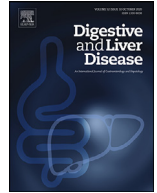




ELSEVIER

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Alimentary Tract

Prevalence and detection rate of celiac disease in Italy: Results of a SIGENP multicenter screening in school-age children

Elena Lionetti^a, Dorina Pjetraj^a, Simona Gatti^a, Giulia Catassi^b, Antonella Bellantoni^c, Massimo Boffardi^d, Mara Cananzi^e, Mauro Cinquettiⁱ, Ruggiero Francavilla^f, Basilio Malamisura^d, Monica Montuori^b, Gianvincenzo Zuccotti^g, Fernanda Cristofori^f, Paola Gaio^e, Tiziana Passaro^d, Francesca Penagini^g, Alessandra Testa^h, Chiara Maria Trovatoⁱ, Carlo Catassi^{a,*}

^a Division of Pediatrics and Center for Celiac Research, DISCO Department, Marche Polytechnic University, Ancona, Italy

^b Pediatric Gastroenterology and Liver Unit, Department of Maternal and Child Health, Sapienza-University of Rome, Rome, Italy

^c Department of Pediatrics, Bianchi-Melacrino Morelli Hospital, Reggio Calabria, Italy

^d Pediatric Unit and Center for Celiac Disease - University Hospital of Salerno, Campus of Cava de' Tirreni, Italy

^e Unit of Pediatric Gastroenterology, Digestive Endoscopy, Hepatology and Care of the Child with Liver Transplantation, Dpt. of Women's and Children's Health, University Hospital of Padova, Italy

^f Pediatric Section, Department of Interdisciplinary Medicine, University of Bari, Italy

^g Department of Pediatrics, Vittore Buzzi Children's Hospital, University of Milan, Italy

^h Clinical Biochemistry Unit, National Research Council, Reggio Calabria, Italy

ⁱ Hepatology Gastroenterology and Nutrition Unit, "Bambino Gesù" Children Hospital, Rome, Italy

^j Department of Pediatrics, "G. Fracastoro" Hospital, AULSS9 Verona, Italy

ARTICLE INFO

Article history:

Received 29 October 2022

Accepted 28 December 2022

Available online xxx

Keywords:

Celiac disease

Prevalence

Mass screening

Case finding

ABSTRACT

Background: Celiac disease is a common lifelong disorder. Recent studies indicate that the number of clinically detected cases has increased over the last decades, however little is known about changes in the prevalence and the detection rate of celiac disease.

Aim: To evaluate the current prevalence and detection rate of celiac disease in Italy by a multicenter, mass screening study on a large sample of school-age children.

Methods: children aged 5–11 years were screened at school by HLA-DQ2 and -DQ8 determination on a drop of blood in six Italian cities; total serum IgA and IgA anti-transglutaminase were determined in children showing HLA-DQ2 and/or -DQ8 positivity. Diagnosis of celiac disease was confirmed according to the European guidelines.

Results: 5994 children were eligible, 4438 participated and 1873 showed predisposing haplotypes (42.2%, 95% CI=40.7–43.7). The overall prevalence of celiac disease was 1.65% (95% CI, 1.34%–2.01%). Only 40% of celiac children had been diagnosed prior to the school screening. Symptoms evoking celiac disease were as common in celiac children as in controls.

Conclusion: In this multicenter study the prevalence of celiac disease in school-age Italian children was one of the highest in the world. Determination of HLA predisposing genotypes is an easy and fast first-level screening test for celiac disease. Without a mass screening strategy, 60% of celiac patients remain currently undiagnosed in Italy.

© 2023 The Authors. Published by Elsevier Ltd on behalf of Editrice Gastroenterologica Italiana S.r.l.

This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>)

1. Introduction

Celiac disease (CeD) is a chronic immune-mediated enteropathy triggered by gluten ingestion in genetically susceptible individuals [1]. Well identified haplotypes in the human leukocyte antigen (HLA) class II region (DQ2 [DQA*0501-DQB*0201] and DQ8 [DQA*0301-DQB1*0302]) confer a large part of the genetic suscep-

Abbreviations: Celiac disease, CeD.

* Corresponding author at: Division of Pediatrics and Center for Celiac Research, DISCO Department, Marche Polytechnic University, via F. Corridoni 60123 Ancona, Italy.

E-mail address: c.catassi@univpm.it (C. Catassi).

