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Long-term health and treatment outcomes in adult celiac disease patients diagnosed by screening in childhood

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Conflict of Interest: none

Background: The diagnostic yield of celiac disease could be improved by screening in at-risk groups, but long-term benefits of this approach are obscure.

Objective: To investigate health, quality of life and dietary adherence in adult celiac patients diagnosed in childhood by screening.

Methods: After throughout evaluation of medical history, follow-up questionnaires were sent to 559 adults with childhood celiac disease diagnosis. The results were compared between screen-detected and clinically-detected patients, and also between originally asymptomatic and symptomatic screen-detected patients.

Results: 236 (42%) patients completed the questionnaires a median of 18.5 years after childhood diagnosis. Screen-detected patients (n=48) had more often celiac disease in the family and type 1 diabetes and were less often smokers and members of celiac societies compared to clinically-detected patients, whereas the groups did not differ in current self-experienced health or health concerns, quality of life or dietary adherence. Screen-detected, originally asymptomatic patients had currently more anxiety than those presenting with symptoms, whereas the subgroups were comparable in other current characteristics.

Conclusion: Comparable long-term outcomes between screen-detected and clinically-detected patients support risk-group screening for celiac disease. However, asymptomatic patients may require special attention.

Key Words: children, diagnosis, gluten-free diet, long-term follow-up, quality of life, screening

Key Summary

Established knowledge on this subject

- Celiac disease is a common, but significantly under-recognized condition.
- Screening could be used to improve diagnostic yield, but the long-term benefits of this approach remain unclear.

New findings of this study

- Currently adult patients diagnosed by screening in childhood were comparable to those found because of clinical suspicion in a variety of health outcomes, including adherence to gluten-free diet and quality of life.
- There were also no differences in most characteristics between originally asymptomatic and symptomatic patients, but the former group had more anxiety in adulthood.

Introduction

During recent decades celiac disease has become a common health problem affecting up to 1–3% of the population.[1,2] Unfortunately, due to the diverse clinical presentation, most sufferers remain undiagnosed.[1,2] Diagnostic efficiency could be improved by risk-group screening, for example among relatives of patients and those with type 1 diabetes.[3] Supporting early diagnosis, screen-detected children may already have advanced disease and a subsequent risk of permanent complications such as impaired growth and reduced bone accrual.[4–7] Delaying diagnosis until later adulthood predisposes to even more severe maladies, including osteoporotic fractures and refractory celiac disease.[8]

Counterweighting the benefits of screening is the burden of demanding treatment. Adhering to a gluten-free diet may negatively affect the quality of life, especially in asymptomatic patients with satisfactory health prior to diagnosis.[9] Despite these challenges, there are some evidence that these children can achieve good dietary adherence and quality of life in a short-term follow-up.[7,10–12] However, long-term data in screen-detected celiac disease patients are very limited.[13,14] It is possible that in puberty the initial "honeymoon period" fades concurrently with the new challenges in life, leading to poor compliance and ill-health.[15,16] The paucity of long-term studies has led to prudence when it comes to screening recommendations.[17]

In the present study, we investigated long-term health and treatment outcomes in adult celiac disease patients diagnosed in childhood. We were particularly interested in patients detected by at-risk group screening, including those with no apparent symptoms.

Methods

Patients and study design

The study was conducted in the Tampere Center for Child Health Research. Data were constructed by combining patients' answers to questionnaires and personal health information collected from medical records, and in some cases, by interviews carried out in the context of an earlier study.[18] The basic cohort comprised 1070 patients gathered from our research database,[18] supplemented by a search with selected diagnosis codes possibly indicating celiac disease in the patient records of Tampere University Hospital, (Figure 1) a tertiary center with a catchment area of ≈120.000 children. Patients with a reported diagnosis made <18 years of age during 1966–2014 were included for further assessment. After evaluation of medical records, 115 patients were found to be deceased and/or have an uncertain diagnosis. Of the remaining 955 patients with a proven childhood diagnosis, 559 were currently alive and ≥18 years and were sent the study questionnaires. A repeat questionnaire was sent to all non-responders after two months. (Figure 1)

For the subsequent analyses, the responders were divided into 1) those diagnosed via risk-group screening including patients suffering from type 1 diabetes or other concomitant autoimmune disease, or having celiac disease in the relatives, and 2) those found due to clinical suspicion. Screen-detected patients were further classified into asymptomatic and symptomatic based on the evaluation of symptoms at diagnosis before initiation of gluten-free diet. All study variables were compared between the above-mentioned groups.

Altogether 110 healthy adults comprised the control group for comparison of current symptoms and quality of life.[19] Their median age was 49 (range 23–87) years and 81% were females. Controls were recruited among the friends and close neighborhood of known celiac

disease patients. None of the controls had suspicion of celiac disease or known celiac disease in close relatives.

Medical history

Medical data were collected regarding the clinical and histological presentation of celiac disease at the time of diagnosis. Information was gathered on the main reason for celiac disease suspicion and presence of gastrointestinal or extra-intestinal symptoms. Furthermore, possible complications, as well as the presence of celiac disease-related or other coexisting disease and celiac disease in first-degree relatives were noted. Abnormalities in laboratory values or physician's examination were also recorded, but were considered as signs instead of symptoms.

Poor growth was defined as disturbed height and/or weight development compared to expected growth as described in detail elsewhere.[5] Body mass index was calculated as height/weight^2 (kg/m^2). Anemia at diagnosis was defined based on the age- and gender-dependent reference values for hemoglobin.

