 studies in only adolescents (ages 12–18 years) (28,32–34) and 5 on only children (ages <12 years) (8,10,11,13,16).

### Outcomes

Nine studies used the CDDUX questionnaire (15,18,24–27,29,31,32). One study reported the unstandardized score (24) and 1 did not report the total CDDUX score (32). According to a previous study, the quality of life by CDDUX questionnaire is categorized as very poor (score 1–20), poor (score 21–40), neutral (score 41–60), good (score 61–80), or very good (score 81–100) (15). The standardized total score of HRQOL was reported in the range of 30.20 and 67.12. The meta-analysis of 6 studies revealed that the mean score of HRQOL using CDDUX was 58.81 (49.62–51.49).

Eight studies used the PedsQL questionnaire (6,7,12,13,16,23,26,30). In this questionnaire, a score of 100 represents the best possible quality of life, a score of 0 the worst (35). The mean and standard deviation of HRQOL total score was reported in 5

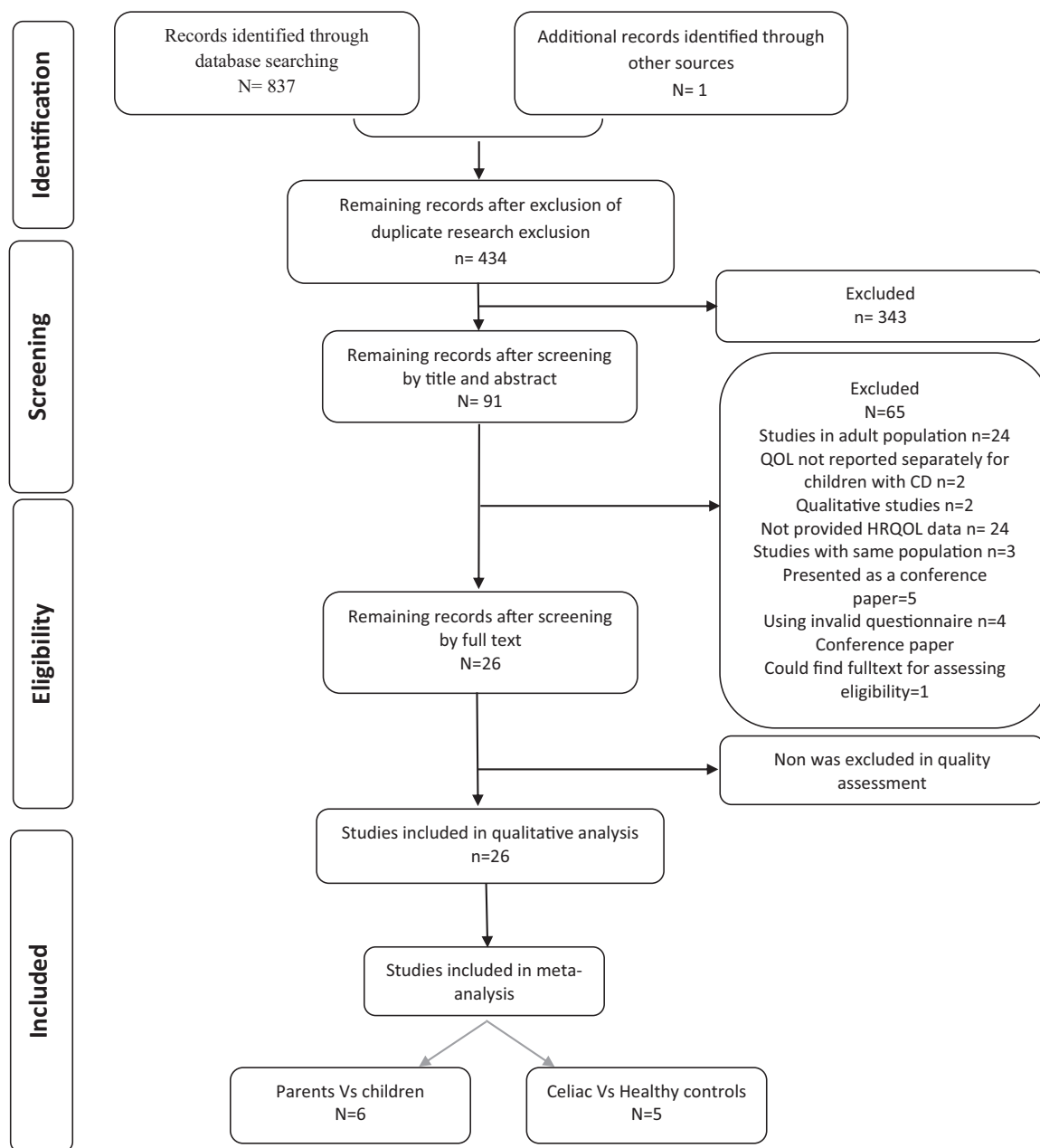


FIGURE 1. Flow diagram of studies for inclusion in the systematic review.

studies (7,12,16,26,30). The meta-analysis of these studies showed that the HRQOL score was 77.29 (95% CI: 73.47–81.11).