<https://doi.org/10.1016/j.dld.2022.12.023>

1590-8658/© 2023 The Authors. Published by Elsevier Ltd on behalf of Editrice Gastroenterologica Italiana S.r.l. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>)

Please cite this article as: E. Lionetti, D. Pjetraj, S. Gatti et al., Prevalence and detection rate of celiac disease in Italy: Results of a SIGENP multicenter screening in school-aged children, *Digestive and Liver Disease*, <https://doi.org/10.1016/j.dld.2022.12.023>

tibility to CeD [2]. An average 1% prevalence of CeD in the general population is reported, with remarkable differences between countries [3]. The clinical presentation of CeD is highly variable and ranges from gastrointestinal symptoms and extraintestinal manifestations to asymptomatic cases. CeD is diagnosed by a combination of serum disease-related antibodies and evidence of villous atrophy at the small-intestinal biopsy. Currently, the only effective treatment for CeD is a lifelong, strict, gluten-free diet (GFD) [1].

Due to the heterogeneity of the clinical presentation, a large proportion of CeD-affected subjects escape diagnosis and remain exposed to the risk of late complications such as osteoporosis and intestinal tumors [1]. In the recent literature there is a vibrant debate on which strategy may be the most suitable for early identification of hidden cases of CeD, particularly mass screening or active case-finding, i.e. offering test to individuals with certain symptoms or conditions that may be associated with CeD. While the first strategy is more effective but complex and expensive, the latter is easier to perform but less sensitive [4,5].

Recent studies suggest a general increase in the number of CeD patients that are diagnosed on clinical ground (CeD incidence) in the last decades, particularly in Western countries [6]. This is mainly due to increased awareness of CeD among physicians and general population, as well as increased availability of easy-to-perform serological testing for CeD. Nevertheless, little is known about changes in CeD prevalence and detection rate (% ratio between clinically diagnosed cases and overall CeD prevalence) over time. In Italy a previous study performed in two areas of North and Middle Italy reported a prevalence of CeD of 1.58% in school-age children, with a significant increase of prevalence over the past 25 years [7].

The purpose of the present study was to re-evaluate the CeD prevalence and detection rate in Italy on a nationwide/multicenter basis, in a large sample of school-age children screened at school by an innovative screening algorithm based on the determination of CeD predisposing genes (HLA -DQ2 and -DQ8) as the first-level test.

2. Methods

2.1. Study-design

This is a multi-center, nationwide, cross-sectional study performed by a Study Group of the Italian Society for Pediatric Gastroenterology, Hepatology and Nutrition (SIGENP) between May 2017 and February 2020 in school-age children living in six Italian cities (Milan, Padua, Rome, Reggio Calabria, Cava de' Tirreni, Bari) scattered through the country. The study design is the same of a previous survey conducted by some of us (S.G., E.L., G.C., C.C.) in two urban areas of Italy (Ancona and Verona) from May 2015 to December 2016 [7].

Briefly, eligible participants were primary school students aged 5–11 years screened at school by HLA-DQ2 and -DQ8 determination on a drop of whole blood taken by capillary draw. Exclusion criteria were (a) previous diagnosis of CeD, and (b) being on a GFD for any reason. Children positive for CeD-compatible HLA haplotypes were invited to return at the outpatient clinic to perform a full clinical evaluation and blood drawing to determine total serum IgA and IgA class anti-tissue transglutaminase (tTG) (or IgG class anti-deamidated gliadin peptide antibodies [DGP] in children showing levels of serum IgA lower than 2 standard deviations [SD] the normal value for gender and age). Parents were asked to provide basic demographic information, family history, and to complete a symptom questionnaire. Symptoms suggestive of CeD over the past 3 months were assessed and included: recurrent abdominal pain, constipation, frequent diarrhea, recurrent vomiting, growth failure, poor appetite, iron deficiency anemia, oral aphtho-

sis. The second-level evaluation was considered positive in children showing either (1) IgA anti-tTG higher than upper normal limit (UNL) or (2) selective IgA deficiency (SIgAD = total serum IgA lower than 5 mg%) associated with IgG anti-DGP positivity. Anti-endomysial antibody (EMA) was determined on a second serum sample in cases showing IgA anti-tTG positivity. According to the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) 2012 criteria [8], a small intestinal biopsy was recommended in children showing either (a) EMA positivity and IgA anti-tTG levels higher than 1x and lower than 10x the upper normal limit or (b) IgG anti-DGP positivity and SIgAD. The diagnosis of CeD was eventually determined in children showing either: (1) IgA anti-tTG, EMA positivity and villous atrophy (Marsh-Oberhuber grade 3 lesion) at the small intestinal biopsy; (2) IgA anti-tTG levels higher than 10x UNL and EMA positivity, in 2 different samples; (3) IgG anti-DGP positivity, SIgAD and villous atrophy (Marsh-Oberhuber grade 3 lesion) at the small intestinal biopsy; Potential CeD was diagnosed in subjects with IgA anti-tTG and EMA positivity in two different samples, and a Marsh-Oberhuber grade 0–1 enteropathy at the small intestinal biopsy. Subjects showing isolated IgA anti-tTG positivity (EMA negative) were left on a gluten-containing diet and re-evaluated after 3–6 months.

The study was approved by the Ethical Committees of participating Centers, and informed consent from the parents/caregivers was obtained.