Severity of histological damage was classified based on the pathologic report. In our hospital practice, the degree of villous atrophy is evaluated from several well-oriented biopsy samples and further categorized as partial, subtotal or total (Marsh IIIa–c).

Questionnaires

Currently adult patients completed three surveys, including a specifically designed study questionnaire and two questionnaires evaluating gastrointestinal symptoms and quality of life.

The study questionnaire comprised items on sociodemographic and lifestyle characteristics such as work and study situation, membership in a celiac society, regularity of physical exercise, smoking, presence of children, and celiac disease in the family. The presence of celiac-related comorbidities and other chronic diseases was evaluated. Current self-experienced health was categorized as excellent, good, moderate or poor; and concerns about health as none/minor or moderate/severe. Furthermore, patients reported experience of self-assessed possibly celiac disease-related symptoms and everyday life restrictions caused by the treatment. Adherence to a gluten-free diet was classified as strict, occasional lapses, regular lapses or no diet; and frequency of follow-up as regular or none/very occasional.

The Psychological General Well-Being (PGWB) questionnaire evaluates health-related quality of life, which is subsequently divided into anxiety, depression, positive well-being, self-control, general health and vitality.[20] Altogether 22 questions are rated from 1 to 6 higher scores representing better well-being. Total score is a sum of all scores the values being between 22 and 132, and the sub-dimensions are calculated as sums of scores of selected questions. For example, vitality describes person's energy level, and the score is comprised as a sum of questions about overall energy, activity and tiredness, and experience of resting after night sleep.[20]

Gastrointestinal Symptom Rating Scale (GSRS) consists 15 questions, which evaluate common gastrointestinal symptoms and their severity.[21] Each question is scored with seven-point Likert scale from asymptomatic (1) to severe symptoms (7). Total score is calculated as a mean of all 15 items. Further, the questions are divided to five sub-dimensions being abdominal pain, indigestion, diarrhea, constipation and reflux, which are calculated as means of selected questions.

Ethical aspects

The Regional Ethics Committee of Tampere University Hospital approved the research protocol (Ethical committee code R16091, 05/31/2016), and ethical guidelines of the 1975 Declaration of Helsinki were conformed. Patients participating earlier interviews or answering the questionnaires fulfilled informed consent.

Statistics

Non-parametric numeric values are reported as medians with quartiles, and compared between the groups with Mann-Whitney U or Kruskal-Wallis test. Bonferroni correction was used in pair-wise post-hoc comparisons. Categorized values are reported as numbers and percentages, and compared with Chi Square or Fisher's Exact test. Significance was set at P value <0.05. Statistical analyses were carried out with SPSS version 23 (IBM Corporation, Armonk, NY). Data were available on >90% of patients unless otherwise stated.

Results

Altogether 237 (42%) currently adult patients answered the questionnaires. (Figure 1) The responders were more often girls, suffered less frequently type 1 diabetes and had more celiac disease in the family than the non-responders (n=322), while the groups did not differ significantly in other diagnostic variables such as clinical presentation and the main reason for diagnostic evaluations. (eTable 1)

Of 236 responders with available information on diagnostic approach, 48 (20%) had been found by screening and 188 (80%) due to clinical suspicion. (Table 1) Screen-detected patients were diagnosed at significantly older age and during more recent years. They also

had fewer symptoms and growth disturbances at diagnosis, but although their hemoglobin levels were higher, there was no significant difference between the groups in the presence of anemia. The groups were also comparable in gender and degree of villous atrophy. (Table 1)

In subgroup analysis, screen-detected patients presenting with symptoms at diagnosis (n=21) were younger (9.5 vs 12.1 yr, p=0.098) and more often girls (86% vs 56%, p=0.025) and had more anemia (33% vs 7%, p=0.031) than asymptomatic subjects (n=27). The subgroups did not differ in the year of diagnosis, presence of growth disturbances, median hemoglobin or degree of villous atrophy (data not shown).

In current comparison at a median of 18.5 years (IQR 12.7, 30.7 years) after the diagnosis, the presence of celiac disease in the family and type 1 diabetes were more common in screen-detected patients, whereas they were less often members of celiac societies and current smokers than those found due to clinical suspicion. (Table 2) The groups were comparable in age, work and study situation, presence of other concomitant diseases and children, frequency of physical exercise and body composition (Table 2), as well as in experienced health, concerns about health, presence of symptoms, daily restrictions caused by the treatment, dietary adherence and implementation of follow-up. (Table 3) There were no differences between the subgroups of symptomatic and asymptomatic patients in the afore-mentioned variables. (Table 4)

Screen-detected and clinically detected patients were comparable in respect of current quality of life and symptoms as measured by PGWB and GSRS, but both groups showed lower vitality (Figure 2A) and screen-detected patients more abdominal pain and reflux (Figure 2B) compared to non-celiac controls. When the analyses were repeated in the subgroups, PGWB

anxiety and vitality scores were lower than controls in those who were asymptomatic at diagnosis (Figure 2C), while there were no differences in GSRS (data not shown). Increased anxiety was also seen in patients with other than celiac-related co-morbidities such as malignancies, eating disorder and depression, and in smokers, whereas coexisting type 1 diabetes or thyroid disease were not associated to anxiety and it did not correlate with time from the diagnosis (data not shown).

Discussion

Our main finding was that celiac disease patients diagnosed in childhood by screening and due to clinical suspicion are comparable in most measured adulthood health outcomes. The results give further support to screening among at-risk children. However, a subgroup of patients asymptomatic at diagnosis are at an increased risk of later anxiety and may require special support during the follow-up. Whether benefits of screening overcome the possible burden of the dietary treatment cannot be answered with certainty by this study design, but it is important to bear in mind that also asymptomatic screen-detected patients have risk to develop permanent complications.

