Rate, Risk Factors, and Outcomes of Nonadherence in Pediatric Patients With Celiac Disease: A Systematic Review

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BACKGROUND AND AIMS: **The only treatment for celiac disease is strict adherence to a gluten-free diet (GFD). We performed a systematic review to investigate the rate of adherence to a GFD in children with celiac disease, risk factors that affect adherence, and outcomes of non-adherence.**

METHODS: **We searched PubMed, Cochrane Library, EBSCO, and Scopus for studies through January 2019. We included observational studies of ≥50 children diagnosed with celiac disease and recommended for placement on a GFD. We collected data on adherence assessment (self-report, serology tests, structured dietary interview, biopsies, or assays for gluten immunogenic peptides), risk factors, and outcomes related to adherence. Findings were presented with medians, range, and a narrative synthesis.**

RESULTS: **We identified 703 studies; of these, 167 were eligible for full-text assessment and 49 were included in the final analysis, comprising 7850 children. Rates of adherence to a GFD ranged from 23% to 98%. Comparable rates (median rates of adherence, 75%–87%) were found irrespective of how assessments were performed. Adolescents were at risk of non-adherence and children whose parents had good knowledge about celiac disease adhered more strictly. Non-adherence associated with patient growth, symptoms, and quality of life.**

CONCLUSION: **In a systematic review of 49 studies of children with celiac disease, we found substantial variation in adherence to a GFD among patients. Rate of adherence was not associated with method of adherence measurement, so all methods appear to be useful, with lack of consensus on the ideal metric. Studies are needed to determine the best method to ensure adherence and effects on long-term health.**

Keywords: Compliance; Follow-Up; Food Intolerance; Wheat.

Celiac disease is a chronic autoimmune disease affecting about 1% of the population.[1] The clinical presentation varies from gastrointestinal symptoms prominent form to nongastrointestinal or atypical or asymptomatic presentation. The majority of cases remain undiagnosed.[1,2] The disease develops in genetically predisposed individuals in which dietary gluten or related prolamins trigger and maintain an inflammatory response primarily in the small intestine causing a T cell–mediated enteropathy.[1]

The mainstay of treatment is a gluten-free diet (GFD). A GFD implies eating food completely free from wheat, rye, barley, and products with added gluten.[3] Oats have been suggested to be tolerable for the majority of patients.[4] As these grains are staple foods in large parts of the world, the availability of uncontaminated naturally gluten-free foods may be limited, especially processed foods. The alternative is commercially prepared substitutes, which are more expensive than their gluten-containing counterparts.[3,5] Thus, strict adherence to a GFD can be challenging in everyday life and has been shown to be a burden with negative impact on quality of life.[6,7] Among adults the proportion following a strict GFD varies between 42% and 91%.[8] The reasons for suboptimal adherence are less well understood. Factors related to disease characteristics, quality of life and social environment, knowledge and sociodemography may

Abbreviations used in this paper: GFD, gluten-free diet; IQR, interquartile range.

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affect adherence.[3,8,9] Better understanding of which factors affect adherence among children is important to facilitate their treatment and guide intervention studies.

Remission of the gluten-induced enteropathy, as achieved by a strict GFD in the majority of children, has been shown to reduce symptoms, morbidity and reduce health care needs.[1,2,10] It is also suggested that strict GFD adherence reduces the risk of future complications such as osteoporosis, small bowel lymphoma, cardiovascular diseases, and untimely death, although the evidence is limited.[9,11] The proposed benefits of a strict GFD in children with celiac disease and the indications that adherence is not achieved among many patients prompted us to perform a systematic review to investigate the rate of adherence to a GFD in children with celiac disease, risk factors that affect adherence, and outcomes of nonadherence.

What You Need to Know

Background

We performed a systematic review to investigate the rate of adherence to a gluten-free diet (GFD) in children with celiac disease, risk factors that affect adherence, and outcomes of nonadherence.

Findings

In a systematic review of 49 studies of children with celiac disease, we found substantial variation in adherence to a GFD among patients. Rate of adherence was not associated with method of adherence measurement, so all methods appear to be useful, with lack of consensus on the ideal metric. Studies are needed to determine the best method to ensure adherence and effects on long-term health.

Implications for Patient Care

There is a range in adherence to a GFD among children with celiac disease. Both reported and biological measures of adherence are useful in clinical practice. Parent education appears to increase adherence.

Materials and Methods

We performed a systematic review following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Statement and MOOSE guidelines (Guidelines Meta-Analyses and Systematic Reviews of Observational Studies) (Supplementary File 1) and registered a protocol with Prospero (http://www.crd.york.ac.uk/PROSPERO/ ID:CRD42015017149).

Search Strategy

We searched the databases PubMed (MEDLINE and PubMed Central), Cochrane Library, EBSCO (PsycINFO and CINAHL), and Scopus (EMBASE and MEDLINE) for studies published through April 2015 and an update in PubMed was performed for studies through January 2019. Search terms were a combination of *celiac*, *gluten-free diet*, *adherence*, and *child* and their related words (Supplementary File 1). No language restriction was imposed during the search. Reference lists of included full text articles published during 2013–2018 were scrutinized for additional studies.