2.2. HLA genotyping

For HLA-DQ2/-DQ8 determination, a quick HLA-DQ typing test (Celiac Gene Screen; Biodiogene, Palermo, Italy) was used. The Celiac Gene Screen identifies the alleles DQB1*02 codifying for the beta chain of the DQ2 antigen and the DQB1*0302 alleles codifying for the DQ8 beta chain, as previously described in details [9]. A validation study showed a 100% concordance of this test with the conventional assay [10]. This method allows a yes/no assessment of HLA-DQ2 and -DQ8 genes but does not define the different HLA-DQ2 and -DQ8 haplotypes/genotypes. Based on this assessment, the children were classified as having no risk of CeD (lack of HLA-DQ2 and HLA-DQ8), or CeD predisposition (the presence of HLA-DQ2 and/or HLA-DQ8).

2.3. Serological assays

All serum samples were kept frozen at -20°C until analysis by one of us (M.B.) in the Clinical Chemistry Unit at the Cava de' Tirreni Hospital. IgA anti-tTG and IgA EMA antibodies were determined by an ELISA test (Eu-tTG IgA; Eurospital SpA, Trieste, Italy) and an indirect immunofluorescence assay (Anti-endomysium; Eurospital SpA), respectively. IgG anti-DGP were performed by an ELISA test (α -Gliadin-Pep IgG; Eurospital SpA). Samples showing IgA anti-tTG <16 UA/mL, IgG anti-DGP <15 UA/mL and EMA titer $<1:5$, were considered negative. Total serum IgA concentration was determined by nephelometric technique (N Latex IgA; Siemens Healthcare Diagnostics, Siemens Healthcare GmbH, Erlangen, Germany).

2.4. Small intestinal biopsies

Small bowel biopsy was performed by upper gastrointestinal endoscopy under deep sedation. At least 4 biopsy samples were taken from the second or third part of the duodenum and at least 1 from the duodenal bulb. Lesions in the small intestine were graded according to the Marsh-Oberhuber classification [11].

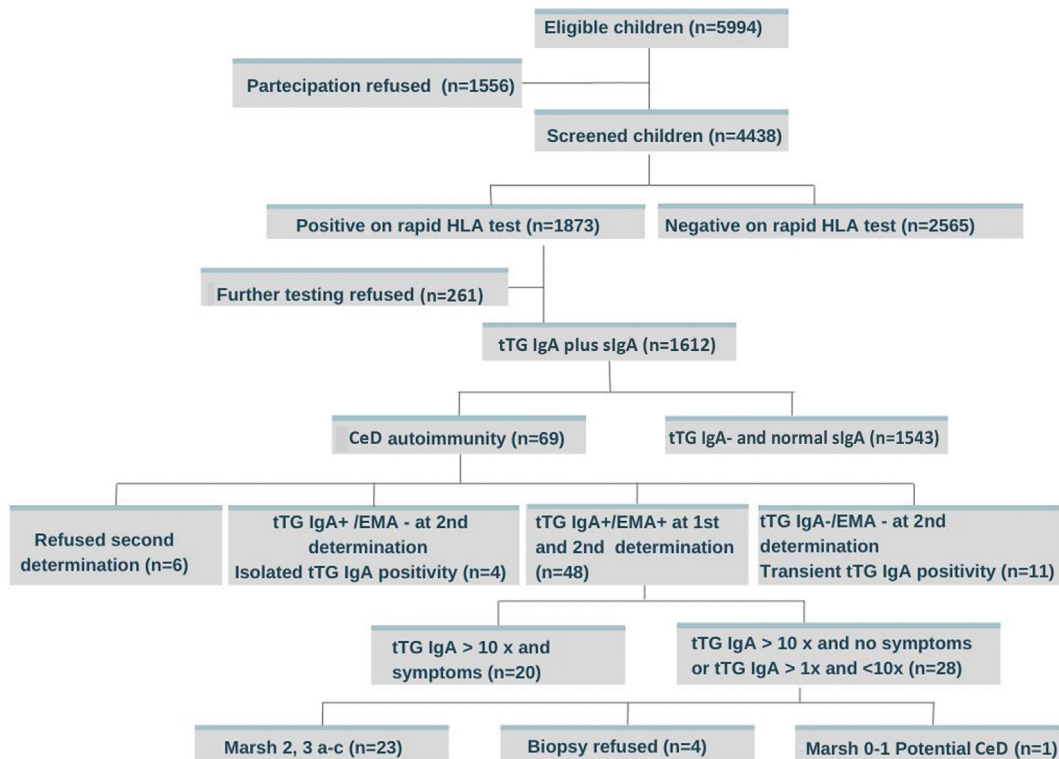


Fig. 1. Study flow diagram. CeD: celiac disease; EMA: anti-endomysial antibody; sIgA: serum IgA; tTG: tissue transglutaminase.