As regards to the rationale of screening, it was of particular importance that we found no differences in dietary adherence between screen- and clinically detected celiac disease patients. Earlier long-term studies investigating this issue are scant. In a study by Roma et al, 88% of screen-detected children adhered to a gluten-free diet compared to 58% of the whole study cohort after four years on diet.[22] Fabiani et al. reported a mere 23% of screen-detected adolescents to maintain a strict diet after five years compared to 68% of those found because of malabsorptive symptoms.[15] Besides these pediatric studies, we and Mahadev et al. have observed similar dietary adherence patterns between cohorts of screened and clinically

detected adults of whom some were diagnosed as children.[23,24] However, subjects with a childhood diagnosis were not evaluated separately. A few more adult studies have assessed adherence in originally pediatric patients, but it is unclear whether screen-detected subjects were included.[13,25]

Drawing firm conclusions from this limited number of studies is challenging, but adherence is likely to be markedly dependent on the variability prevailing in knowledge of celiac disease and the availability of gluten-free products.[26,27] Furthermore, it is important to realize that Fabiani et al. published their study as far back as 2000, since which the gluten-free diet has become popular and easier to maintain.[28] More studies in different populations are needed, but we here demonstrated that, in favorable circumstances, achieving good long-term dietary adherence is possible in screen-detected patients. Furthermore, screened patients had similar or even better health-related behavior, when for example smoking was less common among them. However, one explanation for this could be higher proportion of those with type 1 diabetes among screen-detected compared to clinically found, since these patients are advised to avoid smoking especially strictly to prevent diabetes-associated long-term complications.

A gluten-free diet is necessary to achieve remission in celiac disease, but can be challenging in many respects. Here, screen-detected and clinically identified patients did not differ in quality of life or experience of everyday life restrictions caused by the treatment. Nevertheless, dietary restriction might be particularly burdensome in screen-detected patients, who often consider themselves healthy before the diagnosis and may lack the experience of a positive treatment response.[29,30] Earlier, Fabiani et al. observed screen- and clinically detected adolescents to be comparable in the experience of anxiety and depression.[15] In addition, van Koppen et al. reported comparable quality of life between healthy controls and 32 screen-

detected children after 10 years on diet.[14] However, even at that point these patients were still in early adolescence (<15 years) and the treatment mainly the parents´ responsibility.

Clinical presentation and particularly absence of symptoms may affect the experience of a celiac disease even more than the original reason for diagnostic evaluations.[17] Hitherto the lack of evidence on the long-term benefits of screening particularly in asymptomatic patients has led to considerable caution, and for example the US Preventive Services Task Force has demanded more prospective studies before releasing screening recommendations.[17] In practice, however, the required studies are particularly laborious and may take decades to complete with sufficient power. Our center has a long tradition in celiac disease research, which enabled us to obtain an unique cohort of adults diagnosed by childhood screening from as far back as the 1970s.[18,31]. Another issue important to realize when discussing screening is that it is not a synonym for absence of symptoms, as many of these patients are not asymptomatic but simply unrecognized,[7,10,23] as was also seen in almost half of our patients. As regards truly asymptomatic cases, it was noteworthy that they did not report more restrictions in daily life or most aspects of quality of life.

There are important arguments favoring celiac disease screening already in childhood. Notwithstanding the less severe clinical presentation, we observed that screen-detected and even asymptomatic children can already have severe histological damage. This confirms our earlier findings, and demonstrates that these otherwise unidentified patients are at risk of permanent complications similarly to those found in clinical practice.[7] In fact, some asymptomatic children here already had signs of anemia and poor growth, and others have reported such patients to suffer from osteopenia and underachievement.[4,32] Furthermore,

although more studies are needed, an early initiated gluten-free diet might reduce the risk of other autoimmune diseases.[33,34]

Although most of our results support childhood screening, certain challenges remain. We found an absence of symptoms to predispose to increased anxiety in adulthood, which is in accord with our previous observation in a small subgroup of asymptomatic adults.[9] It is logical that these individuals find it difficult to adapt to the diagnosis and life-long dietary restriction, particularly if its justification is unclear. Alternatively, owing to the absence of warning symptoms, they might be afraid of inadvertent gluten exposure and the subsequent development of complications. It is therefore important to explain why treatment could be rational in asymptomatic celiac disease, and to underline the good prognosis when dietary adherence is successful.

Strengths and limitations

The major strength of the present study is the large cohort of adults with biopsy-proven celiac disease diagnosed in childhood. We also succeeded in collecting comprehensive medical data at diagnosis together with a variety of sociodemographic, health and lifestyle factors at present. The use of validated questionnaires in the evaluation of symptoms and quality of life increases the reliability and generalizability of the results.[9,19–21,23,27]

There were also limitations. A relatively low response rate to questionnaires predisposes to selection bias. This common problem in postal surveys was likely further aggravated by the long interval between the diagnosis and the current study. For example, it is possible that patients who had better dietary adherence answered more often the questionnaires and thus skewed the results. However, the fact that responders and non-responders were comparable in

most features reduces the risk of bias. Another limitation was incomplete data in a part of the study variables at the time of diagnosis. Finally, the non-celiac controls were older and more often females than celiac disease patients, which may affect the comparability of quality of life.[35]

Conclusions

We provided previously lacking evidence regarding the long-term health outcomes in screen-detected celiac disease. Of particular importance was that even asymptomatic children can attain good adulthood quality of life while maintaining a strict gluten-free diet. However, physicians should bear in mind that in some patients the absence of symptoms at childhood diagnosis may predispose to later anxiety. We do not regard this as a counterargument to screening, but encourage to take clinical presentation into account when planning the long-term follow-up. At this point we feel that affected children and their families have at least a right to be aware of the underlying celiac disease, and be in a position to consider treatment options. Without screening a substantial number of sufferers remain undiagnosed, with often unrecognized symptoms and an increased risk of complications.