Eligibility Criteria for Studies and Participants

We included published studies of any quantitative design reporting adherence to a GFD. We restricted the studies to those with 50 or more participants who were recommended for placement on a GFD. If a full-text paper was not obtainable but the abstract presented sufficient data, the study was included but reported separately. Similarly, with full text in a language other than English. Only studies with data on children and adolescents (19 years of age or younger when adherence was measured) diagnosed with celiac disease according to well-defined criteria who were recommended a GFD were included. In case of multiple reports from the same study or database, the latest was included. Studies were excluded if the child had nonceliac gluten sensitivity or wheat allergy, or followed a self-prescribed GFD. Case reports, commentaries, reviews, or letters were excluded.

Study Selection and Data Extraction

Eligibility was assessed by A.M. and N.R.R. separately and disagreements were resolved through discussion in the review group and consensus. Reason for exclusion was recorded (Supplementary File 1). Data were collected by A.M. and N.R.R., with the other verifying key data. No authors were contacted for additional data. The data was extracted following a predeveloped form comprising general information, study and participant characteristics, celiac disease diagnosis, adherence to a GFD, and risk factors potentially affecting adherence. We made an addendum to the form to include potential outcomes of nonadherence (Supplementary File 1).

Outcome Data. Adherence to a GFD (outcome measure) was recorded and reported as total number and proportion of adherent children. We grouped adherence depending on method of adherence measurement into the following categories: (1) self- or parent reported, (2) serology tests (sometimes combined with physician assessment), (3) structured dietary interview (sometimes combined with biological measure), (4) small intestinal biopsies, or (5) assays for gluten immunogenic peptides. Dichotomized comparisons were made among those with strict adherence vs the combined group of occasional transgression(s), mostly adherent, poor adherence, and not on a GFD. For serology tests, a value

below the manufacturer's upper limit of normal for each respective test categorized children with normal serology as adherent. For small intestinal biopsies, adherence was defined as no longer Marsh 3, and for assays for gluten immunogenic peptides, the manufacturer's cutoff for negative was used.

Data on Risk Factors and Outcomes Associated With Adherence. We collected data on risk factors and outcomes which had been associated to adherence or nonadherence in the included studies. Type of risk factor or outcome and its characteristics, measurement, and association with adherence were documented. Extracted risk factors were grouped into 6 themes suggested by Hall et al.[8]: sociodemographic factors, disease-related factors, treatment factors, knowledge or attitudes and beliefs, sociocultural and environmental factors, and quality of life and psychosocial well-being. Outcomes were grouped into physical and psychosocial outcomes. The separation between risk factors and outcomes was based on the study authors' description.

Study Quality and Assessment of Risk of Bias

The quality of individual studies (for adherence rates, risk factors, and outcomes) was assessed by A.M., and N.R.R. reviewed the assessments. There was no blinding to the authors or journal of the paper. Assessment was performed using the Newcastle-Ottawa Scale for observational studies.[12] Before starting, we made an adaption of the scale for cohort studies to allow assessment of cross-sectional studies (Supplementary File 1). Evidence was graded on selection, comparability, and exposure or outcome depending on study design and summarized into 1 numerical score. For quality assessment of the adherence rate not all aspects in the scale were applicable, rendering a maximum score of 4 points for cohort and case-control studies and 5 points for cross-sectional studies. For quality assessment of factors maximum score was 9 points. The quality assessment was mainly incorporated into the interpretation of the results.

Data Synthesis

All included studies were presented in table(s) for overview together with a narrative synthesis. Adherence was presented using a Forest plot and summarized as median with interquartile range and full range for all studies as well as subgroups. We analyzed adherence by method of adherence measurement (5 categories presented previously), year of publication and geography (Scandinavia, Europe excluding Scandinavia, North America, Other). We performed a subgroup analysis (not prespecified) removing studies with Newcastle-Ottawa Scale score <3 to investigate the impact of study quality. Data were analyzed using STATA 13.0 (StataCorp, College Station, TX).

Results

Through the systematic literature review, we identified 703 studies in total; 686 through the searches after removal of duplicates and 17 after scrutinizing the reference lists (Supplementary File 1). After screening, 167 studies were eligible for full-text assessment. Of these, we failed to retrieve the full text for 10 (6%), and 21 (13%) had an English abstract but full text in another language. In total, 111 were excluded for various documented reasons (Supplementary File 1). The synthesis utilized the remaining 49 studies, which were also summarized quantitively, and 7 abstracts.

Basic Characteristics of Included Studies

The 49 studies included 7850 children diagnosed with celiac disease and recommended for placement on a GFD. Studies were published between 1985 and 2018, albeit predominantly in the most recent years. They originated from 24 different countries. Median number of participants was 113 (IQR, 101; range 50–825). The Q3 median proportion of women was 64% (IQR, 8%) based on the 35 studies with available data. Characteristics of included studies are summarized in Table 1.