2.5. Analysis

Descriptive statistics were performed on demographic and clinical characteristics in the data set. Results are presented as mean and standard deviation for continuous variables or percentages (%) for categorical variables. Chi-square tests with Yates' correction for continuity and Mann-Whitney tests were used to compare categorical and continuous variables between groups. Data were analyzed by the statistical package Graph Pad Prism version 7.00 for Windows (GraphPad Software, La Jolla, CA). All analyses were conducted at an α -level 0.05 significance.

3. Results

The screening flow-chart and the main results of the study are shown in Fig. 1.

3.1. Screened sample and first-level test

Overall, 5994 children were eligible and 4438 agreed to participate (74%): they were 1002 in Milan, 160 in Padua, 824 in Rome, 1169 in Bari, 428 in Reggio Calabria and 855 in Cava de' Tirreni; 1873 of them showed CeD permissive haplotypes (42.2% of the screened children, 95% CI=40.7–43.7), but 262 of them refused further testing. The total number of children refusing the first- or second-level testing was 1818, with an overall adherence to the screening project of 69.6%. Demographic characteristics of the study participants are shown in Table 1.

3.2. Second-level test

Sixty-nine children showed IgA anti-tTG positivity (69/1612; 4.28%, 95% CI: 3.35–5.39). Six of these refused a second antibody determination (mean anti-tTG 1.5x; SD 0.44, 3 of them were EMA positive), while 11 showed transient, low-grade isolated IgA anti-tTG positivity (mean anti-tTG 2.27x; SD 0.99) that normalized at

Table 1

Demographic characteristics of participating children.

Demographic features	HLA screened children (n = 4438)
Male, n (%)	2248 (50.65%)
Age, mean (SD)	8.14 (\pm 1.30)
Origin, n (%)	
Europe	4320 (97.34%)
Asia	56 (1.26%)
North Africa	21 (0.47%)
Sub-Saharan Africa	12 (0.27%)
Central and South America	28 (0.63%)

6-month follow-up. In 4 of 69 subjects, persistent and isolated IgA anti-tTG positivity was found (mean anti-tTG level 1.3x; SD 0.11; EMA negative), as confirmed at 6-month follow-up.

3.3. Diagnosis of CeD

Forty-eight children had serum CeD autoimmunity confirmed at the second test. Out of these 48 cases, (a) 20 children presented with anti-tTG levels 10-fold higher the upper normal limit (>10) and anti-endomysial antibody (EMA) IgA positivity, so fulfilling the ESPGHAN criteria for a biopsy-sparing CeD diagnosis [8]. (b) 24 patients performed a small intestinal biopsy; of them, 23 (95%) had villous atrophy (Marsh 3a–3c), whereas 1 showed a normal mucosa and a Marsh 1 lesion, and was diagnosed as potential CeD. (c) 4 tTG-IgA and EMA positive children refused to perform the biopsy, but were counted in the CeD group. CeD prevalence was significantly higher in females (n = 40 females, 83%; n = 8 males, 17%, p = 0.001).

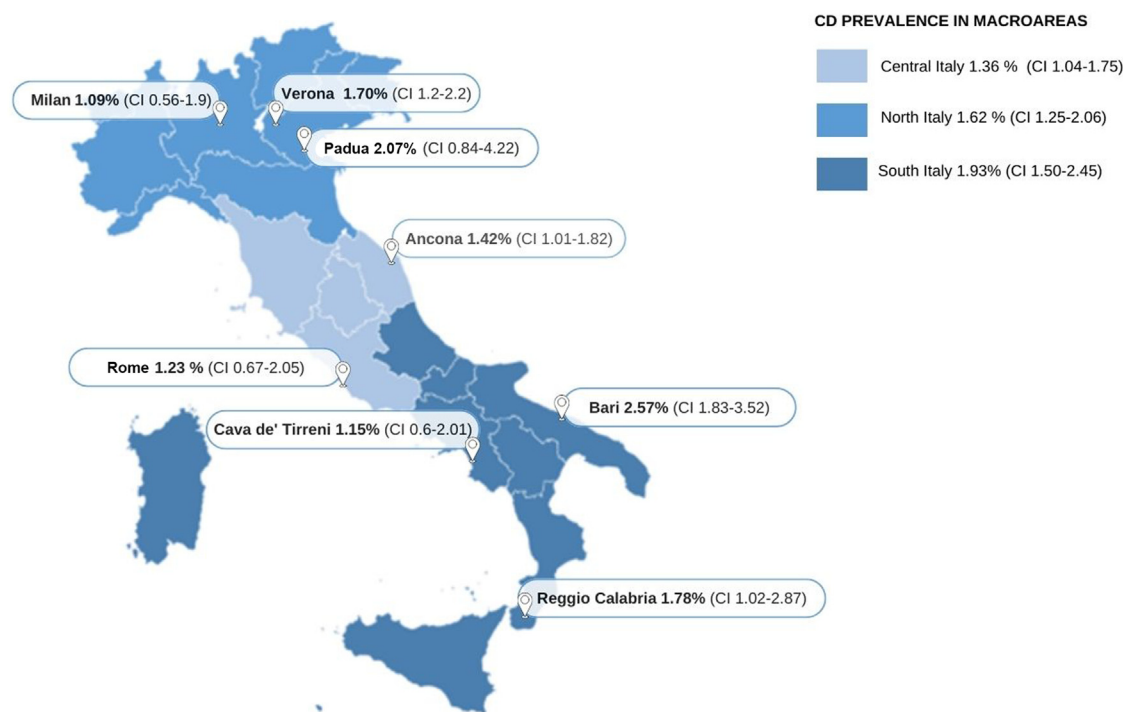
Table 2 shows the demographic and clinical features of CeD children as compared to anti-tTG negative, HLA-DQ2 or DQ8 positive subjects. Approximately half (43.7%) of them did not report any symptom as documented by the clinical notes. Upon history, the most common clinical symptoms in children with CeD