References

1. Rubio-Tapia A, Ludvigsson JF, Brantner TL, Murray JA, Everhart JE. The prevalence of celiac disease in the United States. *Am J Gastroenterol*. 2012;107:1538-1544.
2. Myléus A, Ivarsson A, Webb C, et al. Celiac disease revealed in 3% of Swedish 12-year-olds born during an epidemic. *J Pediatr Gastroenterol Nutr*. 2009;49:170-176.
3. Ludvigsson JF, Card TR, Kaukinen K, et al. Screening for celiac disease in the general population and in high-risk groups. *United Eur Gastroenterol J*. 2015;3:106-120.
4. Björck S, Brundin C, Karlsson M, Agardh D. Reduced bone mineral density in children with screening-detected celiac disease. *J Pediatr Gastroenterol Nutr*. 2017;65:526-532.
5. Nurminen S, Kivelä L, Taavela J, et al. Factors associated with growth disturbance at celiac disease diagnosis in children: a retrospective cohort study. *BMC Gastroenterol*. 2015;15:125.
6. Cellier C, Flobert C, Cormier C, Roux C, Schmitz J. Severe osteopenia in symptom-free adults with a childhood diagnosis of coeliac disease. *Lancet*. 2000;355:806.
7. Kivelä L, Kaukinen K, Huhtala H, Lähdeaho M-L, Mäki M, Kurppa K. At-risk screened children with celiac disease are comparable in disease severity and dietary adherence to those found because of clinical suspicion: a large cohort study. *J Pediatr*. 2017;183:115–121.e2.
8. Viljamaa M, Kaukinen K, Pukkala E, Hervonen K, Reunala T, Collin P. Malignancies and mortality in patients with coeliac disease and dermatitis herpetiformis: 30-year population-based study. *Dig Liver Dis*. 2006;38:374-380.
9. Ukkola A, Mäki M, Kurppa K, et al. Diet improves perception of health and well-being in symptomatic, but not asymptomatic, patients with celiac disease. *Clin Gastroenterol Hepatol*. 2011;9:118-123.
10. Kinos S, Kurppa K, Ukkola A, et al. Burden of illness in screen-detected children with

celiac disease and their families. *J Pediatr Gastroenterol Nutr*. 2012;55:412-416.

11. Webb C, Myléus A, Norström F, et al. High adherence to a gluten-free diet in adolescents with screening-detected celiac disease. *J Pediatr Gastroenterol Nutr*. 2015;60:54-59.
12. Nordyke K, Norström F, Lindholm L, Stenlund H, Rosén A, Ivarsson A. Health-related quality of life in adolescents with screening-detected celiac disease, before and one year after diagnosis and initiation of gluten-free diet, a prospective nested case-referent study. *BMC Public Health*. 2013;13:142.
13. O'Leary C, Wieneke P, Healy M, Cronin C, O'Regan P, Shanahan F. Celiac disease and the transition from childhood to adulthood: a 28-year follow-up. *Am J Gastroenterol*. 2004;99:2437-2441.
14. van Koppen EJ, Schweizer JJ, Csizmadia CGDS, et al. Long-term health and quality-of-life consequences of mass screening for childhood celiac disease: a 10-year follow-up study. *Pediatrics*. 2009;123:e582-8.
15. Fabiani E, Taccari L, Rätsch I-M, Di Giuseppe S, Coppa G, Catassi C. Compliance with gluten-free diet in adolescents with screening-detected celiac disease: a 5-year follow-up study. *J Pediatr*. 2000;136:841-843.
16. Kurppa K, Lauronen O, Collin P, et al. Factors associated with dietary adherence in celiac disease: a nationwide study. *Digestion*. 2012;86:309-314.
17. Bibbins-Domingo K, Grossman DC, Curry SJ, et al. Screening for celiac disease: US Preventive Services Task Force recommendation statement. *JAMA*. 2017;317:1252-1257.
18. Kivelä L, Kaukinen K, Lähdeaho M-L, et al. Presentation of celiac disease in Finnish children is no longer changing: a 50-year perspective. *J Pediatr*. 2015;167:1109-1115.e1.

19. Paarlahti P, Kurppa K, Ukkola A, et al. Predictors of persistent symptoms and reduced quality of life in treated coeliac disease patients: a large cross-sectional study. *BMC Gastroenterol*. 2013;13:75.

20. Dimenäs E, Carlsson G, Glise H, Israelsson B, Wiklund I. Relevance of norm values as part of the documentation of quality of life instruments for use in upper gastrointestinal disease. *Scand J Gastroenterol Suppl*. 1996;221:8-13.

21. Revicki DA, Wood M, Wiklund I, Crawley J. Reliability and validity of the Gastrointestinal Symptom Rating Scale in patients with gastroesophageal reflux disease. *Qual Life Res*. 1998;7:75-83.

22. Roma E, Roubani A, Kolia E, Panayiotou J, Zellos A, Syriopoulou VP. Dietary compliance and life style of children with coeliac disease. *J Hum Nutr Diet*. 2010;23:176-182.