Methodological Quality. Half of the studies (n = 23) were cross-sectional, 16 (33%) were prospective cohorts or clinical studies, and 7 (14%) were retrospective cohorts. Three were case-control studies. Most studies (n = 40) had a Newcastle-Ottawa Scale score higher than half of the maximum score (Table 1). Of the remaining 9 studies, 5 lacked basic information[13–17] and in 4 children constituted a less described subgroup.[18–21] For assessment of risk factors and outcomes, 9 studies had a score below half of the total (Table 1).

Rates of Adherence to a GFD

Among children with celiac disease, rate of adherence to a GFD ranged from 23%[22] to 98%[15,23] with a median rate of 78% (IQR, 27) (Figure 1). The adherence reported from abstracts were all within the range seen from full-text studies (35%–81%). Excluding studies with a low Newcastle-Ottawa Scale score had negligible impact on the findings (data not shown). There was no correlation between adherence and year of study publication. Only 1 study was from the early period,[13] but restricting the analysis to the period of the past 10 or 20 years did not affect the result. Median adherence rate varied with geographical area: Scandinavia 90% (IQR, 11; n = 8), Europe 74% (IQR, 20; n = 22), North America 79% (IQR, 15; n = 7), and other countries 77% (IQR, 43; n = 12).

We found little consensus on what defined "strict" adherence to a GFD, particularly for studies with reported adherence. Two studies defined strict adherence as not knowingly ingesting gluten-containing foods[24,25]; however, several studies did not report a clear definition

Table 1. Characteristics of the Included Studies Reporting Adherence to the GFD

First Author, Reference	Year	Country	Design	Sample	Participant Characteristics	Quality Assessment[a]	Adherence Measurement(s)	Adherence Category[b]	Adherence
Altobelli E[37]	2013	Italy	Cross-sectional, consecutive cases	140	Age 10–18 y, mean 14.2 y, F 79%	4 / FO6	Self-report in questionnaire	1	122 (87)
Bannister EG[31]	2014	Australia	Prospective clinical case study	129	Age 0.9–16.2 y, F 57%,	3	Self-report questionnaire		114 (88)
				150	GFD median 1.4 y		Serology: TG2 <6, DGP <6		97 (65)
				150			Biopsies: Marsh 0	4	124 (83)
Barrio J[29]	2016	Spain	Cross-sectional	428	Age 8–18 y	2 / O4	Parental-report questionnaire	1	414 (97)
Bazzigaluppi E[18]	2006	Italy	Cross-sectional for subgroup of cohort	59	Not included for the subgroup GFD >1 y	1	Dietician inquiry	3	23 (39)
Bellini A[26]	2011	Italy	Cases from case-control study	156	Age 6–16 y, F 69%, GFD >1 y mean 4.3	4 / F8	Self-report questionnaire	1	122 (78)
Benelli E[33]	2016	Italy	Prospective clinical case study	143	Age 0–18 y, median 2.1 y and 2.4 y, F 87%, GFD 1–3 y	4 / F6	Self-report (Biagi 3–4)		141 (99)
							Serology: TG2 negative	2	89 (80)
Bolia R[40]	2018	India	Controls from case-control study	100	Age <19 y, median 8.6 y, F 36%, GFD median 3.2 y	3 / FO6	Serology (TG2 negative) combined with dietary assessment	2	47 (47)
Charalampopoulos D[27]	2013	Greece	Cross-sectional	90	Age 2.2–17.4 y, F 73%, GFD median 4 y	4 / F9	Self-report using 2 Likert-type scale questions	1	40 (44)
Chauhan JC[43]	2010	India	Cross-sectional, consecutive cases	64	Age 2–17 y, GFD >6 mo	3 / FO4	Dietary interview and clinical assessment	3	51 (51)
Comba A[41]	2018	Turkey	Prospective clinical case study	73	Age <19 y, mean 10.4 y, F 64%, GFD 1 y	3 / FO7	Serology TG2 and EMA change to negative	2	45 (62)
Comino I[36]	2018	Spain	Prospective case-control study	114	Subgroup 0–12 y	5 / F7	GIP <.16 μg	5	87 (76)
Czaja-Bulsa G[38]	2018	Poland	Clinical cases	54	Age 0–18 y, GFD mean 104 mo	3 / F6	Self-report during medical interview	1	40 (74)
Errichiello S[19]	2010	Italy	Cross-sectional consecutive cases	121	14–18 y, subgroup of 13–30 y	2 / F4	Dietician assessment	3	89 (74)
Gerasimidis K[34]	2018	United Kingdom	Cross-sectional and prospective clinical cohort	65	Age mean 10 y, F 57%, follow-up 1 y for newly diagnosed	2	Self-report (Biagi 3–4)		61 (94)
				60			Serology TG2 <7		44 (73)
				65			GIP <.16 μg	5	48 (74)
Hogberg L[23]	2004	Sweden	Prospective cohort for adherence (RCT)	92	Age 0.7–17.2 y, GFD mean 1.1 y	4	Serology TG2 <8		80 (87)
							Biopsies	4	90 (98)
Isaac D[62]	2017	Canada	Retrospective hospital-based cohort	487	Age <18 y, mean 9.3 y, F 64% follow-up 6 mo to 6 y	4 / F7	Serology TG2<7		392 (80)
							Dietician assessment	3	429 (88)
Jackson PT[13]	1985	United Kingdom	Cross-sectional	50	Age 0–19 y, F 58%	1 / F4	Parental report	1	30 (60)
Janas RM[45]	2016	Poland	Cross-sectional	248	Age 1–18 y, mean 7 y, F 62%, GFD mean 3 y	2 / FO3	Serology TG2 <8	2	127 (51)