### Patients on Gluten-free Diet Versus a Control Population

Ten studies compared the HRQOL in CD patients and nonceliac control (6–8,11–14,23,28,33). One study used the KINDL questionnaire and showed that HRQOL was significantly lower in celiac patients (14). de Lorenzo et al (11) used the AUQUEI questionnaire and showed that there were no significant differences in HRQOL between celiac patients and healthy

children. Wagner et al (33) compared the HRQOL in healthy controls and CD patients with different compliance status using the ILC questionnaire and reported no significant differences between groups regarding the global rating of this questionnaire. Grootenhuis et al compared the HRQOL in celiac patients and healthy control using the TNO-AZL questionnaire and showed that the social functioning score was significantly lower in celiac patients (8). Myleus et al (28) in a large population-based study showed similar HRQOL in celiac children and nonceliac controls.

Five studies used the PedsQL questionnaire to compare the HRQOL in CD children and healthy controls (6,7,12,13,23). Kara et al (23) reported the results of children and adolescents independently and these data were entered into the meta-analysis separately

TABLE 1. Definitions of health-related quality-of-life questionnaires used in children and adolescents

| Questionnaires       | Definitions                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|----------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| CDDUX                | A celiac disease-specific questionnaire consisting 12 questions and include 3 subscales namely ‘diet,’ ‘communication,’ and ‘having CD’                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| PedsQL               | The PedsQL questionnaire include 23 questions to measuring health-related quality of life (HRQOL) in healthy children and adolescents and those with acute and chronic health conditions. It designed to measure physical functioning (8 items), emotional functioning (5 items), social functioning (5 items), and school functioning (5 items). It is mostly reported as physical health score (8 items) and psychological health score (15 items).                                                                                                                                                                                                                                                      |
| KINDL                | The KINDL is a generic instrument for assessing Health-Related Quality of Life in children and adolescents between 3 and 17 years of age. It provides 24 items.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| AUQUEI               | A pictured child’s quality-of-life self-questionnaire was developed to assess the child’s subjective quality of life. It is 26 items for 3 to 5 years old children, and 33 items for 6 to 11 years old children.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| SF-12                | It is the short form of SF-36 questionnaire and measures physical functioning, role emotion, role physical, body pain, general health, vitality, social functioning, and mental health. It mostly reported as physical composite score and mental composite score                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| TACQOL               | TNO-AZL has a questionnaire to measure quality of life in children (TACQOL). This generic questionnaire has parents form and child form. This questionnaire measuring general aspects of health-related quality of life in 7 scales including physical complaints and motor functioning (physical), autonomous functioning (daily living), social functioning (social), cognitive functioning, and positive moods and negative moods (psychological functioning)                                                                                                                                                                                                                                           |
| CDQOL                | A disease-specific questionnaire consisting of 20 items across 4 clinically relevant subscales (CD-related limitations, dysphoria, health concerns, and inadequate treatment) was used to assess QOL issues specific to CD                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Disabkids-short form | The short-form of the DISABKIDS condition generic module was derived from its parental version. It has the self-report version (child version) and a proxy version (parents’ version). It consists of 12 Likert-scaled items assigned to the 3 domains of the parental version: mental, social, and physical. The items can be combined to produce a total score.                                                                                                                                                                                                                                                                                                                                          |
| KIDSCREEN-52         | The KIDSCREEN instruments a generic 52-item questionnaire that assess children’s and adolescents’ subjective health and well-being. They were developed as self-report measures applicable for healthy and chronically ill children and adolescents aged from 8 to 18 years. It has child and adolescent as well as parent/proxy versions and assess 10 HRQoL dimensions: Physical Wellbeing (5 items), Psychological Wellbeing (6 items), Moods and Emotions (7 items), Self-Perception (5 items), Autonomy (5 items), Parent Relations and Home Life (6 items), Social Support and Peers (6 items), School Environment (6 items), Social Acceptance (Bullying) (3 items), Financial Resources (3 items). |
| ILC                  | Inventory of Life Quality in Children and Adolescents (ILC) is a questionnaire measuring health-related quality of life in not only in children and adolescents (ages 6–18 years) with mental and somatic disorders but also in healthy subjects. The questionnaire exists in a parent and child version and consists of 7 items (9 for patients) rated on a 1 to 5 scale.                                                                                                                                                                                                                                                                                                                                 |

AUQUEI = autoquestionnaire qualité de vie enfant image; CDDUX = celiac disease DUX; CDQOL = celiac disease quality of life; Disabkids-short form = disability kids-short form; ILC = inventory of life quality in children and adolescents; KIDSCREEN = kid screen questionnaire; PedsQL = pediatric quality of life inventory; SF-12 = short-form 12-item health survey; TACQOL = TNO-AZL children’s quality of life questionnaire.

for children and adolescents. According to the Egger’s test (21), no publication bias was observed (Egger test  $P$ -value = 0.76). Considering the presence of heterogeneity ( $I^2 = 71.80$ ,  $P = 0.03$ ), the random effect model was used. The results of the meta-analysis showed that the total score of HRQOL was not significantly different between celiac patients than healthy controls (SMD [95% CI]:  $-0.11$  [ $-0.45$  to  $0.23$ ],  $P = 0.52$ ) (Fig. 2A). Moreover, meta-analyzing of the HRQOL subscores also revealed that there were no significant differences between celiac patients and healthy controls regarding physical (Fig. 2B) and psychological health subscores (Fig. 2C).