23. Mahadev S, Gardner R, Lewis SK, Lebwohl B, Green PH. Quality of life in screen-detected celiac disease patients in the United States. *J Clin Gastroenterol*. 2016;50:393-397.

24. Paavola A, Kurppa K, Ukkola A, et al. Gastrointestinal symptoms and quality of life in screen-detected celiac disease. *Dig Liver Dis*. 2012;44:814-818.

25. Högberg L, Grodzinsky E, Stenhammar L. Better dietary compliance in patients with coeliac disease diagnosed in early childhood. *Scand J Gastroenterol*. 2003;38:751-754.

26. White LE, Bannerman E, Gillett PM. Coeliac disease and the gluten-free diet: a review of the burdens; factors associated with adherence and impact on health-related quality of life, with specific focus on adolescence. *J Hum Nutr Diet*. 2016;29:593-606.

27. Viljamaa M, Collin P, Huhtala H, Sievänen H, Mäki M, Kaukinen K. Is coeliac disease screening in risk groups justified? A fourteen-year follow-up with special focus on compliance and quality of life. *Aliment Pharmacol Ther*. 2005;22:317-324.

28. Newberry C, McKnight L, Sarav M, Pickett-Blakely O. Going gluten free: the history and nutritional implications of today's most popular diet. *Curr Gastroenterol Rep*. 2017;19:54.

29. Uutela T, Hannonen P, Kautiainen H, Hakala M, Paananen M-L, Häkkinen A. Positive treatment response improves the health-related quality of life of patients with early rheumatoid arthritis. *Clin Exp Rheumatol*. 2009;27:108-111.

30. Leffler DA, Kelly CP. The cost of a loaf of bread in symptomless celiac disease. *Gastroenterology*. 2014;147:557-559.

31. Mäki M, Kallonen K, Lähdeaho M-L, Visakorpi JK. Changing pattern of childhood coeliac disease in Finland. *Acta Paediatr*. 1988;77:408-412.

32. Verkasalo MA, Raitakari OT, Viikari J, Marniemi J, Savilahti E. Undiagnosed silent coeliac disease: a risk for underachievement? *Scand J Gastroenterol*. 2005;40:1407-1412.

33. Ventura A, Magazzù G, Greco L. Duration of exposure to gluten and risk for autoimmune disorders in patients with celiac disease. SIGEP Study Group for Autoimmune Disorders in Celiac Disease. *Gastroenterology*. 1999;117:297-303.

34. Sategna Guidetti C, Solerio E, Scaglione N, Aimo G, Mengozzi G. Duration of gluten exposure in adult coeliac disease does not correlate with the risk for autoimmune disorders. *Gut*. 2001;49:502-505.

35. Casellas F, Rodrigo L, Vivancos JL, et al. Factors that impact health-related quality of life in adults with celiac disease: a multicenter study. *World J Gastroenterol*. 2008;14:46-52.

Figure Legends

Figure 1. Flowchart of the study. [a]Patients were gathered from our research database and supplemented by a search in the patient records with ICD-7-10 diagnosis codes K90.0, 579A, 579.0, 269.00, 269.98 and 286.00 possibly indicating celiac disease; [b]Patients with incorrect diagnosis code were found to have e.g. hemophilia A, cow´s milk allergy, primary lactose intolerance or von Willerbrandt disease.

Figure 2. Psychological General Well-Being (A, C) and Gastrointestinal Symptom Rating Scale (B) sub-scores in adults. Celiac disease patients were first divided into those diagnosed in childhood via risk-group screening (n=48) and due to clinical suspicion (n=188) (A-B), and the group of screen-detected patients was then further divided into those who were asymptomatic (n=27) and symptomatic (n=21) at diagnosis (C). The corresponding values for 110 non-celiac adults are shown for comparison. Higher scores indicate either better psychological well-being (A, C) or more severe symptoms (B). Differences between the groups were evaluated by Kruskal-Wallis test and Bonferroni correction was used in pair-wise post-hoc comparisons. Median (horizontal line), IQR (box), and minimum and maximum values (vertical line) of the scores are presented for each patient group.