Johansson K[52]	2019	Sweden	Retrospective hospital-based cohort	363	Age <18 y, F 64%, median follow-up 2 y	3 / F5	Dietician structured assessment and serology	3	325 (90)
Kalyoncu D[14]	2015	Turkey	Prospective cohort of clinical cases	67	Age 1–16 y, F 60%	1 / O6	Clinical assessment and serology	2	76 (55)
Khurana B[44]	2015	India	cross-sectional consecutive cases	50	Age 5–18 y, median 9.1 y, F 56%	3 / FO4	Dietician structured assessment and serology	3	37 (74)
Kinos S[48]	2012	Finland	Prospective cohort of clinical cases	129	Age 1–15 y, F 67%, GFD 1 y	3 / F6	Self-report questionnaire	1	104 (81)
Kurppa K[20]	2012	Finland	Cross-sectional	94	Age 2–17 y, subgroup of 2–89 y	2 / F4	Structured dietary interview and serology	3	76 (81)
MacCulloch K[24]	2014	Canada	Cross-sectional	126	Age 2–18 y, F 64%, GFD mean 3 y	3 / F6	Self-report/parental report questionnaire	1	88 (70)
Mager DR[42]	2018	Canada	Cross-sectional multicenter	228	Age 3–18 y, mean 10.4 y, F 68%, CD duration 2.3 y	4 / FO7	Self-report Serology TG2<7	 2	161 (71) 180 (79)
Mehta P[28]	2018	United States	Clinical retrospective cohort	66	Age 2–19 y, mean 10–12 y, F 71%, GFD mean 1.2–1.5 y	3 / F6	Dietician structured assessment (scoring)	3	35 (53)
Meyer S[15]	2017	Israel	Cross-sectional	126	Age 8–18 y, Mean 12.3 y, F 65% 68% GFD >3 y	1	Parental report	1	123 (98)
Mozer-Glassberg Y[51]	2011	Israel	Retrospective cohort (chart review)	251	Age <18, F 60%, subgroup with follow-up	4 / F6	Serology TG2 and/or EMA	2	211 (84)
Myleus A[63]	2014	Sweden	Cross-sectional	90	Age 12 y, F 68%, GFD median 7.3 y	4 / O5	Serology TG2 <5	2	83 (92)
Norsa L[16]	2015	Italy	Cross-sectional	116	Age <18 y, mean 11 y, F 63%, follow-up 5.6 y	1	Parental report	1	112 (97)
Nurminen S[30]	2019	Finland	Clinical cohort/ database	511	Age <18 y, mean 7.6 y, F 65%	4	Structured dietary interview and serology	3	460 (90)
Radlovic N[32]	2009	Serbia	Clinical cases prospective	90	Age 0.5–7.5 y, F 62%, GFD mean 3 y	4 / O6	Biopsies in 87% Marsh 0–1	4	78 (87)
Rashid M[53]	2005	Canada	Cross-sectional	168	Age 2–15 y, F 58%, median diagnosis 3 y	3	Self-reported in questionnaire	1	160 (95)
Reilly NR[50]	2011	United States	Retrospective cohort of clinical cases	166	Age 1.3–19 y, F 53%, mean follow-up 3 y	3 / FO6	Serology Sustained normal TG2	2	126 (76)
Roma E[25]	2010	Greece	Cross-sectional, consecutive cases	73	Mean age 10 y, F 60%, GFD 1–15 y	3 / F6	Self-report Normal TG2 and EMA	 2	42 (58) 29 (40)
Saadah OI[55]	2011	Saudi Arabia	Retrospective hospital-based cohort	73	Age 0.5–18 y, mean 9.6 y, F 55%, follow-up 6 mo	3 / O5	Serology TG2 decline >50% or disappearance	2	41 (56)
Salardi S[64]	2017	Italy	Case-control multicenter	201	Age 1–19 y T1DM, GFD 1 y	3 / O6	Serology Normal TG2 or EMA	2	129 (64)
Samasca G[47]	2011	Romania	Clinical cases prospective	50	Mean age 7–11 y, F 66%, follow-up 2 y	4 / F7	Serology TG2 <25 (cutoff for normal)	2	40 (80)