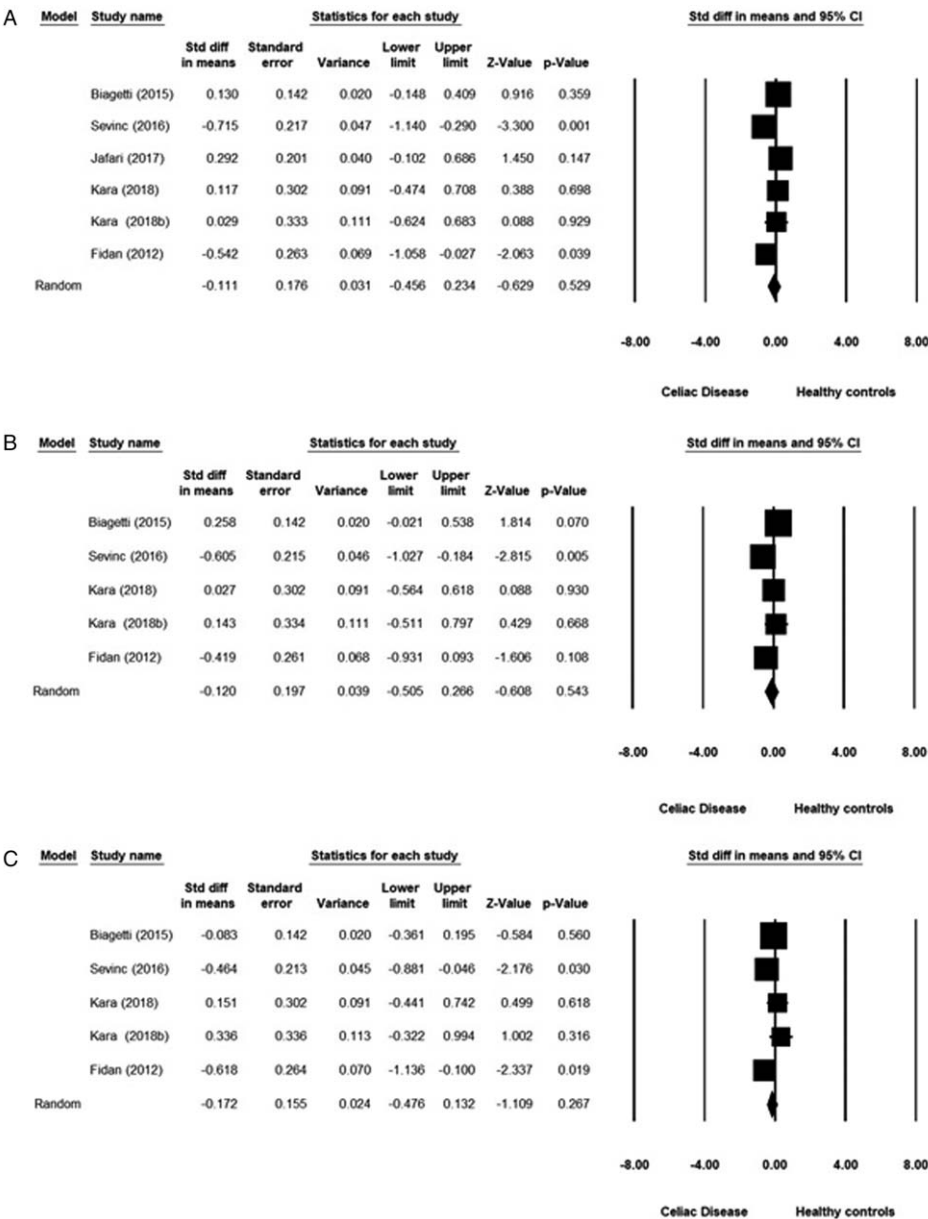
Six studies compared the HRQOL in CD children and the general population (9,10,18,26,30,32). Altobelli et al (10) compared the HRQOL in celiac patients and the general population of Italy using the SF-12 questionnaire and showed that the mental health domain score was significantly lower in children with celiac disease. In a study in The Netherlands, Kolsteren et al showed that the DUCATQOL questionnaire scores was similar in celiac children and a healthy population. However, in the adolescent group, the mean scores of emotional, physical, and home domains were significantly lower in celiac patients compared with healthy controls (9). Mager et al (26) showed comparable HRQOL between CD children and healthy norms. In another study in The Netherlands, van Doorn reported that score of all domains of DUX-25 questionnaire was lower in celiac children compared with a healthy reference group (18). van Koopen et al (32) showed that the HRQOL of

children with symptoms at diagnosis was lower than that of the reference population, however, that of symptom-free children (after 1 year of GDF) was comparable with that of the general population. Shull et al compared the HRQOL in newly diagnosed celiac patients (were not on GFD) and general healthy population [the data were obtained from a previous population-based study (36)] and showed significant differences in total score and physical and psychological health subscores between the 2 groups (30).

Two studies compared the HRQOL in patients with celiac disease and controls with other gastrointestinal (GI) problems and showed no significant differences between the 2 groups (26,30).