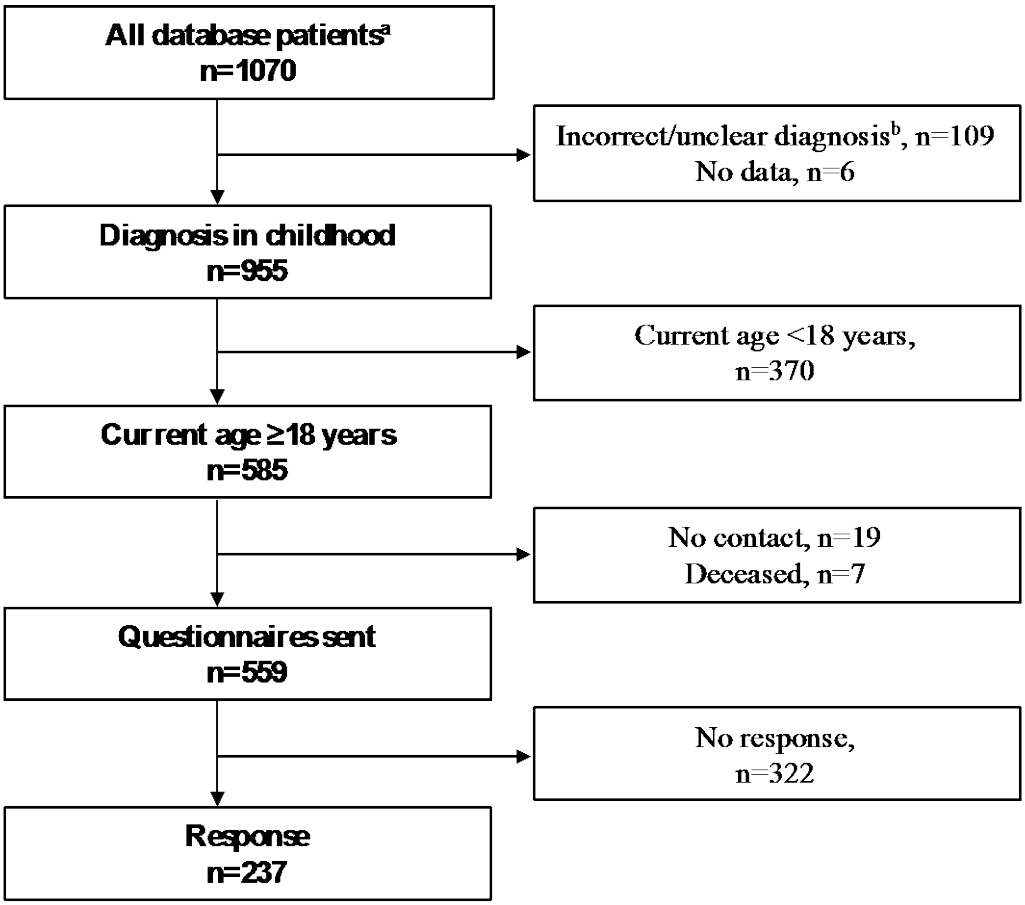
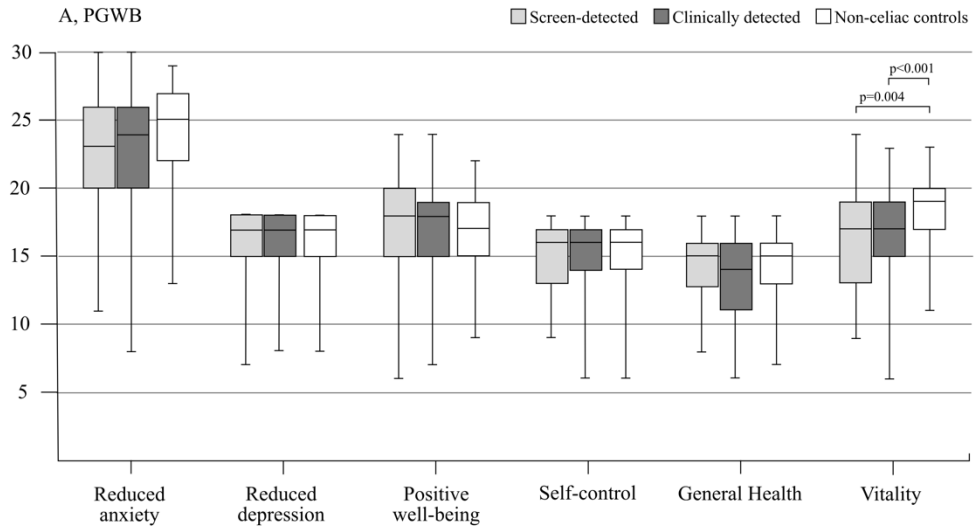
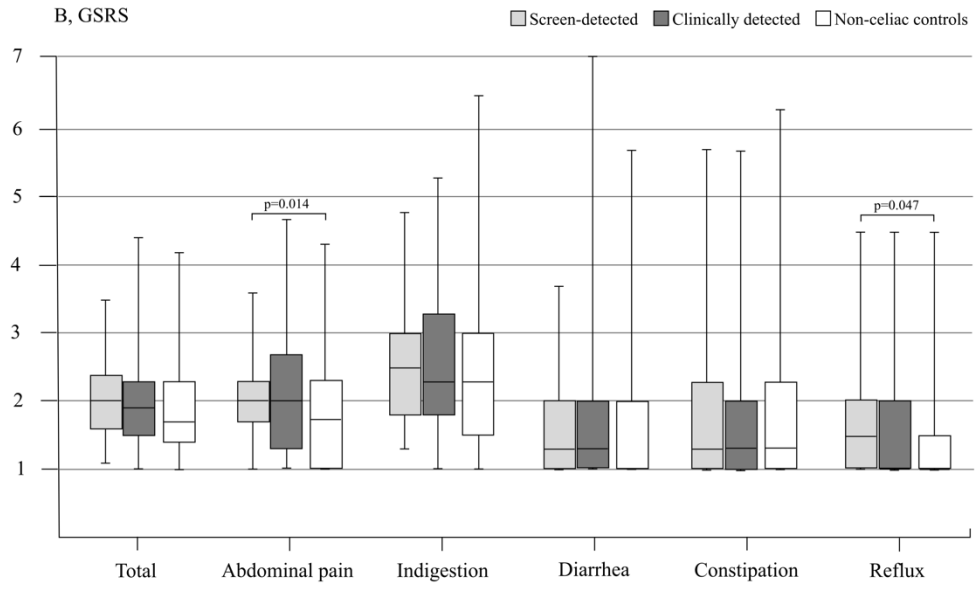

All database patients[a]
n=1070
Incorrect/unclear diagnosis[b], n=109
No data, n=6
Diagnosis in childhood
n=955
Current age <18 years,
n=370
Current age ≥18 years
n=585
No contact, n=19
Deceased, n=7
Questionnaires sent
n=559
No response,
n=322
Response
n=237

Figure 1.