Table 2

Demographic and clinical characteristics of subjects with celiac disease and controls (HLA-positive and Anti-tTG negative).

Demographic and clinical features	Controls (HLA pos, anti tTG neg) n = 1543	Celiac Disease n = 48	p-value
Females, n (%)	749 (48.6)	40 (83.3)	<0.001
Median Age (IQR)	8.1 (7.0–9.2)	8.3 (9.3–7.3)	0.329
Family history of CeD, n (%)	130 (8.4)	7 (14.6)	0.22
No symptoms, n (%)	781 (50.6)	21 (43.7)	0.42
Recurrent abdominal pain, n (%)	247 (16.0)	13 (27.1)	0.066
Constipation, n (%)	279 (18.0)	10 (20.83)	0.766
Frequent diarrhea ^a , n (%)	64 (4.2)	4 (8.3)	0.294
Recurrent vomiting ^b , n (%)	19 (1.23)	0 (0)	0.921
Growth failure, n (%)	64 (4.2)	3 (6.3)	0.721
Poor appetite, n (%)	124 (8.2)	2 (4.1)	0.479
Iron deficiency anemia, n (%)	44 (2.9)	0 (0)	0.486
Oral aphthosis, n (%)	210 (13.6)	6 (12.5)	0.994

IQR, interquartile range; tTG, tissue transglutaminase.

^a Frequent diarrhea was defined as more than 1 episode of loose stools in a week.^b Recurrent vomiting was defined as more than 4 episodes of vomiting in a month.**Fig. 2.** Celiac disease (CeD) prevalence in each center, and in three macroareas: North, Center and South of Italy.

were abdominal pain ($n = 13$, 27.1%) and constipation ($n = 10$, 20.8%). Family history of CeD in a first-degree relative was reported in 14.6% of CeD patient, not significantly different from controls ($p = 0.23$).

3.4. Epidemiology of CeD in Italy

The prevalence of screening-detected CeD in the 1612 children with HLA positivity was 2.98% (95% CI, 2.20%–3.92%) and 1.15% (95% CI, 0.85%–1.52%) in the screened sample.

In order to determine the overall CeD prevalence, cases with previously diagnosed CeD were included in the calculations. Since these cases belonged to the eligible population, all the following calculations were referred to the eligible population. The overall CeD prevalence in the eligible population sample ($n = 5994$) was calculated (1) including the 32 cases of known CeD, and assuming (2) 100% negative predictive value of HLA determination, (3) the same prevalence of CeD in screened children ($n = 4176$) and in those refusing the screening ($n = 1818$). The estimated overall

prevalence of CeD in the eligible study-group was 1.65% (95% CI, 1.34%–2.01%), and was 2.57% (95% CI, 1.83%– 3.52%) in Bari, 1.15% (95% CI, 0.60%– 2.01%) in Cava de' Tirreni, 1.09% (95% CI, 0.56%– 1.90%) in Milan, 2.07% (95% CI, 0.84%– 4.22%) in Padua, 1.78% (95% CI, 1.02%– 2.87%) in Reggio Calabria, 1.23% (95% CI, 0.67%– 2.05%) in Rome samples, respectively. Overall, 60% of the children with CeD were diagnosed by mass screening ($n = 48$) while only 40% ($n = 32$) were diagnosed on clinical ground prior to the screening project.