## Comparison of the Parents and Children Reports

Twelve studies compared the HRQOL score of parent proxy-report and child self-report (15–18,24–27,29–32). One study used the Disabkids questionnaire (17) and showed that parents reported the HRQOL of children significantly lower than what the children feel. Three studies used PedsQL (16,26,30) questionnaires and reported no significant difference between the report of the parents and children. In 8 studies, the HRQOL was assessed using the CDDUX questionnaire (15,18,24,25,27,29,31,32). In 1 study, the CDDUX total score and having CD subscore were not reported (32), and 1 study reported the unstandardized values (24). According to the Egger test (21), no publication bias was observed (Egger test  $P$ -value 0.37). The results



**FIGURE 2.** Forest plot for comparison of health-related quality of life between celiac patients and healthy controls. (A) PedsQLtotal score, (B) physical subscore; (C) psychological subscore.

of meta-analysis showed that parents reported the child total score (SMD [95% CI]: 5.68 [2.66–8.70, 0.07],  $P < 0.001$ ), diet score (SMD [95% CI]: 2.69 [1.17–4.20],  $P < 0.001$ ), and communication scores (SMD [95% CI]: 8.55 [0.42–16.65],  $P = 0.03$ ) significantly lower than that of children (Fig. 3).

Subgroup Analysis: Gluten-free Compliance

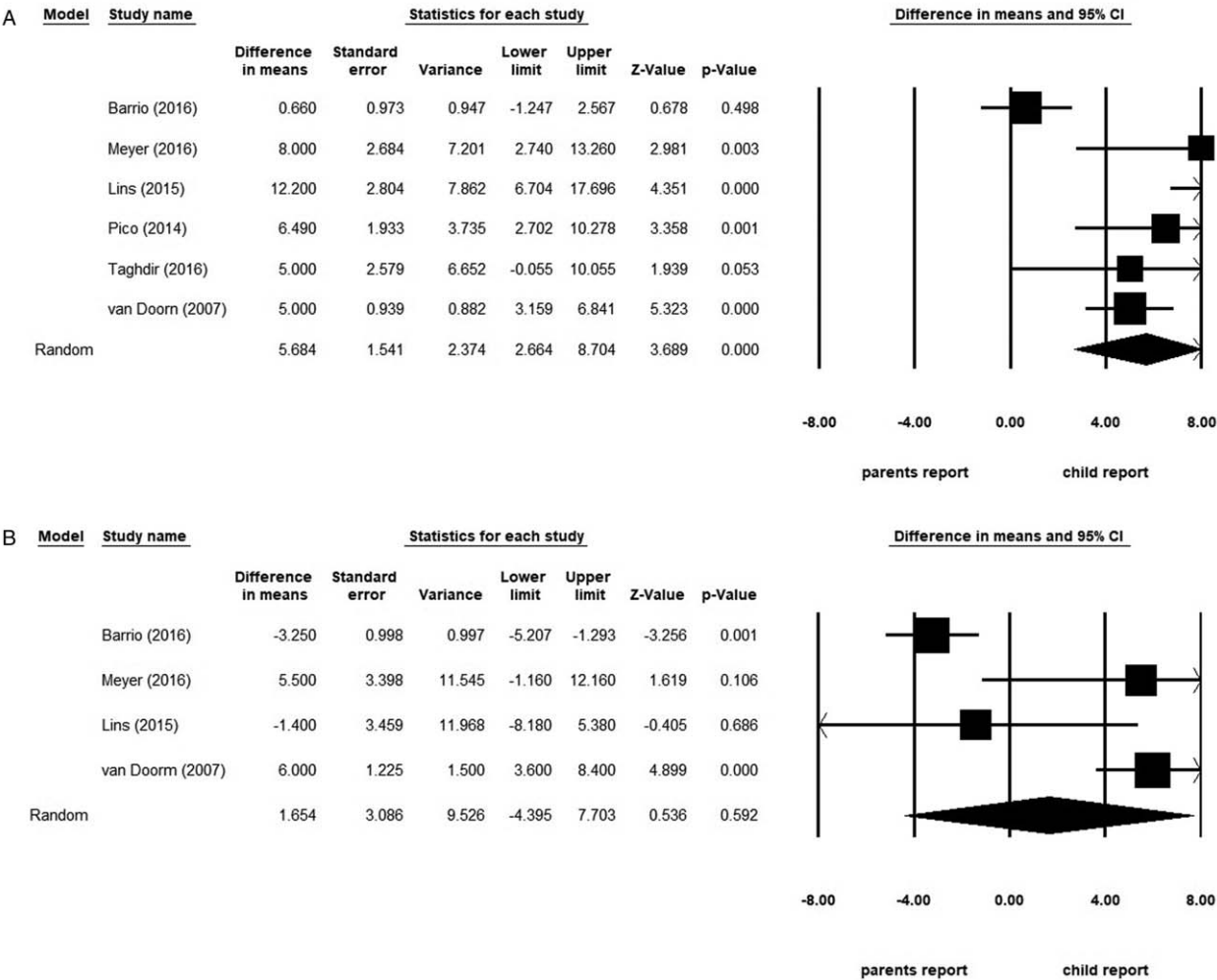
Eleven studies (7,10,11,13–15,24,26,31,33,34) assessed the effect of GFD compliance on HRQOL in children and adolescence. However, various questionnaires were used in this regard. Thus, the meta-analysis could not be done on these data. Out of 11 studies, only 4 showed a significant correlation between HRQOL and GFD compliance (Table 2).

Subgroup Analysis: Age at Diagnosis

Six studies (6,10,11,15,17,33) assessed the association between age at diagnosis and HRQOL in children and adolescents and 3 of them showed a significant negative association. Considering that various questionnaires were used for evaluating HRQOL, the meta-analysis could not be done on these data.