A, PGWB
Screen-detected
Clinically detected
Non-celiac controls
30
25
20
15
10
5
p<0.001
p=0.004
Reduced anxiety
Reduced depression
Positive well-being
Self-control
General Health
Vitality


B, GSRS
Screen-detected
Clinically detected
Non-celiac controls
7
6
5
4
3
2
1
p=0.014
p=0.047
Total
Abdominal pain
Indigestion
Diarrhea
Constipation
Reflux

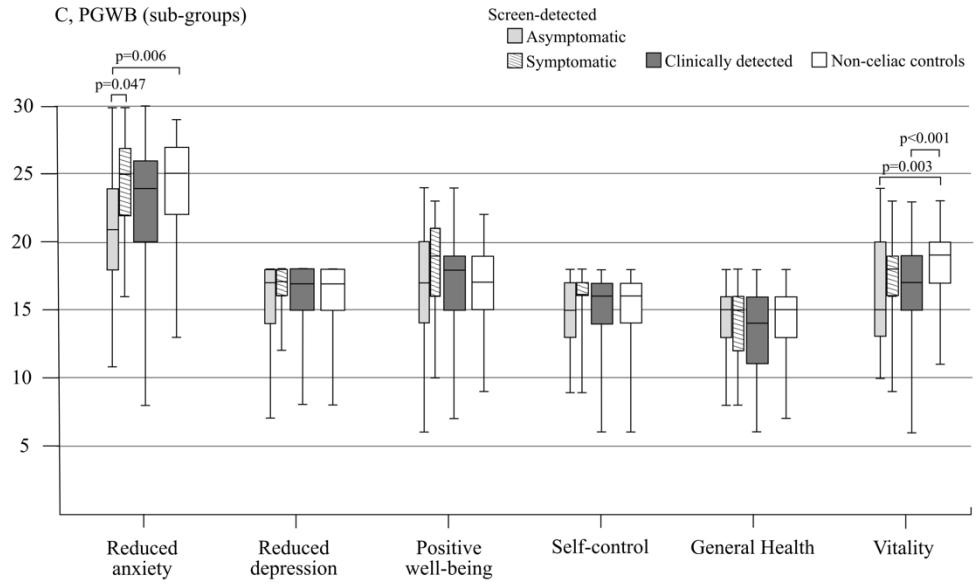

C, PGWB (sub-groups)
Screen-detected
Asymptomatic
Symptomatic
Clinically detected
Non-celiac controls
p=0.006
p=0.047
30
25
20
15
10
5
p<0.001
p=0.003
Reduced anxiety
Reduced depression
Positive well-being
Self-control
General Health
Vitality

Figure 2.

Table 1. Characteristics at time of childhood diagnosis in currently adult celiac disease patients.

	Screen-detected patients, n=48	Clinically detected patients, n=188	P value
Age at diagnosis, median (IQR), years	11.7 (8.1, 14.6)	8.7 (4.5, 13.3)	0.004
Year of diagnosis, median (IQR)	2000 (1992, 2005)	1997 (1983, 2003)	0.017
Girls, No. (%)	33 (68.8)	130 (69.1)	0.957
Symptoms [a], No. (%)	21 (43.8)	151 (86.3)	<0.001
Poor growth, No. (%)	8 (17.4)	88 (51.8)	<0.001
Anemia, No. (%)	9 (18.8)	54 (31.2)	0.091
Hemoglobin, median (IQR), g/l	130 (121, 134) [b]	123 (114, 131) [c]	0.015
Degree of villous atrophy, No. (%)			0.176
Partial	15 (34.1)	52 (31.0) [d]	
Subtotal	21 (47.7)	62 (36.9) [d]	
Total	8 (18.2)	54 (32.1) [d]	

[a] Asymptomatic signs such as poor growth, anemia and other laboratory abnormalities excluded.
[b-d] Data available only from [b] 32, [c] 158, [d] 168 of patients.
IQR, interquartile range.

Table 2. Current sociodemographic and lifestyle characteristics and comorbidities in adult celiac disease patients diagnosed in childhood.

	Screen-detected patients, n=48	Clinically detected patients, n=188	P value
Age, median (IQR), years	26.6 (21.1, 35.2)	27.2 (22.1, 38.1)	0.328
Working full-time, No. (%)	25 (67.6) [a]	93 (62.0) [b]	0.530
Student, No. (%)	19 (39.6)	59 (31.4)	0.281
Member of celiac society, No. (%)	18 (37.5)	104 (56.5)	0.019
Celiac disease in the family, No. (%) [c]	31 (64.6)	72 (40.0)	0.002
Type 1 diabetes, No. (%)	13 (27.1)	5 (2.7)	<0.001
Thyroidal disease, No. (%)	8 (16.7)	15 (8.2)	0.103
Other concomitant disease [d], No. (%)	24 (50.0)	92 (49.5)	0.947
One or more children, No. (%)	18 (37.5)	81 (44.0)	0.416
Current smoking, No. (%)	2 (4.2)	28 (15.2)	0.042
Quit smoking, No. (%)	10 (21.3)	36 (22.0)	0.921
Regular physical exercise [e], No. (%)	29 (60.4)	111 (59.0)	0.863
Body mass index, median (IQR), kg/m^2	24.6 (22.2, 26.7)	23.4 (21.3, 26.6)	0.198

[ab] Data available for only [a] 37 and [b] 149 of patients.
[c] First degree relatives; [d] For example other gastrointestinal disease, rheumatic disease, hypertension, cancer, osteoporosis, psoriasis, depression, eating disorder or asthma; [e] ≥3 times per week.
IQR, interquartile range.