In order to extend the countrywide data on CeD prevalence, we merged the current results with those of a previous study conducted in the years 2015–16 in North/Central Italy, with the same study-design and methods [7]. The following results were obtained on an overall sample of 9008 school-age children screened at school in different areas of Italy (Fig. 2). Overall the percentage of HLA-DQ2 and/or -DQ8 among Italian school-age children was 42.5 (95% CI, 41.5–43.6), 43.7% (95% CI, 42.0–45.5) in subjects from North, 40.4% from Center (95% CI 38.7– 48.1), and 43.8% (95% CI, 41.8 - 45.8) from South Italy, with significant differences between

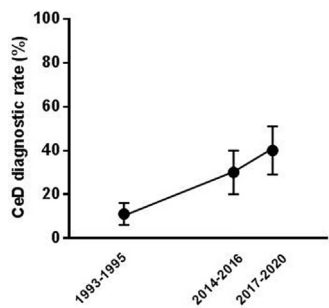


Fig. 3. Celiac Disease% detection rate (ratio between cases diagnosed on clinical ground and the overall prevalence of disease) over time in Italy. All data were collected by means of a targeted mass screening project. CeD: celiac disease.

North vs Center and Center vs South ($p = 0.006$ and $p = 0.01$ respectively). The overall prevalence of CD in Italy was 1.62 (95% CI, 1.39–1.86), 1.62% (95% CI 1.25–2.06) in the North of Italy, 1.36% (95% CI 1.04–1.75) in the Center, and 1.93% (95% CI 1.50–2.45) in the South, with a statistical difference between Central and South Italy ($p = 0.0482$) (Fig. 2).

The prevalence of CeD was 1.58% (95% CI, 1.26–1.90) in the screening project performed in the years 2015–16, not significantly different from that found in the current study (1.65%, 95% CI 1.34–2.01%) performed in the years 2017–20 ($p = 0.68$).

The percentage of CeD cases diagnosed previous to the school screening (detection rate), i.e. the so-called “visible part of the CeD iceberg”, was 40% in this study, significantly higher than the 11% found in a pioneer screening performed in Italy in the years 1992–1994, but not significantly different from the 30% found in the 2015–2016 study ($p = 0.18$) [7] (Fig. 3).

4. Discussion

According to a recent meta-analysis, the pooled world prevalence of serological CeD autoimmunity is 1.4%, while the prevalence of biopsy-confirmed CeD is much lower (0.6%) [12]. However, CeD frequency is widely variable in different countries. This Italian multicenter, cross-sectional study provides accurate data on the prevalence of CeD in a large population sample. The overall prevalence of CeD in Italy was 1.65% (95% CI, 1.34–2.01), one of the highest in the world. In Sweden cross-sectional screening studies have shown a CeD prevalence in school-age children of 2.2 and 2.7% in two different birth cohorts, respectively [13]. In a mass screening project performed in Finland in the early 2000s on school-age children, Mäki and co-workers found a CeD prevalence of 1% [14]. In a population-based study performed in the United States on 22,277 participants (children and adults) from 2009 to 2014, a prevalence of 0.7% was found [15]. In Argentina, a screening study involving 2230 children showed a prevalence of biopsy-proven CeD of 1.26% [16]. In China, CeD prevalence was estimated around 0.27%, with great variability within the country [17–18]. In Japan CeD is so rare (0.05%) [19] that this country may be defined as a “Celiac heaven”. This variable prevalence worldwide is dependent on several factors, either intrinsically related to CeD pathophysiology (population prevalence of HLA predisposing genotypes and amount of gluten consumption) or screening-dependent, such as age of screened subjects and diagnostic algorithm.

The determination of HLA predisposing genes as the first-level screening test was one of the distinctive features of our diagnostic algorithm. A similar procedure has been adopted to select newborns at risk of type 1 diabetes in long-term follow-up studies, particularly the TEDDY study [20]. Since the percentage of HLA-DQ2 and -DQ8 negative CeD patients is negligible (about 0.3%) [21], lack of HLA CeD-predisposing genotypes exclude CeD with

a high level of confidence (very high negative predictive value). Based on our data, the prevalence of CeD in HLA-positive screened subjects (~3%) is comparable to other at-risk groups, e.g. patients with other autoimmune diseases. Therefore, the HLA determination as first-level test “transforms” a mass screening into a case-finding procedure. Need of a single blood drop, quick result and low cost are further advantages of the HLA determination used in our study. Another strong point of our protocol was the application of the recent ESPGHAN diagnostic guidelines [8], requiring clear-cut positivity of CeD serology and, in selected cases only, small intestinal biopsy confirmation. This diagnostic algorithm avoided both overestimation (typical of studies evaluating the prevalence of CeD serological autoimmunity) and underestimation (typical of studies requiring always intestinal biopsy confirmation) of CeD prevalence.