Table 1. Continued

First Author, Reference	Year	Country	Design	Sample	Participant Characteristics	Quality Assessment[a]	Adherence Measurement(s)	Adherence Category[b]	Adherence
Sansotta N[54]	2018	United States	Clinical cohort/ database	258	Age <18 y, median age at diagnosis 8.5 y, F 66%, median follow-up 2.6 y	3 / O5	Self-report during medical interview and improvement in serology	2	238 (92)
Taghdir M[39]	2016	Iran	Cross sectional	65	Age 2–8 y, mean 11.3 y, F 59%, mean age at diagnosis 8.1 y	3 / FO5	Self-report		35 (59)
							Serology-negative TG2 or EMA	2	52 (80)
Tapsas D[46]	2014	Sweden	Cross sectional	316	Age <18.5 y, mean 12 y F 64%, GFD mean 6.9 y	3 / F5	Self-report using a food questionnaire	1	306 (97)
Terrone G[21]	2013	Italy	Cross-sectional	54	Age 4–16 y, GFD for >1 y subgroup	1 / O2	Serology	2	41 (76)
Tokatly Latzer I[17]	2018	Israel	Cross-sectional survey	136	Age 12–18 y	1 / FO3	Self-report (Biagi score 4)	1	44 (32)
Toumi D[65]	2007	Tunisia	Retrospective cohort	67	Age 1–15 y, F 64%, GFD >1 y, mean 4 y	3	Serology-negative EMA	2	21 (31)
Uspenskaya ID[22]	2014	Russia	Cross sectional	71	Age 2.5–16.5, median 10.6 y, F 66%, GFD >1.5 y	3	Special interviews verified with biopsies	3	16 (23)
Usta M[35]	2014	Turkey	Clinical cases prospective	63	Mean age 14.7 y, F 57%, GFD >2 y	4 / O6	3-day diet inventory and EMA	3	38 (60)
Webb C[49]	2015	Sweden	Prospective cohort of screening cases	193	Age 13–14 y, F 57%,	4 / F7	Self-report		158 (82)
				210	GFD 1 y		Serology TG2 <5	2	179 (85)
Zanini B[66]	2010	Italy	Prospective cohort	825	Age <14 y, GFD >1 y subgroup	4	Serology-negative TG2	2	594 (72)
Zifman E[67]	2019	Israel	Prospective clinical cohort	113	Age 2–17 y	4	Dietician and clinical assessment and serology	3	110 (97)

Values are n (%), unless otherwise indicated.

DGP, deamidated gluten peptide; EMA, endomysial antibody; F = female; FO, quality assessment score for risk factors or outcomes; GIP, gluten immunogenic peptide; GFD, gluten-free diet; RCT, randomized controlled trial; TG2, tissue transglutaminase antibodies; T1DM, type 1 diabetes mellitus.

[a]Quality was assessed using the Newcastle-Ottawa Scale for observational studies. Adaption for assessment of a proportion (first number) rendered a lower maximum score (cohort and case-control studies maximum 4 points, cross-sectional studies maximum 5 points). For assessment of factors or outcomes (second number denoted FO# in applicable studies) maximum score was 9.

[b]Adherence was categorized depending on type of measurement into (1) self- or parent reported, (2) serology tests, (3) structured dietary interview, (4) small intestinal biopsies, and (5) assays for GIP. In case of more than 1 measurement, the highest number was recorded.