DISCUSSION

In the present study, we systematically reviewed and meta-analyzed the HRQOL in celiac patients and compared it with that of healthy controls. Moreover, we compared the perspectives of the parents and children about HRQOL. Twenty-six studies were



**FIGURE 3.** Forest plot for comparison of the parents and child report regarding health-related quality of life of celiac children. (A) CDDUX total score, (B) celiac disease score, (C) diet sub score; and (D) communication.

selected for this systematic review that constitutes 2774 children with celiac patients.

According to the results of meta-analysis, the mean HRQOL score was at a neutral level in studies that used the CDDUX and at a good level in studies that used the PedsQL. Moreover, HRQOL was not significantly different between celiac patients and healthy controls. Considering that in the most included studies, the patients were on GFD, it is expected that the patients had a good quality of life. By adherence to the GFD diet, the mucosal healing and the absorption of micronutrients are improved. All included studies in this meta-analysis used the PedsQL questionnaire, which is not a disease-specific questionnaire and makes it possible to compare the results with healthy controls. Previously, Burger et al (5) meta-analyzed the studies comparing HRQOL in adult celiac patients and nonceliac controls. The result showed that there was no significant difference between the 2 groups when the meta-analysis conducted on studies used the PGWB questionnaire for evaluating HRQOL. However, the result of meta-analysis on studies used SF-36 questionnaire showed significant differences between the 2 groups in terms of physical and mental scores. So, it seems that using different HRQOL assessment tools may affect the results of the study.

In addition, we showed that the parents evaluated the child's diet and communication scores lower than children did. This finding is consistent with the result of a previous study in children with celiac disease and type 1 diabetes; Sud et al (37) reported a lower score for the parental perception of psychosocial life compared with children report. Moreover, studies in other childhood chronic diseases also have found that parents rate their child's QOL lower than the child does (38–40). This may be because of the parental anxiety that could result in a lower parent-report of HRQOL compared with the child report. Parental anxiety may stem from the knowledge that children with celiac may face many challenges in different fields including psychiatric, school performance, socioeconomic status, and marital status (41). Parents are aware of the behavioral, emotional, and cognitive difficulties faced by their children. In addition, the disability paradox may be another explanation for this finding. Unlike what the children reported, adults think that a child with a chronic disease is unsatisfied with his/her life. So they underestimated their quality of life (41). One more explanation for this finding could be the overestimation of the HRQOL by children because of this fact that the children were accustomed to the symptoms of the CD (42), which may be observed by the parents. Thus, as suggested by previous systematic