In Italy the previously reported tendency of increasing CeD prevalence in children during the last three decades [7], seems to be slowing down in the last years (from 1.58% in 2014–16 to 1.65% in 2017–20). However, further investigation will be helpful to confirm this trend, as our observation time may be too short and the sample size too small to register a significant variation. Interestingly, our study spotted differences in the prevalence of CeD between Central and South Italy. Similar or even higher regional differences have been reported in other countries. For instance, in India there is great variability in CeD prevalence between the North and the South of the country, and this probably reflects the much higher consumption of wheat in the northern area [22]. Regional variations of CeD prevalence have been registered also in the United Kingdom and USA [15,23]. In particular, in the USA the gradient was inverted, with a higher risk of CeD in those living North of the 40th degree [15]. We speculate that the higher prevalence of CeD in the South of Italy may be related to higher consumption of wheat [24]. The slightly higher prevalence of HLA predisposing genes in the South of Italy may also contribute to explain this finding.

The CeD detection rate reflects the incidence of CeD cases that are newly diagnosed on clinical ground. Our study documented an active trend of increasing CeD detection rate over time (from 30 to 40% of cases during the last years). However, even in a country showing (1) high CeD awareness among primary care doctors and the general audience, (2) an easily accessible gluten-free food and (3) a financial support for patients with CeD, still 60% of affected subjects remain undiagnosed. These data have been confirmed in other countries, where the proportion of clinically detected CeD mostly remains below 30%, and is occasionally very low, e.g. in India and China [5]. The main reasons of low CeD detection rate are the wide clinical variability of CeD, the high frequency of clinically “silent” CeD cases (44% in this study) and poor CeD awareness.

CeD-related symptoms were as common in screening-detected CeD cases and non-CeD children, a finding that had previously been reported [25]. This result further confirms that the case-finding strategy, i.e. serological testing of subjects with CeD-related symptoms, is not enough efficient for CeD detection at the population level. On the other hand, our study confirms that a population-based screening approach is the most effective way to identify asymptomatic patients with CeD and potentially prevent morbidity due to diagnostic delay [26]. Recent data suggest that CeD mass screening is not only very sensitive but does not have a negative impact on the adherence to the GFD [27] and the quality of life [28] even though this last issue is still controversial [29]. Norström et al. recommended CeD mass screening according to the thresholds for cost-effectiveness, especially in population where there is easy accessibility to GFD [30]. Some aspects of CeD mass screening remain to be elucidated, possibly by large prospective studies with long-term follow-up, such as the best target age, the cost/benefit ratio for the Health Care System, and the long-term impact on CeD complications.

Besides the already mentioned precision of our diagnostic algorithm, strengths of this work are the population-based design and the large sample size. Merging the results of this and our previous study [7], more than 9000 subjects were involved in 8 Italian centers, with the first level CeD screening conducted at school and not in a clinical setting. This allowed a realistic estimate of the prevalence rate and a good representation of the countrywide Italian situation. The main limitations were the less than optimal adherence (69.6%), the assumption that CeD frequency was the same in the eligible children who did not participate in the screening and the possibility of missing the occasional CeD patient HLA-DQ2 and -DQ8 negative. Since our population sample was mainly composed by children of European origin, we cannot extrapolate our findings to other minority groups.

In conclusion, the present study shows a high prevalence of CeD (1.65%) among children in Italy. CeD affects more females and is more frequent in the South of Italy. Despite recent efforts for improvement, the CeD detection rate remains low in this country. The weakness of the “case finding” strategy in diagnosing CeD suggests that alternative approaches, particularly a well-designed school screening, should be implemented to offer an early diagnosis and possibly prevent long-term CeD complications.

Conflict of interest

Prof Carlo Catassi has served as scientific consultant for Dr. Schaer Food and NOOS s.r.l. The other co-authors have no conflict to declare.

Sources of funding

This study was funded in part by S.C.S. Consulting, Bologna, Italy.

Acknowledgements

We thank the Italian Society for Pediatric Gastroenterology, Hepatology and Nutrition (SIGENP) for endorsement and logistic support of this nationwide project. The collaboration of Mr. Francesco Fumelli from S.C.S. Consulting (Bologna, Italy) and Dr. Giovanni Maggiore from Biodiogene (Palermo, Italy) is greatly appreciated.