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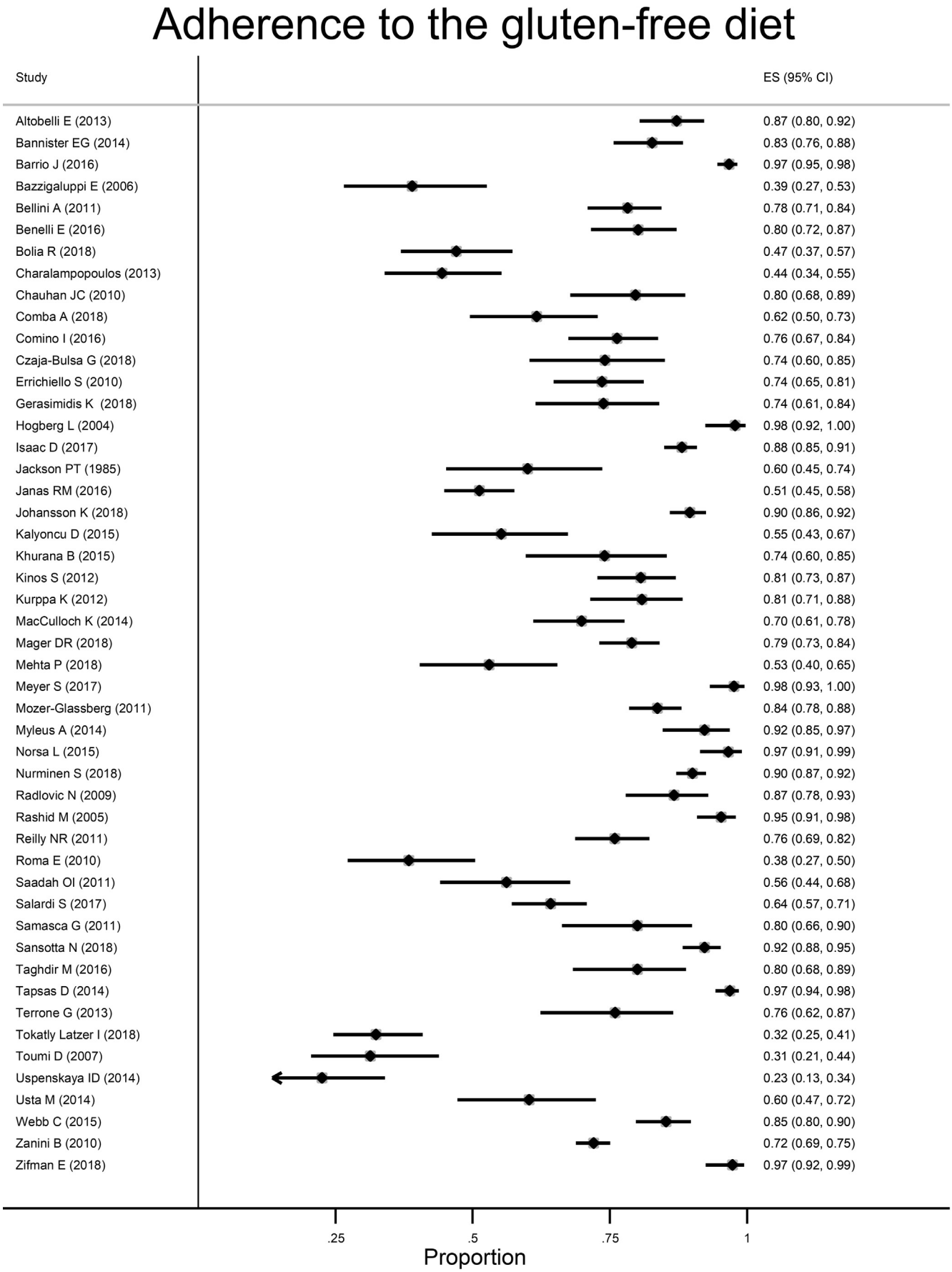

Figure 1. Overall rate of adherence to the gluten-free diet reported in different studies. For studies with more than 1 measure, we included serology test rates instead of self-report, structured dietary interview instead of serology tests, biopsies instead of dietary interview, and assays for gluten immunogenic peptide instead of any of the mentioned measures. CI, confidence interval; ES, •••. Q11

or definition was intrinsically connected to how adherence was assessed (eg, self-report of always GFD or strict compared with often or occasional transgression without further description). In the studies with a clear definition, description, or score, the median was lower (53% vs 88%).[17–19,24,26–28] However, there were differences in whether occasional transgressions, if less than monthly, were still compatible with a definition of strict.[18,19,26,29,30] In the studies included here, mucosal recovery was defined as lack of villous atrophy albeit with different categorization of Marsh 2, illustrating that there are also different understandings on how to use mucosal recovery as a measure of adherence.[23,31,32] There was generally less definition variability when defining adherence with serology tests or assays for gluten immunogenic peptide; the laboratory's upper limit of normal was mostly accepted as the definition of strict adherence, although not all studies presented what cutoff was used (Table 1).

Methods of Adherence Measurement

The highest median adherence was found for biopsies (87%), followed by self-report (81%), structured dietary interview (77%), serology tests (76%), and assays for gluten immunogenic peptide (75%) (Table 2). The most common method of adherence measurement was serology tests, although there were also studies in which more than 1 measure was used, but not clearly reported separately, for example, clinical assessment or self-report supported by biological measures.

Nine studies measured adherence with more than 1 method in the same children, including 2 of the studies using biopsies as adherence measurement (Table 1). Bannister et al[31] used 3 measures with the highest adherence seen in the self-report followed by biopsies and serology tests. However, in this study, adherence as defined by biopsy was defined as Marsh 0 histology. Had those with Marsh 1 been considered adherent, the highest adherence would be for biopsies. Högberg et al[23] regarded Marsh 0–2 as restored morphology. They reported the highest adherence in this study (98%). The second-highest median adherence was based on self-report (81%). Three studies used the Biagi score, a short instrument validated among adults. Two reported adherence rates in the higher range and 1 in the lower.[17,33,34] However, the studies used different score for cutoff, which could explain the disparity and illustrated a difficulty also with validated instruments. Structured dietary interview was performed following different routines and time-frames.[19,20,28,35] Still, among studies reporting more than 1 measure no clear pattern between reported measures (self-report or structured dietary interview) and serology tests was seen (Table 1). Serologic measures carry the advantage of functioning independently from patient knowledge or truthfulness but on the other hand sensitivity to occasional transgressions was suggested to be low.[28] The gluten immunogenic peptide measurement is a noninvasive option that has the advantage of being very specific to gluten intake.[34,36] This measurement reported the lowest adherence rate, suggesting that it finds also those with occasional involuntary gluten exposure (eg. cross-contamination). Both the lowest and highest median adherence rate was based on few studies (Table 2). The remaining 3 methods of adherence measurement showed comparable adherence rates and range.