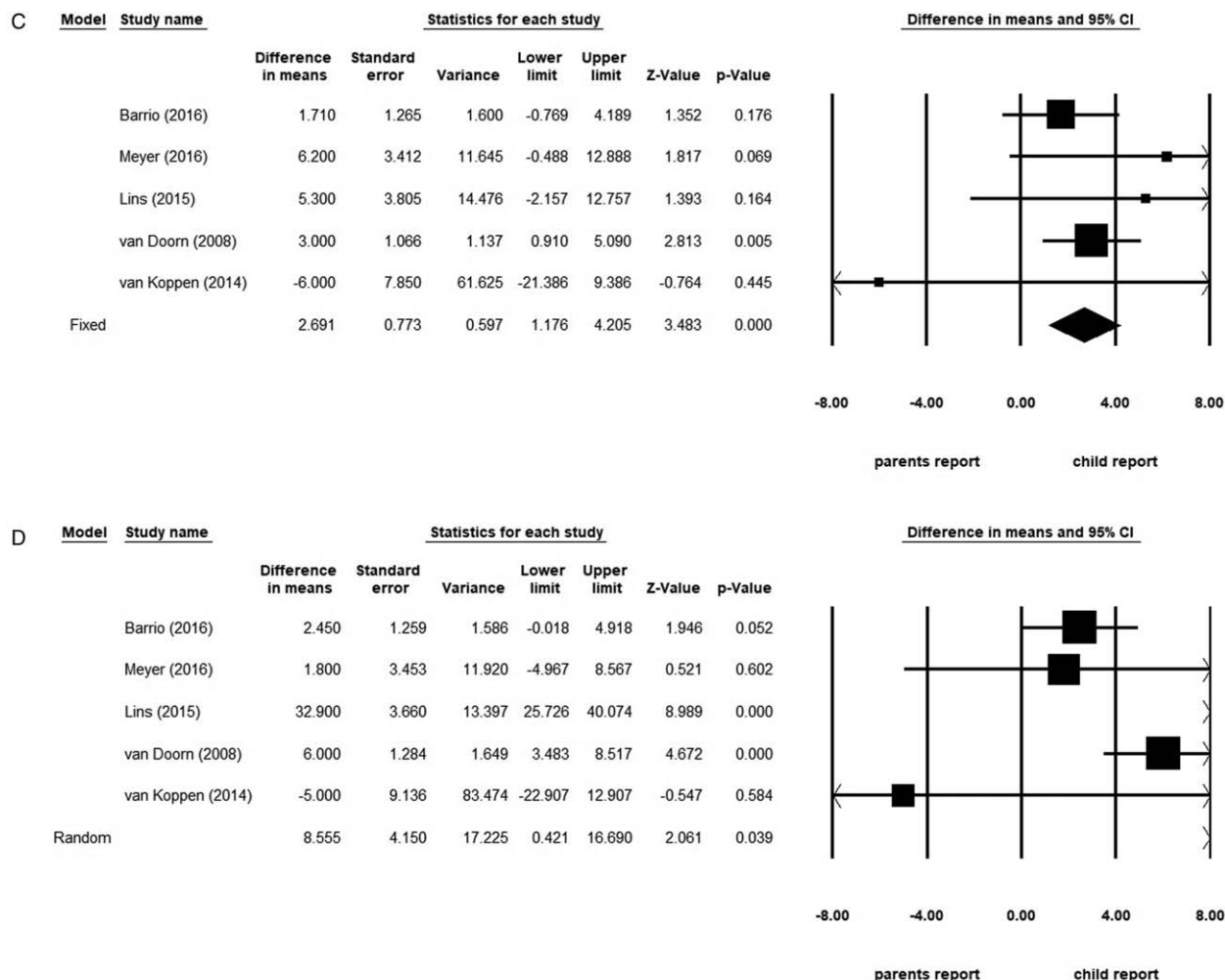


FIGURE 3. Continued.

review in this regard, it is better to acquire relevant information from both parents and children (43).

We also investigated other factors that may affect the quality of life in children with CD, such as age at diagnosis and compliance with the gluten-free diet. Because of the lack of studies, however, the meta-analysis could not be done. Contrary to expectations, only 4 out of 11 studies showed a significant correlation between HRQOL and GFD compliance. This finding is in contrast to the finding of systematic review and meta-analysis conducted on the adult population (5).

Burger et al (5) reported the positive effect of GFD on HRQOL in adult celiac patients. This discrepancy may be because of using various kinds of HRQOL questionnaires. Only 4 out of 11 studies that assessed the compliance effect, used a disease-specific questionnaire and the only 1 showed the significant association between HRQOL and level of adherence to the GFD. Moreover, in terms of the age at diagnosis, 3 of 6 studies showed that the earlier the patients are diagnosed, the higher the HRQOL. However, only 1 of the included studies used a disease-specific questionnaire (15).

The limitations of the present systematic review and meta-analysis were the presence of publication bias and exclusion of studies that had not complete data on HRQOL. In addition, the

limited number of studies included in the meta-analysis may affect the power of meta-analysis. We only included studies that used valid disease-specific or general pediatrics questionnaires. Moreover, we observed high heterogeneity between studies in some meta-analysis that was partly explained by differences in sample size and the age of patients (children vs adolescents). we, however, assessed the quality of life in celiac patients that is the clinically important subject in celiac patients. Also, we have a comprehensive search strategy and the risk of subjective data selection was low.

## CONCLUSIONS

In conclusion, the results of the present study showed that children with celiac disease perceived their HRQOL similar to that of healthy controls. In addition, we showed that in celiac patients, the children's perspectives may differ from those of parents. So, from the research and clinical point of view, both parent's and children's perspectives should be considered for assessing HRQOL. Considering the limitations of some studies and also the availability of CD-specific HRQOL questionnaires, future studies in this regard should use disease-specific questionnaires and also consider the comorbidities and also duration and compliance to GFD.