Table 3. Current health experiences, dietary adherence and follow-up in adult celiac disease patients diagnosed in childhood.

	Screen-detected patients, n=48	Clinically detected patients, n=188	P value
Experienced health, No. (%)			0.633
Excellent	12 (25.0)	45 (24.1)	
Good	30 (62.5)	104 (55.6)	
Moderate	5 (10.4)	34 (18.2)	
Poor	1 (2.1)	4 (2.1)	
Concerns about health, No. (%)			0.137
None or minor	42 (89.4)	148 (80.0)	
Moderate or severe	5 (10.6)	37 (20.0)	
Symptoms related to celiac disease [a], No. (%)	10 (20.8)	44 (24.2)	0.627
Daily life restrictions [b], No. (%)	21 (46.7)	87 (47.0)	0.965
Adherence to gluten-free diet, No. (%)			0.143
Strict	35 (72.9)	150 (80.2)	
Occasional lapses	7 (14.6)	24 (12.8)	
Regular lapses [c]	6 (12.5)	8 (4.3)	
No diet	0 (0.0)	5 (2.7)	
Follow-up of celiac disease, No. (%)			0.467
Regular	14 (29.2)	45 (24.1)	
None or occasional	34 (70.8)	142 (75.9)	

[a] Self-assessment; [b] Experienced to be caused by celiac disease; [c] Lapses every week to month.

Table 4. Current characteristics in subgroups of asymptomatic and symptomatic screen-detected celiac disease patients diagnosed in childhood.

	Screen-detected		
	Asymptomatic, n=27	Symptomatic, n=21	P value
Age, median (IQR), years	27.7 (24.5, 35.6)	25.5 (20.2, 36.8)	0.513
Celiac disease in the family, No. (%)	22 (81.5)	16 (76.2)	0.729
Celiac disease-associated condition [a], No. (%)	12 (44.4)	6 (28.6)	0.260
Other concomitant disease [b], No. (%)	12 (44.4)	12 (57.1)	0.383
One or more children, No. (%)	10 (37.0)	8 (38.1)	0.940
Experienced health, No. (%)			0.424
Excellent	5 (18.5)	7 (33.3)	
Good	17 (63.0)	13 (61.9)	
Moderate	4 (14.8)	1 (4.8)	
Poor	1 (3.7)	0 (0.0)	
Concerns about health, No. (%)			0.063
None or minor	22 (81.5)	20 (100)	
Moderate or severe	5 (18.5)	0 (0.0)	
Symptoms related to celiac disease [c], No. (%)	6 (22.2)	4 (19.0)	1.000
Daily life restrictions [d], No. (%)	11 (45.8)	10 (47.6)	0.905
Adherence to gluten-free diet, No. (%)			0.936
Strict	20 (74.1)	15 (71.4)	
Occasional lapses	4 (14.8)	3 (14.3)	
Regular lapses [c]	3 (11.1)	3 (14.3)	
No diet	0 (0.0)	0 (0.0)	
Follow-up of celiac disease, No. (%)			0.174
Regular	10 (37.0)	4 (19.0)	
None or occasional	17 (63.0)	17 (81.0)	

[a] Type 1 diabetes and/or thyroidal disease; [b] For example other gastrointestinal disease, rheumatic disease, hypertension, cancer, osteoporosis, psoriasis, depression, eating disorder or asthma; [c] Self-assessment; [d] Experienced to be caused by celiac disease; [e] Lapses every week to month.
IQR, interquartile range.

eTable 1. Characteristics at celiac disease diagnosis in adults answering and not answering the study questionnaires.

	Questionnaires answered		
	Yes, n=237	No, n=322	P value
Current age, median (IQR), years	27.0 (22.0, 37.6)	25.9 (21.3, 34.7)	0.130
Age at diagnosis, median (IQR), years	9.7 (5.3, 13.6)	10.1 (6.4, 13.0)	0.529
Year of diagnosis, median (IQR)	1998 (1986, 2004)	1999 (1990, 2005)	0.075
Girls, No. (%)	164 (69.2)	167 (51.9)	<0.001
Main clinical presentation, No. (%)			0.259
Gastrointestinal	123 (52.1)	142 (45.1)	
Extra-intestinal	65 (27.5)	98 (31.1)	
Risk-group screening	48 (20.3)	75 (23.8)	
Symptoms [a], No. (%)	172 (76.8)	226 (75.6)	0.750
In risk-group screened, No. (%)	21 (44.7)	43 (57.3)	0.173
Poor growth, No. (%)	97 (44.7)	115 (38.6)	0.164
Body mass index, median (IQR)	16.5 (15.2, 18.4) [c]	16.6 (15.4, 19.3) [d]	0.264
Anemia, No. (%)	63 (28.4)	63 (23.2)	0.194
Hemoglobin, median (IQR), g/l	124 (115, 131) [e]	127 (118, 134) [f]	0.051
Severity of villous atrophy, No. (%)			0.766
Partial	67 (31.5)	98 (33.6)	
Subtotal	84 (39.4)	106 (36.3)	
Total	62 (29.1)	88 (30.1)	
Type 1 diabetes, No. (%)	16 (8.8)	40 (15.9)	0.029
Celiac disease in the family [b], No. (%)	75 (56.0) [g]	87 (44.2) [h]	0.035

[a] Asymptomatic signs such as poor growth, anemia and other laboratory abnormalities excluded; [b] First degree relatives; [c-h] Data available only from [c] 160, [d] 223, [e] 190, [f] 223, [g] 134 and [h] 197 of patients.
IQR, interquartile range.