Table 2. Rate of Adherence to the Gluten-Free Diet for Different Methods of Measurements

Method of Adherence Measurement	Median Adherence (Interquartile Range) (%)	Range	Studies
Biopsies	87	83–98	3
Self-report	81 (23)	32–98	13
Dietary interview	77 (32)	23–97	12
Serology tests	76 (25)	31–96	19
GIP	75	74–76	2

GIP, gluten immunogenic peptide.

Risk Factors Affecting Adherence to a GFD

Of 49 included studies, 28 had investigated risk factors affecting adherence, comprising 4299 children (Table 1). In total, 20 risk factors had been investigated, but often using different definitions, methods of measurements, and outcome data. A summary of all risk factors is presented in Supplementary File 2.

Sociodemographic Factors. There were 18 studies investigating age in relation to adherence. The most consistent finding was that adherence was lower among adolescents compared with younger children,[20,24,25,27,36–43] although also the opposite was seen,[44,45] and 5 studies showed no association.[13,17,26,28,46] The adherence appears to be comparable in girls and boys, as none of the 13 included studies found a statistically significant differences (Supplementary File 2). No clear pattern was seen with socioeconomic status and GFD adherence; 4 studies suggested higher adherence among those with higher socioeconomic status[39,43,44,47] and 5 studies found no association (Supplementary File 2).

Disease-Related Factors. Overall, our findings suggest that there is no association between adherence and age at diagnosis, family history of celiac disease, comorbidities, and symptomatic disease at presentation (Supplementary File 2). Those children found through screening or with atypical symptoms had no increased risk for nonadherence.[27,28,48,49]

Treatment Factors. Taste of the gluten-free food was suggested to affect adherence.[43] Whether the GFD included oats or not had no impact.[46] There was no clear pattern relating time on a GFD to adherence; 4 studies

found no association, and 2 suggested that longer duration was beneficial,[42,50] but then possibly declining again after 15 years.[46] Three studies investigated different follow-up strategies,[25,51,52] but no preferred strategy could be recommended.

Knowledge, Attitudes, and Beliefs. From 4 studies, we observed that children whose parents had good knowledge about celiac disease and the treatment with a GFD were more likely to adhere strictly. Knowledge was both tested[13,25] and reported as perceived knowledge.[27,43] Furthermore, nonadherent children believed they could be healthy without a GFD to a larger extent than adherent children did.[25]

Sociocultural and Environmental Factors. Being a member in a celiac disease patient society was associated with higher adherence.[13,25,27] The median adherence in studies recruiting the participants from a celiac disease society[15–17,20,27,29,48,53] (n = 8) was somewhat higher (88% vs 76%). No association between adherence and to community size or urban or rural habitation was found.[24,28,42]

Quality of Life and Psychological Well-Being. No study investigated quality of life as a risk factor for suboptimal adherence to a GFD. One study investigated the locus of control showing that those adhering to a GFD believed to a larger extent that events are more contingent on their own behavior compared with those that are not adhering.[26]

Outcomes of Nonadherence to a GFD

In total, 20 studies comprising 2569 children had included findings on outcomes of dietary nonadherence. Three outcomes were investigated in more than 1 study, although definitions were not uniform (Supplementary File 2).

Physical Outcomes. Nonadherence was suggested to affect both gastrointestinal and extraintestinal symptoms, although findings were not conclusive.[21,28,39,54] This was supported by 3 studies, in which 35%–80% of participants reported symptoms at dietary lapses, predominantly abdominal pain.[25,29,46] While no association between adherence and physical health was described,[37] others suggested an association between nonadherence and persisting subtle cardiac dysfunction[40] and low bone density.[35] Findings for endocrinology and nutrition were inconsistent. Seven studies investigated adherence and growth; 3 found no association[17,32,42] and the remaining associated nonadherence with impaired patient growth in at least 1 parameter.[41,44,50,55] Reilly et al[50] suggested that growth after initiation of a GFD is dependent on both adherence to the treatment and patient body mass index at diagnosis, possibly explaining part of the differences.

Psychosocial Outcomes. Quality of life, measured with generic and disease-specific measures, was investigated as an outcome of adherence in 7 studies. The Celiac Disease Dutch Questionnaire[29,39,42,44] suggested higher quality of life among adherent children, but only the largest study showed statistically significant findings.[29] Among studies using different measures, no clear pattern was found.