TABLE 2. Characteristics of included studies

| Author (date)         | Country         | Sample size               | Age range | HRQOL assessment tool | Results                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Conclusion                                                                                                                                                                          |
|-----------------------|-----------------|---------------------------|-----------|-----------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Atobelli E (2013)     | Italy           | Case: 140                 | 10–13     | SF-12                 | PCS score (mean $\pm$ SD):<br>Sample: $54.11 \pm 5.07$<br>Italian average: $54.90 \pm 4.69$<br>MCS score<br>Sample: $45.45 \pm 10.01$<br>Italian average: $54.05 \pm 7.89$                                                                                                                                                                                                                                                                                                                                                    | HRQOL was lower in celiac patients compared with general population of Italy                                                                                                        |
| Alzaben A (2015)      | Canada          | Case: 32                  | 4–18      | Kindl                 | Percent of positive responses to QOL questions:<br>Accepting GFD: 52%<br>GI symptomology after GFD: 71%<br>Adherence to GFD: 77%<br>Embarrassed about asking about GF foods: 81%<br>Give up activities because of diseases: 94%<br>Feeling different from others because of CD: 61%                                                                                                                                                                                                                                           | Fifty-two percentage of patients accepted the gluten-free diet, 94% reported giving up some activities because of having CD and 81 reported being embarrassed about asking GF foods |
| Barrio J (2016)       | Spain           | Case: 266<br>Parent: 428  | 8–18      | CDDUX                 | QOL total score (mean $\pm$ SD)<br>Children: $55.48 \pm 12.72$<br>Parents: $54.82 \pm 12.30$                                                                                                                                                                                                                                                                                                                                                                                                                                  | Both parents and children reported that the celiac disease had no effect on HRQOL                                                                                                   |
| Biagetti C (2015)     | Italy           | Case: 76<br>HC: 143       | 2–18      | PEDSQL                | QOL total score (median [95% CI]):<br>CD group: 84.1 (81.1–87.2)<br>Control: 81.5 (79.7–83.4)                                                                                                                                                                                                                                                                                                                                                                                                                                 | HRQOL was not significantly different in case compared with controls                                                                                                                |
| Bystrom I (2012)      | Sweden          | Case: 156<br>Parents: 156 | 8–18      | Disabkids-short form  | QOL total score (median [95% CI]):<br>CD children: 92 (85.5–96)                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Parents reported the child HRQOL lower than the children themselves did                                                                                                             |
| de Lorenzo (2012)     | Brazil          | Case: 33                  | 4–12      | AUQUEI                | QOL total score (mean $\pm$ SD)<br>CD: $53.48 \pm 6.38$<br>controls: $56.11 \pm 7.38$                                                                                                                                                                                                                                                                                                                                                                                                                                         | HRQOL of celiac children was impaired                                                                                                                                               |
| Fiden T (2013)        | Turkey          | Case: 30<br>HC: 30        | 7–18      | PEDSQL                | QOL Total score (mean $\pm$ SD)<br>CD: $69.10 \pm 17.10$<br>controls: $77.3 \pm 12.9$                                                                                                                                                                                                                                                                                                                                                                                                                                         | There was not significant difference in HRQOL between celiac patients and healthy controls                                                                                          |
| Grootenhuis MA (2007) | The Netherlands | Case: 104<br>HC: 913      | 8–11      | TACQOL                | QOL scores (mean [95% CI]):<br>CD: physical: 25 (24–25.9); Social: 28.7 (28–29.3); motor functioning: 29.3 (28.9–30); autonomy: 31.1 (30.7–31.5); cognitive functioning: 27.3 (26.4–28.3); positive emotions: 13.2 (12.6–13.7); negative emotions: 11.3 (10.7–11.8)<br>Healthy controls: physical: 25.2 (24.9–25.6); social: 29.8 (29.6–30); motor functioning: 30 (29.8–30.2); autonomy: 31.3 (31.2–31.4); cognitive functioning: 28.5 (28.3–28.7); positive emotions: 13.6 (13.4–13.8); negative emotions: 11.7 (11.6–11.9) | HRQOL celiac children was the same as healthy population                                                                                                                            |
| Jafari A (2017)       | Iran            | Case: 50<br>HC: 50        | 7–16      | PEDSQL                | QOL total score (mean $\pm$ SD)<br>CD: $76.8 \pm 13.6$<br>controls: $80.5 \pm 11.3$                                                                                                                                                                                                                                                                                                                                                                                                                                           | There was not significant difference in HRQOL between celiac patients and healthy controls                                                                                          |
| Kara A (2018)         | Turkey          | Case: 40                  | 8–18      | PEDSQL                | QOL total score (median [IQR])<br>CD (children): 80.97 (73.91–89.4)<br>Controls (children): 80.97 (73.91–89.4)<br>CD (adolescents): 80.97 (72.01–87.22)<br>Controls (adolescents): 79.34 (74.72–87.5)                                                                                                                                                                                                                                                                                                                         | Celiac disease significantly affected children and adolescents                                                                                                                      |
| Khurana B (2015)      | India           | Case: 27                  | 5–18      | CDDUX                 | QOL scores: (mean $\pm$ SD)<br>Communication:<br>Compliant: $2.91 \pm 0.66$<br>Noncompliant: $2.51 \pm 0.45$<br>Diet: $2.95 \pm 0.52$<br>Compliant: $2.95 \pm 0.52$<br>Noncompliant: $2.51 \pm 0.33$<br><br>Having CD: $3.21 \pm 0.61$<br>Compliant: $3.21 \pm 0.61$<br>Noncompliant: $2.75 \pm 0.35$                                                                                                                                                                                                                         | There was not statistical association between HRQOL and compliance to GFD                                                                                                           |