References

- [1] Catassi C, Verdu EF, Bai JC, et al. Coeliac disease. *Lancet* 2022;399:2413–26.
- [2] Brown NK, Guandalini S, Semrad C, et al. A clinician's guide to celiac disease HLA genetics. *Am J Gastroenterol* 2019;114:1587–92.
- [3] Makharia GK, Singh P, Catassi C, et al. The global burden of coeliac disease: opportunities and challenges. *Nat Rev Gastroenterol Hepatol* 2022;19:313–27.
- [4] Elwenspoek MMC, Jackson J, Dawson S, et al. Accuracy of potential diagnostic indicators for coeliac disease: a systematic review protocol. *BMJ Open* 2020;10:e038994.
- [5] Catassi C, Lionetti E. Case finding for celiac disease is okay, but is it enough? *J Pediatr Gastroenterol Nutr* 2013;57:415–17.
- [6] King JA, Jeong J, Underwood FE, et al. Incidence of celiac disease is increasing over time: a systematic review and meta-analysis. *Am J Gastroenterol* 2020;115:507–25.
- [7] Gatti S, Lionetti E, Balanzoni L, et al. Increased prevalence of celiac disease in school-age children in Italy. *Clin Gastroenterol Hepatol* 2020;18:596–603.
- [8] Husby S, Koletzko S, Korponay-Szabó IR, et al. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease. *J Pediatr Gastroenterol Nutr* 2012;54:136–60.
- [9] Verma AK, Singh A, Gatti S, et al. Validation of a novel single-drop rapid HLA-DQ2/-DQ8 typing method to identify subjects susceptible to celiac disease. *J Gastroenterol Hepatol Open* 2018;2:311–16.
- [10] Megiorni F, Mora B, Bonamico M, et al. A rapid and sensitive method to detect specific human lymphocyte antigen (HLA) class II alleles associated with celiac disease. *Clin Chem Lab Med* 2008;46:193–6.
- [11] Oberhuber G, Granditsch G, Vogelsang H. The histopathology of coeliac disease: time for a standardized report scheme for pathologists. *Eur J Gastroenterol Hepatol* 1999;11:1185–94.
- [12] Singh P, Arora A, Strand TA, et al. Global prevalence of celiac disease: systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2018;16:823–36.
- [13] Ivarsson A, Myléus A, Norström F, et al. Prevalence of childhood celiac disease and changes in infant feeding. *Pediatrics* 2013;131:e687–94.
- [14] Mäki M, Mustalahti K, Kokkonen J, et al. Prevalence of celiac disease among children in Finland. *N Engl J Med* 2003;348:2517–24.
- [15] Unalp-Arida A, Ruhl CE, Choung RS, et al. Lower prevalence of celiac disease and gluten-related disorders in persons living in Southern vs Northern latitudes of the United States. *Gastroenterology* 2017;152:1922–32.
- [16] Mora M, Litwin N, del Carmen Toca M, et al. Prevalence of celiac disease: multicentric trial among pediatric population from five urban districts in Argentina. *Arch Argent Pediatr* 2012;110:490–6.
- [17] Zhou C, Gao F, Gao J, et al. Prevalence of coeliac disease in Northwest China: heterogeneity across Northern Silk road ethnic populations. *Aliment Pharmacol Ther* 2020;51:1116–29.
- [18] Liang CP, Geng LL, Chen PY, et al. Celiac disease may be rare among children in South China. *J Int Med Res* 2022;50:030006052210769.
- [19] Fukunaga M, Ishimura N, Fukuyama C, et al. Celiac disease in non-clinical populations of Japan. *J Gastroenterol* 2018;53:208–14.
- [20] Rewers M, Hyöty H, Lernmark Å, et al. The Environmental Determinants of Diabetes in the Young (TEDDY) study: 2018 update. *Curr Diab Rep* 2018;18:136.
- [21] Karell K, Louka AS, Moodie SJ, et al. HLA types in celiac disease patients not carrying the DQA1*05-DQB1*02 (DQ2) heterodimer: results from the European genetics cluster on celiac disease. *Hum Immunol* 2003;64:469–77.
- [22] Ramakrishna BS, Makharia GK, Chetri K, et al. Prevalence of adult celiac disease in India: regional variations and associations. *Am J Gastroenterol* 2016;111:115–23.
- [23] West J, Fleming KM, Tata LJ, et al. Incidence and prevalence of celiac disease and dermatitis herpetiformis in the UK over two decades: population-based study. *Am J Gastroenterol* 2014;109:757–68.
- [24] Data available at <https://www.gdowweek.it/indagine-doxa-aidepi-di-che-pasta-siamo-al-sud/>.
- [25] Rosén A, Sandström O, Carlsson A, et al. Usefulness of symptoms to screen for celiac disease. *Pediatrics* 2014;133:211–18.
- [26] Fuchs V, Kurppa K, Huhtala H, et al. Factors associated with long diagnostic delay in celiac disease. *Scand J Gastroenterol* 2014;49:1304–10.
- [27] Kivelä L, Popp A, Arvola T, et al. Long-term health and treatment outcomes in adult coeliac disease patients diagnosed by screening in childhood. *United European Gastroenterol J* 2018;6:1022–31.
- [28] Iorrida D, Valitutti F, Vestri A, et al. Dietary compliance and quality of life in celiac disease: a long-term follow-up of primary school screening-detected patients. *Front Pediatr* 2021;9:787938.
- [29] Leffler DA, Kelly CP. The cost of a loaf of bread in symptomless celiac disease. *Gastroenterology* 2014;147:557–9.
- [30] Norström F, Myléus A, Nordyke K, et al. Is mass screening for coeliac disease a wise use of resources? A health economic evaluation. *BMC Gastroenterol* 2021;21:159.