Discussion

A GFD is currently the only available treatment for celiac disease, and in this systematic review, we investigated the treatment from 3 approaches: the rate of GFD adherence achieved among children, risk factors affecting adherence, and outcomes of nonadherence. We found a substantial variation in rate of adherence, ranging from 23% to 98%, which is larger than seen among adults.[8] While there was little consensus regarding the rate of dietary adherence seen in children with celiac disease across several countries, our findings suggest that the degree of adherence does not differ among patients according to method of measurement. Of risk factors affecting adherence we found that adolescences could be a vulnerable period and parental knowledge about celiac disease was associated with the child's adherence. We found support for nonadherence affecting patient growth, current symptoms, and quality of life, although overall findings for outcomes of nonadherence were inconsistent.

Measurement of adherence poses several challenges in clinical practice, which we observed in comparing the studies included here. Especially the lack of consensus of what defines strict adherence and a validated instrument to measure GFD adherence in children. Our findings showed that serology tests were the most common assessment of adherence, which probably reflects also the clinical practice. It should, however, be emphasized that the serological tests were developed and are approved for the diagnosis of celiac disease, not the follow-up of patients. Which of the currently available serological markers is best to assess adherence remains a subject of debate.[56] Further, a recent meta-analysis revealed that normal serological values do not reflect healing of the mucosa,[57] an important benchmark given the frequency with which failed recovery occurs in children and associated morbidity.[1,58] Although the gluten immunogenic peptides assessment is specific for gluten, the time frame for detection is relatively short.[34] A noninvasive measure of adherence with comparable sensitivity to biopsies in determining mucosal healing has yet to be developed.

We did not find an increase in rate of adherence over time, which was surprising, considering the increase in availability of palatable gluten-free foods in the stores. Both taste and lack of availability has been suggested to be a barriers for adherence.[24,39,43,59] The lack of increase might be due to the higher expenses for gluten free alternatives,[5] although we saw no clear pattern between adherence and socioeconomic status of the family. We found that parental knowledge regarding celiac disease

and the treatment was associated with the child's adherence. Qualitative studies have suggested that appropriate knowledge contributed to adherence, and misunderstandings about celiac disease and the need to educate others were seen as barriers.[59,60] The latter was supported by studies using the Celiac Disease Dutch Questionnaire.[29,39,42,44] Corroborating this, we found that membership in a celiac disease society, which could be an important source of information, was suggested to be associated with better adherence. Adolescents could be a tenuous group regarding GFD adherence, as they might not remember the initial diagnosis and they can make more independent food choices compared with younger children. For those who were not strictly adhering to a GFD, we found support for both physical and psychosocial impact, affecting growth, persisting symptoms, and lower quality of life. On the other hand, diminishing quality of life has also been reported for those handling a GFD with maladaptive eating behaviors.[39,61] Thus, families need both support and to have the concept of strict GFD reinforced to them for the management of celiac disease.

Our study is subject to several limitations. First, adherence to a GFD is not defined uniformly. Owing to the differences in definition and measurement, classification according to type of measurement was difficult and results should be interpreted with caution. We excluded the smallest studies, which could be a limitation. However, the included studies had 50–825 participants, and we found no association between adherence and study size (data not shown). The quality of included studies was relatively high, and excluding studies with lower score did not affect the overall interpretation. However, we cannot exclude that studies with low adherence among participants have remained unpublished, introducing publication bias. The high heterogeneity of our adherence outcomes precluded meta-analysis and median estimates should be interpreted with caution.

In our assessment of risk factors and outcomes, we started from those studies that assessed adherence rate, and thus there could be studies investigating risk factors or outcomes that were not identified through the search strategy. As our purpose was to assess the association between risk factors or outcomes and adherence, the adherence rate was a prerequisite. However, as noted previously, the differences in definitions and measurements constitute a limitation also for this assessment. Several studies[19,24,28,37–39,42,46,48] reported additional barriers to GFD adherence, though without attempting to correlate them with the actual adherence of included children, impairing our ability to analyze the significance of such data. Four of the studies investigating several risk factors[13,17,43,44] were assessed as low quality, so findings should be interpreted with caution. It should be noted that the extraction of outcome data was an addendum to the protocol. For some risk factors and outcomes, it was difficult to disentangle cause from consequence, such as current symptoms and quality of life. We relied on the authors' description in classification, but based on cross-sectional studies, the directionality of these effects cannot be determined. We did not identify any randomized controlled studies or intervention studies fulfilling inclusion criteria.

Conclusions

In a systematic review of 49 studies of children with celiac disease, we found substantial variation in adherence to a GFD among patients (range 23%–98%), as assessed in studies from 24 different countries. Our findings did not relate rates of adherence to method of adherence measurement. This suggests that both self-report and biological measures of adherence are useful, though there is lack of consensus on the ideal metric. The large variation in adherence among children from all geographic areas suggests that children and their caregivers need both support and to have the concept of strict gluten avoidance reinforced to them for the management of their disease. The best method to ensure adherence, particularly in risk groups, needs to be studied and correlated with long-term health outcomes. Both explorative research and testing of theoretical models are applicable. These could thereafter guide intervention studies.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2019.05.046.

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Conflicts of interest
The authors disclose no conflicts.