| Author (date)       | Country         | Sample size                   | Age range | HRQOL assessment tool                            | Results                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Conclusion                                                                                                                                  |
|---------------------|-----------------|-------------------------------|-----------|--------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| Kolsteren M (2001)  | The Netherlands | Case: 92<br>Parents: 92       | 8–16      | TACQOL                                           | QOL scores: (mean $\pm$ SD)<br>Children:<br>CD: emotional: $83 \pm 14.1$ ; physical: $73 \pm 14.3$ ; social: $75 \pm 12.1$ ;<br>home: $71 \pm 7.5$<br>Reference sample: emotional: $86 \pm 13.2$ ; physical: $79 \pm 10.6$ ; social: $83 \pm 10.4$ ; home: $76 \pm 8.3$<br>adolescents:<br>CD: emotional: $68 \pm 12$ ; physical: $68 \pm 14.9$ ; social: $71 \pm 9.3$ ;<br>home: $82 \pm 11.6$<br>Reference sample: emotional: $75 \pm 9.6$ ; physical: $78 \pm 10.6$ ; social: $76 \pm 9.2$ ; home: $93 \pm 9.6$ | HRQOL of celiac children was the same as general population/children reported lower HRQOL compared with parents report                      |
| Lins M (2015)       | Brazil          | Case: 33<br>Parents: 33       | 8–18      | CDDUX                                            | QOL total score (mean $\pm$ SD):<br>CD: $57.6 \pm 12.3$<br>Parents: $45.4 \pm 10.4$                                                                                                                                                                                                                                                                                                                                                                                                                                | Significant difference was found between the score of children and their parents'                                                           |
| Mager D (2018)      | Canada          | Case: 243<br>Parents: 148     | 3–18      | PEDSQL                                           | QOL total score (mean $\pm$ SD)<br>CD: $82.3 \pm 11.5$<br>Parents: $80.8 \pm 13.5$<br>GI controls: $72.6 \pm 13.9$                                                                                                                                                                                                                                                                                                                                                                                                 | Parents and children with celiac had higher HRQOL compared with general population                                                          |
| Meyer S (2016)      | Israel          | Case: 34<br>Parents: 34       | 8–15      | CDDUX                                            | QOL total score (mean $\pm$ SD)<br>Children: $62.6 \pm 12.8$<br>Parents: $57.6 \pm 9$                                                                                                                                                                                                                                                                                                                                                                                                                              | It is better to acquire relevant information from both parents and children                                                                 |
| Myleus A (2014)     | Sweden          | Case: 90<br>Without CD: 12037 | 12        | KIDSCREEN-52                                     | QOL total score (mean $\pm$ SD)<br>CD: $82.2 \pm 12.2$<br>controls: $82.5 \pm 11.3$                                                                                                                                                                                                                                                                                                                                                                                                                                | Children with CD reported similar HRQOL as children without CD                                                                              |
| Pico M (2014)       | Germany         | 102                           | 8–18      | CDDUX                                            | QOL total score (mean $\pm$ SD)<br>Children: $67.12 \pm 14$<br>Parents: $60.63 \pm 13.6$                                                                                                                                                                                                                                                                                                                                                                                                                           | Children reported their HRQOL status better than what their parents perceived                                                               |
| Sevinc E (2016)     | Turkey          | Case: 52<br>HC: 40            | 8–12      | PEDSQL                                           | QOL total score (median [min–max])<br>CD: $87.5 (44.56–100)$<br>controls: $92.30 (84.78–100)$                                                                                                                                                                                                                                                                                                                                                                                                                      | Celiac disease was associated with decreased HRQOL                                                                                          |
| Shull M (2019)      | USA             | 159                           | 2–18      | PEDSQL                                           | QOL total score (mean $\pm$ SD):<br>CD: $76.32 \pm 17$<br>Parents: $75.88 \pm 14.5$<br>Healthy sample: $82.70 \pm 15.4$<br>Non-CD GI: $72.74 \pm 14.8$                                                                                                                                                                                                                                                                                                                                                             | Newly diagnosed children with CD had lower HRQOL score compared with healthy children and similar to that of children with other GI problem |
| Simsek S (2015)     | Turkey          | Case: 25<br>HC: 25            | 9–16      | KINDL                                            | QOL total score (mean $\pm$ SD)<br>CD: $86.0 \pm 12.9$<br>Controls: $94.16 \pm 10.2$                                                                                                                                                                                                                                                                                                                                                                                                                               | HRQOL was significantly lower in celiac patients compared with healthy controls                                                             |
| Stojanovic B (2019) | Serbia          | Case: 116<br>Parents: 116     | 2–12      | PEDSQL                                           | QOL total score (mean $\pm$ SD):<br>CD: $75.89 \pm 20.35$<br>Parents: $74.81 \pm 20.53$                                                                                                                                                                                                                                                                                                                                                                                                                            | The celiac children and their parents reported the child HRQOL similarly                                                                    |
| Taghdir M (2016)    | Iran            | 65                            | 2–18      | CDDUX                                            | QOL total score (mean $\pm$ SD):<br>CD: $30.2 \pm 15$<br>Parents: $25.2 \pm 14.4$                                                                                                                                                                                                                                                                                                                                                                                                                                  | Children with compliance to GFD had better QOL                                                                                              |
| Van Doorn R (2008)  | The Netherlands | 510                           | 8–15      | CDDUX                                            | QOL total score (mean $\pm$ SD):<br>CD: $44 \pm 15$<br>Parents: $39 \pm 15$                                                                                                                                                                                                                                                                                                                                                                                                                                        | Patients had lower quality of life score compared with healthy population                                                                   |
| Van Koppen E (2014) | The Netherlands | Case: 22<br>Parents: 22       | 12–14     | Dux-25 and CDDUX (communication and diet scales) | QOL (DUX-25) total score (mean $\pm$ SD):<br>children: $79 \pm 9$<br>Parents: $76 \pm 10$                                                                                                                                                                                                                                                                                                                                                                                                                          | Parents and children reported a good HRQOL score                                                                                            |
| Wagner G (2007)     | Austria         | 281                           | 12–18     | ILC                                              | QOL total score (mean $\pm$ SD):<br>CD with strict compliant to GFD: $1.69 \pm 0.78$<br>CD with not strict compliant to GFD: $2.06 \pm 0.92$<br>CD with noncompliant to GFD: $2.18 \pm 0.98$<br>Controls: $1.74 \pm 0.75$                                                                                                                                                                                                                                                                                          | Children with good compliance to GFD had higher QOL score.                                                                                  |
| Wolf R (2018)       | USA             | Case: 50                      | 12–18     | CDPQOL                                           | QOL total score (mean $\pm$ SD):<br>CD with high vigilant: $74.6 \pm 14.2$<br>CD with low vigilant: $68.8 \pm 15.2$                                                                                                                                                                                                                                                                                                                                                                                                | HRQOL adolescents who extremely vigilant to GFD was similar to who less vigilant                                                            |

CD = celiac disease; GFD = gluten-free diet; GI = gastrointestinal; HC = healthy controls; HRQOL = health-related quality of life; SD = standard deviation; UC = ulcerative colitis.

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